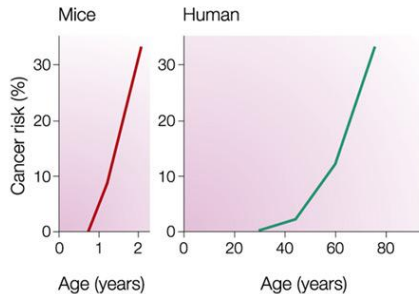


« Mice are not small people »

A. Rangarajan & Weinberg R. Nature Reviews Cancer 3, 952-959. 2003.



Nature Reviews | Cancer



HOW MICE DIFFER FROM HUMANS

- Cancers tend to form in different types of tissue
- Tumours have fewer chromosomal abnormalities
- Ends of chromosomes (telomeres) are longer
- Telomere-repairing enzyme (telomerase) active in cells
- Short lifespan
- Fewer cell divisions (10^{11}) during life than humans (10^{16})
- Metabolic rate seven times higher than humans
- Lab mice highly inbred and genetically similar

Most common age-related neoplasm

Humans in the West = Epithelial

- * Basal-cell carcinoma of skin
- * Breast carcinoma
- * Prostate carcinoma
- * Squamous-cell carcinoma of skin
- * Lung carcinoma
- * Colorectal carcinoma
- * Urinary bladder carcinoma
- * Melanoma
- * Uterine carcinoma
- * Kidney and renal pelvis carcinoma

laboratory mice = Mesenchymal

- * Lymphoma
- * Sarcoma
- * Leukaemia
- * Lung adenoma and carcinoma
- * Hepatoma and hepatic carcinoma
- * Histiocytic sarcoma
- * Fibrosarcoma
- * Haemangiosarcoma
- * Osteosarcoma
- * Leiomyosarcoma

Mice share 99% of their genes with humans.

Mice have a tremendous value as models in human disease.

Main classical MPN murin models (with Myelofibrosis)

Mouse models	Methods	Defect in Human MPN	Type of MPN model	Mouse phenotype	Ref.
TPO ^{high}	RV, Ad, TG	No	PMF (MF 3 month, 7 months survival)	Megakaryocyte hyperplasia and dysplasia, anemia, thrombocytosis, end in pancytopenia, splenomegaly, EMH, osteosclerosis,	Yan et al. Blood 1996-Villeval et al. Blood 1997
GATA ^{low} (MKC-specific hypomorph)	Deletion of regulatory regions	No	PMF (CD1 strain, MF in >1 year)	Megakaryocyte hyperplasia and dysplasia (immature), thrombocytopenia, (anemia), splenomegaly, EMH, osteosclerosis,	Vannucci et al. Blood 2002
LNK-/-	KO	Yes	Myeloid/Lymphoid neoplasm + MF	Megakaryocyte hyperplasia and dysplasia, splenomegaly, Lymphoi/myeloid hyperplasia, leukocytosis, thrombocytosis, EMH, viable	Velazquez et al. J. Exp. Med. 2004
hBACH1 TG	TG	No	Fibrosis	Megakaryocyte dysplasia (immature), thrombocytopenia, EMH	Toki et al. Blood 2005
JAK2 ^{V617F}	RV, TG, KI	Yes	PV, PMF, (ET) MF 1-3 months	Megakaryocyte hyperplasia and dysplasia, <i>anemia, (thrombocytosis), (pancytopenia), splenomegaly, EMH, osteosclerosis, myeloid hyperplasia.</i>	Werning et al. 2006, Tiedt et al. 2008, Akada et al. 2010
MPL ^{W515L}	RV	Yes	PMF (<1 month survival)	Megakaryocyte hyperplasia and dysplasia, thrombocytosis, leukocytosis, splenomegaly, EMH, osteosclerosis, myeloid hyperplasia.	Pikman et al. PLoS Med. 2006
« Trisomy 21 model» Ts65Dn	TG + 104 Chr. 21 orthologs)	?	PMF (≈1 year for MF)	Megakaryocyte hyperplasia and dysplasia, thrombocytosis, mild anemia, EMH, BM granulocyte hyperplasia.	Kirsammer et al. Blood 2008
C- <i>Myb</i> ^{E308G/E308G} (loss of function)	ENU mutagenesis	No	ET - PMF	Megakaryocyte hyperplasia and dysplasia, anemia, thrombocytosis, splenomegaly with myeloid hyperplasia, increase HSC response	Papathanasiou et al. Blood 2010

All involve MKC hyperplasia / dysplasia

Mouse models	Methods	Defect in Human MPN	Type of MPN model	Mouse phenotype	Ref.
TPO ^{high}	RV, Ad, TG	No	PMF (MF 3month, 7 months survival)	Megakaryocyte hyperplasia and dysplasia , anemia, thrombocytosis, end in pancytopenia, splenomegaly, EMH, osteosclerosis,	Yan et al. Blood 1996-Villeval et al. Blood 1997
GATA ^{low} (MKC-specific hypomorph)	Deletion of regulatory regions	No	PMF (CD1 strain, MF in >1 year)	Megakaryocyte hyperplasia and dysplasia (immature) , thrombocytopenia, (anemia), splenomegaly, EMH, osteosclerosis,	Vannucci et al. Blood 2002
LNK-/-	KO	Yes	Myeloid/Lymphoid neoplasm + MF	Megakaryocyte hyperplasia and dysplasia , splenomegaly, Lymphoi/myeloid hyperplasia, leukocytosis, thrombocytosis, EMH, viable	Velazquez et al. J. Exp. Med. 2004
hBACH1 TG	TG	No	Fibrosis	Megakaryocyte dysplasia (immature), thrombocytopenia, EMH	Toki et al. Blood 2005
JAK2 ^{V617F}	RV, TG, KI	Yes	PV, PMF, (ET) MF 1-3months	Megakaryocyte hyperplasia and dysplasia , anemia, (thrombocytosis), (pancytopenia), splenomegaly, EMH, osteosclerosis, myeloid hyperplasia.	Werning et al. 2006, Tiedt et al. 2008, Akada et al. 2010
MPL ^{W515L}	RV	Yes	PMF (<1 month survival)	Megakaryocyte hyperplasia and dysplasia , thrombocytosis, leukocytosis, splenomegaly, EMH, osteosclerosis, myeloid hyperplasia.	Pikman et al. PLoS Med. 2006
« Trisomy 21 model» Ts65Dn	TG + 104 Chr. 21 orthologs)	?	PMF (≈1 year for MF)	Megakaryocyte hyperplasia and dysplasia , thrombocytosis, mild anemia, EMH, BM granulocyte hyperplasia.	Kirsammer et al. Blood 2008
C-Myb ^{E308G/E308G} (loss of function)	ENU mutagenesis	No	ET - PMF	Megakaryocyte hyperplasia and dysplasia , anemia, thrombocytosis, splenomegaly with myeloid hyperplasia, increase HSC response	Papathanasiou et al. Blood 2010

Most involve MPL hyper signaling

Mouse models	Methods	Defect in Human MPN	Type of MPN model	Mouse phenotype	Ref.
TPO^{high} TPO overproduction	RV, Ad, TG	No	PMF (MF 3month, 7 months survival)	Megakaryocyte hyperplasia and dysplasia, anemia, thrombocytosis , end in pancytopenia, splenomegaly, EMH, osteosclerosis,	Yan et al. Blood 1996-Villeval et al. Blood 1997
GATA ^{low} (MKC-specific hypomorph)	Deletion of regulatory regions	No	PMF (CD1 strain, MF in >1 year)	Megakaryocyte hyperplasia and dysplasia (immature), thrombocytopenia, (anemia), splenomegaly, EMH, osteosclerosis,	Vannucci et al. Blood 2002
LNK-/- Negative regulator	KO	Yes	Myeloid/Lymphoid neoplasm + MF	Megakaryocyte hyperplasia and dysplasia, splenomegaly, Lymphoi/myeloid hyperplasia, leukocytosis, thrombocytosis , EMH, viable	Velazquez et al. J. Exp. Med. 2004
hBACH1 TG	TG	No	Fibrosis	Megakaryocyte dysplasia (immature), thrombocytopenia, EMH	Toki et al. Blood 2005
JAK2^{V617F} (gain of function)	RV, TG, KI	Yes	PV, PMF, (ET) MF 1-3months	Megakaryocyte hyperplasia and dysplasia, anemia, (thrombocytosis), (pancytopenia), splenomegaly, EMH, osteosclerosis, myeloid hyperplasia.	Werning et al. 2006, Tiedt et al. 2008, Akada et al. 2010
MPL^{W515L} (gain of function)	RV	Yes	PMF (<1 month survival)	Megakaryocyte hyperplasia and dysplasia, thrombocytosis , leukocytosis, splenomegaly, EMH, osteosclerosis, myeloid hyperplasia.	Pikman et al. PLoS Med. 2006
« Trisomy 21 model» Ts65Dn	TG + 104 Chr. 21 orthologs)	?	PMF (≈1 year for MF)	Megakaryocyte hyperplasia and dysplasia, thrombocytosis, mild anemia, EMH, BM granulocyte hyperplasia.	Kirsammer et al. Blood 2008
C- <i>Myb</i> ^{E308G/E308G} (loss of function)	ENU mutagenesis	No	ET - PMF	Megakaryocyte hyperplasia and dysplasia, anemia, thrombocytosis, splenomegaly with myeloid hyperplasia, increase HSC response	Papathanasiou et al. Blood 2010

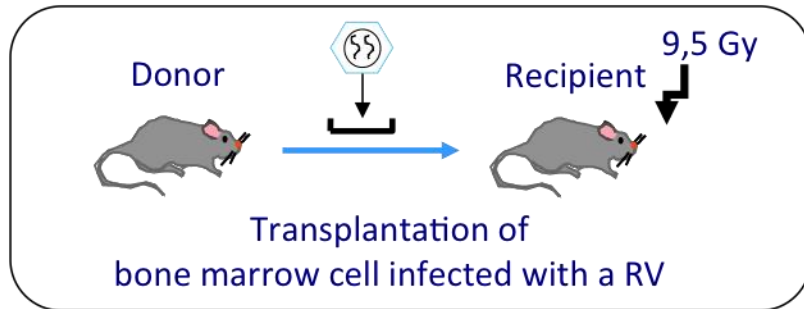
Some involve a blockage of MKC differentiation

Mouse models	Methods	Defect in Human MPN	Type of MPN model	Mouse phenotype	Ref.
TPO ^{high}	RV, Ad, TG	No	PMF (MF 3month, 7 months survival)	Megakaryocyte hyperplasia and dysplasia, anemia, thrombocytosis, end in pancytopenia, splenomegaly, EMH, osteosclerosis,	Yan et al. Blood 1996-Villeval et al. Blood 1997
GATA ^{low} (MKC-specific hypomorph)	Deletion of regulatory regions	No	PMF (CD1 strain, MF in >1 year)	Megakaryocyte hyperplasia and dysplasia (immature), thrombocytopenia , (anemia), splenomegaly, EMH, osteosclerosis,	Vannucci et al. Blood 2002
LNK-/-	KO	Yes	Myeloid/Lymphoid neoplasm + MF	Megakaryocyte hyperplasia and dysplasia, splenomegaly, Lymphoid/myeloid hyperplasia, leukocytosis, thrombocytosis, EMH, viable	Velazquez et al. J. Exp. Med. 2004
hBACH1	TG	No	Fibrosis	Megakaryocyte dysplasia (immature), thrombocytopenia , EMH	Toki et al. Blood 2005
JAK2 ^{V617F}	RV, TG, KI	Yes	PV, PMF, (ET) MF 1-3months	Megakaryocyte hyperplasia and dysplasia, <i>anemia, (thrombocytosis), (pancytopenia), splenomegaly, EMH, osteosclerosis, myeloid hyperplasia.</i>	Werning et al. 2006, Tiedt et al. 2008, Akada et al. 2010
MPL ^{W515L}	RV	Yes	PMF (<1 month survival)	Megakaryocyte hyperplasia and dysplasia, thrombocytosis, leukocytosis, splenomegaly, EMH, osteosclerosis, myeloid hyperplasia.	Pikman et al. PLoS Med. 2006
« Trisomy 21 model» Ts65Dn	TG + 104 Chr. 21 orthologs)	?	PMF (≈1 year for MF)	Megakaryocyte hyperplasia and dysplasia, thrombocytosis, mild anemia, EMH, BM granulocyte hyperplasia.	Kirsammer et al. Blood 2008
C-Myb ^{E308G/E308G} (loss of function)	ENU mutagenesis	No	ET - PMF	Megakaryocyte hyperplasia and dysplasia, anemia, thrombocytosis, splenomegaly with myeloid hyperplasia, increase HSC response	Papathanasiou et al. Blood 2010

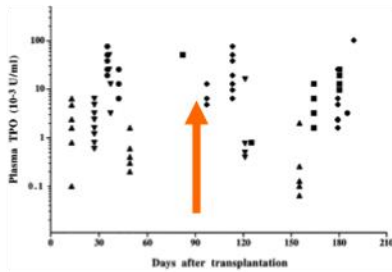
Mouse models	Methods	Defect in Human MPN	Type of MPN model	Mouse phenotype	Ref.
TPO ^{high}	RV, Ad, TG	No	PMF (MF 3month, 7 months survival)	Megakaryocyte hyperplasia and dysplasia, anemia, thrombocytosis, end in pancytopenia, splenomegaly, EMH, osteosclerosis,	Yan et al. Blood 1996-Villeval et al. Blood 1997
GATA ^{low} (MKC-specific hypomorph)	Deletion of regulatory regions	No	PMF (CD1 strain, MF in >1 year)	Megakaryocyte hyperplasia and dysplasia (immature), thrombocytopenia, (anemia), splenomegaly, EMH, osteosclerosis,	Vannucci et al. Blood 2002
LNK-/-	KO	Yes	Myeloid/Lymphoid neoplasm + MF	Megakaryocyte hyperplasia and dysplasia, splenomegaly, Lymphoi/myeloid hyperplasia, leukocytosis, thrombocytosis, EMH, viable	Velazquez et al. J. Exp. Med. 2004
hBACH1 TG	TG	No	Fibrosis	Megakaryocyte dysplasia (immature), thrombocytopenia, EMH	Toki et al. Blood 2005
JAK2 ^{V617F}	RV, TG, KI	Yes	PV, PMF, (ET) MF 1-3months	Megakaryocyte hyperplasia and dysplasia, <i>anemia, (thrombocytosis), (pancytopenia), splenomegaly, EMH, osteosclerosis, myeloid hyperplasia.</i>	Werning et al. 2006, Tiedt et al. 2008, Akada et al. 2010
MPL ^{W515L}	RV	Yes	PMF (<1 month survival)	Megakaryocyte hyperplasia and dysplasia, thrombocytosis, leukocytosis, splenomegaly, EMH, osteosclerosis, myeloid hyperplasia.	Pikman et al. PLoS Med. 2006
« Trisomy 21 model» Ts65Dn	TG + 104 Chr. 21 orthologs)	No	PMF (≈1 year for MF)	Megakaryocyte hyperplasia and dysplasia, thrombocytosis, mild anemia, EMH, BM granulocyte hyperplasia.	Kirsammer et al. Blood 2008
C-Myb ^{E308G/E308G} (loss of function)	ENU mutagenesis	No	ET - PMF	Megakaryocyte hyperplasia and dysplasia, anemia, thrombocytosis, splenomegaly with myeloid hyperplasia, increase HSC response	Papathanasiou et al. Blood 2010

TPO^{high} model $\approx$ MPL constitutive activation (MPL^{W515L})

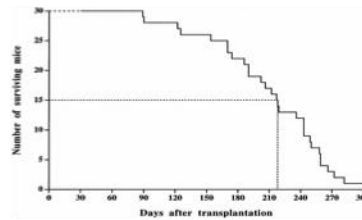
(Yan et al. Blood 1996-Villeval et al. Blood 1997) (Pickman et al. Plos 2006)



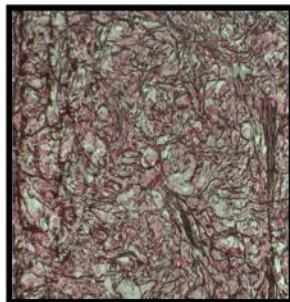
High serum TPO level



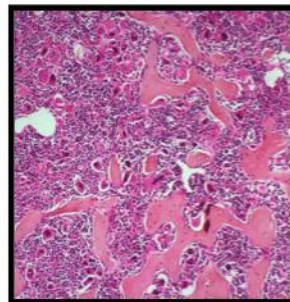
Low survival (7months)



Splenomegaly



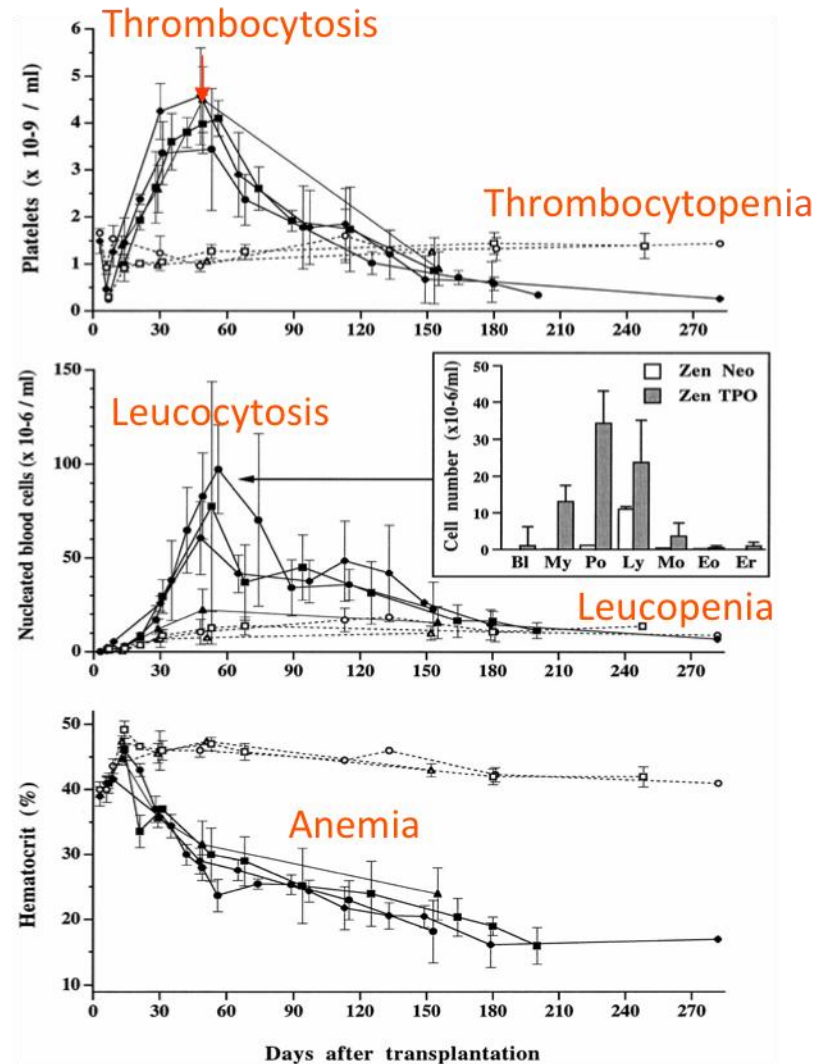
Fibrosis



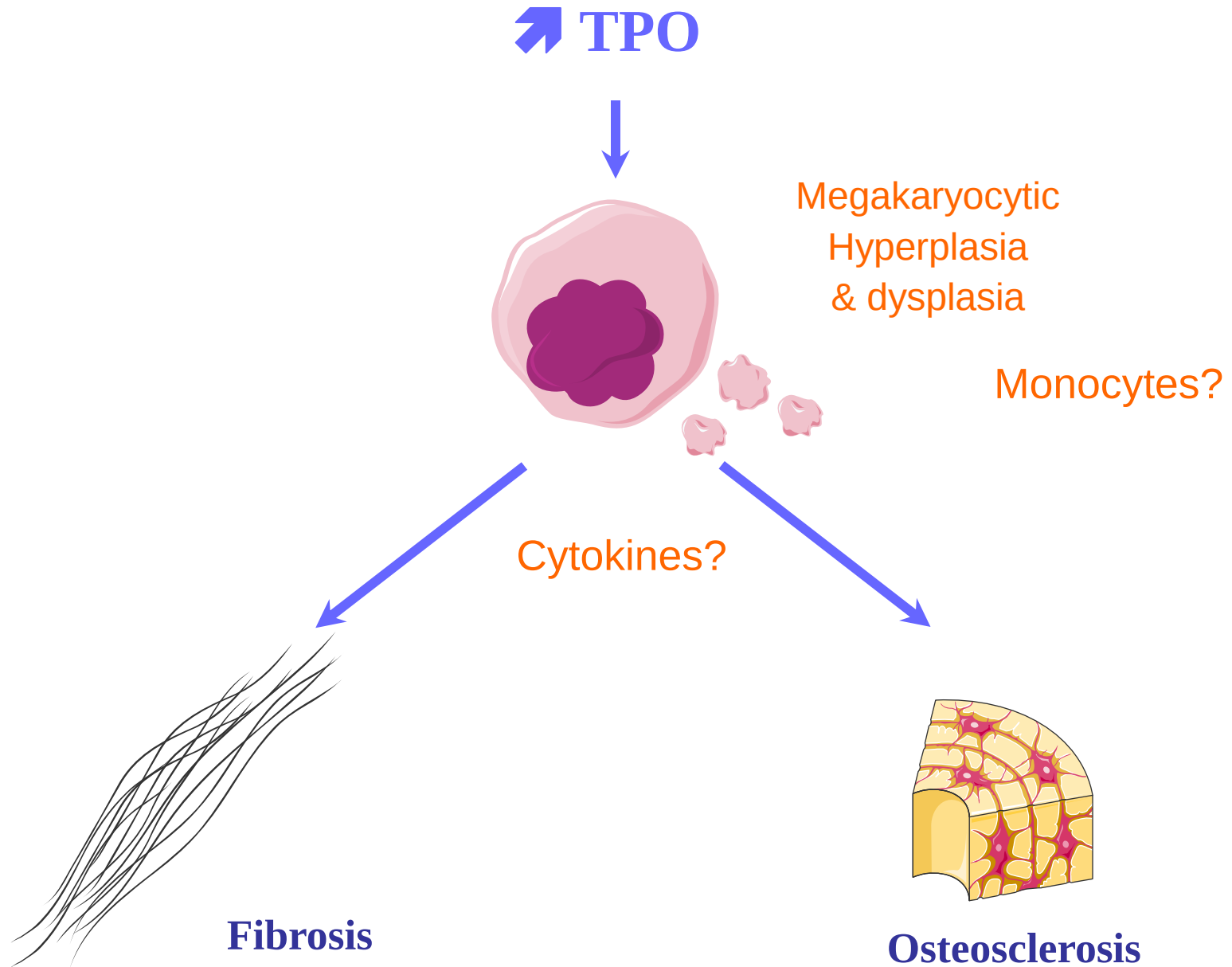
Osteosclerosis

$\approx$ 2-3 month post transplantation

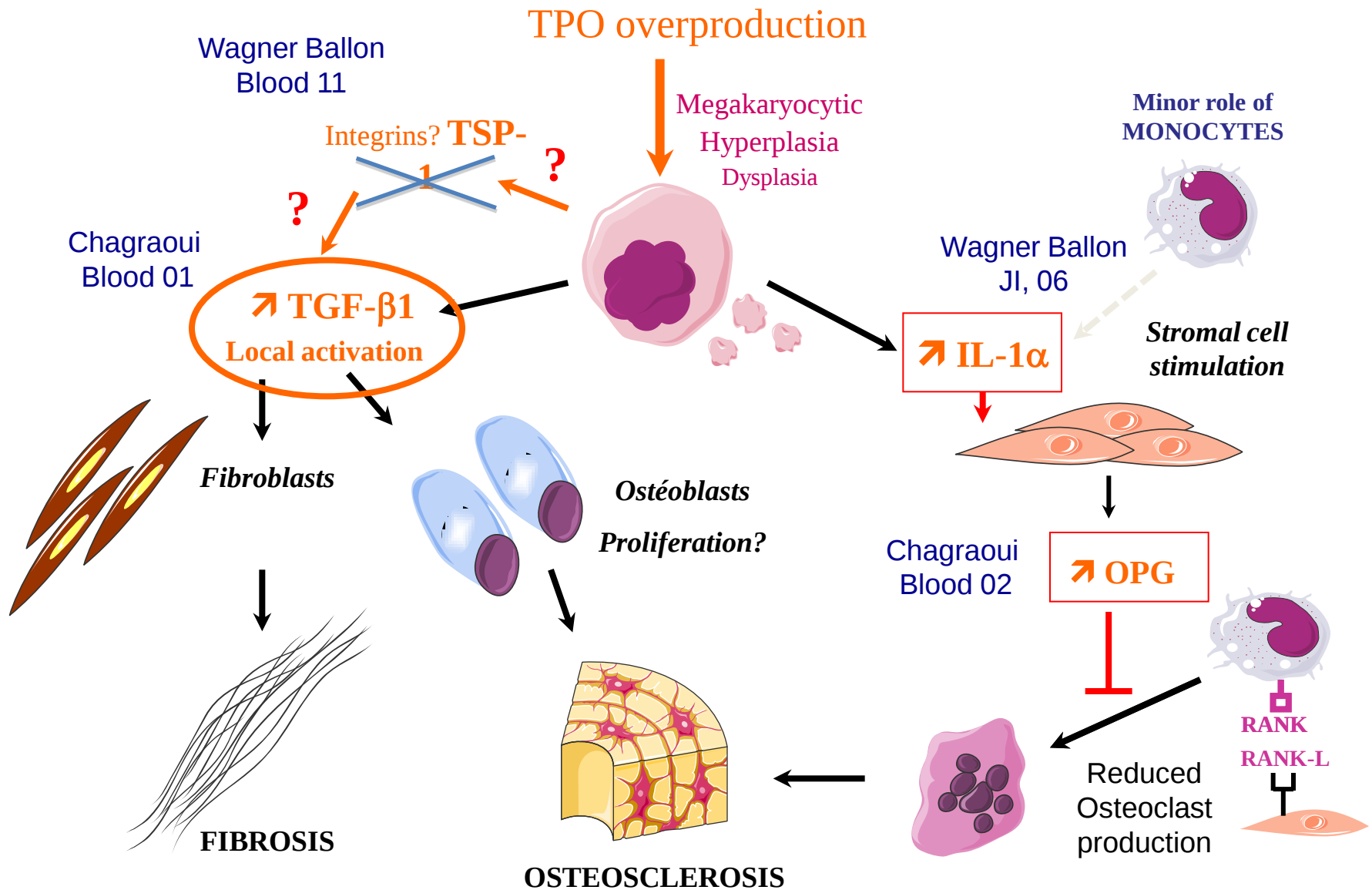
Disease mimicking human PMF



Stromal reaction leading to fibrosis and osteosclerosis



Mediators of fibrosis and osteosclerosis



3 JAK2^{V617F} models

A) Ectopic expression:

- Retrovirally transduced

- Wernig et al. Blood 2006, Lacout et al. Blood 2006, Bumm et al. Cancer Res. 2006, Zaleskas et al. Plos One 2006

- Transgenic

- Tiedt et al Blood 2008, Xing et al. Blood 2008, Shide et al. Leukemia 2008

B) Endogenous expression:

- Knock-in

- Akada et al. Blood. 2010, Marty et al Blood 2010, Li J. et al. Blood 2010, Mullally A et al Cancer Cell 2010