

# Genetics and Targeted Therapy of MPN

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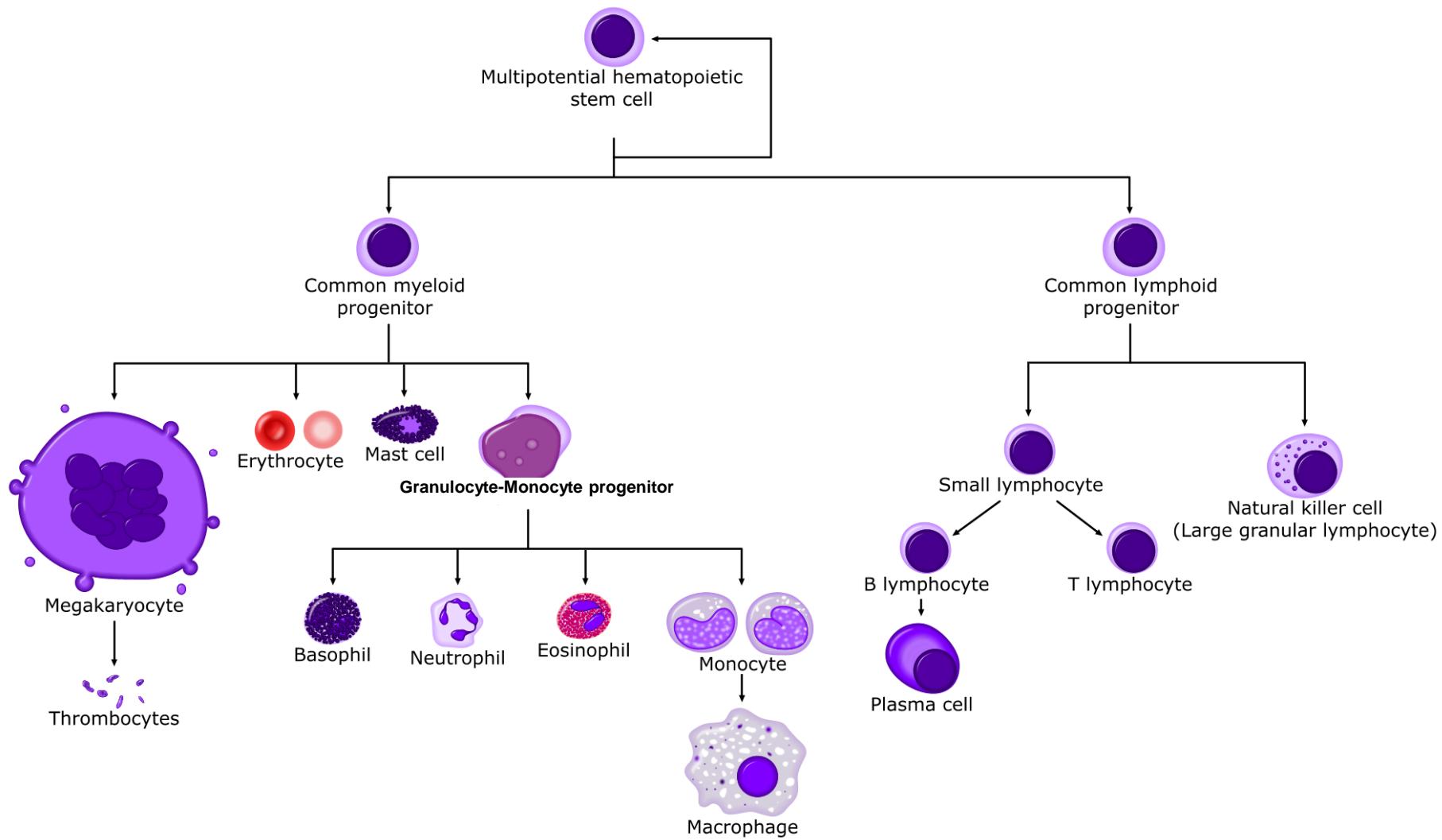
Ann Mullally, MD

10<sup>th</sup> Joyce Niblack Memorial Conference on MPN

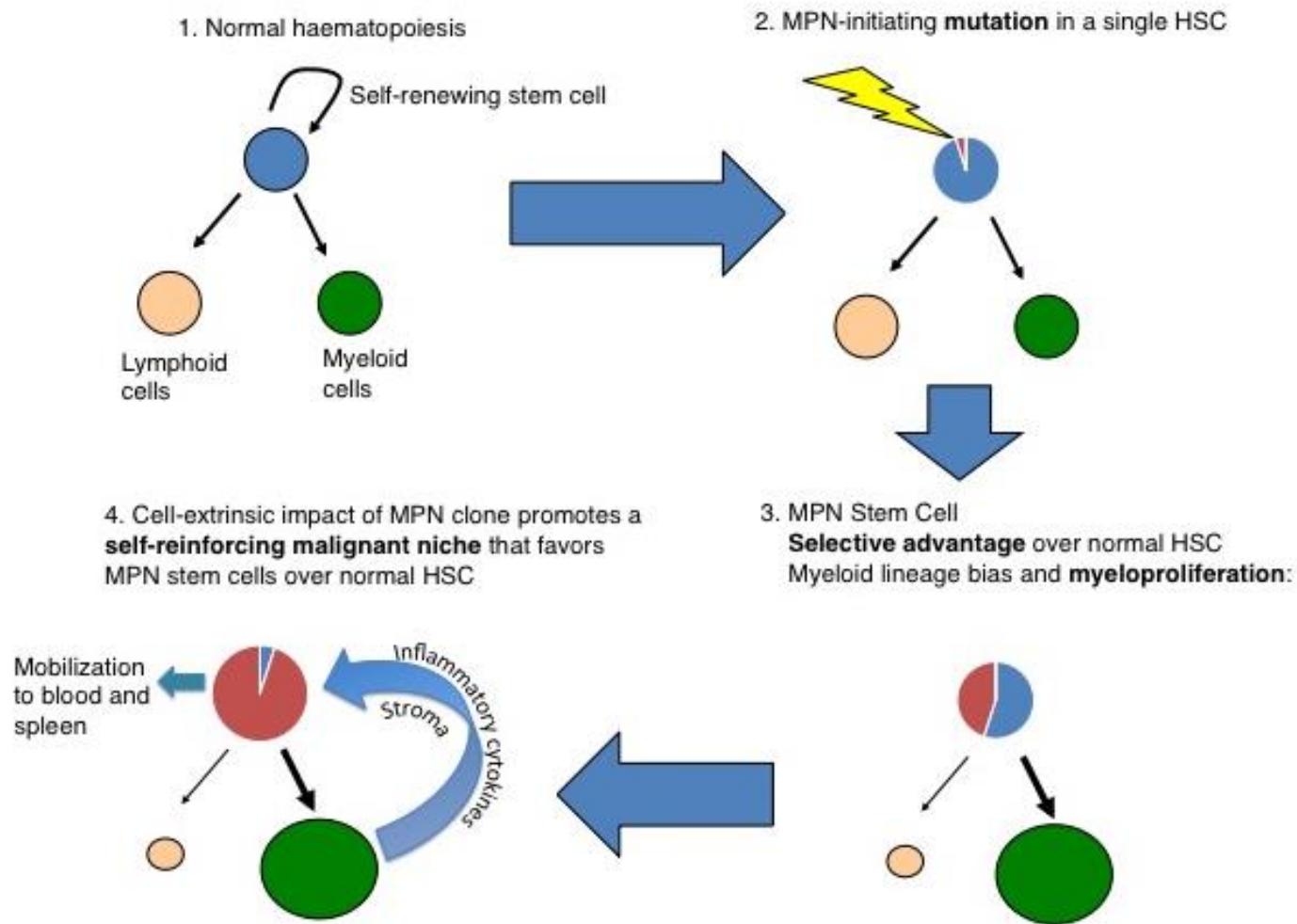
Scottsdale, Arizona

February 25<sup>th</sup>, 2017

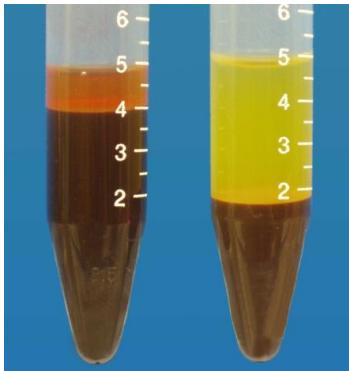
# Hierarchy of blood production



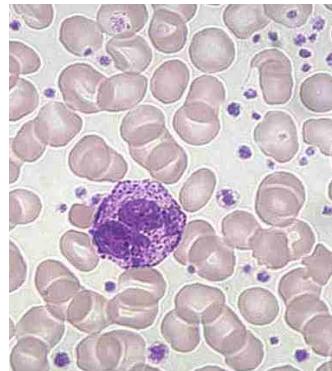
# How is MPN initiated?



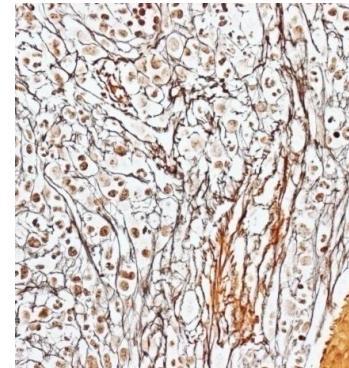
# Genetics of MPN



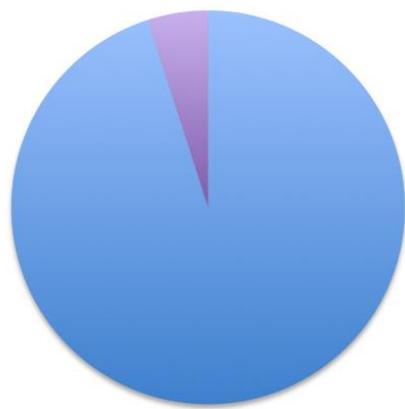
Polycythemia Vera (PV)



Essential Thrombocythemia (ET)



Myelofibrosis (MF)



- █ JAK2 mutation
- █ CALR mutation
- █ MPL mutation
- █ Non-mutated JAK, CALR, MPL

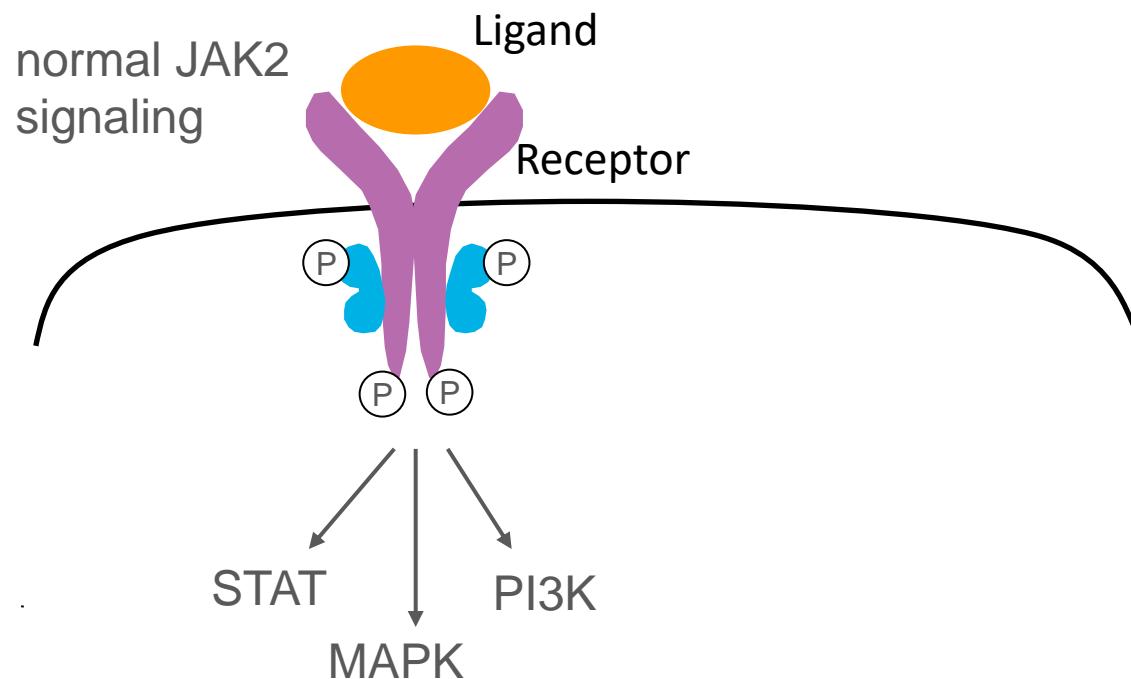
CALR mutation

MPL mutation

Non-mutated JAK, CALR, MPL

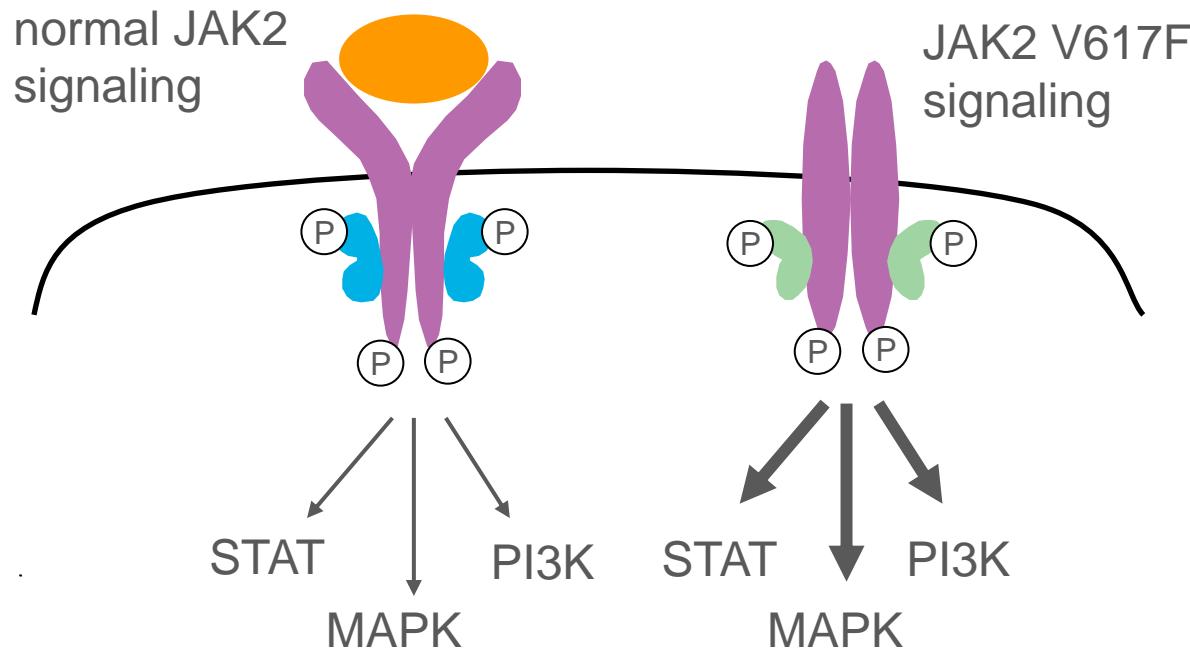
# Janus Kinase 2 (JAK2)

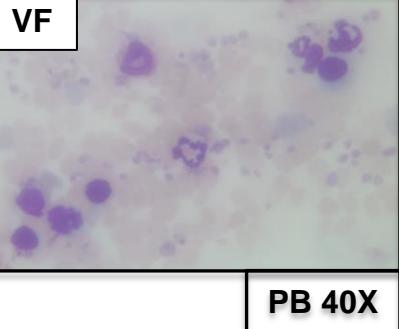
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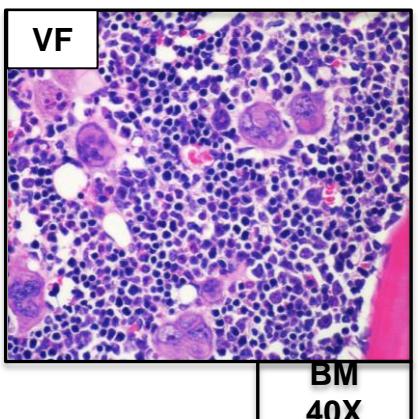
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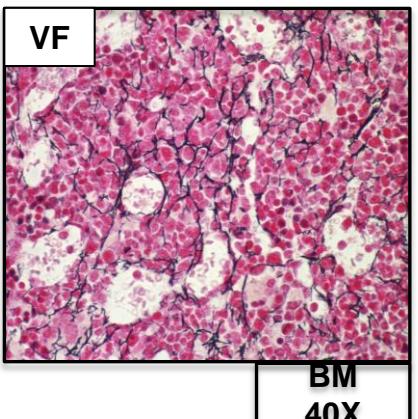




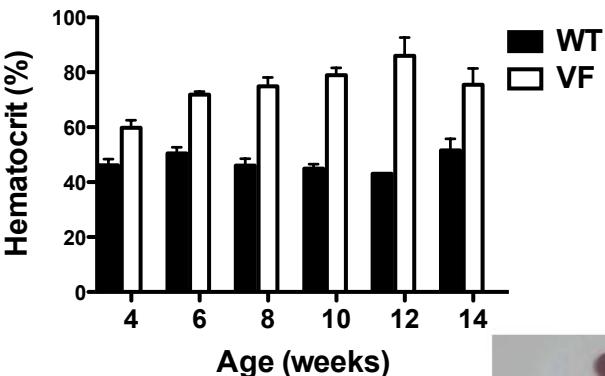
Leukocytosis



Megakaryocytic hyperplasia



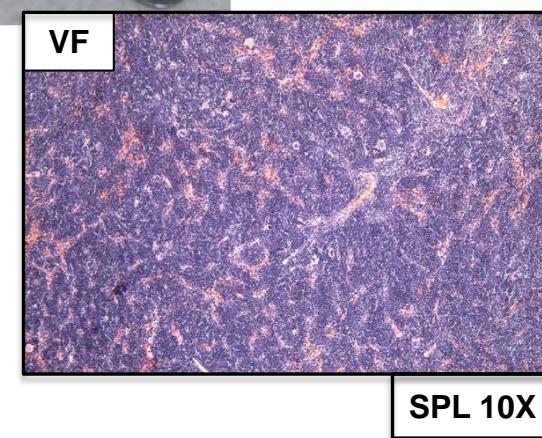
Reticulin fibrosis



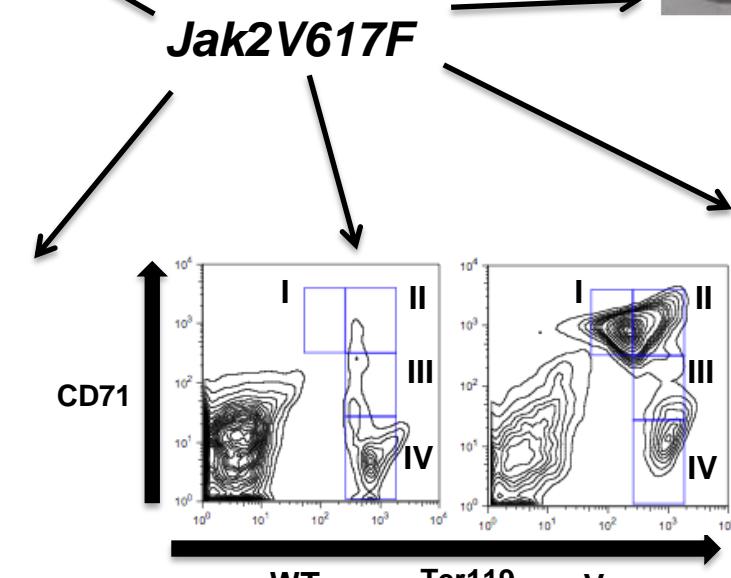
Erythrocytosis



Splenomegaly



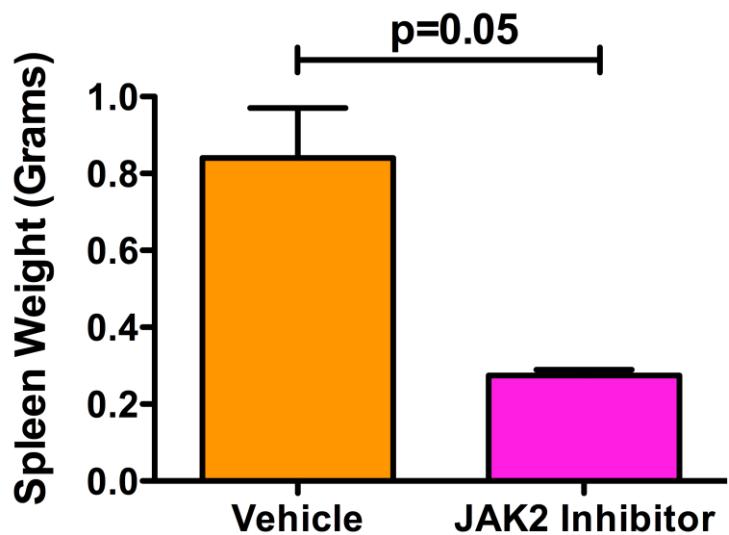
Extra-medullary hematopoiesis



Mullally & Lane et al., Cancer Cell 2010

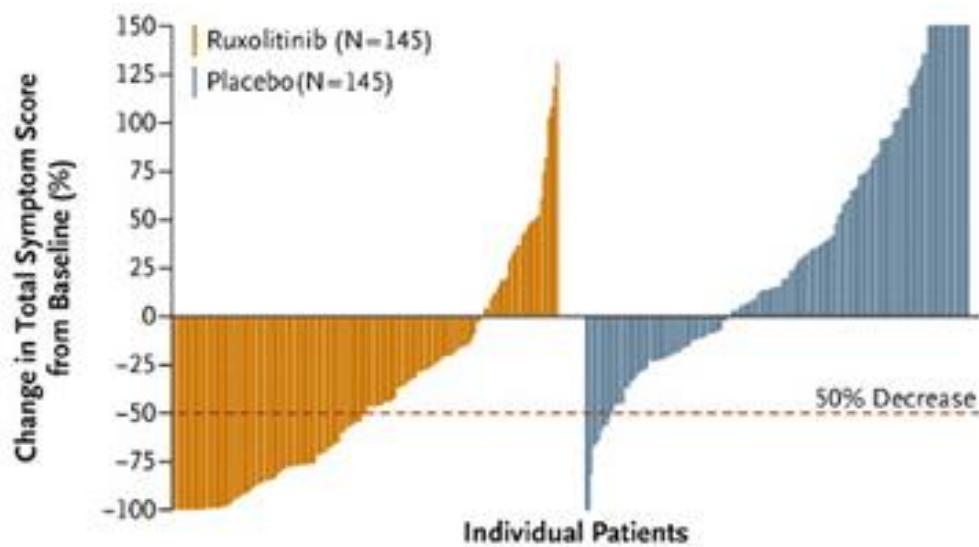
# JAK2 inhibition reduces spleen size

Jak2V617F knockin mouse model

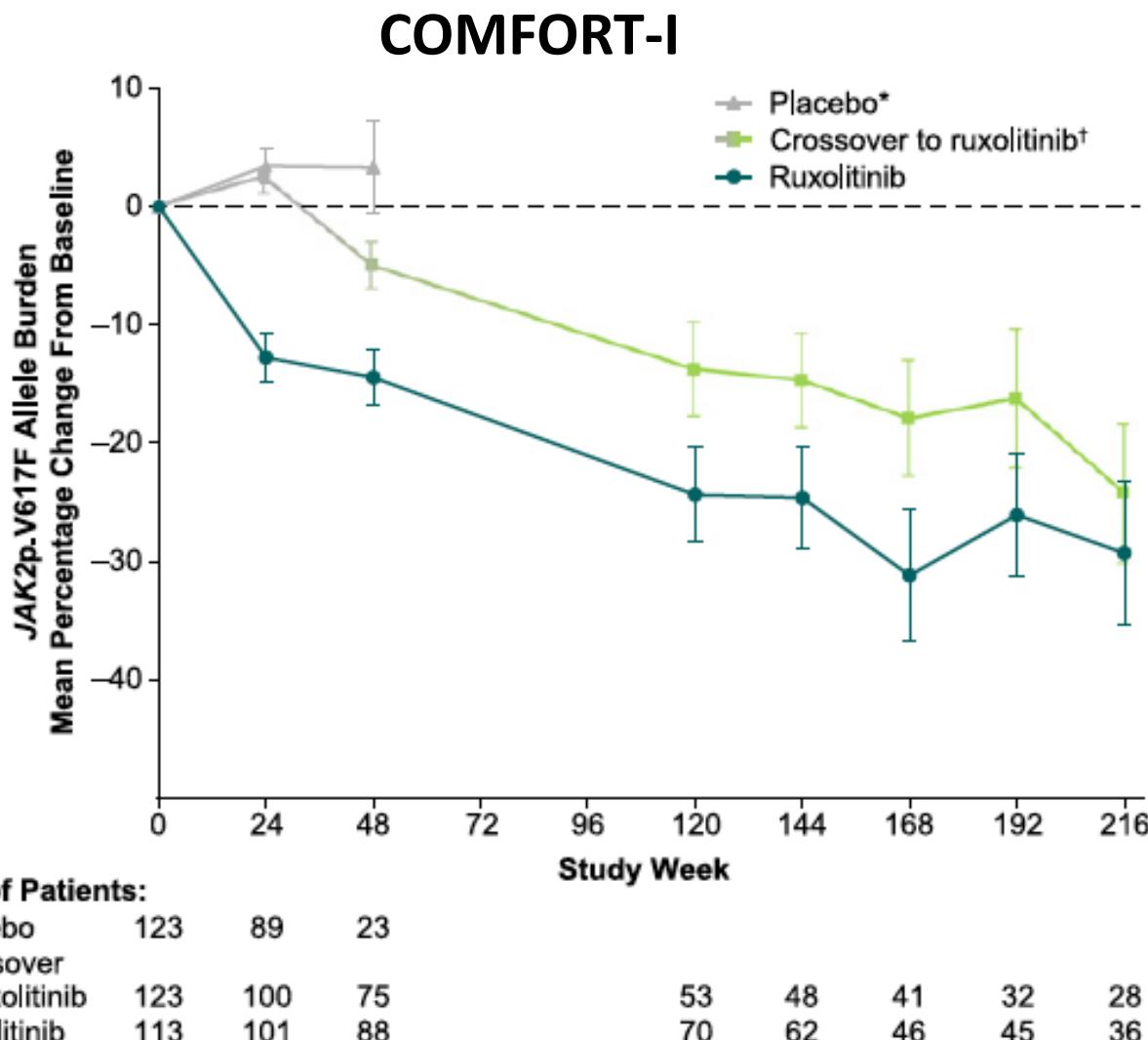


**Jak2 Inhibitor = TG101348 x 6 wks**

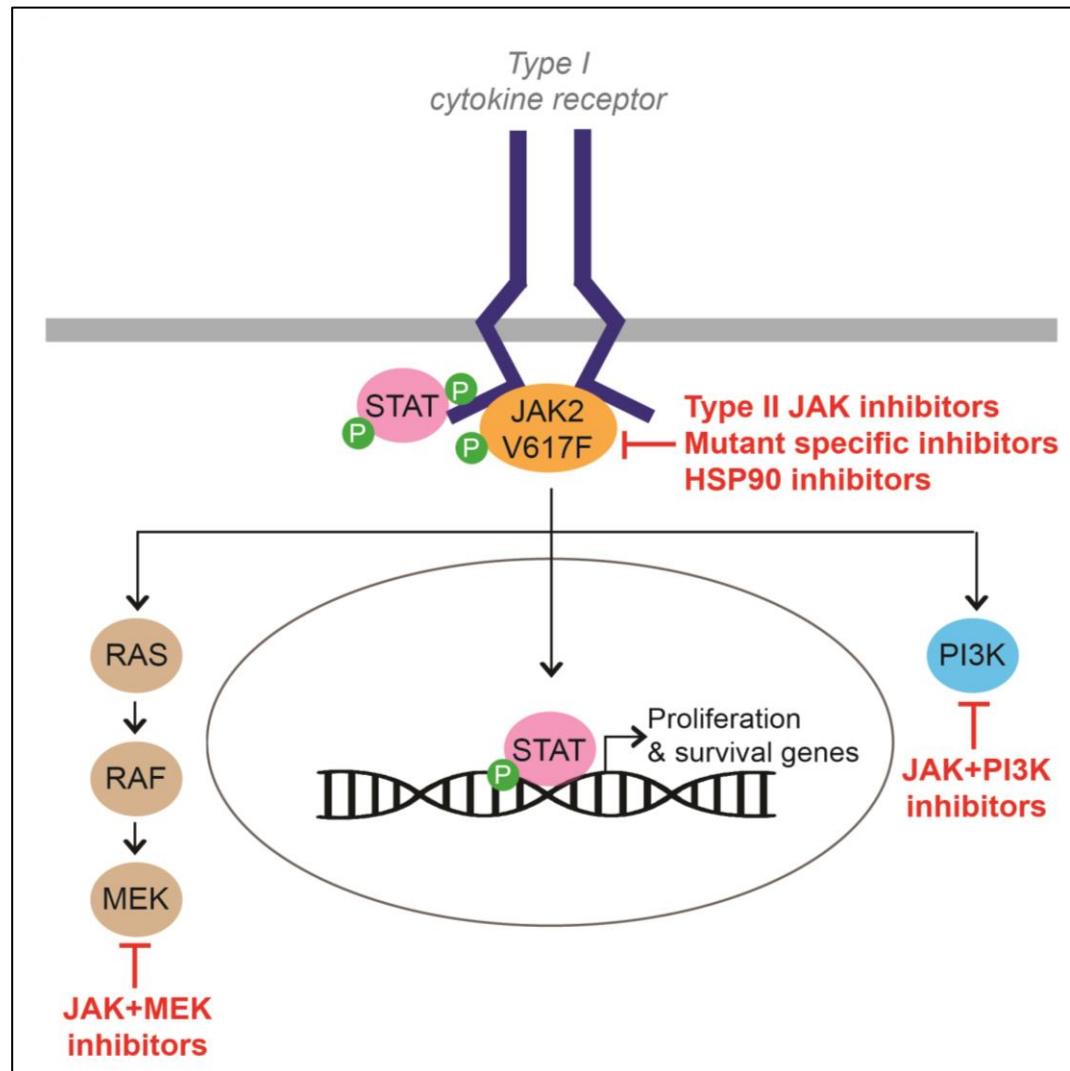
**COMFORT-I**



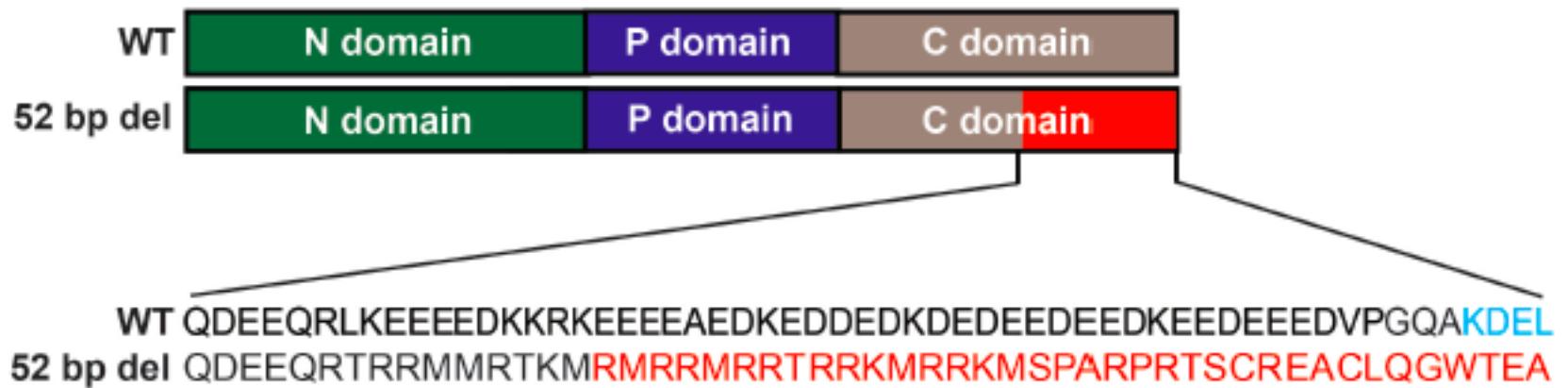
# JAK2 inhibitors: not V617F selective



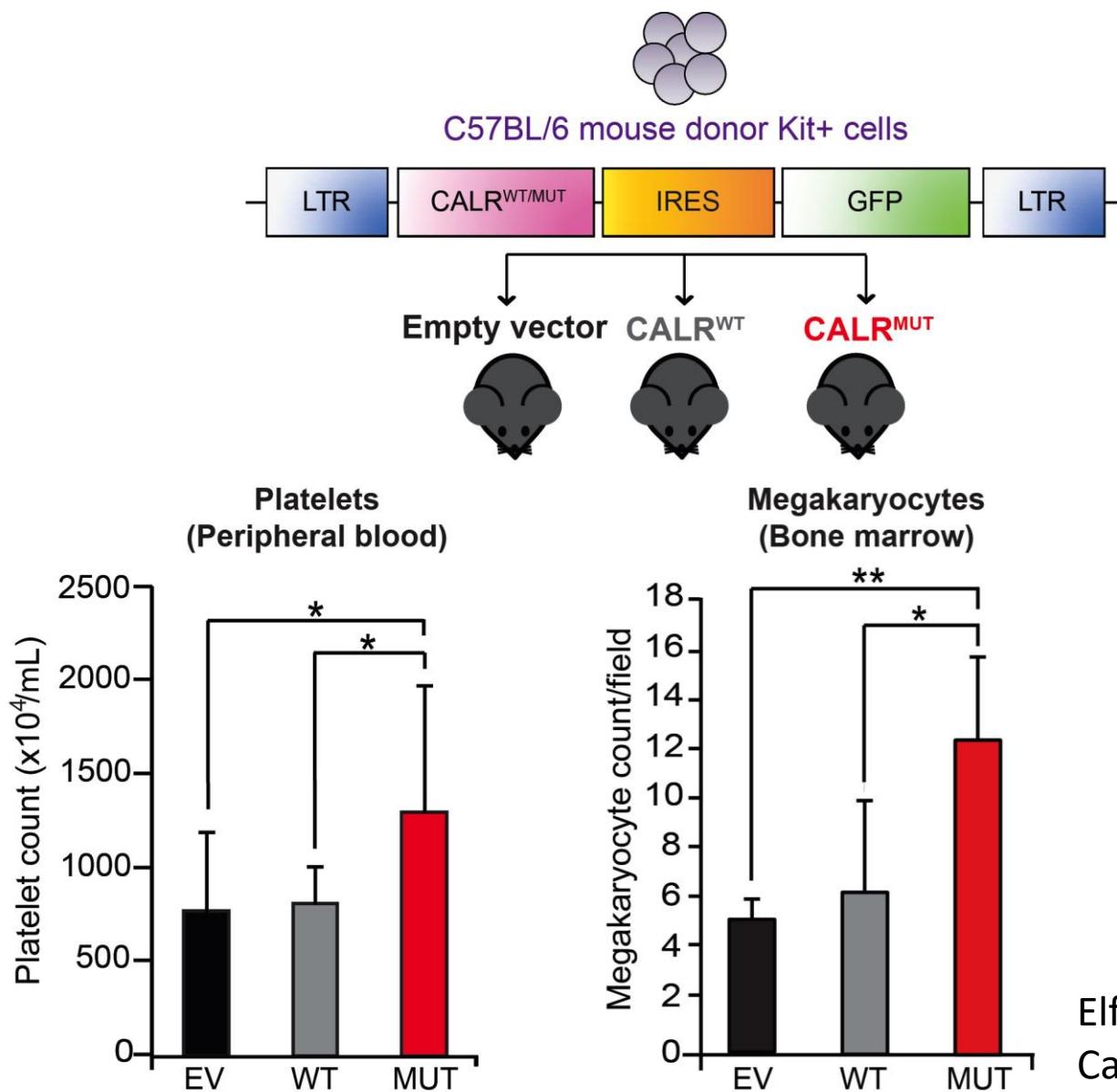
# Improving on JAK2 inhibitors



# Calreticulin (CALR) mutations in MPN



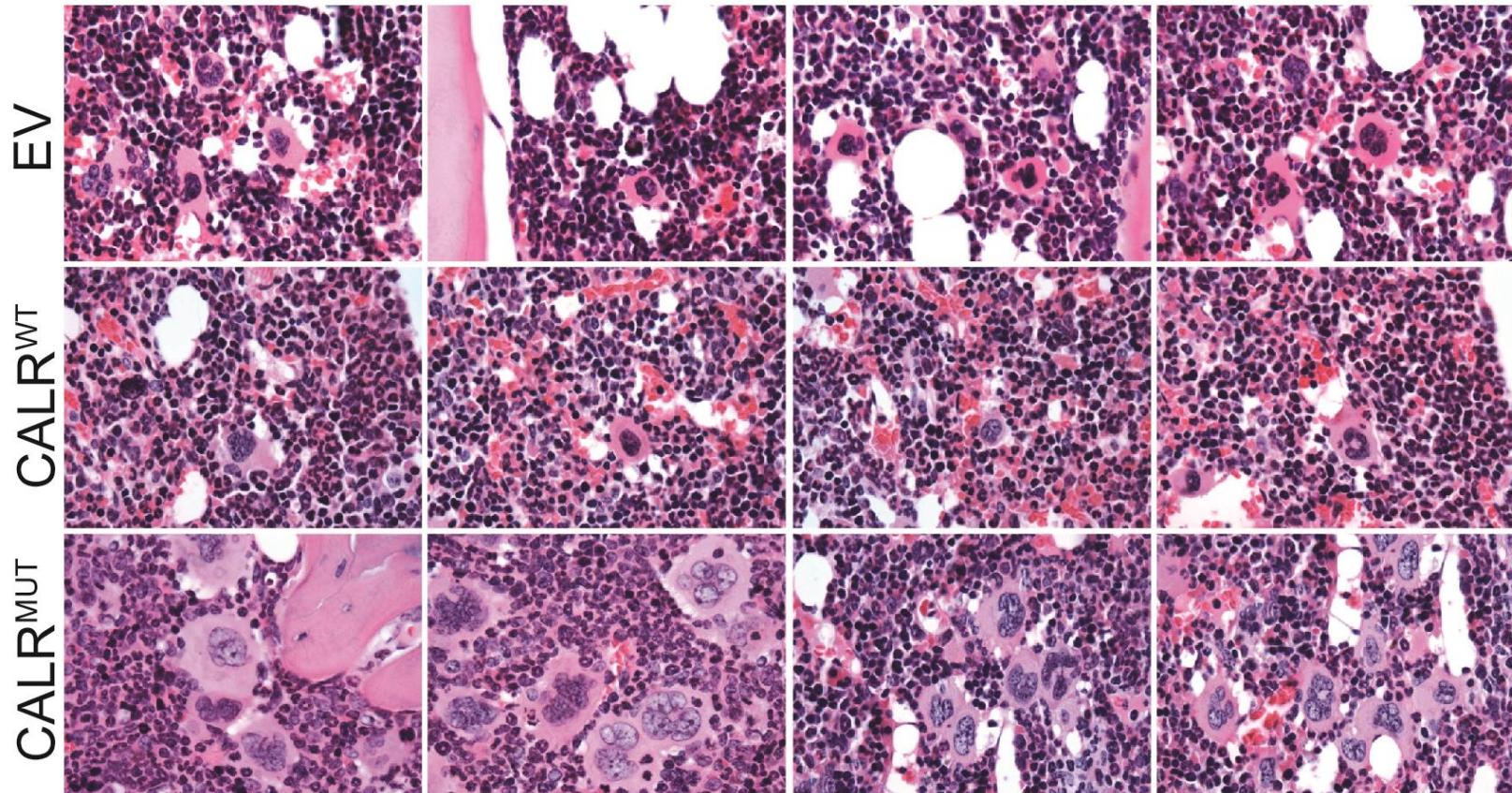
# Mutant CALR induces MPN disease in mice



Elf, Abdelfattah, Chen et al.  
Cancer Discovery 2016

# Megakaryocytic abnormalities in CALR<sup>mut</sup> mice

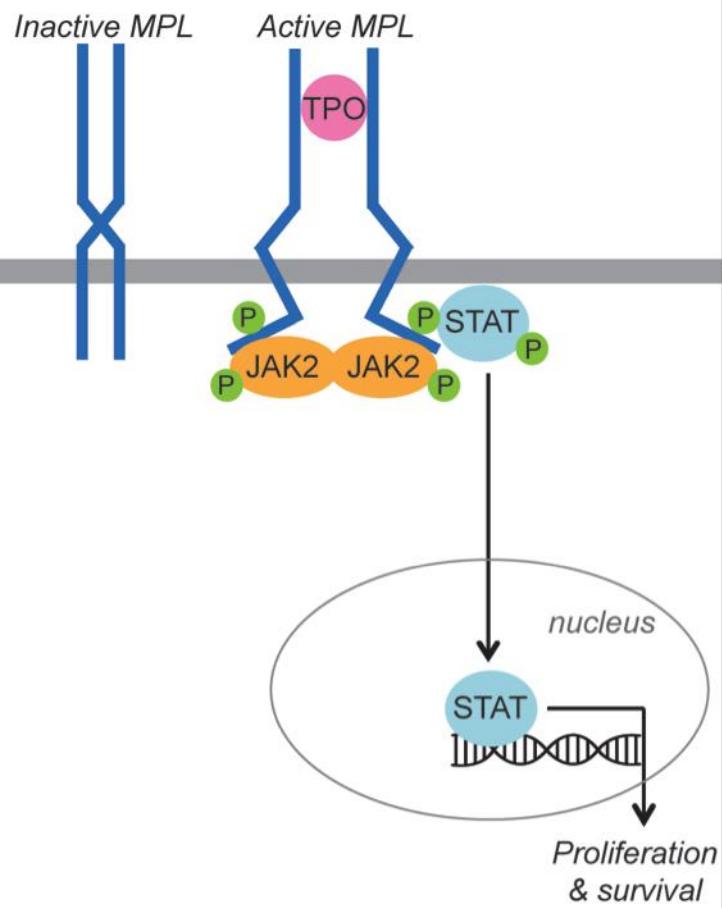
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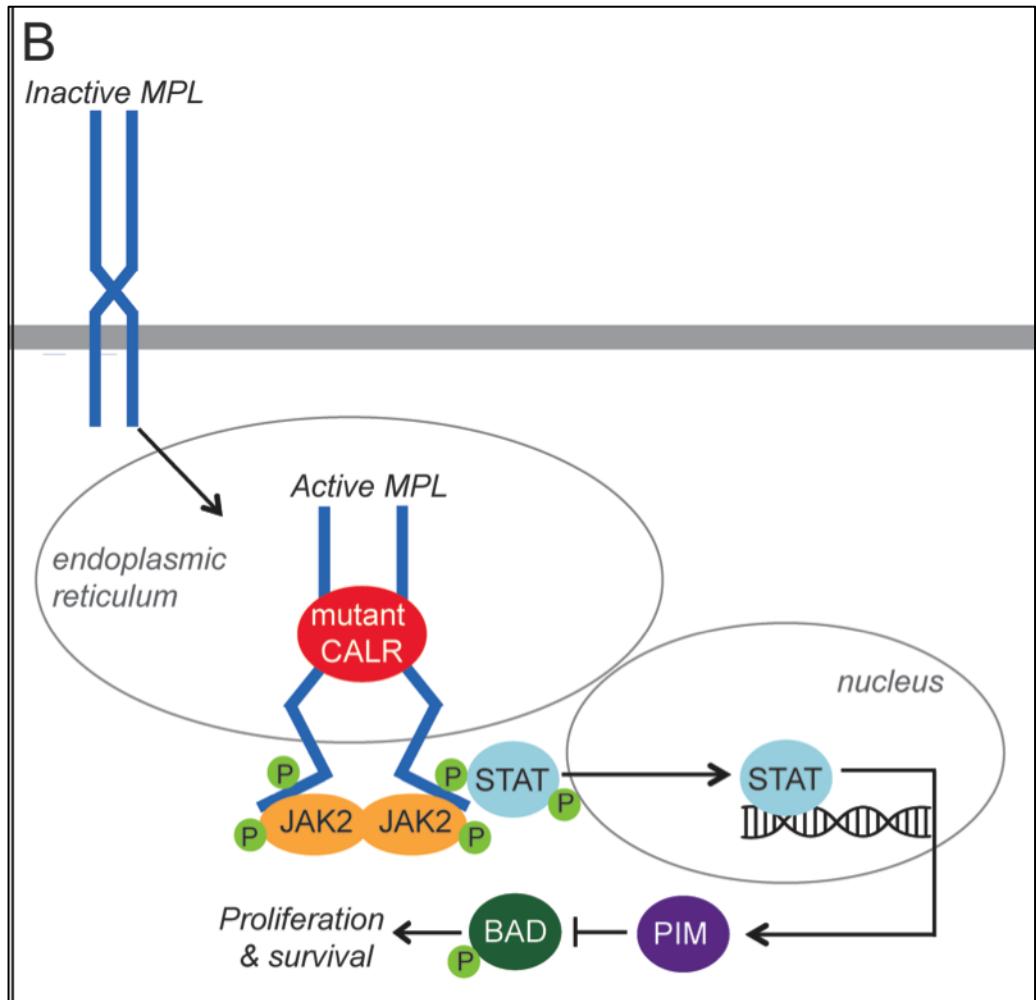
# How does mutant CALR cause MPN?

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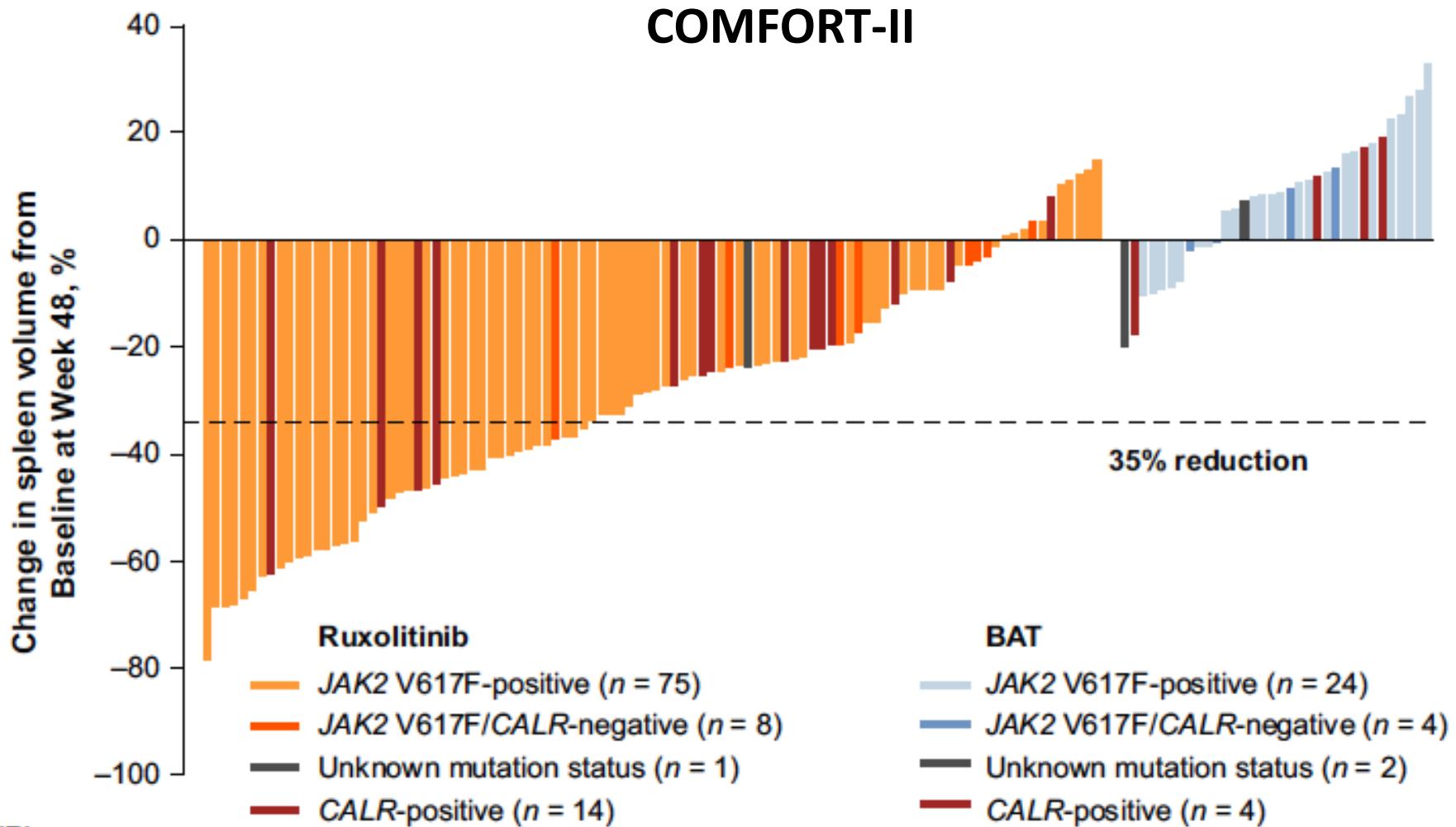
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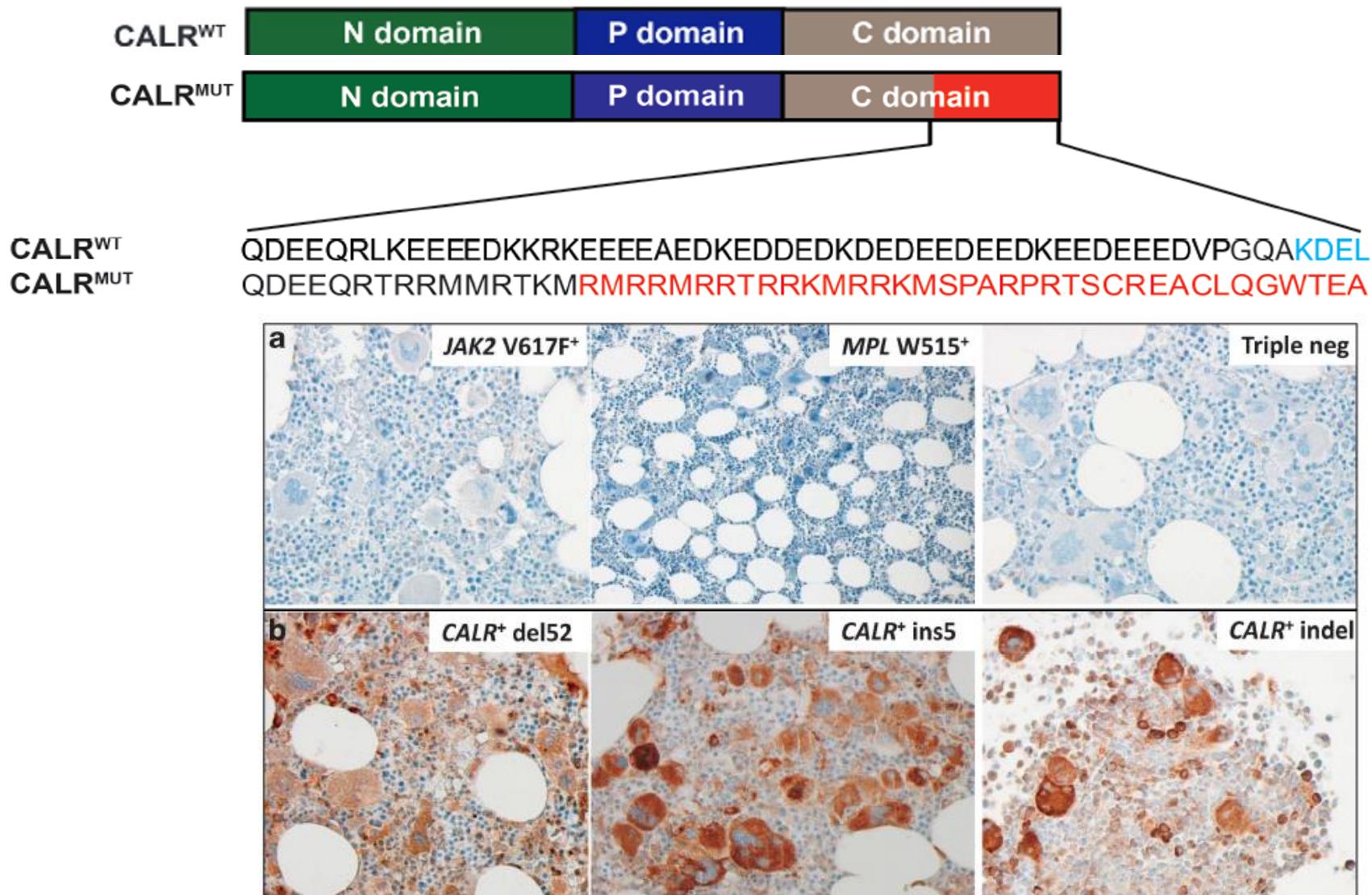
# How does mutant CALR cause MPN?



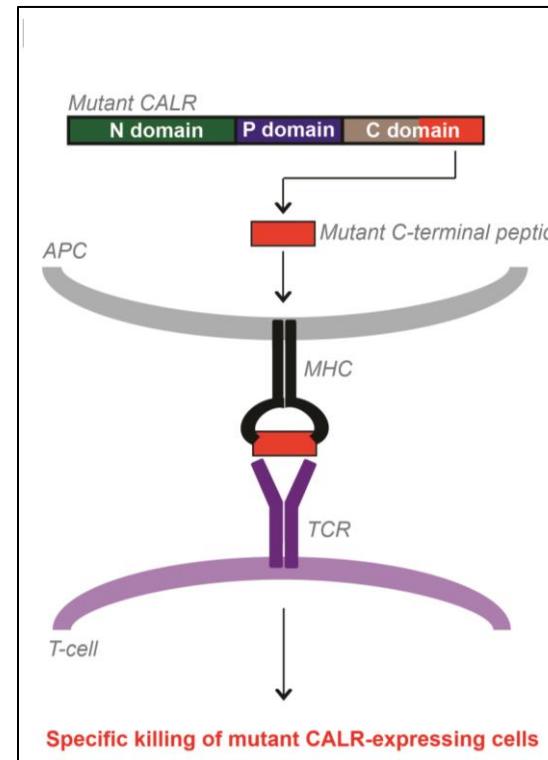
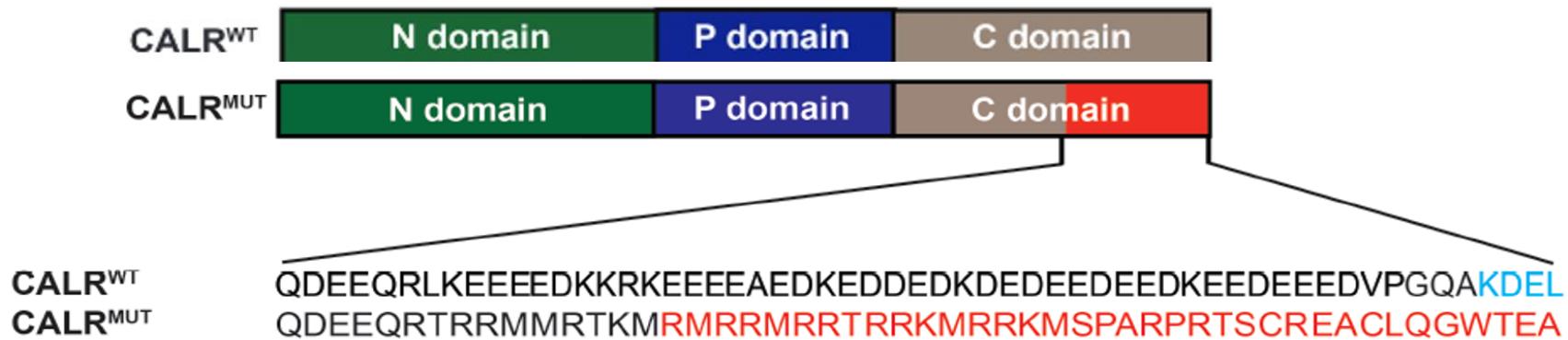
# *CALR*-mutant MF patients demonstrate clinical responses to ruxolitinib



# Mutant-specific C-terminus of mutant CALR



# Could mutant CALR be targeted with immunotherapy?



## Summary

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- MPN is a disease of hematopoietic stem cells
- JAK2, calreticulin (CALR) and MPL account for >90% cases of MPN
- Activated JAK-STAT signaling is a common feature of all MPNs
- A central goal is to improve the ability of current therapies to preferentially targeting MPN cells over normal cells
- CALR-mutant MPN cells may be targets for immunotherapy

# Acknowledgements



Damon Runyon  
**Cancer Research**  
Foundation

MPN RESEARCH FOUNDATION  
advancing research » empowering patients

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for Cancer Research

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