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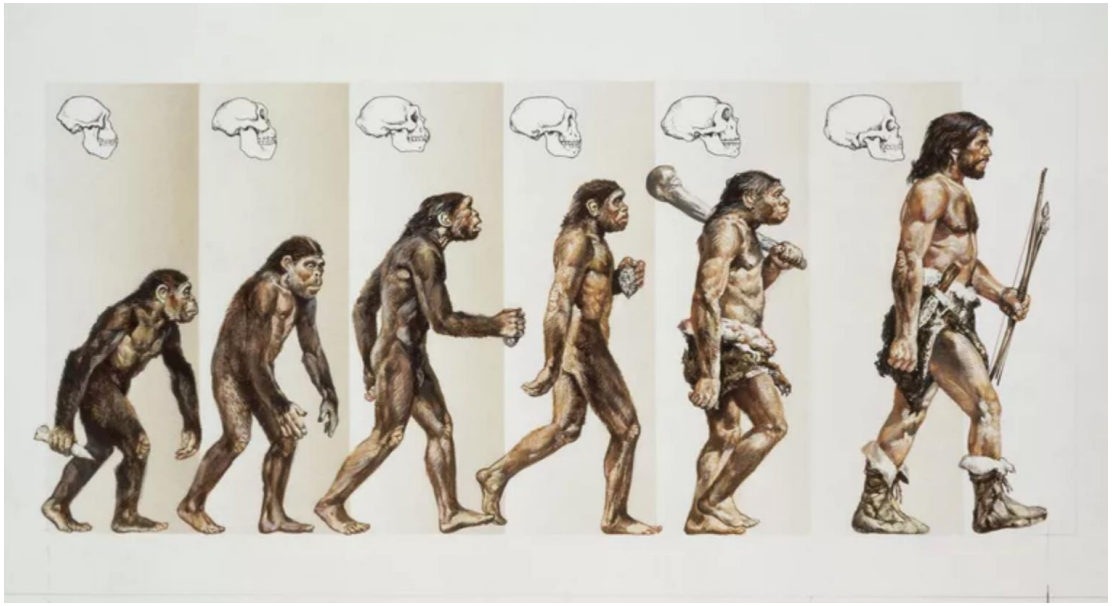

Evolving Targets for MPN Therapy

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12th Joyce Niblack Memorial Conference on MPNs
February 19, 2021

Disclosures

- **Research Funding:** Incyte, Novartis, Kartos, Blueprint Medicines, Deciphera, Abbvie, Celgene, BMS, Protagonist therapeutics, CTI Biopharma, Promedior

- **Advisory Boards/Honoraria:** Incyte, Novartis, Kartos, Blueprint Medicines, Deciphera, Abbvie, Protagonist therapeutics, PharmaEssentia

Evolution of Drugs for MF-Associated Anemia

Immunomodulatory drugs
+/- corticosteroids
(thalidomide, lenalidomide +/- prednisone)

Androgens
(Danazol)

Luspatercept
'erythroid maturation agent (EMA)'

CPI-0610
(BET inhibitor)

Momelotinib
(unanticipated anemia-improving effects by inhibiting activin receptor-like kinase-2 (ALK2)

INCB00928
(ALK2 inhibitor)

Red blood cell transfusions; Erythropoiesis Stimulating Agents (ESAs) (Procrit, Aranesp)

American Society of Hematology
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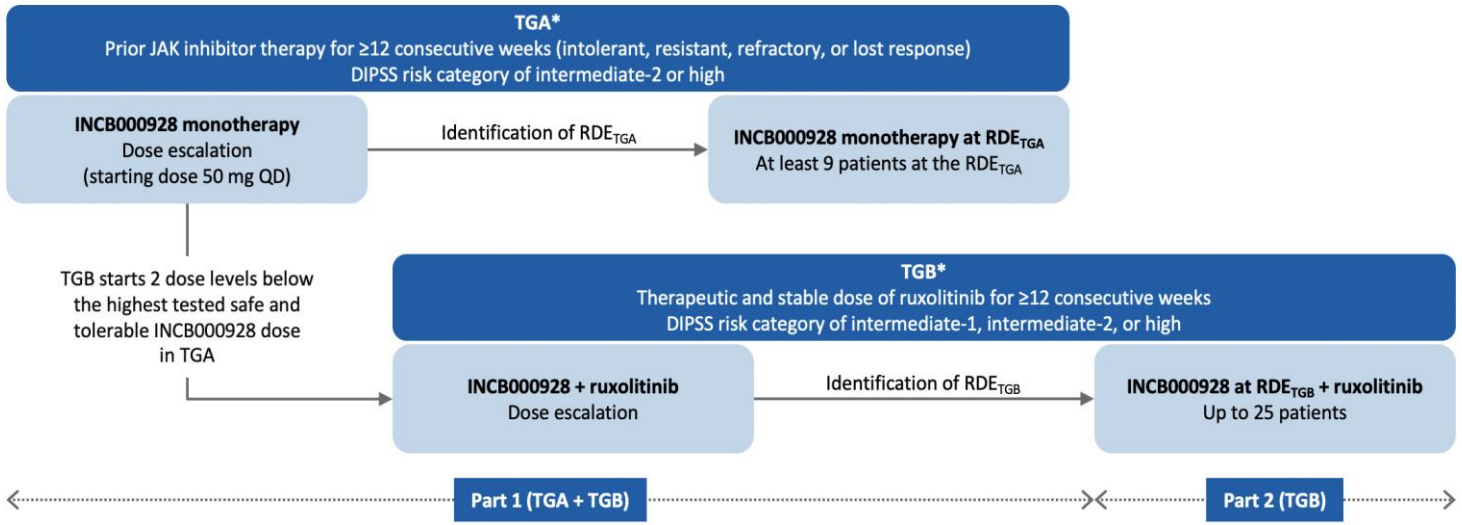
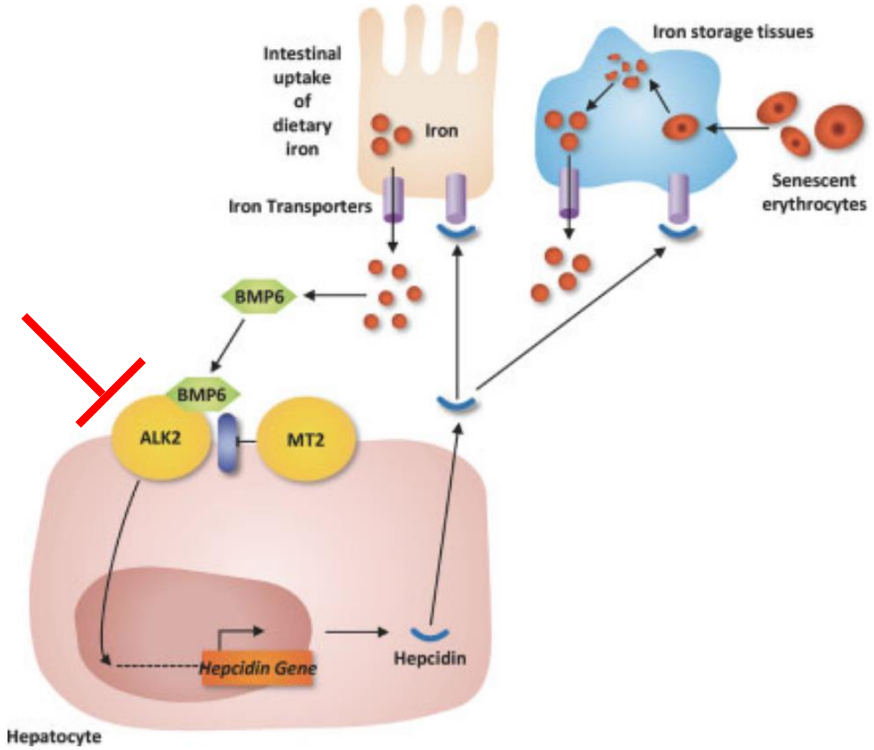
Abstract 3000

A Phase 1/2 Study of INCB000928 as Monotherapy or in Combination With Ruxolitinib in Patients With Anemia Due to Myelofibrosis (INCB 00928-104)

Stephen T. Oh,[1] Jason Gotlib,[2] Sanjay Mohan,[3] Haris Ali,[4] Ekatherine Asatiani,[5] Francis Seguy,[5] Feng Zhou,[6] Srdan Verstovsek[7]

[1]Washington University School of Medicine, St Louis, MO; [2]Stanford Cancer Institute, Stanford, CA; [3]Vanderbilt University Medical Center, Nashville, TN; [4]City of Hope Medical Center, Duarte, CA; [5]Incyte Biosciences International Sàrl, Morges, Switzerland; [6]Incyte Corporation, Wilmington, DE; [7]University of Texas MD Anderson Cancer Center, Houston, TX

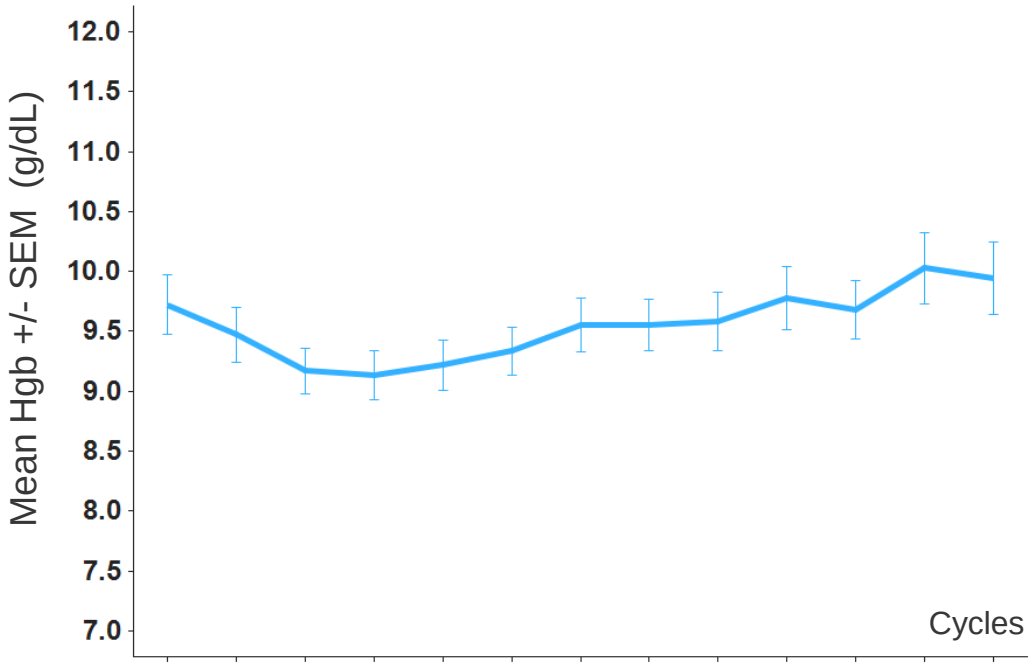




ALK2 inhibition reduces liver hepcidin expression, increases sequestered iron mobilization from cellular stores, and stimulates red blood cell production

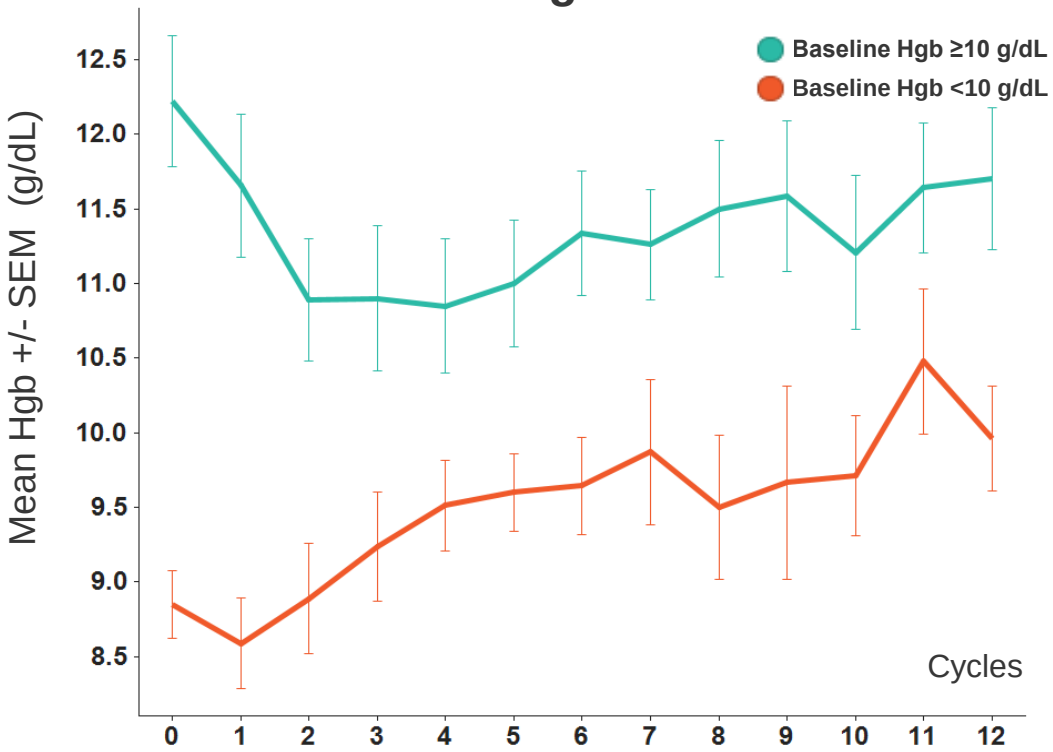
CPI-0610: Hemoglobin improvement observed in patients with baseline hemoglobin <10 g/dL

All patients[1]
Mean Hgb Over Time



N	69	68	68	69	67	66	61	62	59	49	48	43	42

Patients Without Transfusions[1,2]
Mean Hgb Over Time

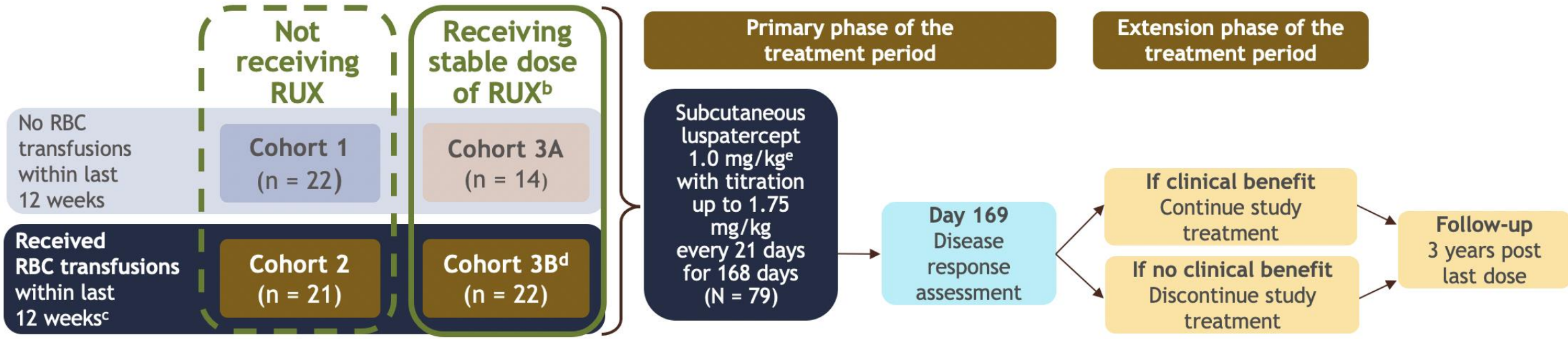


N	18	18	17	18	18	18	17	18	17	14	13	14	14
N	8	8	8	8	8	8	7	7	6	6	7	5	5

[1] Patients on treatment ≥ 12 wks
[2] Received no transfusions 12 wks prior to C1D1 and during treatment
Hgb: Hemoglobin

ACE-536-MF-001 study design[a]

- This study reports the results of the ongoing open-label, phase 2 ACE-536-MF-001 trial evaluating luspatercept in subjects with MF and anemia, focusing on response in subjects requiring RBC transfusions (NCT03194542)

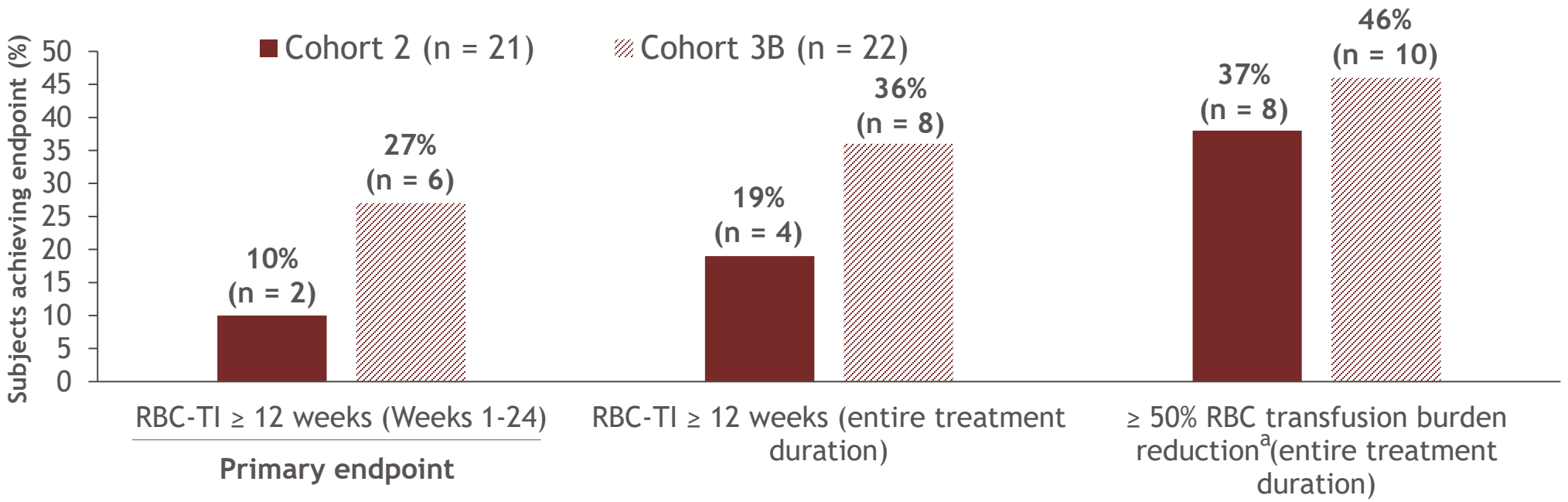


79 subjects with MF and anemia had been enrolled by the data cutoff and were included in this updated analysis (March 29, 2020)

- The analyses presented here focus on response in subjects requiring RBC transfusions (Cohorts 2 and 3B); safety is reported for all 79 subjects on study

As of March 29, 2020, 16 (20%) subjects remain on treatment. [a]Enrolled subjects had primary or post-essential thrombocythemia/post-polycythemia vera myelofibrosis; [b]A stable daily dose of RUX for at least 16 weeks at enrollment; for the 3 subjects enrolled in the expansion cohort in Cohort 3B, subjects were receiving a stable RUX dose for 40 weeks; [c]6-12 RBC units/84 days prior to treatment; or 4-12 units/84 days for the 3 subjects enrolled in the expansion cohort in Cohort 3B; [d]Including 3 subjects enrolled in the expansion cohort; [e]The starting dose was 1.33 mg/kg in the expansion cohort subjects. MF, myelofibrosis; RBC, red blood cell; RUX, ruxolitinib.

Luspatercept: Rates of RBC transfusion independence and ≥ 50% transfusion burden reduction ≥ 12 weeks



Achievement of multiple episodes of response

- Of the RBC-TI ≥ 12-week responders in both Cohorts 2 and 3B, 25% experienced 2 separate episodes of RBC-TI ≥ 12 weeks
- Of the subjects who achieved ≥ 50% reduction in RBC transfusion burden over any 12 weeks, 3 subjects in Cohort 2 (38%) and 2 subjects in Cohort 3B (20%) experienced 2 separate ≥ 12-week response episodes
  - 1 subject (13%) in Cohort 2 experienced 3 separate episodes of RBC-TI ≥ 12 weeks

[a]Defined as RBC transfusion burden reduction by ≥ 50% and by ≥ 4 RBC U for ≥ 12 weeks.

Evolution of Drugs for Blast Phase MPN

Intensive AML-type chemotherapy

Hypomethylating Agents [HMA]
(Azacitidine [Aza], Decitabine [Dec])

HMA + Ruxolitinib
Aza/Rux; Dec/Rux

Targeted Mutation Approaches
(*IDH1*, *IDH2*, *FLT3*, ? *TP53*)

+/-
Transplant

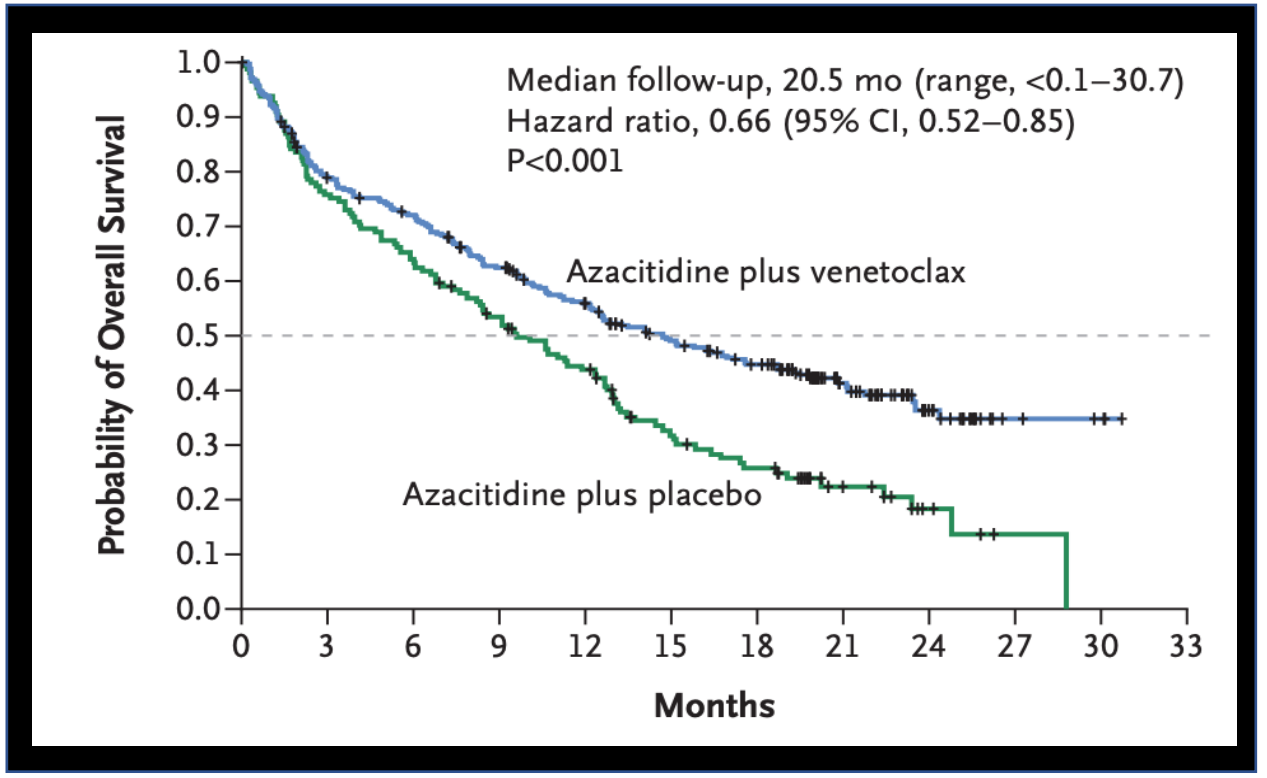
HMA + Ruxolitinib Combinations in Accelerated and Blast Phase MPN

Reference	Patient Population	HMA	Overall Response Rate	Median Overall Survival
Rampal *et al*, *Blood Advances*, 2018	Accelerated and blast phase MPN	Decitabine	53%	7.9 months
Mascarenhas *et al*, *Blood Advances*, 2020	Accelerated and blast phase MPN	Decitabine	44%	9.5 months
Bose *et al*, *Leukemia*, 2020	Blast phase MPN	Decitabine	45%	6.9 months

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 13, 2020 VOL. 383 NO. 7

Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia



Median OS
14.7 vs 9.6 months

DiNardo *et al*, *NEJM*, 2020

The NEW ENGLAND JOURNAL of MEDICINE

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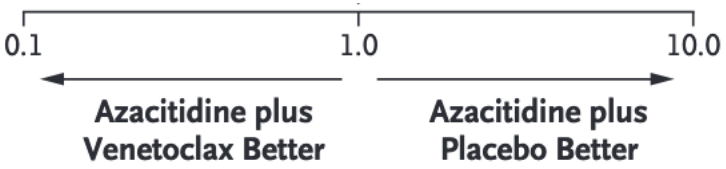
Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia

Subgroup	Azacitidine plus Venetoclax	Azacitidine plus Placebo	Hazard Ratio for Death (95% CI)
	no. of events/total no. (%)		
Type of AML			
De novo	120/214 (56.1)	80/110 (72.7)	0.67 (0.51–0.90)
Secondary	41/72 (56.9)	29/35 (82.9)	0.56 (0.35–0.91)
Cytogenetic risk			
Intermediate	84/182 (46.2)	62/89 (69.7)	0.57 (0.41–0.79)
Poor	77/104 (74.0)	47/56 (83.9)	0.78 (0.54–1.12)
Molecular marker			
FLT3	19/29 (65.5)	19/22 (86.4)	0.66 (0.35–1.26)
IDH1	15/23 (65.2)	11/11 (100.0)	0.28 (0.12–0.65)
IDH2	15/40 (37.5)	14/18 (77.8)	0.34 (0.16–0.71)
IDH1 or *IDH2*	29/61 (47.5)	24/28 (85.7)	0.34 (0.20–0.60)
TP53	34/38 (89.5)	13/14 (92.9)	0.76 (0.40–1.45)
NPM1	16/27 (59.3)	14/17 (82.4)	0.73 (0.36–1.51)
AML with myelodysplasia-related changes			
Yes	56/92 (60.9)	38/49 (77.6)	0.73 (0.48–1.11)
No	105/194 (54.1)	71/96 (74.0)	0.62 (0.46–0.83)



DiNardo *et al*, *NEJM*, 2020

Phase 2 Study of Venetoclax in Combination with Decitabine in Accelerated and Blast-Phase Myeloproliferative Neoplasms

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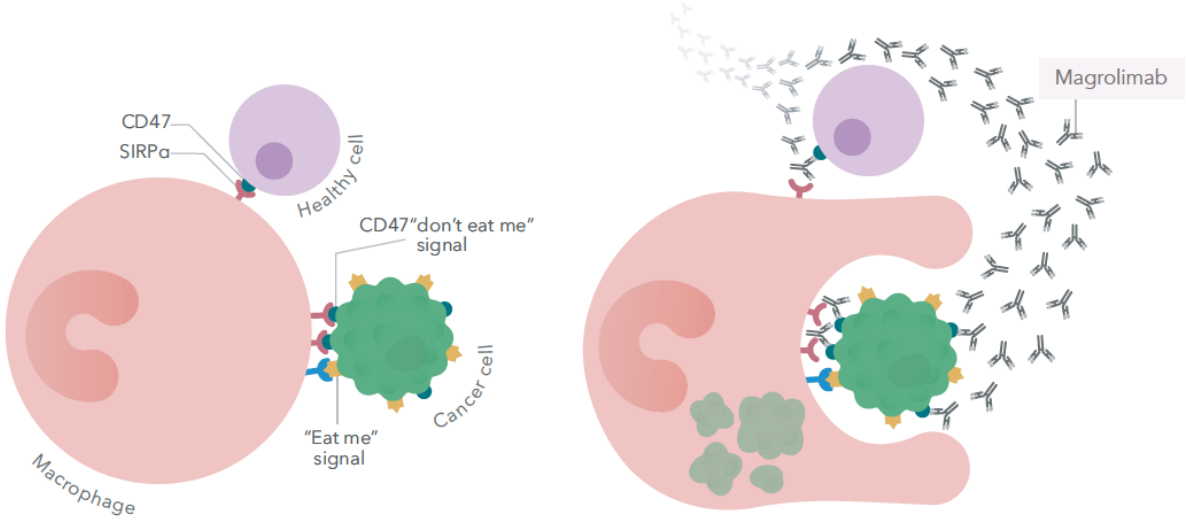
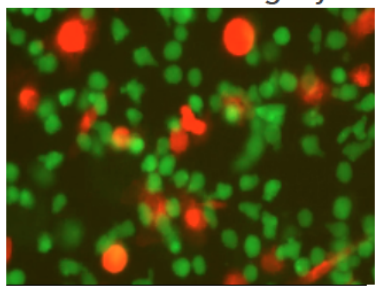
ASH 2020 Abstract #330: Magrolimab in p53 AML

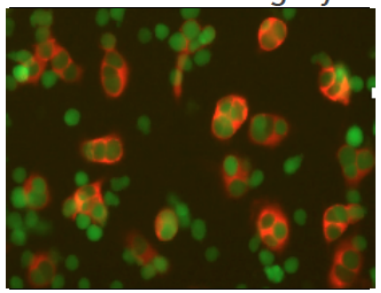
Magrolimab (Formerly 5F9) Is a First-in-Class Macrophage Immune Checkpoint Inhibitor Targeting CD47



Control mAb: No Phagocytosis



Anti-CD47 mAb: Phagocytosis



Macrophages
Cancer cells

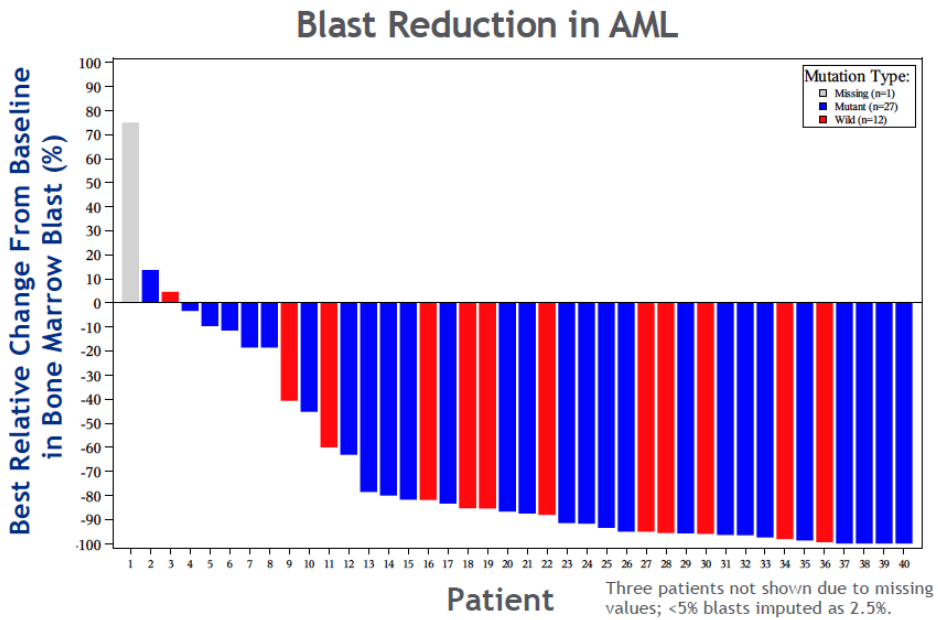
- CD47 is a "do not eat me" signal that is overexpressed in multiple cancers, including acute myeloid leukemia, leading to macrophage immune evasion
- Magrolimab, an IgG4 anti-CD47 monoclonal antibody, eliminates tumor cells through macrophage phagocytosis
- Magrolimab is being investigated in multiple cancers with >500 patients dosed

ASH 2020 Abstract #330: Magrolimab in p53 AML

Magrolimab + AZA Induces High Response Rates in AML

Best Overall Response	All AML (N=43)	*TP53* mutant AML (29)
ORR	27 (63%)	20 (69%)
CR	18 (42%)	13 (45%)
CRi	5 (12%)	4 (14%)
PR	1 (2%)	1 (3%)
MLFS	3 (7%)	2 (7%)
SD	14 (33%)	8 (28%)
PD	2 (5%)	1 (3%)

Response assessments per 2017 AML ELN criteria. Patients with at least 1 post-treatment response assessment are shown



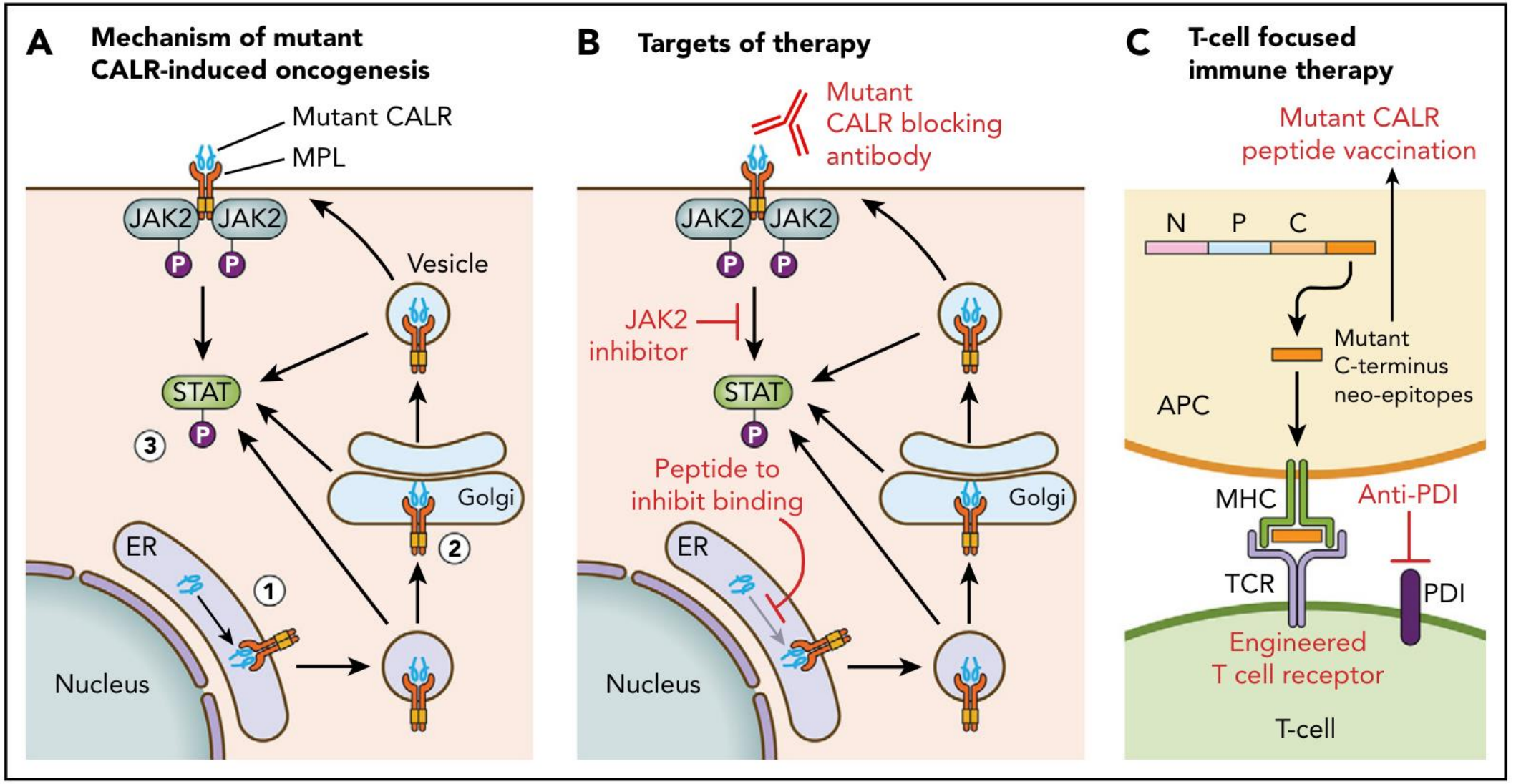
Three patients not shown due to missing values; <5% blasts imputed as 2.5%.

- Magrolimab + AZA induces a 63% ORR and 42% CR rate in AML including similar responses in *TP53*-mutant patients
- Median time to response is 1.95 months (range 0.95 to 5.6 mo), more rapid than AZA monotherapy
- 9.6% of patients proceeded to bone marrow stem cell transplantation
- Magrolimab + AZA efficacy compares favorably to AZA monotherapy (CR rate 18%-20%[1,2])

1. Fenaux P, et al. *J Clin Oncol*. 2010;28(4):562-569. 2. Dombret H, et al. *Blood*. 2015;126(3):291-299.

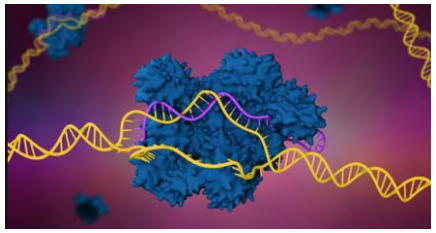
What about CALR?

CALR Therapeutic Targeting



Phase 1 vaccination study in Denmark with a CALR exon 9 peptide vaccine (NCT03566446)

How, Hobbs, Mullally, *Blood*, 2019



Genome Editing in MPNs ?

BRIEF REPORT

CRISPR-Cas9 Gene Editing for Sickle Cell Disease and β-Thalassemia

H. Frangoul, D. Altshuler, M.D. Cappellini, Y.-S. Chen, J. Domm, B.K. Eustace, J. Foell, J. de la Fuente, S. Grupp, R. Handgretinger, T.W. Ho, A. Kattamis, A. Kernytsky, J. Lekstrom-Himes, A.M. Li, F. Locatelli, M.Y. Mapara, M. de Montalembert, D. Rondelli, A. Sharma, S. Sheth, S. Soni, M.H. Steinberg, D. Wall, A. Yen, and S. Corbacioglu

January 2021

Inherited, single-gene diseases
Diseases without increased malignancy potential
Partial correction can lead to dramatic improvement

Issues in MPNs

- Who are the optimal MPN candidates ?
- Often multi-mutated besides *JAK2*, *CALR*, *MPL* (esp. myelofibrosis)
- Risk of secondary acute leukemia from conditioning chemotherapy for infusion of edited autologous CD34+ cells
- Off-target editing; unanticipated effects on MPN hematopoietic stem cells

Aspirational Pursuits…

Article

Inherited myeloproliferative neoplasm risk affects haematopoietic stem cells

https://doi.org/10.1038/s41586-020-2786-7

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Published online: 14 October 2020

Check for updates

Erik L. Bao[1,2,3,4,59], Satish K. Nandakumar[1,2,3,59], Xiaotian Liao[1,2,3,59], Alexander G. Bick[3,5,6,7,8], Juha Karjalainen[9], Marcin Tabaka[3], Olga I. Gan[10,11], Aki S. Havulinna[9], Tuomo T. J. Kiiskinen[9], Caleb A. Lareau[1,2,3,12], Aitzkoa L. de Lapuente Portilla[13], Bo Li[3,14], Connor Emdin[3,5], Veryan Codd[15,16], Christopher P. Nelson[15,16], Christopher J. Walker[17], Claire Churchhouse[3], Albert de la Chapelle[17], Daryl E. Klein[18], Björn Nilsson[3,13], Peter W. F. Wilson[19,20], Kelly Cho[21,22], Saiju Pyarajan[21], J. Michael Gaziano[21,22], Nilesh J. Samani[15,16], FinnGen*, 23andMe Research Team*, Aviv Regev[3,23,24], Aarno Palotie[3,9], Benjamin M. Neale[3], John E. Dick[10,11], Pradeep Natarajan[3,5,25], Christopher J. O'Donnell[7,22], Mark J. Daly[3,9], Michael Milyavsky[26], Sekar Kathiresan[3,5,27] & Vijay G. Sankaran[1,2,3,28]✉

The risk of developing an MPN is increased by 5–7-fold in first-degree relatives of patients with MPNs

> 20 Statistically significant or suggestive gene loci associated with increased MPN risk:

JAK2 46/1, SH2B3, ZNF521 , GATA2 , MECOM, RUNX1 , HMGA1 , ATM , FOXO1 , TET2 , PRKCE, STXBP5L, SMC4, KPNA4, SLC12A7, F2RL1, MAD1L1, MKLN1, FOXG1 DLK1, ***TERT, CHEK2, GFI1B***

Bao *et al*, *Nature* 2020

Gene Variants Associated with Increased MPN Risk and Functional Consequences in Hematopoietic Stem Cells

TERT: (Telomerase Reverse Transcriptase): protein component of the enzyme telomerase which adds DNA to the ends of chromosomes. Telomerase is reactivated or upregulated in the vast majority of cancers.

The top two TERT variants for increased telomere length, TERT rs7705526 and rs2853677 were also the lead variants for MPN risk

---

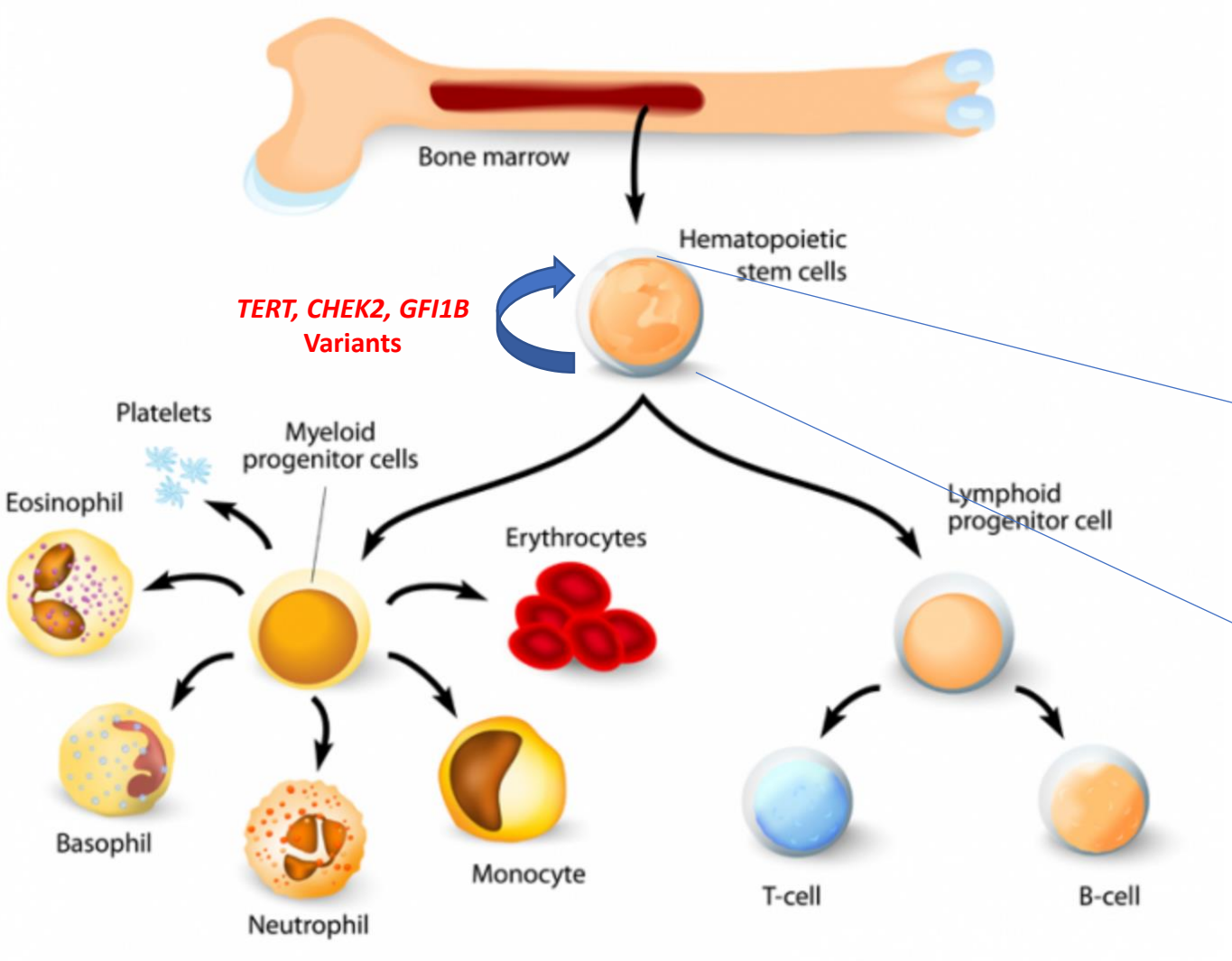
CHEK2: a protein that acts a tumor suppressor. CHEK2 regulates cell division, and can prevent cells from dividing too rapidly. Usually constrains hematopoietic stem cell expansion.

The CHEK2 I157T variant reduces the function of CHEK2, promotes hematopoietic stem cell self-renewal, and may therefore increase MPN risk

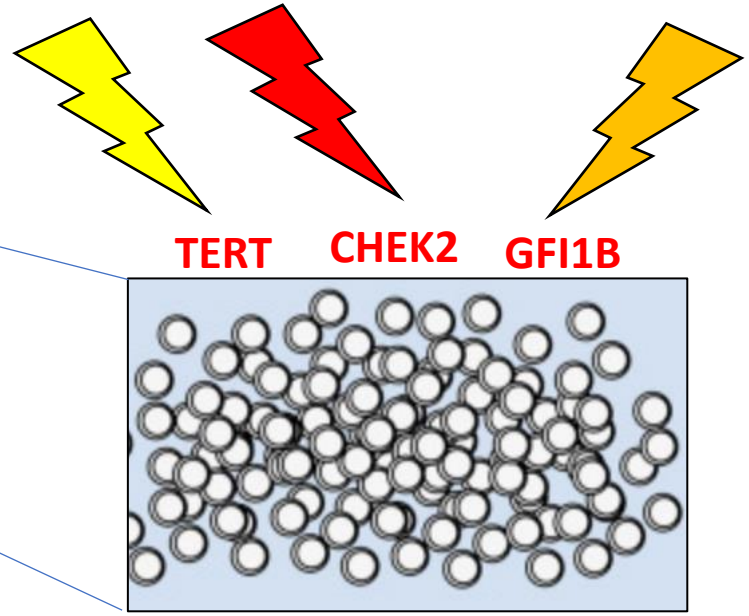
---

GFI1B: a master DNA transcription factor that is necessary for maintaining hematopoietic stem cell quiescence.

The GFI1B rs524137 variant results in decreased expression of GFI1B in hematopoietic stem cells and increases their self-renewal



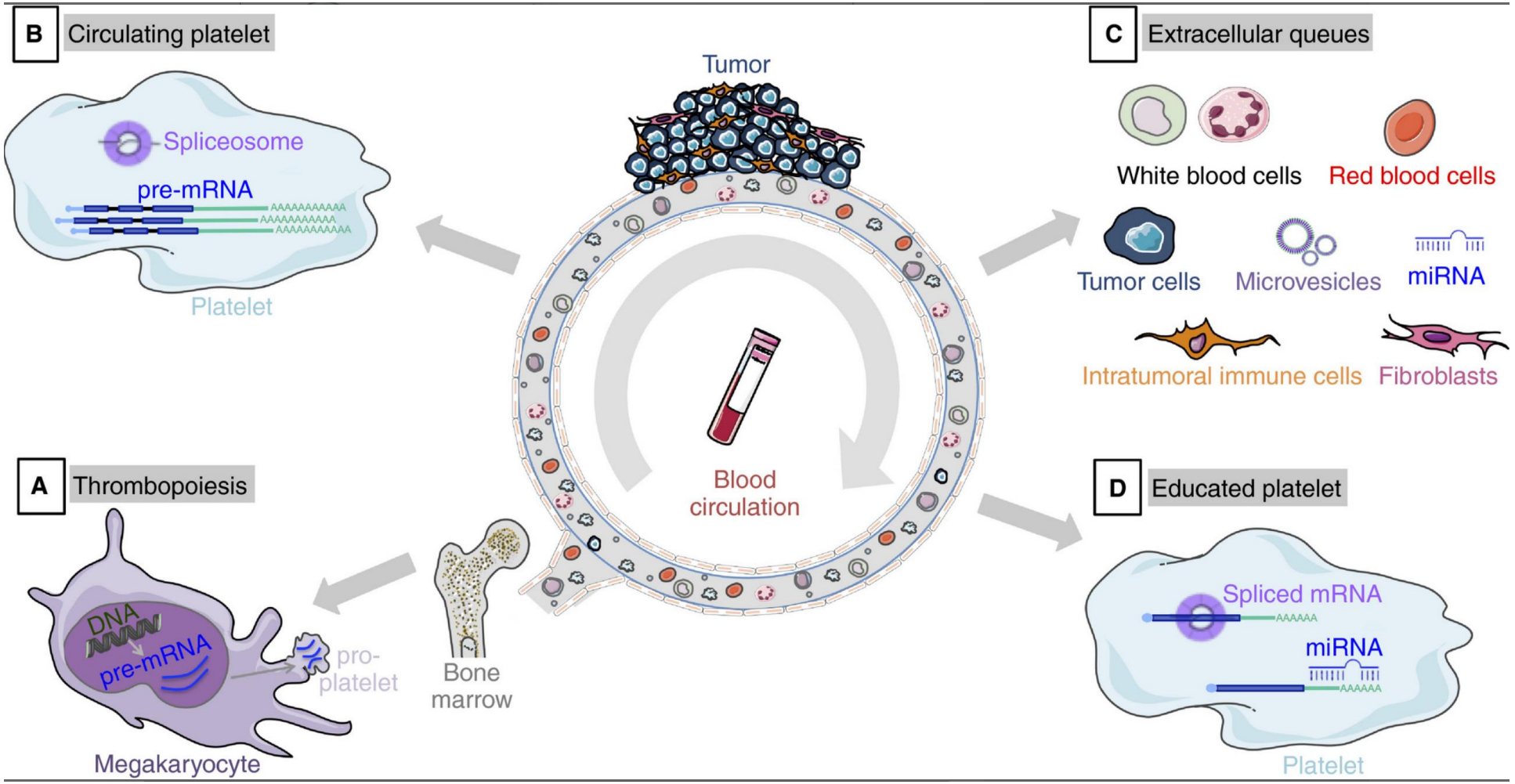
Normal Hematopoiesis



Therapeutic 'correction' of germline variants to mitigate future risk of MPN?

Use of genome editing?

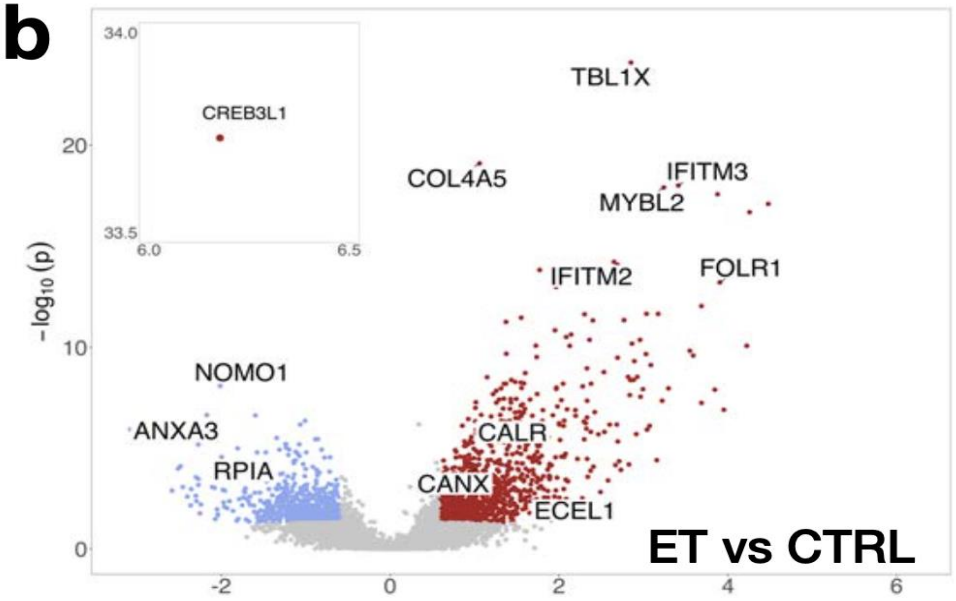
Platelet transcriptome (RNA sequencing) in MPNs

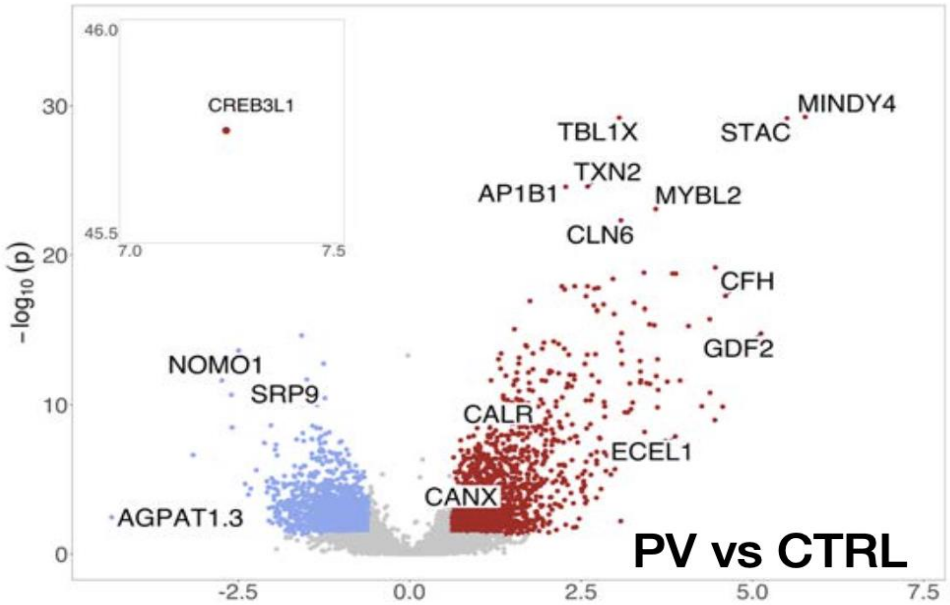


Platelet transcriptome represents a critical biomarker of megakaryocytic activity, and provides a snapshot of the underlying hemostatic, thrombotic, and inflammatory derangements associated with MPNs and the potential impact of treatment

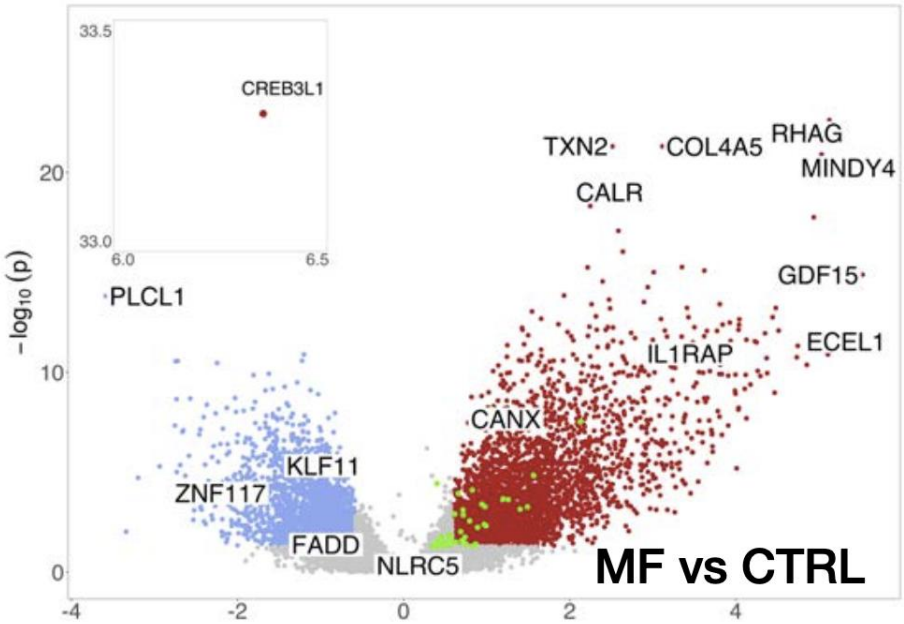
Best *et al*, *J Thromb Haemost*, 2017

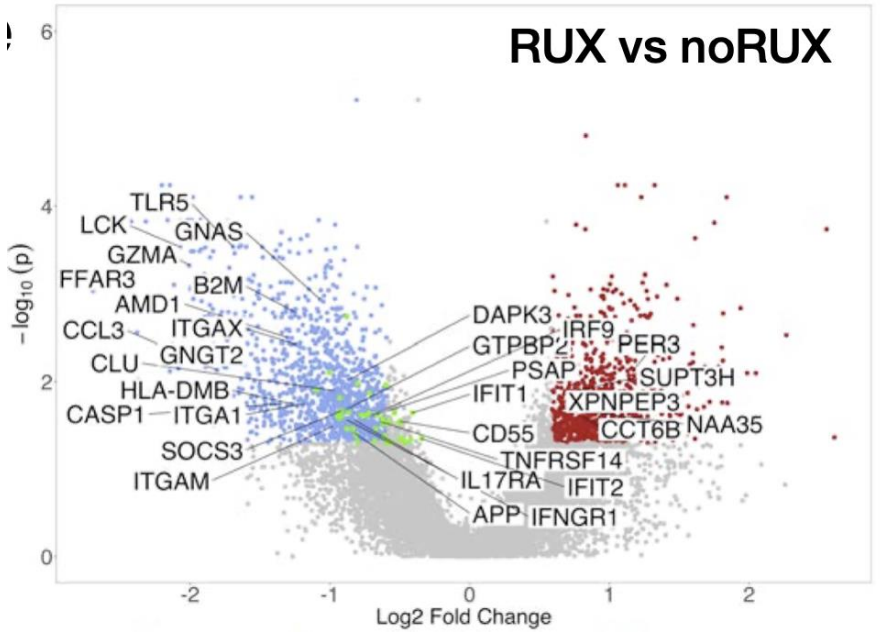
b





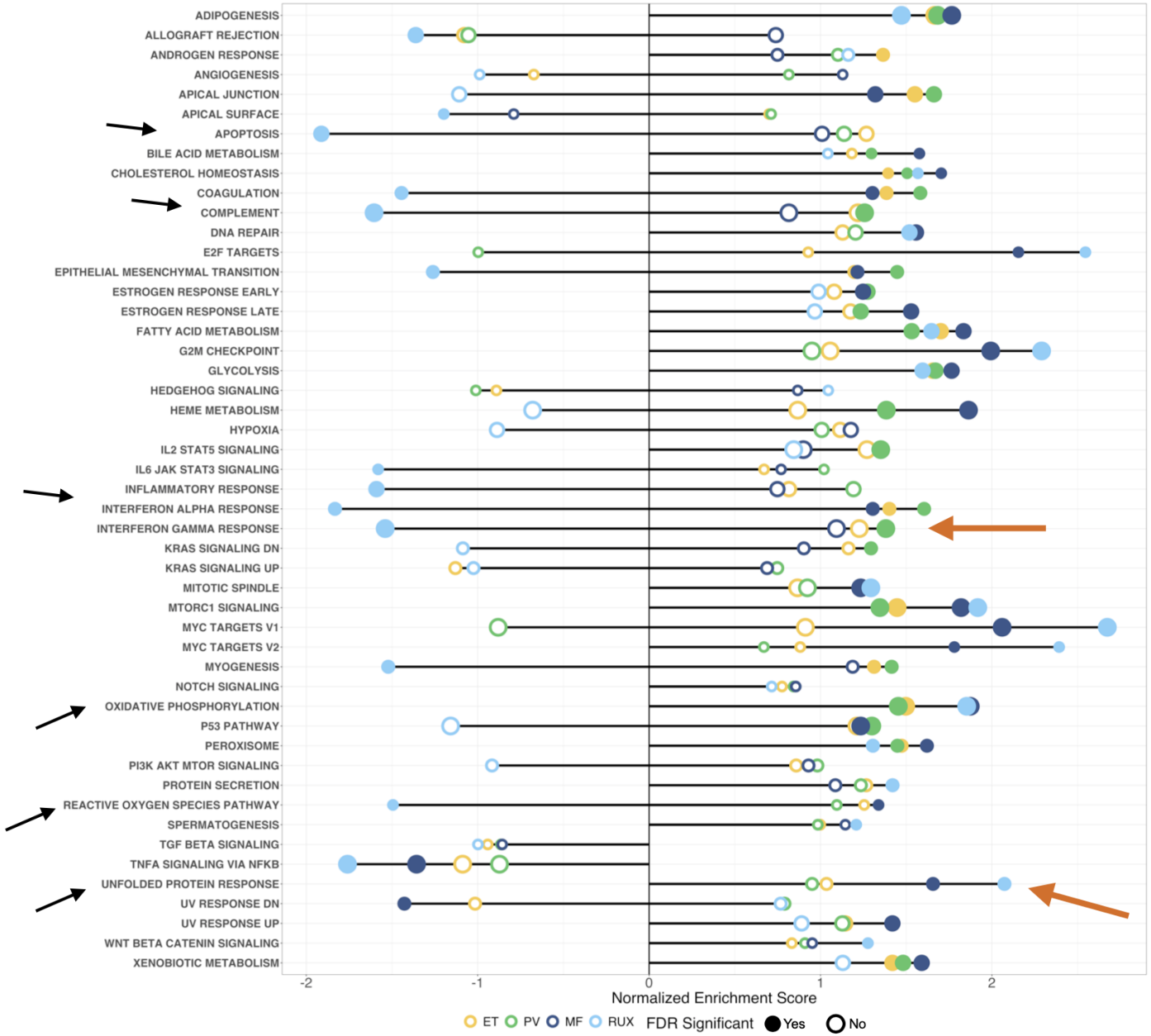
Volcano plots of changes in RNA expression from platelets from ET, PV, & MF patients, and changes on RUX therapy





Work by Dr. Anandi Krishnan, Stanford University School of Medicine

Potential Targets for MPNs



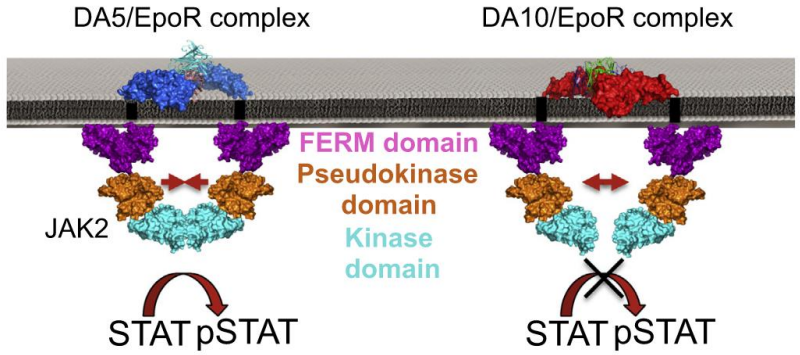
ET
PV
MF
RUX

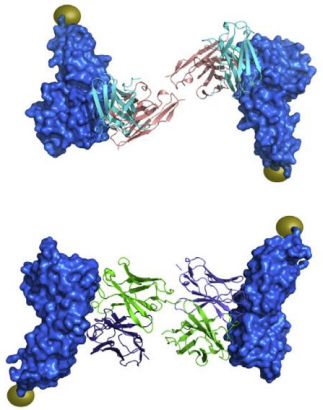
*unpublished data

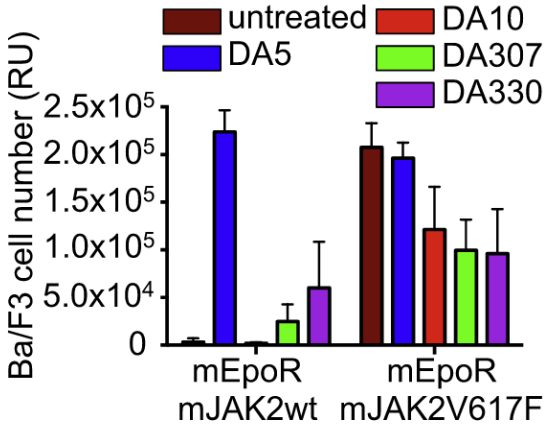
Work by Dr. Anandi Krishnan, Stanford University School of Medicine

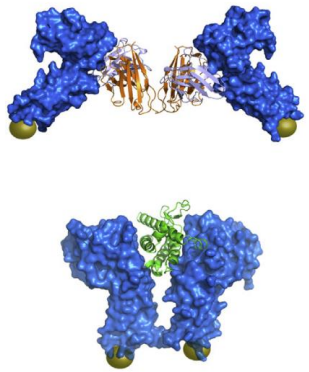
Diabodies, small molecules that can dial-up or dial-down the activity of EPO receptor and TPO receptor (MPL)

EPO Receptor



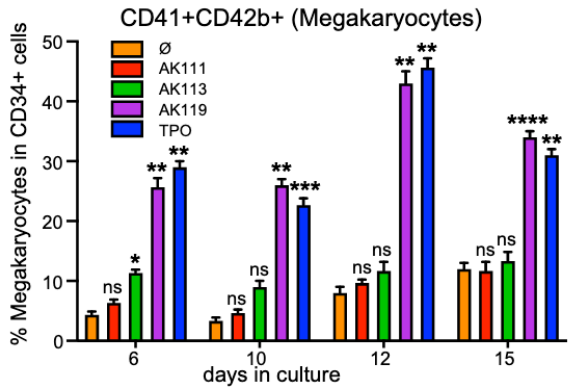


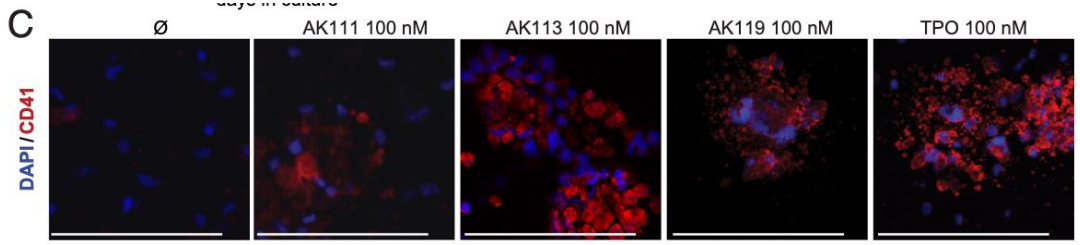


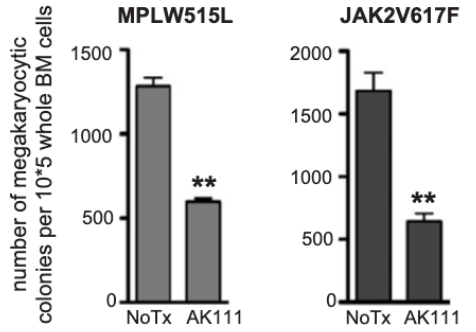


Moraga *et al*, *Cell*, 2015

TPO Receptor (MPL)







ET Patients

Cui et al, PNAS, 2021

Evolving Targets for MPN Therapy

Evolving Treatment Goals

--Spleen size

--Symptoms

--Cytopenias

--BM fibrosis

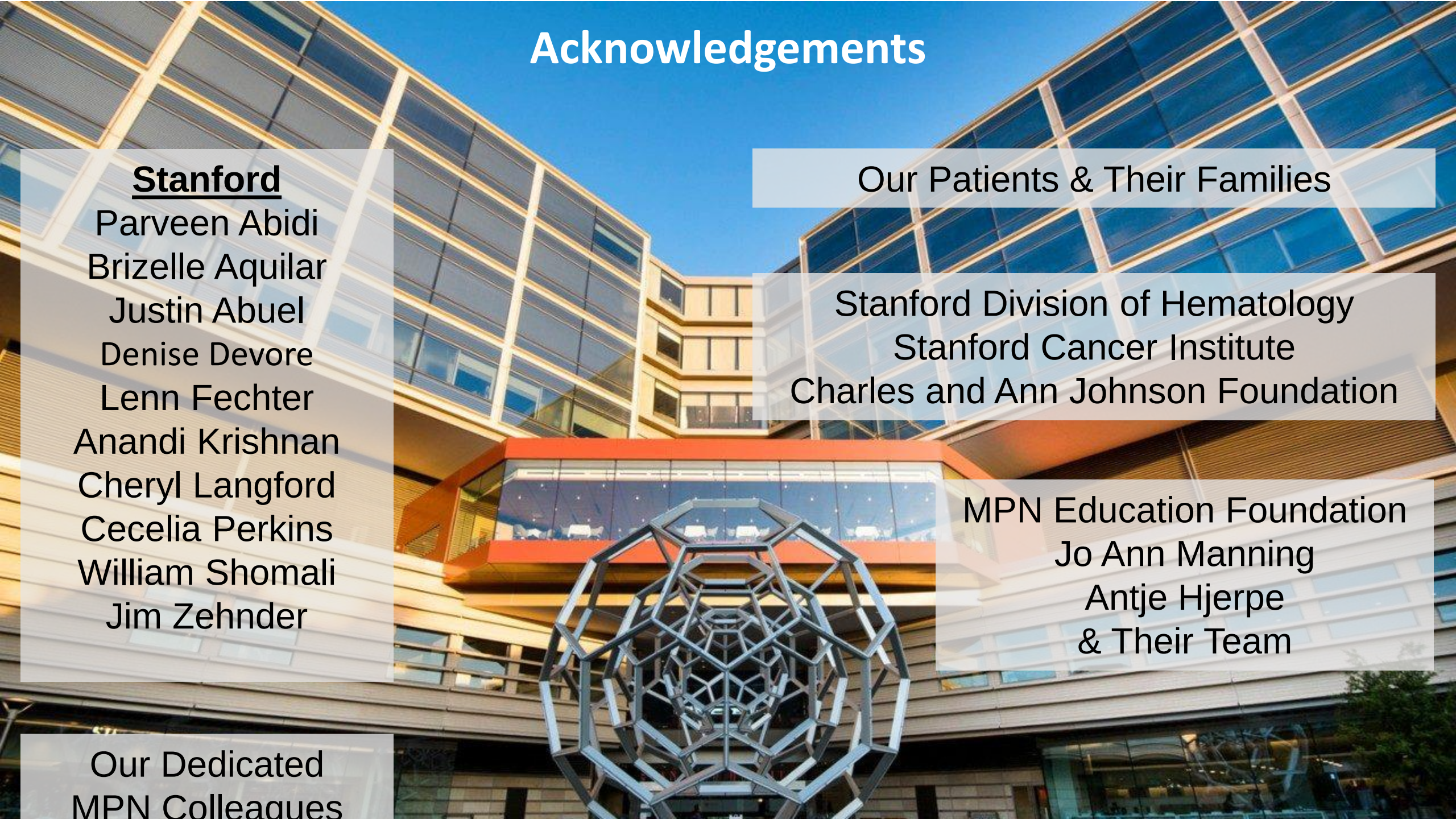
--Mutation burden

-- Survival

-- Leukemic evolution

Making it Happen with
Bench to Bedside Collaboration

Acknowledgements



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MPN Colleagues

Our Patients & Their Families

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