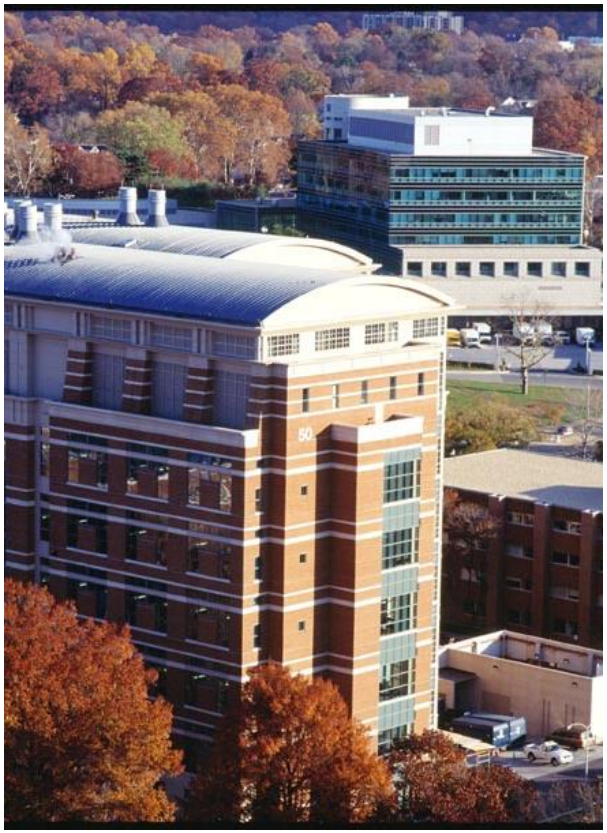
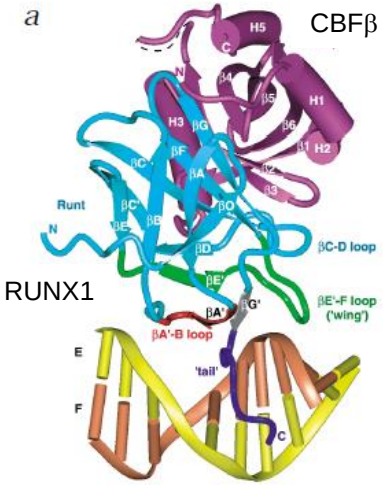
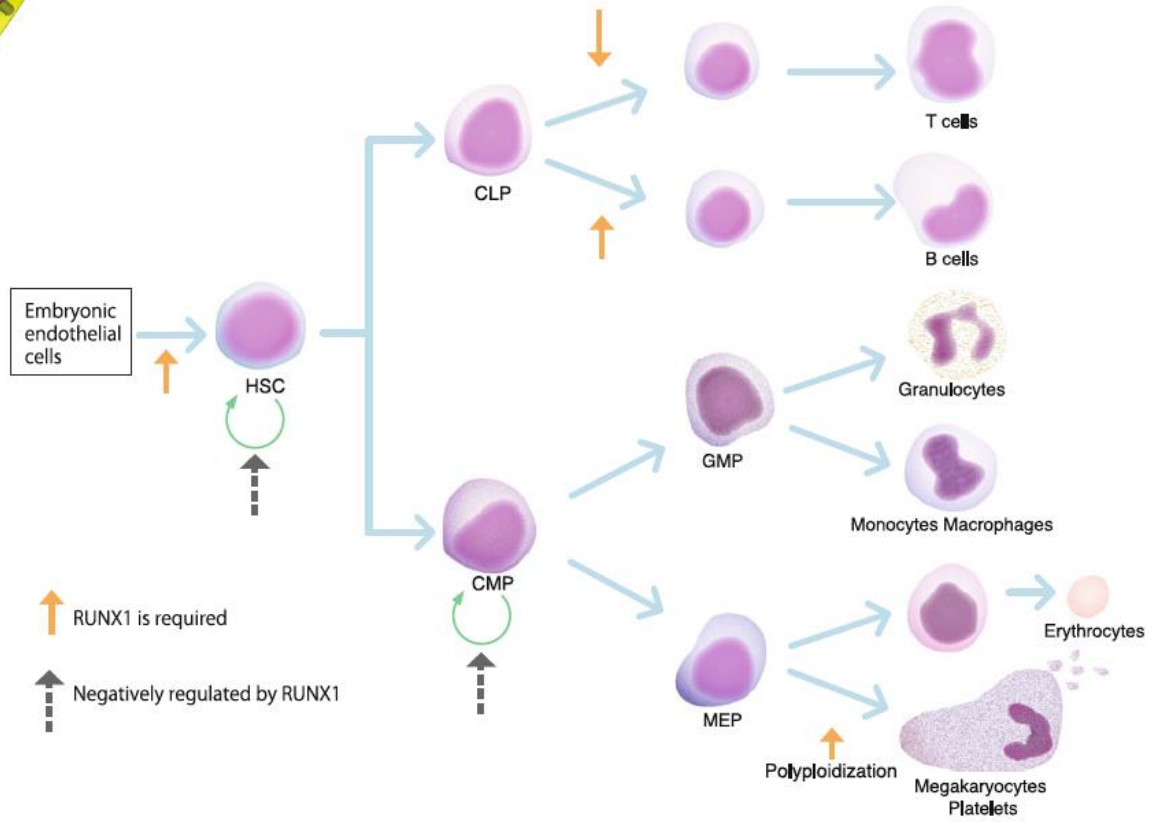


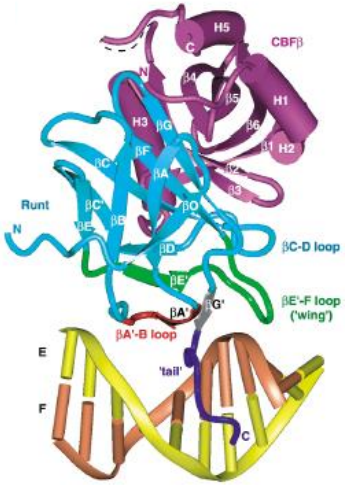
Oncogenesis and Development Section
Translational and Functional Genomics Branch
NHGRI, NIH



CBF complex regulates the differentiation of hematopoietic cells



M. Ichikawa et al, *Int J Hematol*, 2013



TGYGGTY

	Genes	Diseases & Development
a =	*RUNX1 (AML1)*	*leukemia/blood, neurons*
	RUNX2	*CCD/bone*
	RUNX3	*GI cancers/GI, hair, neurons*
b =	*CBFB*	*leukemia/blood, bone, etc.*

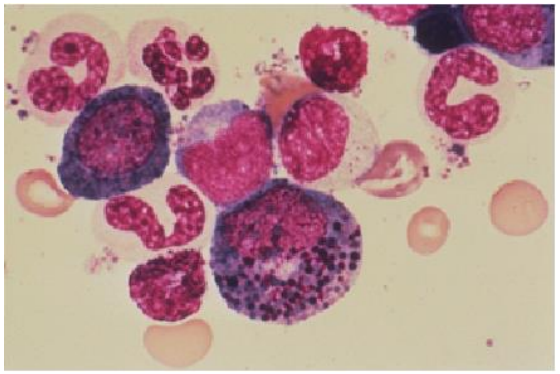
CBF genes in human leukemia

CBFB-MYH11	inv(16)	20-30% of AML
RUNX1-ETO	t(8;21)	
TEL-RUNX1	t(12;21)	20-30% of pediatric-ALL

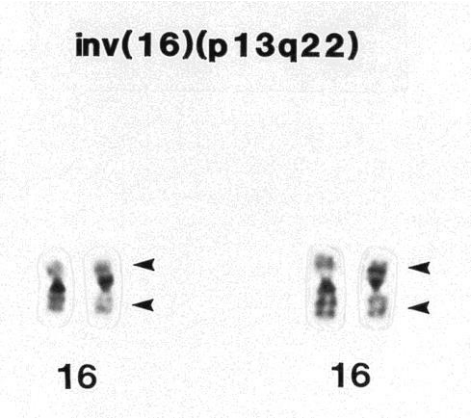
RUNX1 mutations in ~8-13% of de novo AML and 10% of MDS

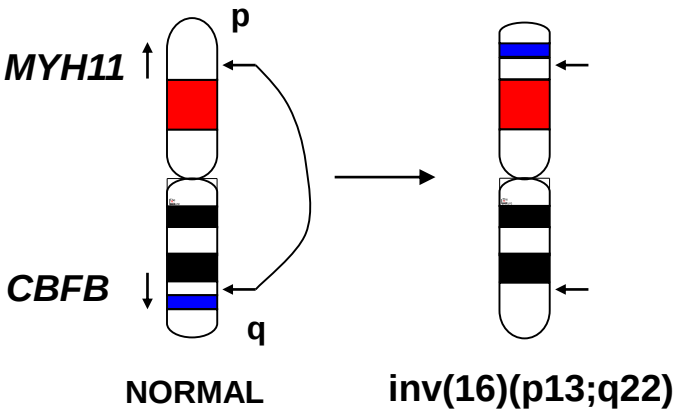
RUNX1 germline mutations lead to FPDMM

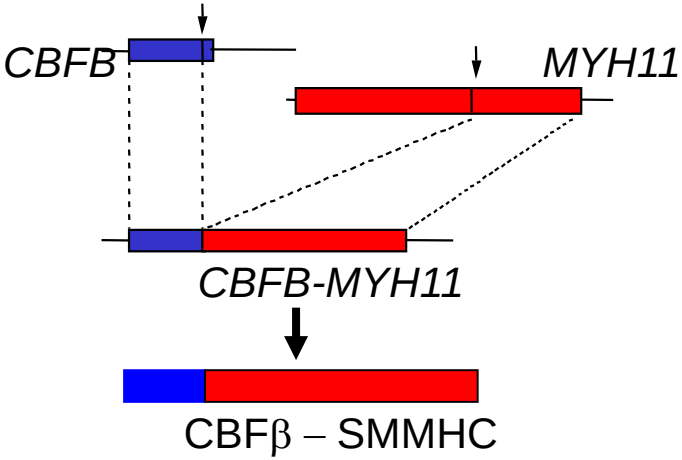
Chromosome 16 inversion in human AML



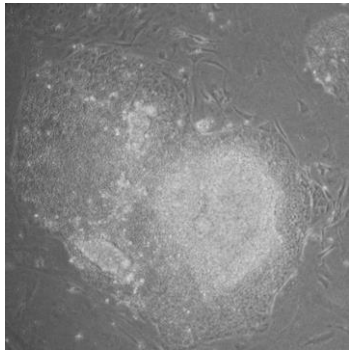
AML M4Eo





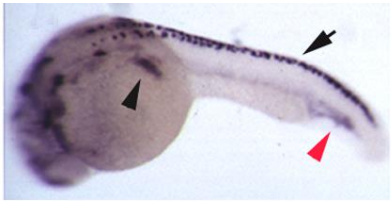


Liu et al., Science 261:1041, 1993

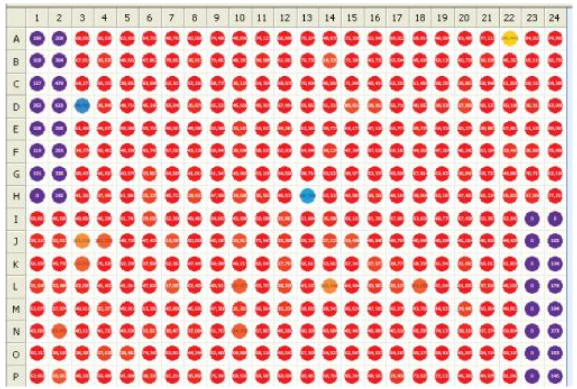


Hematopoiesis

Leukemia

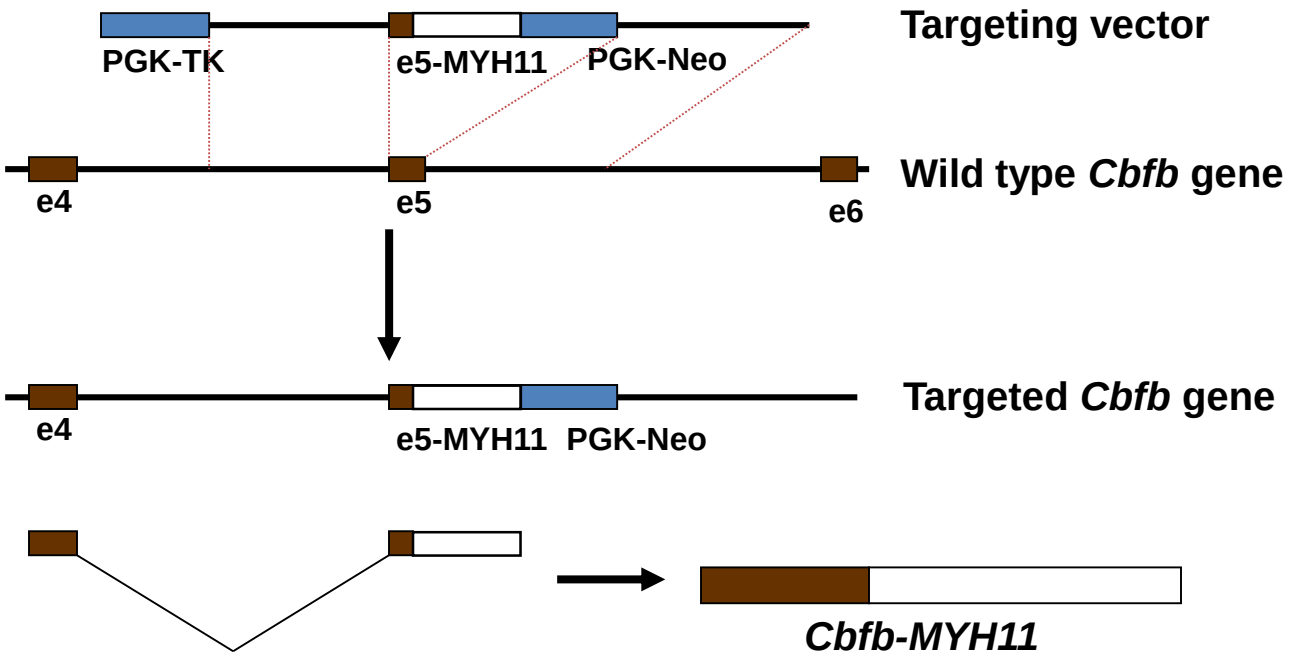


Translational Studies



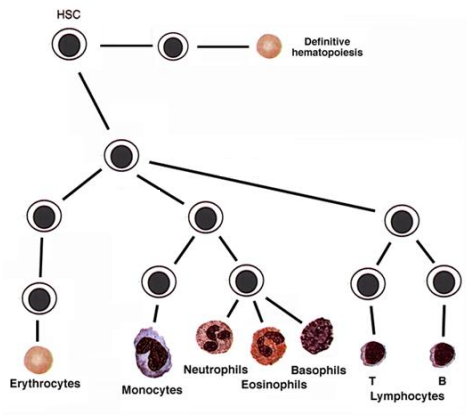
Genomics Genetics

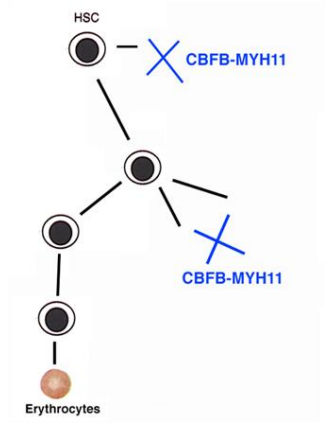
"Knock-in" strategy to recreate *Cbfb-MYH11* fusion in mouse ES cells

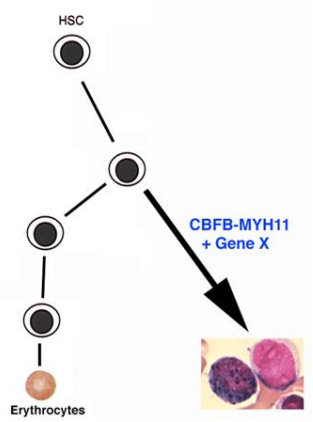


Castilla et al., Cell, 1996

Hematopoietic blockage and leukemogenesis by *CBFB-MYH11*



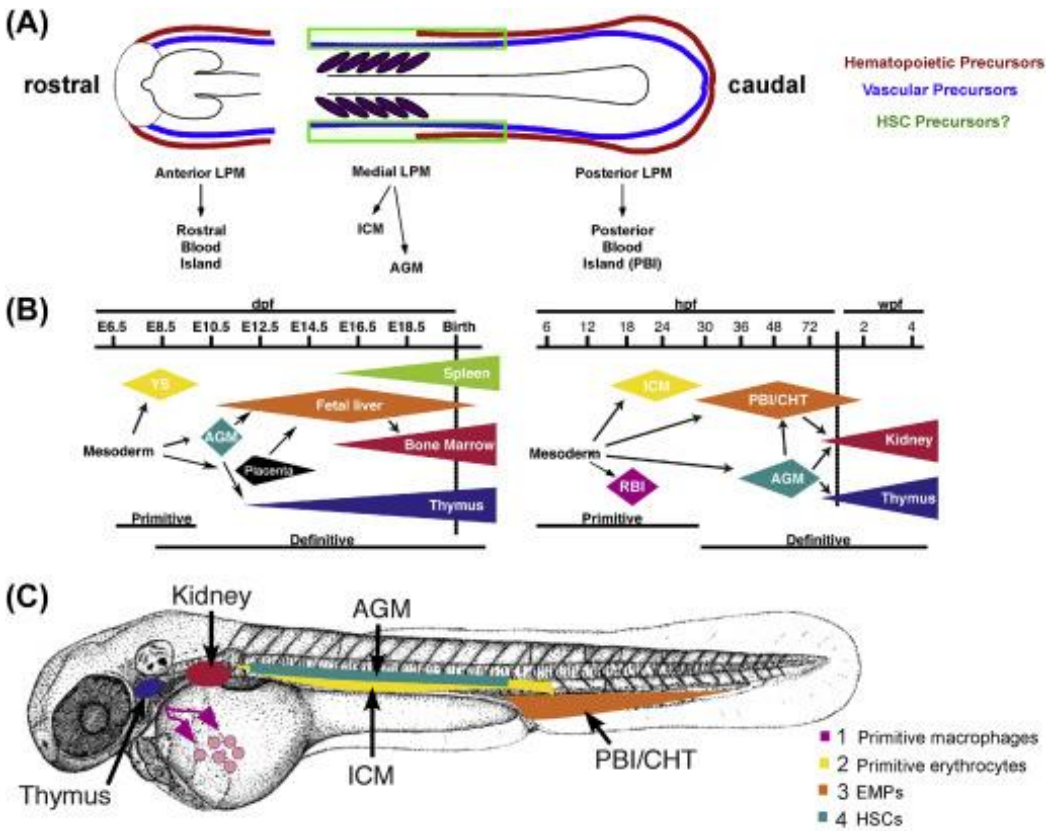




Leukemia

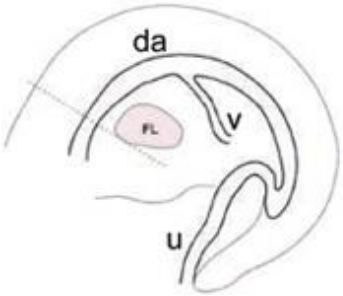
Castilla et al. Cell 1996
Castilla et al. Nat Genet 1999
Kundu et al. Blood 2002
Zhao et al. Blood 2007, 2012
Kamikubo et al., Cancer Cell 2010
Zhen et al., Blood 2017
Fei et al., PNAS 2018

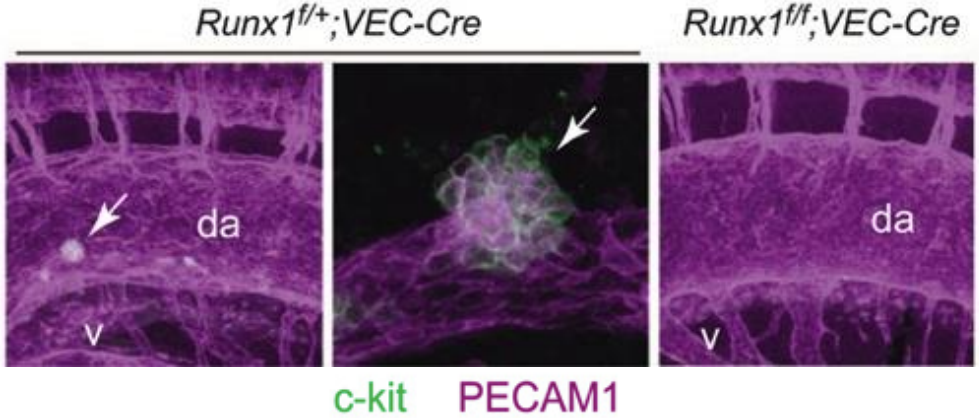
Zebrafish hematopoiesis

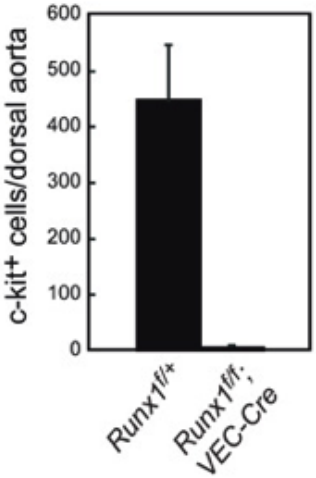


Stachura and Traver, Methods in Cell Biology 2016

Runx1 is required for the emergence of HSCs from AGM

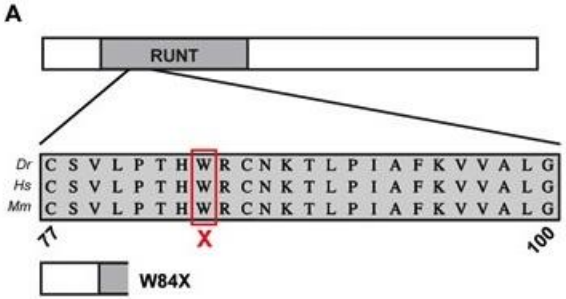




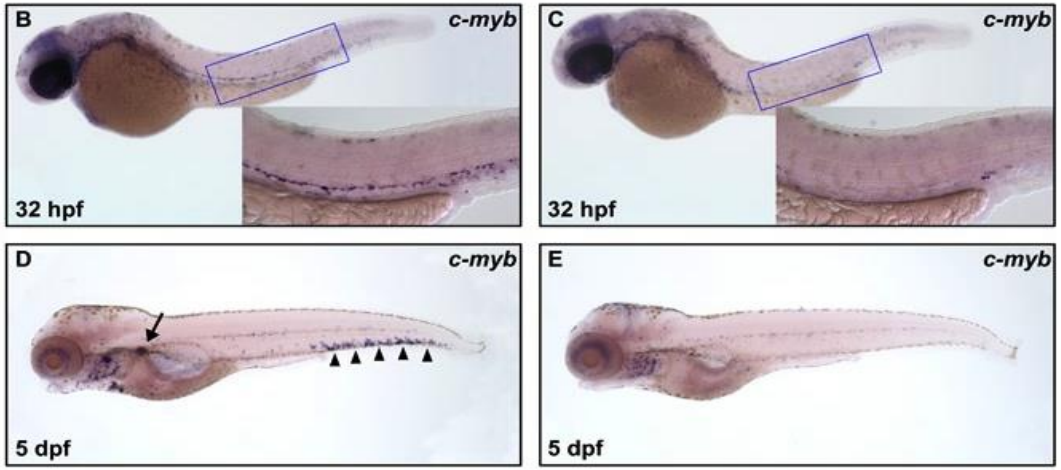


Chen *et al.*, Nature, 2009

ENU-induced point mutation



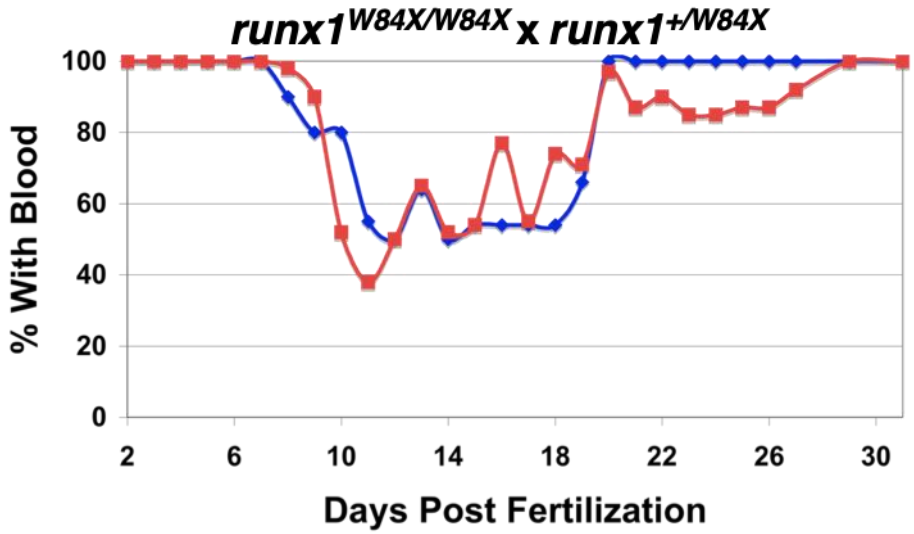
Wild type ***runx1$^{W84X/W84X}$***



Sood et al, Blood,2010

Recovery of hematopoiesis in *runx1*$^{W84X/W84X}$ larvae and survival of *runx1*$^{W84X/W84X}$ adult fish

dpf	Blood cells
1-8	Normal (prim. hemat.)
9-12	Gradual loss
10-18	Absent
14-20	Gradual recovery



Total	*runx1*$^{+/+}$	*runx1*$^{+/-}$	*runx1*$^{-/-}$
267	69	182	16
Expected	25%	50%	25%
Observed	25.84%	68.16%	5.99%

(*runx1*$^{-}$ = *runx1*^{W84X})

Sood et al, Blood,2010

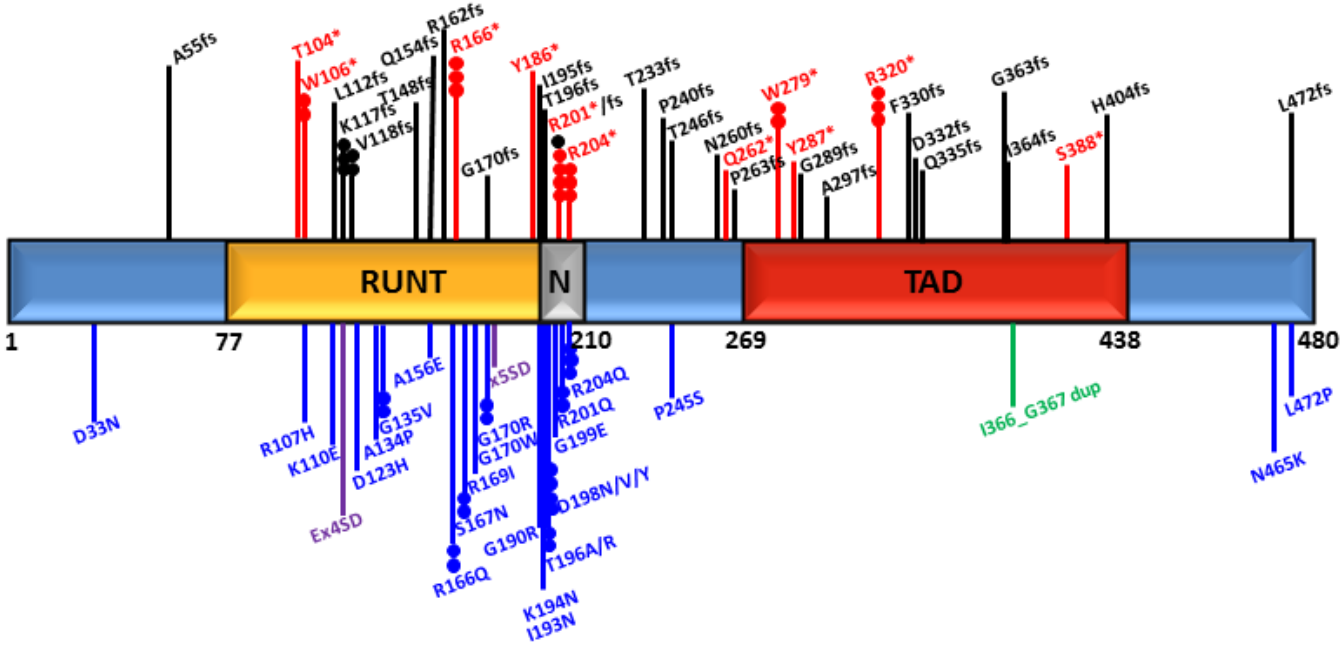
RUNX1 germline mutations lead to familial platelet disorder with associated myeloid malignancy (FPDMM)

- Rare, autosomal dominant disease
- Characterized by
  - Mild to moderate bleeding disorder
  - Immature megakaryocytes
  - Reduced platelet counts (thrombocytopenia)
  - Platelet function defects
  - Tendency to develop acute myeloid leukemia (AML)
    - 25-55% of FPD patients develop AML

Familial platelet disorder with associated myeloid malignancy (OMIM 601399)

***RUNX1* first HM gene, mutations identified 1999**

Over 120 probands reported



Adapted from Brown et al, Semin Hematol. **2017** 54(2):60-68

NIH RUNX1/FPD Clinical Research Program

- Paul Liu
  - Overall program leader
- Lea Cunningham
  - Clinical leader
- Matt Merguerian
  - Clinical Fellow
- Joie Davis
  - Genetic Counselor
- Research Nurse

https://clinicaltrials.gov/ct2/show/NCT03854318?term=RUNX1