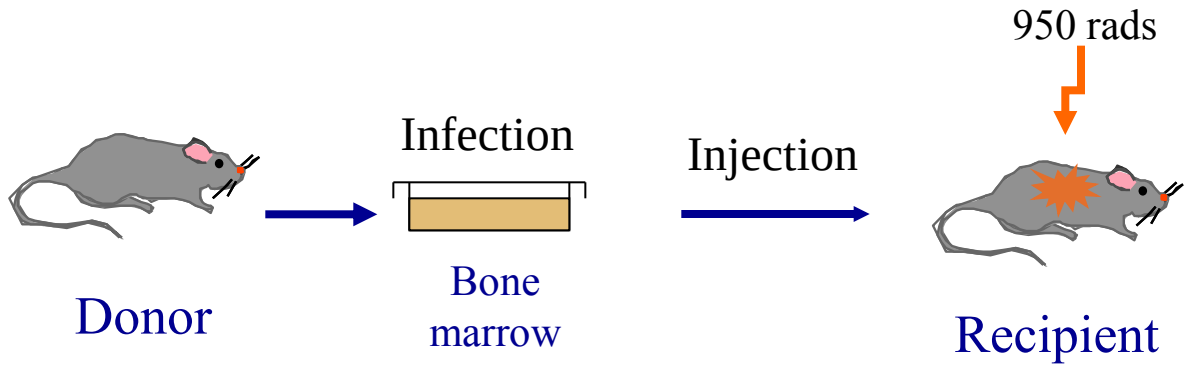
JAK2^{V617F} retroviral model

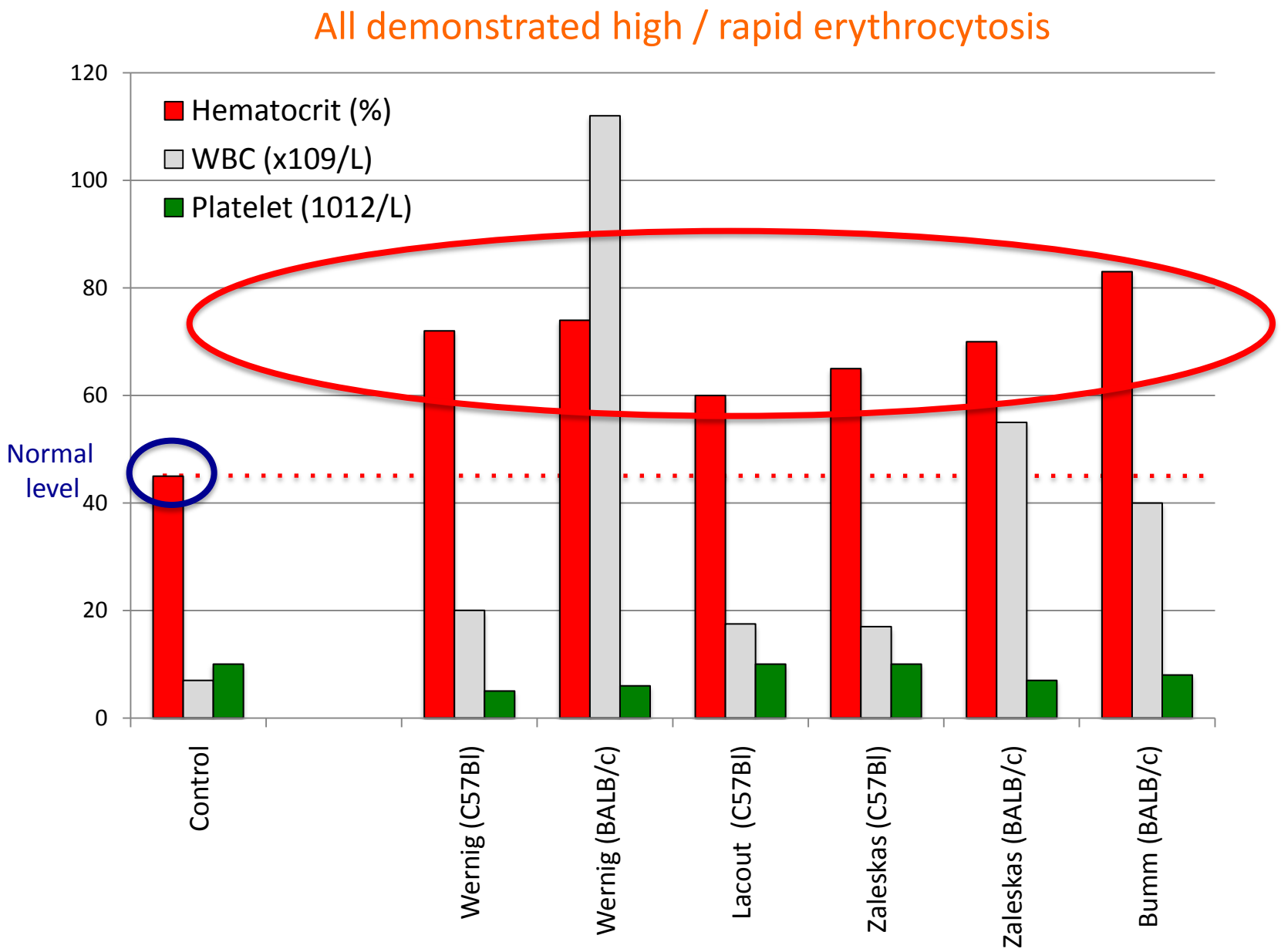
Principle: Adoptive transfer of bone marrow cells infected by a retrovirus expressing JAK2^{V617F}



Over-expression of JAK2^{V617F}
(up to 20-fold the endogenous JAK2^{WT} level)

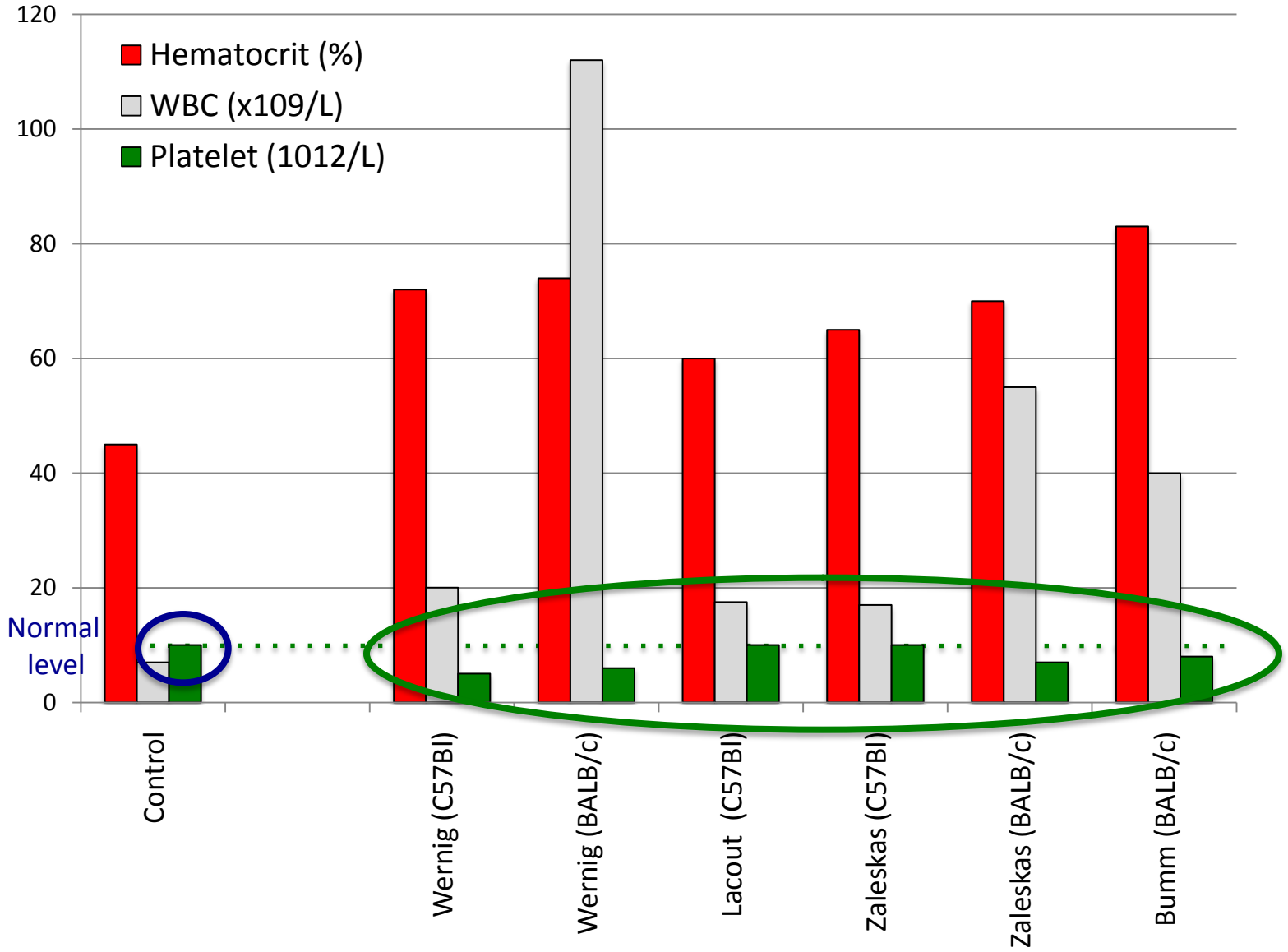
(Wernig et al. Blood 2006, Lacout et al. Blood 2006, Zaleskas et al. Plos One 2006, Bumm et al. Cancer res. 2006)

Retroviral models



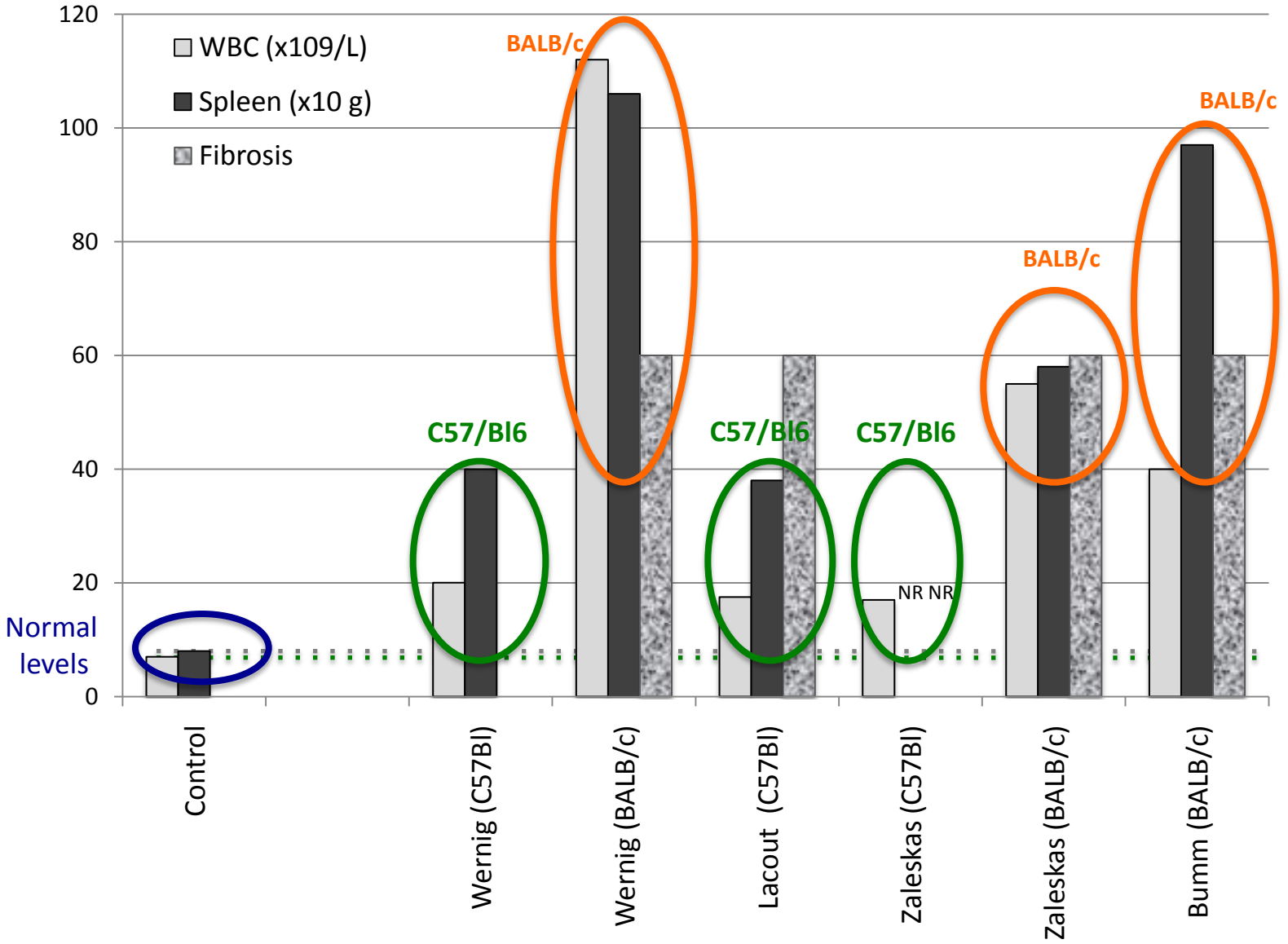
Retroviral models

Normal platelet levels



Retroviral models

Levels of myeloid hyperplasia and fibrosis depended on the mouse strains



Conclusions

1) Direct contribution of JAK2^{V617F} to pathogenesis of human PV

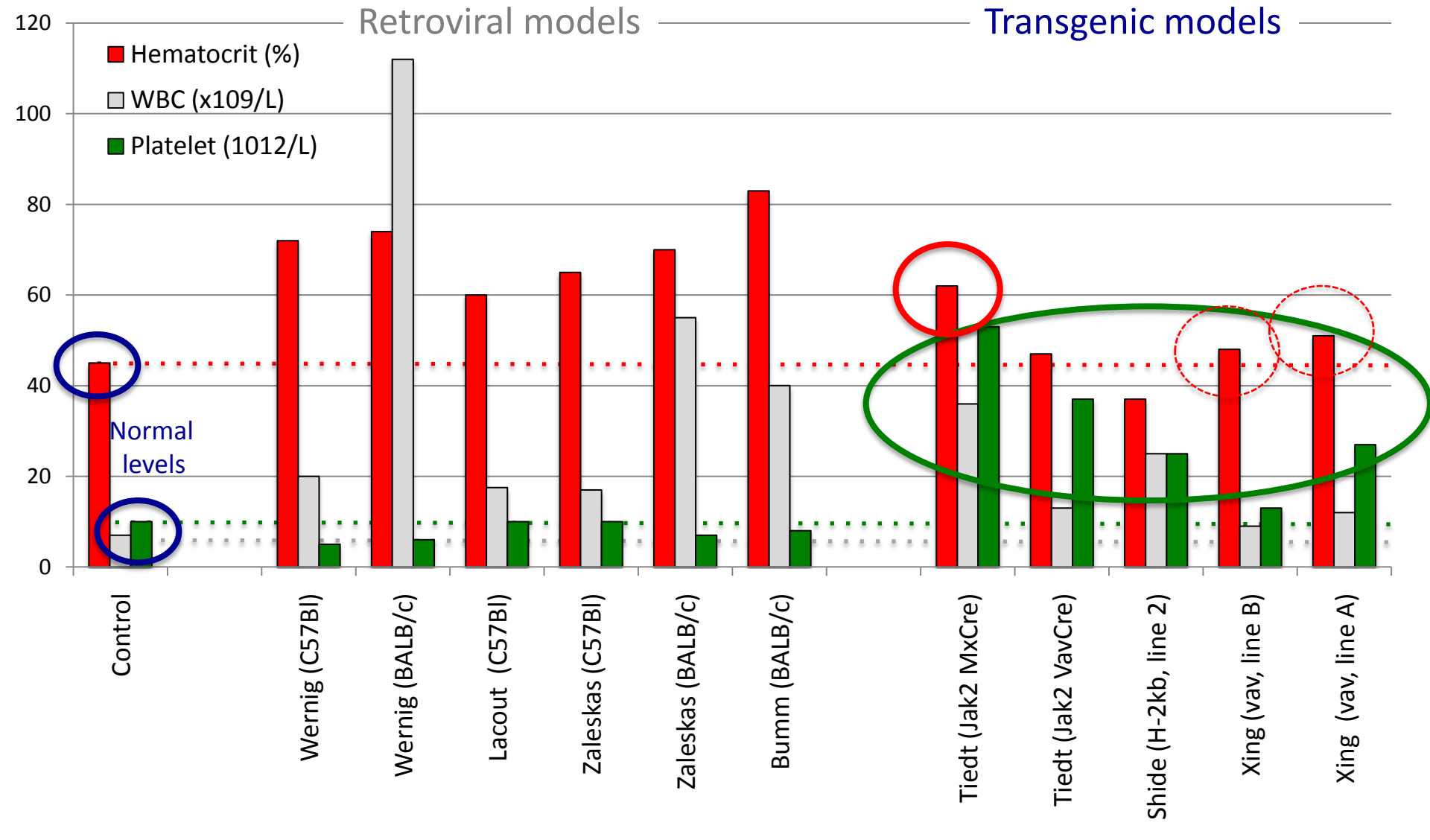
2) Genetic modifiers are involved in the diversity of JAK2^{V617F}-positive MPN.

1) High sustained JAK2^{V617F} expression is sufficient for myelofibrosis. Fibrosis is the "natural" evolution of the disease without the need of an additional defect.

1) High JAK2^{V617F} expression does not induce high platelet level (no ET-phenotype)

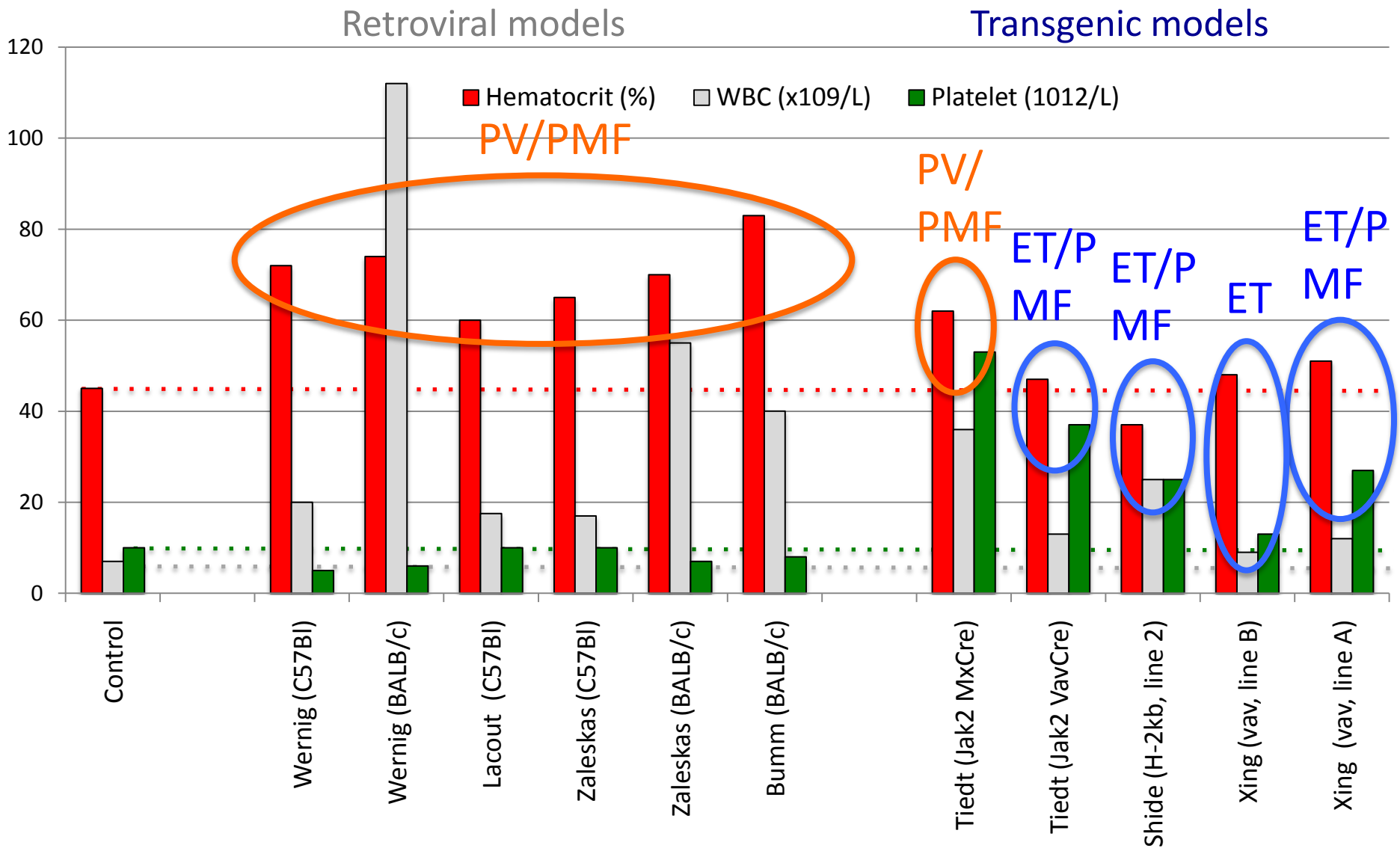
Transgenic models

In contrast to RV models, most TG models developed thrombocytemia with mild or no polycythemia



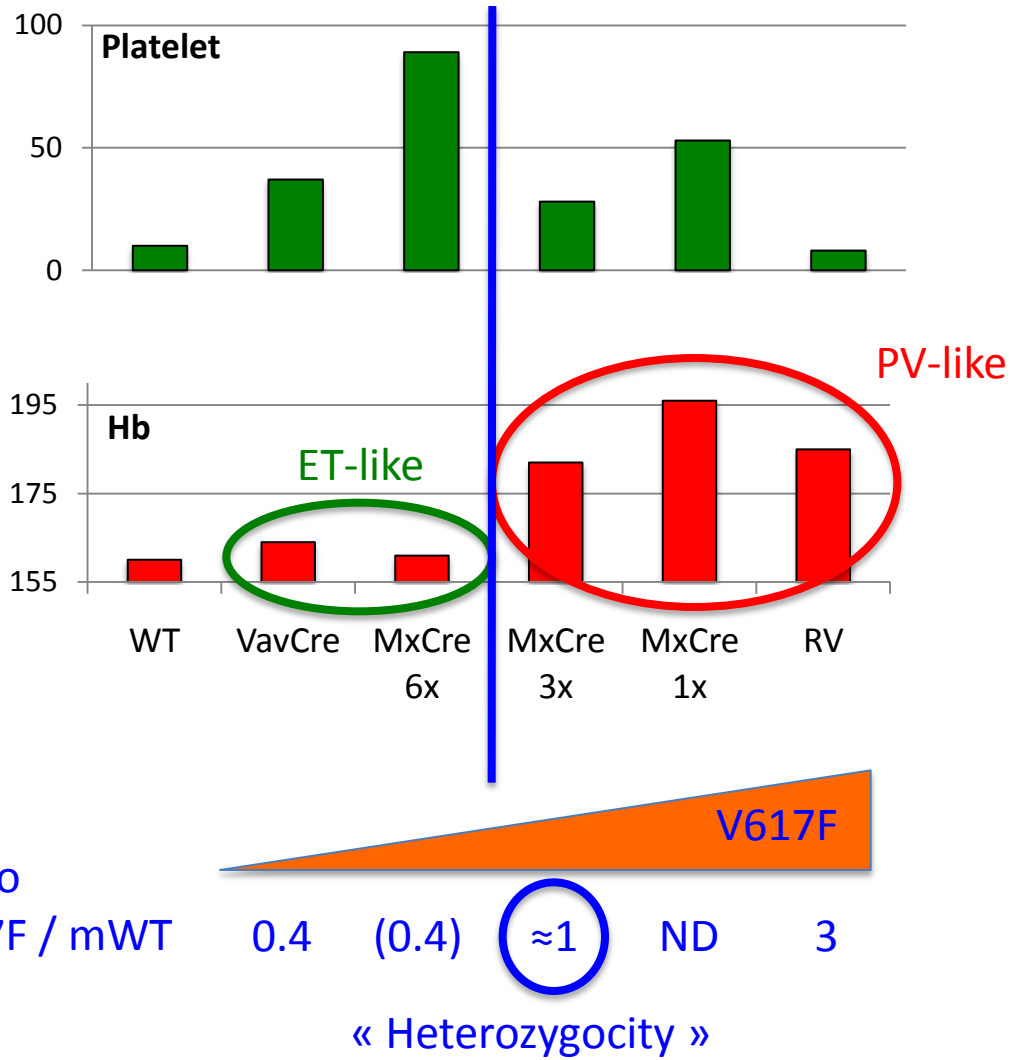
Transgenic models

Most develop ET or «fruste ET»-like phenotypes



MPD phenotypes in TG mice depend on the V617F/WT ratio

(Tiedt et al. Blood 2008)



Dosage hypothesis

KI models

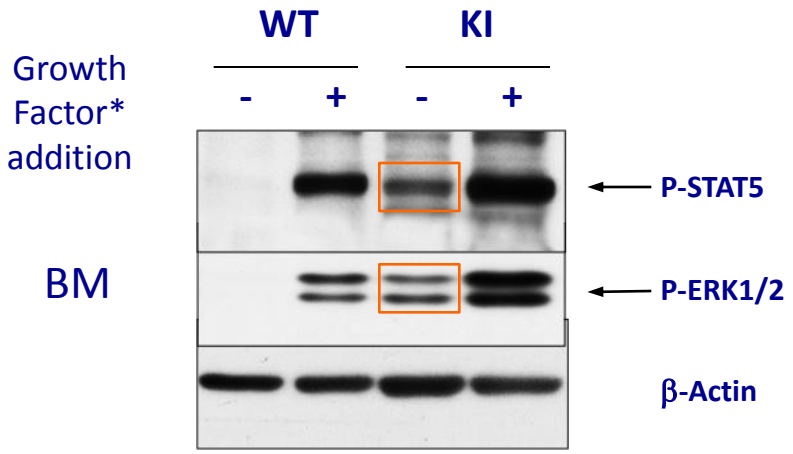
Given the crucial ratio $JAK2^{V617F}$ / $JAK2^{WT}$ in disease phenotype, KI models seem mandatory to faithfully model the human disease

1) Constitutive KI * (Germline) => inherited MPN

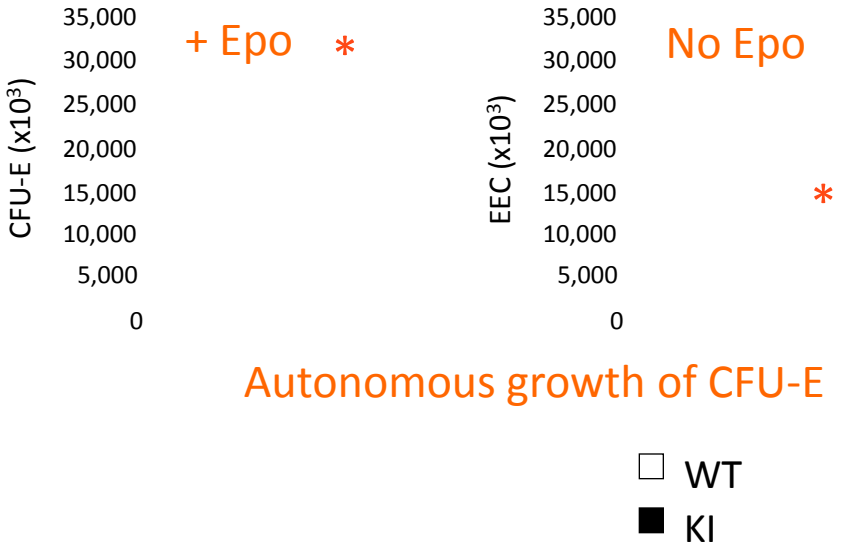
2) Conditional KI (Cre-dependent) => acquired MPN

* Marty et al Blood 2010

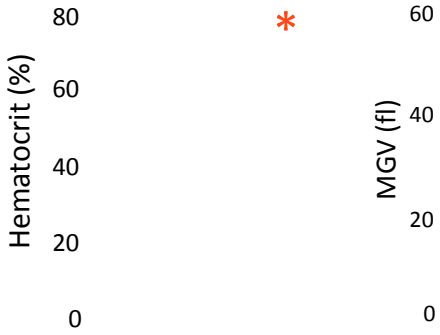
Constitutive KI



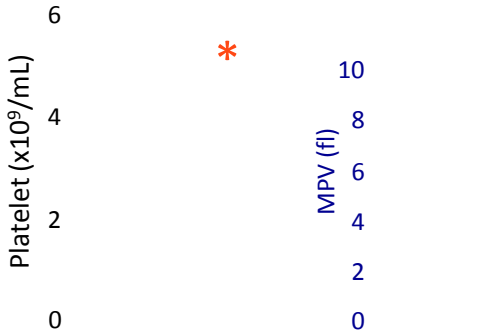
Constitutive activation
JAK/Stat pathway



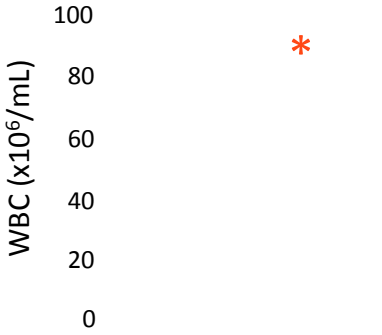
Autonomous growth of CFU-E



Erythrocytosis
(microcytosis)



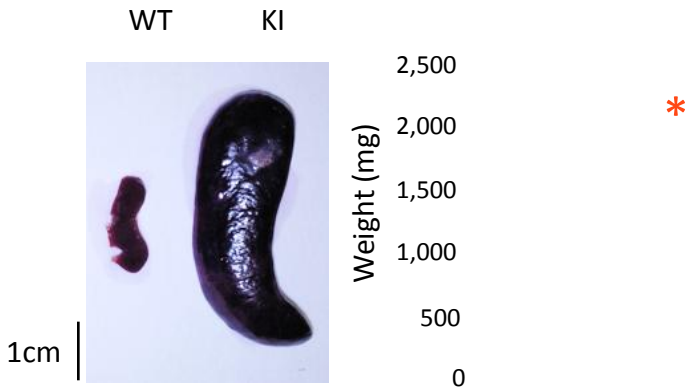
Thrombocytemia
(large platelets)



Leucocytosis

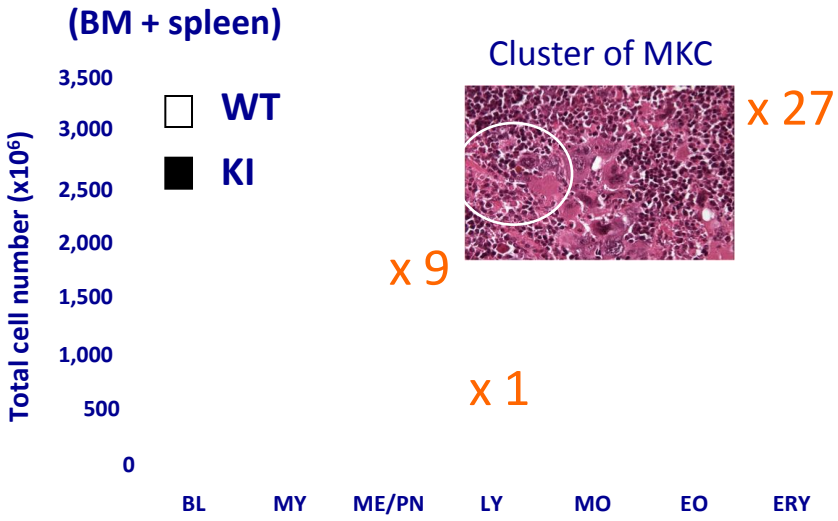
- n=11
- 12±2 weeks of age

Constitutive KI



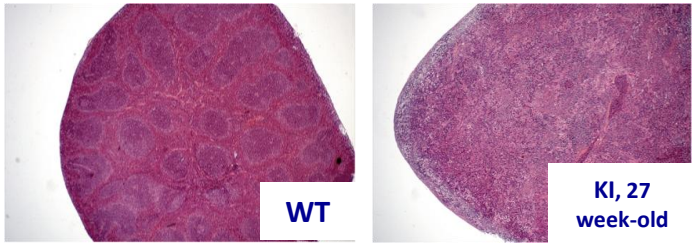
*

Splenomegaly



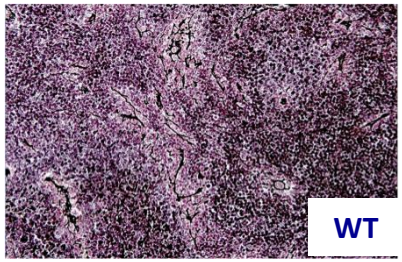
Trilineage hyperplasia (early stage)

HES staining

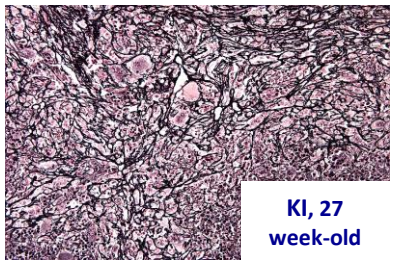


Spreading of the red pulp (myeloid)

Silver staining



Grade I



Grade III
Fibrosis (late stage)

Conclusions

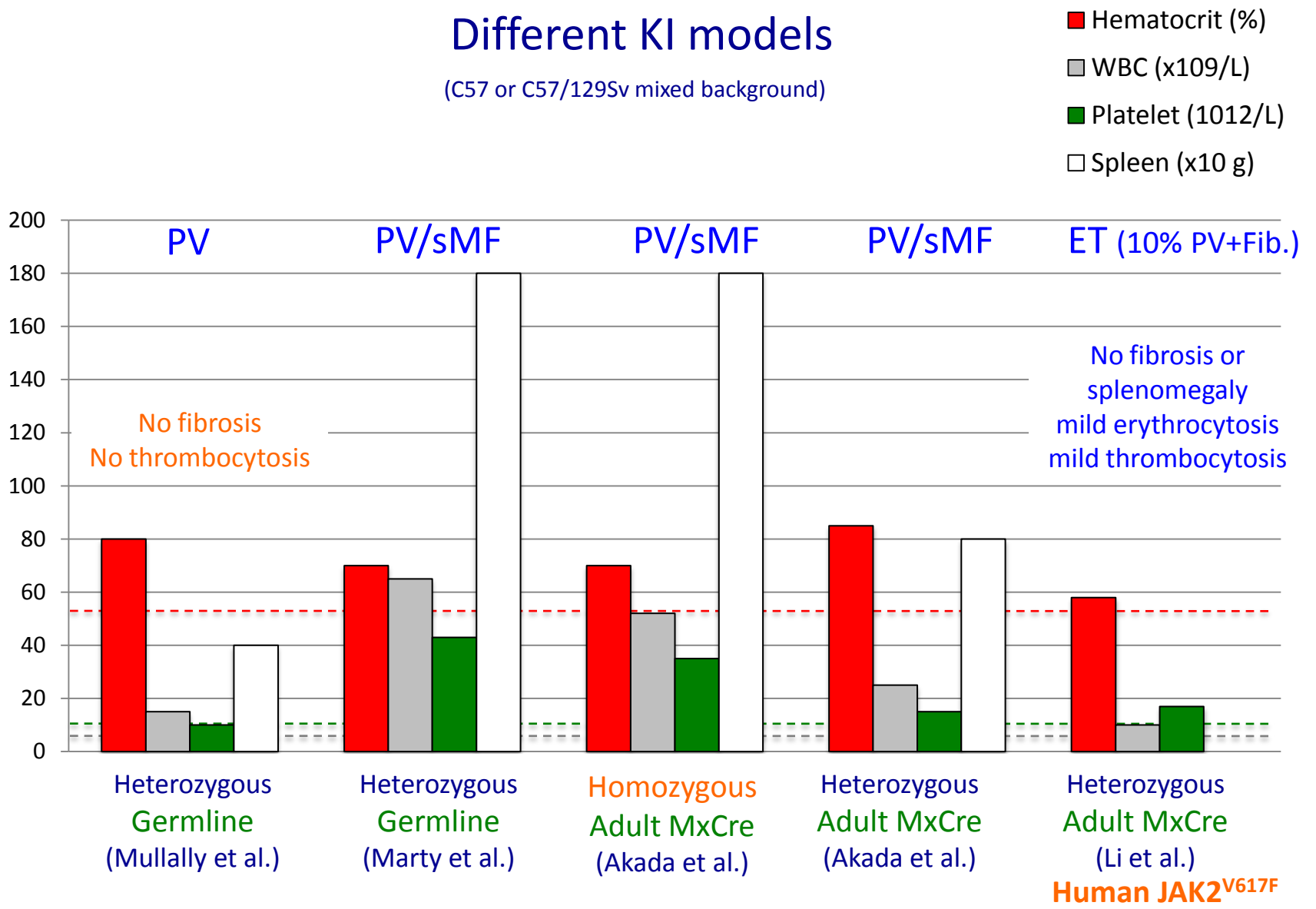
Heterozygous expression of $JAK2^{V617F}$ results in a PV-like disease followed by secondary myelofibrosis

≈

Opposite to what is expected from patient studies where heterozygocity is usually associated with ET and not PV

Different KI models

(C57 or C57/129Sv mixed background)



No change in LSK
"Minor competitive advantage"
(LSK/myeloid)

2-3-fold increase in LSK

Stem cell impairment

Some lessons from animal models

- Heterozygous expression of mJAK2^{V617F} does not lead to ET-phenotype.

Reason unknown, species differences?

- JAK2^{V617F} confers a minor competitive advantage to stem cells

Fits well with a disease appearing late in human life
Would a single stem cell expressing JAK2^{V617F} compete with normal hematopoiesis?
How long will it take for disease appearance?

- JAK2^{V617F} is sufficient for phenotype pleiotropy of MPN (PV / ET and MF) depending on gene dosage and genetic background

Why would other genetic defects be required for MPN?

$\Rightarrow$ For JAK2^{V617F} occurrence in human (initiating/"mutator")
$\Rightarrow$ For clonal dominance if JAK2^{V617F} works differently in human than in mice
=> For accelerating the disease (TET2, EZH2 or ASXL1 frequent in human PMF)

➔ Novel animal models combining JAK2^{V617F} and others defects are needed

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