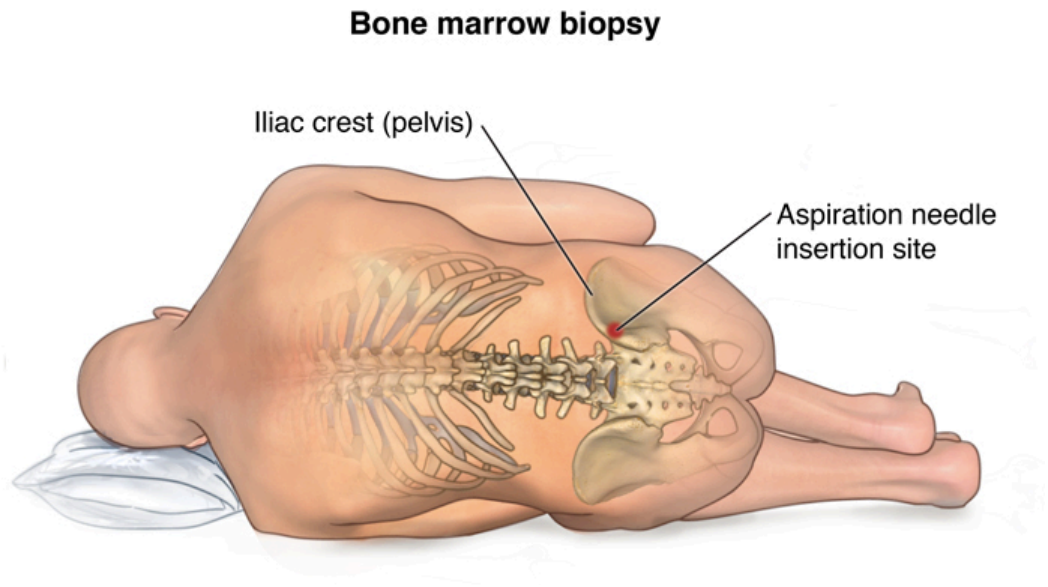
AKERSHUS UNIVERSITETSSYKEHUS

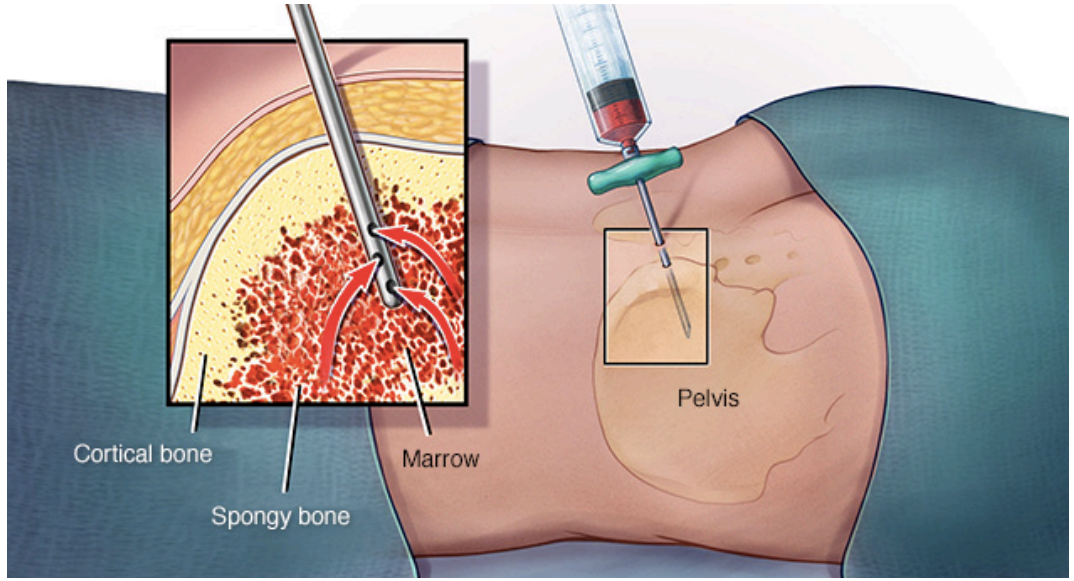
Myeloproliferativ neoplasme (MPN)
12.september 2019

Hoa Tran, avdelingsleder, Avd. for blodsykdommer.

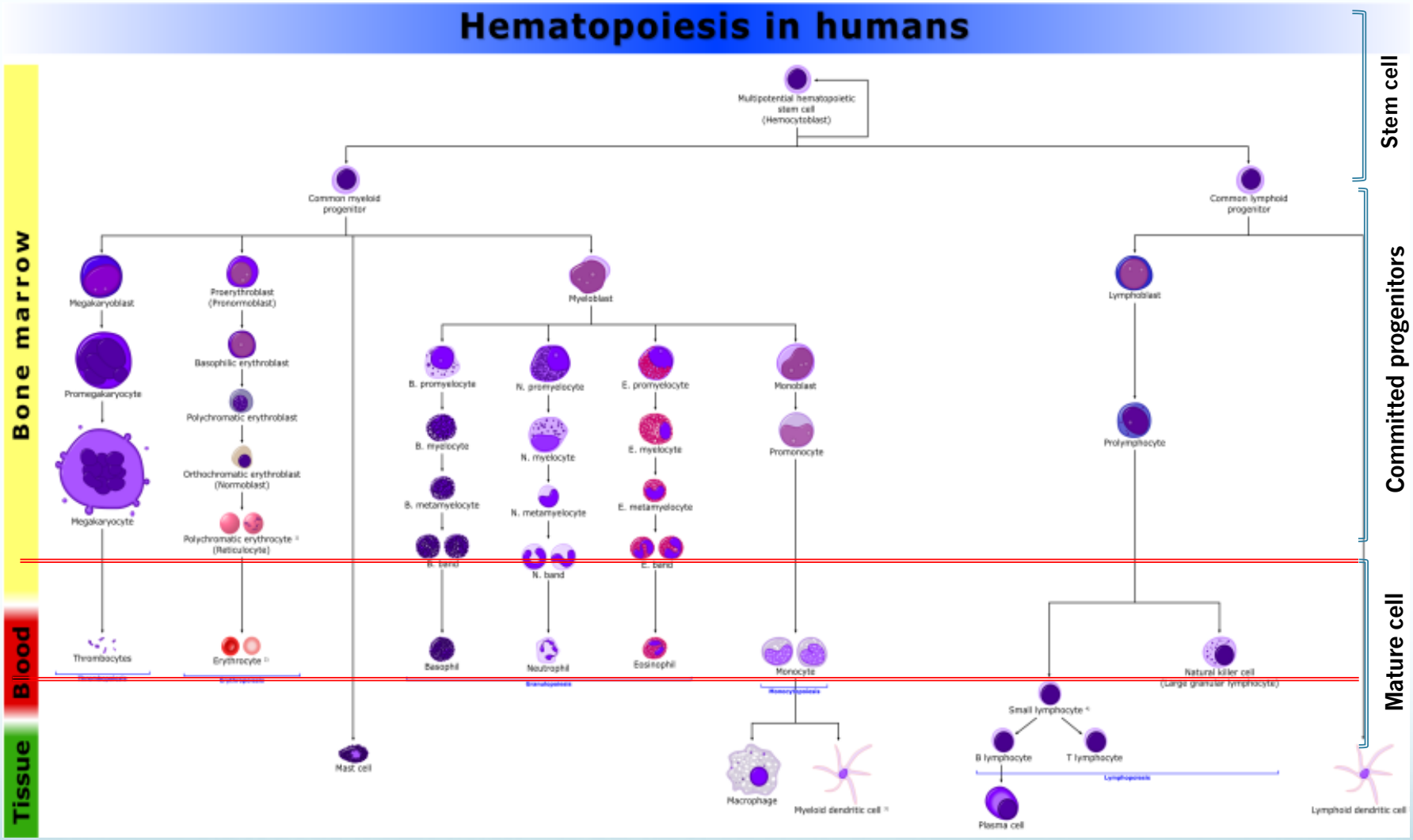
UiO : Universitetet i Oslo

Beinmargsundersøkelse.

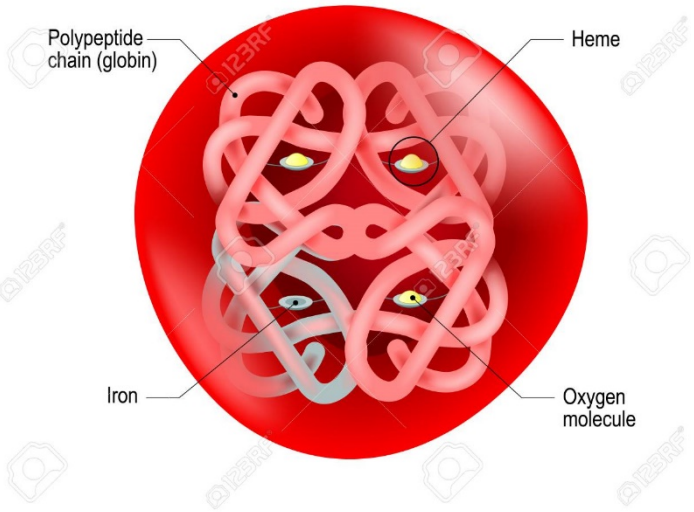




Normal hematopoiese

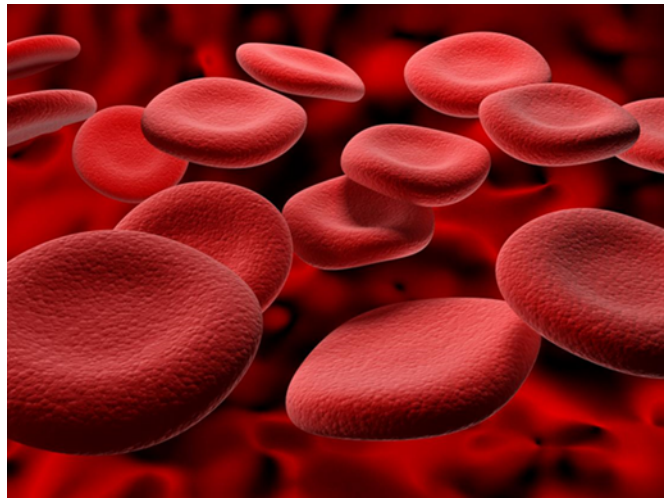


HEMOGLOBIN



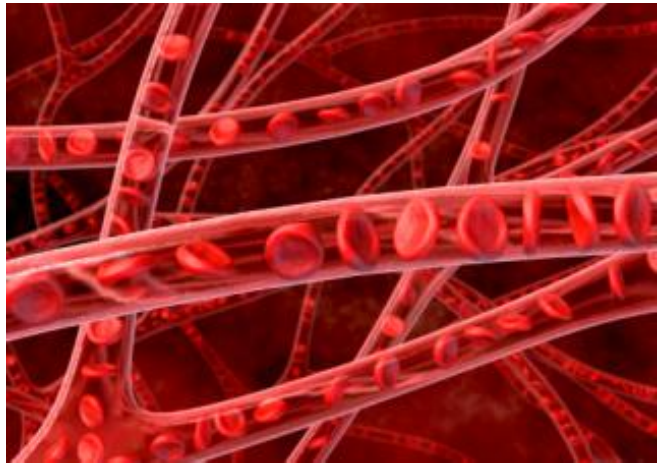
- Hovedoppgaven er transport av O2. Heme-gruppene også reversibelt bindes til CO2, CO og H+ fra karbonsyren som dannes fra CO2 i vevet.

- Hemoglobin består av fire tett foldede globinkjeder, og fire jernholdige heme-grupper bundet til hvert av de fire globinkjedene. Det er heme-gruppen som reversibelt bindes til oksygenmolekylet og som frakter det rundt.



- Formen og den spesielle membranen gjør cellene spesielt egnet til å utføre jobben med å transportere O2 rundt i kroppen.

Røde blodceller /erythrocytter.



Normalområdene for hemoglobin

•Barn til og med 12 år:
- Ved fødselen, 0 - 1 mnd: 14,5 - 22,0 g/dL, 2 - 12 måneder: 10,0 - 13,5 g/dL
- 1 - 12 år: 11,0 - 14,0 g/dL

•Menn: 13,4 - 17,0 g/dL
•Kvinner: 11,7-15,3 g/dL
- Gravide har 5-10% lavere verdier

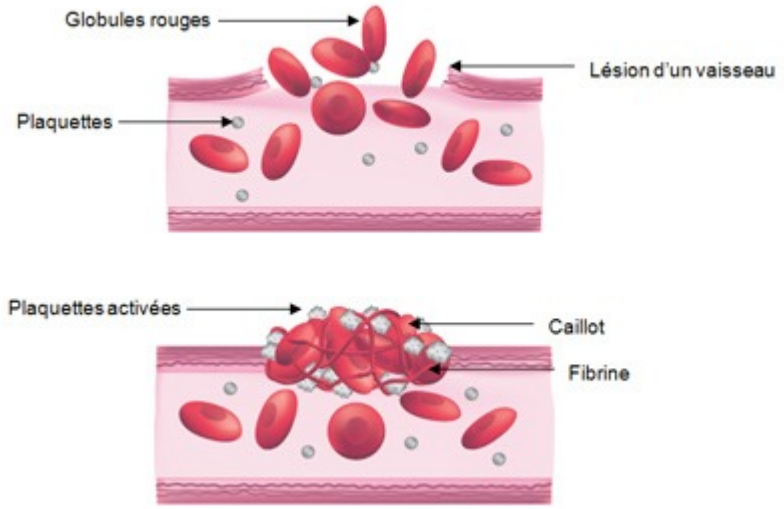
- Erythrocyttene produseres i beinmargen, hovedsaklig kontrollert av hormonet erythropoietin (EPO) som produseres i nyrene.

- Levetid på ca. 120 dager. Fjernes i i milten.

- Også det mannlige kjønnshormonet **testosteron** påvirker erythropoiesen, gjennom å øke produksjonsraten.

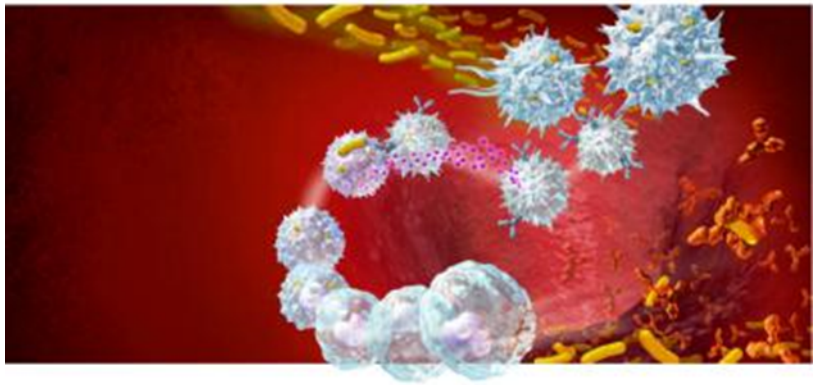
- Hypoksi/ lav oksygen nivå – i høyde /røyking/hjerte-lungesykdommer.

Blodplater



- Å stoppe blødning.
- Å bidrar med i betennelse prosessen, dreper bakterier.
- Normalt – 150 – 390 x 10^{9}/L

Hvite blodceller



Immunforsvaret – beskytter mot infeksjon
Leukocytter - 3,5 – 8,8 x 10^{9}/L

World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia

Myeloproliferative neoplasms (MPN)
Chronic myeloid leukemia (CML), *BCR-ABL1* [+]
Chronic neutrophilic leukemia (CNL)
Polycythemia vera (PV)
Primary myelofibrosis (PMF)
▪ PMF, prefibrotic/early stage
▪ PMF, overt fibrotic stage
Essential thrombocythemia (ET)
Chronic eosinophilic leukemia, not otherwise specified (NOS)
MPN, unclassifiable
Mastocytosis
Myeloid/Lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRA*, *PDGFRB*, or *FGFR1*, or with *PCM1-JAK2*
Myeloid/Lymphoid neoplasms with *PDGFRA* rearrangement
Myeloid/Lymphoid neoplasms with *PDGFRB* rearrangement
Myeloid/Lymphoid neoplasms with *FGFR1* rearrangement
Myelodysplastic/Myeloproliferative neoplasms (MDS/MPN)
Chronic myelomonocytic leukemia (CMML)
Atypical chronic myeloid leukemia (aCML), BCR-ABL1 [+]
Juvenile myelomonocytic leukemia (JMML)
MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
MDS/MPN, unclassifiable
Myelodysplastic syndromes (MDS)
MDS with single lineage dysplasia
MDS with ring sideroblasts (MDS-RS)
▪ MDS-RS and single lineage dysplasia
▪ MDS-RS and multilineage dysplasia
MDS with multilineage dysplasia
MDS with excess blasts
MDS with isolated del(5q)
Myeloid neoplasms with germ line predisposition
Acute myeloid leukemia (AML) and related neoplasms
AML with recurrent genetic abnormalities
▪ AML with t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*
▪ AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11*
▪ APL with *PML-RARA*
▪ AML with t(9;11)(p21.3;q23.3);*MLLT3-KMT2A*
▪ AML with t(6;9)(p23;q34.1);*DEK-NUP214*
▪ AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM*
▪ AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);*RBM15-MKL1*
▪ AML with mutated *NPM1*
▪ AML with biallelic mutations of *CEBPA*
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, NOS
▪ AML with minimal differentiation
▪ AML without maturation
▪ AML with maturation
▪ Acute myelomonocytic leukemia
▪ Acute monoblastic/monocytic leukemia
▪ Pure erythroid leukemia
▪ Acute megakaryoblastic leukemia
▪ Acute basophilic leukemia
▪ Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
▪ Transient abnormal myelopoiesis (TAM)
▪ Myeloid leukemia associated with Down syndrome
Blastic plasmacytoid dendritic cell neoplasm
Acute leukemias of ambiguous lineage
Acute undifferentiated leukemia
Mixed phenotype acute leukemia (MPAL) with t(9;22)(q34.1;q11.2);*BCR-ABL1*
MPAL with t(v;11q23.3); *KMT2A* rearranged
MPAL, B/myeloid, NOS
MPAL, T/myeloid, NOS
B-lymphoblastic leukemia/lymphoma
B-lymphoblastic leukemia/lymphoma, NOS
B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2);*BCR-ABL1*
B-lymphoblastic leukemia/lymphoma with t(v;11q23.3); *KMT2A* rearranged
B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1);*ETV6-RUNX1*
B-lymphoblastic leukemia/lymphoma with hyperdiploidy
B-lymphoblastic leukemia/lymphoma with hypodiploidy
B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3) *IL3-IGH*
B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3);*TCF3-PBX1*
B-lymphoblastic leukemia/lymphoma, BCR-ABL1-like*
B-lymphoblastic leukemia/lymphoma with *iAMP21**
T-lymphoblastic leukemia/lymphoma

* Provisional entity.

Modified with permission of the American Society of Hematology, from Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016; 127:2391. Copyright © 2016; permission conveyed through Copyright Clearance Center, Inc.

UpToDate®

World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia

Myeloproliferative neoplasms (MPN)
Chronic myeloid leukemia (CML), *BCR-ABL1* [+]
Chronic neutrophilic leukemia (CNL)
Polycythemia vera (PV)
Primary myelofibrosis (PMF)
▪ PMF, prefibrotic/early stage
▪ PMF, overt fibrotic stage
Essential thrombocythemia (ET)
Chronic eosinophilic leukemia, not otherwise specified (NOS)
MPN, unclassifiable

Myeloproliferative neoplasme (MPN)

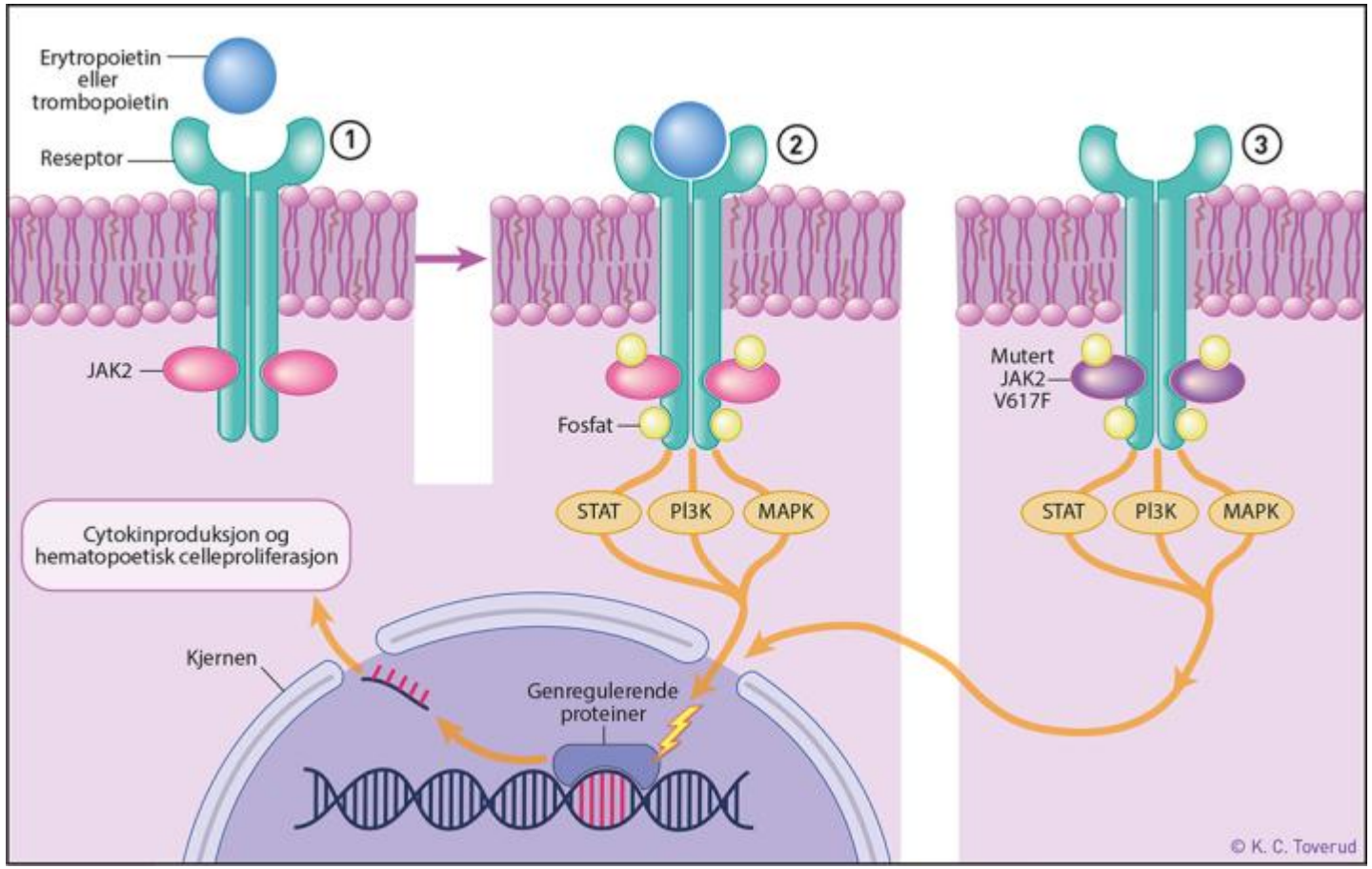
- Polycytemia vera
- Essensiell trombocytose
- Primær myelofibrose.

Hovedmutasjoner ved MPN

- JAK-2- mutasjon/exon 12 (2005).

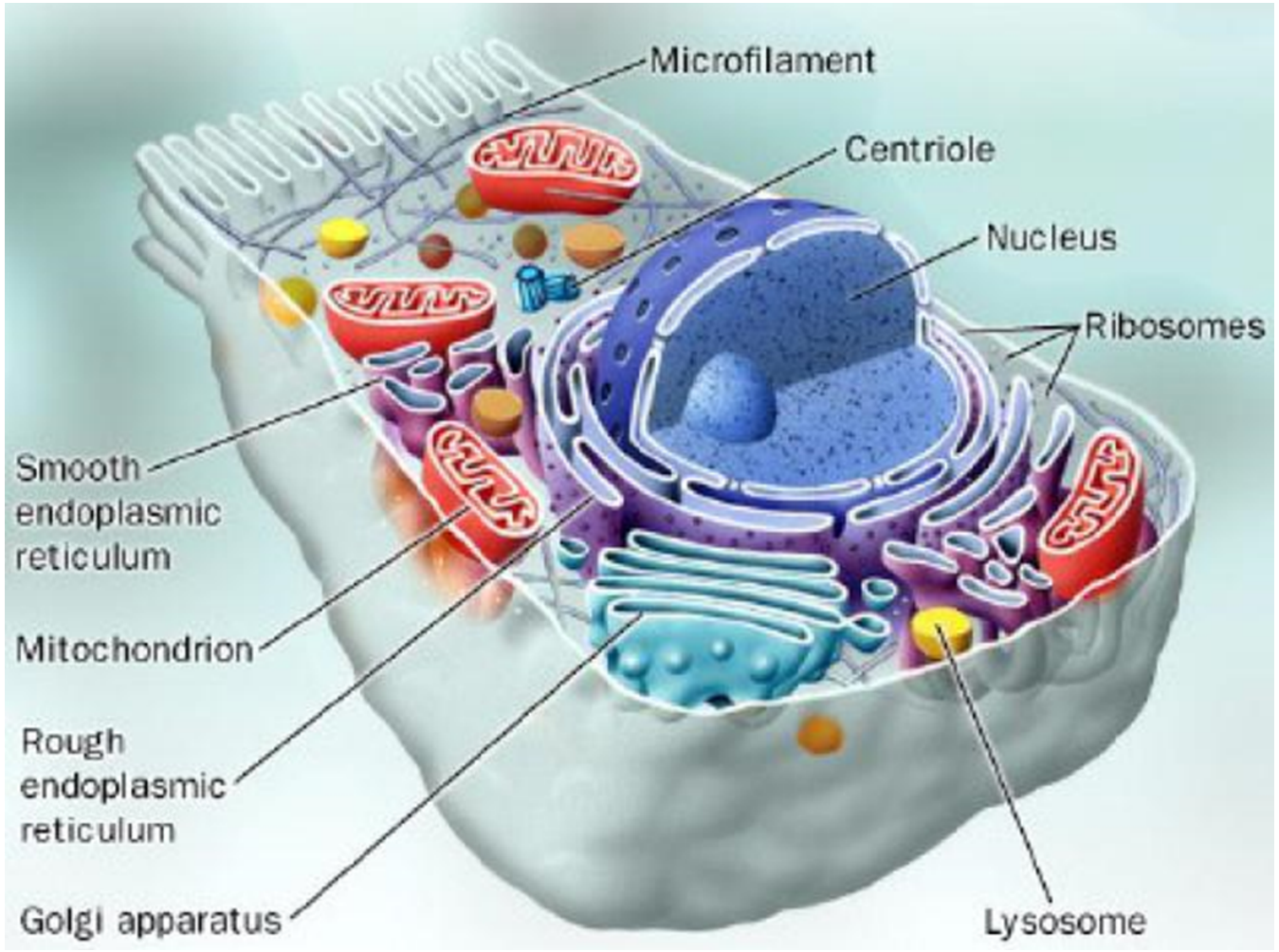
- Calreticulin mutasjon (exon 9 del/insertion) (2013)
  - >50 mutasjoner.
  - Type 1 (53 %) og type 2 (32 %). Ulike prognose ved PMF/ET.

- MPL (Myeloproliferative leukemia virus oncogene mutations/exon 10) kodes for megakaryocytt/trombopoietin reseptor .(2006)



Figur 1 JAK2 er en intracytoplasmatisk ikke-reseptor tyrosinkinase. 1) Inaktiv villtype JAK2-reseptor på overflaten av de hematopoetiske cellene blir stimulert når erytropoietin eller trombopoietin binder seg til den (2). Aktivering av reseptoren fører til konformasjonsendring av denne og binding av fosfat (P) og aktivering av den intracytoplasmatiske delen av reseptoren med påfølgende aktivering av diverse signalveier som STAT (signaltransduser og aktivator av transkripsjon), PI3K (phosphatidylinositol 3-kinase) og MAPK (mitogenaktivert proteinkinase) som fører til celleproduksjon og differensiering.
3) I celler med mutert JAK2 (3) pågår det en konstant signalering av signalveier og dermed økt produksjon av hematopoietiske celler

Tidsskr Nor Legeforen 2013; 133: 1946-50


Microfilament
Centriole
Nucleus
Ribosomes
Smooth endoplasmic reticulum
Mitochondrion
Rough endoplasmic reticulum
Golgi apparatus
Lysosome

Forekomsten av ”driver” mutasjoner

	JAK2V617F (JAK2 exon12.)	CALR1/ CALR2	MPL	Trippel negative
PV	98%			
ET	60 %	22%	3 %	10-15%
PMF	58%	25%	7%	10-15%

Next Generation Sequencing (NGS) «dyp sekvensering»

- Hos MPN pasienter som er negative for JAK2,CALR, og MPL (trippel negative), mutations in LNK, TET2, DNMT3A, IDH1/2, CBL, og ASXL1 gen men også atypiske MPL (S204P) mutasjon har også blitt identifisert.

- Chang et al. identifisert 30 mutasjoner hos 12 av 16 trippel-negative MPN pasienter.

- NGS – identifisere også lav allell byrde and atypical mutasjoner of JAK2 (JAK2V626F and JAK2F556V) og MPL (MPLS204P and MPLY591N).

TABLE 2 | Mutated genes in *BCR-ABL1*-negative myeloproliferative neoplasms (MPNs).

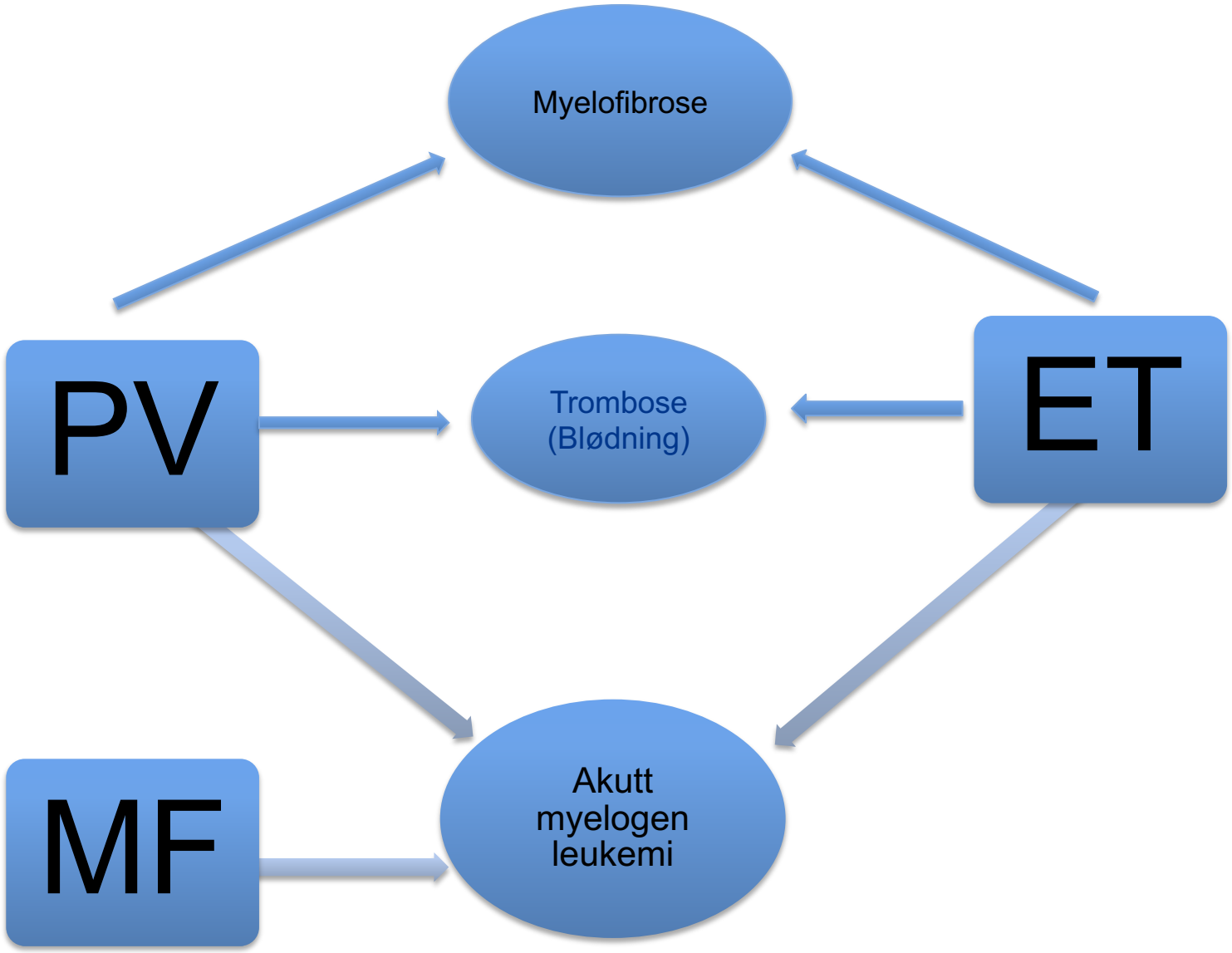
Gene	Pathway relevance	Type of mutation	Frequency of mutation (%, PV, ET, MF)	Prognostic significance	References
ASXL1	Epigenetic regulation	Missense	3–12% in PV 4–11% in ET 22–38% in MF	Adverse in PV and MF	(17, 18, 25, 30, 32, 45, 73–82)
DNMT3A	Epigenetic regulation	Missense	6% in ET 5–10% in MF	None	(18, 32, 73, 74, 76, 77, 82)
EZH2	Epigenetic regulation	Missense	2–12% in PV 3% in ET 12% in MF	Adverse in TE and MF	(18, 25, 32, 73–77, 79, 80, 82)
IDH1	Epigenetic regulation	Missense	10% in PV 1% in ET 1–4% in MF	Adverse in MF	(18, 25, 32, 74–77, 79, 80, 82)
IDH2	Epigenetic regulation	Missense	4% in PV 1–3% in MF	Adverse in PV and MF	(18, 25, 32, 74–77, 79, 80, 82)
TET2	Epigenetic regulation	Insertion/ Deletion Nonsense or Missense	10–25% in PV 16% in ET 17% in MF	Adverse in TE	(18, 32, 73, 74, 76, 77, 82)
SF3B1	mRNA processing	Missense	3% in PV 5% in ET 10% in MF	Adverse in TE	(18, 32, 74, 77, 82)
SRSF2	mRNA processing	Missense	9% in MF <2% ET	Adverse in PV and MF	(18, 25, 32, 74–77, 80–82)
U2AF1	mRNA processing	Missense	1–2% in TE 10–17% in MF	Adverse in TE and MF	(18, 32, 74, 77, 82)
ZRSR2	mRNA processing	Missense	5% in PV 3% in ET 10% in MF	Not known	(18, 32, 74, 77, 82)
CEBPA	Transcriptional regulation	Mutations	6% in PV 4% in ET 9% in MF	Adverse in MF	(18, 32, 82)
RUNX1	Transcriptional regulation	Nonsense Missense Insertion/ Deletion	<5% (PV, ET, MF)	Adverse in MF	(18, 32, 74, 76, 77, 82)
TP53	Transcriptional regulation	Missense or Mutation	<5% (PV, ET, MF)	Adverse in TE	(18, 32, 74, 76, 77, 82)
CBL	Cell signaling pathways	Missense	4% in MF	Adverse in MF	(18, 32, 73, 74, 77, 82)
KIT	Cell signaling pathways	Mutations	3% in PV 2% in ET 1% in MF	Adverse in MF	(18, 32, 82)
NF1	Cell signaling pathways	Deletion	Rare in MF	Not known	(18, 32, 74, 77, 82)
NRAS/KRAS	Cell signaling pathways	Missense	1% in ET 1–4% in MF	Not known	(18, 32, 74, 77, 82)
SH2B3/LNK	Cell signaling pathways	Deletion or missense	9% in PV	Adverse in TE and MF	(18, 32, 73, 74, 77,

Epidemiologi - Norge

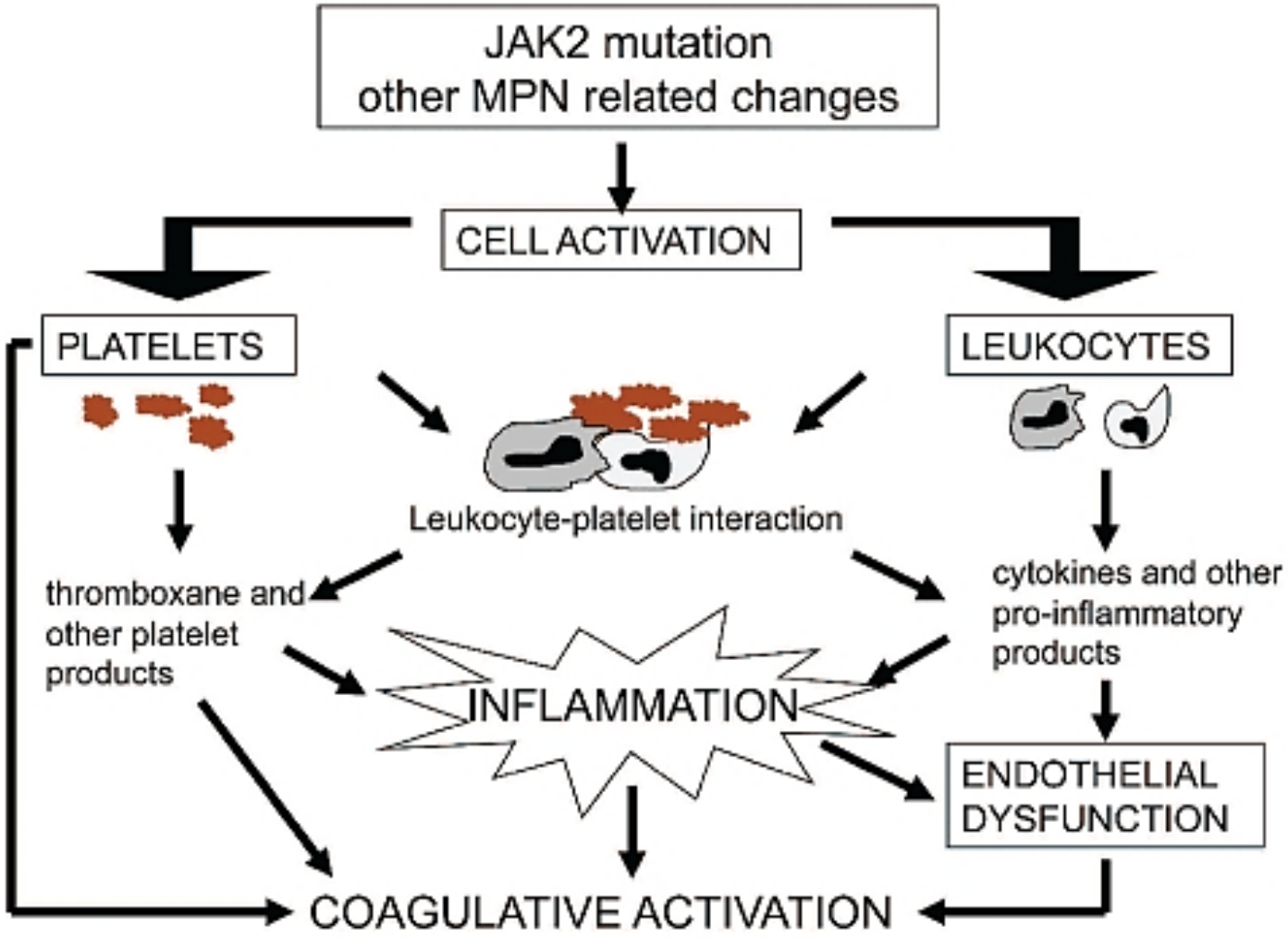
	Antall	Median alder (år)	Insidens (Antall nye tilfelle/10^5
PV	945	70	0,7
ET	762	65	0,9
PMF	418	71	0,5
Total	2344		

Incidence of MPN per 10^5 inhabitants during the period 1995 to 2012 in Norway. Kreftregisteret

Christina Roaldsnes, RN[1*], Anders Waage, MD, PhD[2], Mette Nørgaard, MD, PhD[3*] and **Waleed Ghanima, MD, PhD[4*]**



Komplikasjoner og overgangsformer ved MPN.



Mechanisms which, in myeloproliferative neoplasms (MPN), can increase the thrombotic risk through cell activation and inflammation.

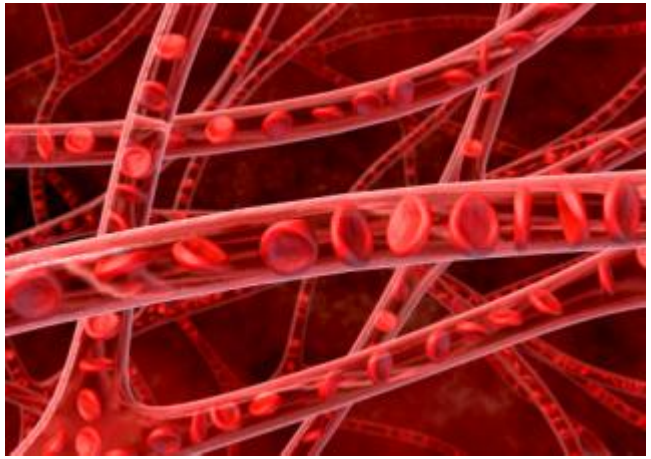
Pathophysiology of thrombosis in myeloproliferative neoplasms

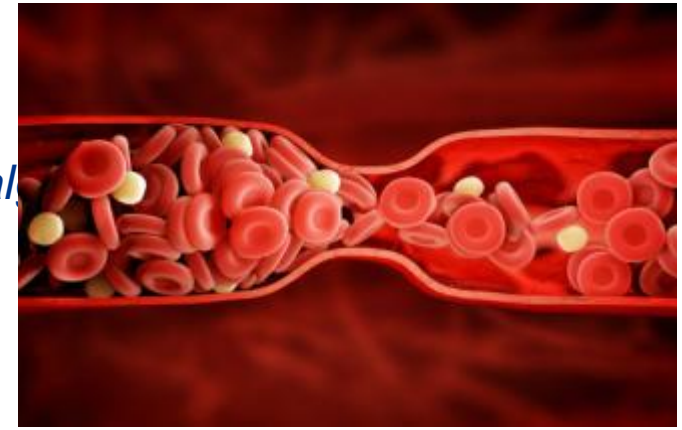
Haematologica. 2011 February;96(2):183-186.

Symptomer ved PV/ET

- *Hodepine*
- *Svette*
- *Øresus/tinnitus*
- *Tåkesyn, blind spot*
- *Svimmelhet*
- *Rød hud*
- *Vekttap*
- *Blødning eller trombose*
- *Metthet følelse*
- *Kløe, spesielt I dusjen*
- *Brennende eller rød flammende hender og føtter (erytromelal*
- *Slapphet*
- *Nattesvette*
- *Beinsmerter*

Asymptomatisk





Utredning ved MPN

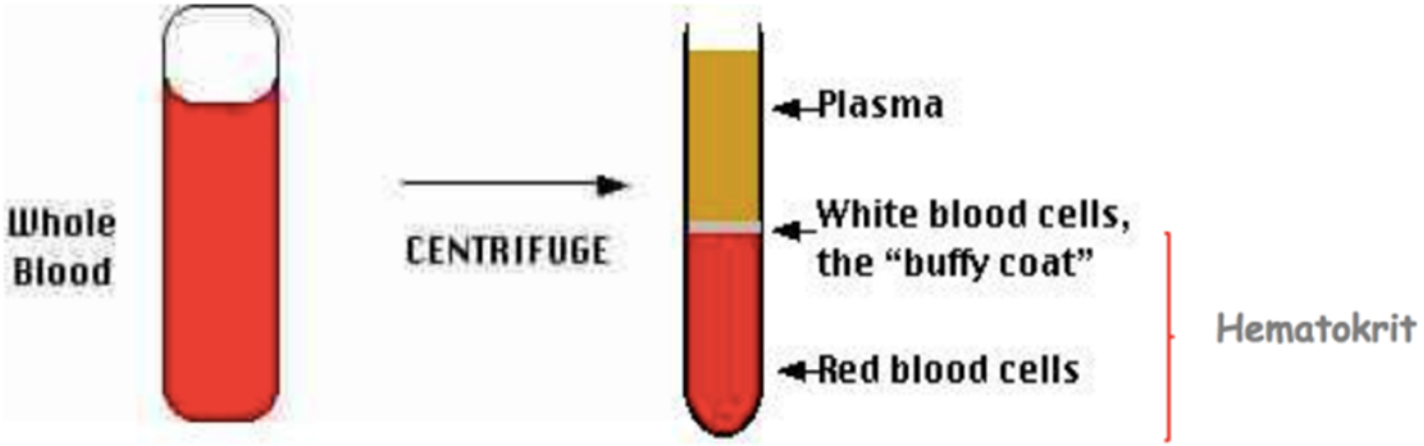
Utredning:

- Blodprøver : BCR-ABL, JAK-2, CALR, MPL, hematologi status, hematokrit, virus serol, kronisk inflammatoriske tilstander.
- Beinmargsundersøkelse: flowcytometri (hårcelle leukemi), aspirat, biopsi, cytogenetikk (myelofibrose).

Behandlingsmål ved MPN

- Reduserer symptomer.
- Reduserer risiko for trombose/blødning.

  Mål: Hematokrit < 0,45, blodplater < 450.
- Reduserer risiko for AML og fibrose utvikling.



Aktuelle medikamenter

- Albyl-E – Blodfortynnende.
- Annen blodfortynnende.
- Kolesterolssenkende.
- Ikke medikamentelle behandling – Blodtapping.
- Hydroksyurea – Hydrea - Cellegift -
- Anagrelid- Reduserer antall blodplater.
- Interferon- Pegasys/Peginteron – Reduserer cellevekst.
- Ruxolitinib – Jakavi – JAK2-hemmer – Reduserer celleproduksjon og miltstørrelse.
- Antihistaminer- Cetirizin/Aurius – mot kløe.

Bivirkninger

- Albyl-E – Blødning, magesår.
- Hydroksyurea – Anemi, kronisk leggsår, kløe, utslett, kreftutvikling ? Utmattelse, smerter.
- Anagrelid – Hodepine, hjertebank, rytme forstyrrelse. Blødning, spes i forb med Albyl-E.
- Interferon – Influensalignende symptomer, muskesskjelett smerter, økning av leverprøver/levercelleskade.
- Ruxolitinib- Diare, beinmargsdepresjon (anemi, trombocytopeni, leukopeni).

"I already diagnosed myself on the Internet.
I'm only here for a second opinion."