Hematopoiesis

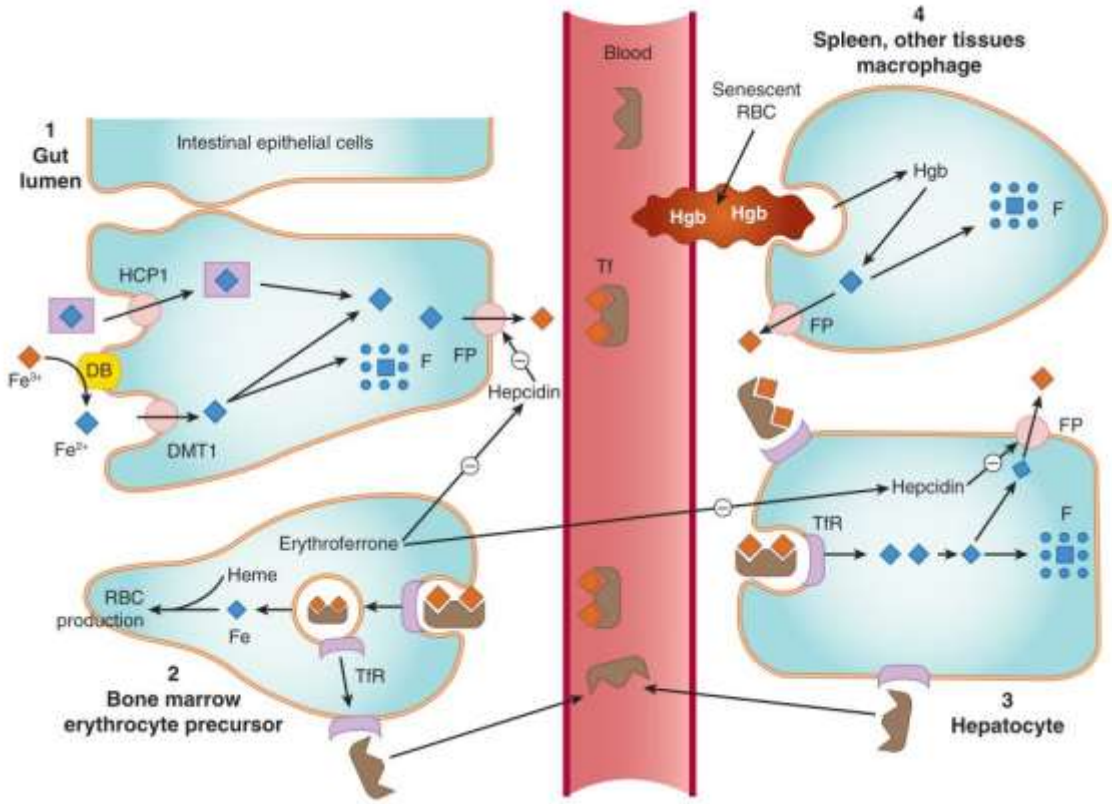
- BM – BLOOD – RES
- BM
  - cell renewal system
    - proliferation
    - differentiation
  - stem cells ⟶ progenitor cells ⟶ mature blood cells
- Required factors
  - minerals – **Fe**
  - vitamins – **folic acid / vitamin B_{12}**
  - **hematopoietic growth factors**
    - myeloid GFs: colony stimulating factors (G-CSF / GM-CSF)
    - erythropoietin
    - megakaryocyte GFs: IL-11 / romiplostim

Anemia

- ↓ erythrocytes / Hgb
- reasons
  - ↓ production
    - lack of nutrients / drugs / irradiation
  - ↑ elimination
    - **blood loss** / hemolysis
- nutritional anemia – deficiency of
  - **iron**
  - **folic acid**
  - **vitamin B_{12}** (deoxyadenosyl-, methyl-, cyano- and hydroxo**cobalamin**)

Iron

- in **hemoglobin** / myoglobin / enzymes (e.g. cytochromes)
- daily intake: ~10-15-20 mg
  - but absorption is only 0.5-1 mg
- **absorption is regulated!**
- distribution
  - transport: **transferrin**
  - store: **ferritin**
  - erythrocytes: **hemoglobin**
- excretion
  - intestinal tract – **highly conserved**



free iron is toxic → complicated system for movement

absorption is controlled – hepcidin ↓

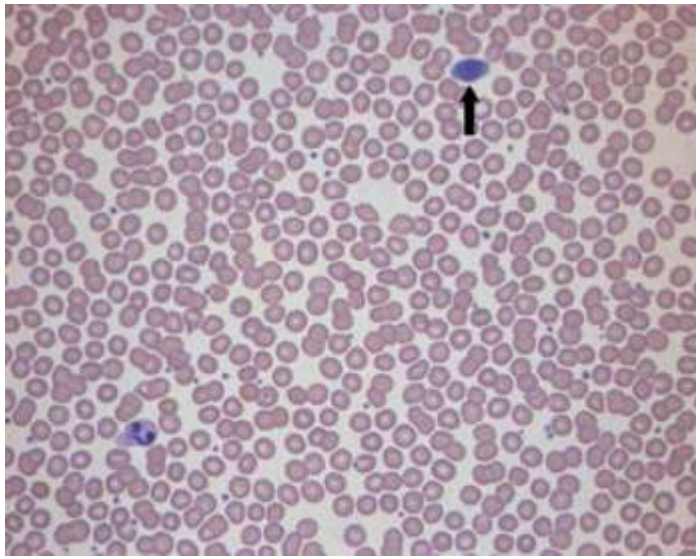
- inorganic, only **ferrous** (Fe^{2+}): DMT1 (divalent metal transporter 1)
- **heme**: HCP1 (heme carrier protein 1)

transport: **transferrin** (Tf)

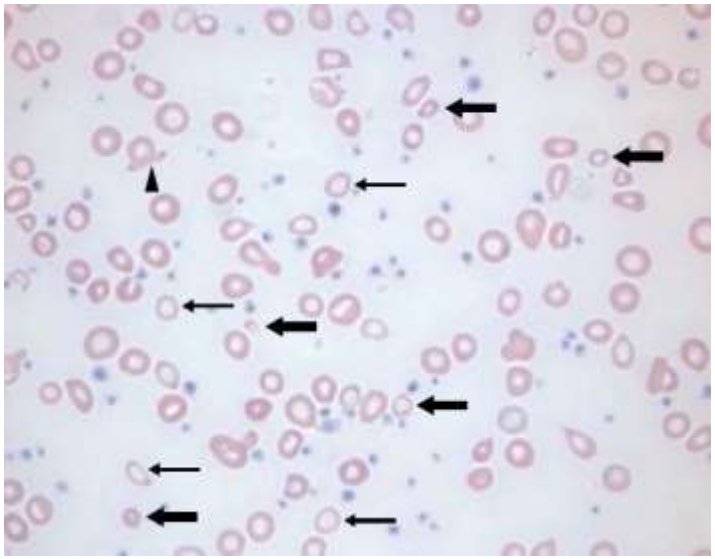
storage: **ferritin** (F; 15-20%) / hemoglobin (~70%), myoglobin, cytochromes, other proteins

Iron deficiency anemia

hypochromic microcytic



normal red cells



severe iron deficiency

treatment: iron supplementation (prevention e.g. in pregnant women)

Iron supplementation

- **oral**
  - **ferrous (Fe^{2+})** – sulfate / gluconate / fumarate
- parenteral (intravenous)
  - free inorganic ferric iron is toxic
  - colloid particles (iron core surrounded by carbohydrate)
    - iron dextran – ferric (Fe^{3+}) hydroxide + dextran
      - high-molecular-weight (**hypersensitivity !!!**)
      - low-molecular-weight (↓ hypersensitivity)
    - ferric (Fe^{3+}) gluconate (Ferrlecit®)
    - ferric (Fe^{3+}) carboxymaltose (Ferinject®)
    - iron sucrose

iv iron suppl.: be prepared for management of anaphylactic shock

Oral iron supplementation

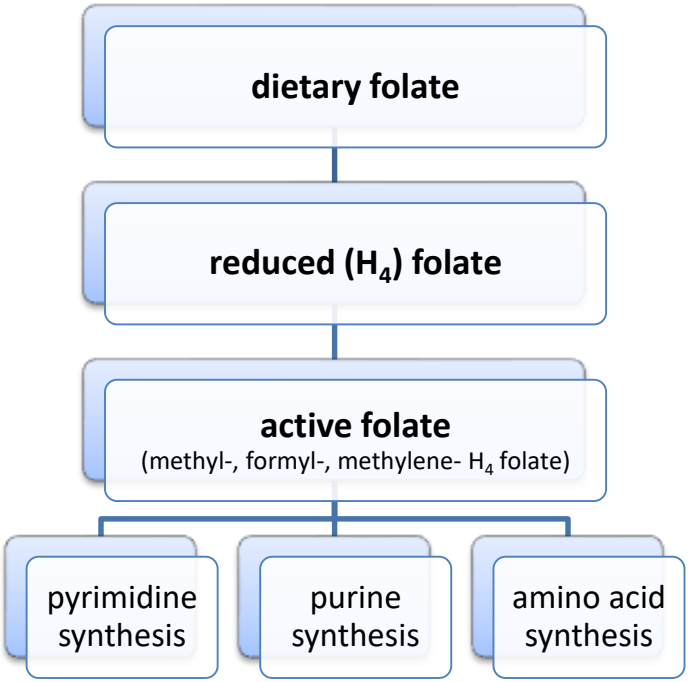
- preferred
- dose
  - traditional: 3x325 mg $FeSO_4$ /day for 4-6 months
  - recent: 15-20 mg Fe daily – similar efficacy & ↓ side effects
- absorption
  - site – primarily duodenum
  - fiber, tea, resins↓
  - vitamin C↑
- adverse effects
  - pain / nausea / constipation or diarrhea / black stools
  - oral overdose
    - in children lethal toxicity – **keep out of reach of children!**

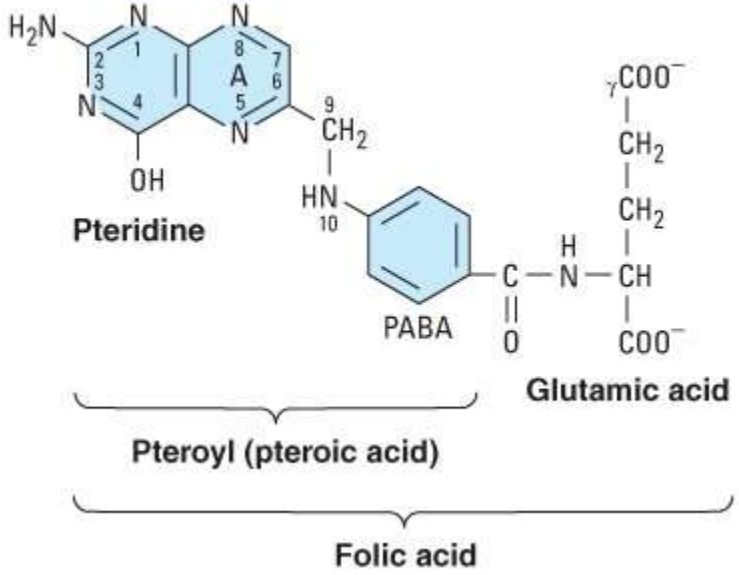
Iron intoxication

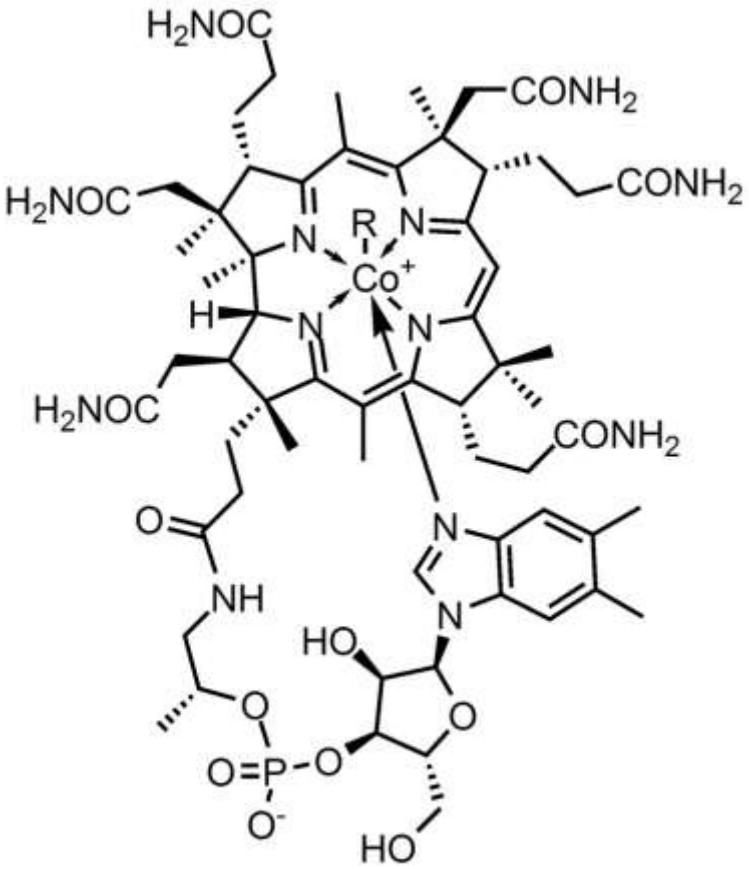
- Acute
  - two phases (gastrointestinal → systemic)
    - necrotizing gastroenteritis, shock → acidosis, coma, death
  - treatment
    - **whole bowel irrigation**
    - gastric lavage rarely / but *activated charcoal is ineffective*
    - DO NOT use ipecac syrup
    - **i.v. deferoxamine**
    - **supportive therapy** (e.g. hydration)
- Chronic (hemochromatosis)
  - deposition in organs
  - reason: excessive absorption (inherited) / transfusions
  - treatment
    - phlebotomy / deferoxamine (parenteral) / deferasirox (oral)

Folic acid and Vitamin B_{12}

- deficiency ⟶ megaloblastic anemia
  - folic acid can compensate for B_{12} (only partial)
  - identify the reason before treatment

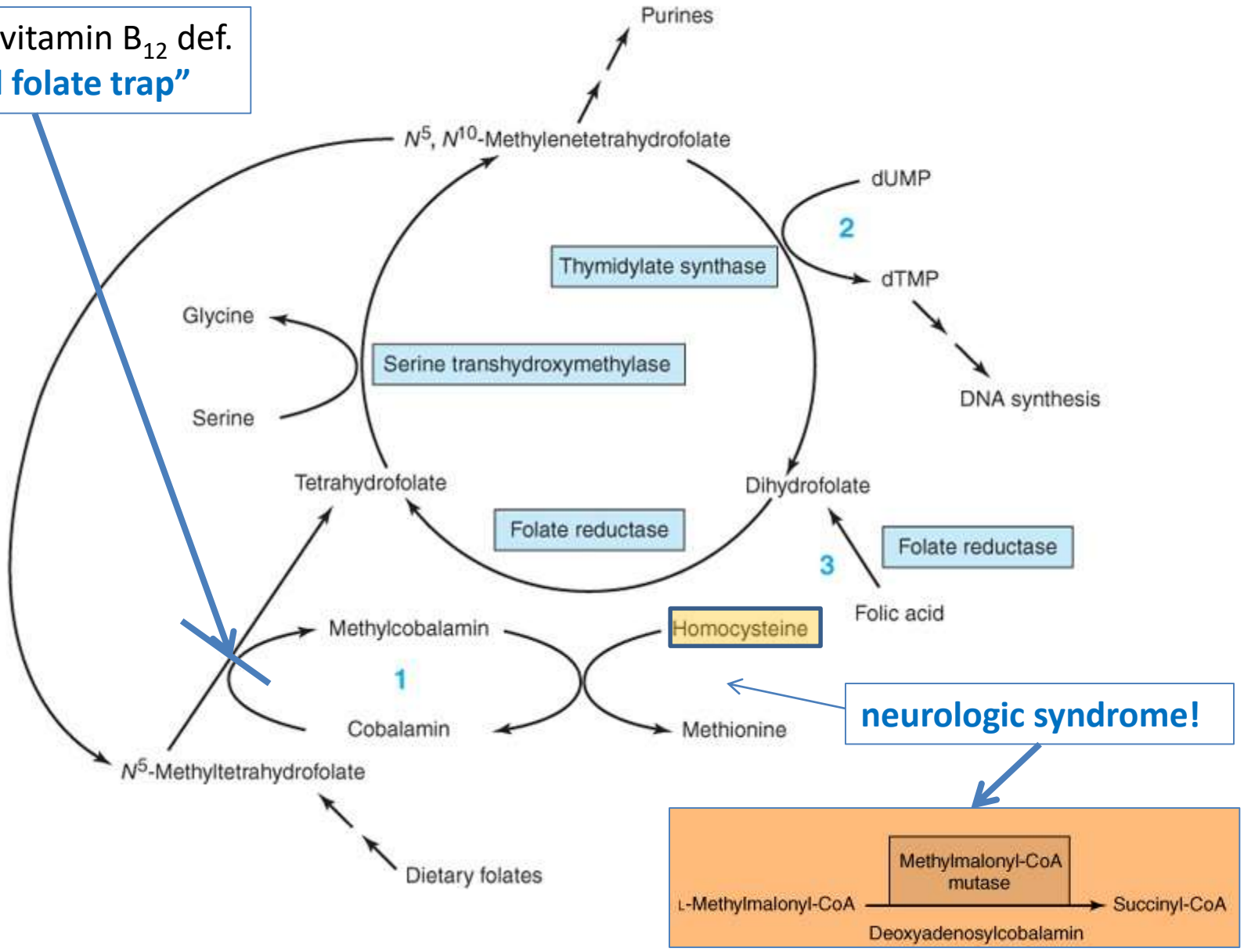






R = 5'-deoxyadenosyl, Me, OH, CN

blocked in vitamin B_{12} def.
"methyl folate trap"



neurologic syndrome!

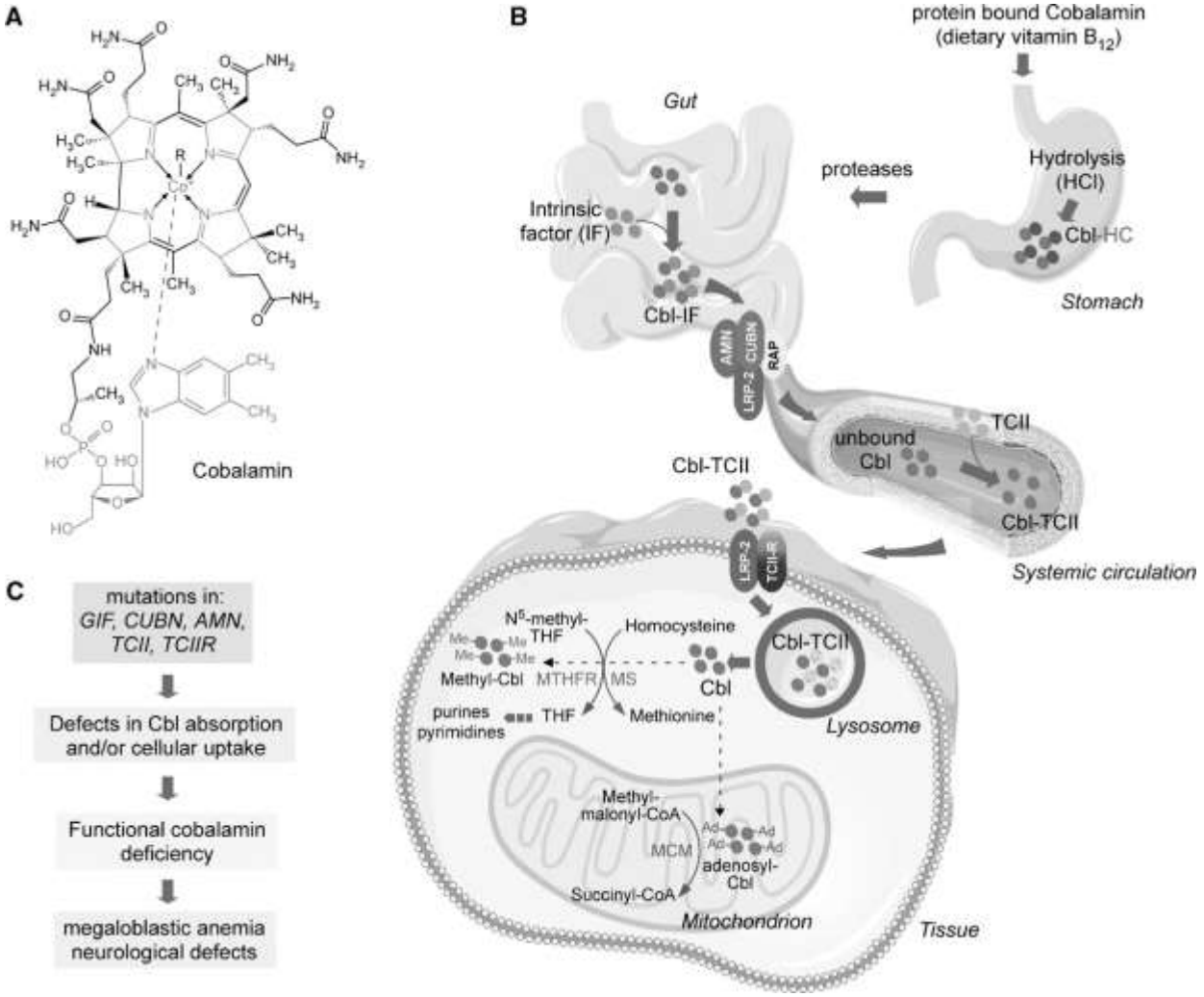
Folic acid

- inadequate intake ⟶
  - in pregnancy
    - neural tube birth defects (spina bifida)
  - megaloblastic anemia
  - ↑ homocystein
- absorption: good (jejunum)
  - oral supplementation / enriched food (?)
- dose
  - 50-500 µg + 400 µg daily (in women)
- elimination
  - catabolism / excretion – low stores
- drug interactions
  - trimethoprim / pyrimethamine / methotrexate / N_20
  - cholestyramine / phenytoin

Vitamin B_{12}

- source: meat / dairy products / egg
- absorption
  - with intrinsic factor
    - secreted in stomach
    - absorbed in distal ileum
- requirement
  - ≈ 2 µg / day – stored: ≈ 3000-5000 µg
- excretion is not significant
- deficiency ← pernicious anemia / gastrectomy / malabsorption syndromes / IBD (Crohn's) / small bowel resection
  - food-cobalamin malabsorption syndrome – no cobalamin release from food
- supplementation: **parenteral**
  - **hydroxocobalamin /** cyanocobalamin
  - but new routes of cobalamin administration – e.g. nasal

Cobalamin (cbl) absorption and metabolic pathway



Hematopoietic growth factors

- endogenous glycoproteins
  - control/induce proliferation/differentiation of **progenitor cells** in bone marrow
  - may have effects on **other cells** (nonhematologic too!)
- produced by recombinant DNA technology
  - **biological therapy** (see next slide)
- currently available
  - **erythropoietin**
    - epoetin /darbepoetin / PEG-epoetin-β
  - **filgrastim /pegfilgrastim** (G-CSF) / sargramostim (GM-CSF)
  - **IL-11 (oprelvekin) / romiplostim / eltrombopag** /thrombopoietin

Biological therapy / biological products

- biological origin
- large molecular weight
- biotechnological production
- chemical structure is not always exactly defined
- "biosimilarity“

- special regulations are necessary during the development of
  - innovative or
  - generic (correctly: **biosimilar**) drugs
- main reasons:
  - the active ingredient cannot be defined exactly
  - some can be extremely human specific (e.g. TGN1412)
- names
  - biological, biologic, biological drug, product, therapy
  - biological therapy
  - biological response modifier
  - biological product: FDA

erythropoietin (rHuEPO)

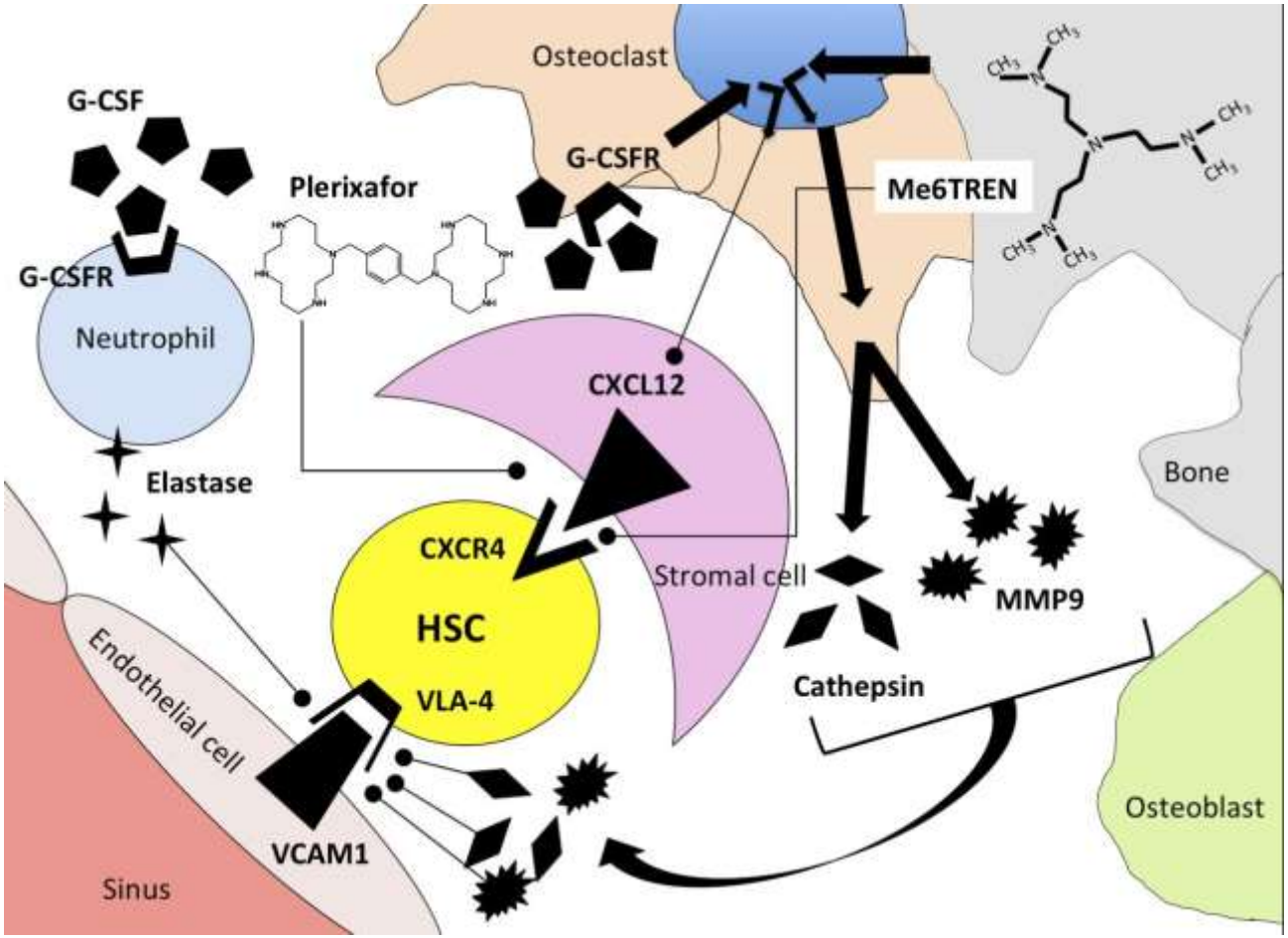
- endogenous – produced in kidney
  - in anemia EPO level is high (except in chronic renal failure)
- effects
  - stimulates erythroid proliferation and differentiation
  - reticulocytosis / Hgb ↑ / transfusions ↓
- indications
  - anemia
    - **chronic renal failure**
    - cancer chemotherapy
    - zidovudine (AZT) therapy (in HIV infection)
    - other (e.g. heart failure)
- dosing
  - i.v. / s.c.
  - 3x weekly / once weekly (darbepoetin-α) / monthly (PEG-epoetin-β)
  - target Hgb levels < 110 g/L
    - if > 110 g/L then risk ↑ of hypertension / stroke / AMI / fatal CV compl.
  - iron supplementation
- no other serious adverse effects

filgrastim

(G-CSF – **G**ranulocyte **C**olony **S**timulating **F**actor)

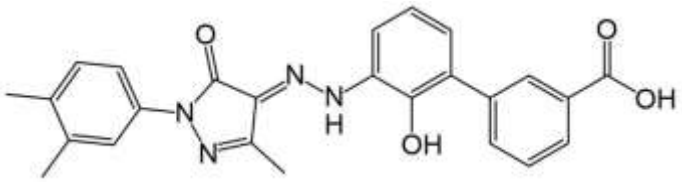
- non-glycosylated – produced in E.coli
- **pegfilgrastim**
  - pegylated (PEG = **P**oly**E**thylene **G**lycol)
    - increased half life
- indications
  - **neutropenia**
    - cancer chemotherapy / BM transplantation
    - congenital neutropenia / agranulocytosis
  - **mobilization of hematopoietic progenitors** into peripheral blood (PBSC transplantation) – see **plerixafor** (CXCR4 inhibitor, Mozobil®)
- dosing
  - i.v. or s.c.
  - daily or weekly (pegfilgrastim)
- adverse effects
  - bone pain / allergic reactions (rare) / splenic rupture (rare)
  - better tolerated than GM-CSF

Plerixafor's mechanism of action



Megakaryocyte growth factors

- interleukin-11 (IL-11) / **oprelvekin**
  - recombinant / *E. coli* / non-glycosylated
  - ind.: secondary prevention of chemotherapy induced thrombocytopenia (in nonmyeloid malignancies)
  - tox.: fluid retention / dilutional anemia / hypokalemia / arrhythmia
- thrombopoietin receptor agonists (Mpl)
  - **romiplostim**: peptide → *sc. injection*
    - ind.: chronic immune thrombocytopenia if no response
  - **eltrombopag**: small molecule → *oral*
    - ind.: chronic immune thrombocytopenia if no resp / hep. C
    - tox.: hepatotoxicity (hep C !) / portal vein thrombosis (in liver dis.)



eltrombopag