The Physician-Scientist: Rewards & Challenges

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Ulster Medical Society Meeting

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@MullallyLab

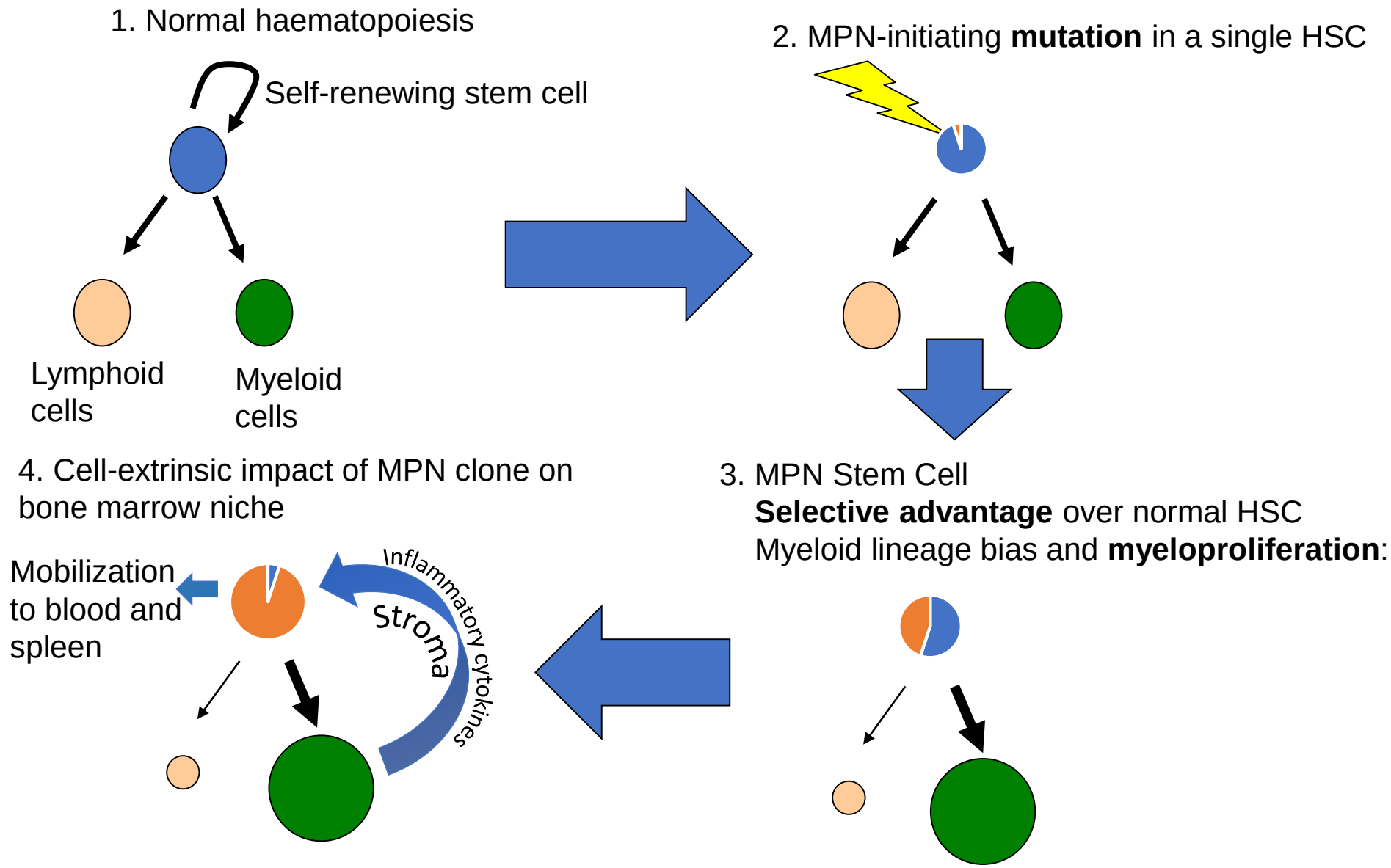
Dana-Farber Cancer Institute

BROAD INSTITUTE

Seminar Overview

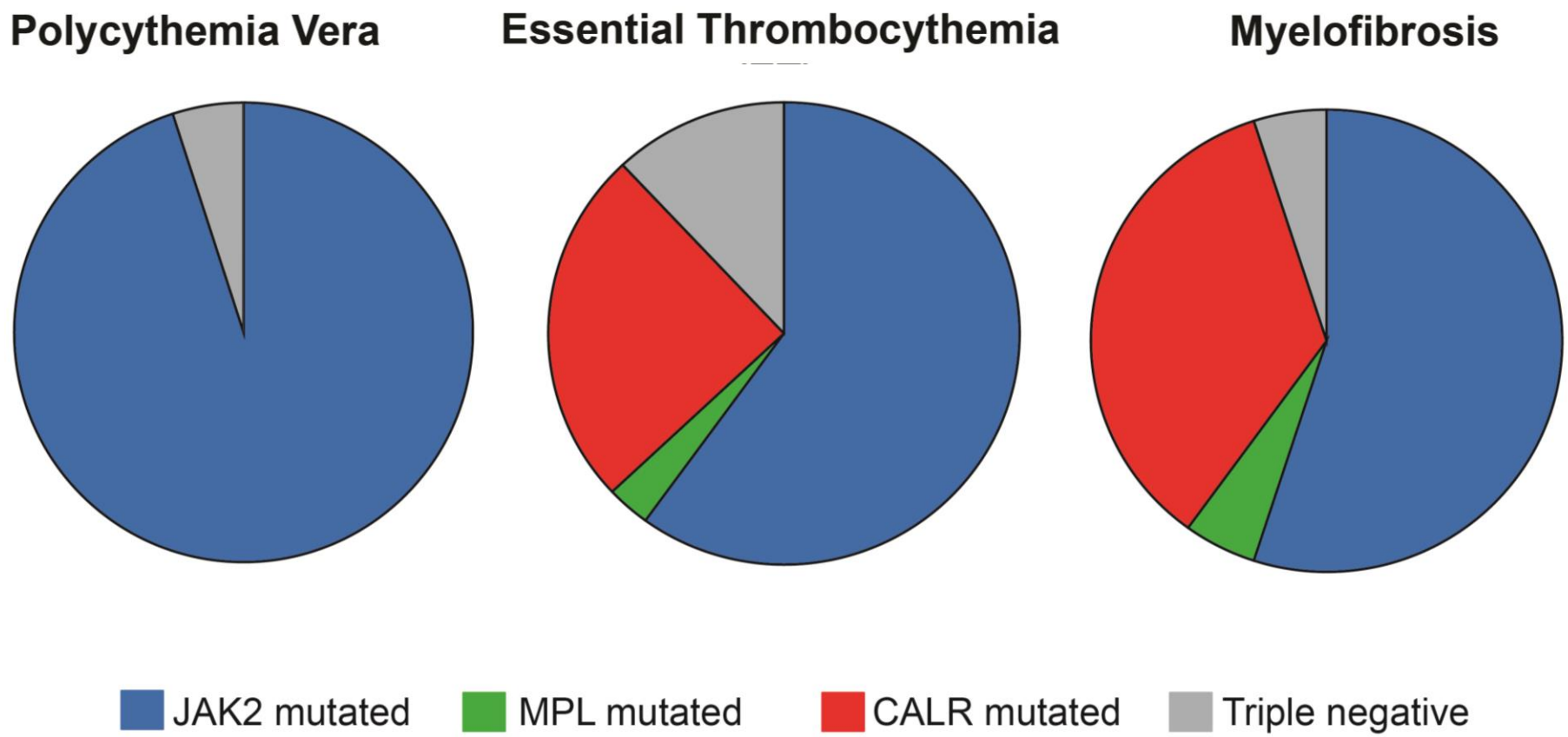
- Lab story #1: *JAK2*
- Lab story #2: *CALR*
- Challenges for the physician-scientist

Myeloproliferative Neoplasm (MPN) Stem Cells



Mead & Mullally. *Blood* 2017; Mar 23;129(12):1607-1616..

MPN Disease-Initiating Mutations



Baxter et al. *Lancet.* 2005 Mar 19-25;365(9464):1054-61.
James et al. *Nature*. 2005 Apr 28;434(7037):1144-8.
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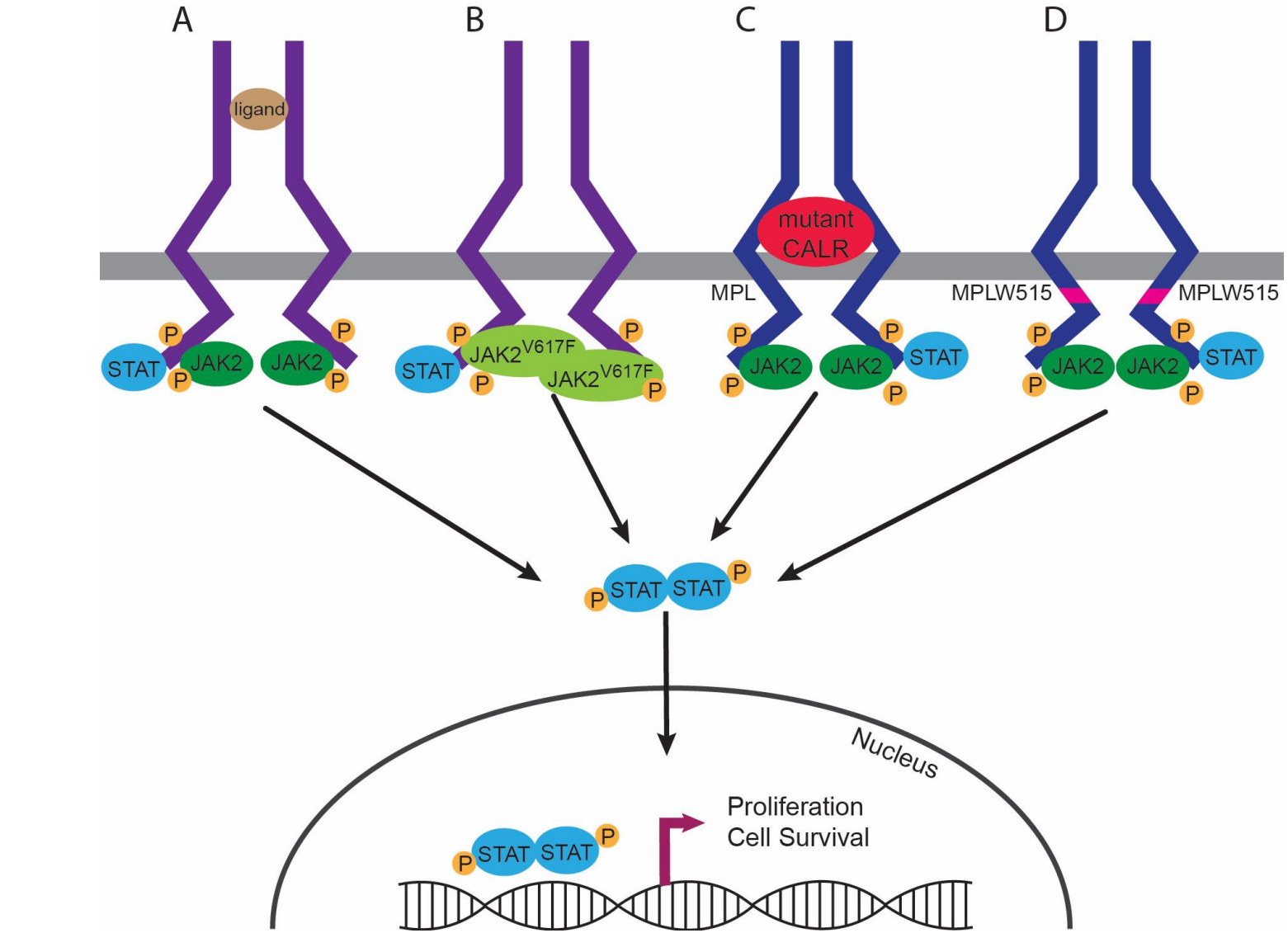
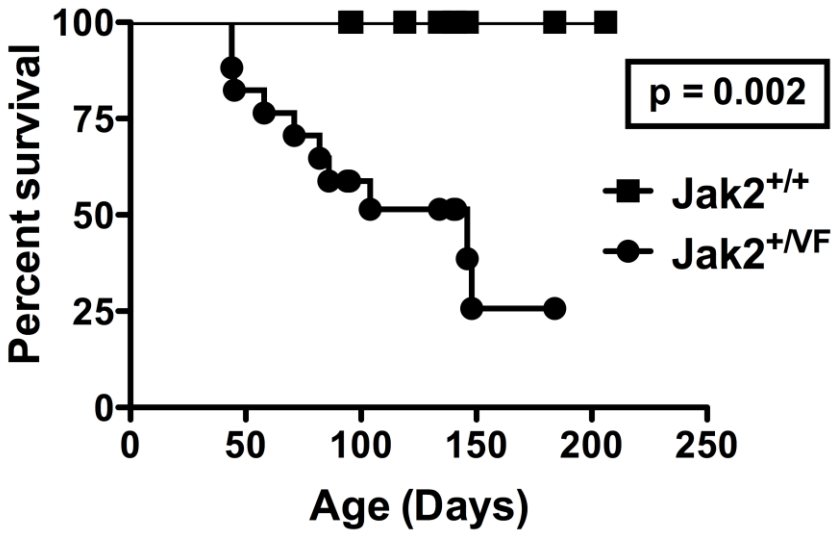
Levine et al. *Cancer Cell*. 2005 Apr;7(4):387-97.
Pikman et al. *PLoS Med.* 2006 Jul;3(7):e270.
Klampfl et al. *NEJM.* 2013 Dec 19;369(25):2379-90.
Nangalila et al. *NEJM.* 2013 Dec 19;369(25):2391-2405

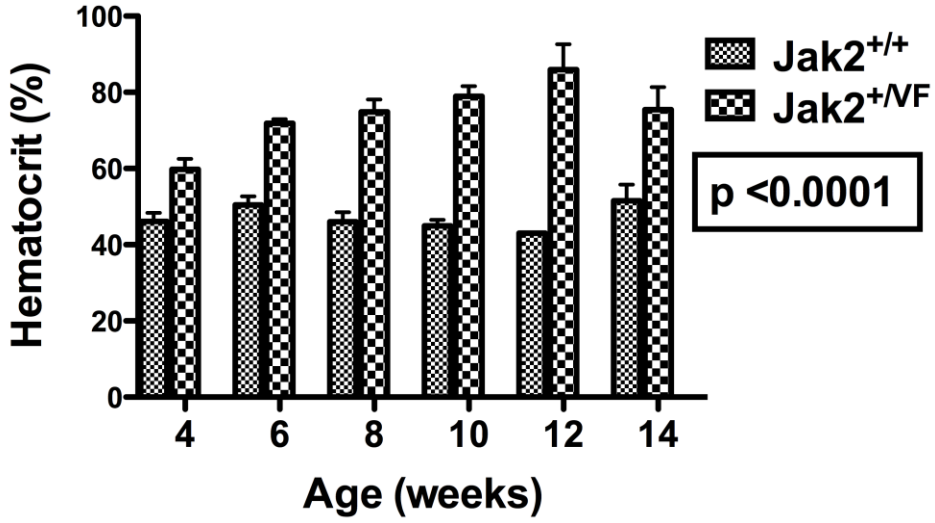
Activated JAK-STAT signaling central to MPN pathogenesis

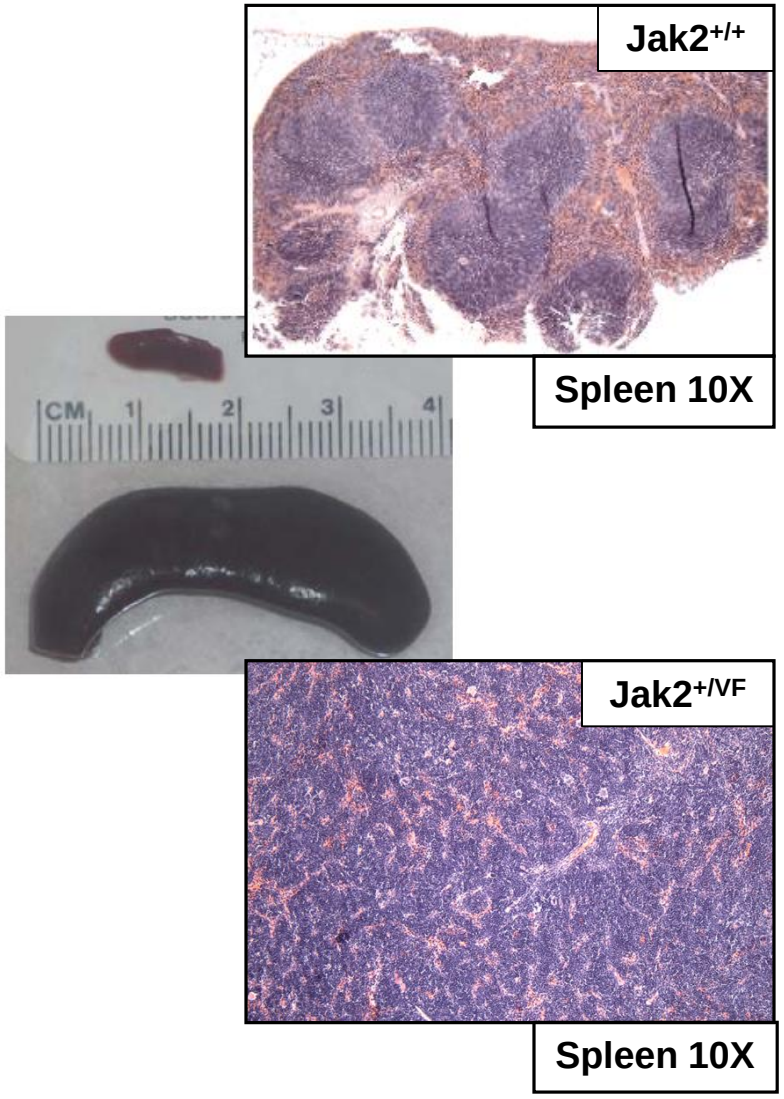


Hobbs, Rozelle, Mullally. *Hematology/Oncology Clinics.* 2017 Aug;31(4):613-626

Jak2V617F *alone* is sufficient to engender MPN in mice







Mullally & Lane et al. *Cancer Cell*. 2010 Jun 15;17(6):584-96.

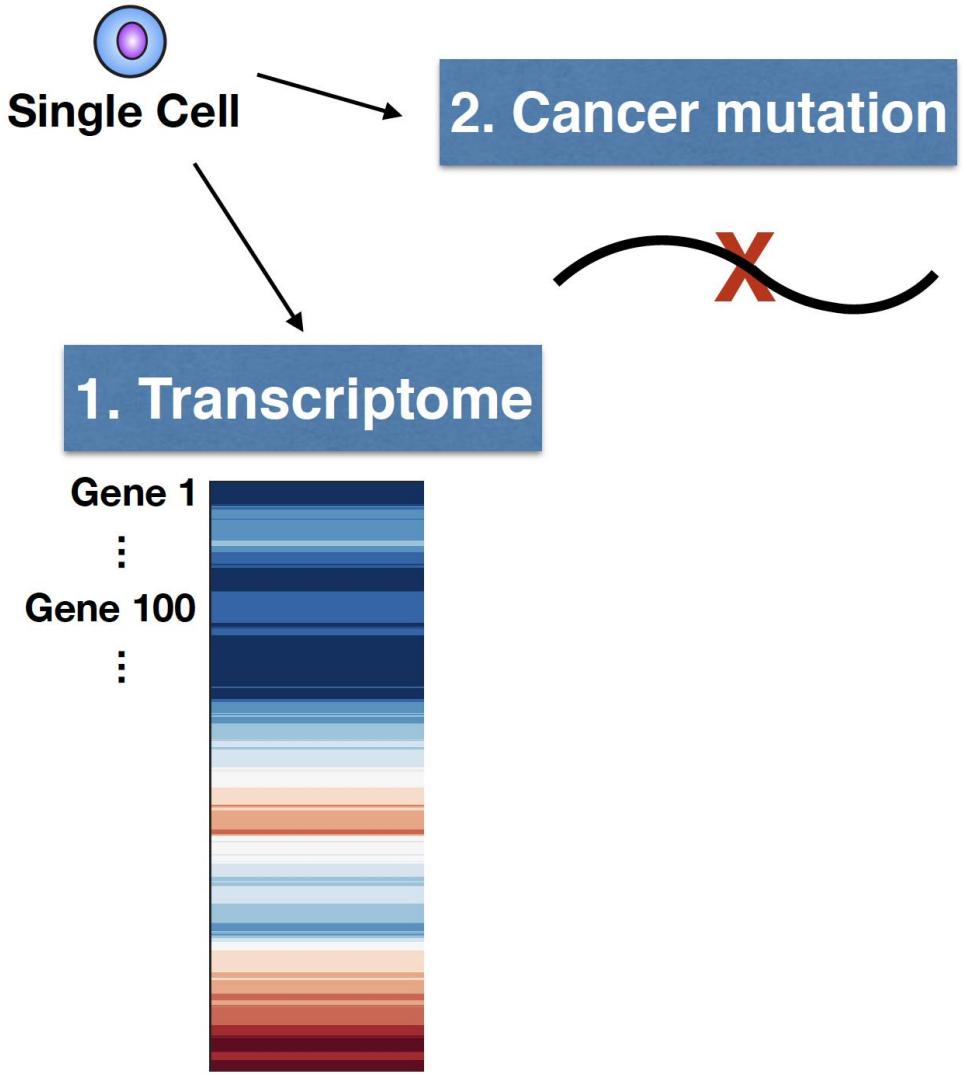
MPN phenotypic mutations are sufficient to cause MPN

Next generation Sequencing (NGS) data on approx. 750 MPN samples @ DFCI

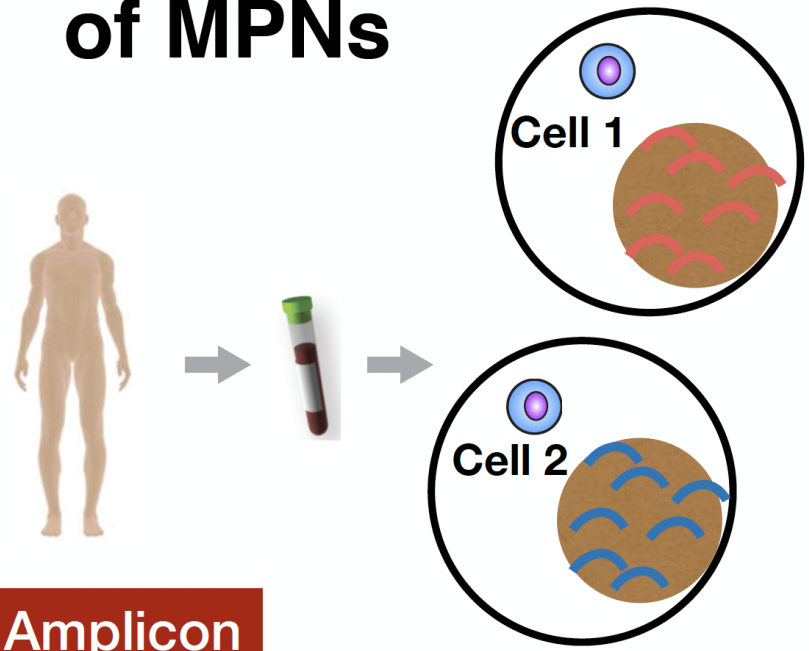
Patient case report

55yo M presents with erythrocytosis and pruritus
Severe coronary artery calcification on CT (no CV risk factors)
His father died at age 45 from acute MI (no CV risk factors)
NGS sequencing (PB) shows: JAK2-V617F VAF = 68%, TET2S268* = 32%

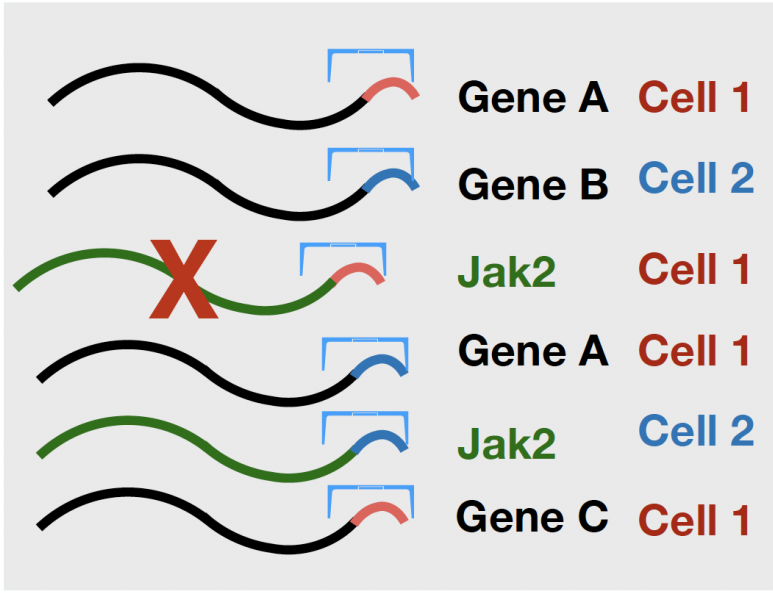
In each patient, identify the mutant cells and characterize them



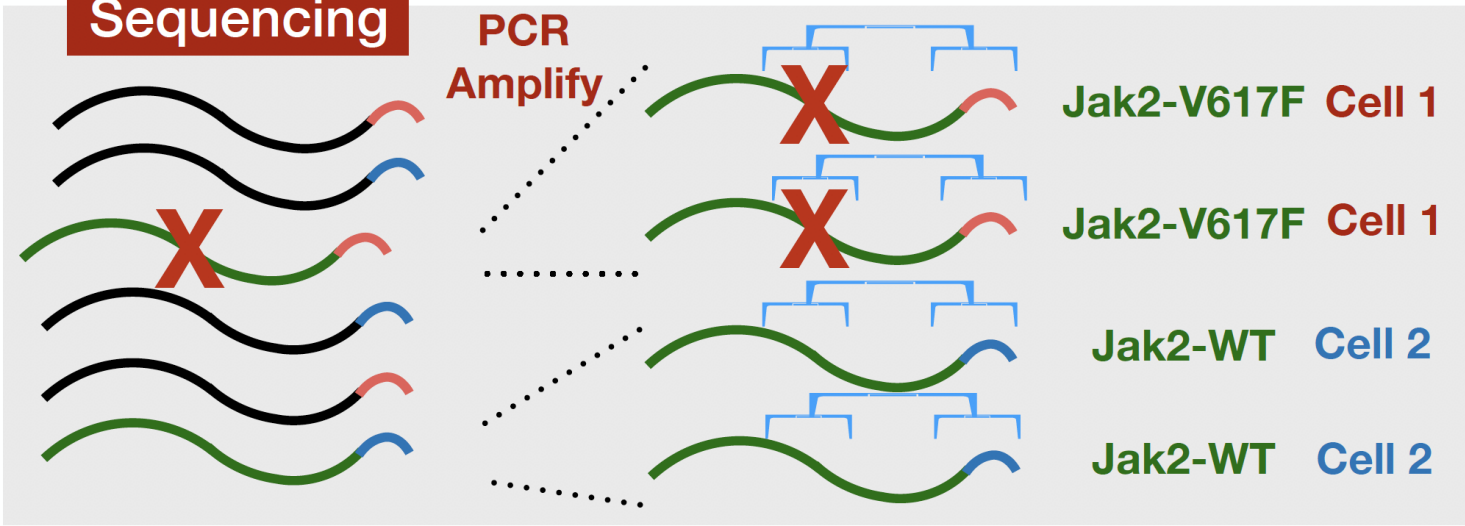
Single-cell profiling of MPNs

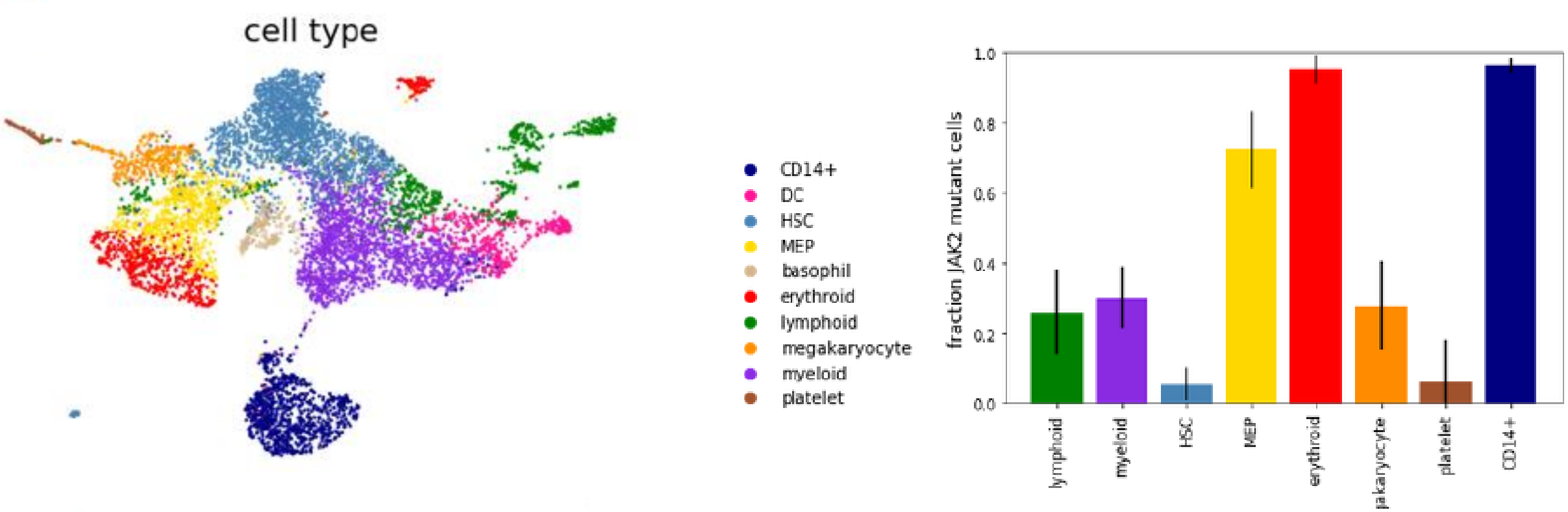


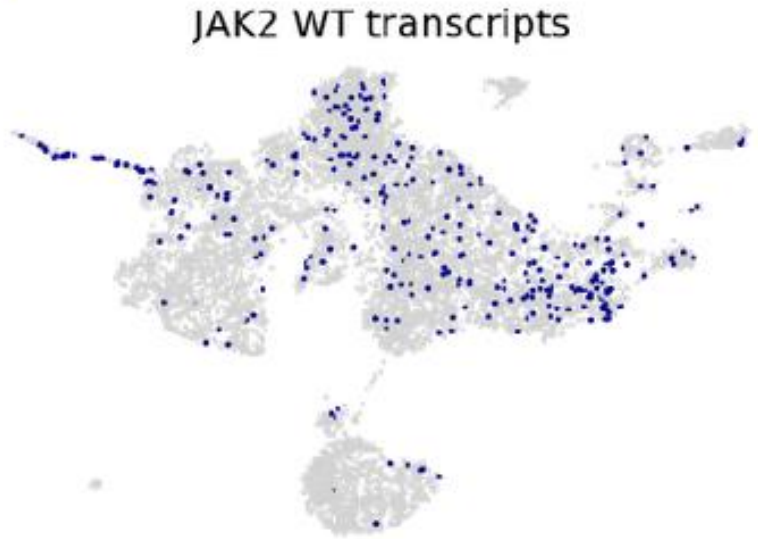
1. Full transcriptome sequencing

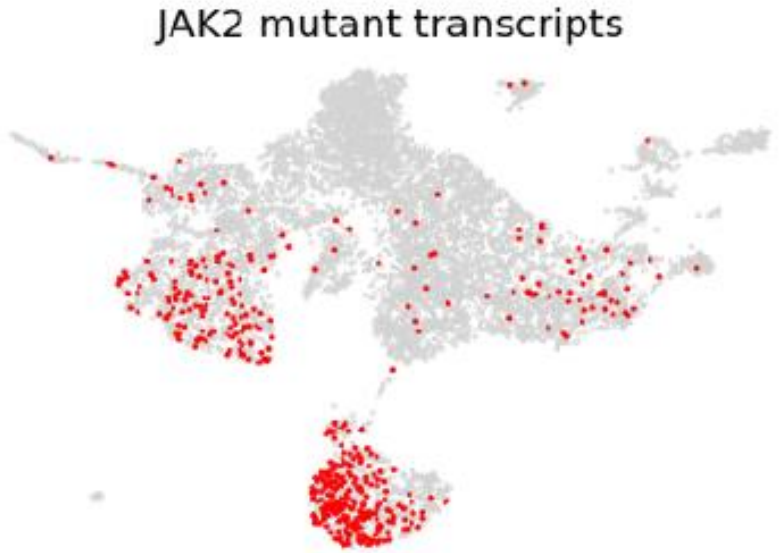


2. Amplicon Sequencing

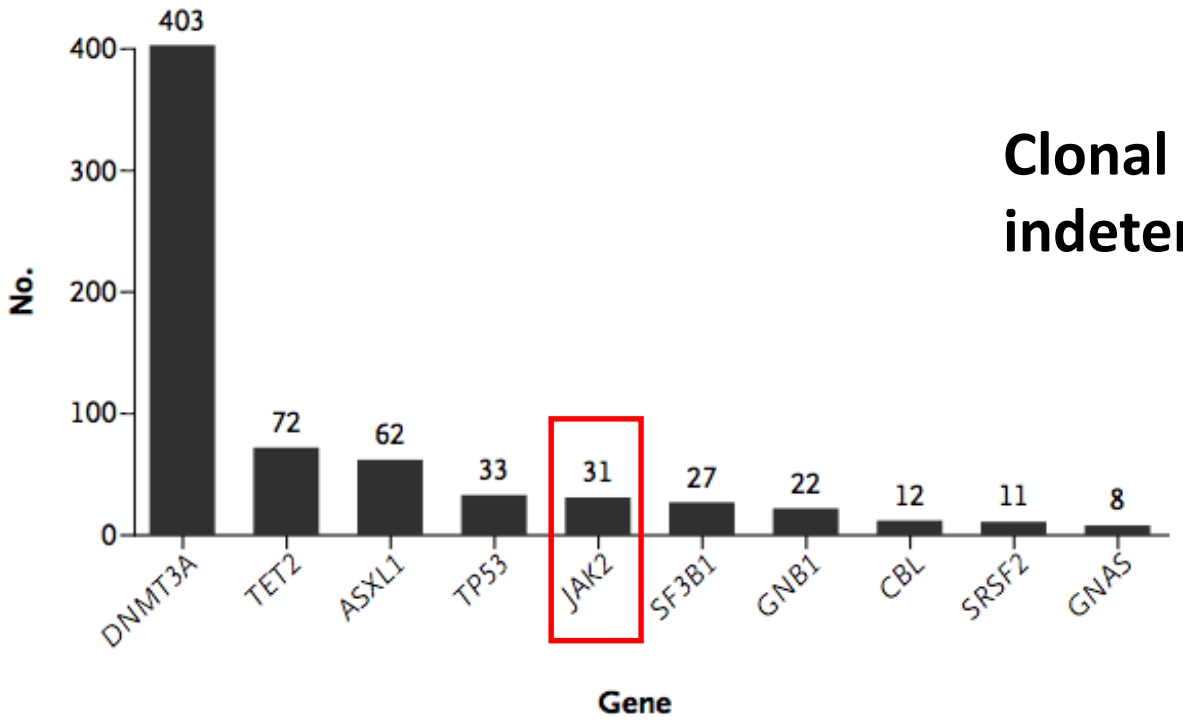



cell type
CD14+
DC
HSC
MEP
basophil
erythroid
lymphoid
megakaryocyte
myeloid
platelet
fraction JAK2 mutant cells
1.0
0.8
0.6
0.4
0.2
0.0
lymphoid
myeloid
HSC
MEP
erythroid
megakaryocyte
platelet
CD14+


JAK2 WT transcripts


JAK2 mutant transcripts

JAK2V617F is sufficient to engender clonal hematopoiesis



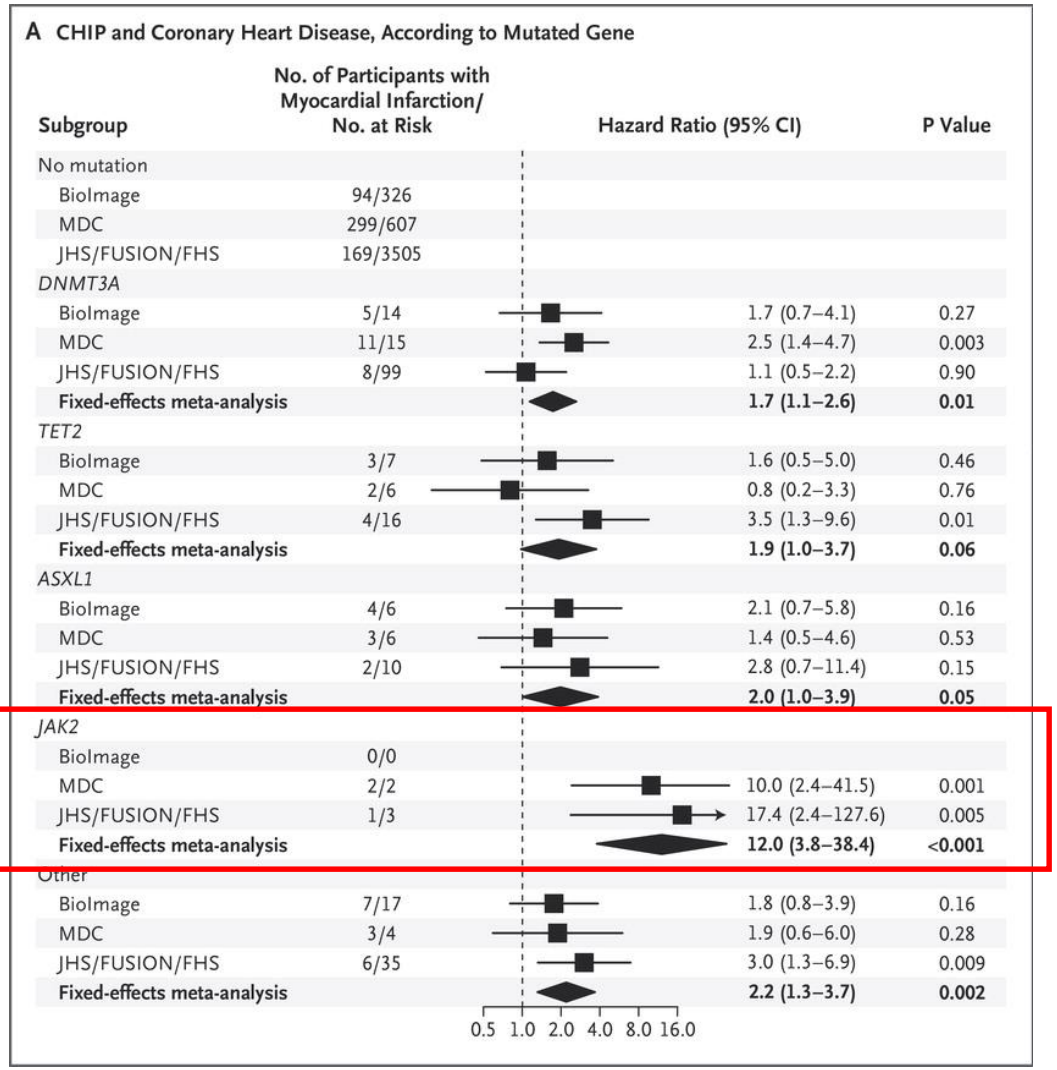
Clonal hematopoiesis of indeterminate potential, CHIP

- Analyzed 17,182 whole-exomes
- Individuals WITHOUT a hematological malignancy
- Peripheral blood DNA source
- Assessed for variants in 160 known “blood cancer genes”

Jaiswal et al. *N Engl J Med*. 2014 Dec 25;371(26):2488-98.

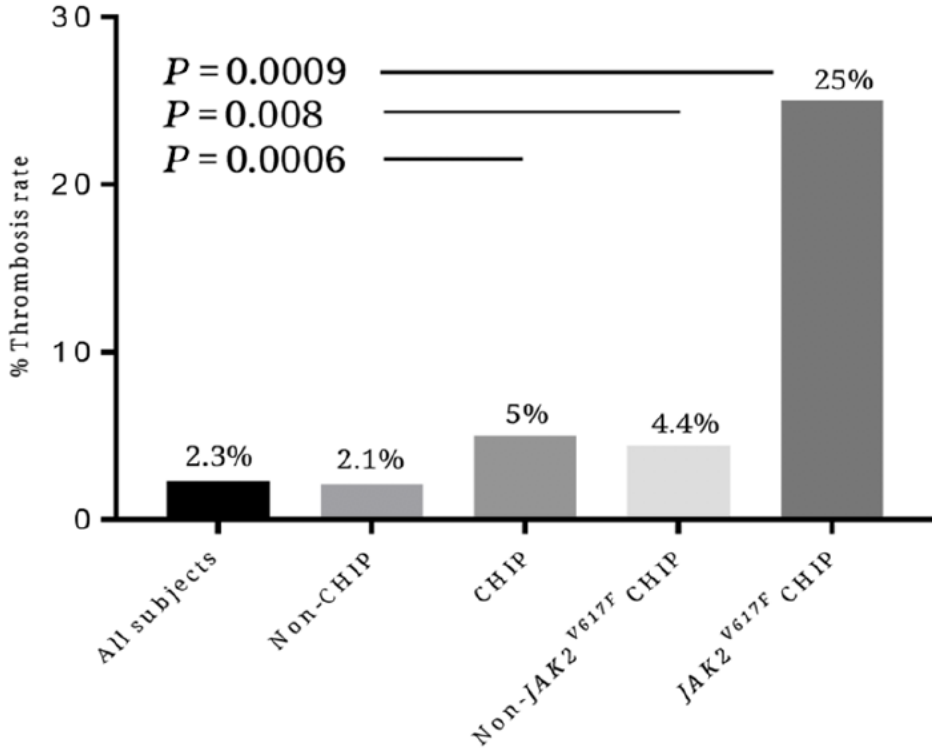
Genovese et al. *N Engl J Med*. 2014 Dec 25;371(26):2477-87.
Xie et al. *Nat Med.* 2014 Dec;20(12):1472-1478.

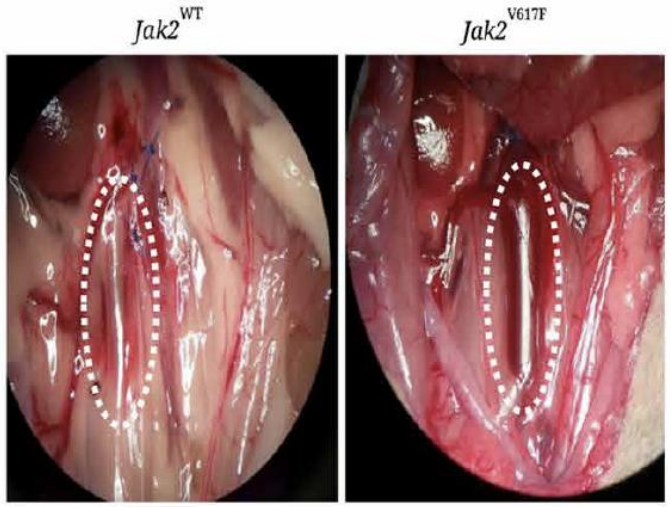
JAK2V617F+ CHIP is clinically relevant - I

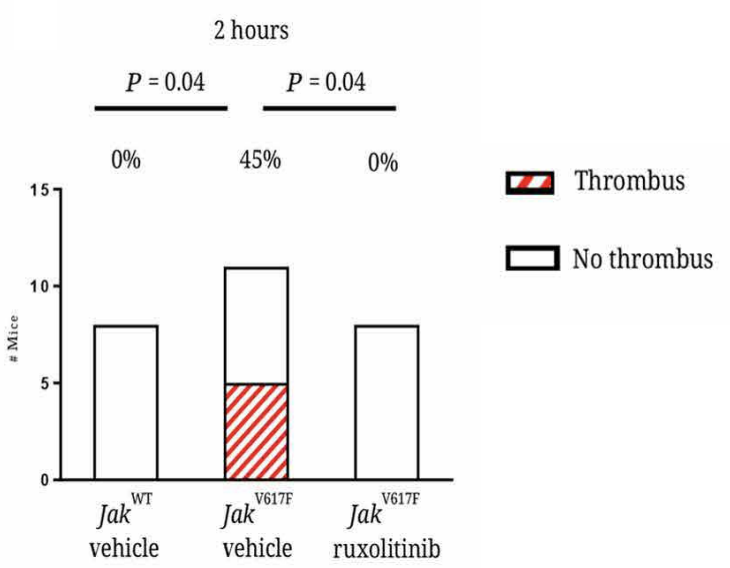


Jaiswal et al. *N Engl J Med*. 2017 Jul 13;377(2):111-121.

JAK2V617F+ CHIP is clinically relevant - II

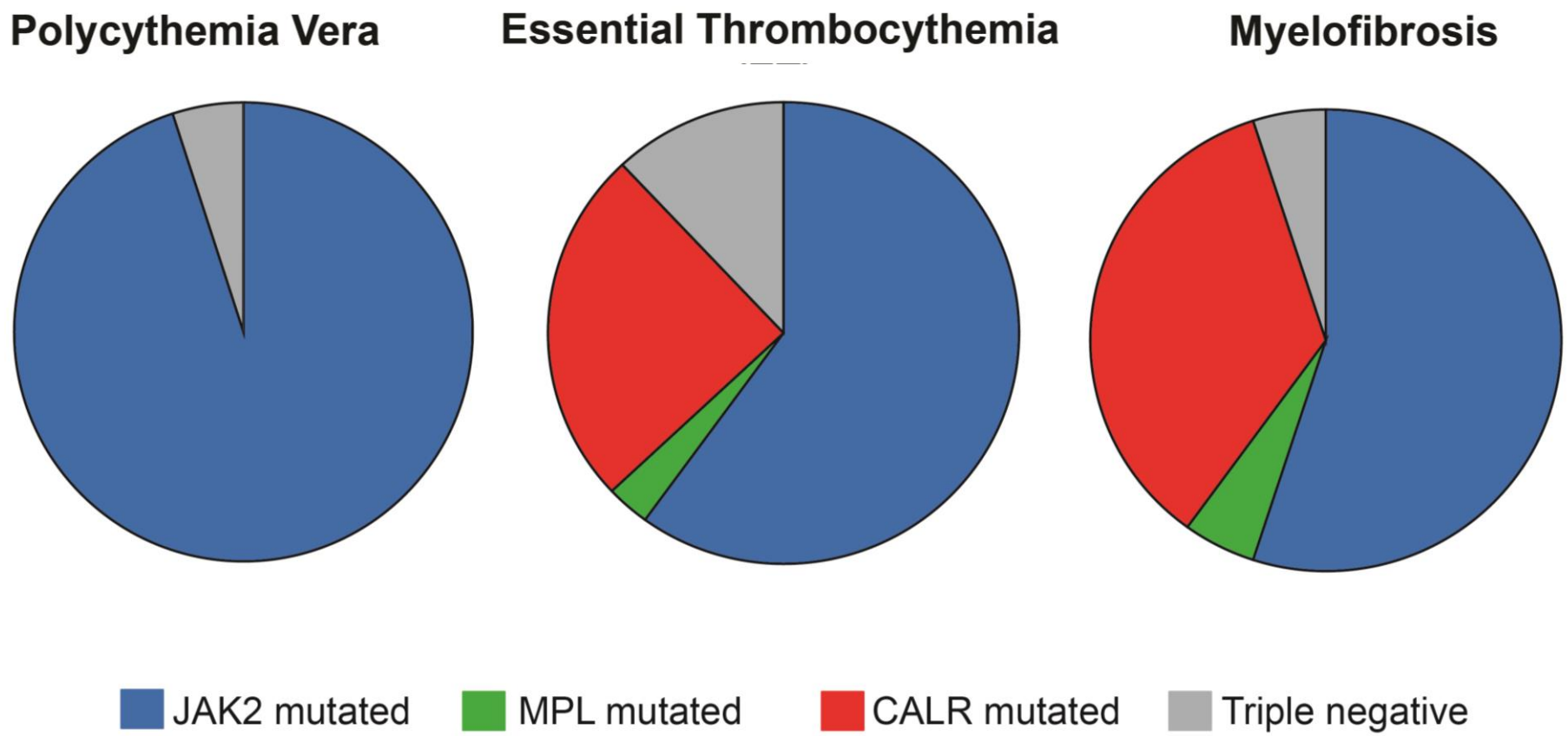






Wolach et al. *Sci Transl Med*. 2018 Apr 11;10(436).

MPN Phenotypic Driver Mutations



Baxter et al. *Lancet.* 2005 Mar 19-25;365(9464):1054-61.
James et al. *Nature*. 2005 Apr 28;434(7037):1144-8.
Kralovics et al. *N Engl J Med*. 2005 Apr 28;352(17):1779-90.
Levine et al. *Cancer Cell*. 2005 Apr;7(4):387-97.
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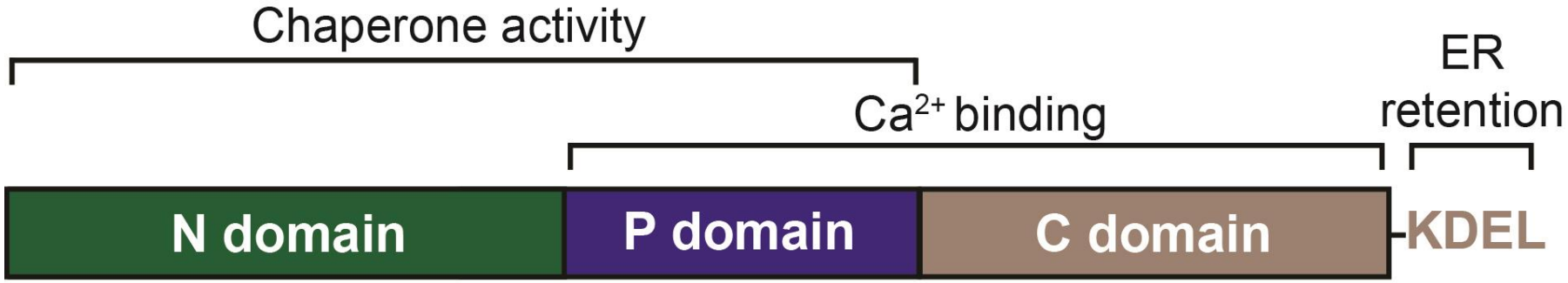
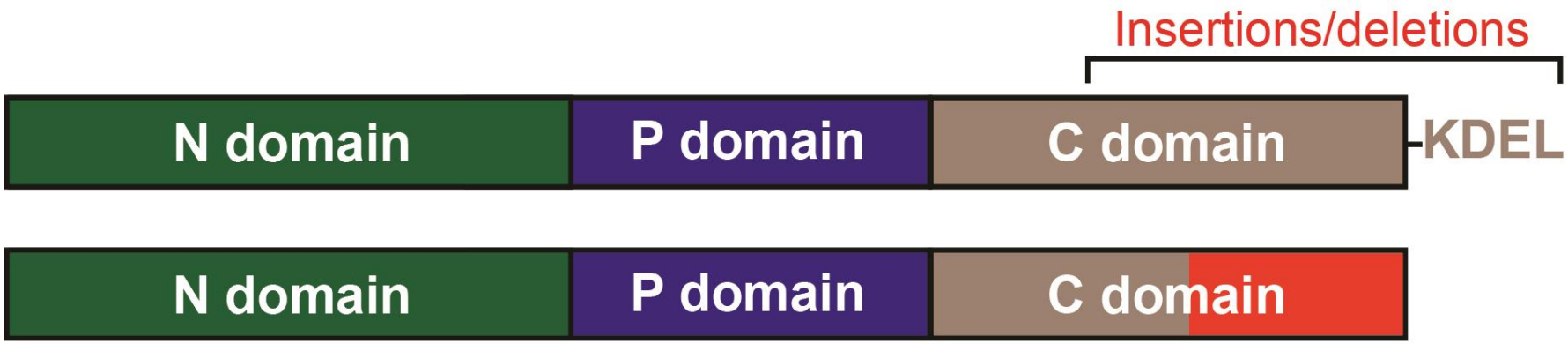
Klampfl et al. *NEJM.* 2013 Dec 19;369(25):2379-90.
Nangalila et al. *NEJM.* 2013 Dec 19;369(25):2391-2405

Calreticulin (CALR)



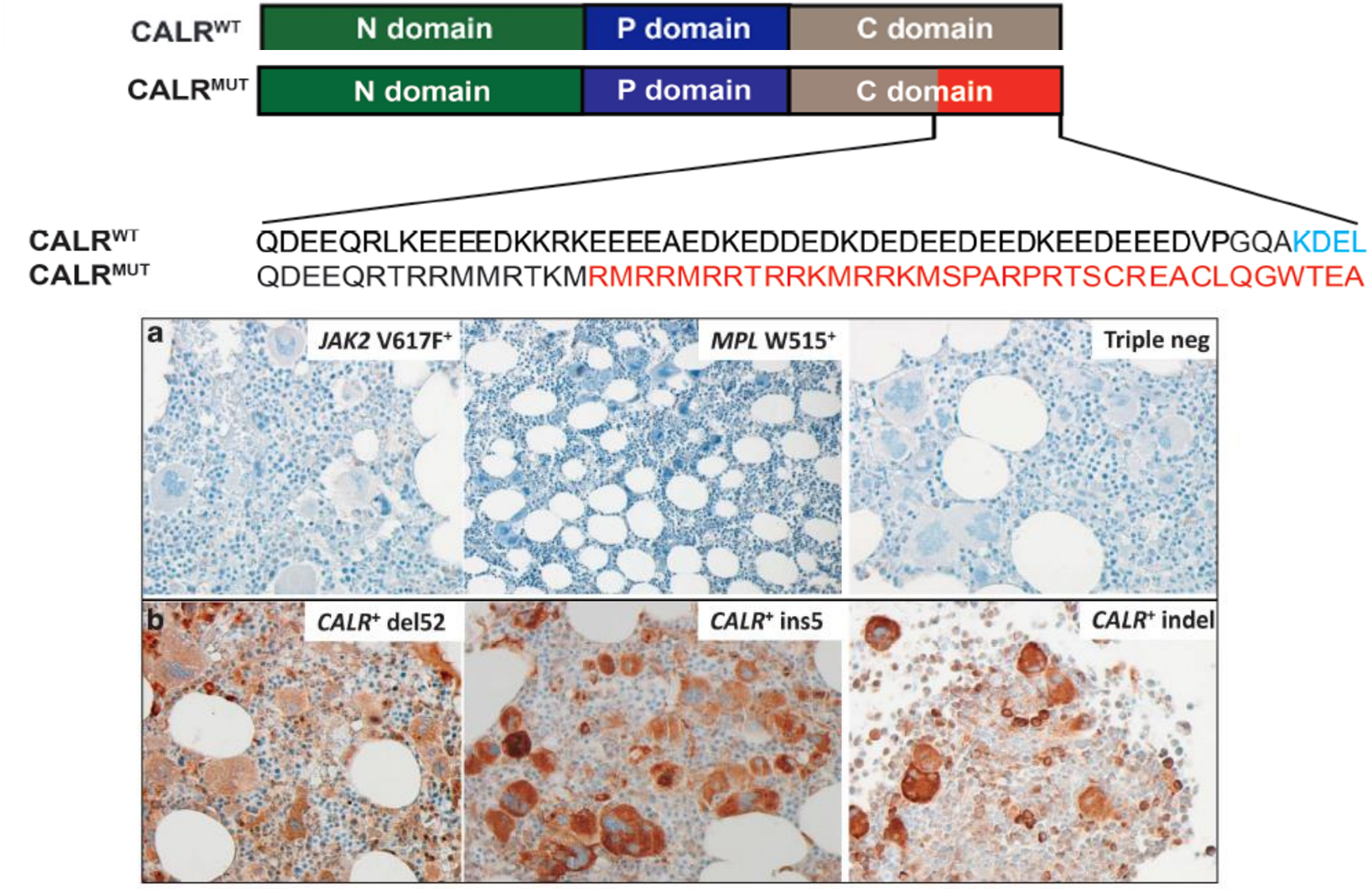
- Endoplasmic reticulum (ER) resident protein
- Quality control of protein folding in the ER
- Binds and stores Ca^{2+}

CALR mutations in MPN



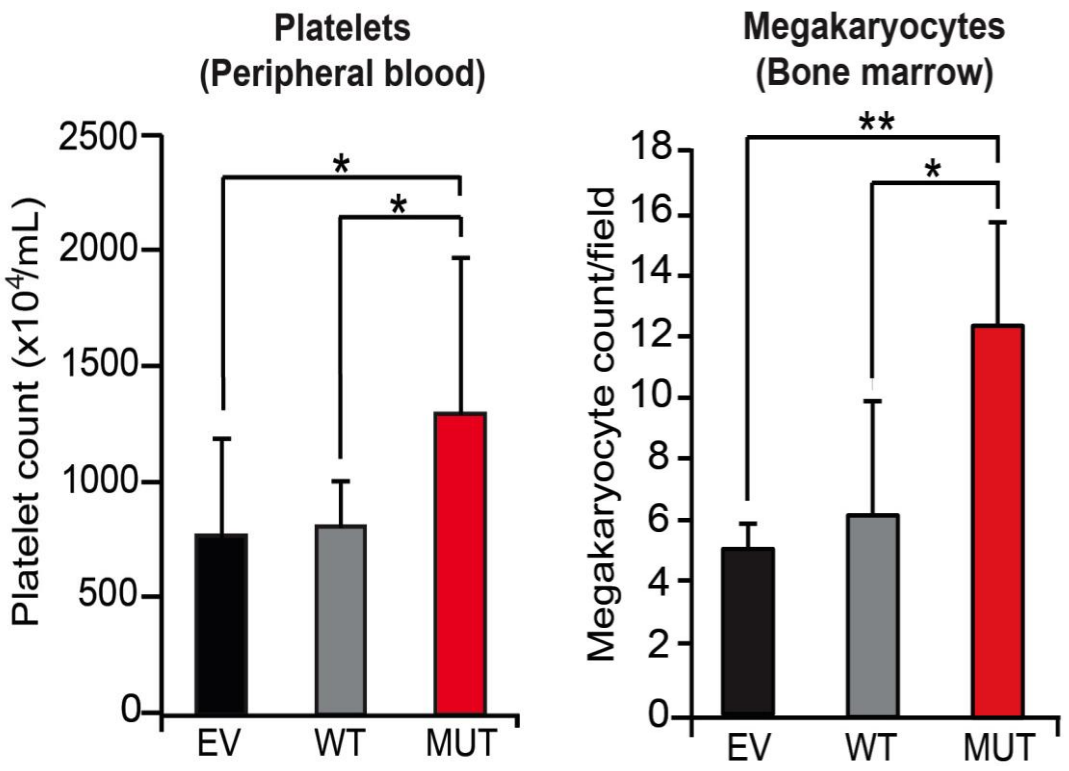
- Mutations occur as heterozygous insertions and/or deletions in exon 9
- ALL mutations cause a +1 bp frameshift leading to:

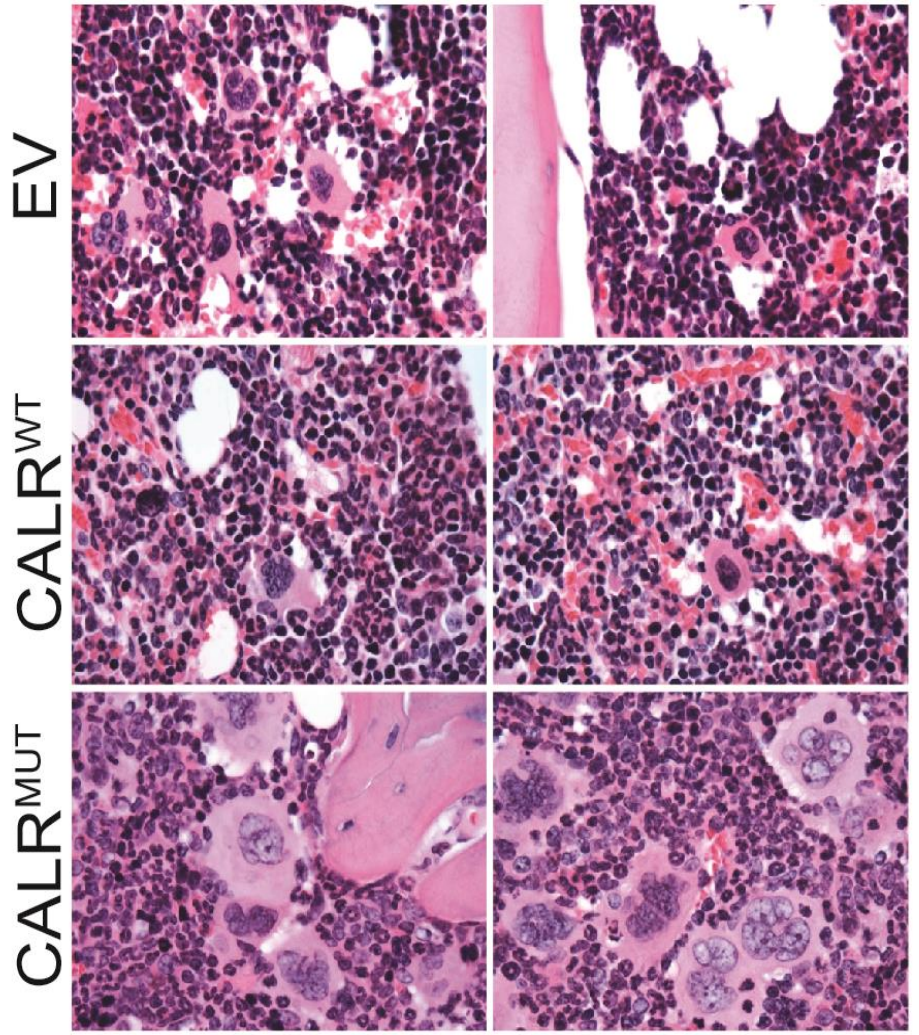
Mutant-specific C-terminus of mutant CALR



Vannucchi et al. *Leukemia*. 2014;28:1811–8.

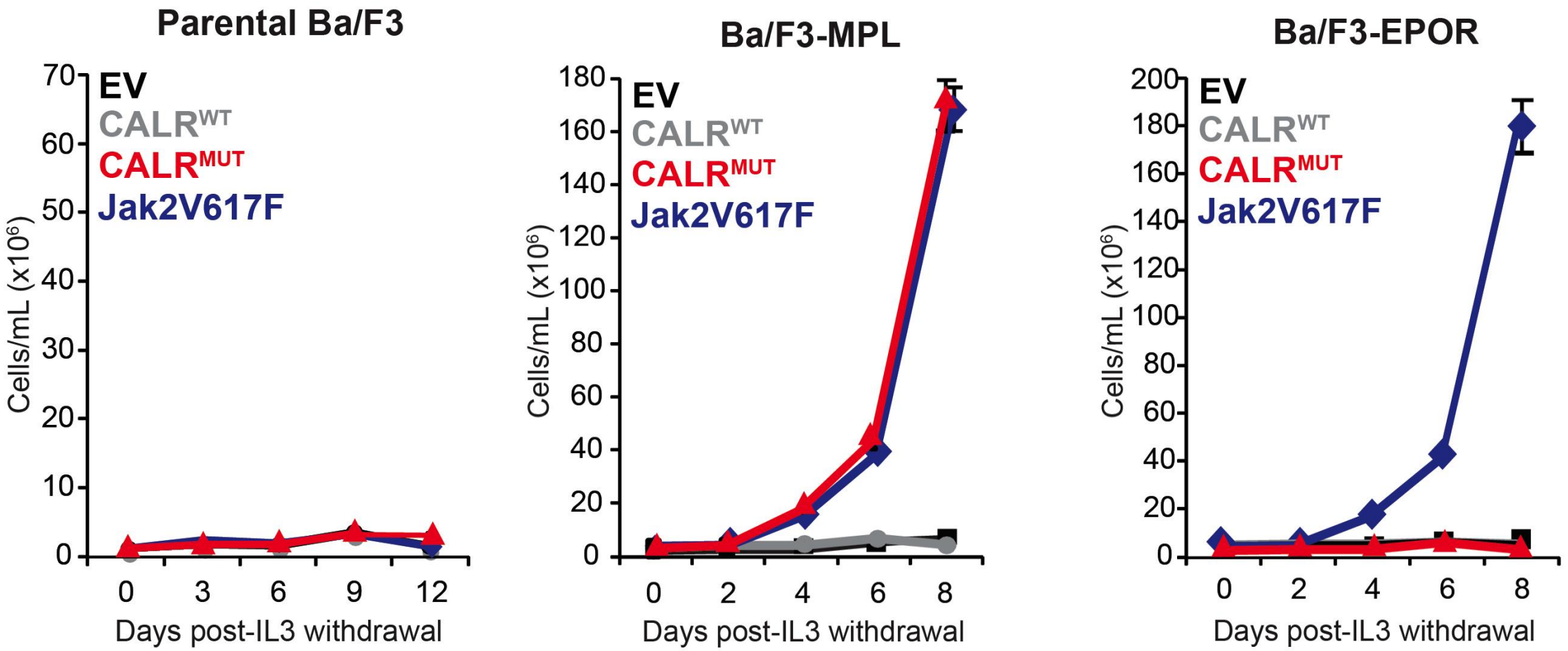
Mutant *CALR* alone is sufficient to engender MPN





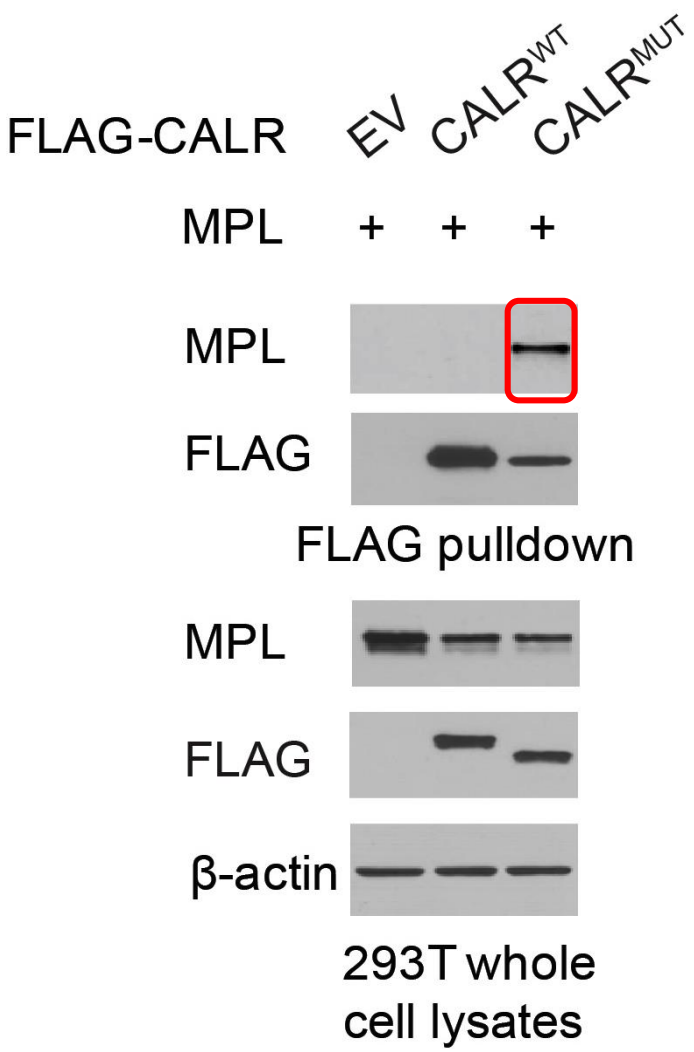
Elf et al. *Cancer Discovery*. 2016; Apr;6(4):368-81.

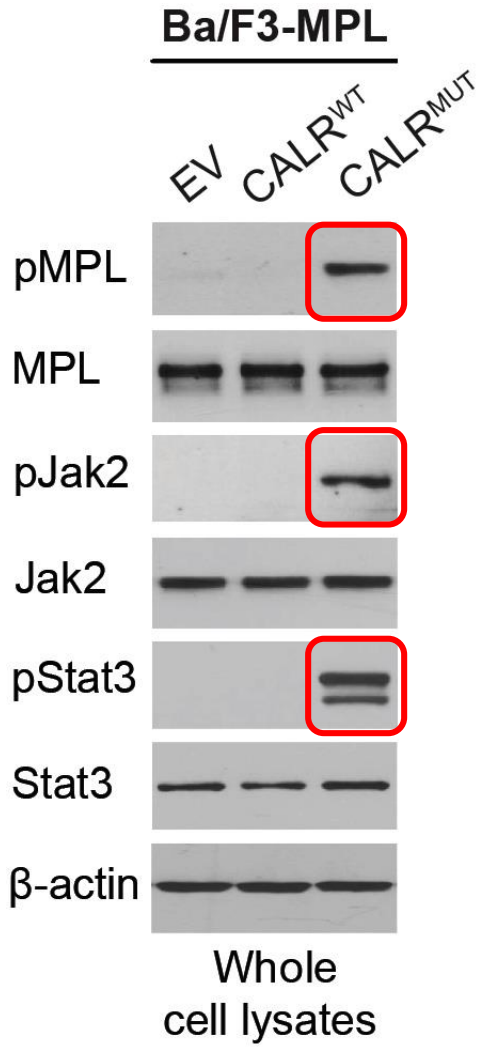
MPL is required for mutant CALR-mediated transformation



Elf, Abdelfattah & Chen et al. *Cancer Discovery*. 2016; Apr;6(4):368-81.

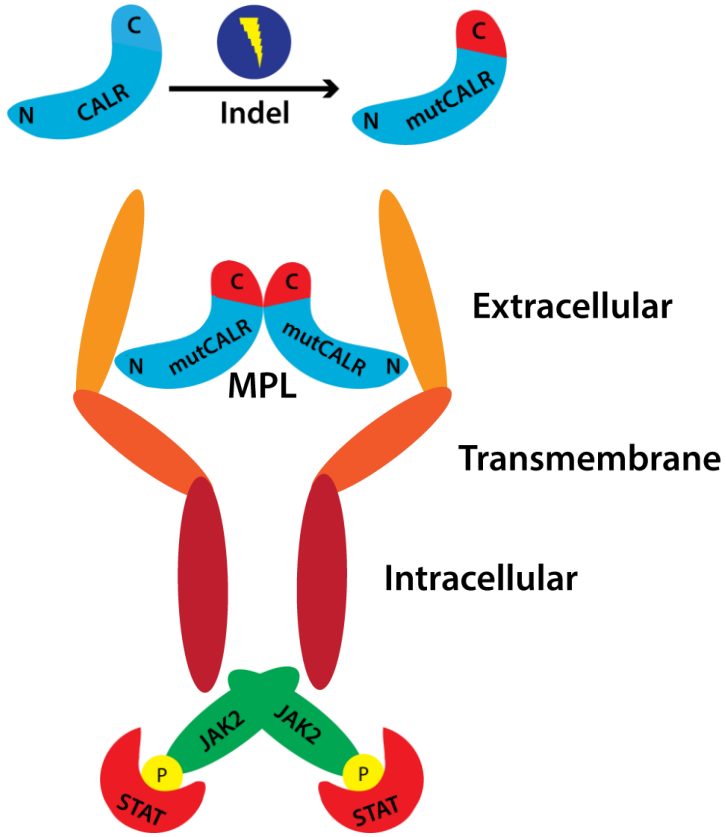
Mutant CALR binds MPL and activates JAK-STAT signaling to induce MPN

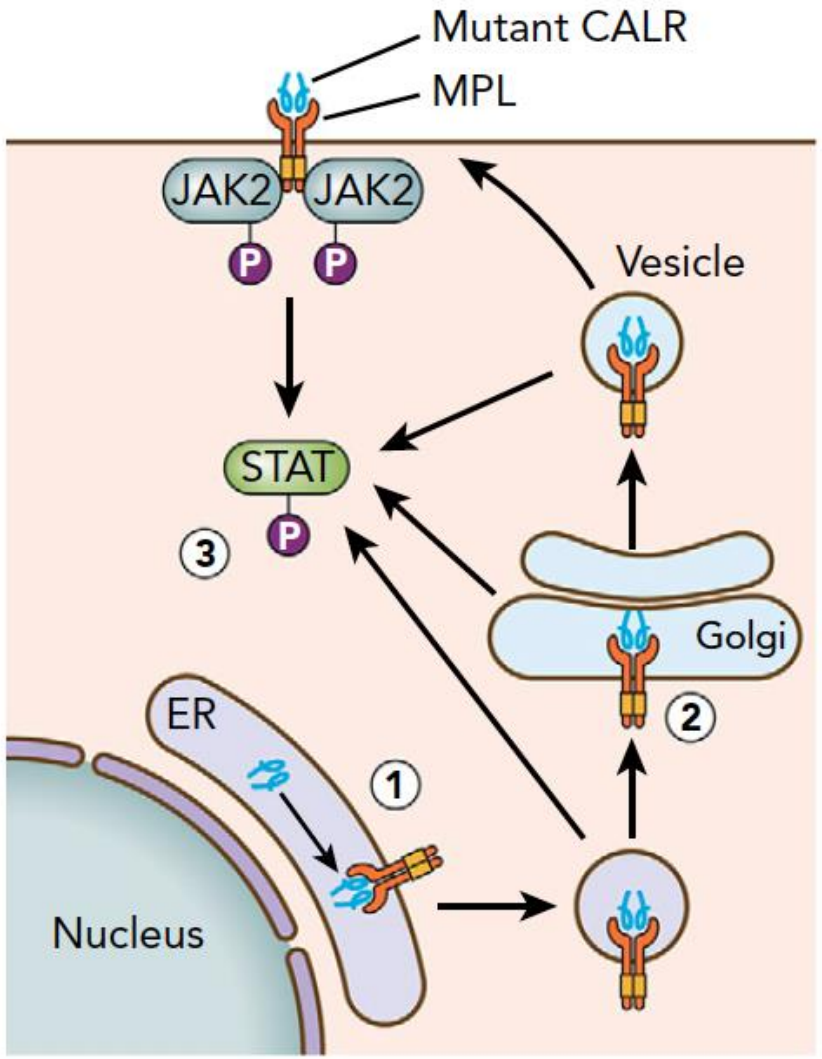




Elf, Abdelfattah & Chen et al. *Cancer Discovery*. 2016; Apr;6(4):368-81.

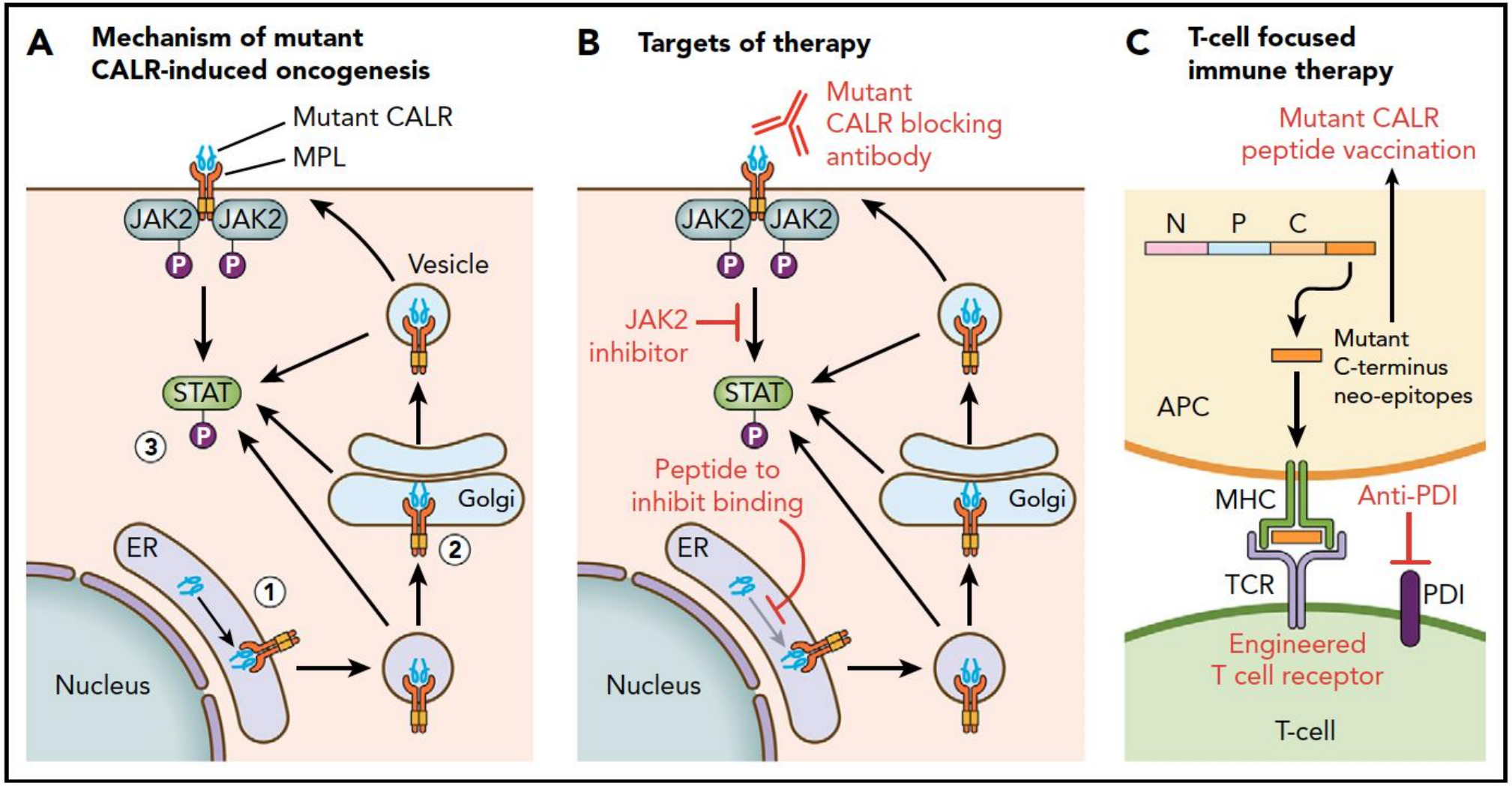
Mechanism of mutant CALR induced oncogenesis





How, Hobbs & Mullally. Blood Spotlight 2019.

Exploiting mutant CALR mechanistic insights for therapeutic benefit



How, Hobbs & Mullally. Blood Spotlight 2019.

Saving the Endangered Physician-Scientist — A Plan for Accelerating Medical Breakthroughs

Mukesh K. Jain, M.D., Vivian G. Cheung, M.D., Paul J. Utz, M.D., Brian K. Kobilka, M.D., Tadataka Yamada, M.D., and Robert Lefkowitz, M.D.

NEJM Perspective 2019

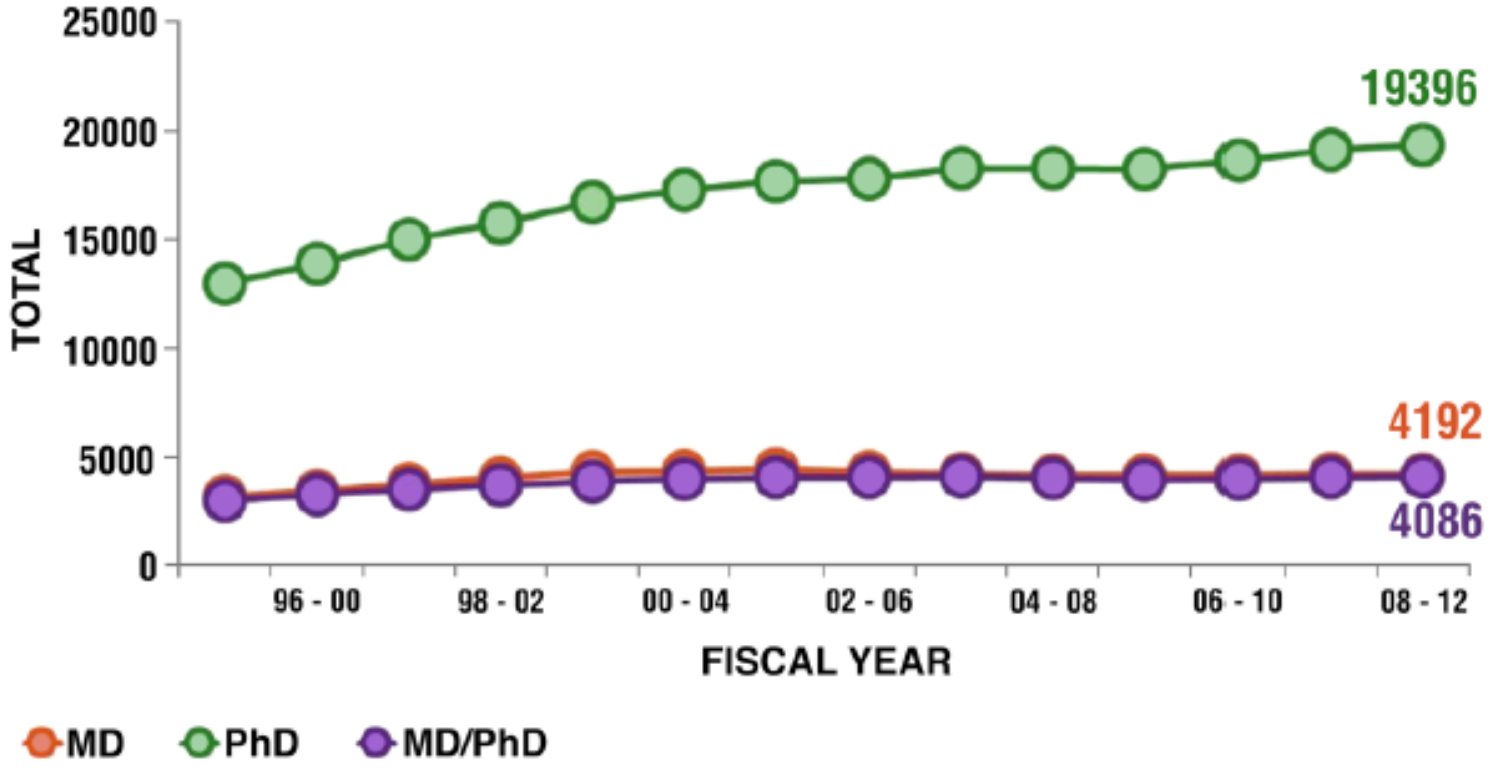
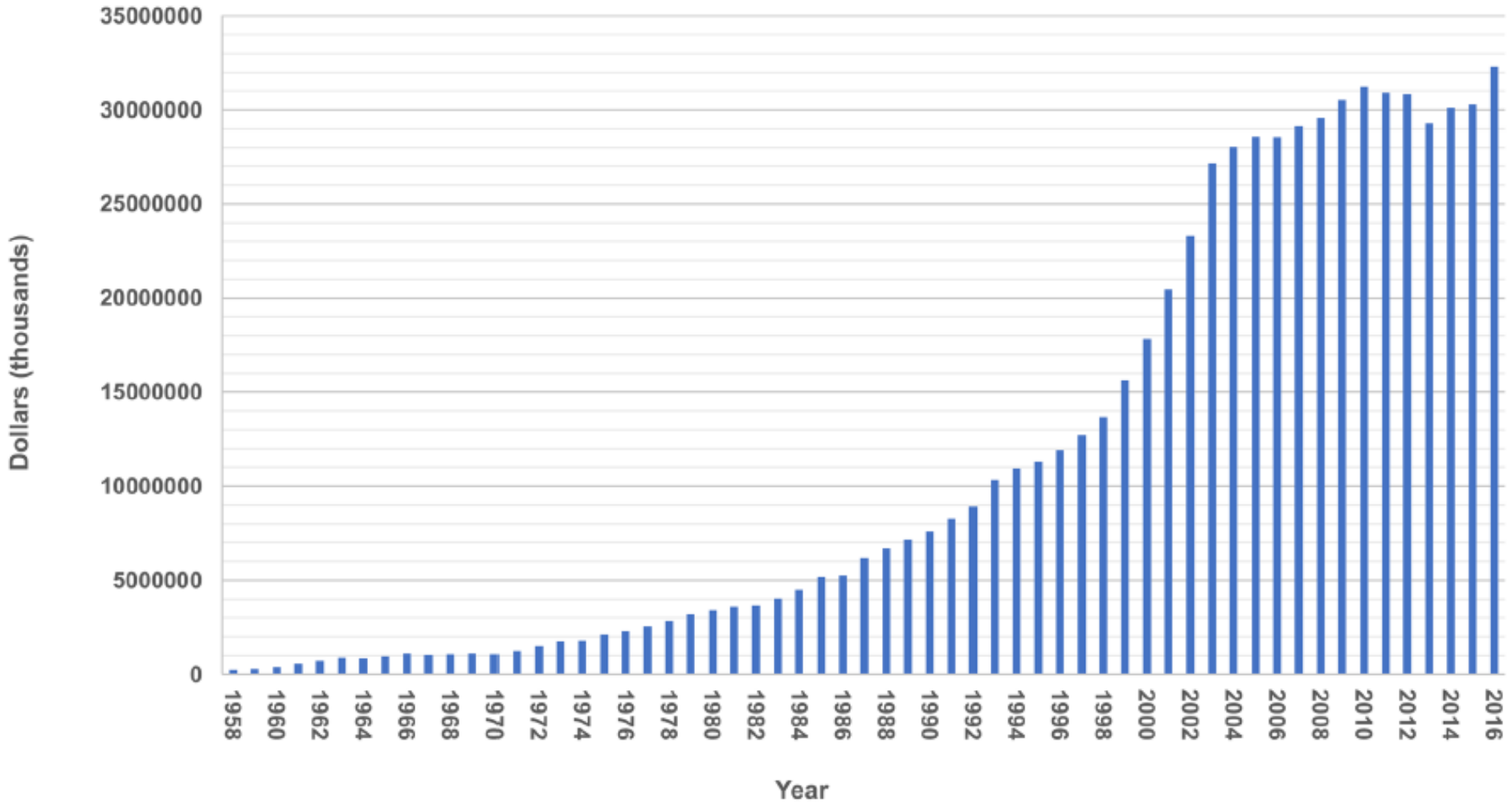


Table 1. Issues Contributing to the Declining Numbers of Physician-Scientists.*

Level	Issues
Individual	Student debt
	Child care and family responsibilities
	Increasing length of time spent in training before being independent
Institutional	Negative effects of health care finances on research support
	Reduced patient contact time that precludes evaluation of difficult cases
	Decreasing numbers of, and decreasing exposure to, physician-scientist mentors
	Insufficient protected time for research
	Absence of organized physician-scientist career-development programs across specialties
	Inflexible family-leave policies
National	Decreased or stagnant federal and nonfederal research funding
	Increased specialization in medicine and science, leading to a widening gap between clinicians and researchers
	Limited available funding for loan repayment programs, particularly for trainees in basic science disciplines
	Increasingly challenging requirements for board certification and maintenance of certification
	Lack of diversity in the physician-scientist workforce
	Discrepancies in salary and benefits offered during clinical versus scientific training, in part owing to ACGME policies

National Institutes of Health Budget: 1959 to 2016



Why Aren't There More Women Leaders in Science?

Medical school applicants

Dean

Dept Chair

Full Time Professor

Dr. Gwen Nichols, CMO, Leukemia & Lymphoma Society
Scientific American 2018

Acknowledgements

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Nouran Abdelfattah (HMS BBS)
Dr. Michele Ciboddo (Pavia)
Anastasia Kosmidou (Ulm)
Kaisa Pakari (Heidelberg)

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