

# **Haematology and blood transfusion**

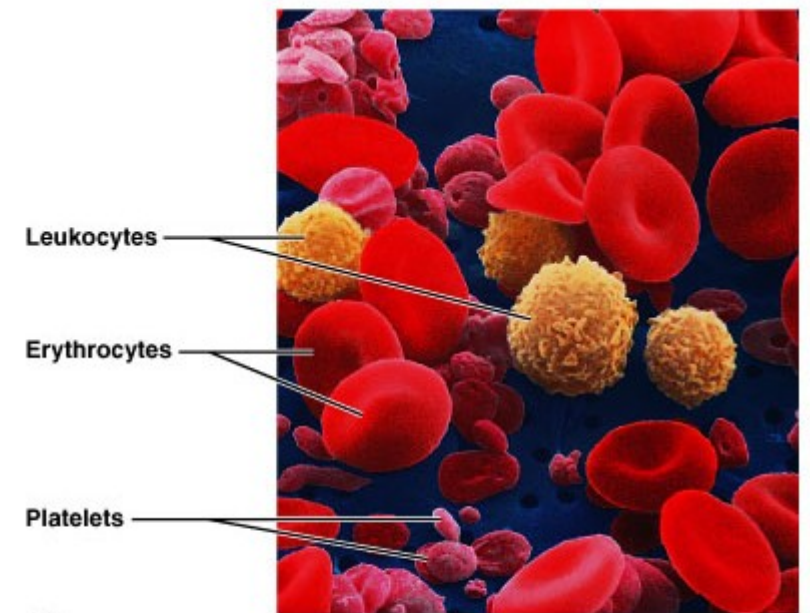
Andrea Knight, PhD  
knight@med.muni.cz

# Definition & function

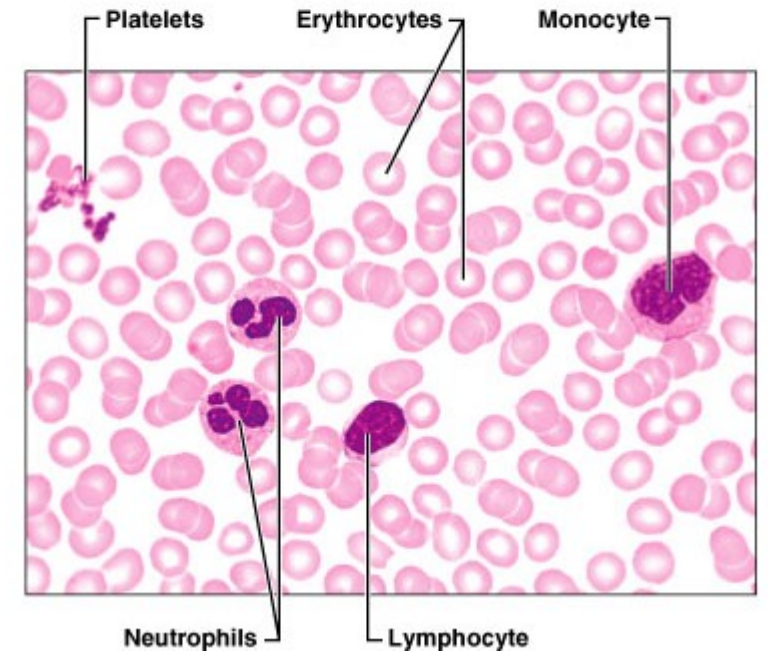
- the branch of medical science concerning blood and blood-forming tissues
- study of morphology, diagnosis, treatment, prognosis & prevention
- pathophysiology
  - Variations from normal blood element counts, function
  - Malignant disorders – leukaemia, lymphoma, myeloma
  - Haemoglobinopathies
- bone marrow and stem cell transplantation
- blood transfusion & blood banking

# Organs & tissues

- peripheral blood
- bone marrow
  
- spleen
- lymph nodes
- liver

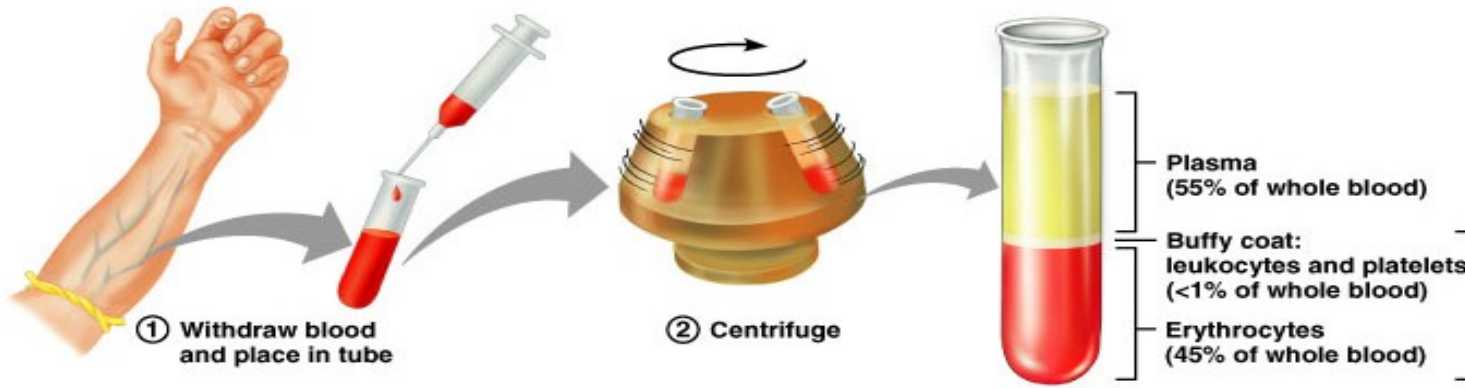


(a)



# Composition of blood

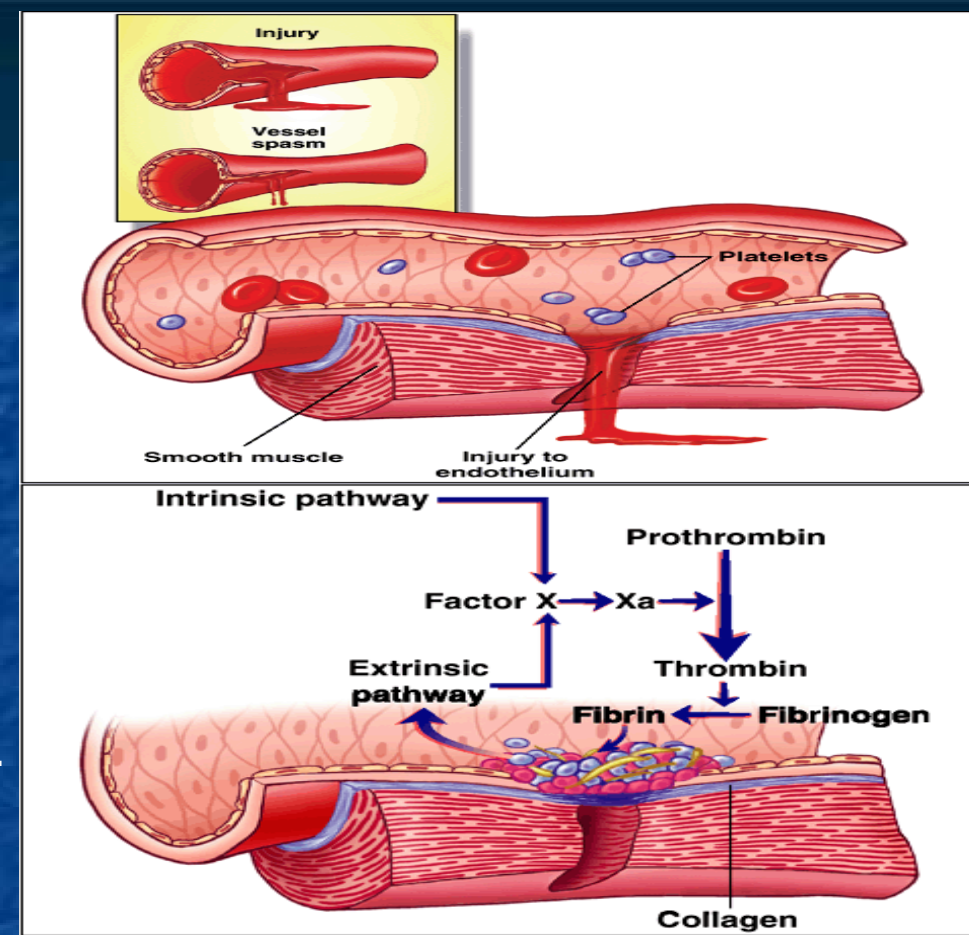
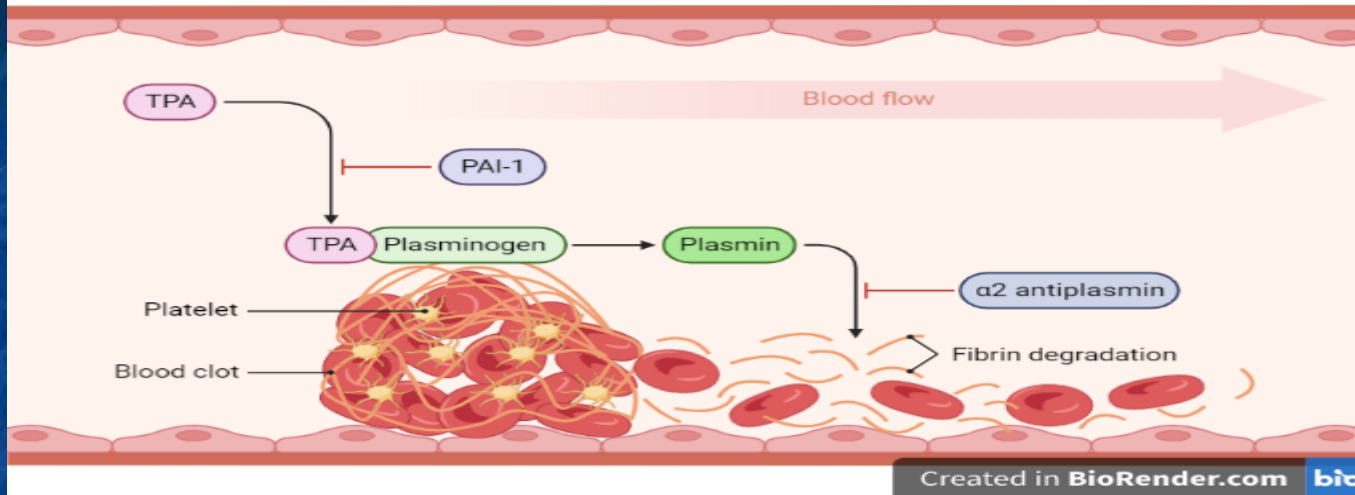
- Specialized connective tissue
- Blood cells (elements) suspended in plasma
- Blood volume: 5-6 litres in males and 4-5 litres in females
- Clinically important hematocrit
  - % of blood volume consisting of erythrocytes (red blood cells) to plasma volume
  - Male average 44-47; female average 39-42
  - Plasma contains water, ions, proteins: albumin, globulins, fibrinogen...
- Serum
  - Blood that is allowed to stand will clot
  - plasma without the clotting factors



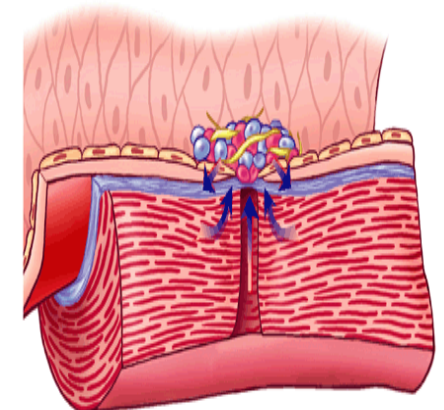
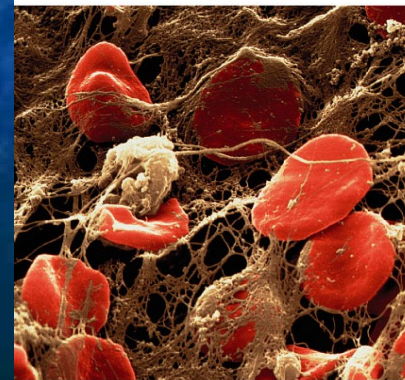
- Density gradient centrifugation
- Solution: Lymphoprep, Ficoll (1.077 g/ml)
  - layered over with whole blood or bone marrow as 1:1 volume
  - spin at 2,200 rpm for 20min, NO BRAKE
- Buffy coat



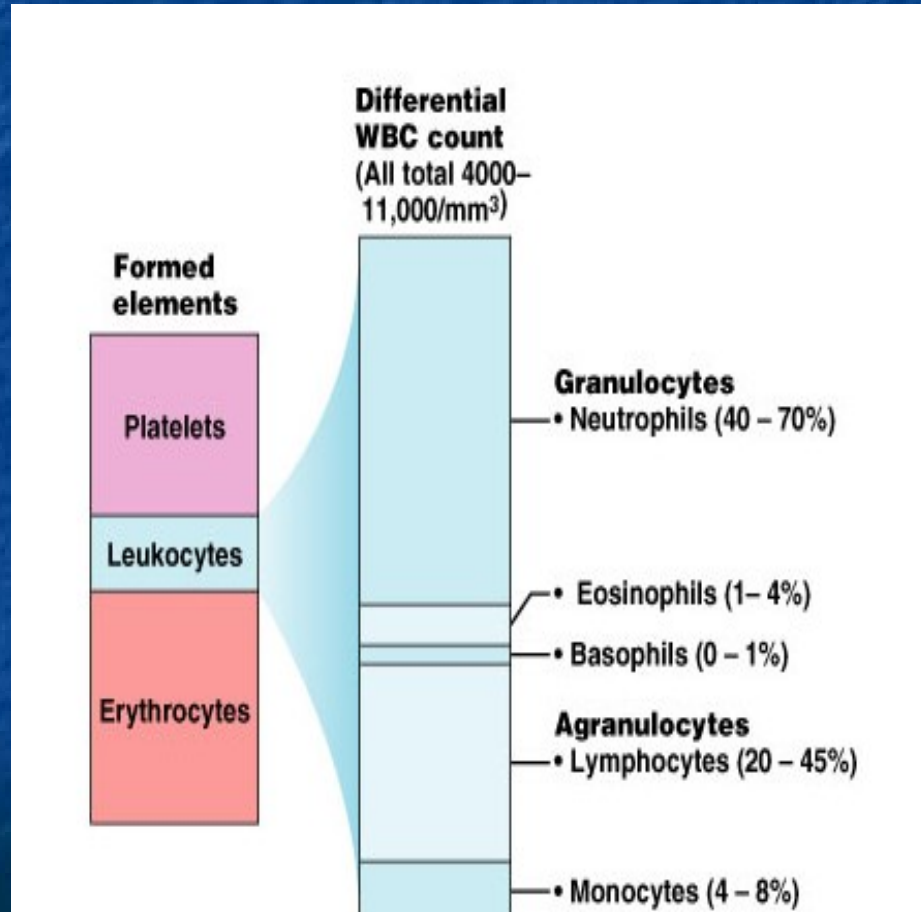
# Process of Blood Clot Formation



- Process in which blood changes from liquid to an insoluble clott
- conversion of [fibrinogen](#) into [fibrin](#) by the [serine protease](#) enzyme [thrombin](#).
- **Coagulation factors** are generally indicated by [Roman numerals](#)
- **Cofactors**: calcium, phospholipids
- **Fibrinolysis** - blood clots are broken down & resorbed
  - [TPA tissue plasminogen activator](#) (serine protease) - conversion of plasminogen to plasmin
  - **Hyperfibrinolysis** (excessive bleeding, increased vascular permeability)
  - **Hypofibrinolysis** (thrombosis, embolism)
  - DVT, stroke, heart attack
  - Decreased platelet numbers (thrombocytopenia)



# CBC test = complete blood count



Parameter	Male	Female
<b>Haemoglobin</b> g/dL	13.5 - 18.0	11.5 - 16.0
<b>WBC</b> x10 <sup>9</sup> /L	4.00 - 11.00	4.00 - 11.00
<b>Platelets</b> x10 <sup>9</sup> /L	150 - 400	150 - 400
<b>MCV</b> fL	78 - 100	78 - 100
<b>PCV, packed cell vol hematokrit</b>	0.40 - 0.52	0.37 - 0.47
<b>RBC</b> x10 <sup>12</sup> /L	4.5 - 6.5	3.8 - 5.8
<b>MCH, mean cell hemoglobin</b> pg	27.0 - 32.0	27.0 - 32.0
<b>MCHC</b> g/dL	31.0 - 37.0	31.0 - 37.0
<b>RDW</b>	11.5 - 15.0	11.5 - 15.0
<b>Neutrophils</b>	2.0 - 7.5	2.0 - 7.5
<b>Lymphocytes</b>	1.0 - 4.5	1.0 - 4.5
<b>Monocytes</b>	0.2 - 0.8	0.2 - 0.8
<b>Eosinophils</b>	0.04 - 0.40	0.04 - 0.40
<b>Basophils</b>	< 0.1	< 0.1

## Cell count variations from normal

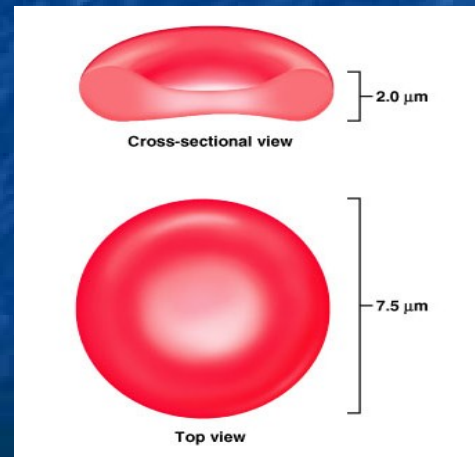
- Lymphopenia : **too few** lymphocytes
- Neutropenia: **too few** neutrophils
- Thrombocytopenia : **too few** platelets
  
- Neutrophilia: **too many** neutrophils
- Thrombocytosis: **too many** platelets
- Leucocytosis : **too many** WBC
- Erythrocytosis, Polycythemia: **too many** RBC



# Erythrocytes

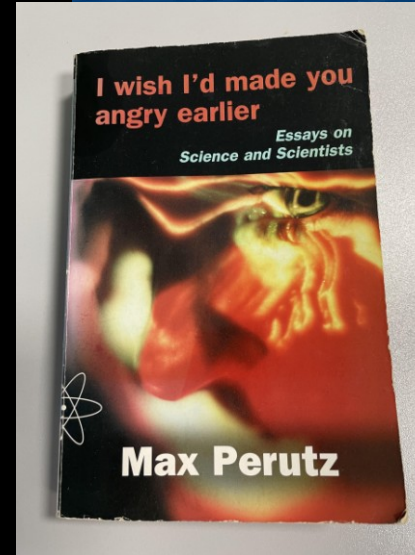
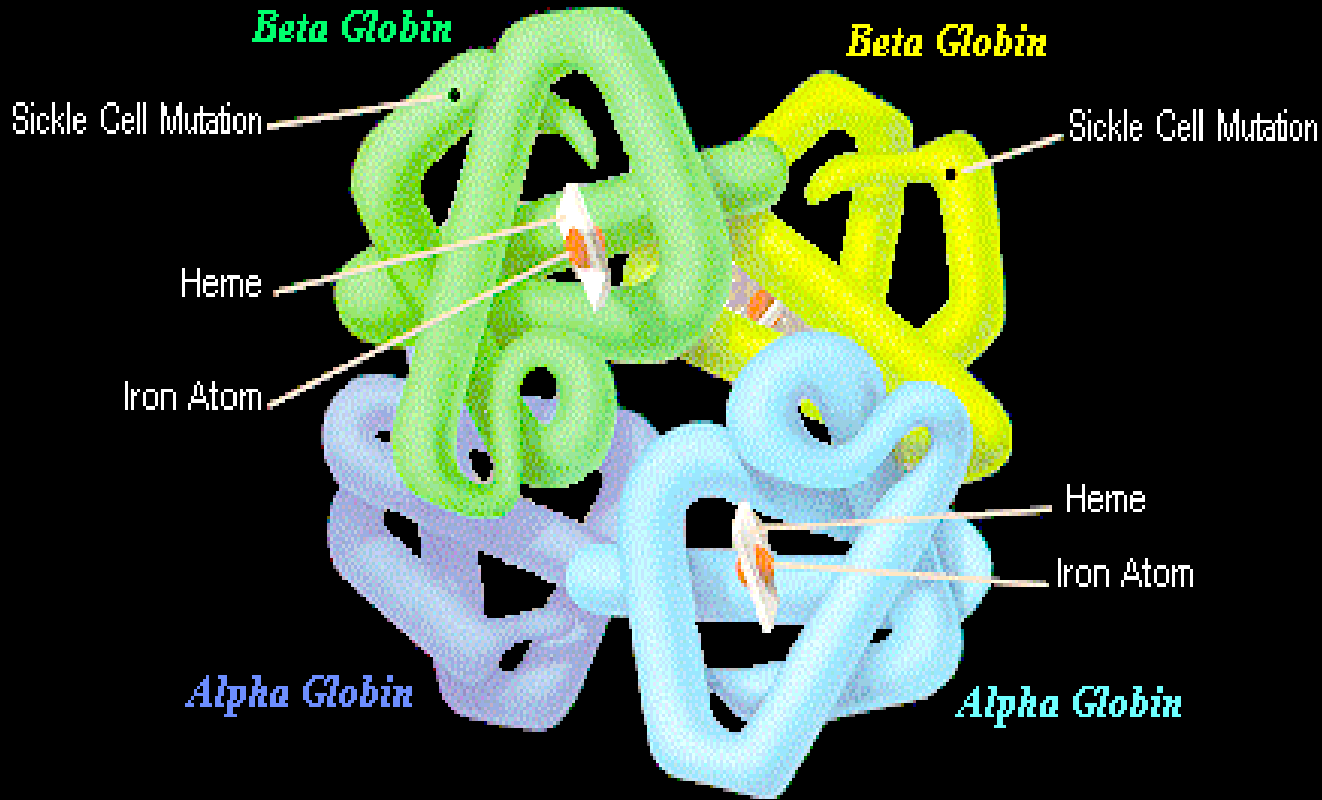
- Also called red blood cells (RBC)
- Biconcave discs and flexible
- Plasma membrane but no nuclei or organelles
- Packed with **hemoglobin** molecules
  - Oxygen carrying protein
  - 4 chains of amino acids, each with iron which is binding site for oxygen/CO<sub>2</sub>
  - young RBC still containing ribosomes are called **reticulocytes**
- Lifespan 100-120 days

Parameter	Male	Female
<b>Haemoglobin</b> g/L	135 - 180	115 - 160
<b>RBC</b> x10 <sup>12</sup> /L	4.5 - 6.5	3.8 - 5.8



1962 [Nobel Prize](#) for Chemistry for his [X-ray diffraction](#) analysis of the structure of [hemoglobin](#) (share with John Kendrew)

## HEMOGLOBIN



Heterotetramer

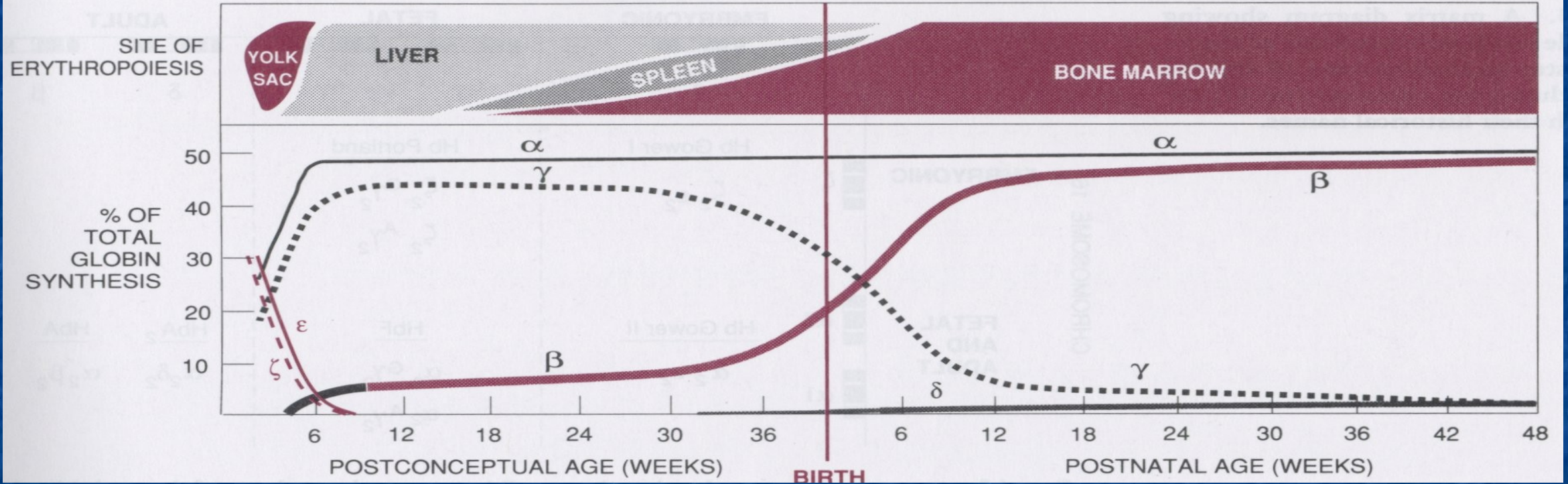
HbA<sub>1</sub>  $\alpha_2\beta_2$  96-98%

HbA<sub>2</sub>  $\alpha_2\delta_2$  2%

HbF  $\alpha_2\gamma_2$  this dominates until 6 weeks of age

postnatally, Hb A dominates through life

# Erythropoiesis

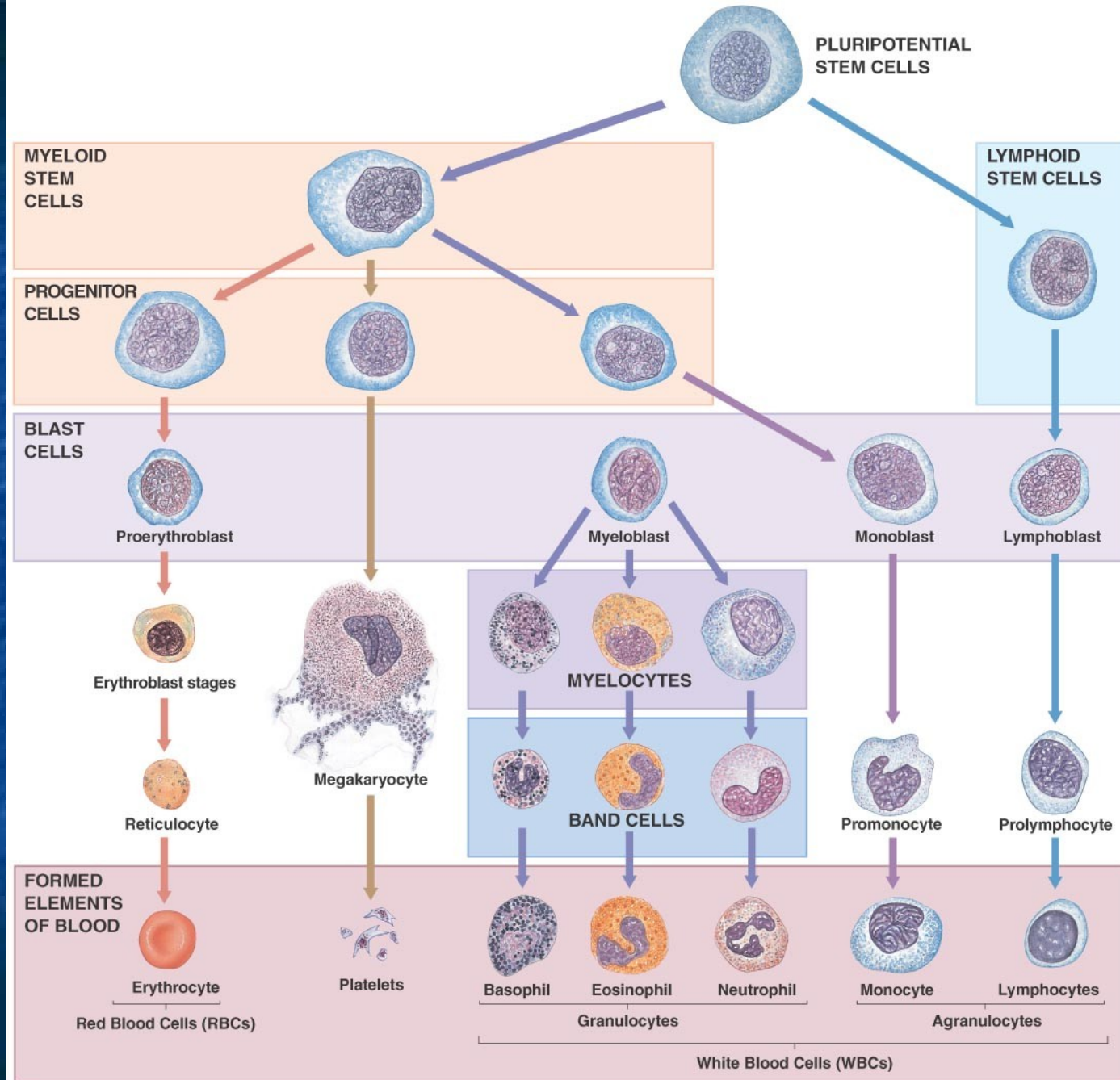


# Methemoglobin

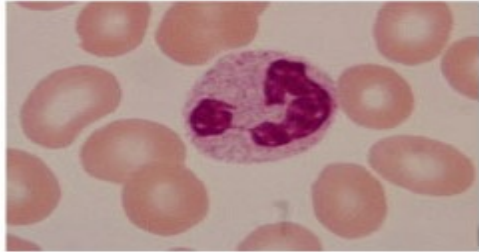
- MetHb is the derivative of Hb, in which the iron of the heme group is oxidized from  $\text{Fe}^{2+}$  to  $\text{Fe}^{3+}$
- MetHb is no longer completely capable of reversibly binding  $\text{O}_2$  (brown)
- MetHb forms continuously (present in RBC 1-2% c HB)
  - must be reduced actively by normal red cell metabolism or by ascorbic acid
  - cyanosis & fatigue 10%, coma & fatal 50-70%
  - nitrates in food and water, medication-local anesthetics, G6PD deficiency

# Hematopoiesis

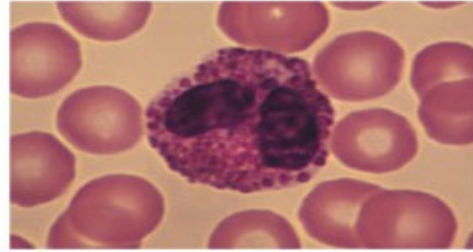
- Formation of blood cells
- Occurs mostly in red bone marrow
- All cells arise from the same pluripotent hematopoietic stem cells
- MSCs form fat cells, osteoblasts, chondrocytes, fibroblasts and muscle cells...



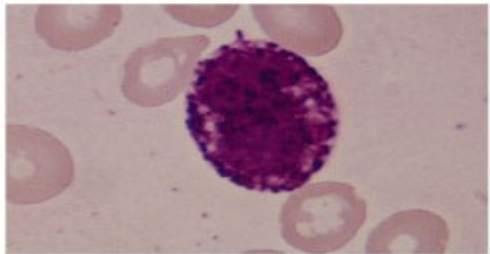
# Leukocytes



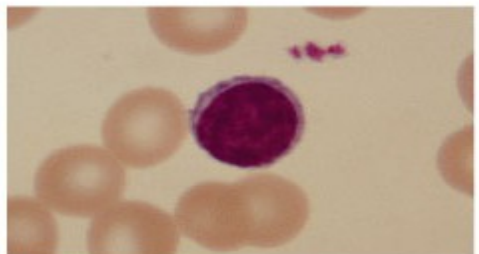
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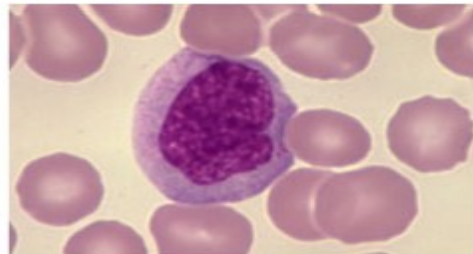
(b)



(c)



(d)




(e)

- A) Granulocytes
  - Granules, lobed nuclei
  - All phagocytic
  - Neutrophil: Nuclei of 2-6 lobes
  - Eosinophil: Nuclei bi lobed
  - Basophil: Dark purple granules
- D) lymphocyte
  - Large nucleus
  - T, B lineage
  - NK cells
- E) monocyte diff. into MØ

CD numbers (clusters of differentiation)

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the gene annotation report
- 3 **Browse**  
the gene report layouts
- 4 **Build**  
your own gene report

Details »

**Search genes here:**


CD123

Press Ctrl-Enter or click **Search**

**Example Searches**  
(click to try these samples)

- Gene Symbol(s)
- Wildcard queries
- Gene Ontology
- Affymetrix IDs
- Interpro
- Genomic interval

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"Register, set up some views, and you'll be finding all sorts of useful annotations for your genes or regions of interest."

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### News and Musings

**No trick, this new plugin is quite the treat** by ginger  
 Check out the new PanDrugs plugin from @pandrug\_cnio—the clean design neatly and intuitively provides information on drugs that relate to your gene of interest. Thanks to the good folks at Centro Nacional de Investigaciones Oncológicas, this awesome new resource is ... [\[view more\]](#)

**Gene Wiki Data, BioThings, Mark2Cure, & more! A review of 2017 in the Su Lab**  
**BioGPS Spotlight on the Sheep Gene Expression Atlas**  
**A look back at 2016 for BioGPS**  
**MyGene.info 2016 Year-end review**

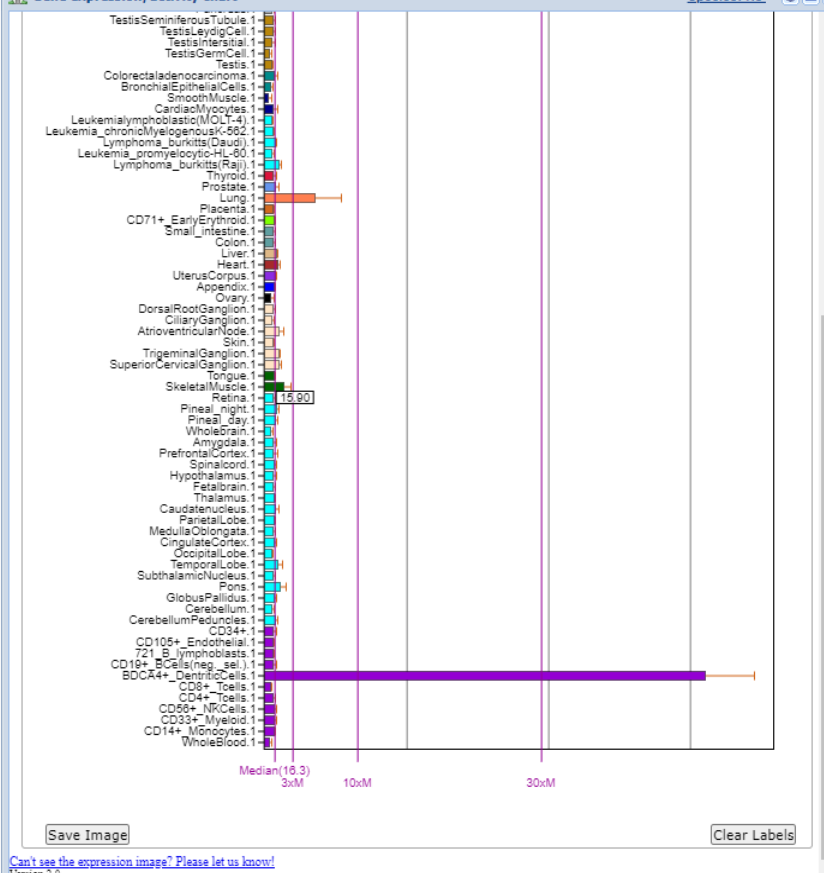


## Gene Report

### IL3RA (interleukin 3 receptor subunit alpha)

Species: Hs

#### Gene expression/activity chart



Median(16.3) 3xM 10xM 30xM

[Save Image](#) [Clear Labels](#)

Can't see the expression image? Please let us know!  
Version 2.0

#### Gene Identifiers

Species: Hs

<b>Symbol:</b>	IL3RA
<b>Description:</b>	interleukin 3 receptor subunit alpha
<b>Accessions:</b>	3563 (NCBI Gene) ENSG00000185291 (Ensembl) P26951 (UniProt) 430000 (OMIM) 48088 (HomoloGene)
<b>Aliases:</b>	CD123, IL3R, IL3RAY, IL3RX, IL3RY, hIL-3Ra
<b>Genome Location:</b>	chrX:1336616-1382689 (hg38)
<b>Function:</b>	<b>Molecular Function</b> cytokine receptor activity (GO:0004896) interleukin-3 receptor activity (GO:0004912) protein binding (GO:0005515) cytokine binding (GO:0019955) <b>Biological Process</b> cytokine-mediated signaling pathway (GO:0019221) cellular response to interleukin-3 (GO:0036016) interleukin-3-mediated signaling pathway (GO:0038156) <b>Cellular Component</b> plasma membrane (GO:0005886) external side of plasma membrane (GO:0009897) integral component of membrane (GO:0016021) receptor complex (GO:0043235)
<b>Interpro:</b>	Short hematopoietin receptor, family 2, conserved site (IPR003532) Immunoglobulin-like fold (IPR013783) Type I cytokine receptor, cytokine-binding domain (IPR015321) Fibronectin type III superfamily (IPR036116) IL-3 receptor alpha chain, N-terminal (IPR040907)
<b>Transcripts:</b>	NM_001267713.2 NM_002183.4 XM_005274431.5 XM_005274432.1 XM_005274780.5 XM_005274781.1 XM_017029491.2 XM_017030043.2 ENST00000331035 ENST00000381469 ENST00000432757 NP_001254642.1 NP_002174.1 XP_005274430.4

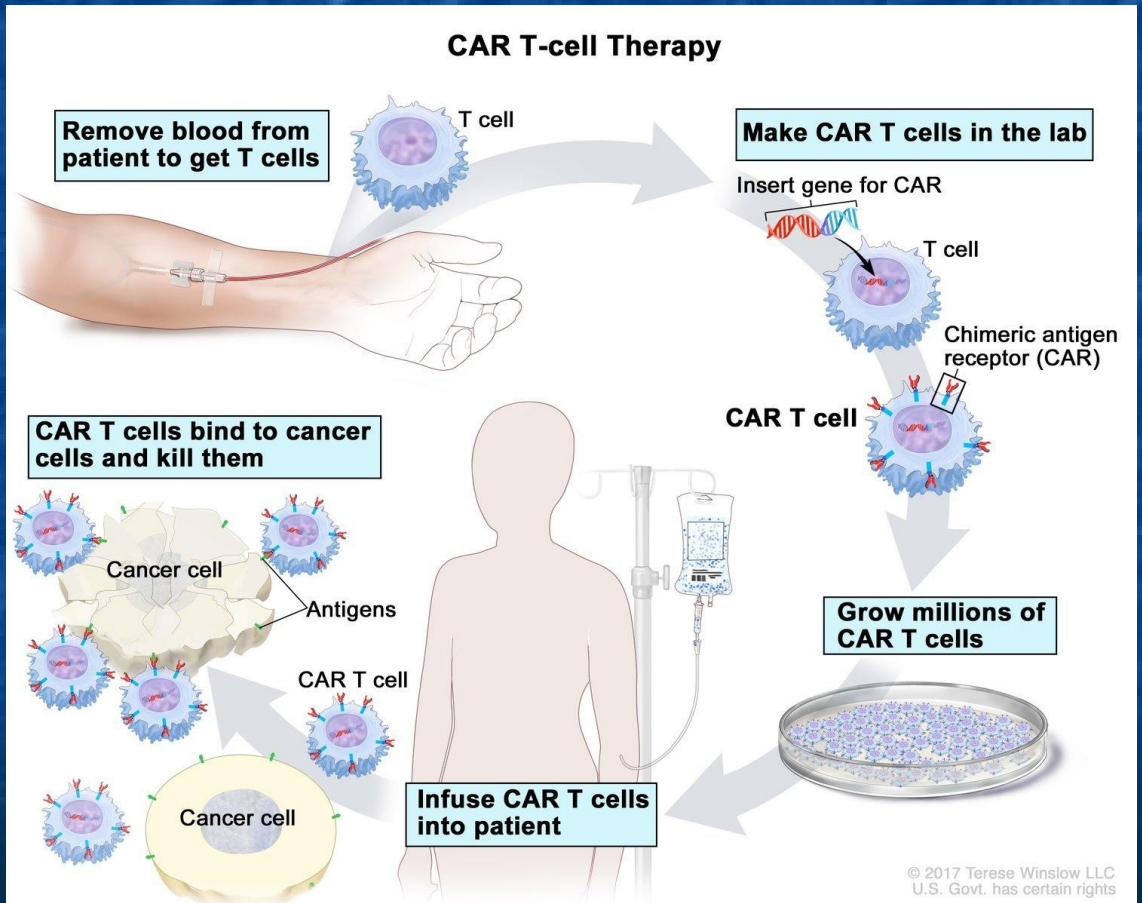
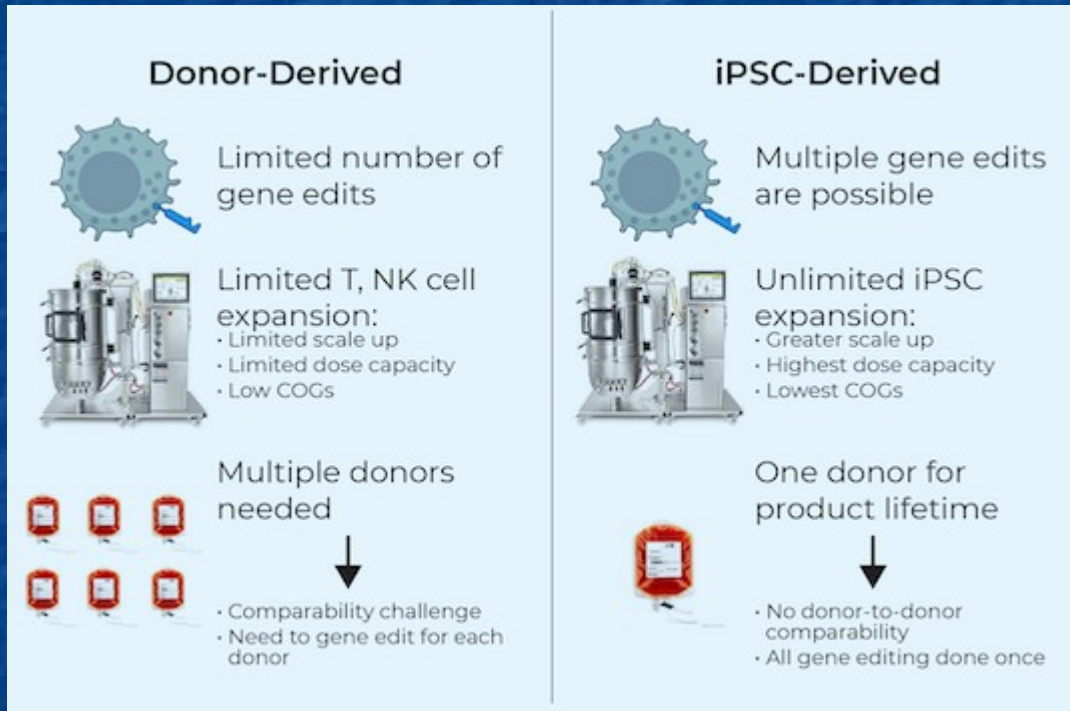
**Gene Wiki** Species: Hs

# Bone marrow

- Red marrow (medulla ossium rubra)
  - Consists mainly of haematopoietic tissue
  - Site of haematopoiesis (red and white blood cells, platelets)
- Yellow marrow (medulla ossium flava)
  - Made up of fat cells
- With age more red BM is converted to yellow BM
- BM stroma
  - Creates a microenvironment
    - Fibroblasts, MØ, adipocytes, Osteoblasts, osteoclasts, Endothelial cells
- Mesenchymal Stem cells (MSC)
  - Pluripotent stem cells that can differentiate *in vitro* and *in vivo* into a number of cell types incl. osteoblasts, chondrocytes, myocytes, adipocytes
- Induced pluripotent stem cells (iPSC)
  - type of pluripotent stem cells that can be generated directly from a adult somatic cell
  - by Oct3/4, Sox2, Klf4, and c-Myc transcription factors (Yamanaka factors, Nobel prize 2012)
  - The Advanced Therapies 2023 congress



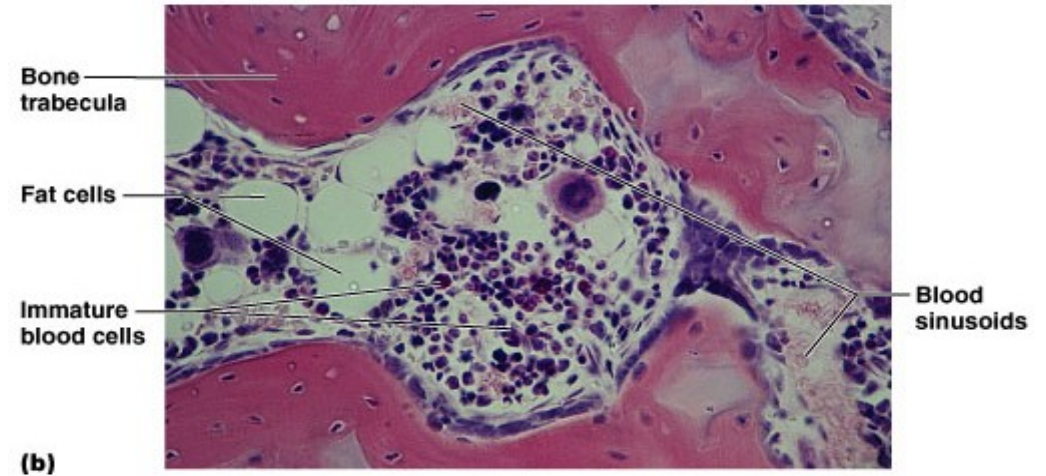
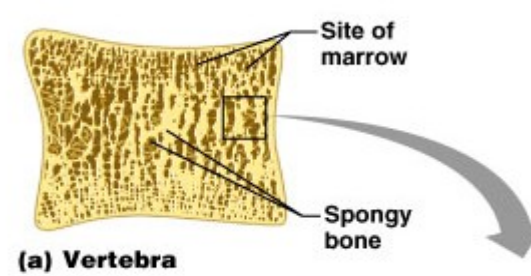
# T cell therapy



Century Therapeutics, Inc.

# Examination of bone marrow

- Invasive procedure
- BM sample obtained via biopsy or aspiration (sternum, pelvis)
- Used to newly diagnose & confirm suspected pathology
- To examine haematopoiesis
- Parallel to analysis of venous PB drawn



# Bone marrow harvest for transplantation

- BM is collected (pelvis under general anesthesia) and infused back:
  - Autologous Tx - same patient
  - Allogeneic Tx
    - Matched sibling
    - Matched Unrelated Donor (MUD)
  - Donor – recipient compatibility (MHC/HLA alleles)
  - Donor registers around the world

# The Anthony Nolan Trust

- <http://www.anthonynolan.org>
  - story of Anthony Nolan (1971-1979)
  - born with a rare Wiskott-Aldrich syndrome
  - only cure was Tx but no donor was available
  - Shirley Nolan (1942-2002) and her legacy to start a donor register
  - Currently over 750 000+ potential donors fully typed
  - Important charity – please log-in & donate
  - Research Institute & project Allostem
    - major EU grant involved 13 countries including CZ
    - (Prof. Bartunkova, Prague)
  - Essential clinical and research contribution to EBMT




# MHC proteins

- Major Histocompatibility Complex, locus on chr. 6
    - Highly polymorphic
    - Enormous MHC allelic diversity
  - HLA, human leukocyte antigens
    - Transplant antigens to prevent graft rejection
  - HLA I. class (HLA-A, B, C)
    - Expressed on all nucleated cells
  - HLA II. class (HLA-DP, DQ, DR)
    - Expressed on cells of IS
  - MHC III. class
    - Complement
- 
- Prof. S Marsh at ANRI, President of the European Federation for Immunogenetics
  - Allele frequencies vary in different populations and ethnic groups

# Haematopoietic stem cell transplantation

- Stem cell transplantation derived from:
  - BM
  - peripheral blood
  - cord blood
- **Autologous Tx**
  - Requires extraction/apheresis of stem cells (HSC)
  - Stored in the liq. nitrogen
  - Patient undergoes high-dose chemo ± radiotherapy
  - Established as the second-line treatment for lymphoma
- **Allogeneic Tx**
  - HLA matching
  - Recipient's immunosuppression
    - Calcineurin inhibitors (cyclosporin, tacrolimus)
    - Corticosteroids (methylprednisolone, dexamethasone, prednisolone)
    - Cytotoxic immunosuppressants (azathioprine, chlorambucil, cyclophosphamide, methotrexate)
  - Full ablative vs **Reduced intensity conditioning (RIC)**
  - RIC pioneered by **Prof Stephen Mackinnon** at University College London
  - Numerous clinical trials ongoing

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X

#### Country ⓘ

▼

X

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# Cell storage for transplantation

- Cells frozen in 5-10% DMSO/human serum
  - DMSO, Dimethyl sulfoxid
  - Prevents the formation of ice crystals during the freezing process
- Stored at liquid nitrogen ( $-196^{\circ}\text{C}$ ) for months/years
- Decreasing the temperature as  $1^{\circ}\text{C}$  per minute over night at  $-80^{\circ}\text{C}$  in the Mr Frostie containing isopropyl alcohol





# Post HSCT

- Cytokine storm
- **Graft-versus-host disease (GvHD)** as a major complication post SCT
  - T cells present in the transplant recognize the host's (recipient's) cells as foreign
  - Minor histocompatibility antigens
  - **Acute** within 100 days as major challenge to transplant mortality and morbidity (grade 1-4)
  - **Chronic** as moderate to severe
  - Skin, liver, gut and GI tract, lung
  - Donor T cells mediate **graft -versus-tumour effect** (versus leukaemia, lymphoma or myeloma)

# Graft – versus - tumour effect

- GvL (versus leukaemia)
  - Most prominent in CML patients, (also in ALL)
- GvM (myeloma)

*Cytotherapy*, 2012; 14: 1110–1118

**informa**  
healthcare

## **Human Vdelta1 gamma-delta T cells exert potent specific cytotoxicity against primary multiple myeloma cells**

ANDREA KNIGHT, STEPHEN MACKINNON & MARK W. LOWDELL

*Department of Haematology, Royal Free Hospital, University College Medical School London, UK*

### **Abstract**

*Background aims.* Human gamma-delta ( $\gamma\delta$ ) T cells are potent effector lymphocytes of innate immunity involved in anti-tumor immune surveillance. However, the V $\delta$ 1  $\gamma\delta$  T-cell subset targeting multiple myeloma (MM) has not previously been investigated. *Methods.* V $\delta$ 1 T cells were purified from peripheral blood mononuclear cells of healthy donors and patients with MM by immunomagnetic sorting and expanded with phytohemagglutinin (PHA) together with interleukin (IL)-2 in the presence of allogeneic feeders. V $\delta$ 1 T cells were phenotyped by flow cytometry and used in a 4-h flow cytometric cytotoxicity assay. Cytokine release and blocking studies were performed. Primary myeloma cells were purified from MM patients' bone marrow aspirates. *Results.* V $\delta$ 1 T cells expanded from healthy donors displayed prominent cytotoxicity by specific lysis against patients' CD38<sup>+</sup> CD138<sup>+</sup> bone marrow-derived plasma cells. V $\delta$ 1 T cells isolated from MM patients showed equally significant killing of myeloma cells as V $\delta$ 1 T cells from normal donors. V $\delta$ 1 T cells showed similarly potent cytotoxicity against myeloma cell lines U266 and RPMI8226 and plasma cell leukemia ARH77 in a dose-dependent manner. The interferon (IFN)- $\gamma$  secretion and V $\delta$ 1 T-cell cytotoxicity against myeloma cells was mediated in part through the T-cell receptor (TCR) in addition to involvement of Natural killer-G2D molecule (NKG2D), DNAX accessory molecule-1 (DNAM-1), intracellular cell adhesion molecule (ICAM)-1, CD3 and CD2 receptors. In addition, V $\delta$ 1 T cells were shown to exert anti-myeloma activity equal to that of V $\delta$ 2 T cells. *Conclusions.* We have shown for the first time that V $\delta$ 1 T cells are highly myeloma-reactive and have therefore established V $\delta$ 1  $\gamma\delta$  T cells as a potential candidate for a novel tumor immunotherapy.

# SCT and CMV

- HCMV cytomegalovirus
- Common beta-herpes virus (HHV5)
- Primary infection followed by a latent infection
- Vigorous immune response, persistent suppression of viral replication
- CMV seropositivity associated with **immune senescence** of virus-specific CD4+ and CD8+ T cells (**Prof. Paul Moss, Graham Pawelec, Mark Wills**)
- Multiple strategies to evade the host immune system
- Immunocompetent vs immunocompromised host

- Donor+ Recipient+
- D+ R-
- D- R+
- D- R-

8th International Congenital CMV Conference  
& 18th International CMV Workshop

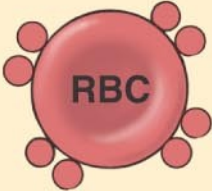
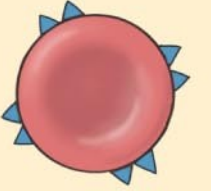
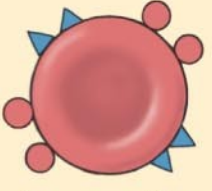



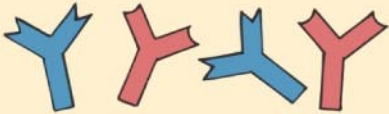
28 March - 1 April 2022



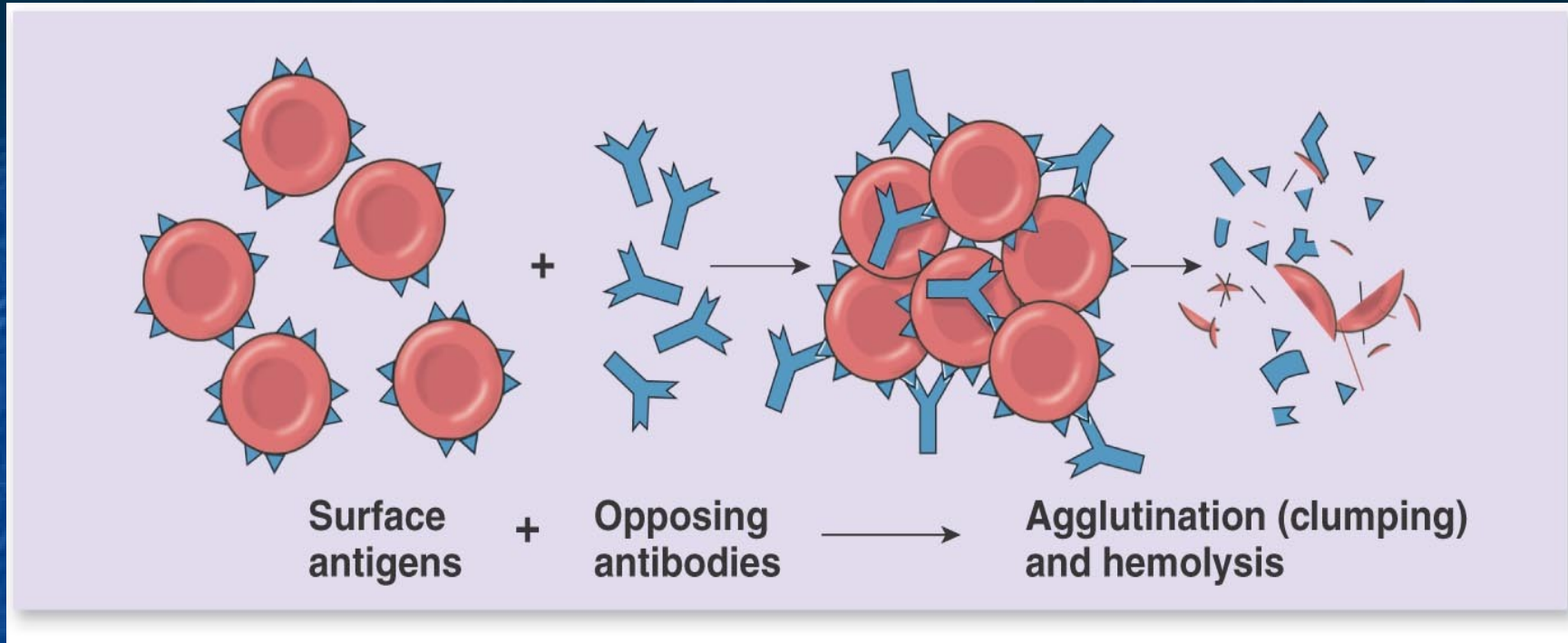
# Blood transfusion

- process of receiving blood intravenously
- to replace a lost blood component (red blood cells, plasma, platelets or clotting factors)
- donated blood processed/separated by centrifugation
- tested for infections (HIV 1, 2, HTLV 1, 2, Hep B, C, syphilis, CMV)
- stored in Blood Bank
- compatibility testing between D and R
- typing of recipient's blood determines the ABO blood groups and Rh status
- sample tested for any alloantibodies that may react with donor blood

# ABO blood groups

TYPE A	TYPE B	TYPE AB	TYPE O
 <p>RBC</p> <p>Surface antigen A</p>	 <p>Surface antigen B</p>	 <p>Surface antigens A and B</p>	 <p>Neither A nor B surface antigens</p>
 <p>Anti-B antibodies</p>	 <p>Anti-A antibodies</p>	<p>Neither anti-A nor anti-B antibodies</p>	 <p>Anti-A and anti-B antibodies</p>

(a)



- If a blood transfusion is given to a person who has antibodies to that type of blood, then the transfused blood will be attacked and destroyed (transfusion reaction)

# ABO blood group types

## ■ Europe:

- A 45%
- B 16%
- AB 6%
- O 33%

**TABLE 20.4 Differences in Blood Group Distribution**

Population	Percentage with Each Blood Type				
	O	A	B	AB	Rh+
<b>U. S. (average)</b>	46	40	10	4	85
Caucasian	45	40	11	4	85
African-American	49	27	20	4	95
Chinese	42	27	25	6	100
Japanese	31	39	21	10	100
Korean	32	28	30	10	100
Filipino	44	22	29	6	100
Hawaiian	46	46	5	3	100
<b>Native North American</b>	79	16	4	<1	100
<b>Native South American</b>	100	0	0	0	100
<b>Australian Aborigines</b>	44	56	0	0	100

# Rh blood group system

- consists of 50 defined blood-group antigens
- The commonly used terms *Rh factor*
  - *Rh positive* (85%)
  - *Rh negative* (15%) refer only to the *D antigen*
- We either have or don't have it on the surface of red cells
- Condition of hemolytic disease of the newborn
  - Incompatibility between mother and the fetus



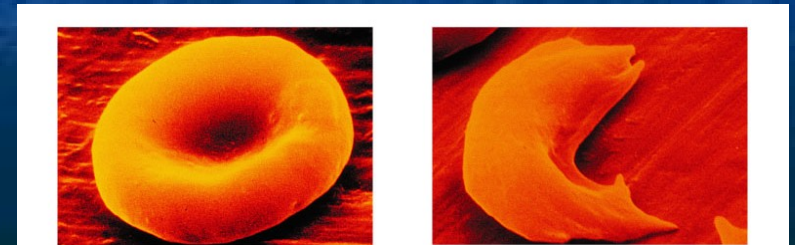
# Haematological disorders

# Disorders of Erythrocytes

- **Polycythemia:** high RBC, increased Hb and hematokrit
- **Anaemia:** low RBC
- over 400 types of anaemia
- develops when:
  - Decrease in the total number of red blood cells (RBC)
    - **Blood loss** — pregnancy, Acute: trauma and surgery, Chronic: many types of cancers (colon, bladder carcinomas), IBD patients
    - **Decreased production of RBC - result of BM failure & differentiation of stem cells**
    - **Increased destruction of RBC**
  - Decrease of the amount of haemoglobin and/or its reduced ability to carry oxygen

# Disorders of Erythrocytes - Hemoglobinopathies

- are inherited single-gene disorders
- characterized by decreased and/or unstable haemoglobin
  - Thalassemia
    - usually results in underproduction of normal globin proteins often through mutations in regulatory genes
    - Beta; subtypes major (both beta globin genes missing) and intermedia
    - Alpha; subtypes Hb H and hydropsis fetalis
    - Minor; either alpha or beta globin gene missing
  - Sickle cell disease
    - Estimated that 7% of world's population (~420 million) are carriers
    - Inheritance of two abnormal B-globin gene (chr 11)
    - The gene defect is a SNP (single nucleotide polymorphism) where GAG changes to GTG and results in glutamic acid being substituted by valine (E6V)



# G6PD Deficiency

- Glucose-6-phosphate dehydrogenase deficiency
  - enzyme involved in the pentose phosphate pathway
  - important in red blood cell metabolism
- Perhaps most common, world-wide congenital abnormality
  - > 300 variants identified
  - X-linked inheritance
- Common G6PD deficient variants are associated with an acute intermittent hemolysis and anaemia
- vast majority never symptomatic!

# Disorders of Platelets

## ■ Thrombocytopenia

- normal platelet count ranges from 150,000 - 450,000 per  $\mu\text{L}$
- platelet count below 50,000 per  $\mu\text{L}$
- occasional bruising, nosebleeds, bleeding gums
- !! internal bleeding
- many causes: decreased production or increased destruction (SLE, HIV)
  - Vitamin B12 or folic acid deficiency
  - Leukaemia, MDS
  - Decreased production of thrombopoietin by the liver in liver failure
  - Bacterial, viral infections, sepsis
  - Hereditary: Fanconi anemia
- Treatment depending on the cause
  - Corticosteroids
  - Platelet transfusion

# Disease of the bone marrow

- Congenital defects
- Aplastic anemia
- Malignancies
  - Leukaemia
  - Lymphoma
  - Multiple myeloma

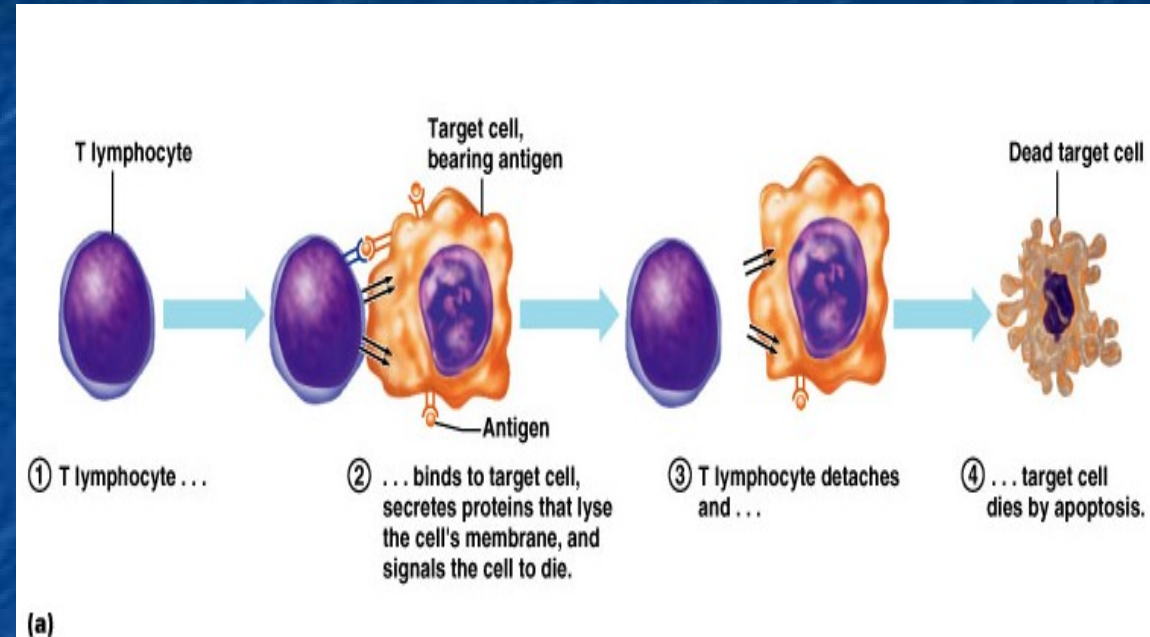
# Congenital defects

## ■ Dyskeratosis congenita (DKC)

- is a rare progressive congenital disorder resembling premature aging
- Essen. bone marrow failure syndrome
- DKC typically develop between ages 5-15 years
- is a result of one or more mutations in the long arm of the chr X **in the gene DKC1**
- Heiss NS, [Knight SW](#), Vulliamy TJ, et al." May 1998, *Nat. Genet.* **19** (1): 32–38

# Haematological Malignancies

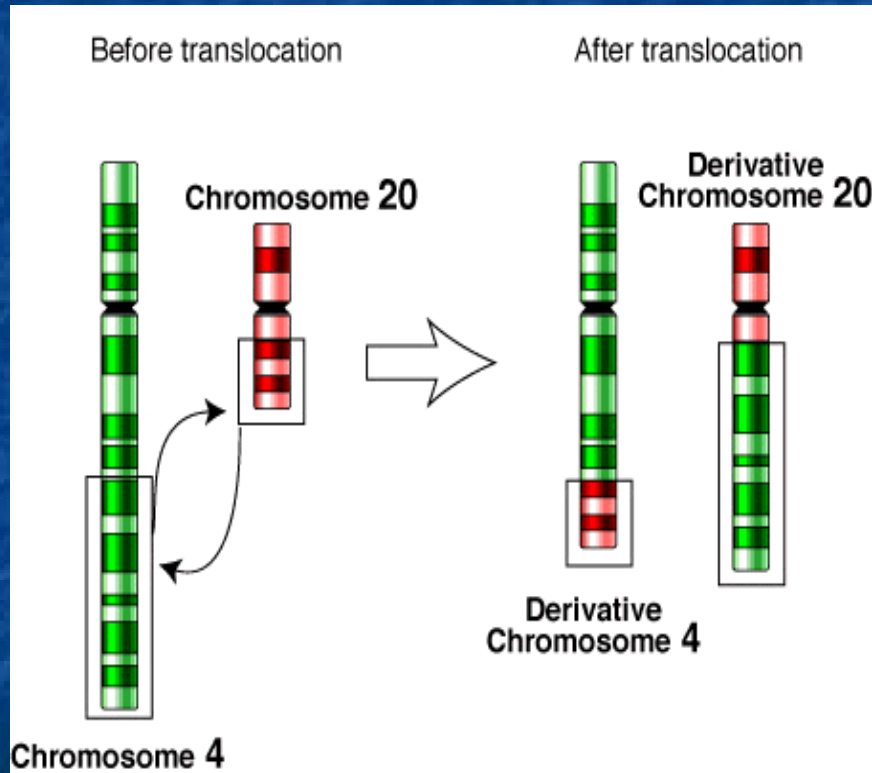
- Understand the pathogenesis
  - Genetic alterations including translocations, mutations, SNPs...
  - Leukaemogenesis
    - Hereditary factors (Fanconi A, Down sy)
    - Radiation, chemicals, drugs
    - Virus related (EBV, CMV)
    - Retrovirus mediated (HTLV-1)
    - Age related
    - Oncogenes, tumour suppressor genes
- Understand the pathophysiology
- Able to list down the laboratory investigations required for diagnosis
- Therapy & clinical trials
- Research !



Stress ligands  
Immune surveillance  
Tumour evasion  
Shedding  
Trogocytosis



# Leukaemia and chromosomal translocations



- Ionising radiation can cause breakage of the phosphodiester backbone of both strands of DNA
- Double-strand breaks are very efficiently repaired
  - Potential loss of genetic material
  - Double-strand ends recognised as "foreign" DNA and destroyed
- If double-strand breaks occur in two different chromosomes then possibility for incorrect repair taking place

# Frequent translocations

B-ALL	t(1;19)	5%
B-ALL (in children)	t(12;21)	22%
T-ALL	t(5;14)	20%
T-ALL	1p32 deletion	25%
AML	t(15;17)	13%
AML	t(8;21)	7%
CML	t(9;22)	99%

# Leukaemia I.

- heterogenous group of malignant disorders which is characterised by uncontrolled clonal and accumulation of blasts in the bone marrow and body tissues
- Excessive production of WBC
- Often non fully differentiated cells called "blasts"
- WBC have abnormal function
  - Resistant to apoptosis
  - Excessive proliferation
  - Tumour microenvironment in the bone marrow
- Disruption of normal haematopoiesis in bone marrow

# Leukaemia II.

- Classification

- **Acute**

- Acute lymphoblastic leukemia (T-ALL & B-ALL)
- Acute myeloid leukemia

- **Chronic**

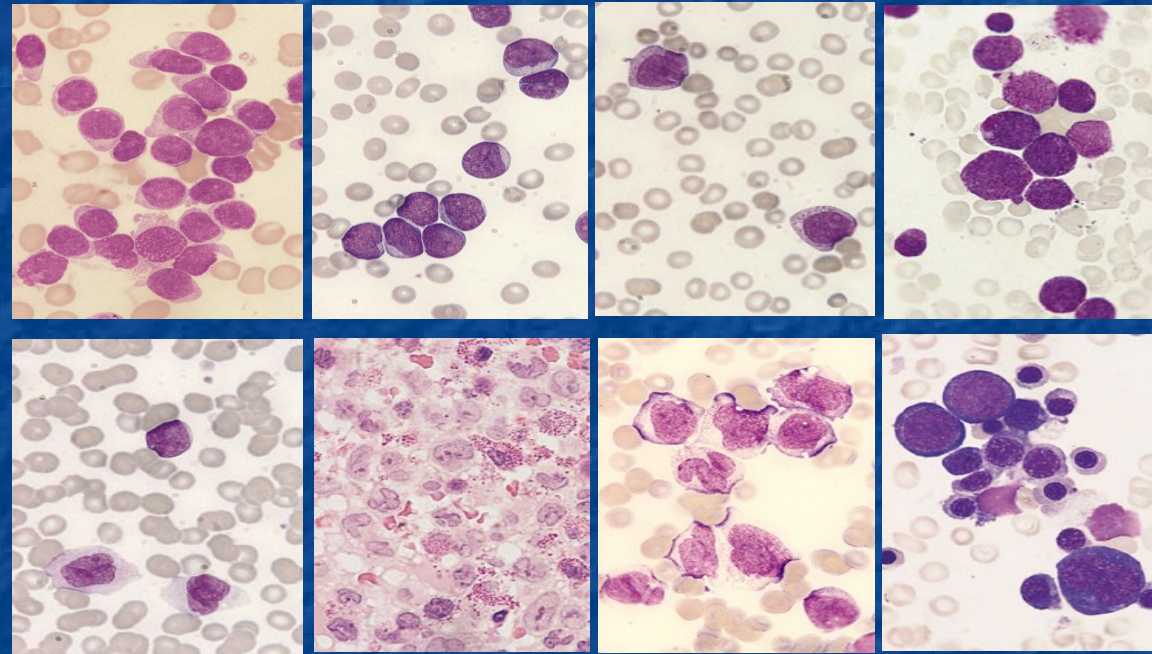
- Chronic myeloid leukemia
- Chronic lymphocytic leukemia

# Acute Lymphoblastic Leukaemia

- Cancer of the blood affecting the white blood cell *LYMPHOCYTES*
- Commonest in the age 2-10 years
- Peak at 3-4 years.
- Incidence decreases with age, and a secondary rise after 40 years.
- In children - most common malignant disease
- 85% of childhood leukaemia

# Acute Myeloid Leukaemia

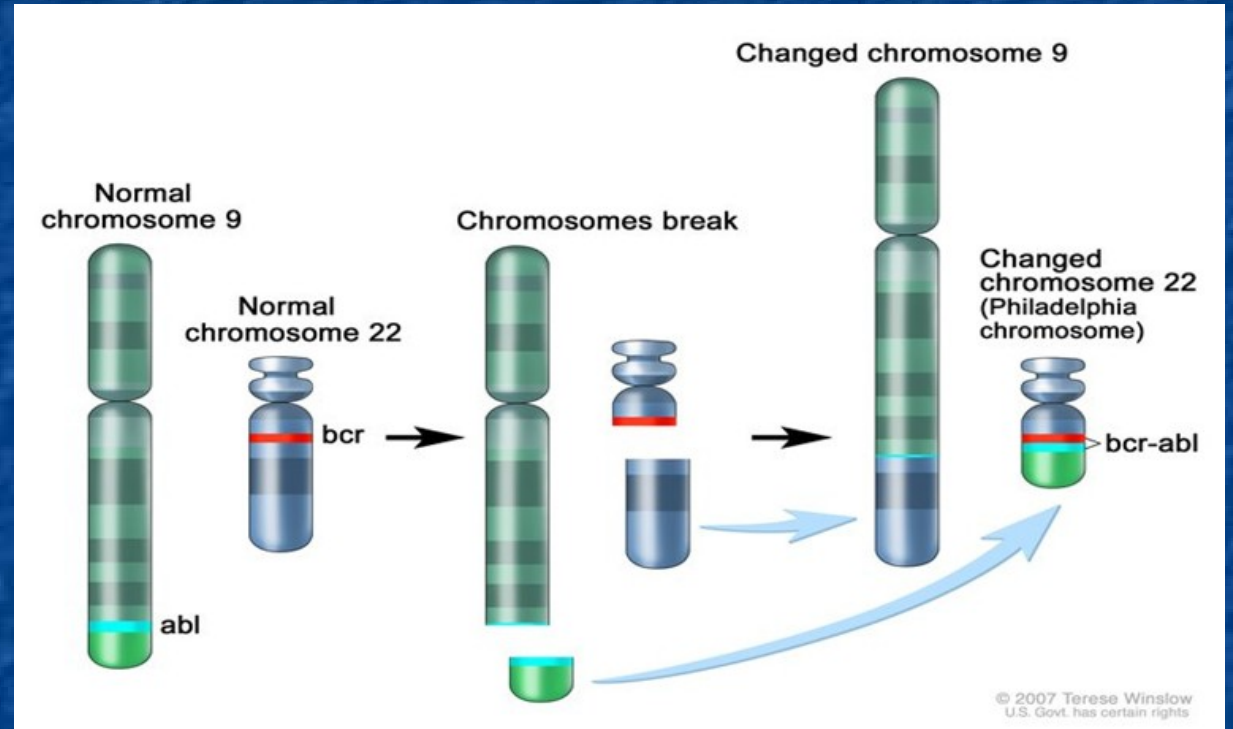
- Arise from the malignant transformation of a myeloid precursor
- Rare in childhood (10%-15%)
- The incidence increases with age
- 80% in adults
- FAB classification
  - M0 Undifferentiated blasts
  - M1 AML without maturation
  - M2 AML with maturation
  - M3 Acute promyelocytic leukemia
  - M4 Acute myelomonocytic leukemia
  - M5 Acute monocytic leukemia
  - M6 Acute erythroblastic leukemia
  - M7 Acute megakaryoblastic leukemia



From lecture by Dr NJ Dodd BS967-7-SP: Session 6  
[courses.essex.ac.uk/bs/bs967/restricted/NJD%20Leukaemia.ppt](https://courses.essex.ac.uk/bs/bs967/restricted/NJD%20Leukaemia.ppt)

# Molecular biology of CML

- Philadelphia Chromosome (Ph)
- t(9;22) balanced translocation
- disruption of the ABL (Chr 9) and BCR (Chr 22) genes
- formation of two hybrid genes
  - 5'BCR/3'ABL
  - 5'ABL/3'BCR
- BCR/ABL mRNA,
- p210 'fusion' oncoprotein as constitutively active tyrosine kinase resulting in the permanent activation of the RAS pathway



[visualsonline.cancer.gov/addlb.cfm?imageid=7153](http://visualsonline.cancer.gov/addlb.cfm?imageid=7153)

# New CML Treatment

- Design compounds that specifically target the p210 protein
- p210 is CML specific
- imatinib (Gleevec, Glivec, STI571)
- specifically inhibits the ABL kinase
  - imatinib inhibits the growth of CML cells in culture
  - progression-free survival at 24 months is 87%
- Prof John Goldman Hammersmith Hospital London
- Prof John Barret NIH Washington
- Prof Francois Mahon Bordeaux
- Prof Mayer FN Brno
- New generations of the TKI – dasatinib, nilotinib

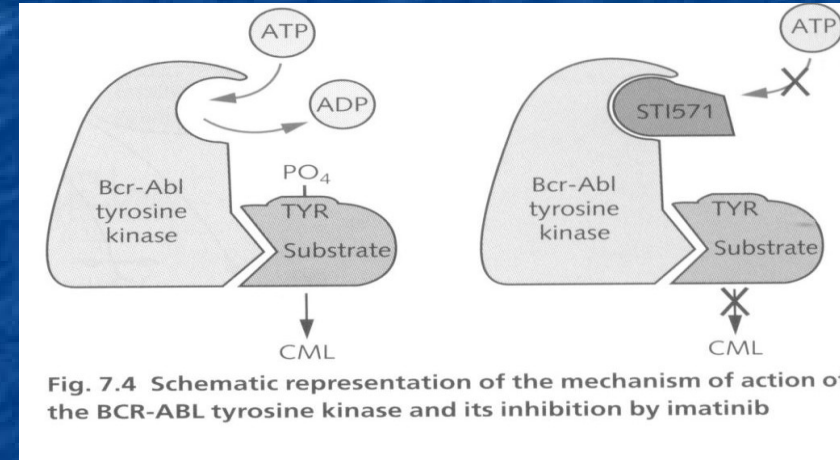


Fig. 7.4 Schematic representation of the mechanism of action of the BCR-ABL tyrosine kinase and its inhibition by imatinib

*Molecular Haematology Provan & Gribben*

Cancer Immunology, Immunotherapy  
<https://doi.org/10.1007/s00262-022-03312-3>

RESEARCH



**Expansions of tumor-reactive Vdelta1 gamma-delta T cells in newly diagnosed patients with chronic myeloid leukemia**

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# Chronic lymphocytic leukaemia

- Most common leukaemia in the Western countries
  - lymphocytosis of  $> 5000$  cells/ $\mu$ l for
  - $> 3$  months
- Flow cytometry of peripheral blood (phenotype CD19, CD5, CD23)
- Bone marrow biopsy
- Staging according to Rai (I-IV)
- Mutated IgVH
- Del11q (ATM)
- Del17p
- Del13q (RB1)
- +12
- TP53
- Prof Michael Doubek, IHOK, FN Brno

# Multiple Myeloma

- B cell malignancy of plasma cells CD38+CD138+ in the bone marrow
- Pre-malignant stage:
  - MGUS – monoclonal gammopathy of undetermined significance
  - Progression of 1% per annum
- Bone marrow biopsy
- Therapy (IMiDS)
- Prof. Roman Hájek FN Ostrava

# Questions