Human Dendritic Cell Laboratory

Newcastle University

www.hudendritic.org

Erdheim Chester Disease: cancer, but not as we know it

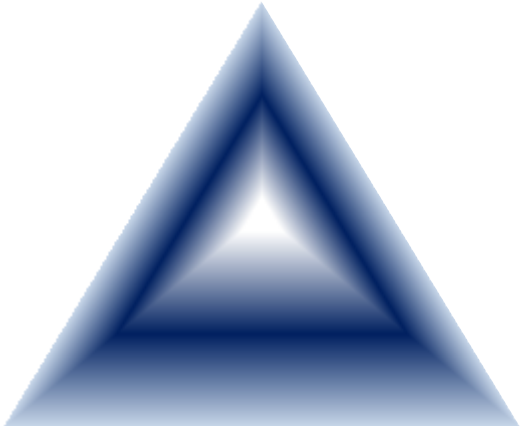
6th Annual International ECD Medical Symposium
Orlando, FL | November 14 – 16, 2018

Biologist

Somatic mutation

Selective growth or survival advantage

Interaction with immune system



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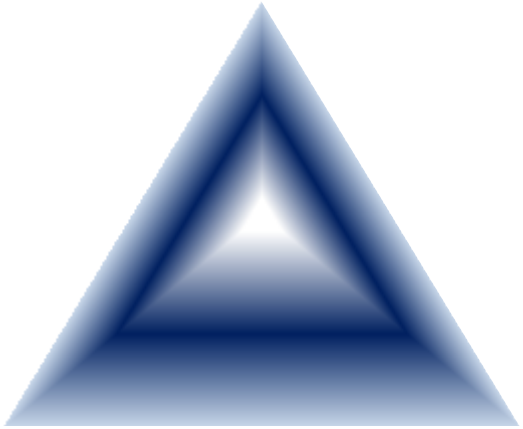

Clinician

Serious condition

Biopsy, stage and treat

Organ dysfunction

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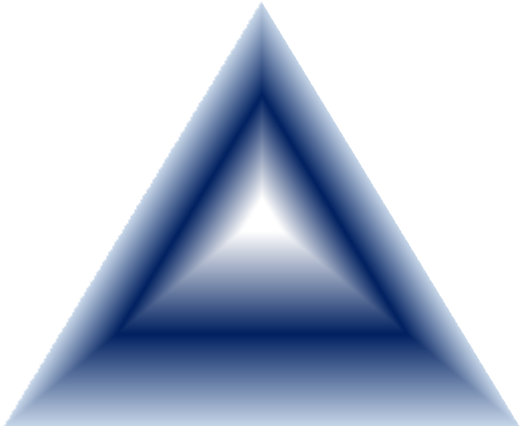


Clinician

Serious condition

Biopsy, stage and treat

Organ dysfunction

Patient

Feel unwell

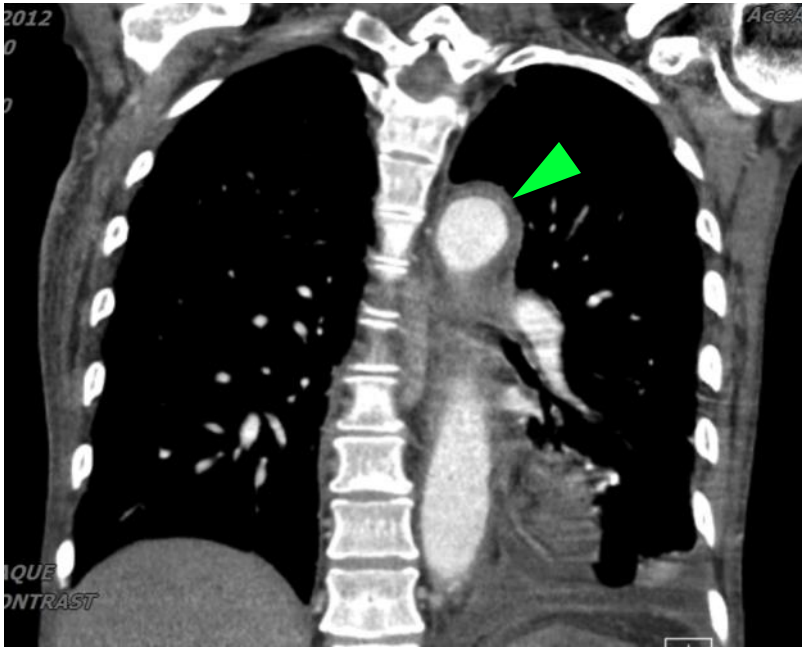
Require intensive therapy

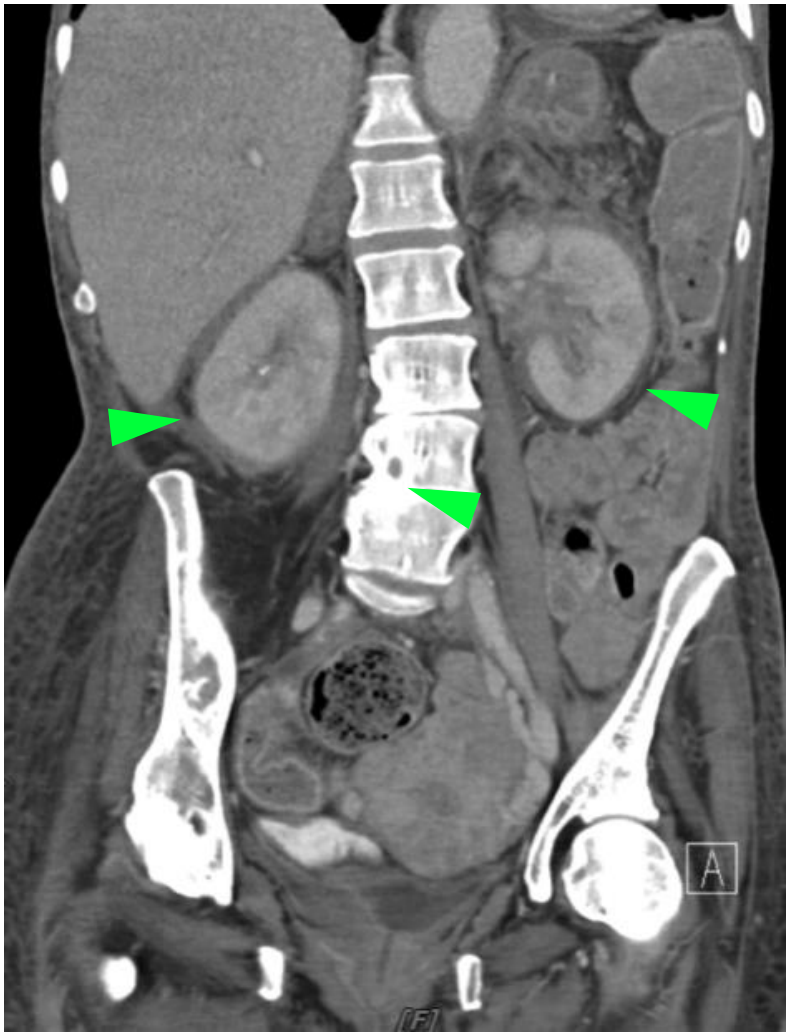
Might not survive

Mrs B

- 59 year old retired
- Skin rash for 2 years
- Biopsy: Langerhans cell histiocytosis (treated topically)
- Lower limb edema, heart failure
- CT: aortitis and retroperitoneal fibrosis
- 2 months later dysarthria and ataxia – MRI brain: vertebral infarct
- Retroperitoneal biopsy: Erdheim Chester Disease

Mrs B: CT

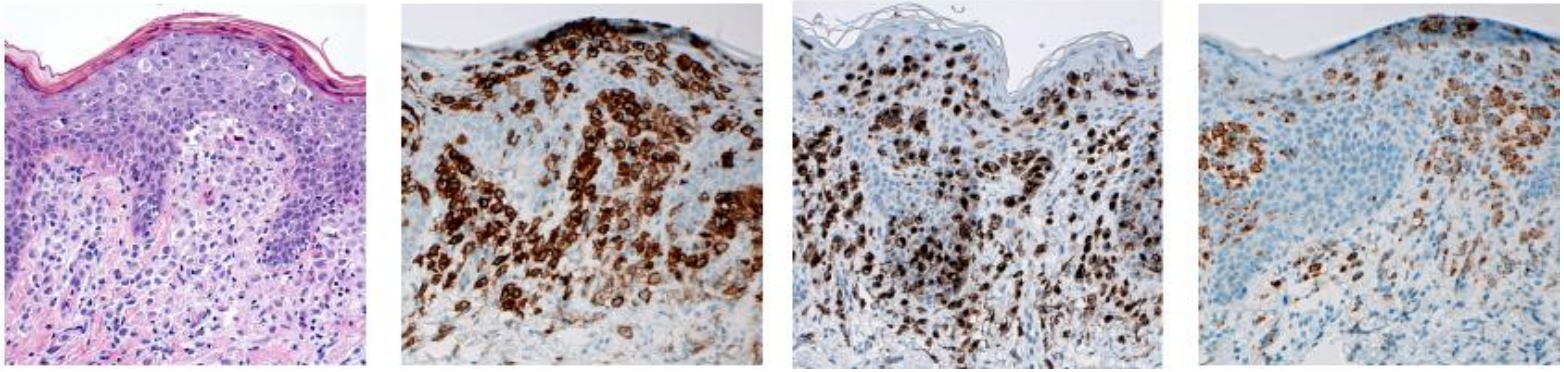




Mrs B: Pathological diagnosis

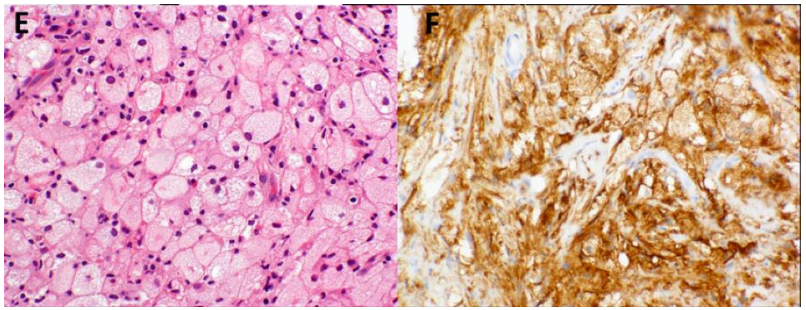
Skin LCH

H&E | CD1a | Lang | BRAF^{V600E}



Perinephric ECD

H&E | CD68



Foamy macrophages

BRAF V600E in blood and skin

Mrs B: Treatment and outcome

- Cladribine 5mg/m^2 x 5 days every 4-6 weeks
- After second course patient required admission with chest infection
- Patient was refused hematology ward ‘we can’t admit this patient to a regional leukemia unit – its not our disease’
- 8 weeks recovering on general medical ward
- Patient: ‘No-one has heard of my disease and no-one seems interested’
- Bone marrow suppression (plts 24)
- Skin breaking down – LCH still active
- Repeat CT – progression of ECD now involving coeliac axis and causing arterial insufficiency to bowel
- Referred for V600E Basket study but did not make performance status
- Palliative care at home - died

Clinical and Radiologic Responses to Cladribine for the Treatment of Erdheim-Chester Disease. (2017) Goyal, G., Shah, M.V., Call, T.G., Litzow, M.R., Hogan, W.J. & Go, R.S. ***JAMA Oncol***, 3, 1253-1256. PMID: 28253394

Vemurafenib for BRAF V600-Mutant Erdheim-Chester Disease and Langerhans Cell Histiocytosis: Analysis of Data From the Histology-Independent, Phase 2, Open-label VE-BASKET Study. (2018) Diamond, E.L ***JAMA Oncol***, 4, 384-388. PMID: 29188284

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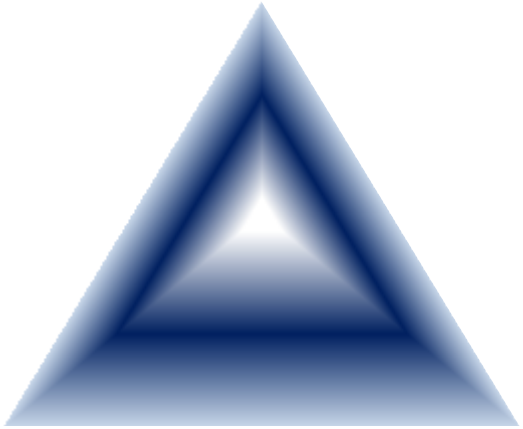
Selective growth or survival advantage



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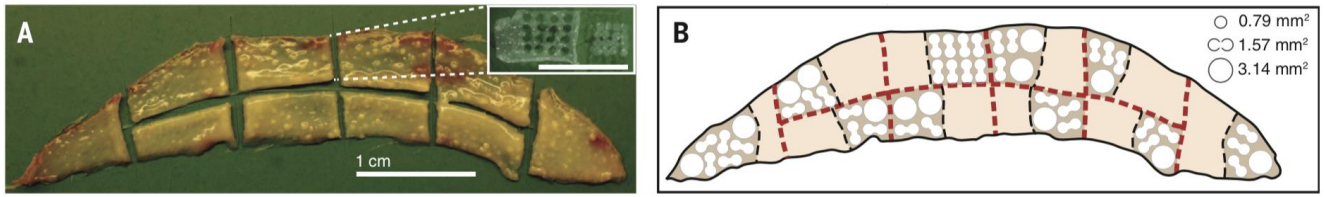
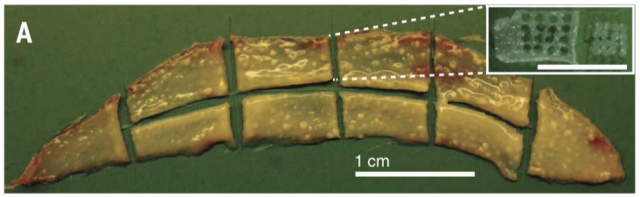
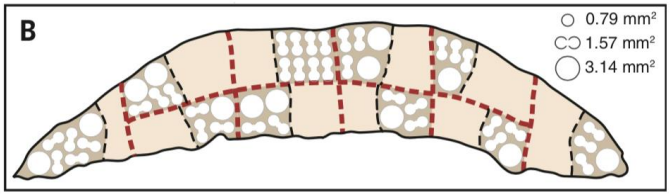
Healthy tissues harbor frequent cancer-related somatic mutations

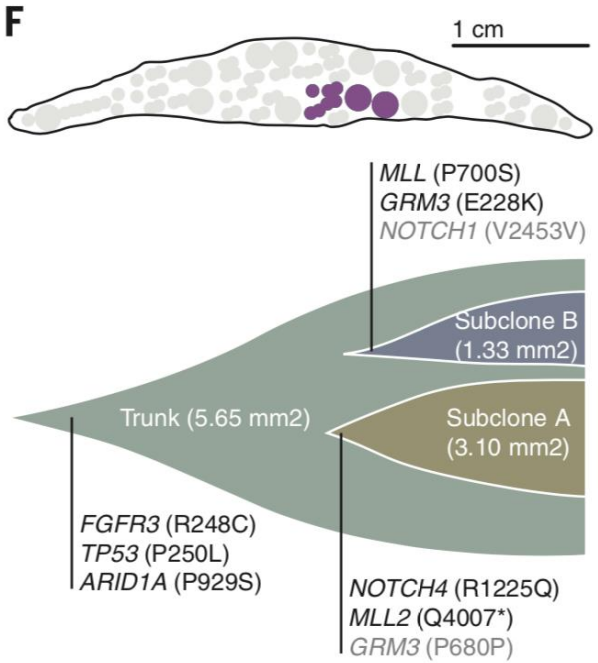


Tumor evolution. High burden and pervasive positive selection of somatic mutations in normal human skin. (2015) Martincorena, I. ***Science***, 348, 880-886. PMID: 25999502

Healthy tissues harbor frequent cancer-related somatic mutations







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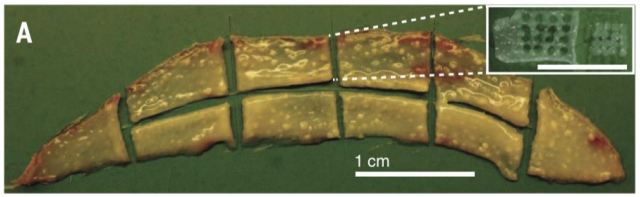

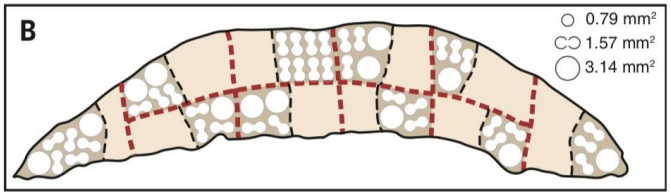

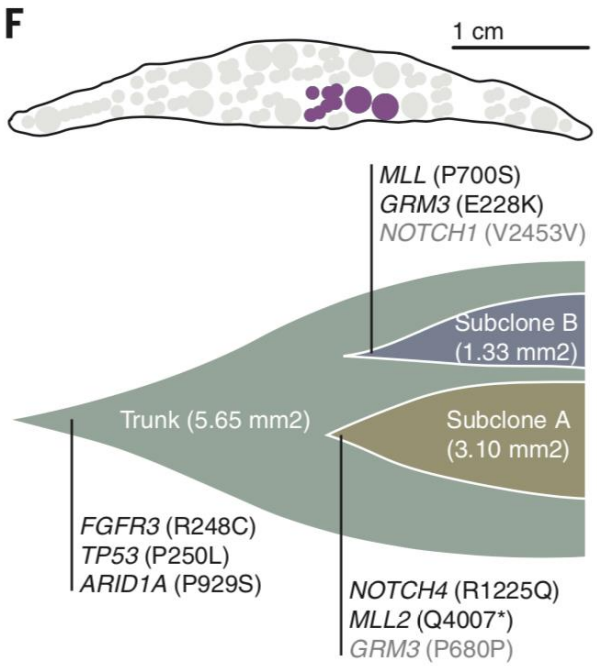

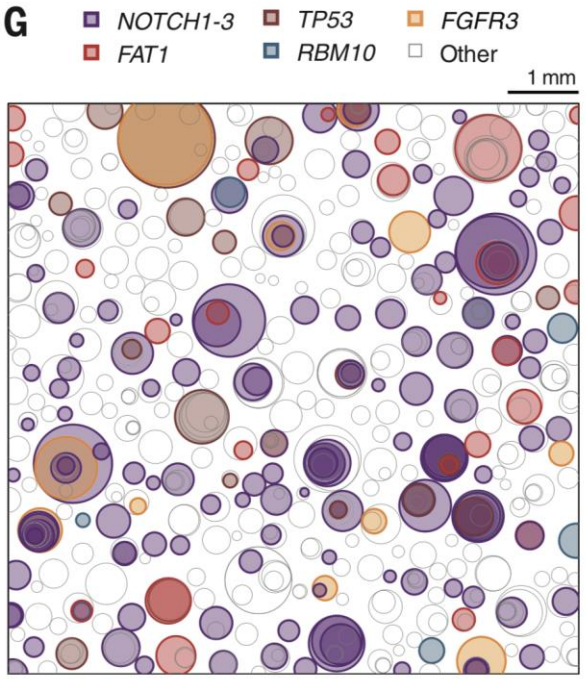

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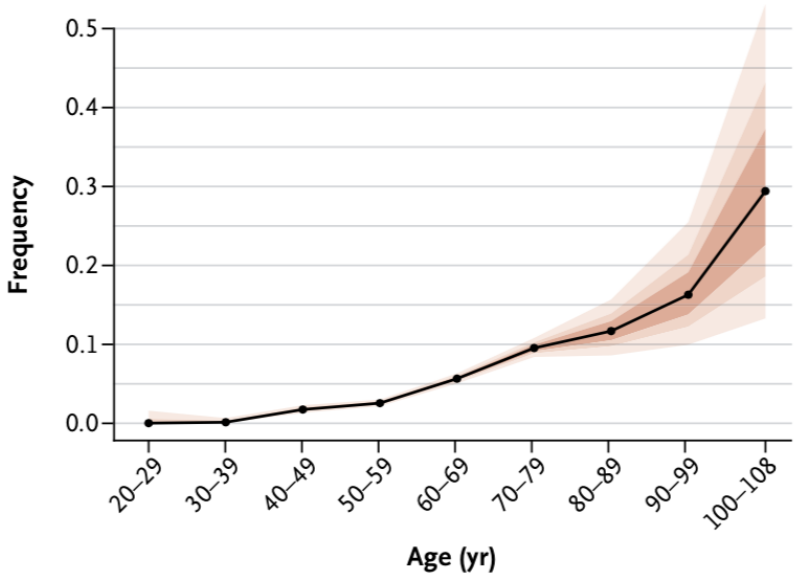
Clonal hematopoiesis

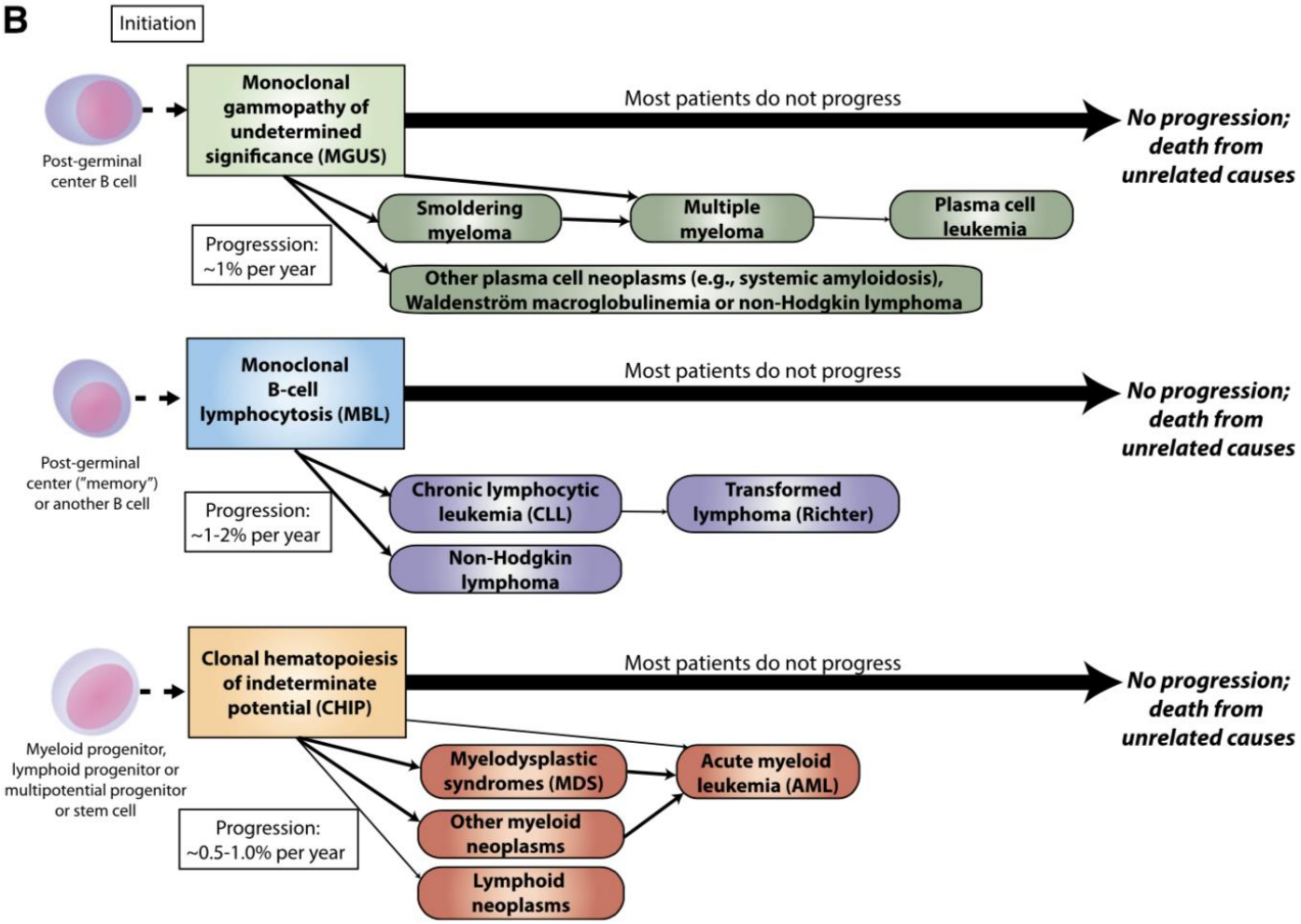


No. with Mutation	0	1	50	138	282	219	37	14	5
Total	240	855	2894	5441	5002	2300	317	86	17

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

Age-related clonal hematopoiesis associated with adverse outcomes. (2014) Jaiswal, S. ***N Engl J Med***, 371, 2488-2498. PMID: 25426837

Clonal disorders may not progress

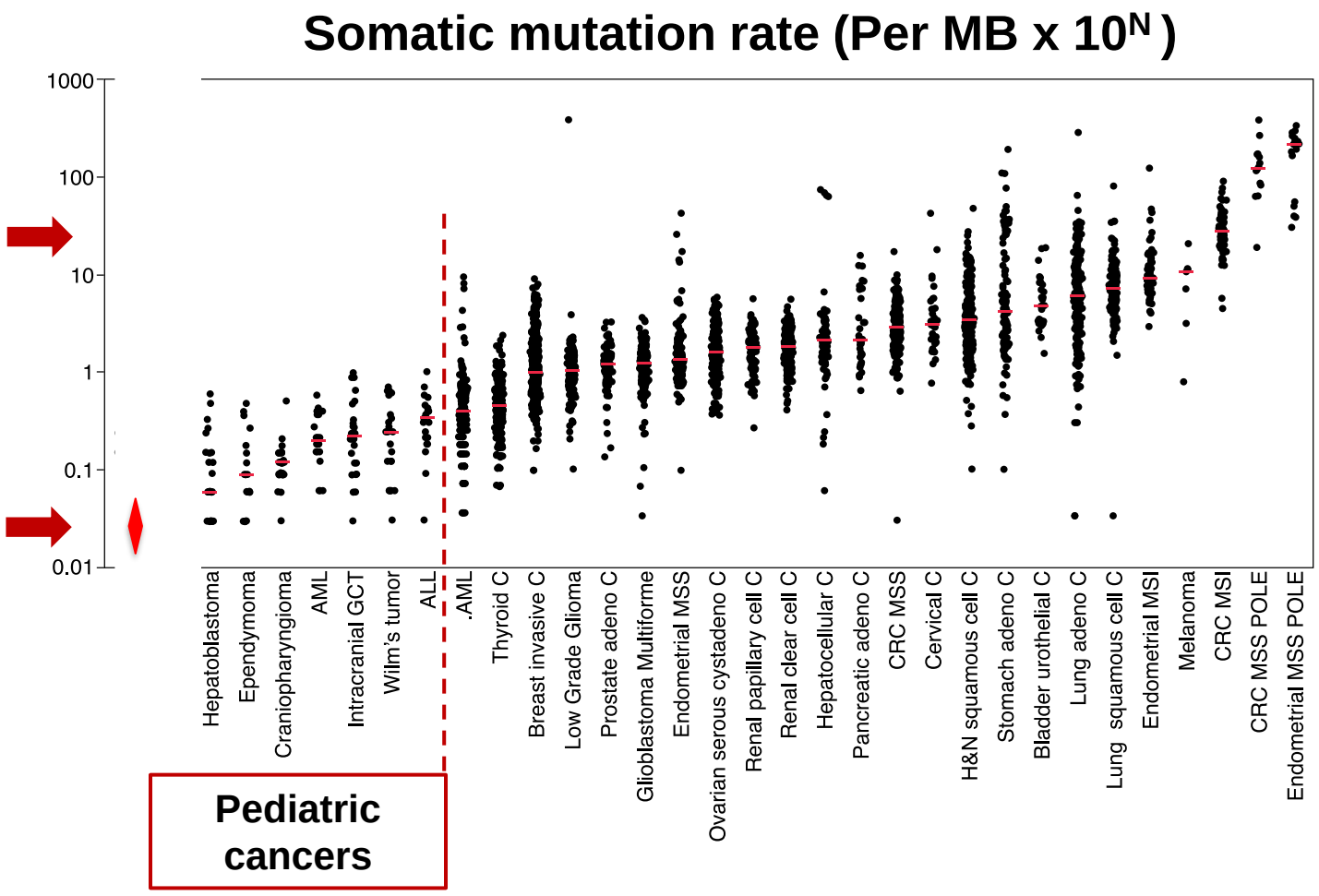


Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes. (2015) Steensma, D.P. ***Blood***, 126, 9-16. PMID: 25931582

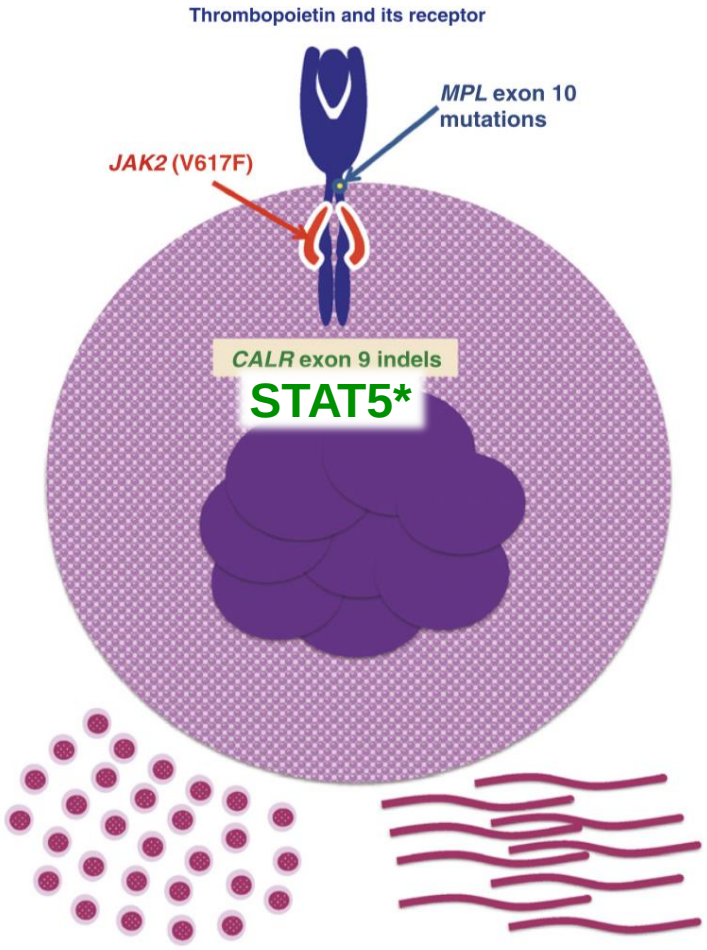
Spectrum of somatic mutation in cancer

Melanoma: 1000x more mutations

Histiocytosis
ONE mutation per genome
(0.03 per MB)



Hematopoietic one-hit wonders



From Janus kinase 2 to calreticulin: the clinically relevant genomic landscape of myeloproliferative neoplasms. (2014) Cazzola, M. & Kralovics, R. ***Blood***, 123, 3714-3719. PMID:

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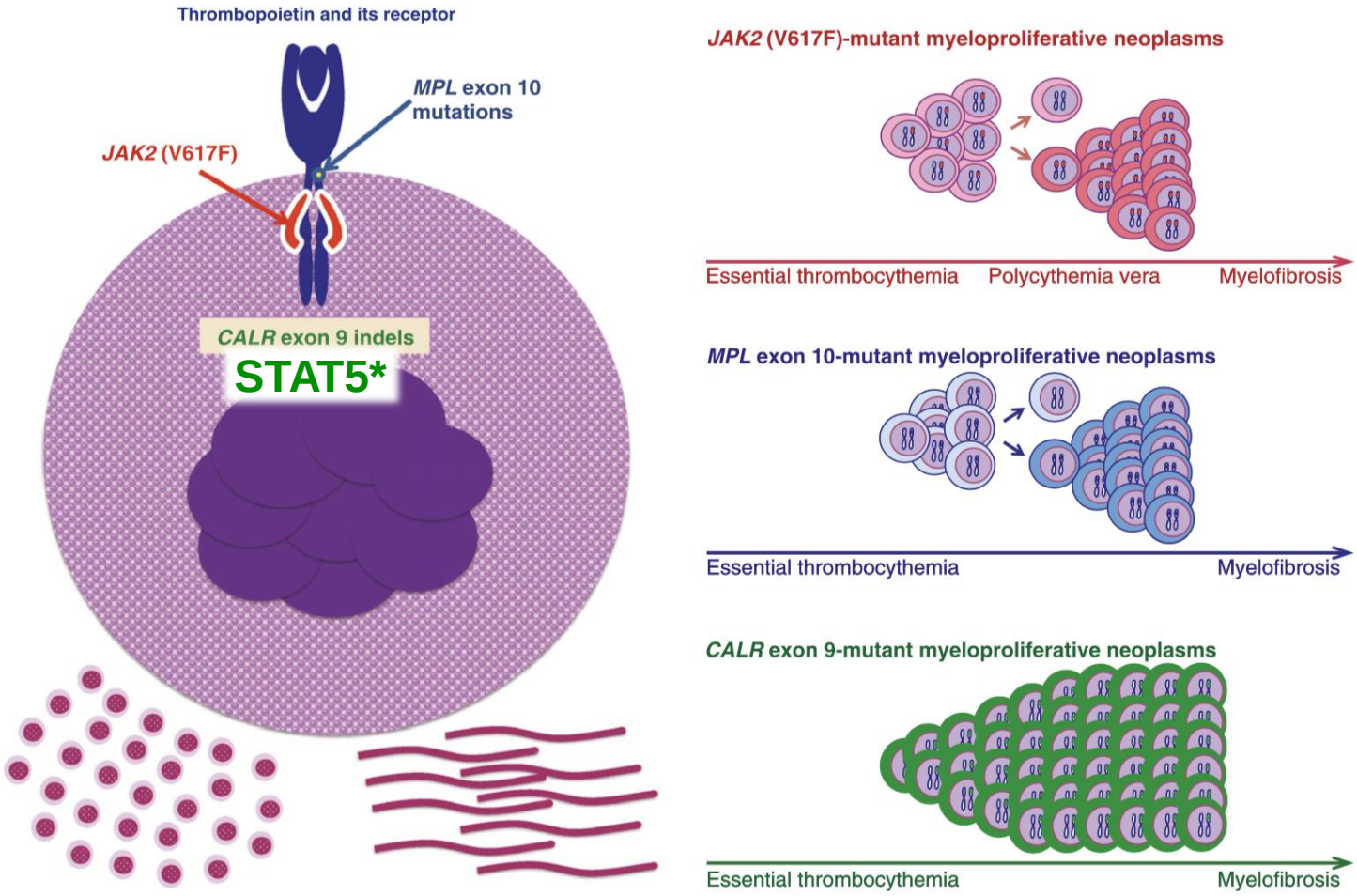

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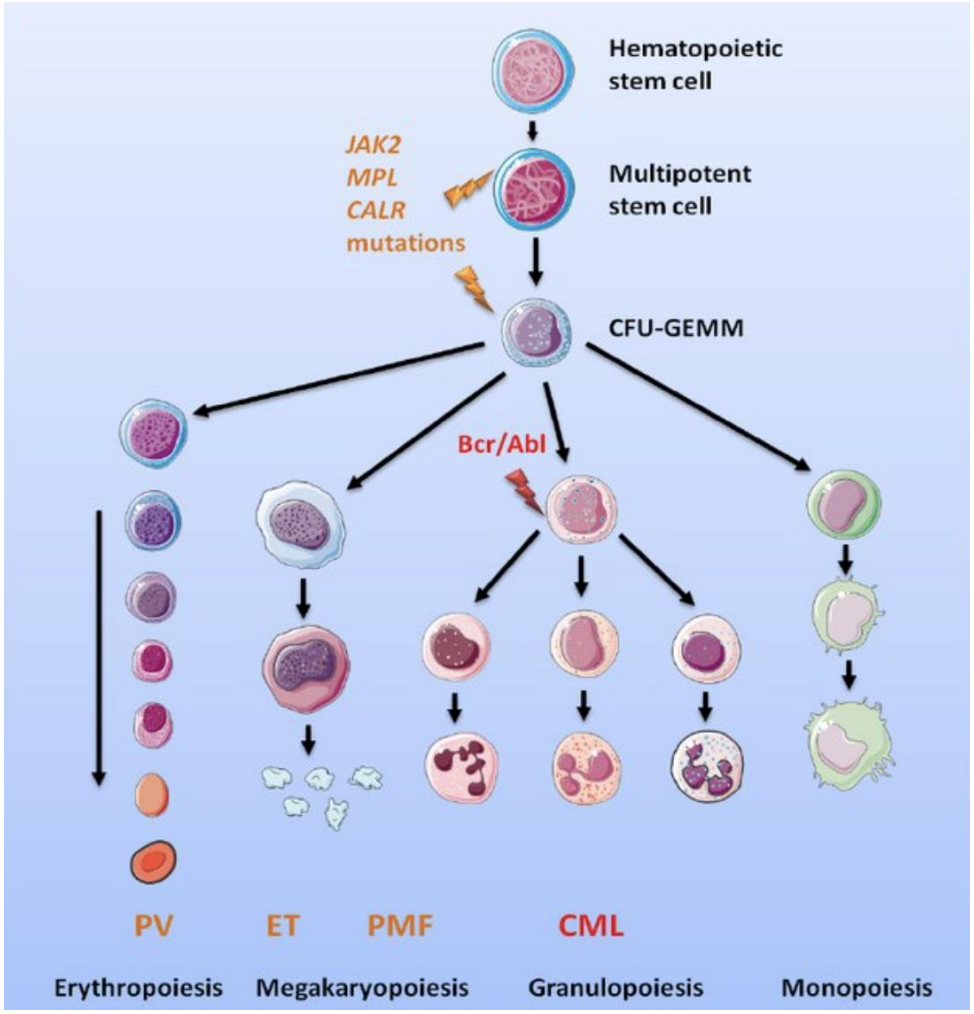

The Hepatocyte Growth Factor (HGF)/Met Axis: A Neglected Target in the Treatment of Chronic Myeloproliferative Neoplasms. (2014) Boissinot, M., Vilaine, M. & Hermouet, S. ***Cancers (Basel)***, 6, 1631-1669.

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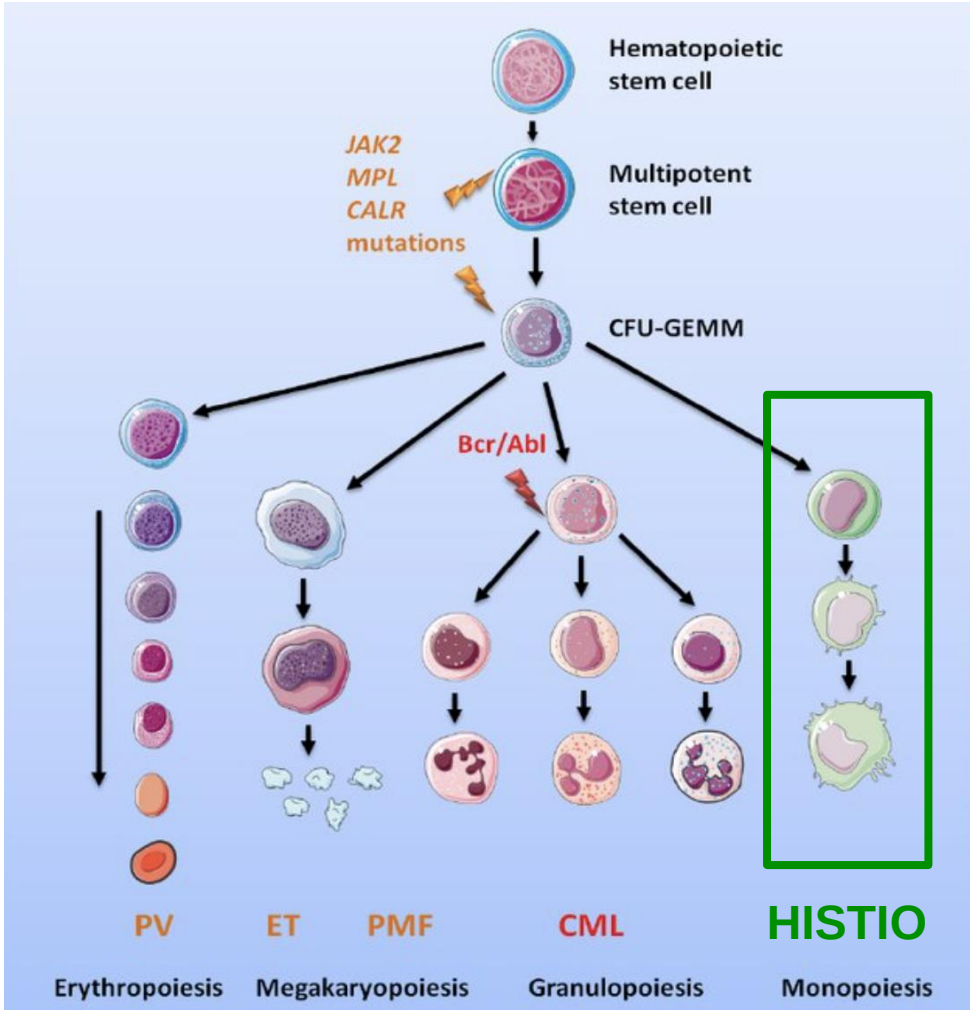

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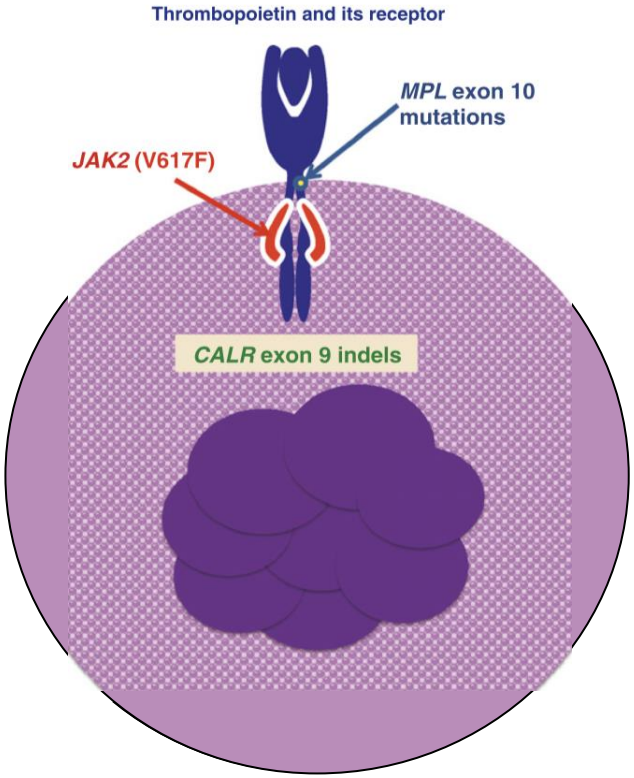
Expanding the spectrum of MPNs



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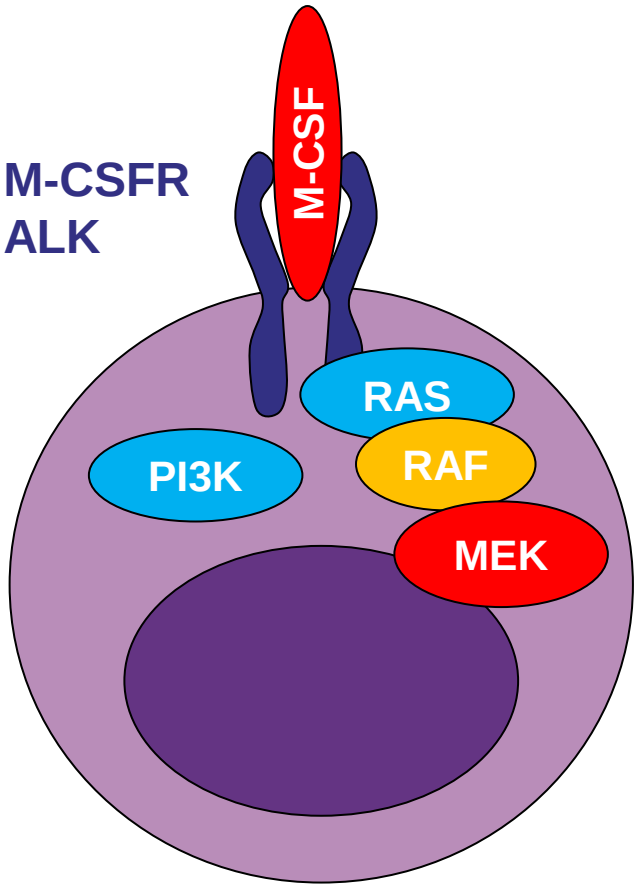
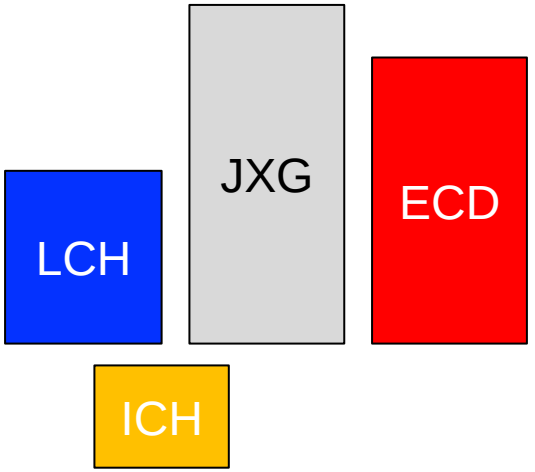
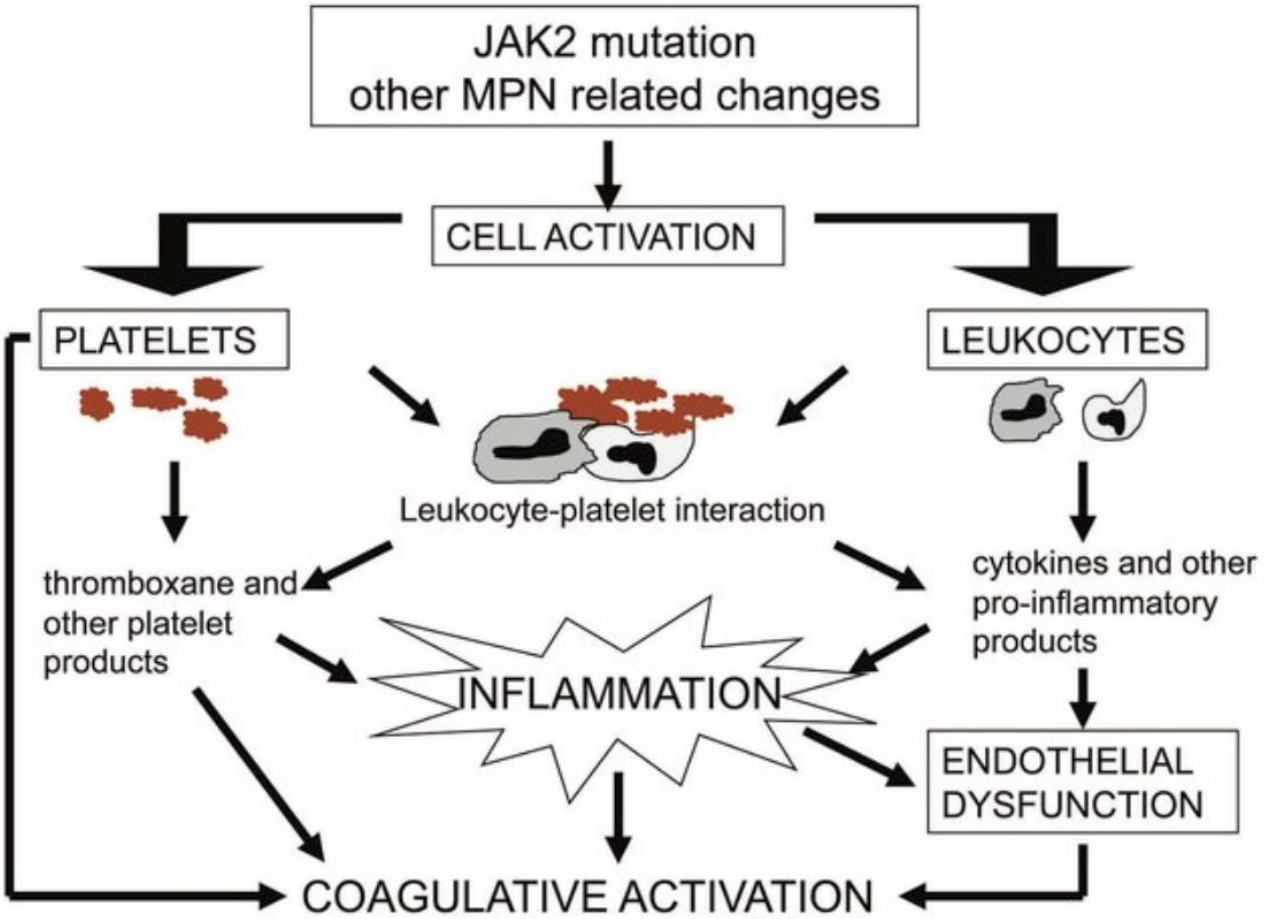


M-CSFR
ALK
RAS
RAF
MEK
PI3K

ETV3-NCOA2



Clonality and systemic inflammation



Pathophysiology of thrombosis in myeloproliferative neoplasms. (2011) Landolfi, R. & Di Gennaro, L. ***Haematologica***, 96, 183-186. PMID: 21282719

Clonality and systemic inflammation

Self-Reported Constitutional Symptoms in 458

Symptom	All patients (N=458)
Fatigue	*84%*
Bone Pain	*47%*
Fever	*18%*
Pruritus	*50%*
Night Sweats	*56%*
Symptomatic Splenomegaly	*54%*
Weight Loss (>10%)	*20%*

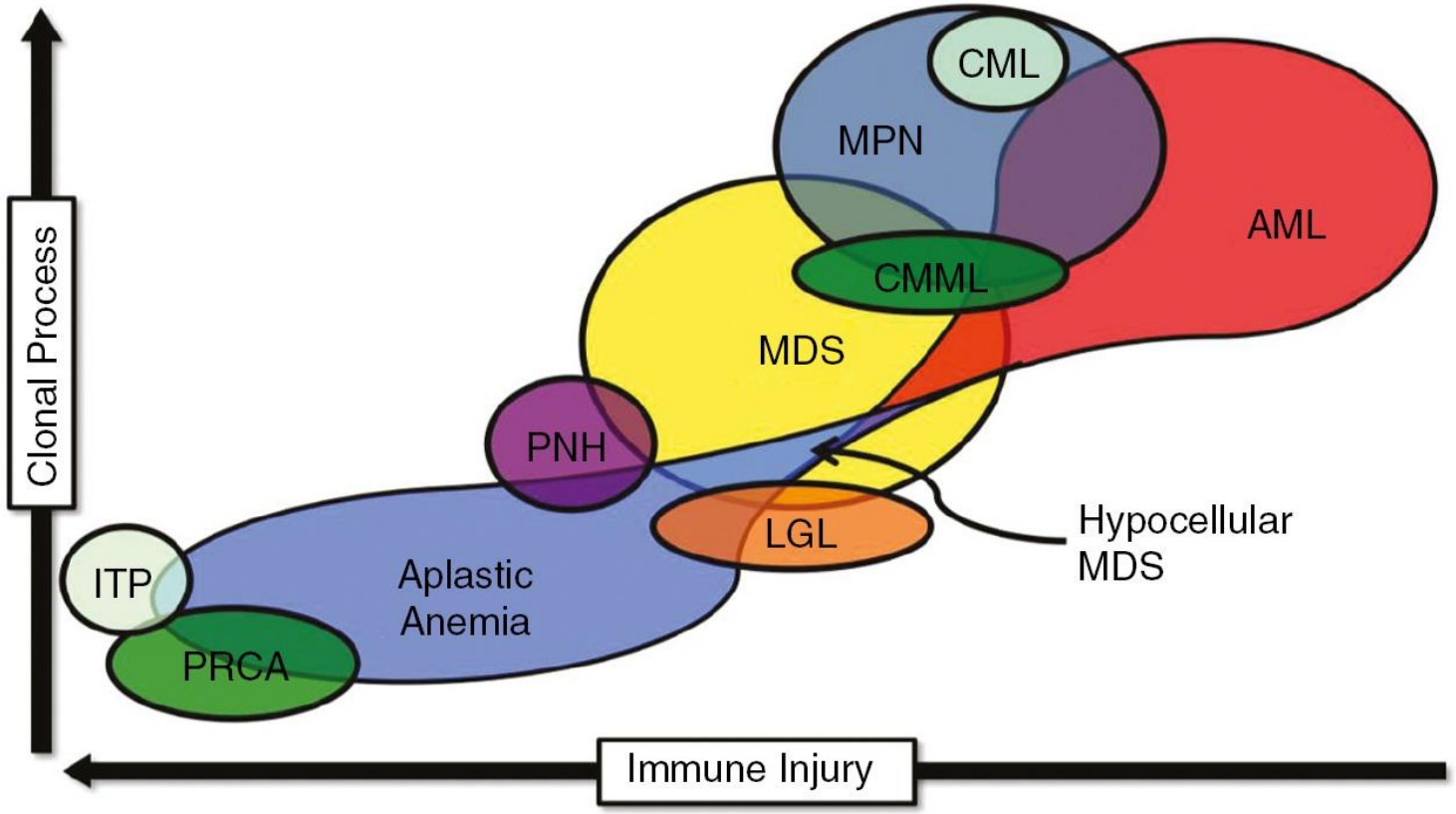
PMF (Primary Myelofibrosis)

Post PV MF (Post Polycythemia Vera Myelofibrosis)

Post ET MF (Post Essential Thrombocythemia Myelofibrosis)

The Myelofibrosis Symptom Assessment Form (MFSAF): an evidence-based brief inventory to measure quality of life and symptomatic response to treatment in myelofibrosis. (2009) Mesa, R.A. ***Leuk Res***, 33, 1199-1203. PMID: 19250674

Clonality and immunity



14. Myelodysplastic/myeloproliferative neoplasm overlap syndromes. Aaron T. Gerds, Ramon V. Tiu, Mikkael A. Sekeres. *In Managing Myeloproliferative Neoplasms.* Editors Ruben A. Mesa, Claire N. Harrison. Cambridge University Press 2016

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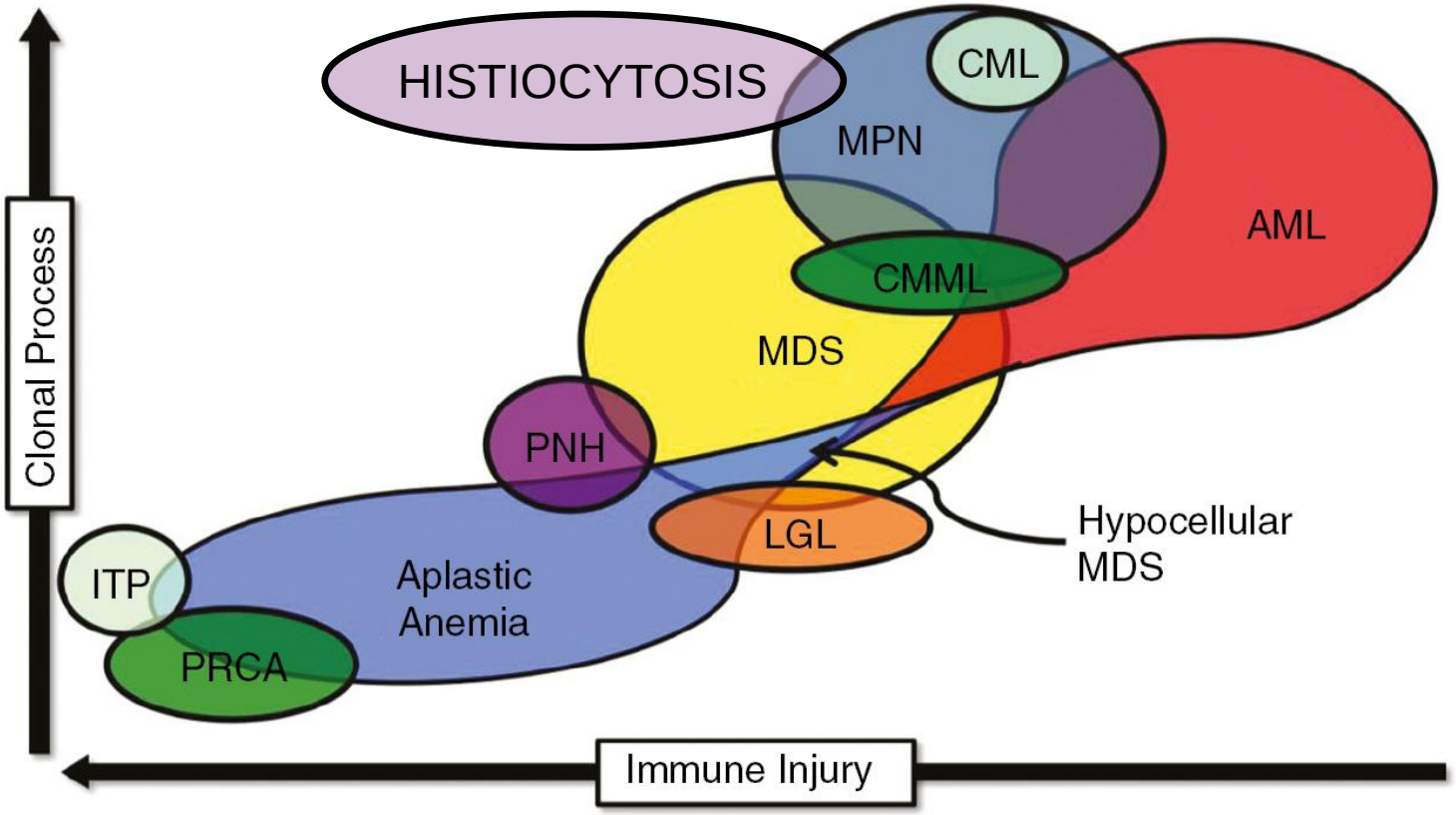

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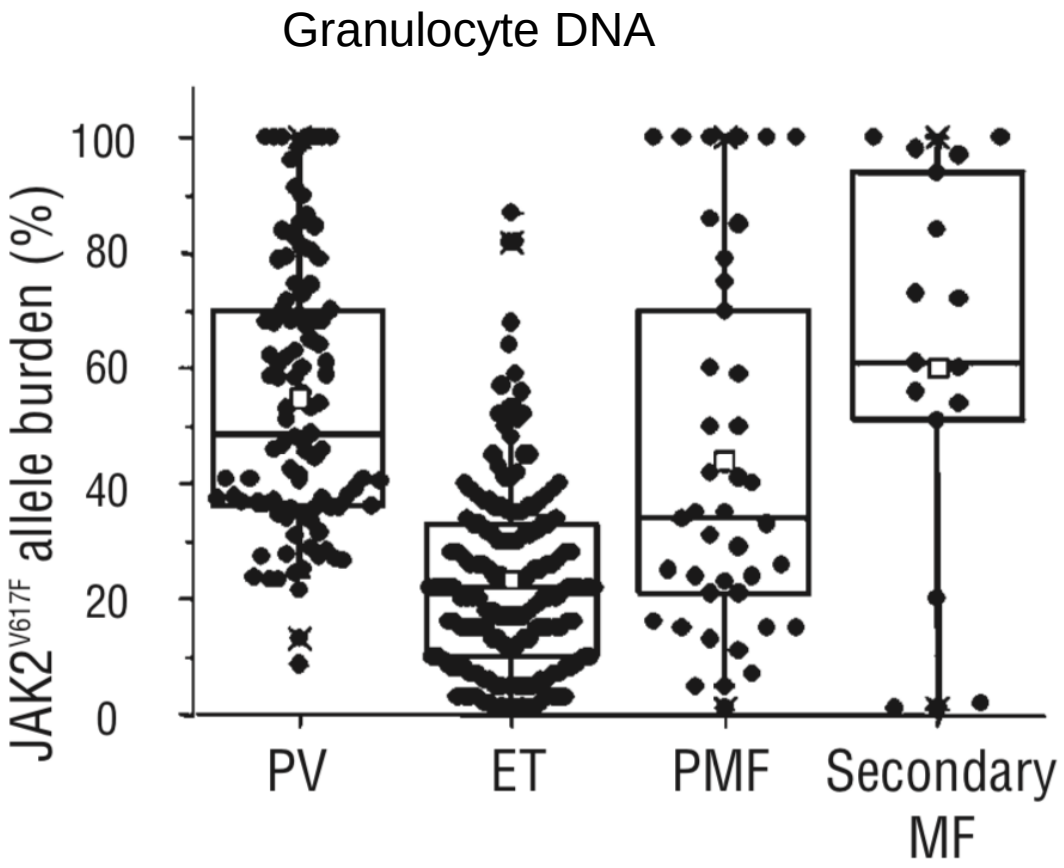
Mutated allele burden in MPNs



Influence of JAK2V617F allele burden on phenotype in essential thrombocythemia. (2008) Antonioli, E. ***Haematologica***, 93, 41-48. PMID:

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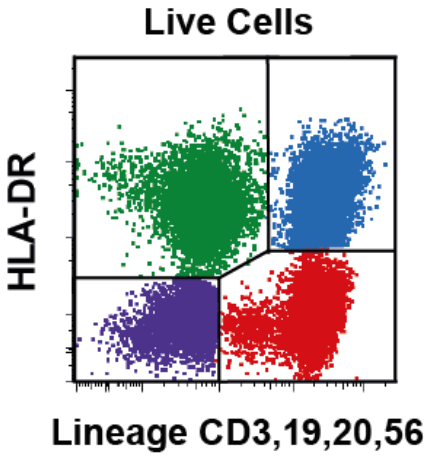
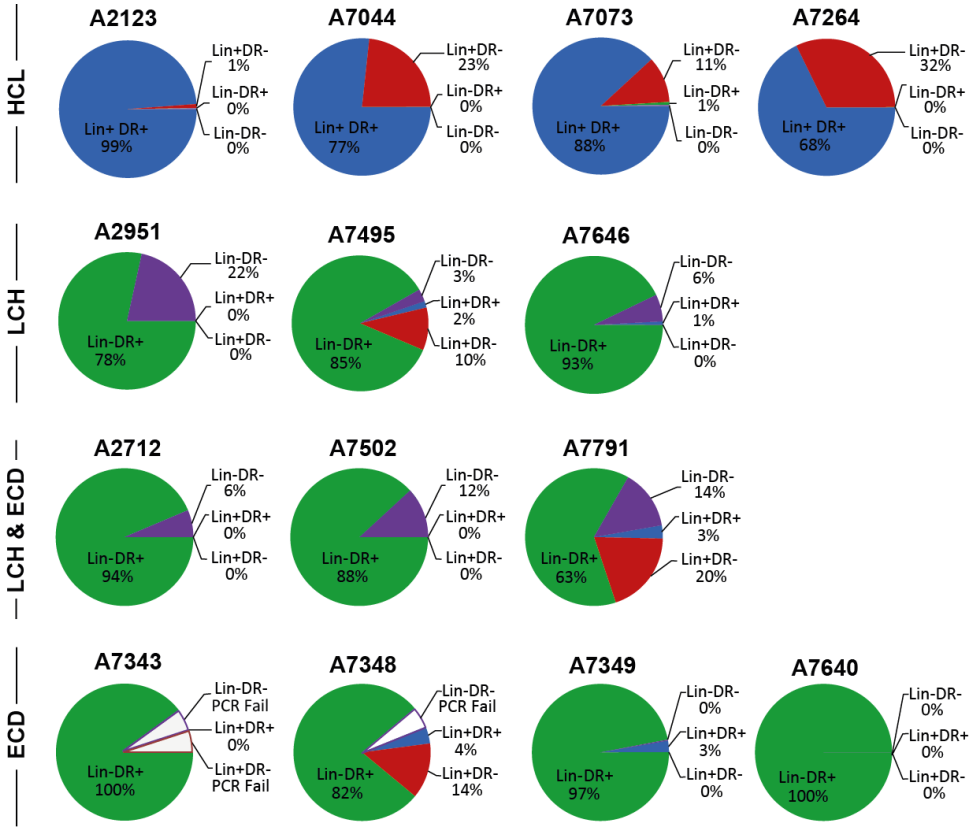
Where are the mutated alleles?





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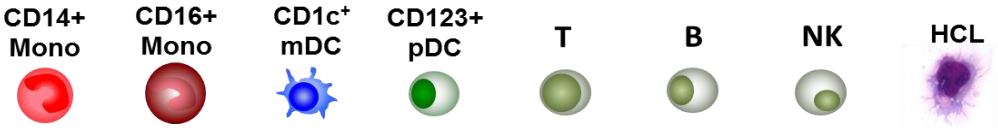
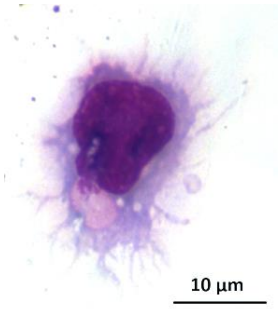
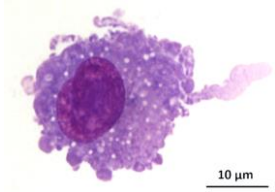
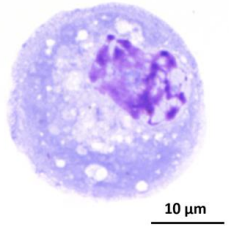
Where are the mutated alleles?

% mutant alleles









Patient		Myeloid					Lymphoid			
Disease	Patient	Neuts	14+	16+	11c+1c+	123+	T Cells	B Cells	NK	HCL Cells
HCL	A2123	0.00	0.00	0.00	0.00	0.00	0.00	0.05	0.40	22.85
	A7044	0.00	0.00	0.00	0.00	0.00	0.00	0.35	1.06	73.65
	A7073	0.00	nt	nt	nt	nt	0.01	26.87	0.10	38.21
	A7264	0.00	0.00	0.00	0.00	0.00	0.03	0.29	0.01	29.34
LCH	A2951	0.00	4.82	45.61	4.96	0.90	0.03	0.16	0.00	n/a
	A7495	0.00	17.74	39.48	7.94	1.04	0.00	0.00	0.00	n/a
	A7646	0.00	1.70	2.66	1.15	0.22	0.00	0.00	0.00	n/a
LCH/ECD	A2712	0.00	0.14	4.07	0.11	0.06	0.01	0.00	0.00	n/a
	A7502	0.00	0.17	0.20	0.08	0.00	0.00	0.00	0.00	n/a
ECD	A7348	nt	0.38	1.36	1.63	0.00	0.00	0.00	0.00	n/a
	A7349	nt	1.42	0.47	1.06	0.00	0.00	0.00	0.00	n/a
	A7640	0.00	0.08	0.16	0.00	0.00	0.00	0.00	0.00	n/a
	A7343	nt	0.00	0.07	0.00	0.00	nt	0.00	0.00	n/a

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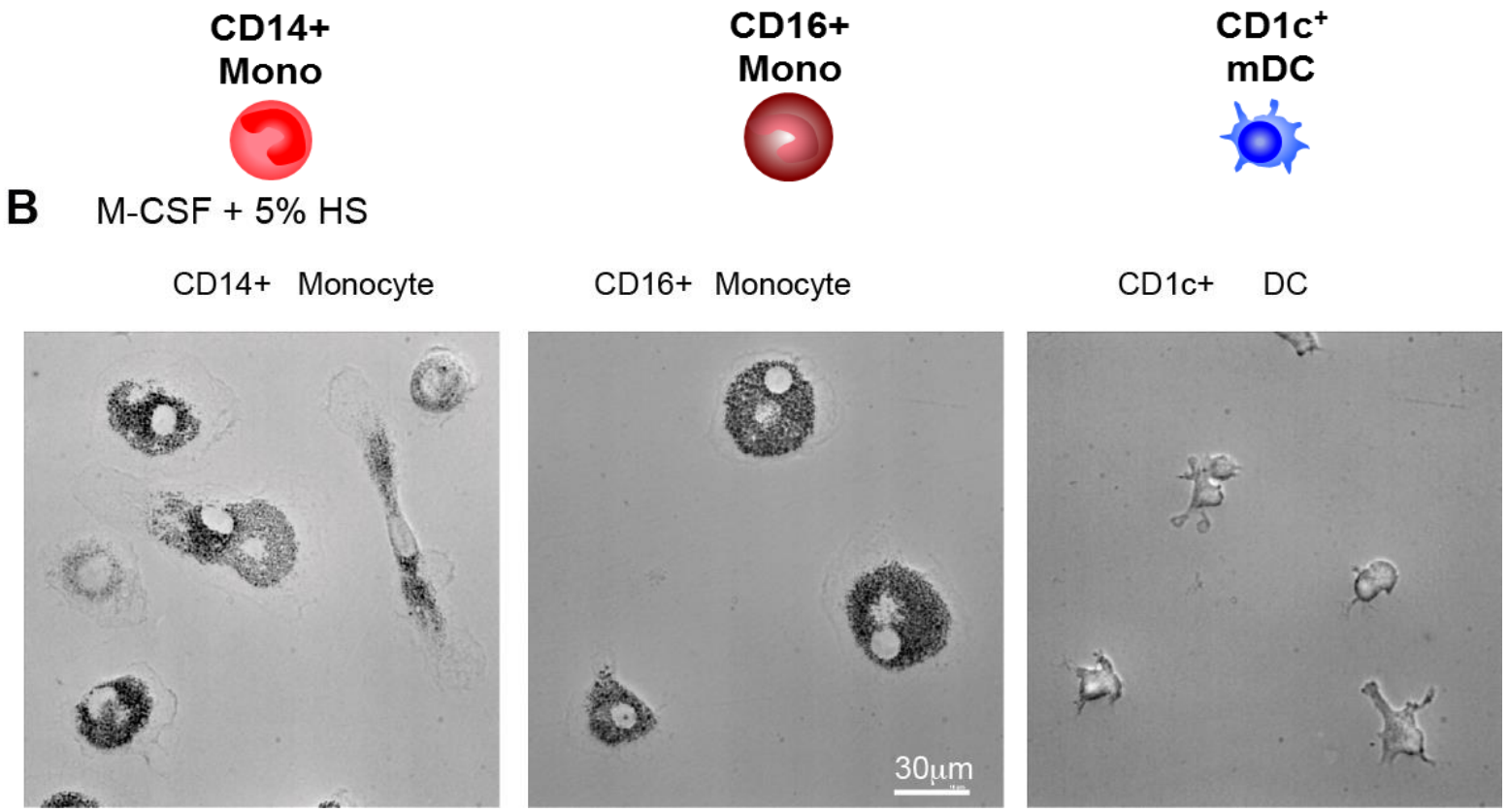
Both monocytes make a foam cell



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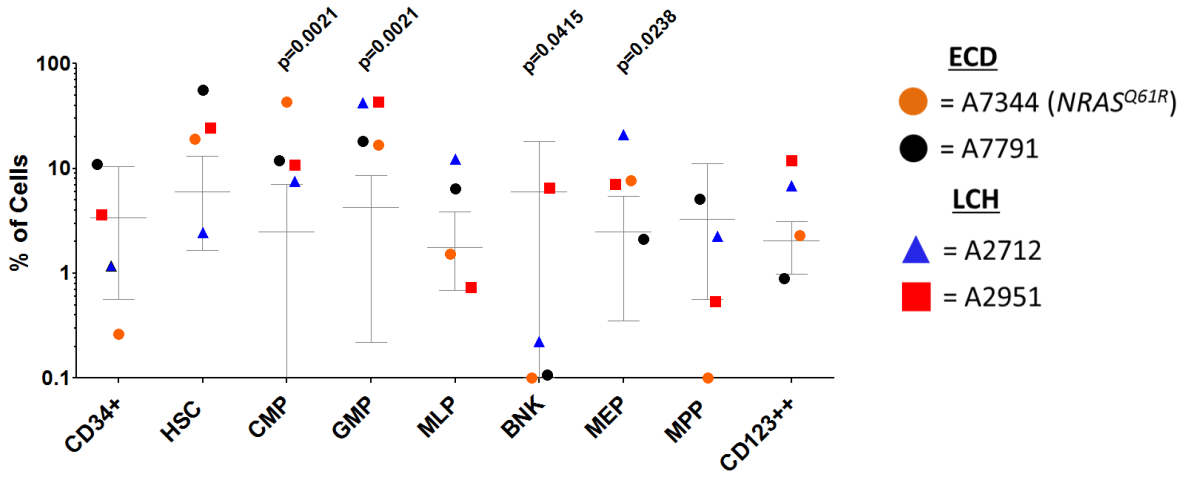
BM origin . . .



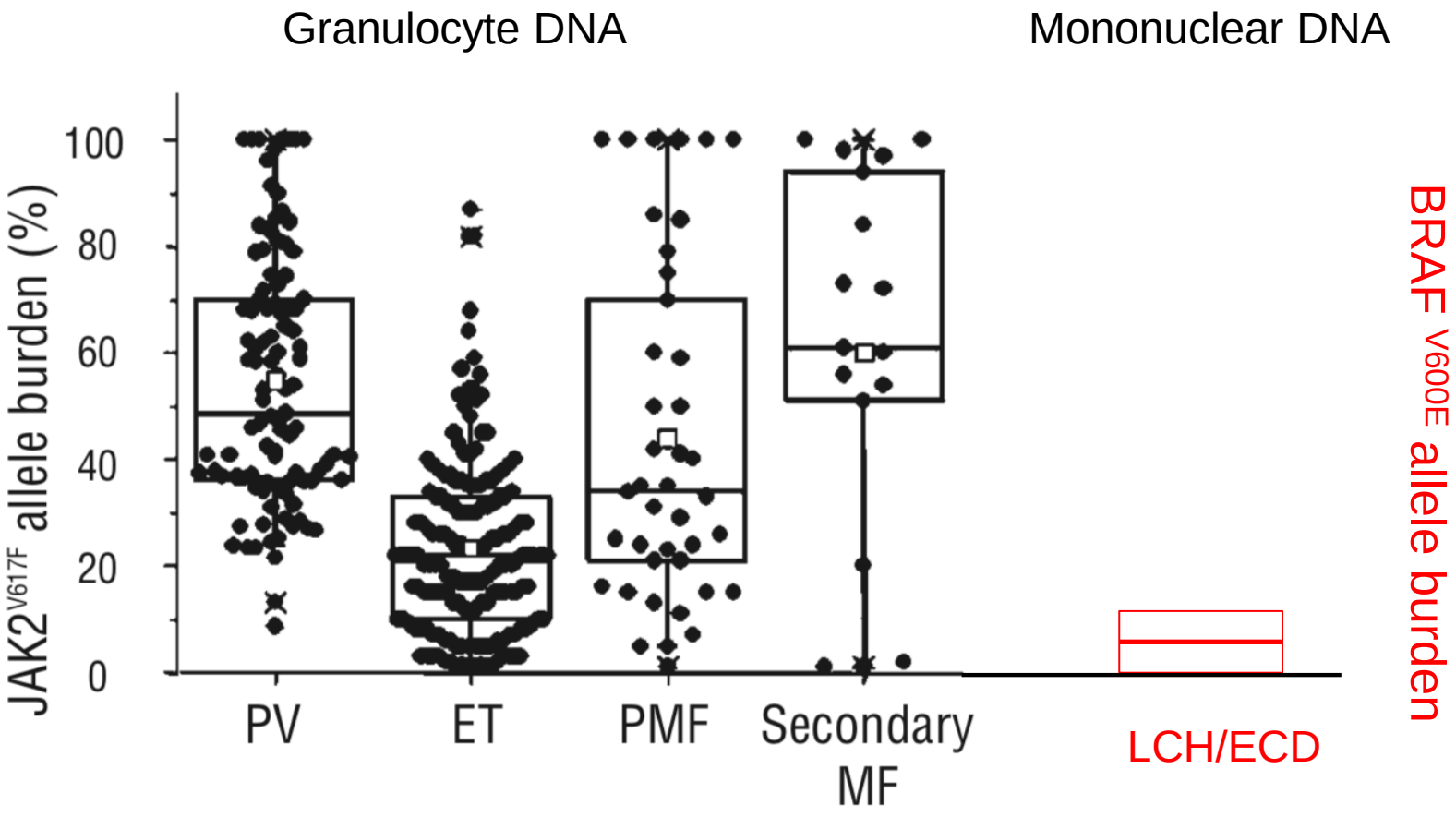
% BRAF^{V600E}

Disease	Patient	HSC	CMP	GMP	MLP	B/NK	HCL
HCL	A7264	0.57	nt	nt	nt	nt	33.37
LCH	A2712	0.47	4.56	0.61	0.00	0.00	n/a
	A2951	0.61	12.67	1.33	0.20	0.00	n/a
ECD	A7991	0.10	0.35	0.48	0.01	nt	n/a
	A7344*	29.00	21.00	63.00	0.00	0.00	n/a

*$NRAS^{Q61R}$ Mutation Sanger Sequencing Prep by Rachel Dickinson

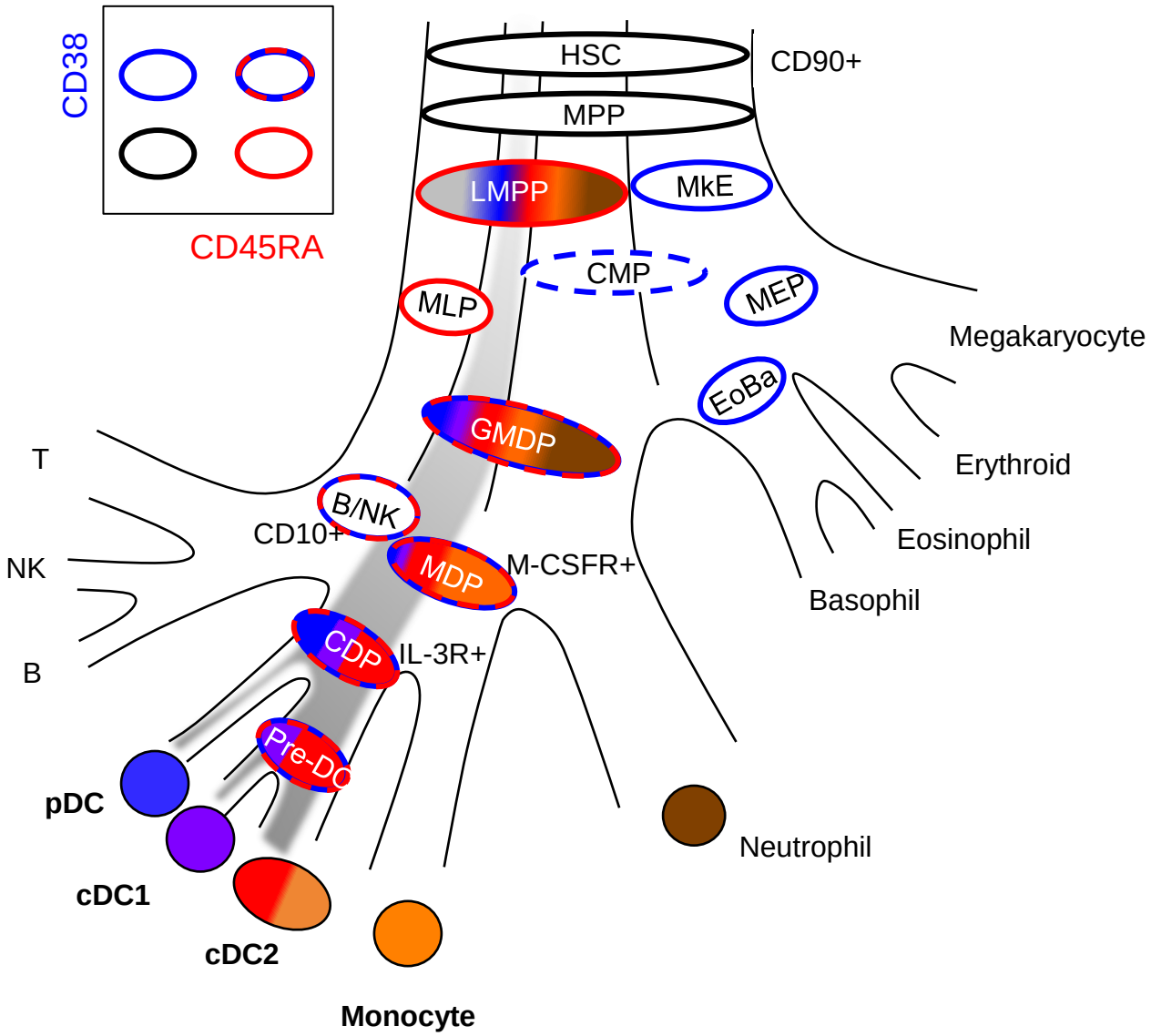
Hematopoietic origin of Langerhans cell histiocytosis and Erdheim-Chester disease in adults. (2017) Milne, P. ***Blood***, 130, 167-175. PMID: 28512190

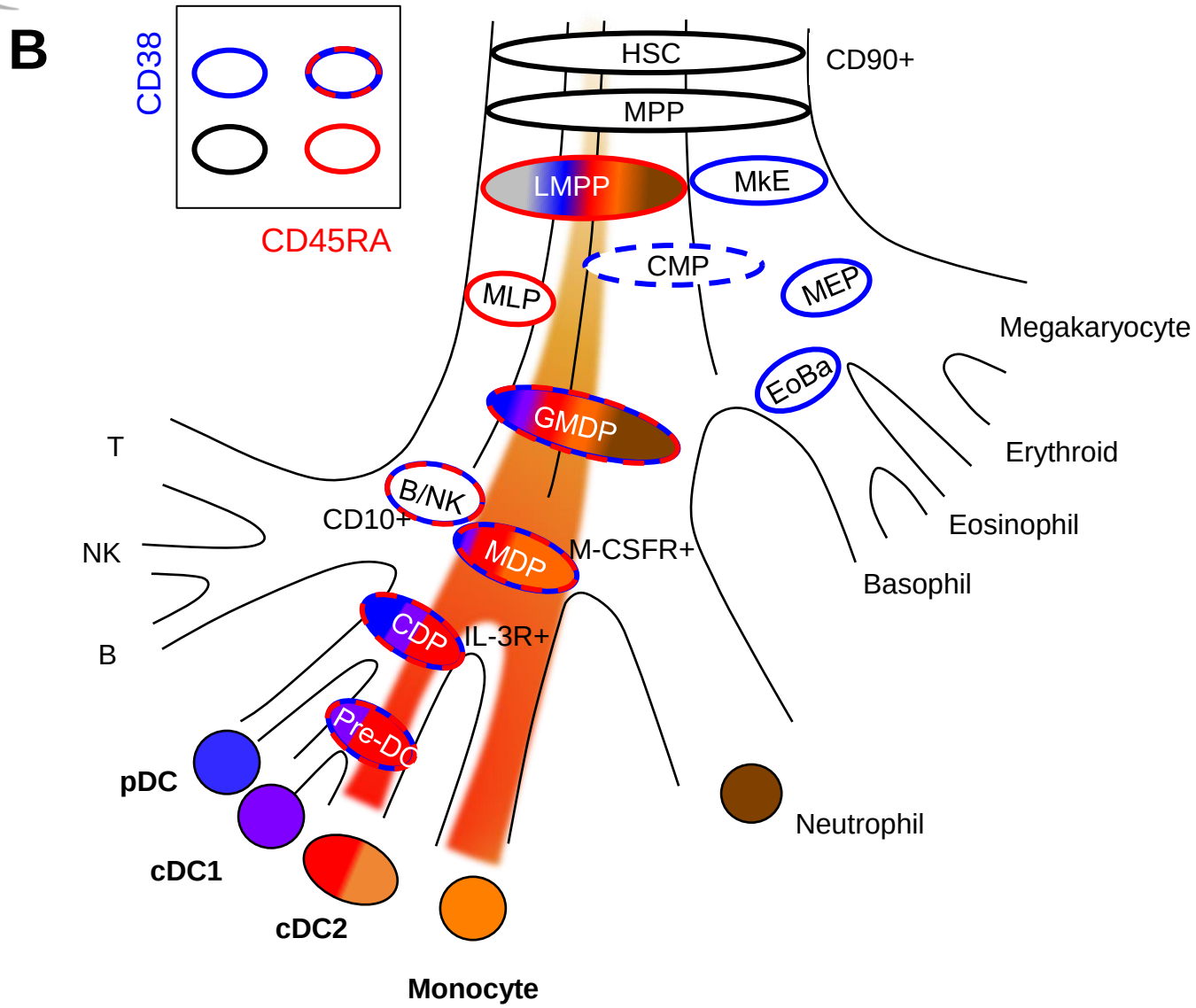
Mutated allele burden in MPNs



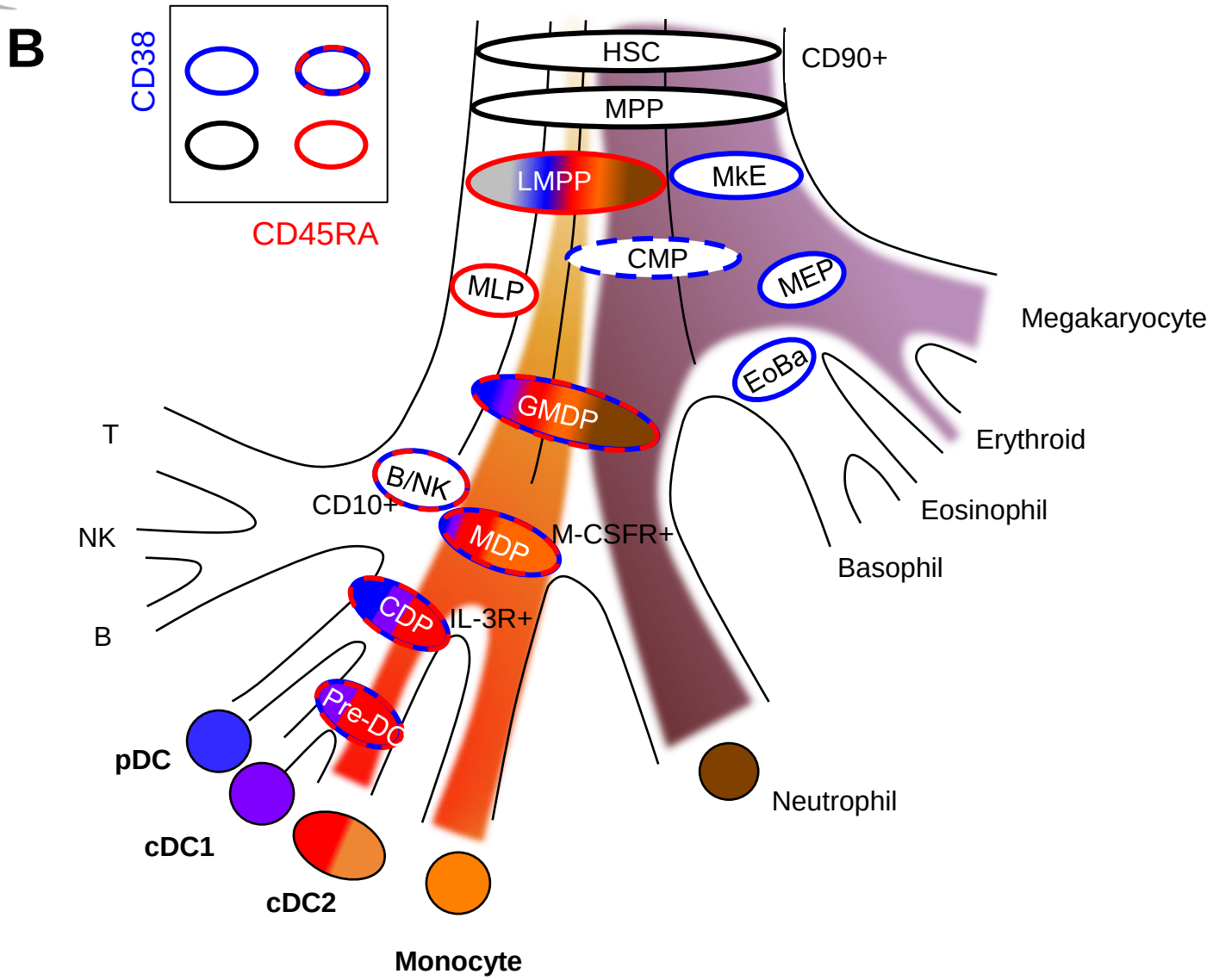
Influence of JAK2V617F allele burden on phenotype in essential thrombocythemia. (2008) Antonioli, E. ***Haematologica***, 93, 41-48. PMID:

B


CD38
CD45RA
HSC
CD90+
MPP
LMPP
MkE
CMP
MEP
MLP
Megakaryocyte
EoBa
GMDP
Erythroid
T
B/NK
CD10+
Eosinophil
NK
MDP
M-CSFR+
Basophil
CDP
IL-3R+
B
Pre-DC
pDC
Neutrophil
cDC1
cDC2
Monocyte



BRAF-mutated lineages



BRAF-mutated lineages

JAK2-mutated lineages

Human Dendritic Cell Laboratory

Newcastle University

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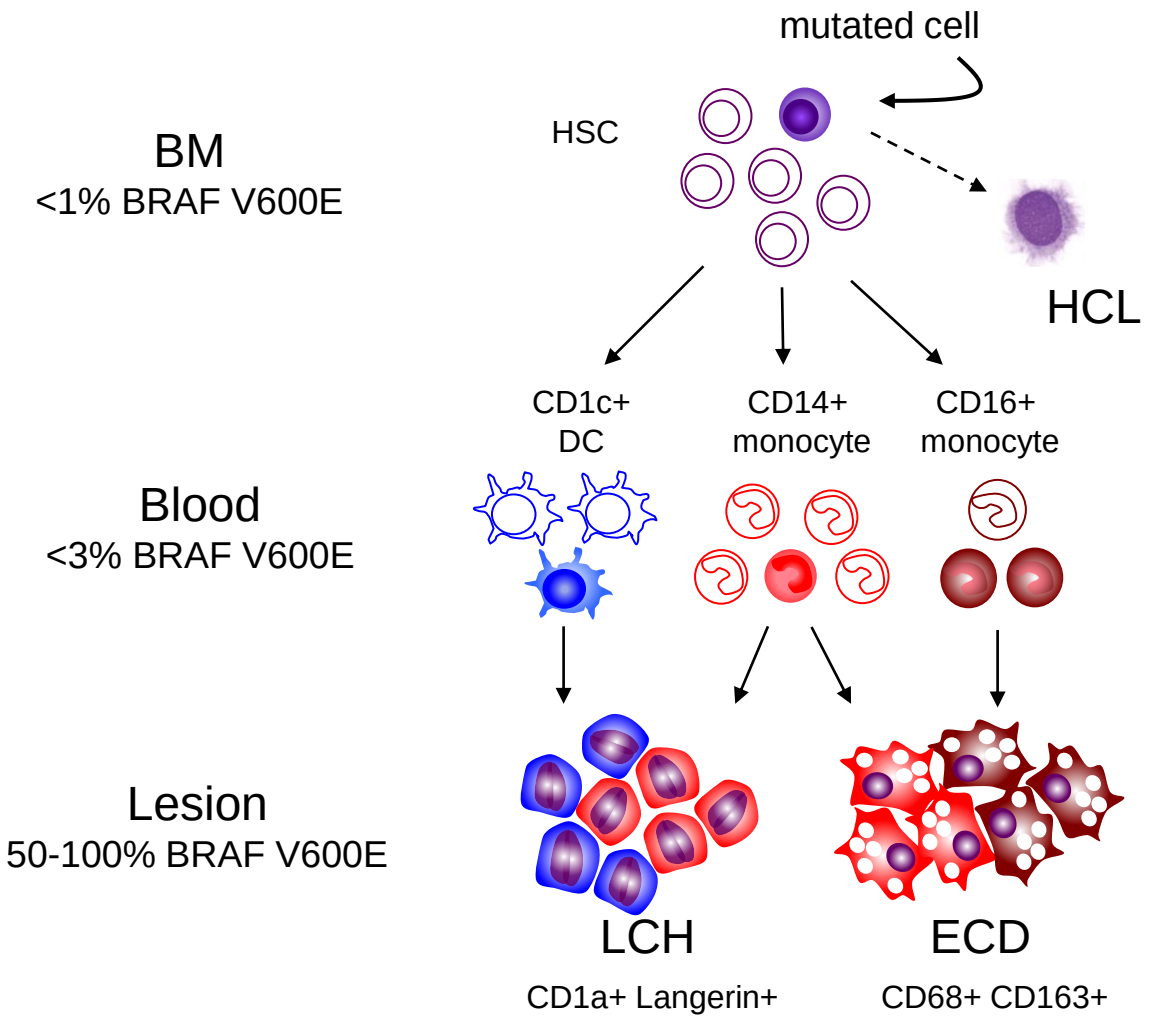
MS histiocytosis is a haematopoietic neoplasm . . .but

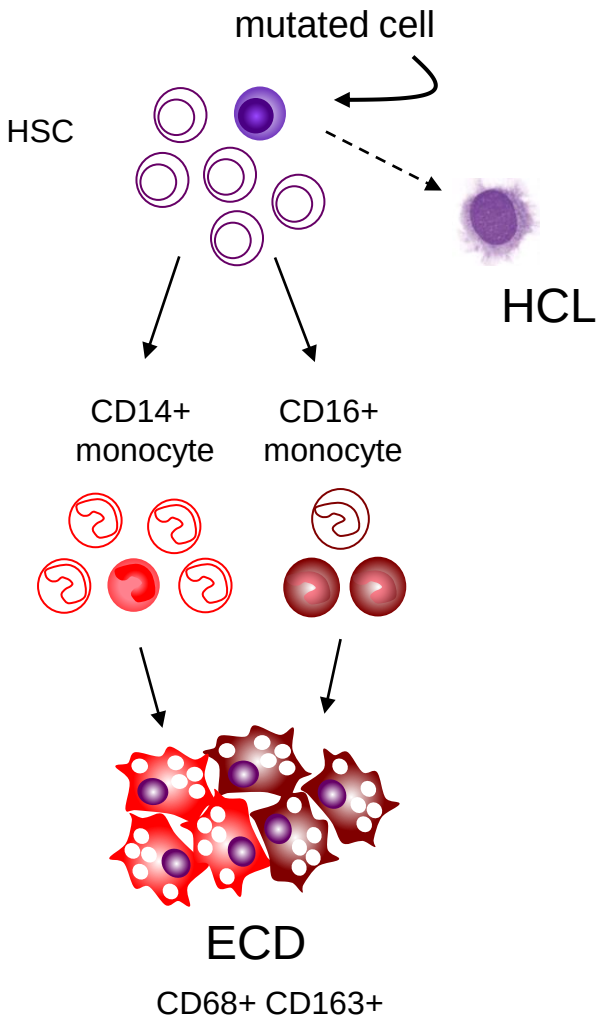


MS histiocytosis is a haematopoietic neoplasm . . .but

BM
<1% BRAF V600E

Blood
<3% BRAF V600E

Lesion
50-100% BRAF V600E



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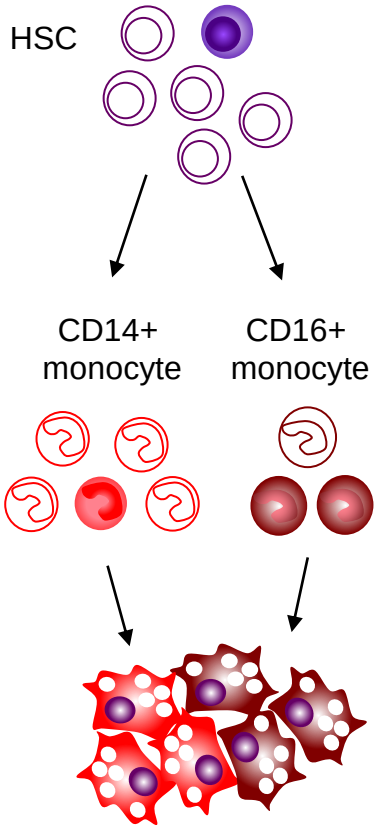
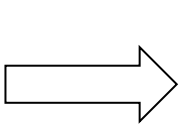
MS histiocytosis is a haematopoietic neoplasm . . .but why doesn't this happen?

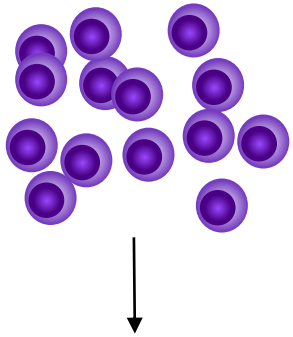
BM
<1% BRAF V600E

Blood
<3% BRAF V600E

Lesion
50-100% BRAF V600E







Leukaemia

Selective advantage for progenitor cells

Human Dendritic Cell Laboratory

Newcastle University

www.hudendritic.org

Histiocytosis is a haematopoietic neoplasm

BM

<1% BRAF V600E

No selective advantage

Blood

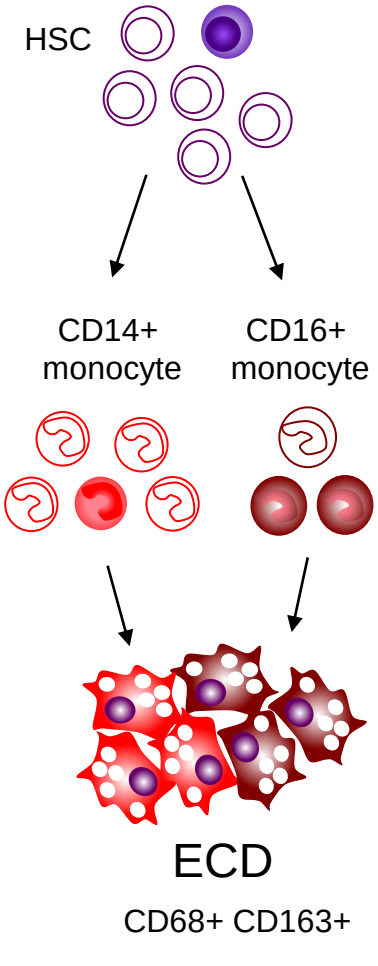
<3% BRAF V600E

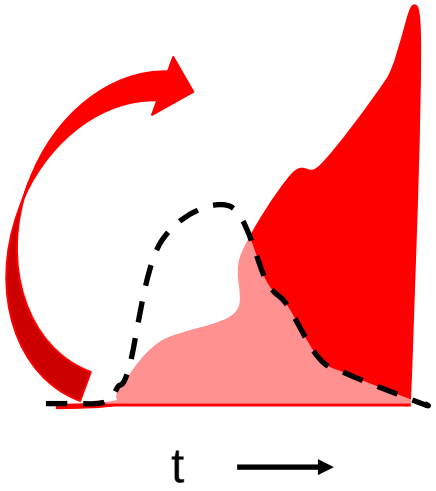
Low selective advantage

Lesion

50-100% BRAF V600E

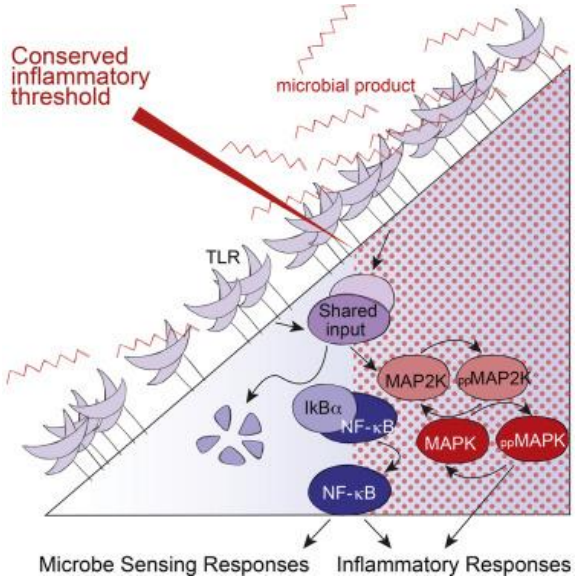
Selective advantage for BRAF^{V600E}





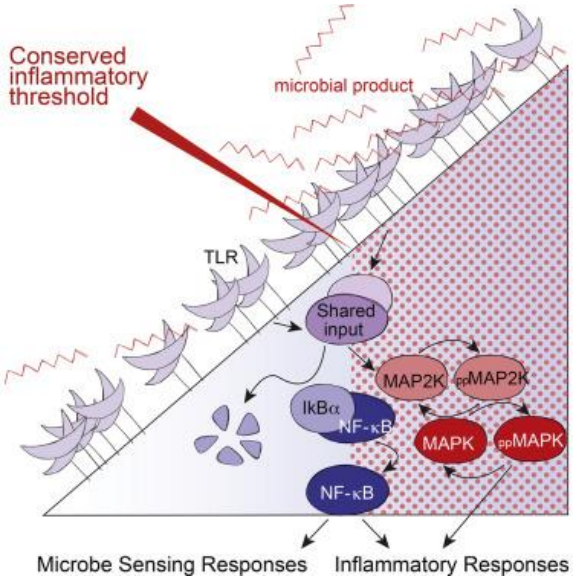
Uncontrolled and persistent activation of immunity

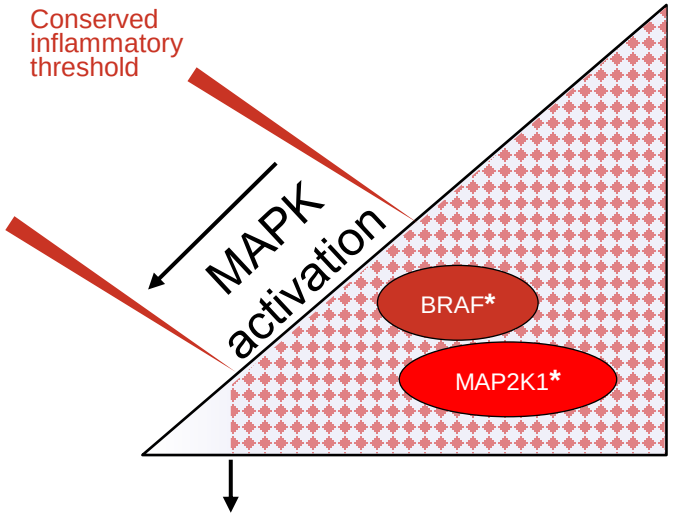
MAPK pathway sets the threshold of macrophage activation



Distinct NF-κB and MAPK Activation Thresholds Uncouple Steady-State Microbe Sensing from Anti-pathogen Inflammatory Responses Rachel A. Gottschalk, Cell Systems Volume 2, Issue 6, Pages 378-390 (June 2016)

MAPK pathway sets the threshold of macrophage activation

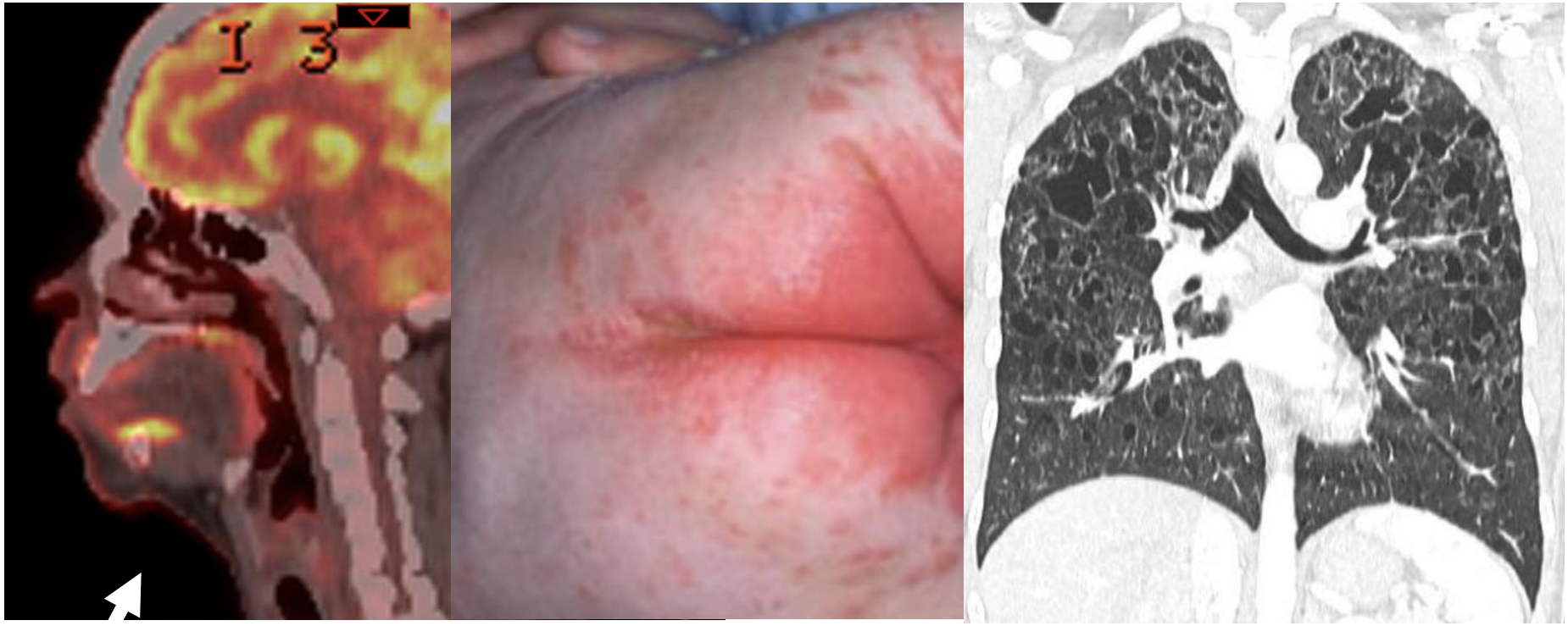




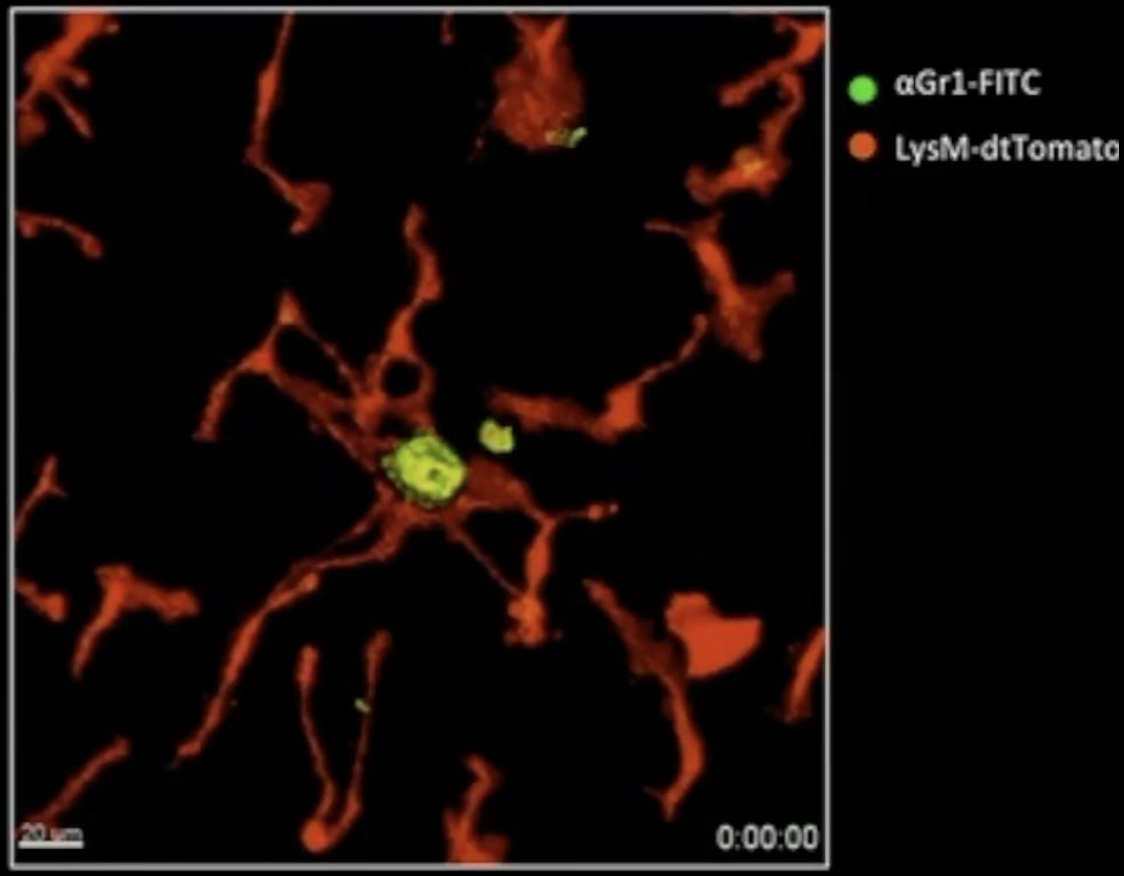
Inflammatory response at a lower threshold

Distinct NF-κB and MAPK Activation Thresholds Uncouple Steady-State Microbe Sensing from Anti-pathogen Inflammatory Responses Rachel A. Gottschalk, Cell Systems Volume 2, Issue 6, Pages 378-390 (June 2016)

Local inflammation exacerbates histiocytosis



Tissue Resident Macrophages “Cloak” Tissue Damage Before Neutrophils Arrive

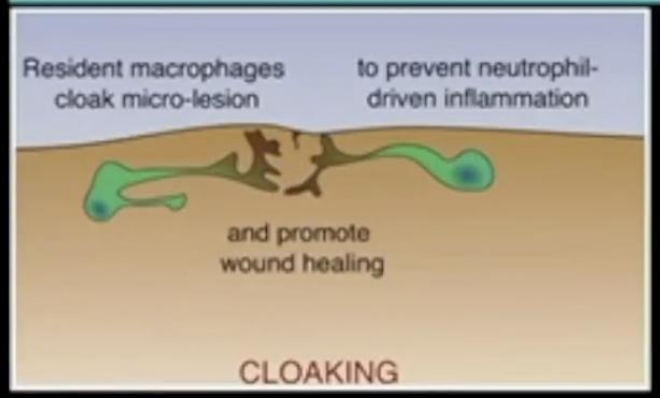


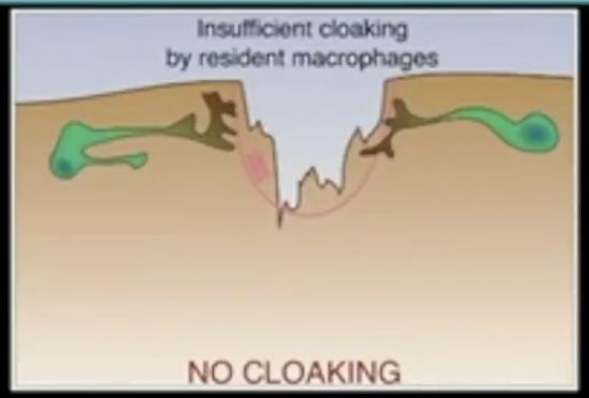
EMBL Keynote Lecture - Imaging the Immune System, Ron Germain

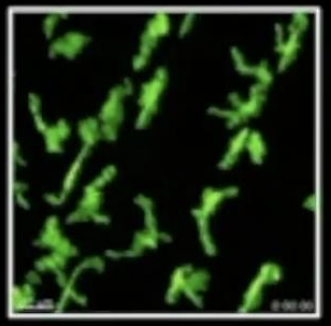
Endocytic Activity of Cloaking Macrophages Remove Cell Debris

EMBL Keynote Lecture - Imaging the Immune System, Ron Germain

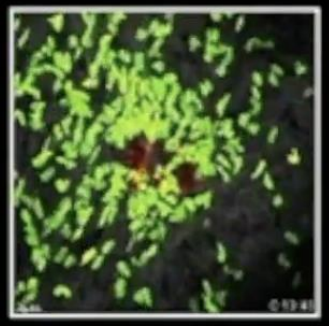
Difference Between Prevention of Inflammatory Tissue Damage and Resolution of Such Damage







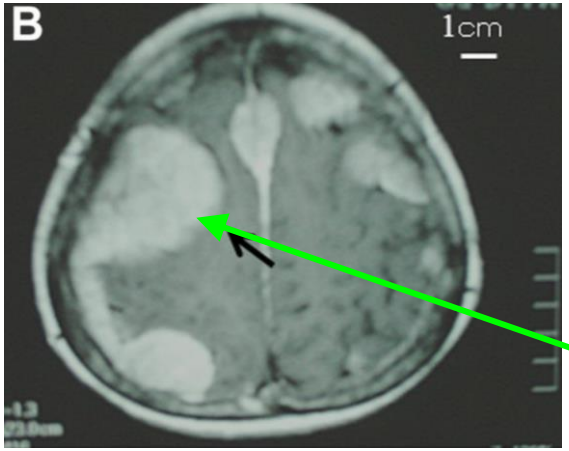
NO INFLAMMATION
=> PREVENTION

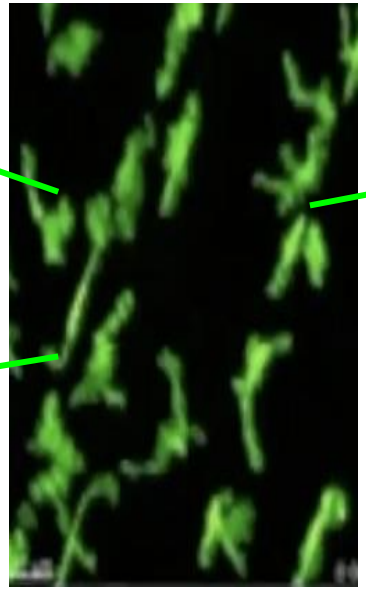


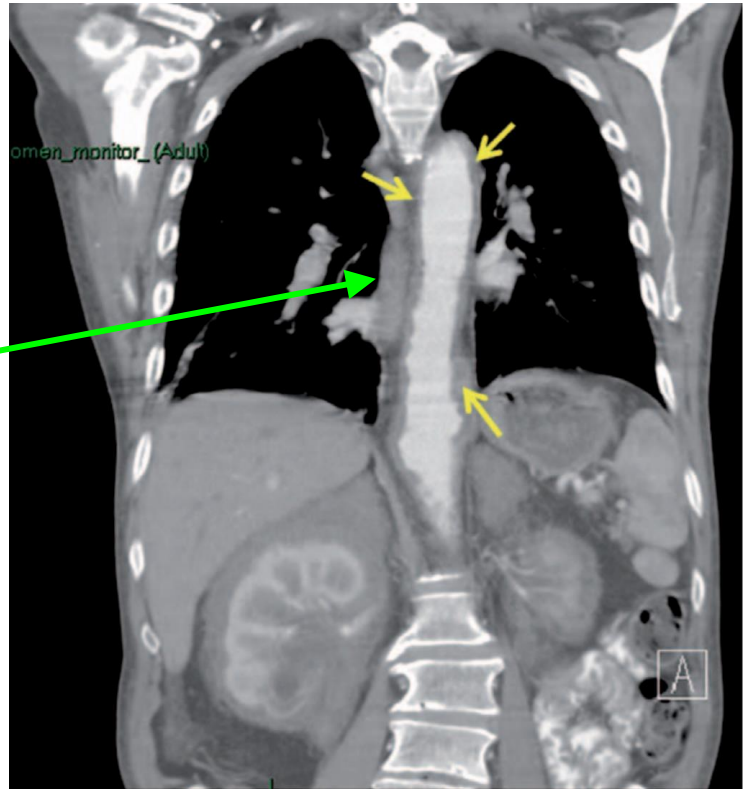
INFLAMMATION
=> RESOLUTION needed

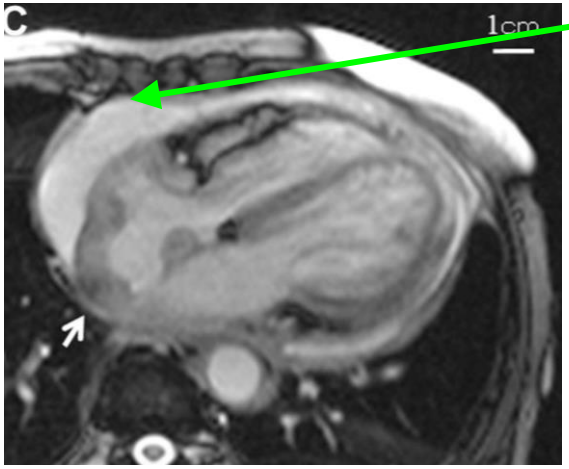
EMBL Keynote Lecture - Imaging the Immune System, Ron Germain

Impaired cloaking function of fascial macrophages promotes ECD?



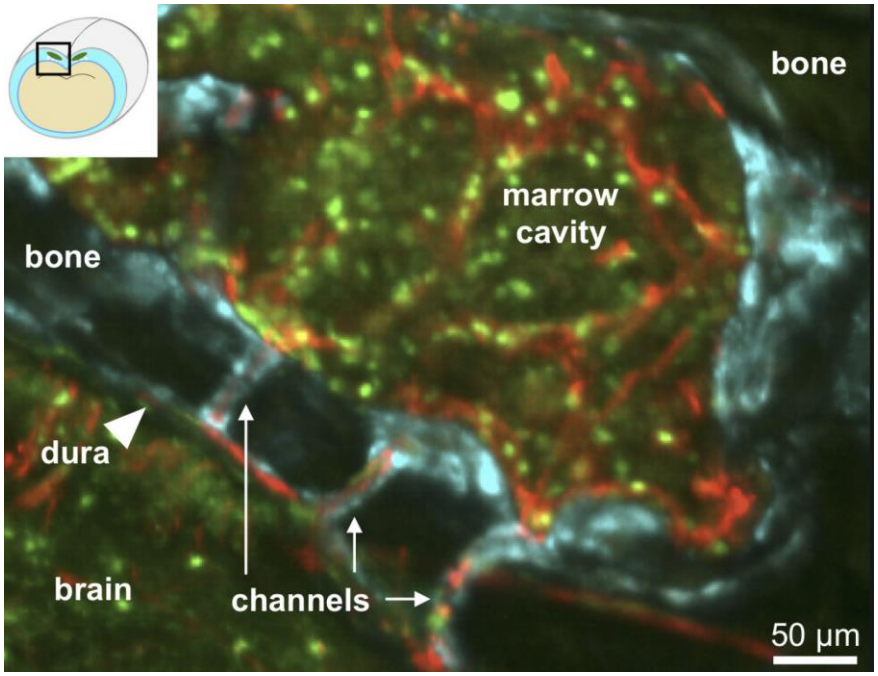




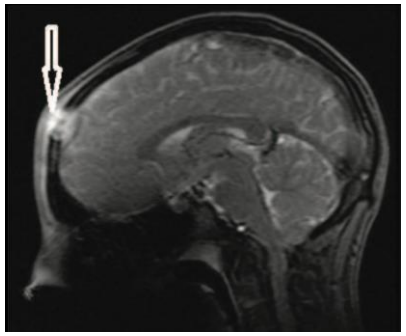


Direct channels connect the skull bone marrow and the brain surface

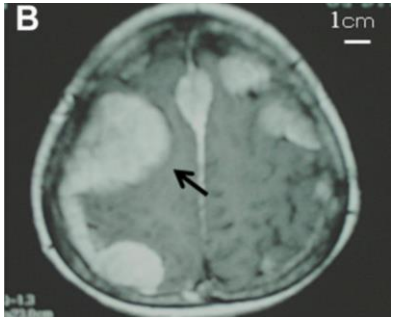
Inflammatory cells in the brain are more likely to originate from the skull than the tibia

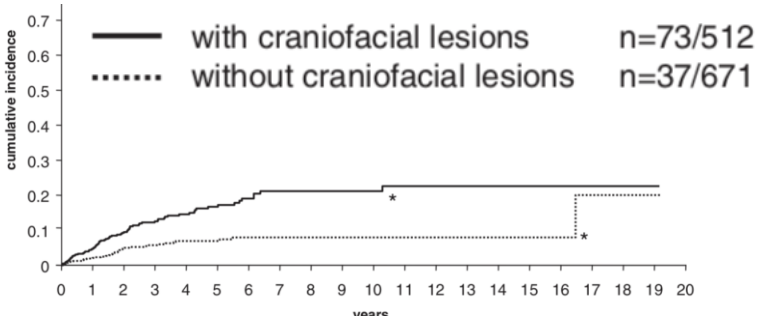


LCH

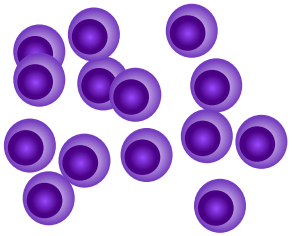


ECD





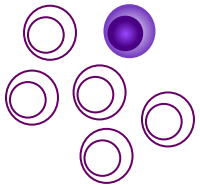
Herisson F, Frodermann V, Courties G et al. Direct vascular channels connect skull bone marrow and the brain surface enabling myeloid cell migration. *Nat Neurosci*. 2018;21 (9):1209-1217.



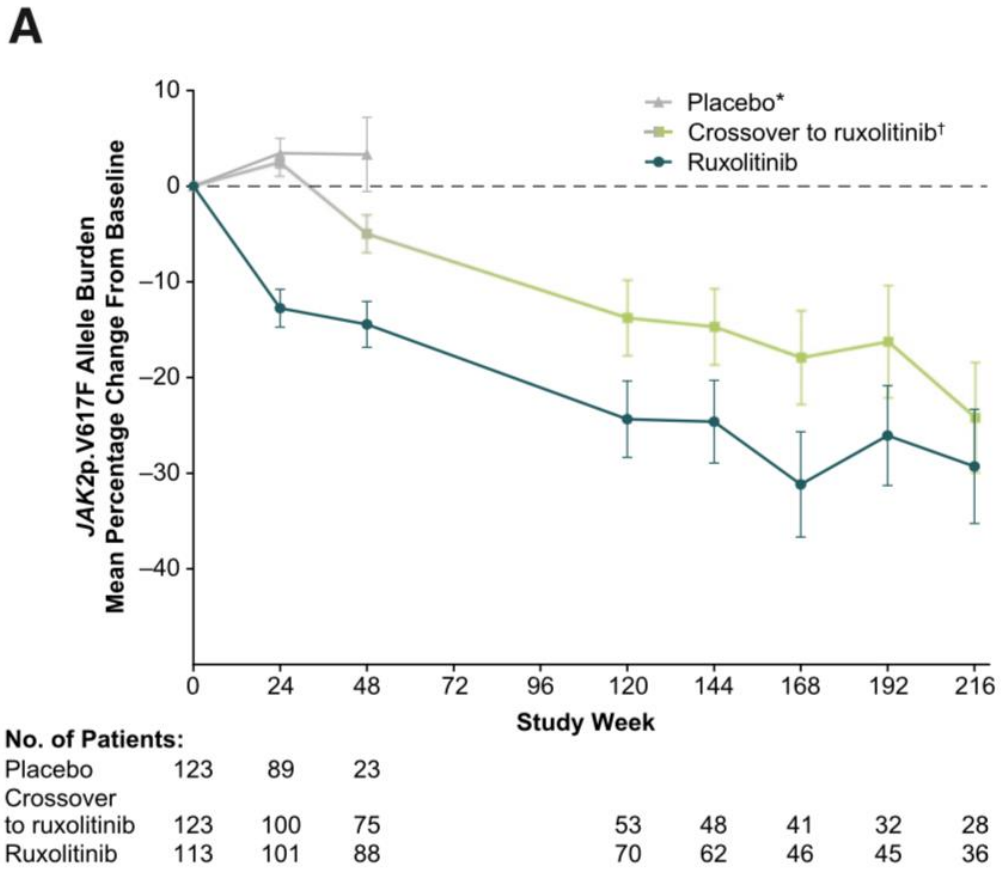
Leukaemia

Selective advantage for progenitor cells

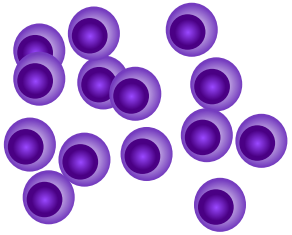
Targeted therapy



Disadvantage for mutated progenitor cells



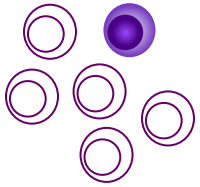
The effect of long-term ruxolitinib treatment on JAK2p.V617F allele burden in patients with myelofibrosis. (2015) Deininger, M. ***Blood***, 126, 1551-1554. PMID: 26228487



Leukaemia

Selective advantage for progenitor cells

Targeted therapy

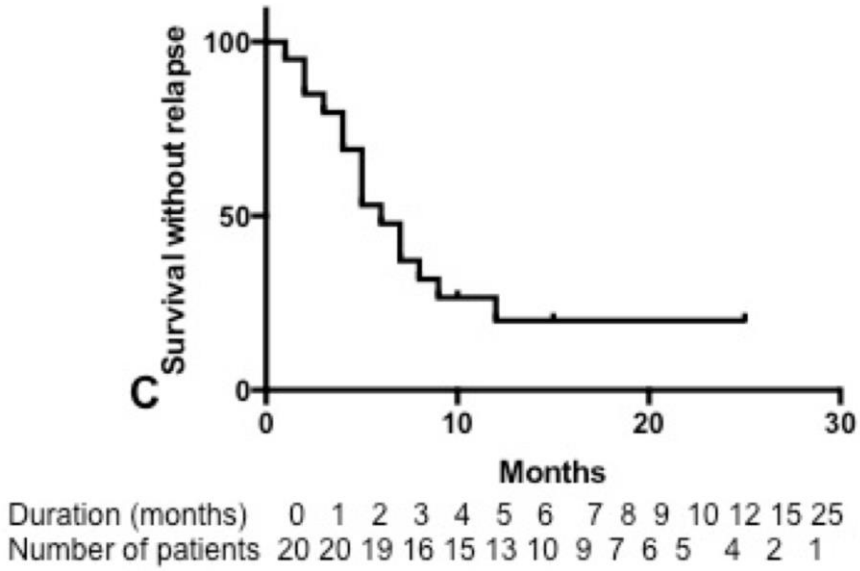


Disadvantage for mutated progenitor cells

What happens to the mutated allele burden if we give a targeted inhibitor to MS-histiocytosis?

Targeted inhibition of MAPK may not eradicate histiocytosis

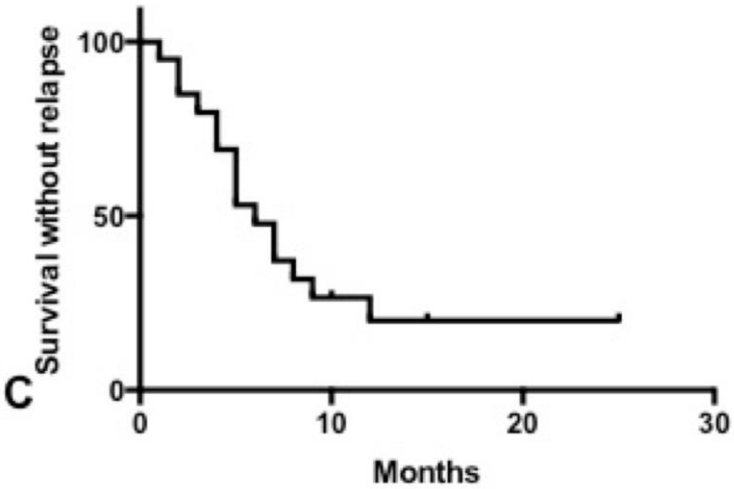
ECD



Targeted therapies in 54 patients with Erdheim-Chester disease, including follow-up after interruption (the LOVE study). (2017) Cohen Aubart, F., ***Blood***, 130, 1377-1380. PMID: 28667012

Targeted inhibition of MAPK may not eradicate histiocytosis

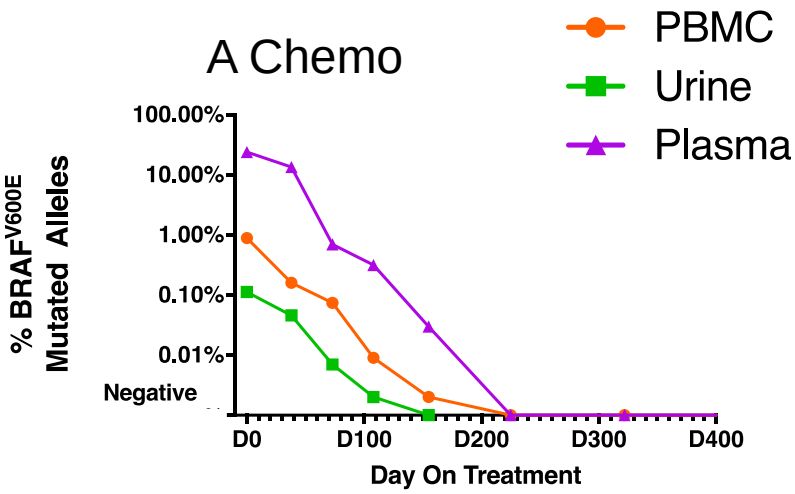
ECD

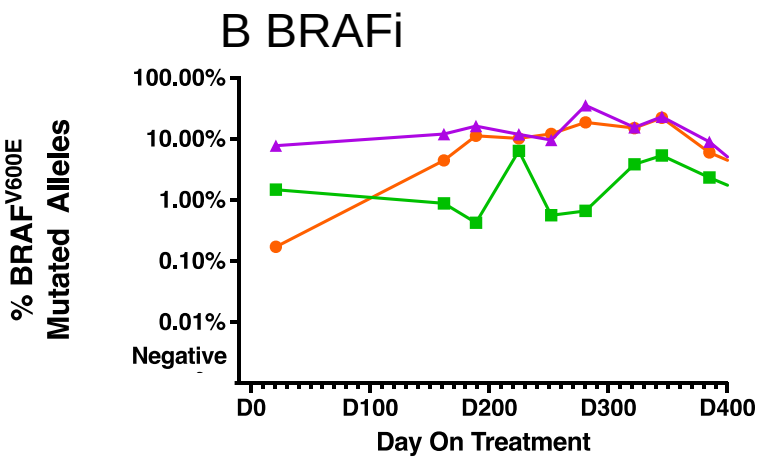


Duration (months)	0	1	2	3	4	5	6	7	8	9	10	12	15	25
Number of patients	20	20	19	16	15	13	10	9	7	6	5	4	2	1

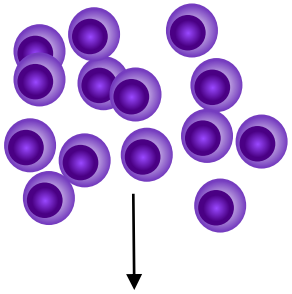
Targeted therapies in 54 patients with Erdheim-Chester disease, including follow-up after interruption (the LOVE study). (2017) Cohen Aubart, F., ***Blood***, 130, 1377-1380. PMID: 28667012

LCH





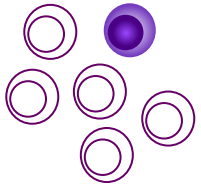
Targeted therapy does not eradicate histiocytosis



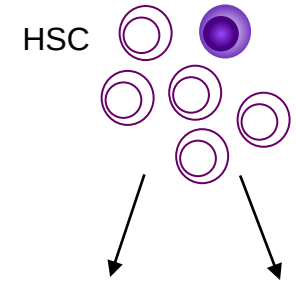
Leukaemia

Selective advantage for progenitor cells

Targeted therapy

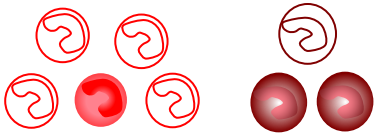


Disadvantage for mutated progenitor cells



CD14+ monocyte

CD16+ monocyte



No selective advantage

Selective advantage for BRAF^{V600E}

Lessons from MPN:
1) Germline variants will modify disease

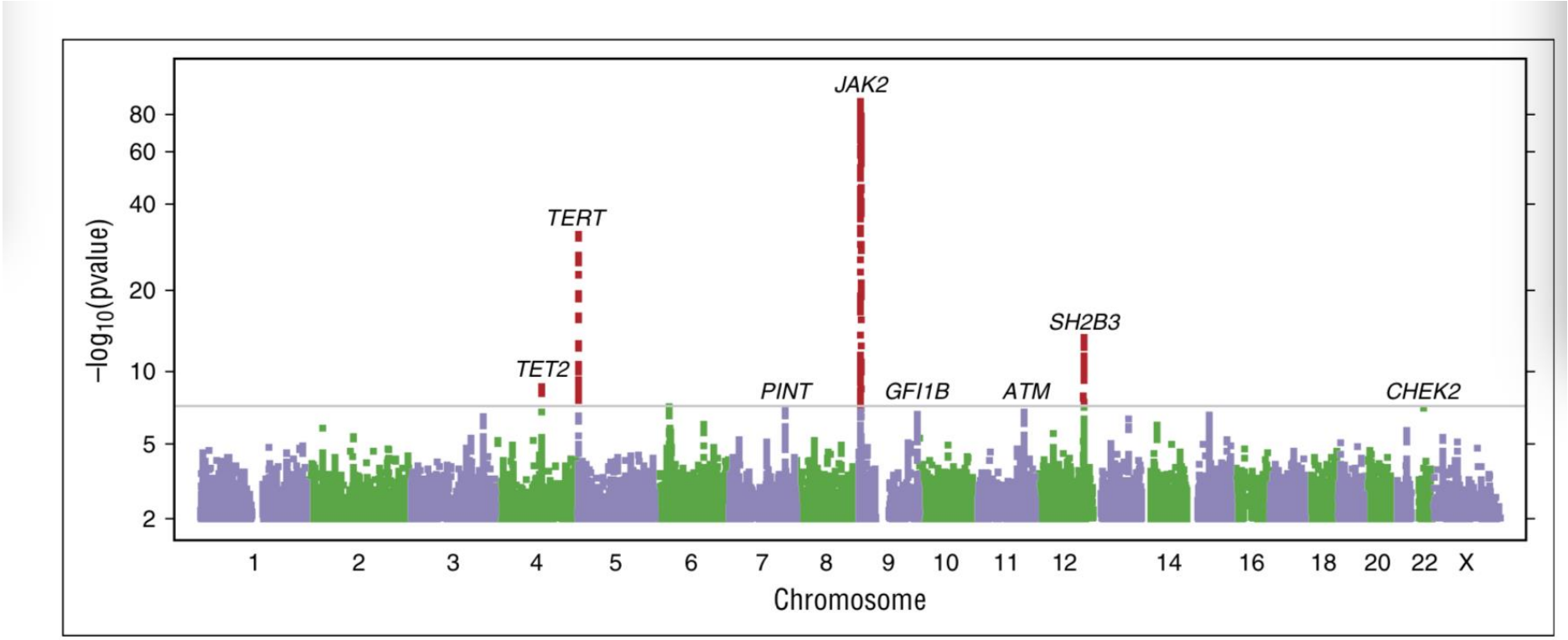
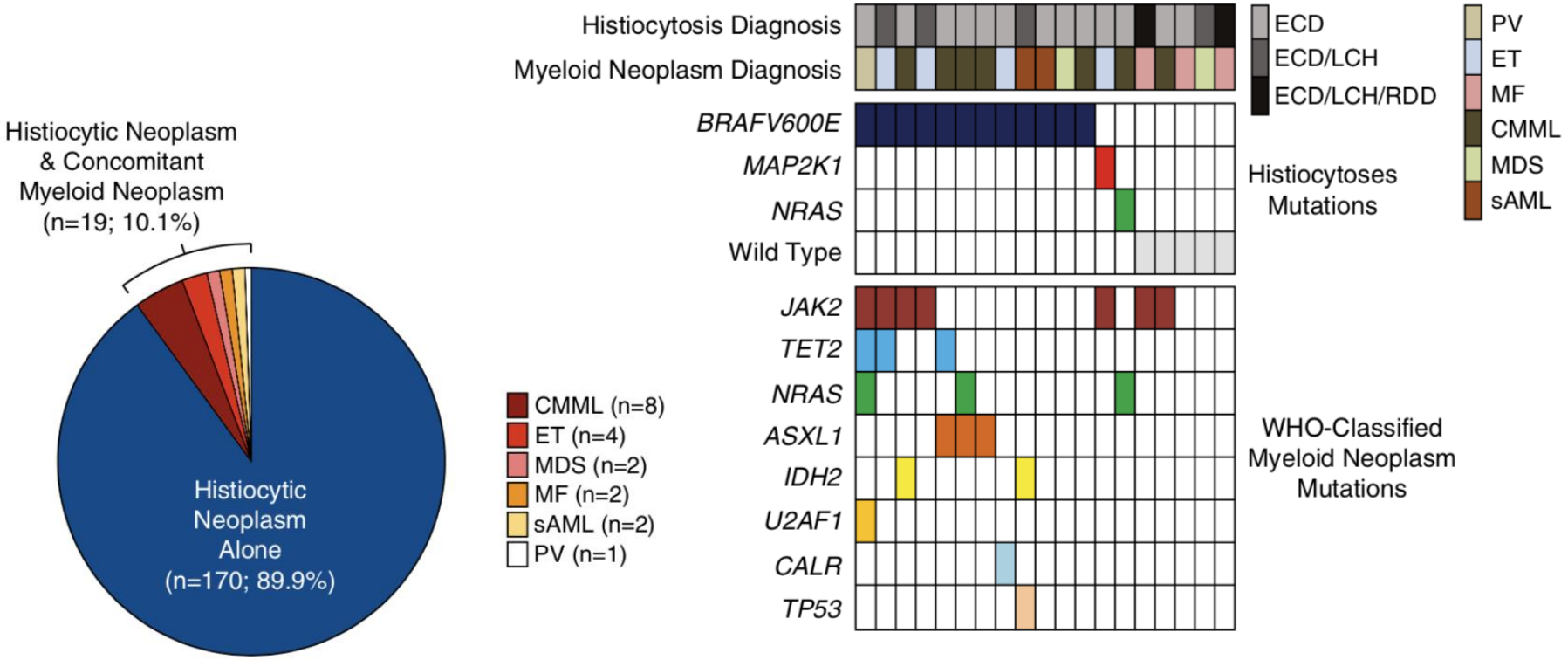


Figure 2. Manhattan plot of the combined GWAS of MPN cases and V617F carriers. Results with $P < 5 \times 10^{-8}$ (conventional threshold for genome-wide significanc are shown in red. We have also labeled suggestive results ($P < 1 \times 10^{-6}$) discussed in the text. Gene labels are provided for cross referencing with other results and are r intended to suggest a causal basis for the observed associations.

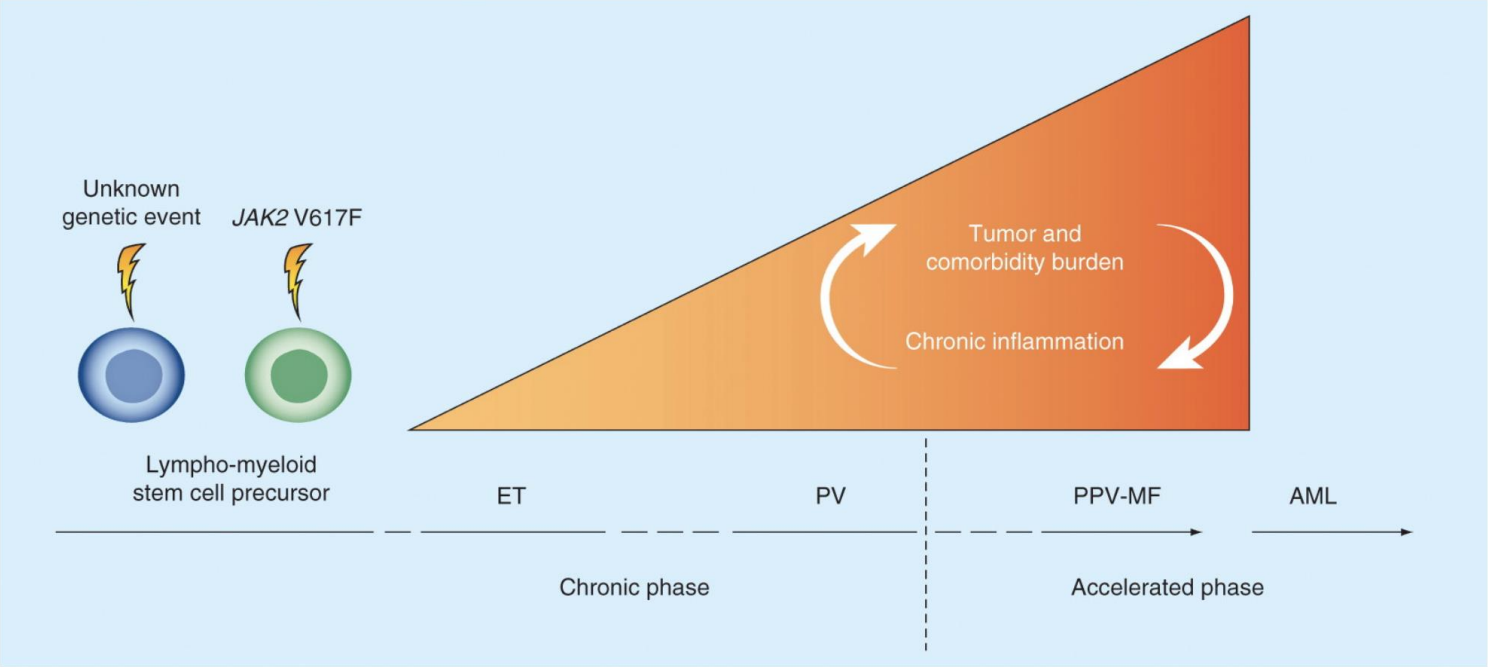
Germ line variants predispose to both JAK2 V617F clonal hematopoiesis and myeloproliferative neoplasms. (2016) Hinds, D.A. ***Blood***, 128, 1121-1128. PMID: 27365426

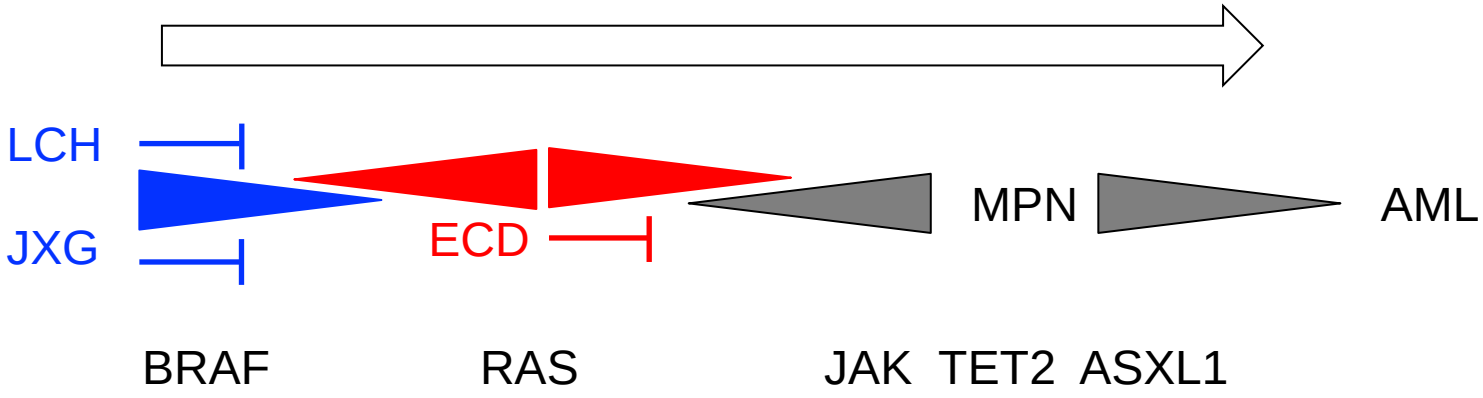
2) There will be an interaction with clonal haematopoiesis



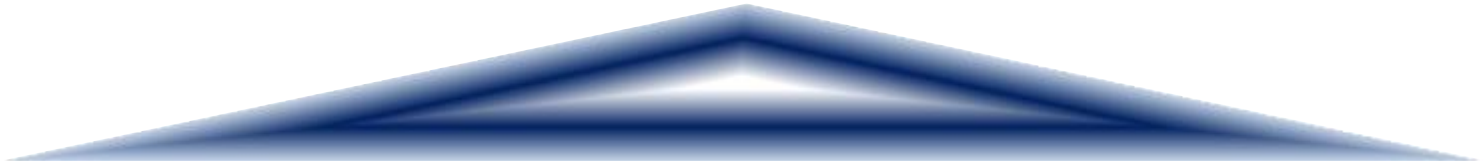
High prevalence of myeloid neoplasms in adults with non-Langerhans cell histiocytosis. (2017) Papo, M., ***Blood***, 130, 1007-1013. PMID: 28679734

3) Pathology will evolve





A cancer spectrum

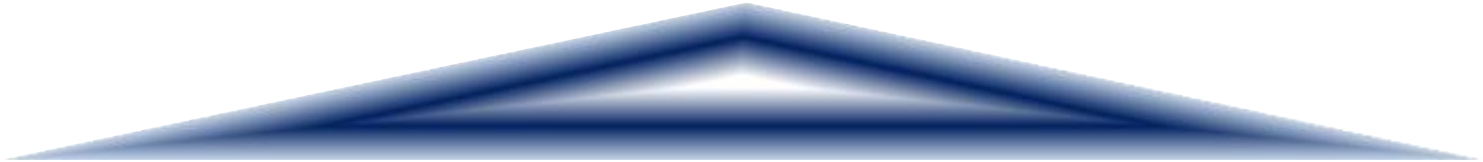


Cancer cancer
Complex genome
Forms a tumor
Kills by organ dysfunction

Ageing
Somatic mutation
Clones detectable
Low grade inflammation

A cancer spectrum

Inflammatory myeloid neoplasia
Specific somatic mutations
Inflammatory feedback loops
Bizarre systemic manifestations



Cancer cancer
Complex genome
Forms a tumor
Kills by organ dysfunction

Ageing
Somatic mutation
Clones detectable
Low grade inflammation

It is not how old you are
but how you are old - Jules Renard

Jules Renard 1864-1910

I don't know if God exists, but it would be better for His reputation if He didn't.

Jules Renard 1864-1910

Jules Renard 1864-1910

Not everybody can be an orphan.

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Erdheim-Chester disease

Search Database | ICD-O-3 Code Lists

This neoplasm is not reportable.

Name

Erdheim-Chester disease

Not Reportable

This neoplasm is not reportable

Alternate Names

ECD
Lipogranulomatosis
Lipoid granulomatosis
Lipid (cholesterol) granulomatosis
Polyostotic sclerosing histiocytosis

Definition

Erdheim-Chester disease (ECD) is a clonal systemic proliferation of histiocytes, commonly having a foamy (xanthomatous) component, and contain Touton giant cells (considered to be a non-Langerhans cell histiocytosis).

Acknowledgements

Paul Milne
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Sarah Pagan
Clare Lendrem

CANCER RESEARCH UK

Together we are Histio UK

HISTIOCYTOSIS ASSOCIATION™
A Rare Community

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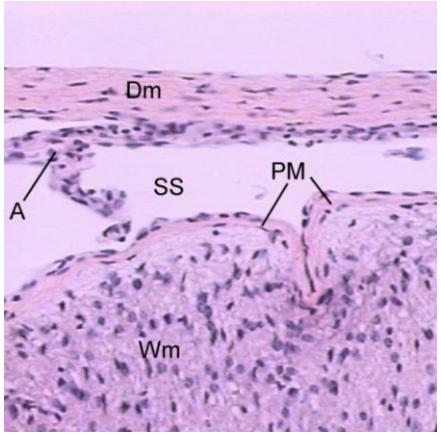
Serosal macrophages – the substrate of ECD?

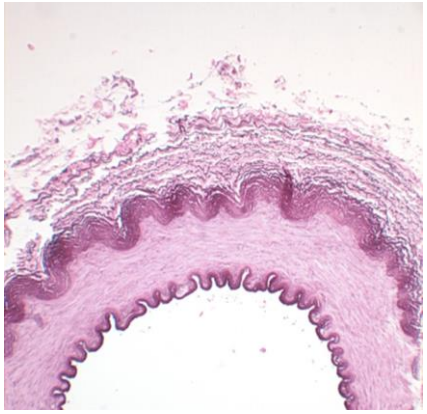
- Helicopter parent function of macrophages
- Abnormal response to damage
- Failure of cloaking
- Recruitment of BM-derived cells
- Inflammation and fibrosis

Pleura

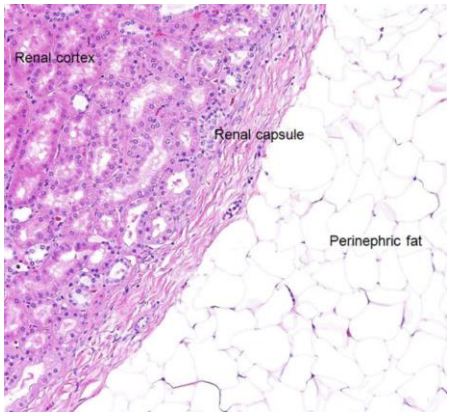
Dura



Adventia



Renal capsule



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Distinct NF-κB and MAPK Activation Thresholds Uncouple Steady-State Microbe Sensing from Anti-pathogen Inflammatory Responses

Rachel A. Gottschalk, Andrew J. Martins, Bastian R. Angermann, Bhaskar Dutta, Caleb E. Ng, Stefan Uderhardt, John S. Tsang, Iain D.C. Fraser, Martin Meier-Schellersheim, Ronald N. Germain

Cell Systems

Volume 2, Issue 6, Pages 378-390 (June 2016)

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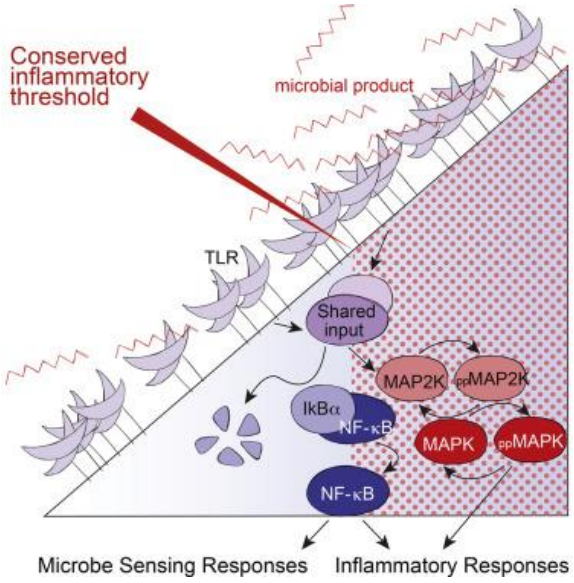

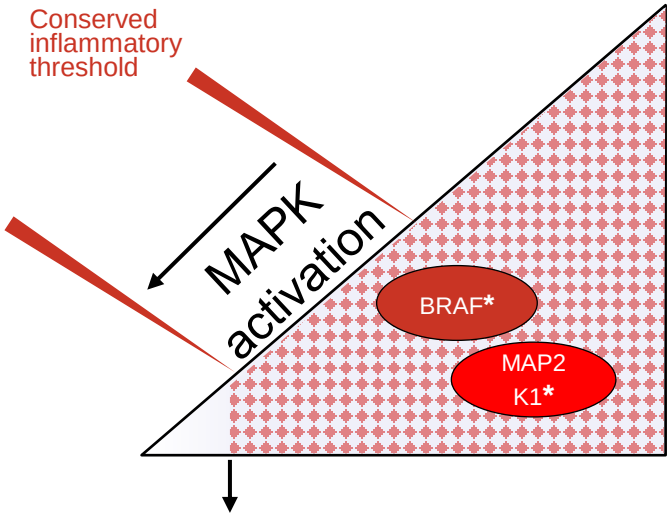

Inflammatory response at a lower threshold

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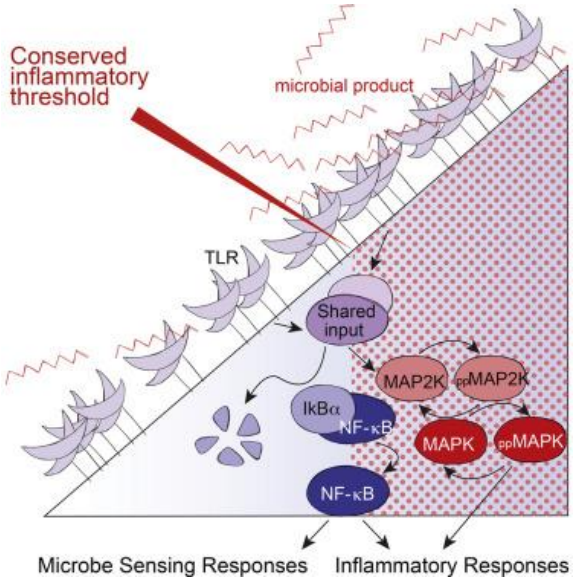

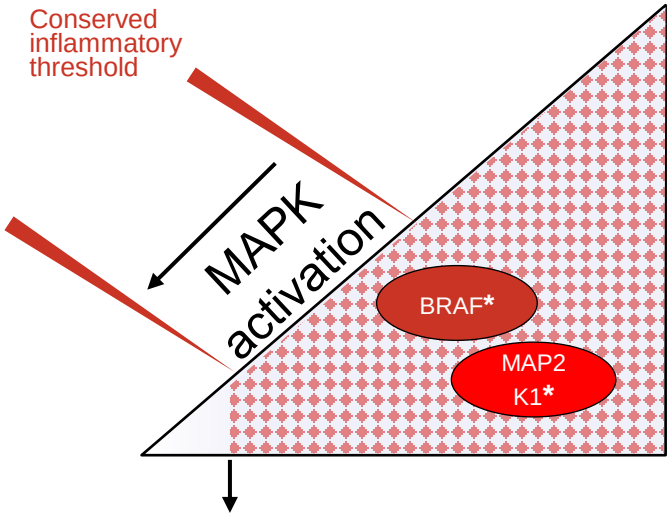

Inflammatory response at a lower threshold

Overview

- A case B-D – see BJH lecture
- What is cancer?
  - Somatic mutation rate in all tissues
  - Alternate states of the genome
  - Ageing gracefully
  - Waddington landscape for cancer???
  - How does chemo work in myeloid neoplasia? Non stem cell disease. Selective pressure etc
- Myeloid pathology – lessons from MPN – constitutional symptoms in myelofibrosis
- Future questions
  - Drug dosing – do we need to hit it hard like cancer – maybe not
  - CNS penetrance
  - Nature of cell-free DNA – progenitor vs tumour
  - Exit strategies from targeted therapy – usually don't talk about exit in cancer
  - Immunotherapy question

Also from NCI pages

- The genetic changes that contribute to cancer tend to affect three main types of genes—proto-oncogenes, tumor suppressor genes, and DNA repair genes.
- Proto-oncogenes are involved in normal cell growth and division. However, when these genes are altered in certain ways this allows cells to grow and survive when they should not.
- Many cancers form solid tumors, which are masses of tissue. Cancers of the blood, generally do not form solid tumors.
- Cancer cells may be able to influence the normal cells, molecules, and blood vessels that surround and feed a tumor—an area known as the microenvironment.
- Tumors can also use the immune system to stay alive and grow.

Autoimmune disease and MPN

Al Ustwani O, Ford LA, Sait SJ, et al. Myelodysplastic syndromes and autoimmune diseases—case series and review of literature. Leuk Res 2013;37(8):894-9

Kristinsson SY, Landgren O, Samuelsson J, et al. Autoimmunity and the risk of myeloproliferative neoplasms. Haematologica 2010;95(7):1216-20

Hasselbalch HC. The role of cytokines in the initiation and progression of myelofibrosis. Cytokine Growth Factor Rev 2013;24:133-45

Reads

- Review recent literature
- Implications for patients
  - stress of diagnosis vs access to benefits – appreciation of serious nature

Mod Pathol 2018 Sep. 31:1479-1486. 10.1038/s41379-018-0052-4

Expression of the transcription factor ZBTB46 distinguishes human histiocytic disorders of classical dendritic cell origin.

Satpathy, AT, Brown, RA, Gomulia, E, Briseño, CG, Mumbach, MR, Pan, Z, Murphy, KM, Natkunam, Y, Chang, HY, Kim,

Department of Pathology, Stanford University School of Medicine, Stanford, CA, 94305, USA. satpathy@stanford.edu.

Onco Targets Ther 2017. 10:521-526. 10.2147/OTT.S121615

Effective BRAF inhibitor vemurafenib therapy in a 2-year-old patient with sequentially diagnosed Langerhans cell histiocytosis and Erdheim-Chester disease.

Váradi, Z, Bánusz, R, Csomor, J, Kállay, K, Varga, E, Kertész, G, Csóka, M

NCI definition

- ***cancer*** listen (KAN-ser)
- A term for diseases in which **abnormal cells divide without control and can invade nearby tissues**. Cancer cells can also spread to other parts of the body through the blood and lymph systems. There are several main types of cancer. Carcinoma is a cancer that begins in the skin or in tissues that line or cover internal organs. Sarcoma is a cancer that begins in bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue. Leukemia is a cancer that starts in blood-forming tissue, such as the bone marrow, and causes large numbers of abnormal blood cells to be produced and enter the blood. Lymphoma and multiple myeloma are cancers that begin in the cells of the immune system. Central nervous system cancers are cancers that begin in the tissues of the brain and spinal cord. Histiocytosis is a cancer?

Haematopoietic 'plasticity'

Really reflects lymphomyeloid haematopoiesis – WHO2016 puts them in lymphoid malignancy

Feldman AL, Arber DA, Pittaluga S, et al. Clonally related follicular lymphomas and histiocytic/dendritic cell sarcomas: evidence for transdifferentiation of the follicular lymphoma clone. Blood. 2008;111(12):5433-5439.
Shao H, Xi L, Raffeld M, et al. Clonally related histiocytic/dendritic cell sarcoma and chronic lymphocytic leukemia/small lymphocytic lymphoma: a study of seven cases. Mod Pathol. 2011;24(11):1421-1432.
Chen W, Jaffe R, Zhang L, et al. Langerhans cell sarcoma arising from chronic lymphocytic lymphoma/small lymphocytic leukemia: lineage analysis and BRAF V600E Mutation Study. N Am J Med Sci. 2013;5(6):386-391.
Ratei R, Hummel M, Anagnostopoulos I,
et al. Common clonal origin of an acute B-lymphoblastic leukemia and a Langerhans' cell sarcoma: evidence for hematopoietic plasticity. Haematologica. 2010;95(9): 1461-1466.
Shao H, Xi L, Raffeld M, et al. Clonally related histiocytic/dendritic cell sarcoma and chronic lymphocytic leukemia/small lymphocytic lymphoma: a study of seven cases. Mod Pathol. 2011;24(11):1421-1432.
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Letterer-Siwe

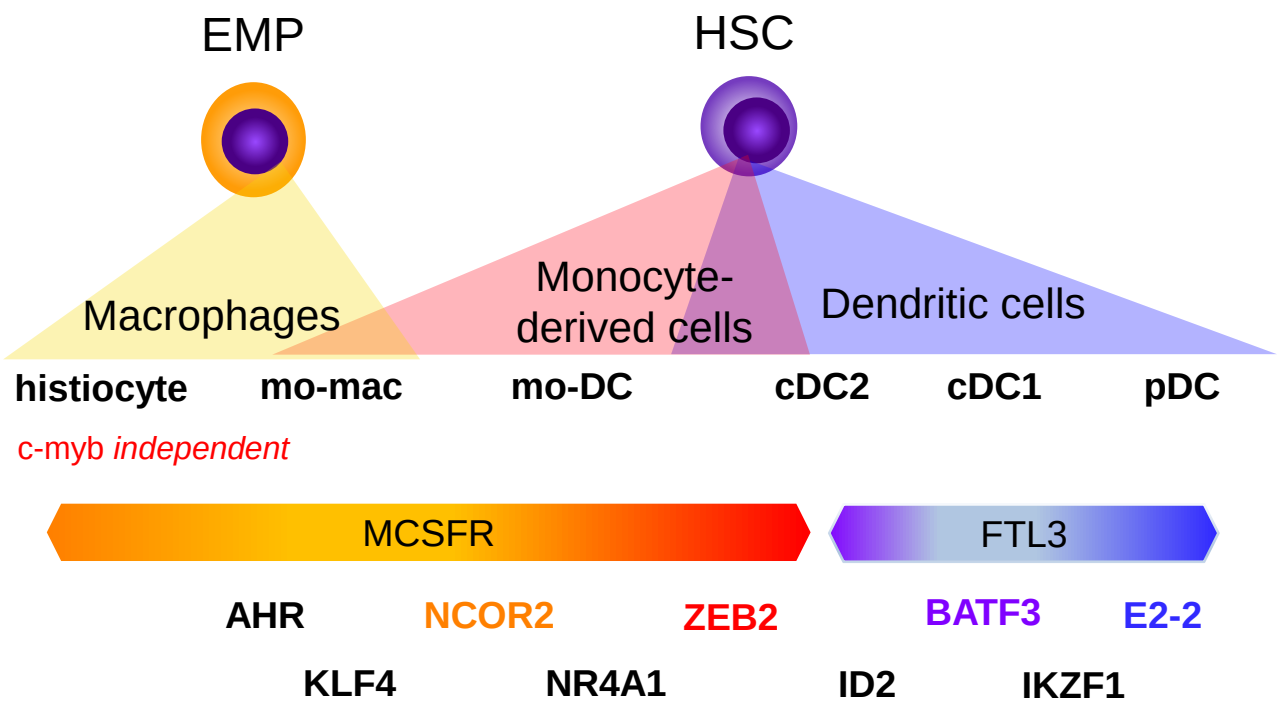
Eosinophilic granuloma

Hand-Schuller Christian

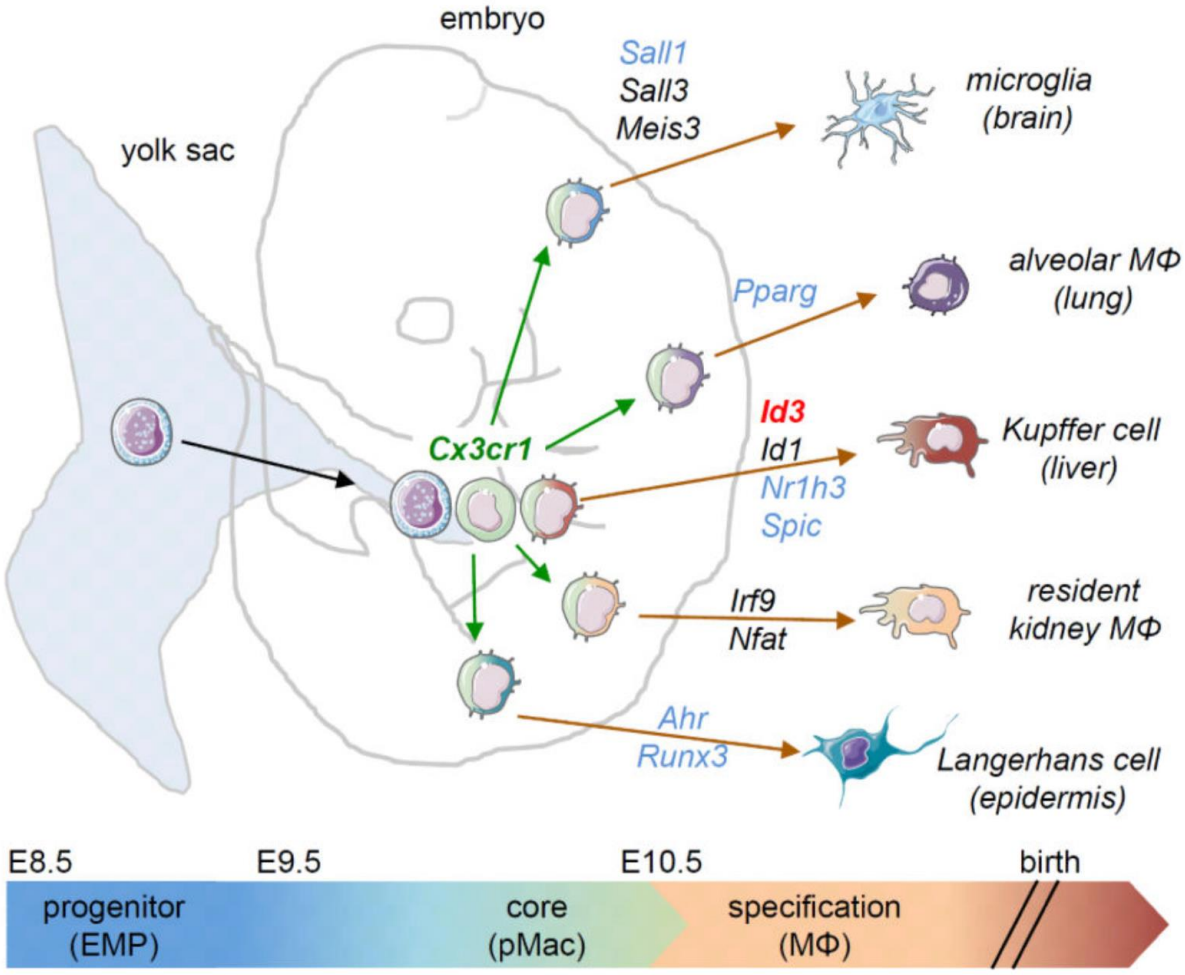
Erdheim Chester Disease

The mononuclear phagocyte system

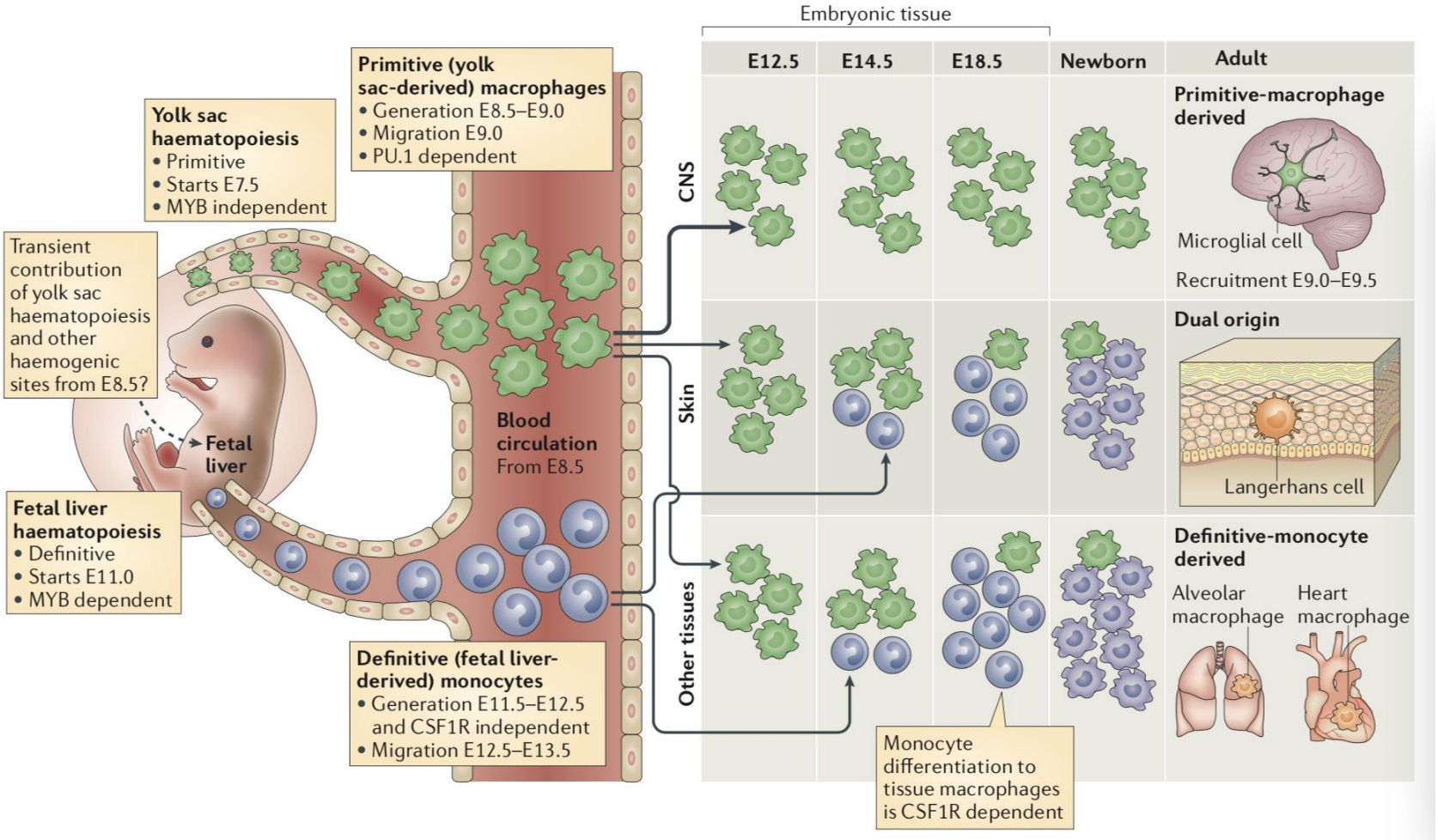
Dual origin of macrophages



Primitive macrophages colonise every tissue

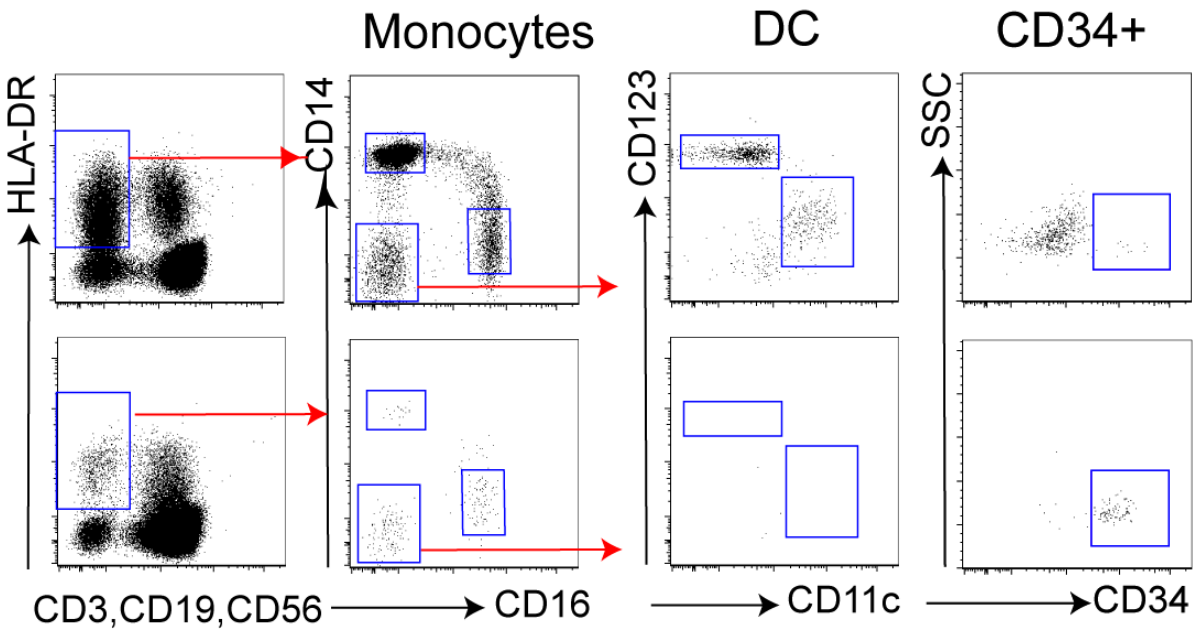


Fetal liver monocytes contribute except in the brain



Human macrophages are long-lived

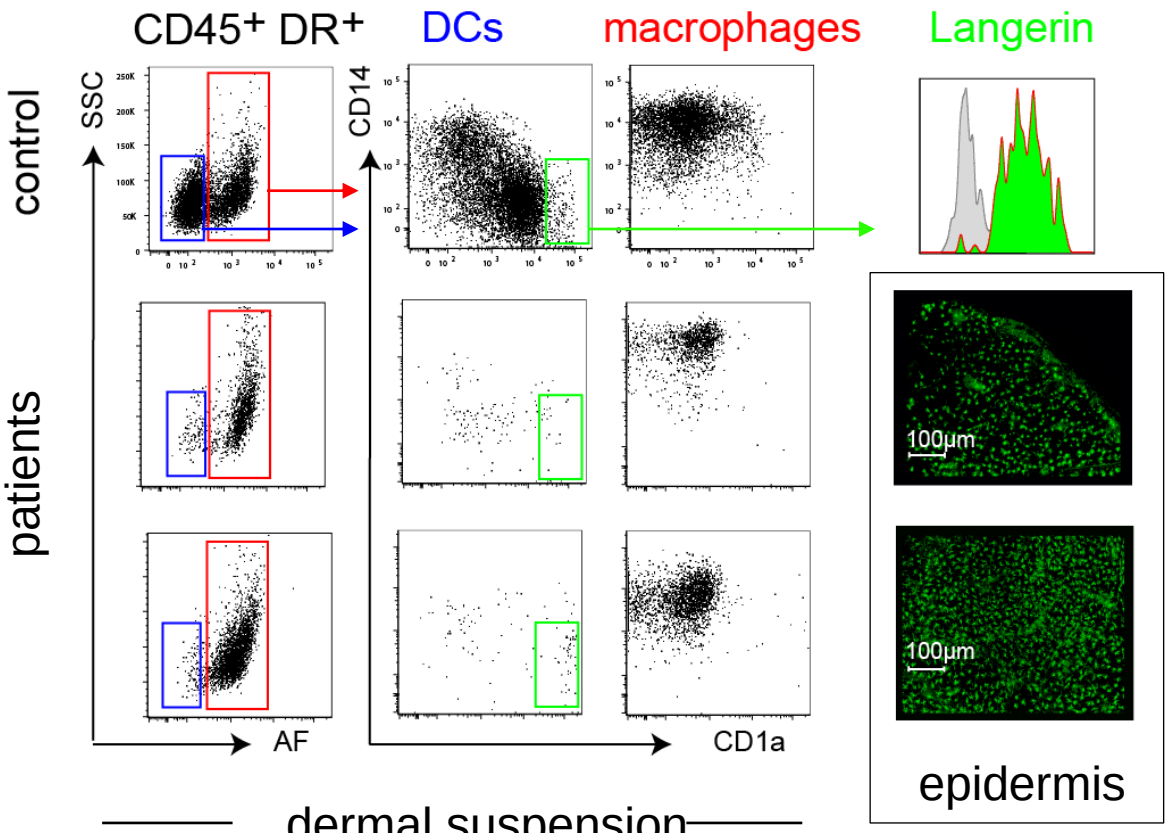
Control

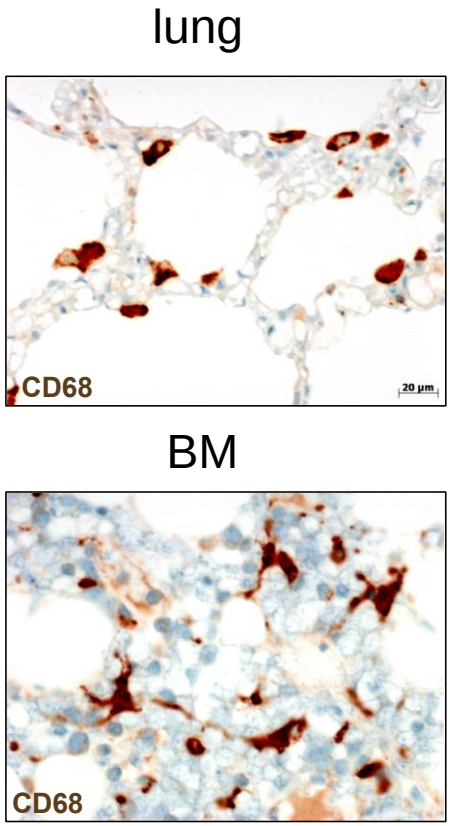


Patient with *GATA2* mutation

Bigley et al. *J Exp Med* 208, 227-234 (2011).

Human macrophages are long-lived





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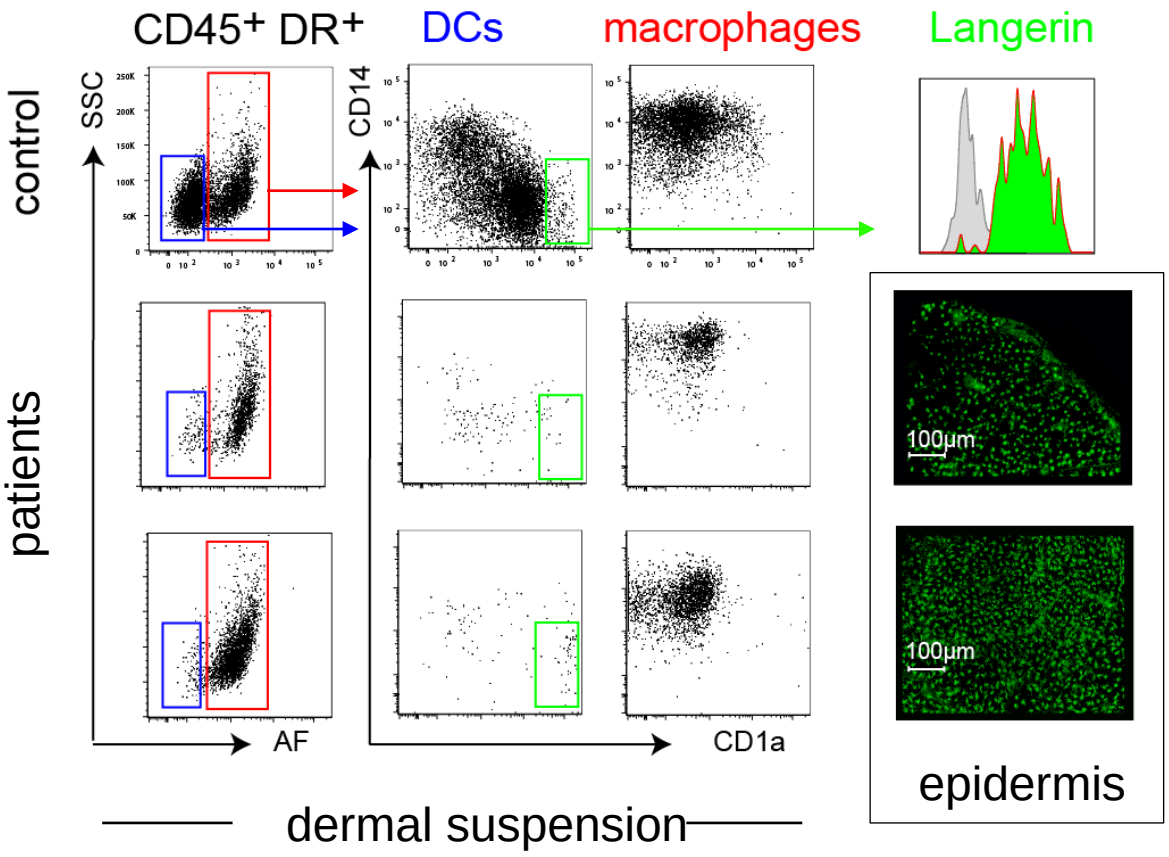

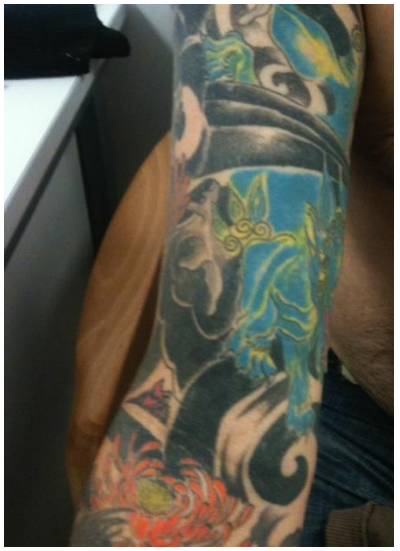

Tattoo pigment
- stable for decades
- even after HSCT

Bigley et al. *J Exp Med* 208, 227-234 (2011).