LEUKOCYTES, LEUKOPENIA, LEUCOCYTOSIS, LEUKAEMIA

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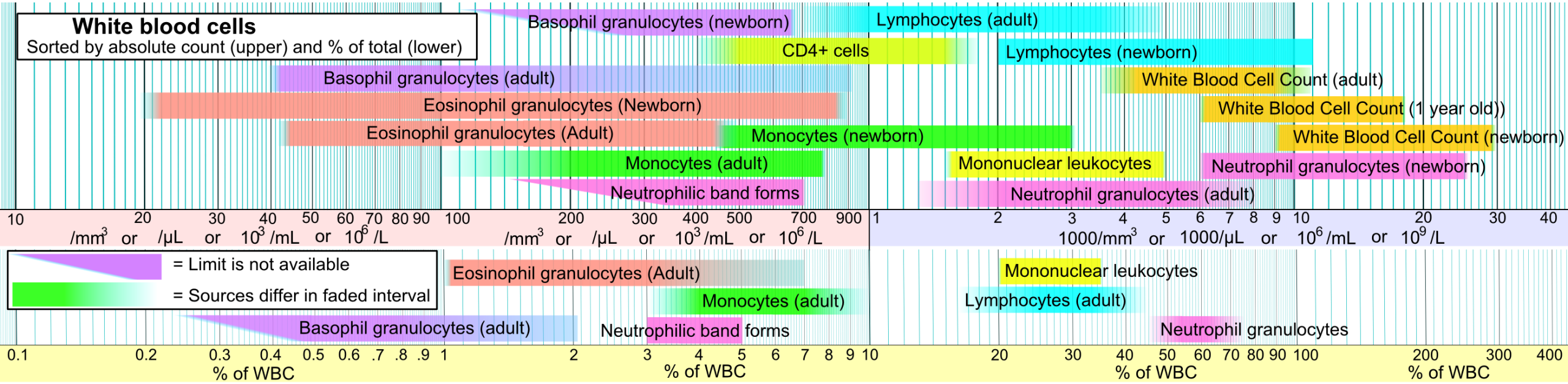
PHYSIOLOGICAL DATA OF WHITE BLOOD CELLS



https://upload.wikimedia.org/wikipedia/commons/b/b5/Reference_ranges_for_blood_tests_-_white_blood_cells.png

LEUKOPENIA, NEUTROPENIA, LYMPHOPENIA

- Leukopenia - <4000 cells/µl
- Neutropenia - <1500 cells/µl
- Lympho(cyto)penia – adults <1000 cells/µl (symptomatic <300 cells/µl) vs. children <3000 cells/µl

- Causes
  1. Decreased production
  2. Increased destruction or cells utilisation

When you haven't been paying attention to the lecture and the professor asks you what labs you would like to order

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LEUKOPENIA

- Drop in one or more white blood cells subpopulations in peripheral blood
- It is a SYMPTOM!!!

- „Leukopenia“ and „neutropenia“ might be used interchangeably -> neutrophiles comprise 50-75 % of all leukocytes in adults

- Agranulocytosis – clinical manifestations of severe neutropenia
  - Fatigue, fever, severe to fatal course of (even mild) diseases
  - Oral cavity – mucosa ulcers –gingiva and pharynx

LEUKOPENIA CAUSES

Decreased production

- Aplastic anaemia
- Genetics
- Autoimmune disorders
- Medication induced
- Onkohematologic diseases
  - Leukaemia and lymphomas

Increased utilisation and/or destruction

- HIV infection
- Onkohematologic diseases
  - Leukaemia and lymphomas

NEUTROPENIA AND AGRANULOCYTOSIS

- Neutrophils
  - 50–75 % of all leukocytes
  - Non-specific defence, „first-contact troops“
  - Exposure to viruses, bacteria, physical and chemical factors, malignancies
  - Functions – DEGRANULATION, phagocytosis, chemotaxis and inflammatory response regulation
- Neutropenia degrees
  - Mild – 1000 – 1500 cells/µl
  - Moderate – 500 – 1000 cells/µl
  - Severe - <500 cells/µl (AGRANULOCYTOSIS, some sources state <100 cells/µl)
  - Critical - <100 cells/µl -> extreme morbidity and mortality risk

AGRANULOCYTOSIS

- Congenital (rare)
  - AD, ar, X-rec. – genes ELANE, HAX1, WAS (X-rec.), G6PC3, etc.
  - Autoimmune neutropenia
- Decreased production
  - Chemotherapy – destruction/"crippling" of hemopoietic stem cell – e.g. Adriamycin, doxorubicin, cyclophosphamide, cisplatina, paclitaxel, carboplatina, etc.
  - Onkohematological diseases – myelodysplastic sy., leukaemia, lymphomas, etc.
  - Nutrients deficiency – vit. B9, B12
- Increased destruction
  - Autoimmune diseases – e.g. systemic lupus erythematosus, Crohn disease, rheumatoid arthritis
  - Drug-induced – idiosyncratic drug reactions

ELANE – elastase, neutrophile expressed, HAX1 – hemopoietic cells specific substrate Lyn 1 associated protein X1, G6PC3 – glucose-6-phosphatase catalytic subunit

The risk categories of chemotherapy regimen to induce febrile neutropenia (FN)

Cancer type	FN risk category (%)/Chemotherapy regimen		
	< 10	10–20	> 20
Breast cancer	AC	FEC/docetaxel	AC- docetaxel
	Epirubicin/cyclophosphamide ± lonidamide	FEC-120	Docetaxel-AC
		FEC-100	
	Doxorubicin/cyclophosphamide–paclitaxel	Cyclophosphamide/mitoxantrone	Doxorubicin/docetaxel
	CMF	Paclitaxel (every 21 days)	Doxorubicin/paclitaxel
	Doxorubicin/cyclophosphamide	DDG doxorubicin/Cyclophosphamide-paclitaxel	TAC
			TCH
	FAC 50	Doxorubicin/vinorelbine	
		AC	
Small cell lung cancer	CAV - PE	Etoposide/carboplatin	ACE
		CAV	Topotecan
		Etoposide/carboplatin	ICE
		Paclitaxel/carboplatin	VICE
		Tirapazamine/cisplatin/etoposide/irradiation	DDG CAV -PE
		CODE	

https://pmc.ncbi.nlm.nih.gov/articles/PMC7721096/table/tb003/

The risk categories of chemotherapy regimen to induce febrile neutropenia (FN)

Cancer type	FN risk category (%)/Chemotherapy regimen		
	< 10	10–20	> 20
Non-small cell lung cancer	Gemcitabine/cisplatin	Paclitaxel/cisplatin	Docetaxel/carboplatin
		Vinorelbine/cisplatin	
		Paclitaxel/carboplatin	
		Cisplatin/docetaxel	
		Etoposide/cisplatin	
		Docetaxel	
Non-Hodgkin lymphoma		ACOD	DHAP
		(R)-CHOP	ESHAP
		Fludarabine/mitoxantrone	R-ESHAP
		Dose adjusted EPOCH	
		Mega dose-CHOP	VAPEC-B
		(R)-GEM-P	ACVBP
		(R)-GEMOX (elderly patients)	(R)-Hyper-CVAD
		GDP	ICE/R-ICE
		CHP	Stanford V
			MOPPEB-VCAD
			FC
			FCR
Hodgkin's disease			BEACOPP
			ABVD
			CEC
			IGEV
Ovarian cancer	Gemcitabine/cisplatin	Paclitaxel/carboplatin	Docetaxel
			Topotecan

https://pmc.ncbi.nlm.nih.gov/articles/PMC7721096/table/tb003/

The risk categories of chemotherapy regimen to induce febrile neutropenia (FN)

Cancer type	FN risk category (%)/Chemotherapy regimen		
	< 10	10–20	> 20
Urothelial cancer		Paclitaxel/carboplatin	MVAC
			DDGc MVAC
			BOP--VIP-B46
Germ cell tumours		Cisplatin/etoposide	VeIP
		BEP - EP	
Colorectal cancer	Irinotecan	FOLFOX	
	IFL	FOLFIRI	
Gastric cancer		Docetaxel-irinotecan	DCF
		FOLFOX	TC
		LVFU-cisplatin	TCF
		LVFU-irinotecan	ECF
			ECX
			EOF
			EOX
Esophagal cancer		Irinotecan/cisplatin	
Other malignancies	Doxorubicin/cisplatin (endometrial cancer)	Gemcitabine/irinotecan (pancreatic cancer)	TIC (head and neck cancers)
		FOLFIRINOX (pancreatic cancer)	
	TAP (endometrial cancer)	Stanford V (Hodgkin's lymphoma)	MAID (sarcoma)
	TPF (laryngeal cancer)	Paclitaxel/cisplatin (cervical cancer)	
		Gemcitabine/docetaxel (occult primary- adenocarcinoma)	

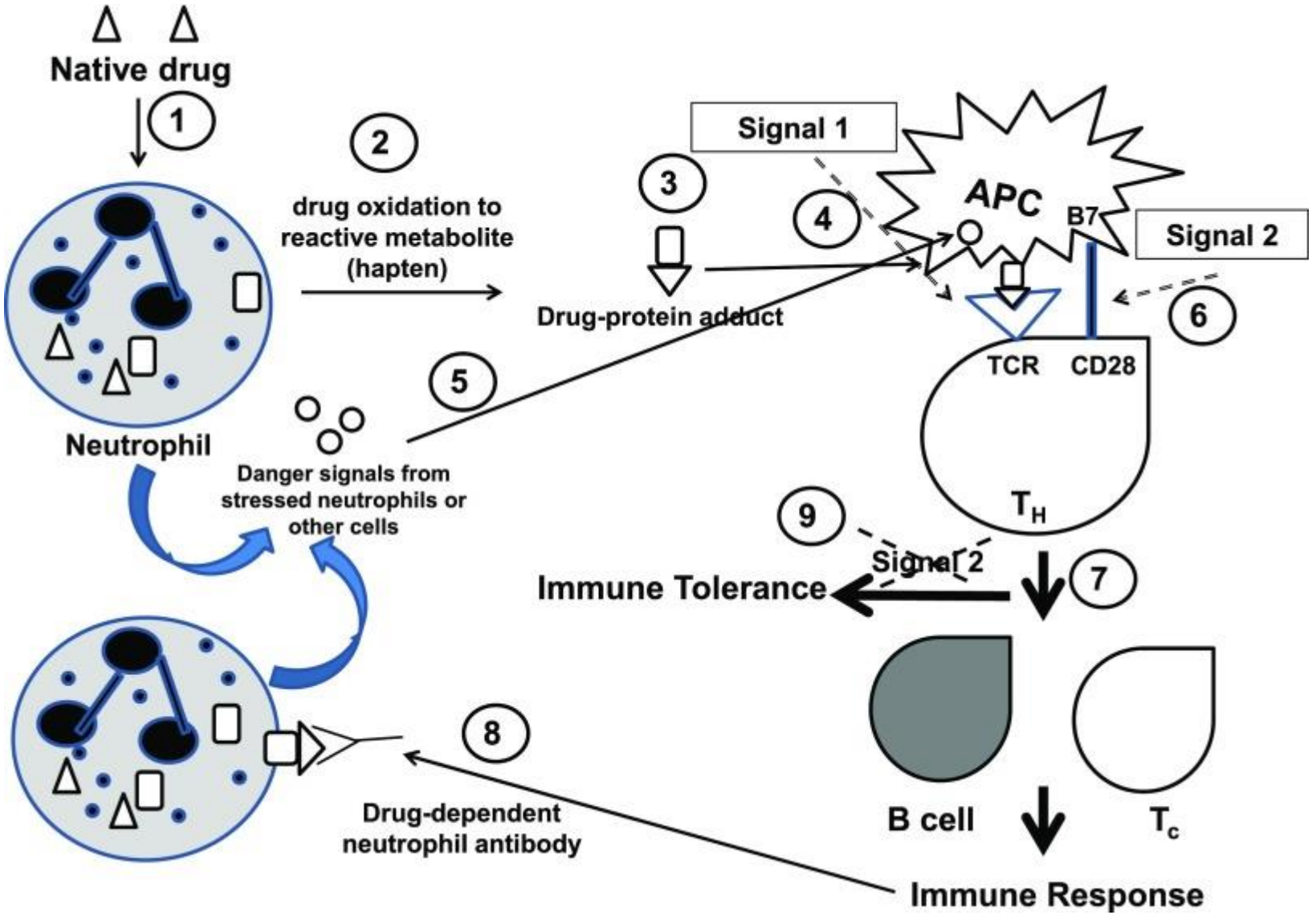
DD, dose-dense; DDG, dose-dense with G-CSF; AC, Cyclophosphamide+Adriamycin; FEC, Epirubicin+Cyclophosphamide+Fluorouracil; CMF, Methotrexate+Cyclophosphamide+Fluorouracil; TAC, Docetaxel+Epirubicin+Cyclophosphamide; TCH, Docetaxel+carboplatin+trastuzumab; ACE, Etoposide+Epirubicin+Cyclophosphamide; CAV, Vincristine+Etoposide+Epirubicin; PE, Etoposide+Cisplatin; ICE, Ifosfamide+Epirubicin+Cyclophosphamide; VICE, Ifosfamide+carboplatin+etoposide+vincristine; CODE, Vincristine+Etoposide+Cisplatin+Epirubicin; CHOP, cyclophosphamide++vincristine+doxorubicin+ponisone; GDP, gemcitabine+dexamethasone+cisplatin/carboplatin; CHP, cyclophosphamide+doxorubicin,+prednisone; DHAP, cisplatin+cytarabine+dexamethasone; ESAP, cytarabine+etoposide+ 6-mercaptopurine+cisplatin; ABVD, doxorubicin+bleomycin+vinblastine+dacarbazine; BEACOPP, etoposide+doxorubicin+cyclophosphamide+vincristine+bleomycin+prednisone+procarbazine; EPOCH, etoposide+vincristine+cyclophosphamide+doxorubicin+prednisone; StanfordV, doxorubicin+vincristine+nitrogenmustard+vinblastine+bleomycin+etoposide+prednisone; MAID, mesner+doxorubicin+ifosfamide+dacarbazine; IGEV, Isophosphoramide+gemcitabine+vinorelbine+prednisone; FOLFOX, oxaliplatin+fluorouracil+calciumleucovorin; FOLFIRI, Irinotecan+fluorouracil+calciumleucovorin; DCF, Docetaxel+cisplatin+fluorouracil; TCF, Taxol+cisplatin+fluorouracil; ECF, Epirubicin+cisplatin+fluorouracil; EOF, Epirubicin+oxaliplatin+ fluorouracil; EOX, Epirubicin+oxaliplatin+capecitabine; ECX, Cisplatin+capecitabine+epirubicin; BEP, Bleomycin+etoposide+cisplatin; TPF, Taxol+cisplatin+fluorouracil; FOLFIRINOX, Irinotecan+oxaliplatin+fluorouracil + calcium leucovorin.

https://pmc.ncbi.nlm.nih.gov/articles/PMC7721096/table/tb003

DRUG INDUCED (IDIOSYNCRATIC) NEUTROPENIAS

1. Hapten hypothesis
   - A condition to create a covalent bond with neutrophils surface glycoproteins
   - Drugs undergoing biotransformation -> more reactive metabolites, longer elimination half-time
   - „Allo-antigen“ established -> DDABs targeting neutrophils produced
   - „Myeloperoxidase“ hypothesis -> biotransformation process may be also in neutrophils (partial – cells affected down to promyelocyte)
2. „Danger“ hypothesis – „two signals“ hypothesis
   - A hapten – signal 1, „danger“ signal 2 – HSPs, hyaluronans fragments
     - Signal 2 as the decisive -> absence leading to immunotolerance vs. presence to neutrophiles destruction
   - „Stressed “ neutrophiles -> „danger“ signals produced
   - Drugs conjugates -> inflammasome activation -> IL-1β and IL-18 produced

DDABs – drug-dependent antibodies, HSPs – heat shock proteins



https://pmc.ncbi.nlm.nih.gov/articles/PMC6142577/figure/F1/

DRUG INDUCED (IDIOSYNCRATIC) NEUTROPENIAS

- HLA antigens association -> immune system „participation“
  - Grave‘s disease -> HLA-B*38:02 ev. HLA-DRB1*08:03.
- CAVE! – decreased neutrophils count at onset of therapy - <1500 bb/µl

NEUTROPENIA AND AGRANULOCYTOSIS SIGNS

- Repeated and prolonged infections
- Fever (severe, often >38 °C)
- Fatigue
- Pharyngitis
- Lymphadenopathies (often painful)
- Oral cavity and perianal ulcerations
- Pain, swelling and rush at infection site
- Diarrhoea
- Burning sensation during urination, painful urination, urgencies; vaginal discharge, pruritus, pain

GENERAL RULES OF NEUTROPENIA/AGRANULOCYTOSIS MANAGEMENT

General rules

- Discontinuation of medication causing neutropenia/agranulocytosis (consider benefit-to-risk ratio or dosage alteration)
- Corticosteroids to contain autoimmunity to be considered
- G-CSF administration
  - Some clinical trials showed benefit (neutropenia duration decreased from cca. 9 days to 4-5 days)
  - Controversial, careful consideration

Infection prevention

- Strict hygiene rules
  - Not sharing dinnerware, hands cleaning, own towels, etc.
- Getting vaccinations available
- Gardening with gloves only
- Meat to be separated from vegetables, to be processed as the last part of meal
- To avoid animal faeces (cats, dogs, bunnies, etc.) and diapers change (if necessary, gloves and a surgical mask to be used)
- Prophylactic medication administered (respiration, urogenital, probiotics!)
- Administration to hospital in case of severe agranulocytosis (strict aseptic and antiseptic protocol)

LYMPHOPENIA

- Decrease in one or more lymphocytes subpopulations under physiological levels for that certain age group
  - Adults <1000 cells/µl
  - Children below 2 years of age <3000 cells/µl
    - Adults have a neutrophils prevailing with 25 % lymphocytes only vs. 67-38 % lymphocytes in children depending on their age
- Classification
  - T-lympho(cyto)penia – CD4+ „officers and generals“ and CD8+ „melee fighters, special commandos“
  - B-lympho(cyto)penia – antibodies production, „long-range artillery“
  - NK-lympho(cyto)penia – „police“ – destruction of infected, invaded and altered cells

LYMPHOPENIA CAUSES

Acute lymphopenia

- Acute viral infection (influenza H1N1, SARS-CoV-2, hepatitis)
- Starvation
- Physical/psychical stress
- Corticosteroids administration
- Chemotherapy/radiotherapy
- Ionising radiation exposure (nuclear power plant disaster, „dirty“ bomb)

Chronic lymphopenia

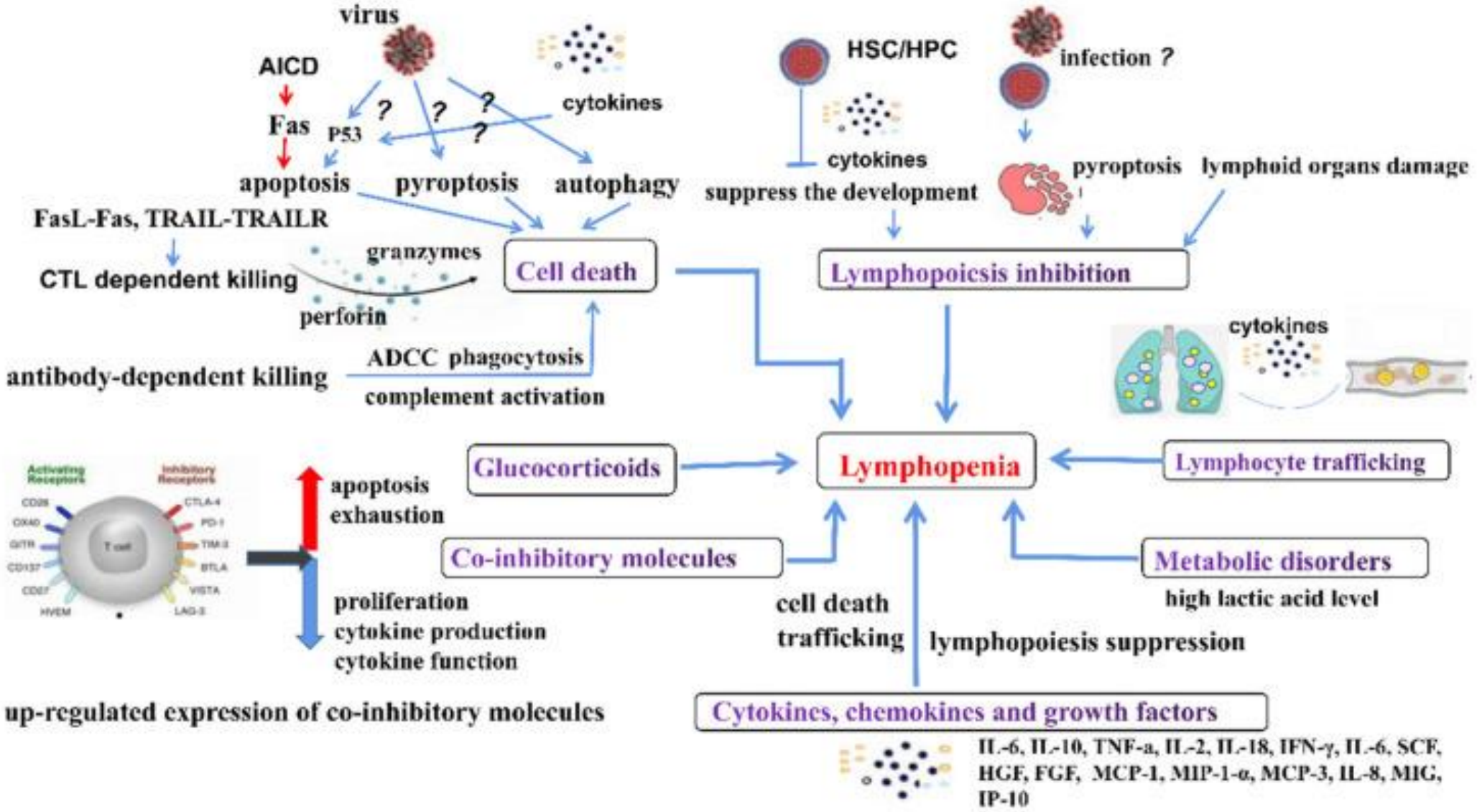
- Genetics
  - Monosomy 22q11.2 (DiGeorge sy.), Wiscott-Aldrich sy., SCID, ataxia teleangiectatica, WHIMs
- Malnutrition
- Autoimmune diseases – e.g. lupus erythematosus, rheumatoid arthritis, myasthenia gravis
- Chronic infections e.g. HIV, miliary TBC
- Leukaemia and lymphomas
- Long-term corticosteroids use, Cushing syndrome
- Sarcoidosis

SCID – severe combined immunodeficiency, WHIMs – warts, hypogammaglobulinemia, infections and myelokathexis – mature neutrophiles and T-, B- and NK-lymphocytes retention in bone marrow; gain-of-function (?AD) CXCR4 receptor mutation (with ligand SDF-1; stroma-derived factor), for cell release into peripheral blood an inactivation of this receptor is necessary)

LYMPHOPENIA PATHOMECHANISMS (SELECTED EXAMPLES)

1. Transient lymphopenia during viral infections
   - Cytokines selection affected, lymphopoiesis blocked, cell death induction
   - Possible cell death types of lymphocytes for this scenario
     - Apoptosis – direct infection e.g. MERS-CoV, HIV, measles
     - Pyroptosis – e.g. HIV, SARS-CoV-2 ->↑↑↑IL-1β
     - Autophagy – detection of gp41 in non-infected CD4+ lymphocytes in HIV+ patient
     - ADCC – viral antigens targeting antibodies attack also infected cells (surface antigen match)
     - Viral-specific CD8+ cytotoxic Ly -> FasL/FasR and TRAIL/TRAILR interaction
     - Dendritic cells – FasL/FasR – influenza virus H5N1 upregulated FasL on dendritic cells -> viral-specific CD8+ Ly destruction
     - Activation-induced cell death -> SARS-CoV-2, RSV, CDV -> FasL expression indirectly proportional to CD4+ count -> surrounding T-Ly destruction

TRAIL(R) – TNF-related apoptosis inducing ligand (receptor), CDV – „canine distemper virus“



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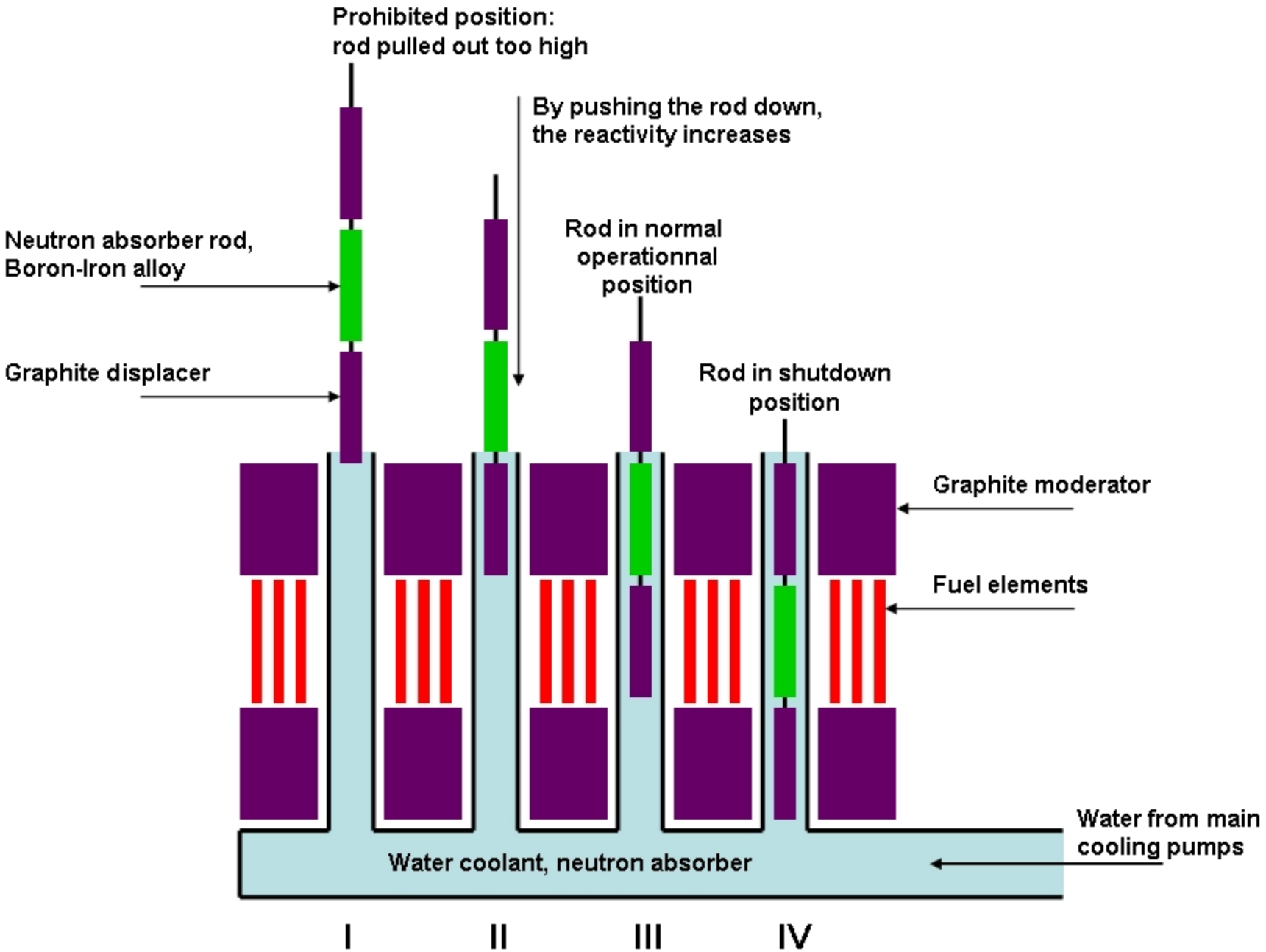
CYTOKINES EFFECT ON SUPPRESSION OF LYMPHOCYTES COUNT

- IL-6
  - Chronic infections, hemopoiesis inhibition – STAT-3 cascade activated
- IL-10
  - T-Lymphocytes proliferation suppression, T-lymphocytes „exhaustion“ induction, CD9+ regulatory B-lymphocytes activated
- TNF-α, interferons
  - Apoptosis induction (TNF-α, IFN-γ), lymphocytes recirculation reduction (IFN-α)
- Hemopoiesis limitation with granulocytes preferred, thymus involution
- Lymphocytes redistributed to infected places and lymphatic nodes
- Co-inhibitory molecules upregulated – e.g. CTLA-4. PD-1 („lymphocytes exhaustion“ markers)
- CAVE! – corticosteroids in patient with initial lymphopenia may induce temporary improvement but will backfire ultimately („Chornobyl control rods“)

CTLA-4 – cytotoxic T-lymphocyte associated protein 4, PD-1 – „programmed death“ protein 1



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LYMPHOCYTES EXHAUSTION SCHEME, CYTOKINE STORM INDUCTION AND EXTENSIVE NEUTROPHILES ACTIVATION IN CORTICOSTEROIDS ADMINISTRATION DURING LYMPHOPENIA

MDSC – myeloid-derived suppressor cells

Sufficient lymphocytes count at onset

- CD4+ Lymphocytes
- CD4+ Lymphocytes
- CD8+ Lymphocytes
- CD8+ Lymphocytes
- CD4+ memory cells
- CD8+ memory cells
- B-cell memory cells

- Neutrophils
- MDSC
- Lymphocytes defficiency
- Corticosteroids
- Neutrophils
- REGULATED REPONSE

Lymphocytopenia at onset

- CD4+ Lymphocytes
- CD4+ Lymphocytes
- CD8+ Lymphocytes
- CD8+ Lymphocytes
- CD4+ memory cells
- CD8+ memory cells
- B-cell memory cells

- Neutrophils
- MDSC
- Lymphocytes defficiency
- Corticosteroids
- MDSC
- Neutrophils
- Neutrophils
- SIRS/CYTOKINE STORM

LYMPHOCYTES SENESCENCE AND EXHAUSTION

Senescence

- Too many lymphocytes cell divisions
- CD57 upregulated -> apoptosis-prone
- Decreased IL-2 production

- HIV+ patients contain high counts of senescent T-Ly, HIV infection effect questionable

Exhaustion

- Prolonged antigen exposure
- PD-1 upregulated
  - Also on APC, e.g. macrophages and dendritic cells
- T-lymfocytov donwregulation
- TCR (T-cell receptor) intracellular signalisation downregulation
- Immunologic memory and tollerance interference
- HIV -> ↑PD-1 in both CD4+ and CD8+ cells
- Circulating and effector memory subpopulation decrease (Ki-67+)

SYMPTOMS OF LYMPHOPENIA AND ITS MANAGEMENT

Signs and symptoms

- General – repeated bacterial, viral, parasitic, fungal infections, SIRS-prone
- HIV/malignancy -> enlarged lymphatic nodes, spleen
- Respiratory infection -> cough, catarrh, fever
- Immunity disorders -> lymphatic nodes and tonsils shrinking
- RA/SLE -> joints pain, rash

Management

- Treating the triggering cause
- Gammaglobulines when low antibodies levels detected
- Bone marrow transplantation (hereditary conditions, oncohematologic diseases)
- HIV –> effective antiretroviral therapy
- CAVE! -> lymphopenia may aid to autoimmune disease establishment (tolerance-breaking condition)

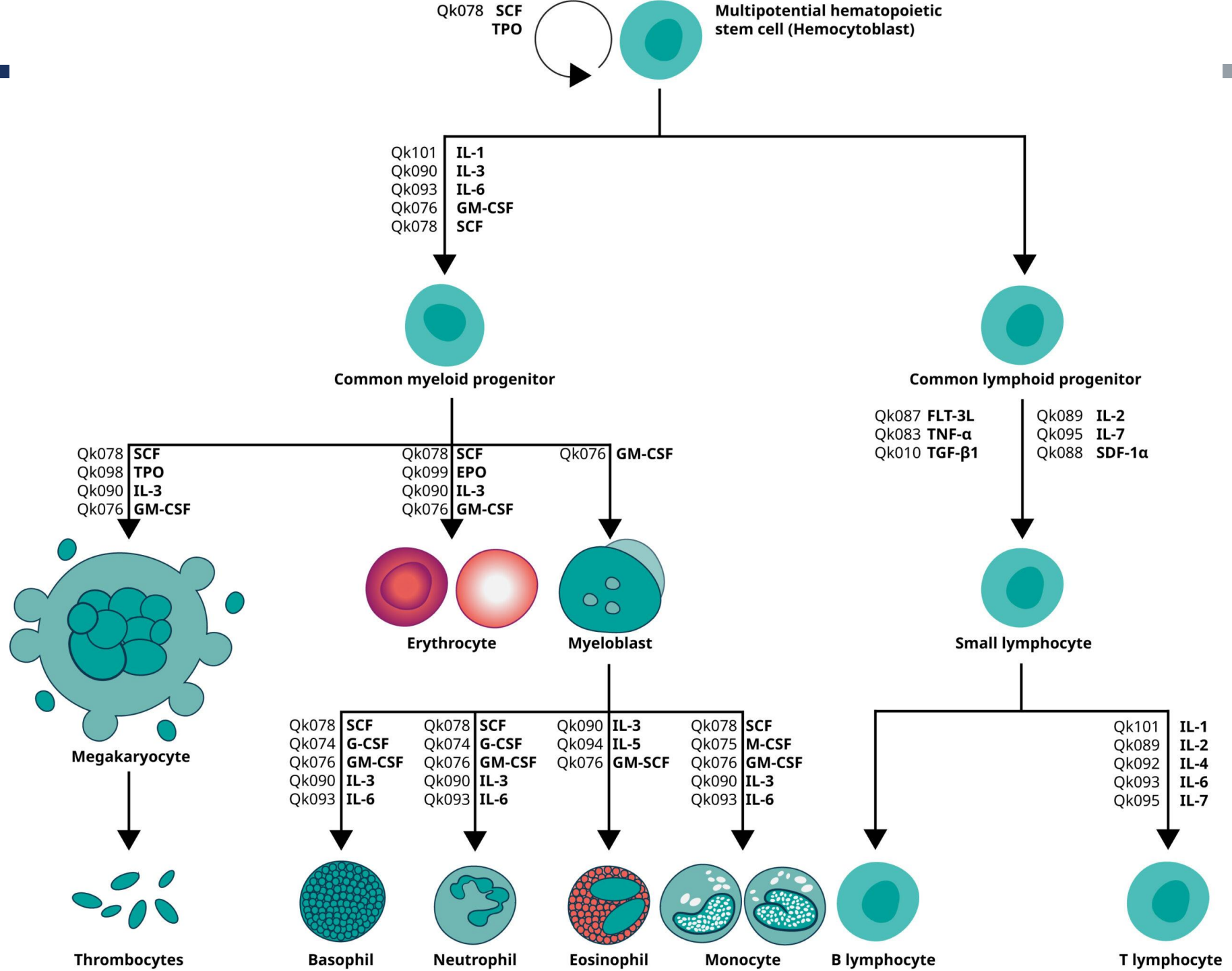
LEUCOCYTOSIS

- Elevation of leukocytes in peripheral blood >10 000 cells/µl
  - Equally or selective (neutrophilia, eosinophilia, basophilia, lymphocytosis, monocytosis)
- Causes
  - Neutrophilia – bacterial infections, pyogenic infections, sterile inflammation, MI, burns
  - Eosinophilia – allergy, parasitic infections, malignancies (Hodgkin, non-Hodgkin lymphomas), systemic autoimmune disease (SLE), vasculitis
  - Basophilia – CML (rare)
  - Monocytosis – chronic infections (TBC, bacterial endocarditis, rickettsiosis, malaria), systemic autoimmunity (SLE), IBD (ulcerous colitis), chronic myelomonocytic leukaemia (immature)
  - Lymphocytosis – chronic infections (TBC, brucellosis), viral infections (hepatitis, CMV, EBV), pertussis, ALL and CLL (leukaemia)
  - Immature forms – leukaemia and lymphomas*

*as for teaching purposes leukaemia and lymphomas are stated separately

LEUCOCYTOSIS DEVELOPMENT MECHANISMS

1. Increased bone-marrow synthesis and „storage pools“ release
   - Metamyelocyte lost mitotic ability -> „band“ transformation -> 3–5 % of circulating neutrophils
2. Decreased leukocytes adhesions to blood vessel walls
   - 50 % neutrophils circulate and 50 % adhering during physiological conditions
3. Decreased leukocytes extravasation
4. Increased bone-marrow precursors count
   - More efficient reaction to G-CSF, GM-CSF, cytokines effect, e.g. TNF-α, IL-2, IL-7, TGF-β1; IL-1, IL-3, IL-4, IL-5, IL-6



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LEUKEMOID REACTION

- Elevation of peripheral leukocytes >50 000 bb/µl
- Temporary condition mostly
- Causes
  - Severe infections – *C. difficile,* miliary TBC, Shigellosis (*S. dysenteriae*)
  - „Hyperinflammation" - ↑↑IL-6
  - Therapeutic (iatrogenic) – e.g. corticosteroids therapy, minocyclin, G-CSF, GM-CSF
  - Rare – mesenteric inflammatory pseudotumor (benign neoplasia), alcoholic steatohepatitis, haemorrhage (massive, retroperitoneal)
  - Correlation/unclear causality – ATRA-therapy, asplenia, diabetic ketoacidosis, hepatic necrosis, trisomy of ch. 21 (cca. 10 % incidence), paraneoplastic syndrome (extremely rare)

ATRA – all-*trans*-retinoic acid

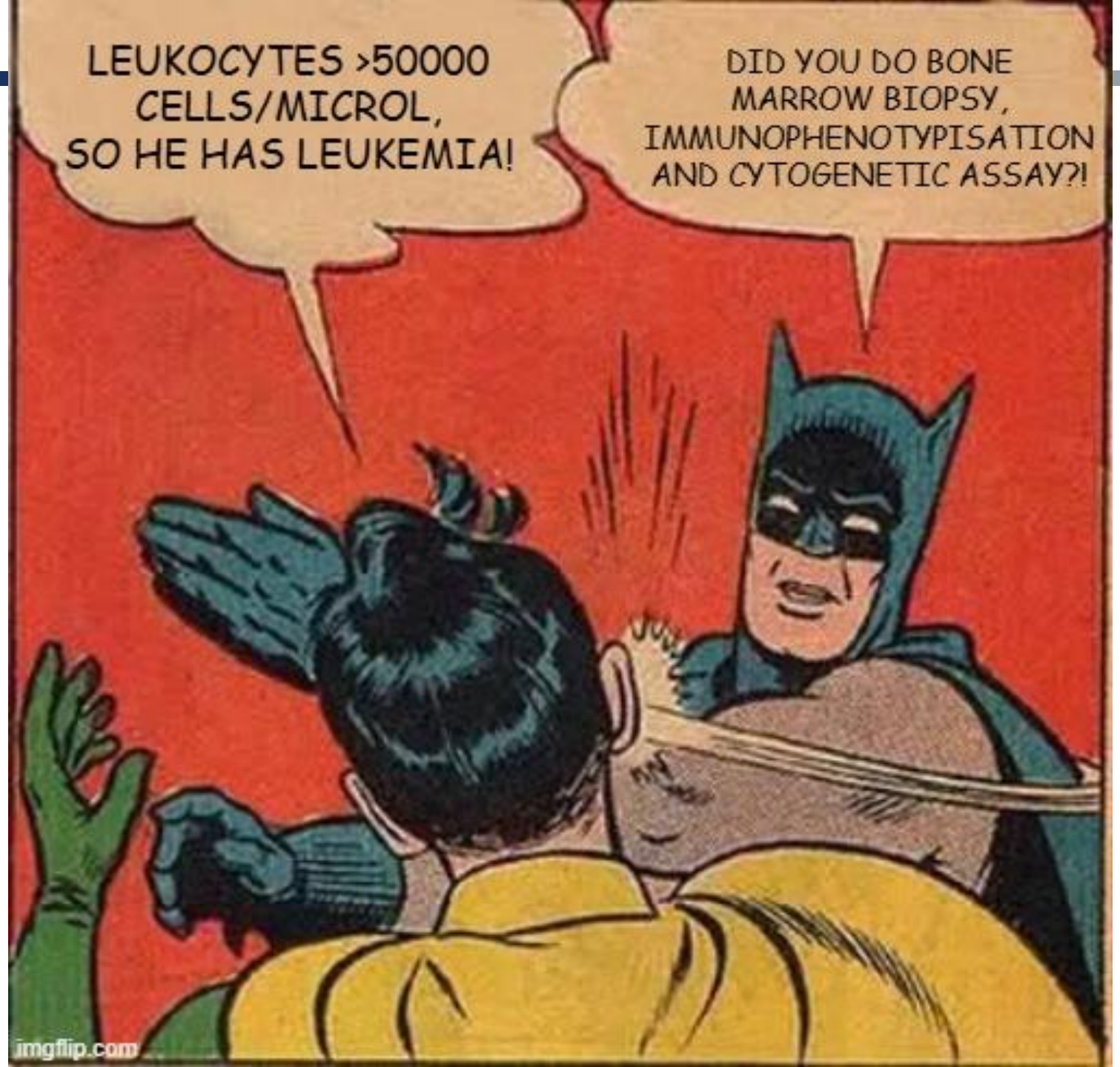
LEUKEMOID REACTION

- Characteristics
  - Peripheral blood - POLYCLONAL neutrophils (also less mature forms – metamyelocytes, „bands“)
    - Chronic myeloid leukaemia - monoclonal neutrophils (immunophenotypisation assessed)
    - Lymphoid leukemoid reaction also possible
  - ↑S-ALP (leukaemia - ↑ - CNL but ↓ - CML)
  - Vit. B12 in physiological range (leukaemia and G-CSF administration - elevated – liver supplies mobilised)
  - Bone-marrow biopsy - hypercellular, yet physiological
    - Leukaemia and oncohematologic disorders – monoclonal pathologic occupation mostly

- CAVE! – leukemoid reaction means no oncohematological disease usually but observation is necessary (possible leukaemia onset)!

DIF. DG. AMONG LEUKEMOID REACTION AND CNL WITH CML RESPECTIVELY

Condition / Parameter	Leukemoid reaction (LR)	Chronic myeloid leukaemia (CML)	Chronic neutrophilic leukaemia (CNL)
Peripheral blood	Neutrophils, „left"-shift („bands")	Immature precursors and cells, Basophils, eosinophils	Extreme neutrophilia, No immature cells!
S-Leu-ALP	↑	↓	↑
S-vit. B12	Varying or ↑	↑	↑
Bone marrow biopsy	Myeloid hyperplasia, physiol. Maturation and morphology	Basophilia, eosinophilia, monocytosis, ↑blasts, reticullin fibrosis	Similar morphology to LR, packed bone marrow, ↑reticullin
Cytogenetic assay	No genetic abnormalities	Bcr-abl	Various genetic abnormalities (cca 37 % of all cases)
Immunopheno-typisation	CD13+, CD15+, CD34-, HLA-DR-	CD13+, CD15+, CD34-, HLA-DR+	CD13+, CD15+, CD34-, HLA-DR+
Serum G-CSF	↑	↓	↓
Cell clonality	Polyclonal	Monoclonal	Monoclonal



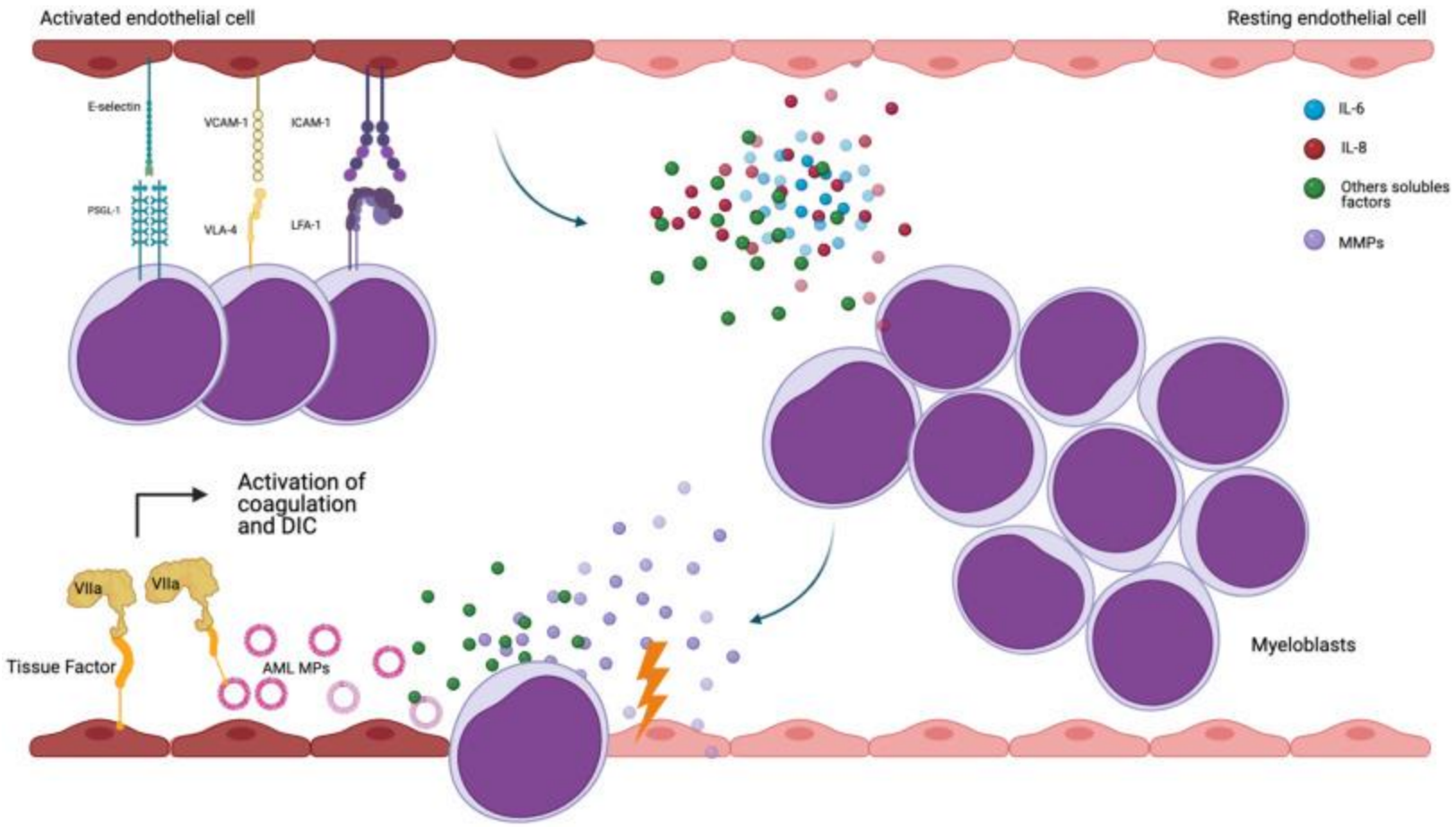
Source: author's work ☺

LEUKOSTASIS (ALIAS SYMPTOMATIC HYPERLEUCOCYTOSIS)

- Leukocytes and immature precursors rise in peripheral blood >100 000 cells/µl (hyperleucocytosis definition)
  - Acute myeloid leukaemia (AML) may manifest these symptoms even with lower counts (from 30 000 cells/µl) -> larger leukemic cells (volume)
- Always states leukaemia or oncohematological disease presence (leukaemisation)!
  - Present during diagnostics
    - AML (10–20 %), ALL (20–30 %)
    - CML (rare, symptoms may not manifest even at 200 000 – 300 000 cells/µl), (CLL (?, rare) -> frequent hyperleucocytosis
- Severe to life-threatening condition – immediate administration to hospital and intervention necessary
  - Poor prognosis – mortality 20–40 % when untreated (pulmonary complications, transitory ischemic attack, stroke (mainly ischemic), CVS collapse)

HYPOTHESES, MECHANISM AND MANIFESTATION OF LEUKOSTASIS

- Hypotheses
  1. Elevation of rigid blasts count -> microcirculation obstruction
  2. „Hypoxic theory" – tissue hypoxia -> ↑mitotic blasts activity -> ↑cytokines production -> endothelial damage and subsequent haemorrhages -> ↑blasts migration to capillaries
- Mechanism – capillaries obstruction and tissue hypoxia emergence
- Manifestation
  - Pulmonary – dyspnoea, cough, hypoxia (artificial ventilation often necessary); Chest X-ray – diffuse alveolar or interstitial infiltrates, stethoscope - rumbles
  - CNS – confusion, blurred vision, vertigo, ataxia, tinnitus, headache, disorder of consciousness (somnolence to coma); seizures, focal neurologic functions deficiency (e.g. arm)
  - Ophthalmology – retinal oedema and haemorrhages, blood vessels dilation
  - Tissue – pain in various body parts, (?)fever
  - Rare – priapism (erection without stimulation or lasting for hours after cessation of stimuli)



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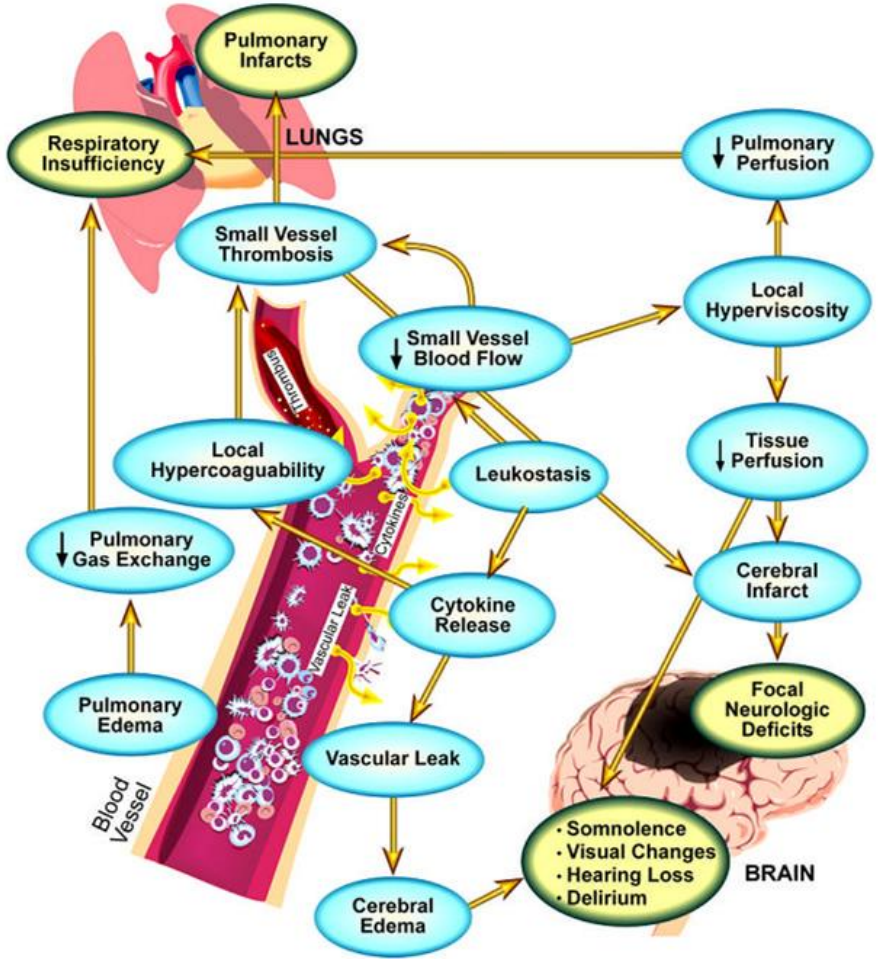
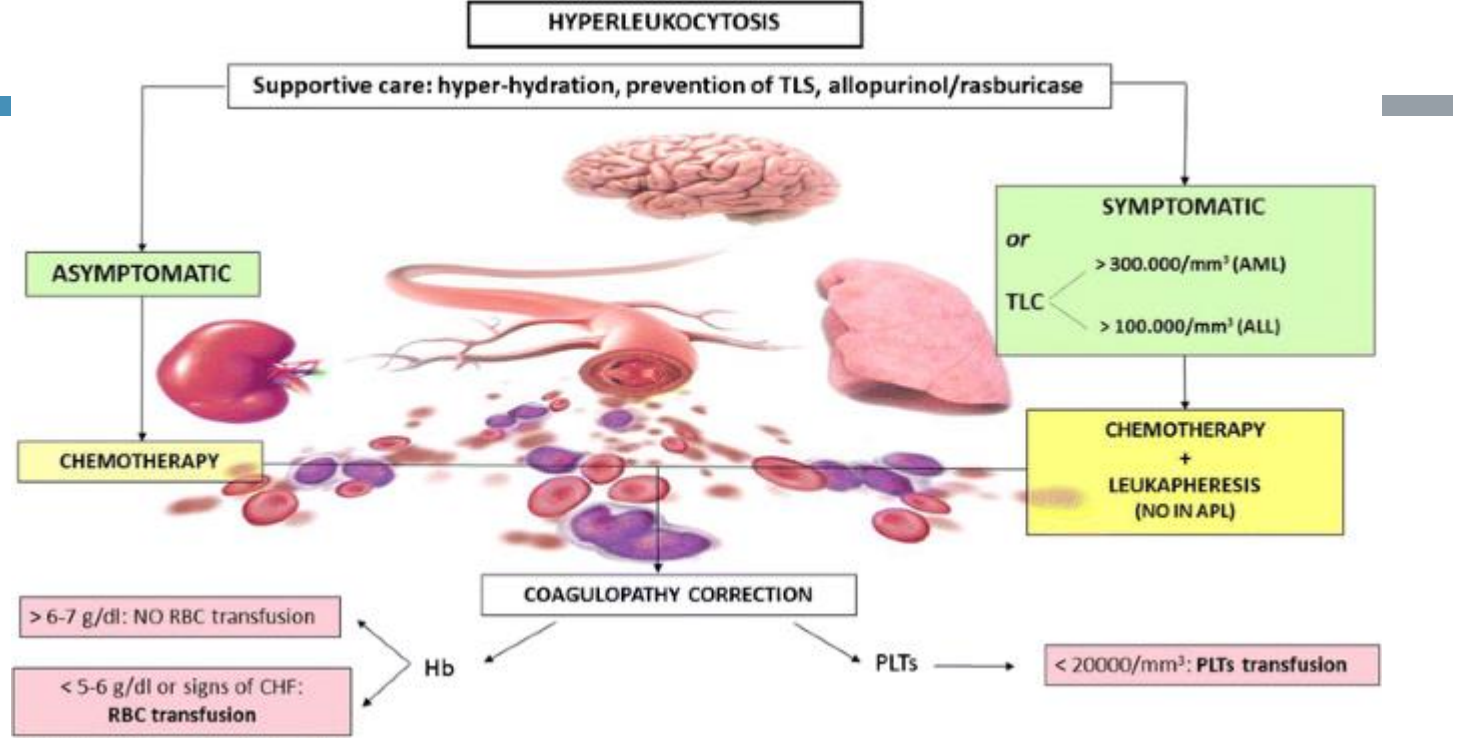
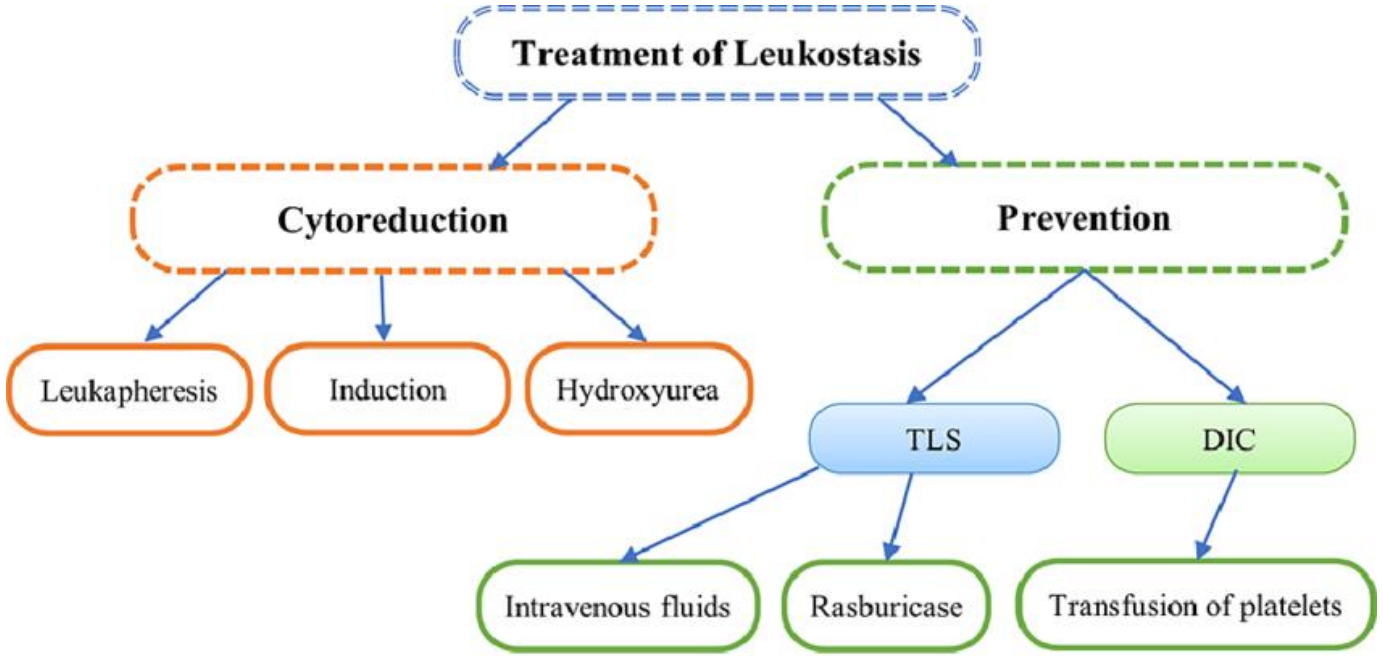


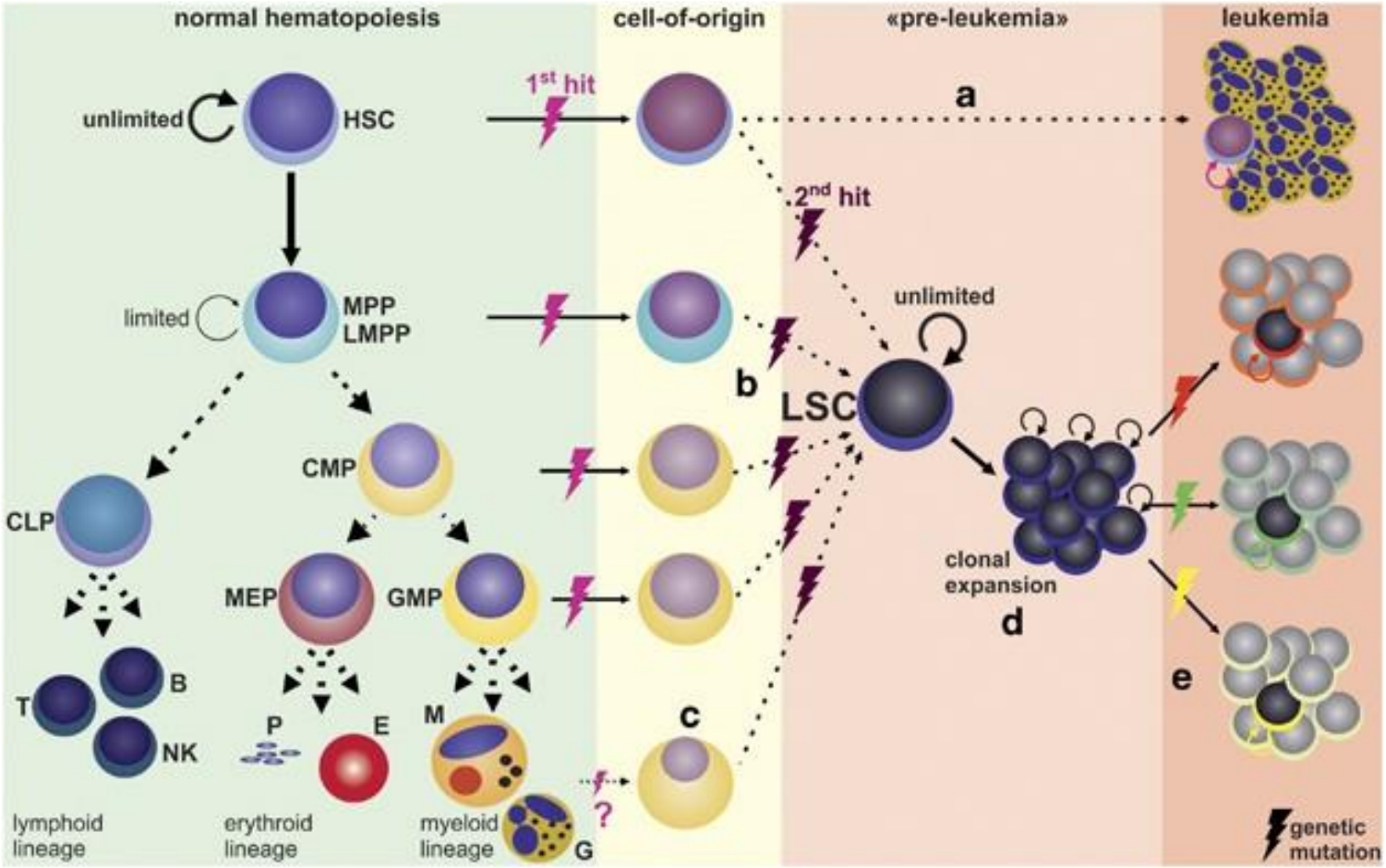




https://www.researchgate.net/publication/379195520/figure/fig4/AS:11431281230993721@1711199151555/Treatment-of-leukostasis-the-arrows-indicate-based-on.png
https://telemedicina.med.muni.cz/pediatric-oncology/res/photogallery/1-hyperleukocytosis-02.jpg
https://media.springernature.com/lw685/springer-static/image/art%3A10.1007%2Fs11864-015-0387-8/MediaObjects/11864_2015_387_Fig1_HTML.gif

LEUKAEMIA AND LYMPHOMAS – GENERAL CHARACTERISTICS

- Oncohematologic diseases
- „Founder cell“ – monoclonal
- Bone marrow occupation and destruction -> haematopoiesis decreased
- Non-specific symptoms usually
  - Fatigue, tiredness, repeated subfebrilities and fevers (ev. „night chills“ or periodic fever), unexplained weight loss or cachexia
  - Frequent infections
  - Anaemia – normocytic normochromic (anaemic hypoxia)
  - Thrombocytes functions affected – petechiae, purpuras, ecchymosis, bleeding manifestations
  - Lymphadenopathy (one or more groups)
- BONE MARROW BIOPSY IS DECISIVE FOR DIAGNOSIS CONFIRMATION!



https://media.springernature.com/full/springer-static/image/art%3A10.1038%2Fcdd.2014.89/MediaObjects/41418_2015_Article_BFcdd201489_Fig1_HTML.jpg

Pathophysiology Behind the Leukemias

https://calgaryguide.ucalgary.ca/wp-content/uploads/2020/01/Pathophysiology-Behind-the-Leukemias.jpg

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Point Mutation (in DNA) + Chromosomal Abnormality (duplication, loss, recombination error)

→ Combinations of these genetic defects causes reduced tumor suppressor gene expression and/or increased oncogene expression

→ In White Blood Cells and their precursors:
- Lack of cell growth inhibition and / or apoptosis.
- Over stimulation of cell division/growth

→ Neoplastic blood cell incapable of regulated cell division

→ Neoplastic cells uncontrollably divide in a monoclonal way: one neoplastic cell originates all successive cells

	Initiating Mutational Event
ALL	Any combination of mutations, chromosomal alterations, or other genetic abnormalities that creates a neoplastic cell (incapable of regulating cell growth/division).
AML	
CLL	
CML	Translocation between Chr 9 and Chr 22 → Philadelphia chromosome (abnormal Chr 22) → BCR-ABL1 oncogene (along with other genetic abnormalities)

Genes regulating differentiation/maturation <u>disrupted</u>, affected neoplastic cells are incapable of further differentiation/maturation

- Specific mutations cause slower disease progression → CML: Chronic Myeloid Leukemia → Degeneration during CML's "blast crisis"
- Specific mutations cause rapid division and buildup of existing neoplastic cells → Acute/rapid disease progression. → <u>ALL</u>: Acute Lymphoblastic Leukemia, <u>AML</u>: Acute Myeloid Leukemia

Genes regulating maturation remain <u>intact</u> (affected neoplastic cell is capable of further differentiation/maturation) → Some neoplastic cells <u>take time to mature</u> further → **less rapid disease progression** (more indolent disease); cells don't die → <u>CLL</u>: Chronic Lymphoid Leukemia

Note:
Although it is tempting to group the leukemias together for study purposes, it is best to learn the 4 main types of leukemias independently of one another, as they have a uniquely different pathophysiology and clinical presentation

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LEUKAEMIA AND ONCOHEMATOLOGICAL DISEASES CLASSIFICATION

Leukaemia

1. Acute myeloid leukaemia
2. Chronic myeloid/myelocytic leukaemia
3. Acute lymphocytic/lymphoblastic leukaemia
4. Chronic lymphocytic leukaemia

Lymphomas and other

- Hodgkin lymphoma
- Non-Hodgkin lymphoma

- Myelodysplastic syndrome
- Polycytemia vera rubra
- Essential thrombocytemia
- Myelofibrosis
- Mastocytosis

ACUTE MYELOID LEUKEMIA

- Onkohematological disease from immature myeloid precursors in bone marrow and peripheral blood
  - Include states with overt production of red blood cells, platelets and their precursors - megakaryocytes
- Epidemiology and statistics
  - Cca. 22 000 patients dg. per year 2025 estimated in USA (cca. 11 000 deaths)
    - 217 new cases in Slovakia in 2023 (incidence 2,6/100000 inhabitants/year)
  - Men affected slightly more
  - Age of onset usually >45 years
  - 33 % of leukaemia (although 1 % of malignancies)

AML PATHOMECHANISM

- Multistep process
  - „Preleukaemic HSPC“ creation (NPM1, TET2, SMC1A) -> driver and key mutations acquired -> leukemic haematopoiesis

- Genetic preconditioning
  - Low genetic burden compared to other leukaemia however with high penetrance!
    1. Somatic mutations (acquired during life)
    - Signal and kinase cascades (FLT3, „RASopathies“), epigenetic modifiers (DNMT3A, TET2, IDH1, -2, MLL/KMT2A), transcription factors (CEBPA, RUNX1), RNA-splicing factors (SRSF2), tumour-suppressor genes (-TP53) and nucleophosmin (NPM1)
    2. Gametic/“germline“
    - M. Down (GATA1 gene), RUNX1, DDX41

FLT3 – Fms-like tyrosine kinase 3, DNMT3A – DNA-methyltransferase 3α, TET2 – Tet methylcytosinedioxygenase 2, IDH1, 2 – isocitrate dehydrogenase 1, 2; MLL/KMTA2 – mixed lineage leukaemia/histone-lysine N-methyltransferase 2A, CEBPA – CCAAT/enhancer-binding protein alpha, RUNX1 – Runt-related transcription factor 1, SRSF2 – serine/arginine-rich splicing factor 2
Note – examples are stated here, complete gene list is more extended, suggested further reading - https://link.springer.com/content/pdf/10.1007/s11864-022-01021-8.pdf

AML PATHOMECHANISM

- Epigenetic mechanisms
  - Methylation dysregulation - DNA – DNMT3A^{R882H} hypomethylated with „dominant phenotype “, TET2 „loss-of-function“, MLL fused gene hypomethylation (CpG sequences)
  - Non-coding RNA alterations
    - Micro-RNA – miR-145 and miR-146 deletion, miR-9 and miR-155 upregulated -> selective advantage for clones, adaptation and inflammatory response adjusted in favour of blasts
    - Long non-coding RNA (LncRNA) – conformation affect, may be as „oncogenes/TSG“ - HOTAIR (*cis*-HOTAIRM1), RUNXOR (RUNX1 promotor to enhancer interactions and translocations, chromosomal „looping“)
- Microenvironment alteration
  - Dicer1 deletion, VEGF-A secretion, interleukins secretion, CXCL12 reduced, GAS6 upregulated, WNT-ligands upregulated

GAS6 – growth arrest signal 6, Dicer1 – dsRNA endoribonuclease

GENES INVOLVED IN AML DEVELOPMENT EXAMPLES (ACUTE PROMYELOCYTIC LEUKAEMIA)

Abbreviation	Genome position	Abbreviation origin
PML	15q22	ProMyelocytic Leukaemia
PLZF	11q23	PromyeLocytic Zinc Finger
AML1	21q22	Acute Myeloid Leukaemia
c/EBPα		CAAT/Enhancer Binding Protein
CBFβ	inv16	Core-Binding Factor

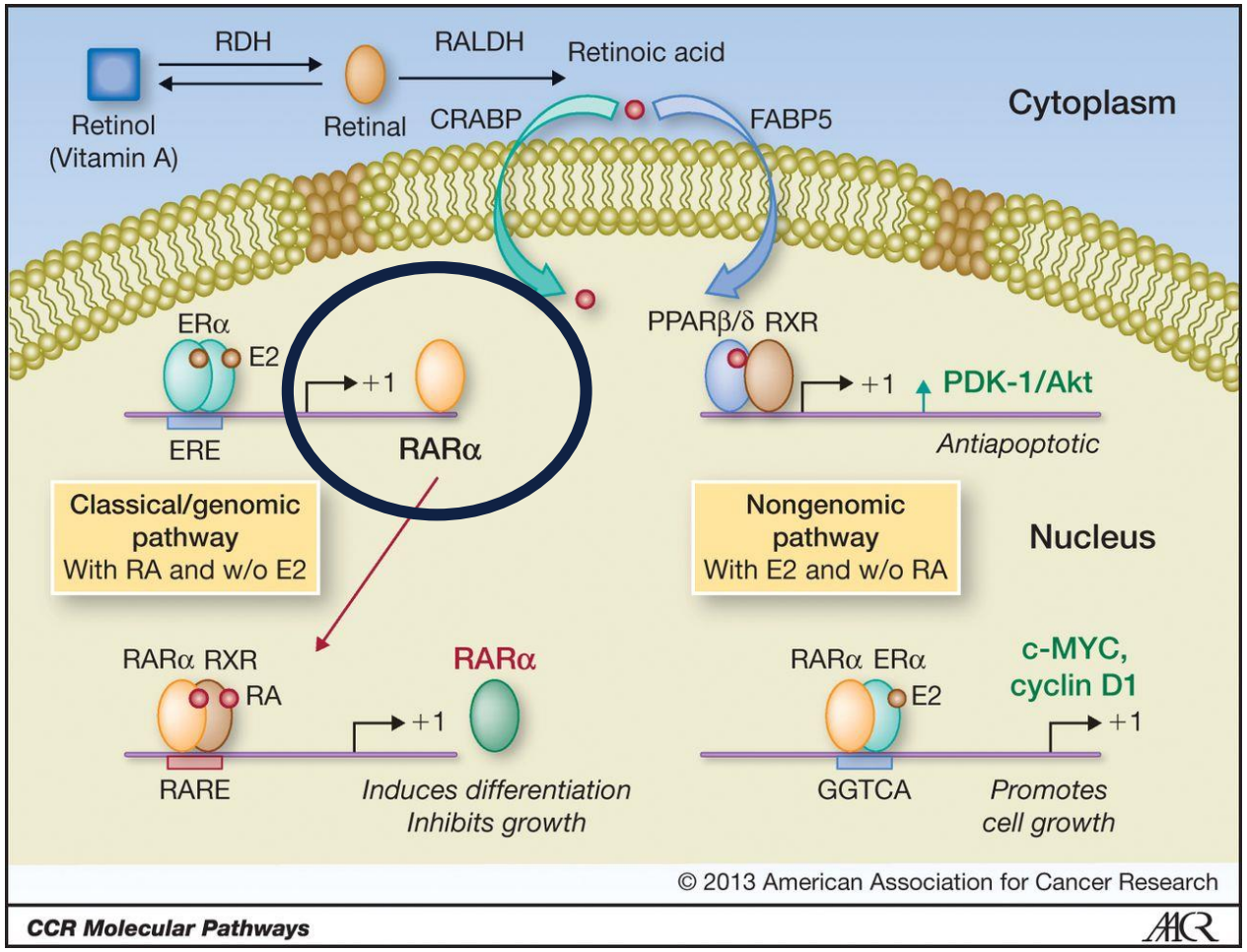
PROMYELOCYTIC LEUKEMIA – T(15,17)

- PML is transferred to Ch 17 and fused with RARα (steroid/thyroidal receptors family) -> fusion gene PML-RARα
- RARα (retinoid acid receptor) + vit. A -> all-trans retinoic acid (ATRA) -> physiological bound to specific DNA segments -> maturation enhanced
- PML-RARα is not fulfilling its function -> Leu stays in the stage of promyelocyte

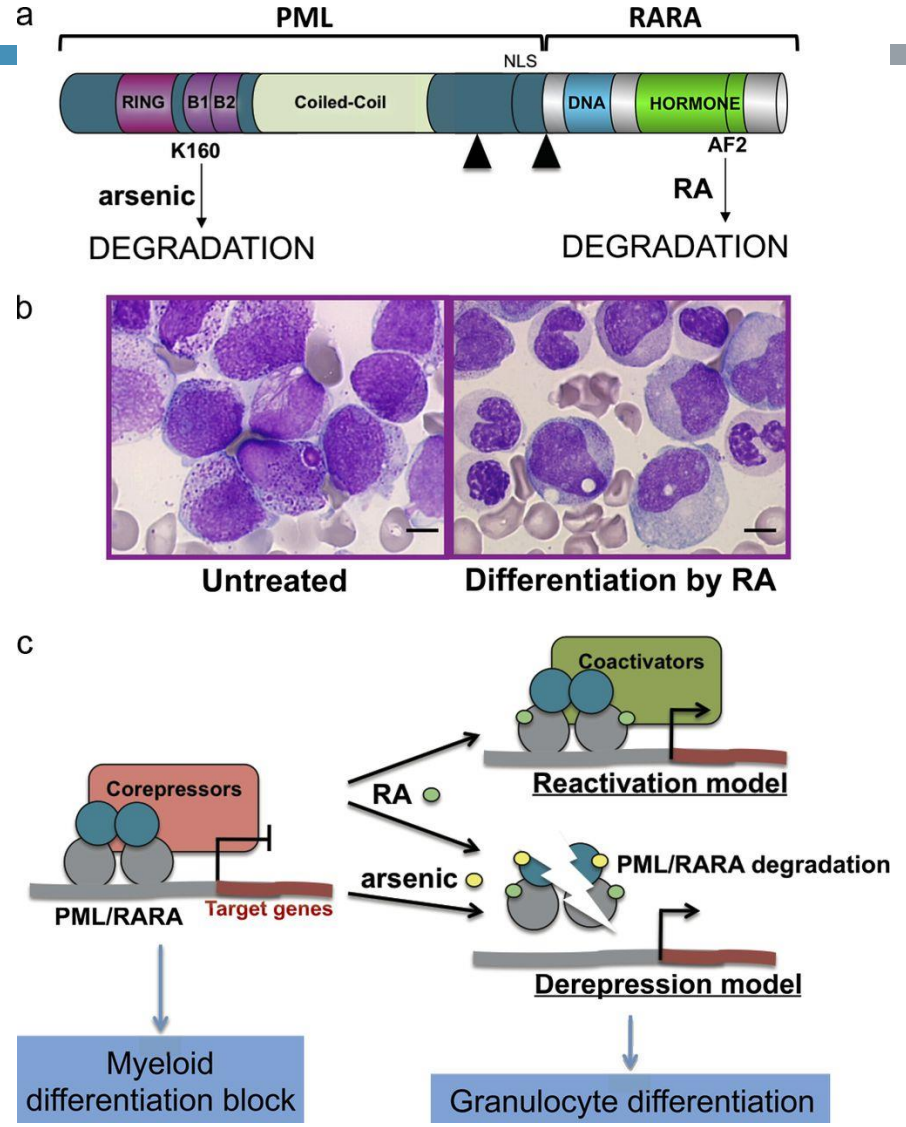
- PML -> forms nuclear bodies (membrane-less organelles) -> clustered location
- RARα -> diffuse location in the nucleus (applies for the fusion gene as well)

- ATRA-high dose treatment might inhibit fusion gene - remission
- Resistance may develop – another mutation gain? (PLZF is resistant to ATRA treatment) – PLZF-RARα; NPM1-RARα, ZBTB16-RARα (t11,17), TTMV-RARα (viral origin), STAT5B-RARα, and NUP98-RARG

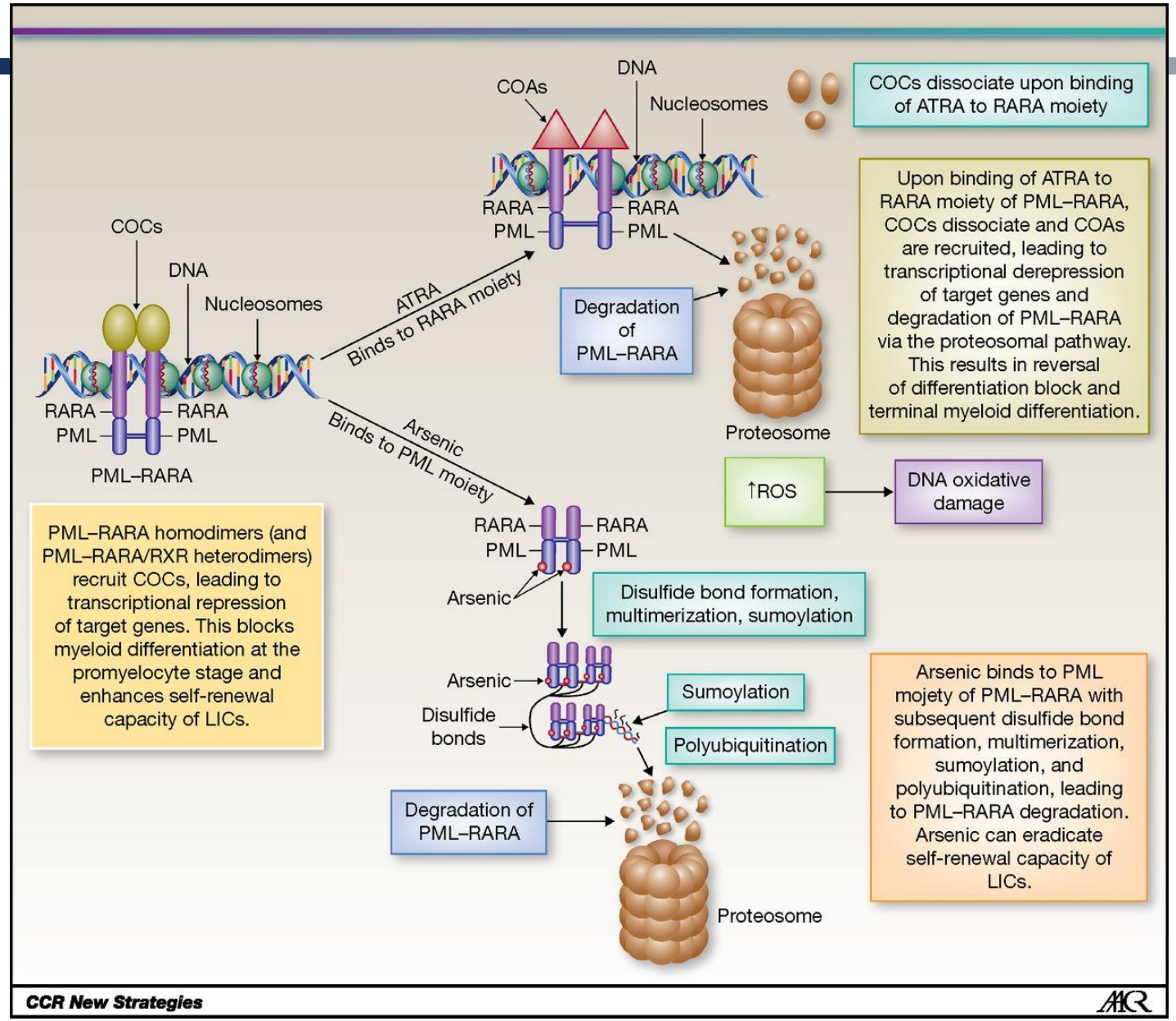
NPM1 – nucleophosmin 1, ZBTB16 – zinc finger and BTB domain containing protein 16, TTMV – torque teno minivirus, STAT5 – signal transducer and transcription activator 5, NUP98 – nuclear complex pore protein/nucleoporin 98 and 96 precursor



http://clincancerres.aacrjournals.org/content/clincanres/19/7/1651/F1.large.jpg?width=800&height=600&carousel=1



http://jcb.rupress.org/content/jcb/198/1/11/F1.large.jpg



http://clincancerres.aacrjournals.org/content/clincanres/20/19/4985/F1.large.jpg

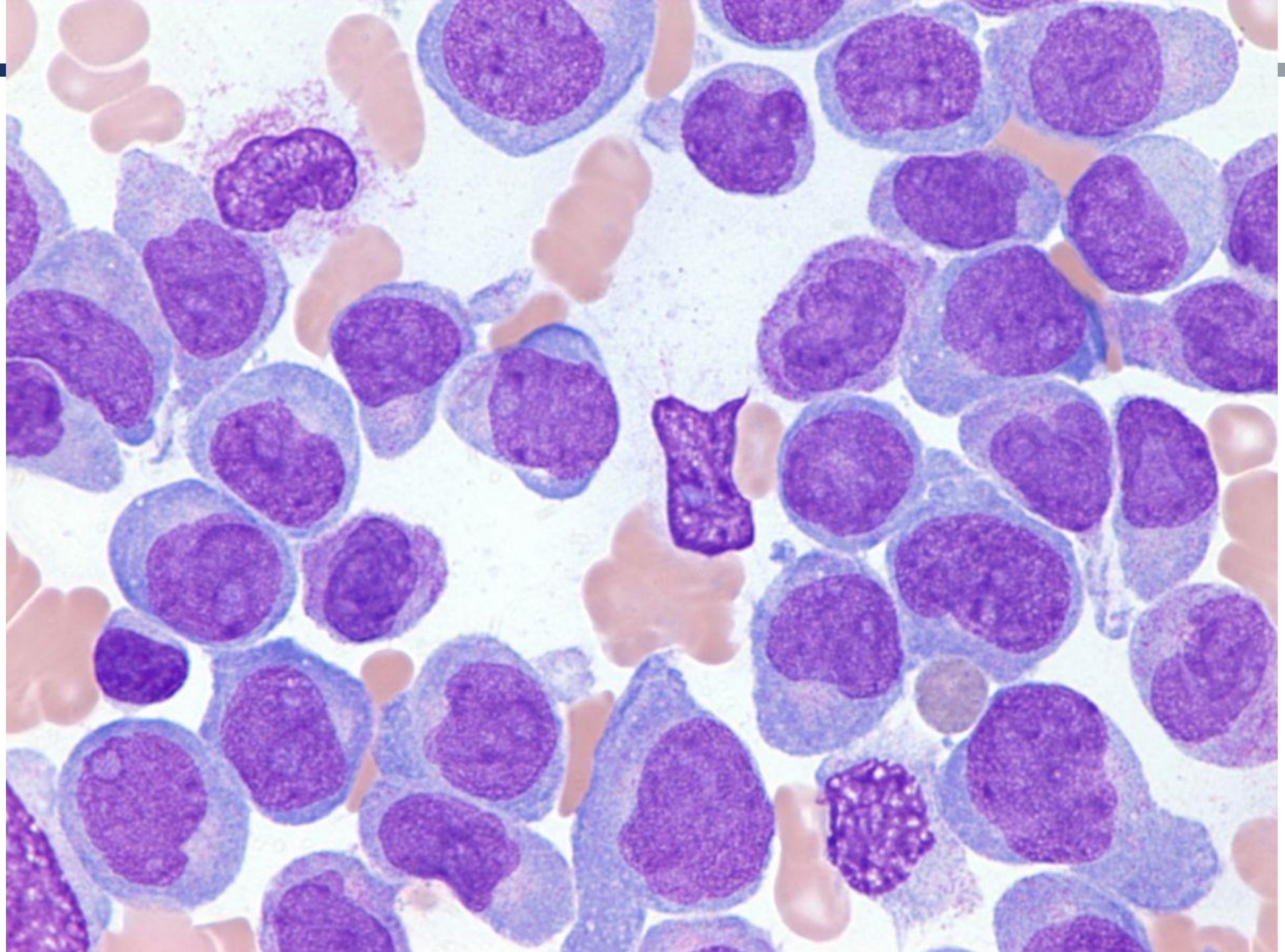
AML THERAPY EVASION

- Blasts acquiring resistance to chemotherapy -> selection pressure -> chemoresistant AML established

1. Fatty acids-rich microenvironment -> leukemic stem cells (LSC) homing to gonadal adipose tissue
   - Scavenger receptor CD36 and FABP4 expression -> oxidative metabolism
2. Endosteal region migration of chemoresistant LSCs
   - E-selectin and CXCL12/SDF-1 expressed, adhesion molecules CD44 expression, VLA4-VCAM1 axis upregulation, CXCL12R and CXCL4R upregulation

- Prognosis
  - Complete remission - 50–80 % patients (relapse within 3 year usually, 60 % in favourable prognosis types, 85 % in poor prognosis types)
  - 5-year survival – cca. 29,5 % (adults) vs. 66 % (children and teenagers <19 years of age)

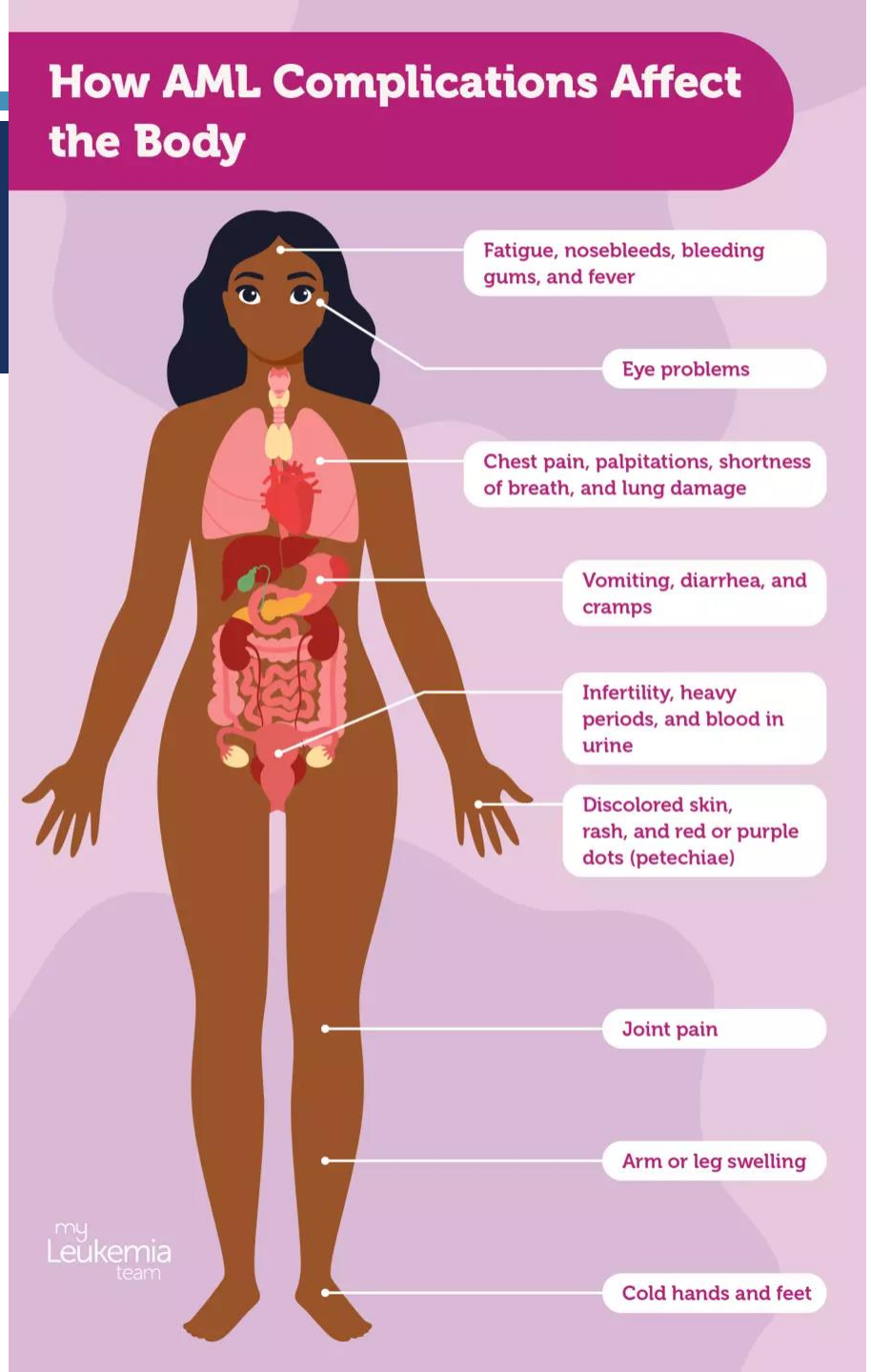
CXCL12/SDF-1 – CXC-motif chemokine 12/stromal cell derived factor-1, VLA4 - integrin



https://stjude.scene7.com/is/image/stjude/aml-leukemia-bm-m4?fit=crop,1&wid=1200

AML SYMPTOMS AND MANIFESTATIONS

- Haematopoesis disorders
  - Normocytic normochromic anaemia
  - Leucocytosis with functional leukopenia
    - Prone to bacterial, fungal infections of skin and mucosa
  - Thrombocytopenia -> bleeding manifestations
  - DIC risk – blasts presence
- Leukemic invasion
  - Hepatomegaly, splenomegaly, lymphadenopathy
- Leukostasis symptoms



https://cdn.myhealthteams.com/graphic/65086ee7fe9c0e0a2fc68441/woriginal/MyLeukemiaTeam_ComplicationsFromAcuteMyeloidLeukemia_Graphic-8aa00c4332a348bf15e8bec3c81763cc.webp?1695051492

ACUTE LYMPHOCYTIC/LYMPHOBLASTIC LEUKAEMIA

- Oncohematological disease typical with elevation of immature lymphocytes form in bone marrow and peripheral blood
- Epidemiology and statistics
  - Peak – 2–5 years of age (USA – 2025 estimate – incidence 6100 cases, mortality 1400 cases)
    - 2015 – 7.7/100000 children vs. 1/100000 adults per year (CZE)
  - Men affected slightly more
  - Prognosis
    - Children – favourable (60 % of all ALL)
    - Adults – poor (80 % deaths to ALL despite 40% of ALL cases)

FACTORS LEADING TO ALL DEVELOPMENT

- Genetics
  - Children – hyperploidy (51 – 65 chromosomes in blasts - 25 % children vs 11 % adults), t(12,21)/TEL-AML1 (ETV6-RUNX1 – 20–25 % children vs <3 % adults)
    - These mutations are with favourable prognosis
  - Adults – Ph+ (Philadelphia chromosome, t(9,22 – BCR-ABL – 25 % adults vs 5 % children), hypoploidy (<46 Ch in cells – 5 % adults vs. 5 % children)
    - These mutations are associated with poor prognosis
- Environmental factors
  - Children – unknown, genetics (Down sy, Klinefelter sy, Fanconi anaemia, neurofibromatosis, ataxia teleangiectatica, Bloom syndrome, Li-Fraumeni sy – one allele p53 loss inherited)
  - Adults – chemical (benzene), biological (HTLV-1, EBV), radiation, malignancy treatment in early age (chemotherapy)

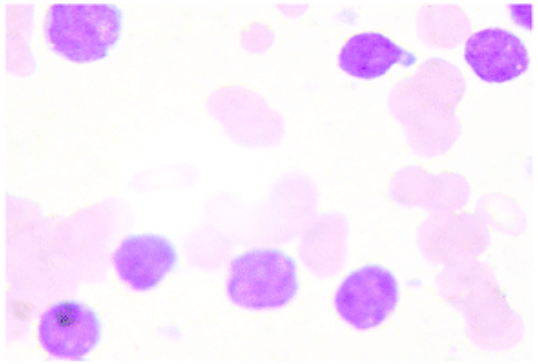
ETV6 – Ets-leukaemia virus 6

ALL MECHANISM AND ITS PROGRESS

1. Genetic abnormalities accumulation in B- and T-cells precursors
2. „Founder cell" transformation -> leukemic stem cells (LSCs) -> bone marrow invasion and destruction
3. Physiological haematopoesis suppression -> leucocytosis (even normal count or leukopenia) with functional pancytopenia
4. Peripheral blood invasion
5. Lymphatic nodes migration and spleen occupation -> lymphadenopathy and splenomegaly
6. High turnover of tumour cells -> ↑LDH

CAVE! – possible blast migration to CNS -> intracranial bleeding, seizures, neuropathies, leukoencephalopathy, thrombosis, meningitis (even lethal!), long-term cognitive functions deficiency -> intrathecal chemotherapy as a prophylaxis and treatment

FAB classification of lymphoblastic leukaemia



L1 Lymphoblastic leukaemia with homogeneous structure

Frequency:

Between 25% and 30% of cases in adults, and 85% of cases in children.

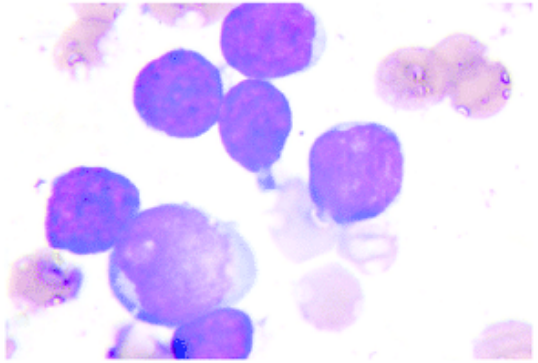
Morphology:

Blasts are homogeneous, nucleus is regular, chromatin is homogeneous, small or no nucleoli, scanty cytoplasm, and mild to moderate basophilia.

Immunophenotype

B:	T:
• CD19	•CD3
•CD22	•CD7
•CD79a	•CD5
•CD10	•CD2
•CD20	•CD4

•Cytoplasmic or superficial immunoglobulin



L2 Lymphoblastic leukaemia with varied structure

Frequency:

Accounts for 70% of cases in adults, and 14% in children.

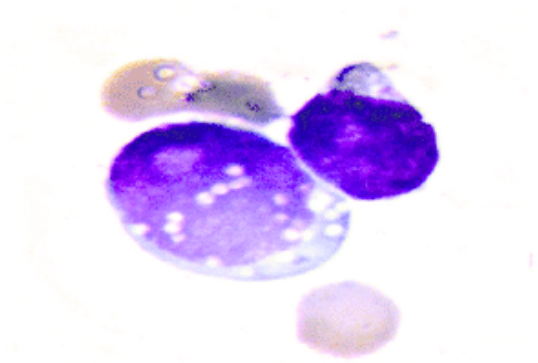
Morphology:

Nucleus is irregular, heterogeneous chromatin structure, large nucleoli.

Immunophenotype

B:	T:
•CD19	•CD3
•CD22	•CD7
•CD79a	•CD5
•CD10	•CD2
•CD20	•CD4

•Cytoplasmic or superficial immunoglobulin



L3 Burkitt's leukaemia

Frequency:

Rare subtype, accounting for less than 1% to 2% of cases.

Morphology:

Large blasts, prominent nucleoli, stippled homogeneous chromatin structure, abundant cytoplasm, abundant cytoplasmic vacuolation (bubble type) covering the nucleus.

Immunophenotype

B:	T:
•CD19	•CD3
•CD22	•CD7
•CD79a	•CD5
•CD10	•CD2
•CD20	•CD4

•Cytoplasmic or superficial immunoglobulin

ALL according to cells origin	ALL percentage
B-cell precursors	80–85 %
T-cell precursors	10–15 %
NK-cells precursors	0–1 %

2015

https://www.researchgate.net/profile/Adrian-Santoyo-Sanchez/publication/284069311/figure/fig1/AS:404129794019330@1473363459583/French-American-British-FAB-classification-of-acute-lymphoblastic-leukaemia-FAB.png

4th edition	5th edition
B-lymphoblastic leukemia/lymphoma, NOS	Unchanged
B-lymphoblastic leukemia/lymphoma with hyperdiploidy	B-lymphoblastic leukemia/lymphoma with high hyperdiploidy
B-lymphoblastic leukemia/lymphoma with hypodiploidy	Unchanged
B-lymphoblastic leukemia/lymphoma with *iAMP21*	Unchanged
B-lymphoblastic leukemia/lymphoma with t(9;22)(q34;q11.2); *BCR-ABL1*	B-lymphoblastic leukaemia/lymphoma with *BCR::ABL1* fusion
B-lymphoblastic leukemia/lymphoma, *BCR-ABL1*-like	B-lymphoblastic leukemia/lymphoma with *BCR::ABL1*-like features
B-lymphoblastic leukemia/lymphoma with t(v;11q23.3); *KMT2A*-rearranged	B-lymphoblastic leukemia/lymphoma with *KMT2A* rearrangement
B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*	B-lymphoblastic leukemia/lymphoma with *ETV6::RUNX1* fusion
B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3); *TCF3-PBX1*	B-lymphoblastic leukemia/lymphoma with *TCF3::PBX1* fusion
B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.1); *IGH/IL3*	B-lymphoblastic leukemia/lymphoma with *IGH::IL3* fusion
B-lymphoblastic leukemia/lymphoma with other defined genetic abnormalities	B-lymphoblastic leukemia/lymphoma with other defined genetic abnormalities

5th edition
B-lymphoblastic leukemia/lymphoma with *ETV6::RUNX1*-like features
B-lymphoblastic leukemia/lymphoma with *TCF3::HLF* fusion

B-cells classification changes according to WHO (left, 4th ed. – 2017, 5.thed. - 2022 respectively)
New diagnoses for 5th ed. (right and top)

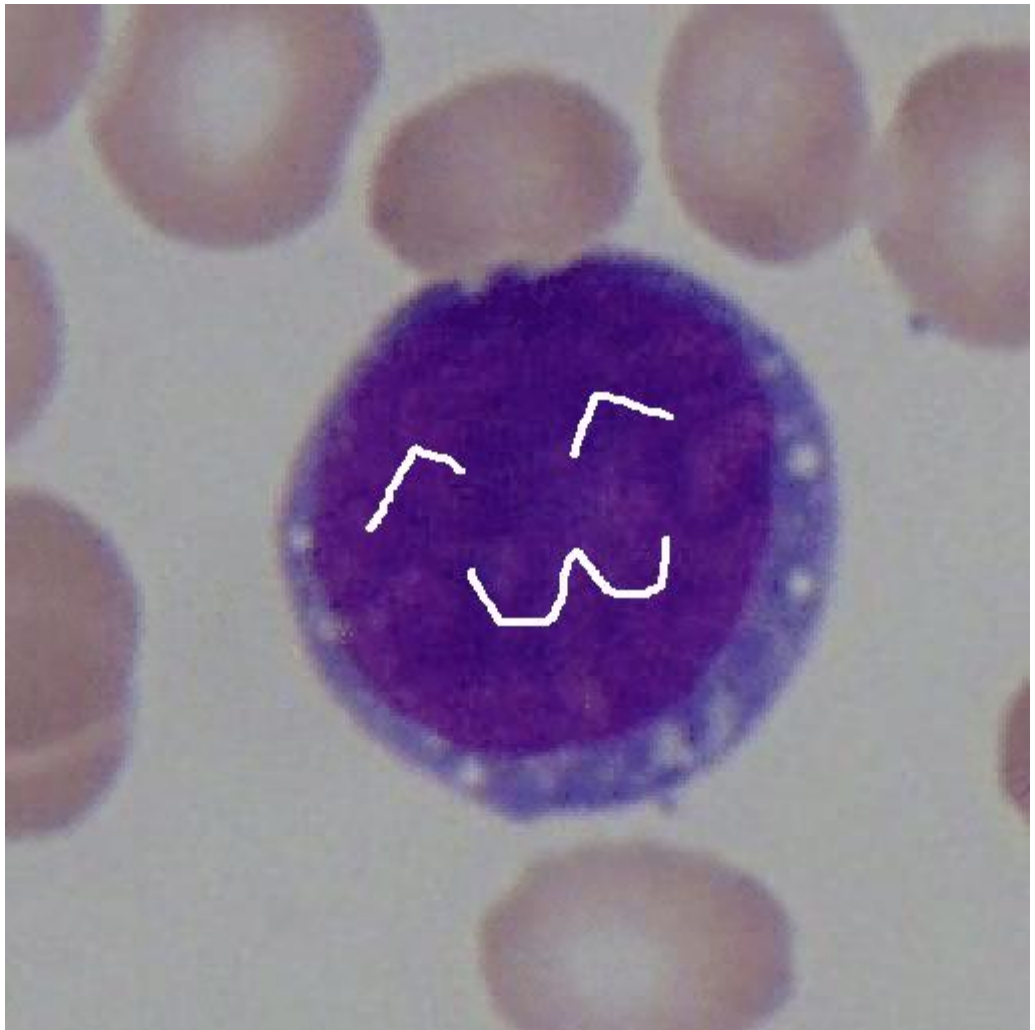
https://lymphoblastic-hub.com/medical-information/the-5th-edition-of-the-world-health-organization-classification-of-haematolymphoid-tumors-key-updates-to-all-classification

T-CELL ALL CLASSIFICATION - WHO (4TH ED. – 2017, 5TH ED. – 2022)

4th edition	5th edition
T-lymphoblastic leukemia/lymphoma	T-lymphoblastic leukemia/lymphoma, NOS
Early T-cell precursor lymphoblastic leukemia	Early T-precursor lymphoblastic leukemia/ lymphoma
NK-lymphoblastic leukemia/lymphoma	Entity deleted

https://lymphoblastic-hub.com/media/images/aa/d0/who-all-figure3.png
https://img.freepik.com/premium-vector/cartoon-cute-anime-girl-crying-illustration-creative_638892-439.jpg

THOSE TYPOS… – „A CUTE LYMPHOCYTIC LEUKAEMIA“



ALL MANIFESTATIONS

- Haematopoesis affected
  - >20 % blasts in peripheral blood and bone marrow
  - Functional pancytopenia -> anaemia; prone to infections; bleeding manifestations (skin, GIT)
  - DIC imminent! – blasts in peripheral circulation
  - Bone pain – bone marrow invasion
- Lymphadenopathy (multiple groups together)
- Hepato- and splenomegaly
- „Night chills“, subfebrilities, fevers

ALL TREATMENT IN CHILDREN AND ADULTS (JUST FYI) – AMERICAN CANCER SOCIETY

Children

1. Induction
   - L-asparaginase, vincristine, dexamethasone (if high-risk (HR) + anthracyclines – e.g. daunorubicine)
   - If Ph-Ch+ - imatinib
2. Consolidation
   - According to ALL type – e.g. methotrexate, 6-merkaptopurine, vincristine, L-asparaginase (if HR – doxorubicine, etoposide, cyclophosphamide, cytarabine)
   - Sometimes a „second wave" treatment necessary – delayed consolidation
3. Maintenance
   - 6-merkaptopurine (daily), methotrexate (weekly) p.o.; vincristine + corticosteroids i.v. (á 4–8 weeks)
4. Radiotherapy (bone marrow ablation)
5. Bone marrow transplantation

Adults

1. Induction
   - Vincristine + dexamethasone/prednisone – doxorubicin/daunorubicine
   - If Ph-Ch+ - imatinib, dasatinib
2. Consolidation (intensification)
   - Imatinib
   - Immunotherapy - blinatumomab
3. Maintenance (2 years)
   - 6-merkaptopurine, methotrexate (Ph-Ch+)
4. Radiotherapy (bone marrow ablation)
5. Bone marrow transplantation (possible even during phase 2)

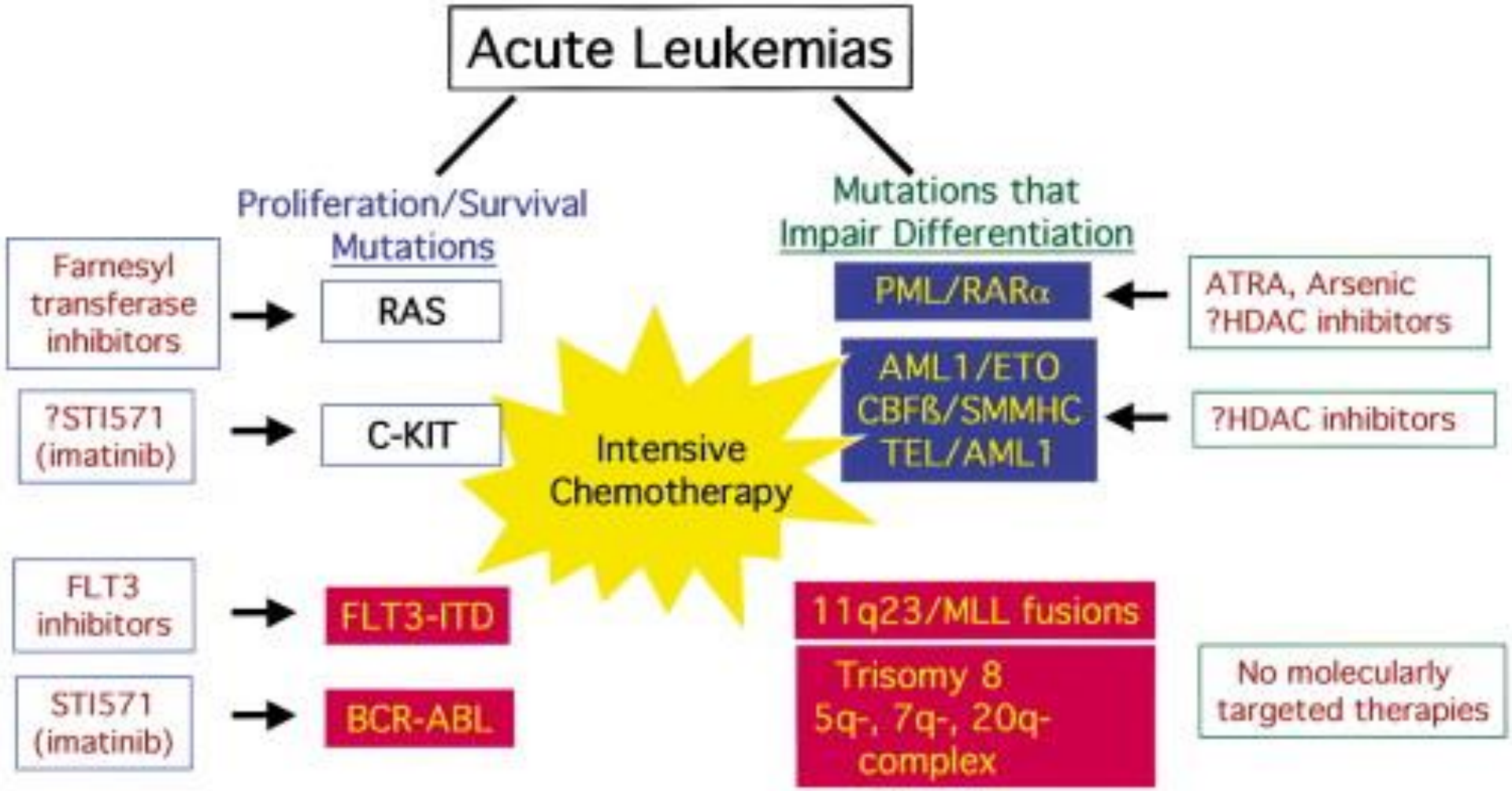
PROGNOSIS OF ALL AND TREATMENT OF RESISTANT FORMS

Children

- Prognosis
  - Remission – 90–98 %
  - Relapse – cca. 10 %
- Recurrent and resistant ALL treatment
  - CAR-T-cell treatment (chimeric antigen receptor)
  - Drug and antibody conjugate – inotuzumab ozogamicin

Adults

- Prognosis
  - Remission – 80–90 %
  - Relapse – 40–45 %
- Recurrent and resistant ALL treatment
  - CAR-T – B-cell-ALL
  - Ph-Ch+ - imatinib
  - KMT2A+ - revumenib
  - Nelarabine – T-cell ALL



HDAC – histone deacetylase https://www.cell.com/cms/10.1016/S1535-6108(02)00081-8/asset/e39034e4-7311-44be-b4e5-cf41a700ee3c/main.assets/gr1.jpg

CHRONIC MYELOID LEUKAEMIA

- Oncohematological disease typical with increase in myeloid precursors of higher maturity degree compared to AML
- Epidemiology
  - USA 2025 estimate – incidence 9 500 cases, mortality cca. 1 300 cases
  - 50 % patients aged 65+, rarely in children or <40 years of age
- Fusion gene BCR-ABL1 establishment typical
  - T(9;22)(q34;q31)
  - Chromosome 22 contain several points of possible breaks and translocations – variations e13a2 and e14a2 (210 kDa)
    - Variations 190 kDa (e1a2 – B-cell-ALL), resp. 230 kDa (chronic leukaemia)
  - This gene solely allows leukemic transformation

CML PATHOMECHANISM

1. BCR-ABL1 fusion gene -> protein
   - Tyrosine kinase activity
   - Cascades JAK/STAT, PI3K/AKT, RAF, MYC and RAS/MEK stimulated -> proliferation, cell survival and resistance to apoptosis cell advantage
   - BCR-ABL negative CML -> SETBP1, ASXL1, NRAS/KRAS, SRSF2, CSF3R, U2AF1 gene mutations, etc.
2. Leukemic stem cells development -> chronic phase

SETBP1 – Set binding protein 1, ASXL1 – additional sex chromatin human homologue 1, NRAS – neuroblastoma RAS viral homologue, KRAS – Kirsten rat sarcoma virus, SRSF2 – serine/arginine-rich splicing factor 2
U2AF1 – U2 small nuclear RNA auxiliary factor 1

CML COURSE

1. Chronic phase (3–5 years, 85 % patients during dg.)
   - <10 % bone marrow blasts, possible anomalies in peripheral blood (↑Tr, ↑Leu - ↑Neu, ↑Ba, ↑Eo, „left“ shift)
   - „Myelocyte bulge“ – myelocytes prevail over mature metamyelocytes
   - Asymptomatic patient or non-specific symptoms – weight loss, fever/“night chills“, weakness, splenomegaly
2. *Accelerated phase (7–12 months without treatment)*
   - *Additional mutations acquired – p53-; CDKN2A-; GATA2-; RUNX1; IKZF1; ASXL1; WT1*
   - *Additive cytogenetic abnormalities (ACA) mark worse prognosis and increasing severity (5–10 % in chronic phase vs. 80 % v blastic phase)*
   - *Anaemia development, symptoms from chronic phase more intense of starting to manifest*

CDKN2A –cycline-dependent kinase inhibitor 2A; GATA2 – GATA-binding protein 2; RUNX1 –Runt-related transcription factor 1; IKZF1 – Ikarus family zinc finger 1; ASXL1 – Additional sex chromatin human homologue 1; WT-1 – Wilms tumour 1

CML COURSE

3. Blastic phase (blastic crisis; 3–6 months; survival median 1.8 years)
   - Bone-marrow and peripheral blasts >20 %
   - High cells turnover -> ↑K^+, ↑LDH, ↑uric acid
   - Organs infiltration -> lymphadenopathy, splenomegaly, bone pain
   - Sternal bone „softening“ -> haematopoiesis bone marrow expansion to phylogenetic older locations
   - AML/ALL transformation

Chronic Myeloid Leukemia (CML): *Pathogenesis and Clinical Presentation*

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Translocation of a Chr 9 segment onto Chr 22, creating a Philadelphia chromosome (Chr 22) containing the BCR-ABL1 fusion gene

Mutations from ionizing radiation

Other genetic abnormalities

These genetic abnormalities accumulate in the earliest cell of the blood cell differentiation sequence: the pluripotent hematopoietic stem cell

Hematopoietic stem cell division in the bone marrow becomes unregulated → Multifactorial causes, most with unclear mechanisms → Weight loss, malaise, fever/ chills, night sweats

https://calgaryguide.ucalgary.ca/wp-content/uploads/2015/05/CML.jpg

1. Chronic Stage (85% of clinical presentation): Hematopoietic stem cell division/differentiation in the bone marrow results in ↑ production of multiple blood cell lines (detectable on CBC, but patients are usually asymptomatic at this stage)

- Neoplastic division of platelet precursor cells → Thrombocytosis
- Neoplastic division of WBC precursor cells, especially neutrophil precursors → **Leukocytosis:**
  · Neutrophilia, basophilia, & eosinophilia
  · "Left shift": ↑ neutrophil & band production
  · Disorderly WBC differential: i.e. "myelocyte bulge"
  → Trapping of WBC's in the spleen enlarges the spleen → **Splenomegaly:**
  · Left upper quadrant pain
  · Early satiety (large spleen compresses the stomach)
  · Associated hepatomegaly (if spleen is overfilled & WBCs spill over into liver)

Acquired ↑ genetic abnormalities

2. Accelerated Stage
More and more immature precursor cells ("blasts") divide and accumulate in bone marrow (where 10-19% of blood cells are "blasts".) Blasts start to spill over into the peripheral blood

Dividing "blasts" limit the space and resources available for RBC synthesis → Anemia → *↓ oxygenation of blood means blood is less red & body tries to compensate* → Pallor, Dyspnea, Tachycardia

Acquired ↑ genetic abnormalities

3. Blast crisis (transformation into AML/ALL)
Neoplastic blast cells have filled up the bone marrow (where >20% of blood cells are blasts). More blasts spill out into the peripheral blood.

- High turnover of these cancerous cells → excess cell lysis → Release of intracellular contents (uric acid, K+, LDH) into plasma
  - · Hyperkalemia
    · High (LDH) → Gout
  - Hyperuricemia → Acute Kidney Injury
- Expanding marrow pushing on bone → Bone pain
- Bone marrow expands into sternum → Sternal tenderness

Legend: Pathophysiology | Mechanism | Sign/Symptom/Lab Finding | Complications

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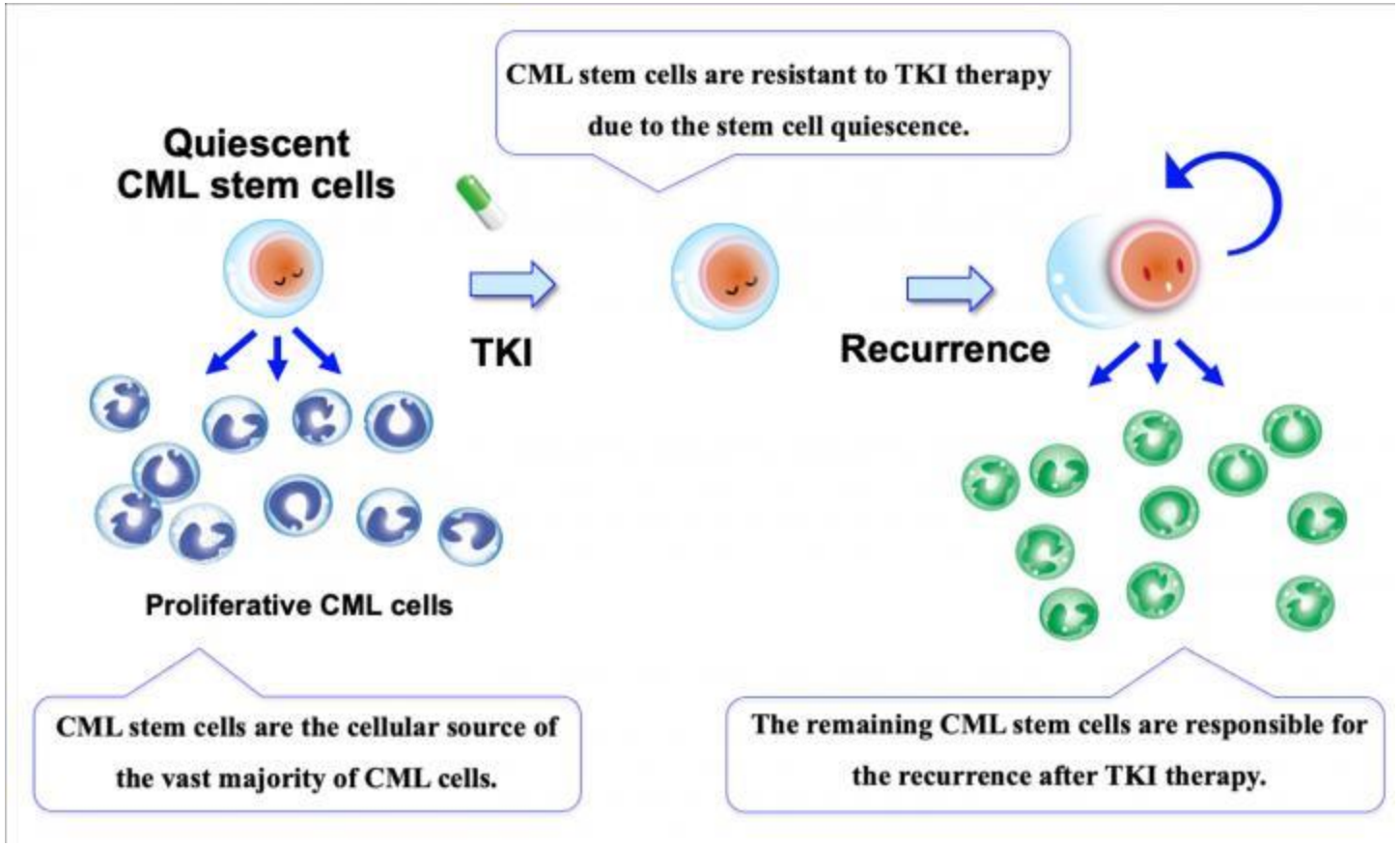
CML TREATMENT AND PROGNOSIS

- Treatment
  - GOLDEN STANDARD – Tyrosine kinases inhibitors - Imatinib mesylate, dasatinib, nilotinib, etc.
  - Chemotherapy, immunotherapy
  - High-dose ChT + bone marrow transplantation
  - Donor lymphocytes transfusion -> bone marrow transplantation success increased– „graft vs. host" – donor lymphocytes attack acceptor blasts
  - Surgery - splenectomy
- Prognosis
  - 5-year survival – 90 % (85 % survive for 10 years)
  - Remission – 40–60 %, relapse 60 % (most in 6 months after treatment termination, imatinib – responding well)



https://genengnews.com/wp-content/uploads/2020/09/Sep18_2020_KazuhitoNaka_CMLstemcells.jpg

CHRONIC LYMPHOCYTIC LEUKAEMIA

- Oncohematologic disease typical with leukocytes increase in bone-marrow and peripheral blood (also organs infiltration often) – monoclonal B-cells
  - Partial preservation of signalisation, B-cell receptor (BCR) including
  - Packing of monoclonal B-cells -> oppression of healthy cells, defective defensive functions, CD5+, CD23+
- Classification
  - Slowly progressing CLL (indolent)
  - Fast progressing CLL (aggressive)
- Epidemiology and statistics
  - USA 2025 estimate – incidence 24 000, mortality 4 500 cases
  - Average age during diagnosis - 70 years of age, rarely <40 years of age

CLL PATHOMECHANISM

1. Monoclonal-B-lymphocytosis – „pre-leukemic condition“
   - Definition – „low-grade“ (<500 MBLy-Ly/µl) vs „high-grade“ (500 – 5000 MBLy/µl)
   - Genetics - „first hit“
     - Classic factors (SNP, partial monosomies) – locus 13q21.33-22.2, m-del q11, m-delq13, m-del p17; 47, XX/XY,+12;
     - NOTCH1, BIRC3, SF3B1, MYD88, ATM a TP53 factors mutations
     - V(D)J components mutations – e.g. IVGH4-59/61 („low-grade“) vs. IGHV1-69, IGH2-5, IGHV3-23, etc. („high-grade“) -> genomic transformation failure (antibodies production necessity) -> „second hit“
   - Environmental factors influence (benzene; EBV; chemotherapy in medical history)
   - Packed MBLy in bone marrow and their release into periphery
   - Asymptomatic, average CLL/SLL transformation time is 6.4 years

„m-“ marking partial monosomy, SLL – small-cell lymphoma

CLL PATHOMECHANISM

2. CLL transition
   - CLL may start even without MBLy
   - Genetic and epigenetic abnormalities accumulation -> bone-marrow microenvironment change
   - Environmental factors – as in MBLy + insecticides, Agent Orange, radiation
   - Survival cascades regulation -> „Goldilocks and three bears“ -> BCR, NF-κB
   - Bone-marrow occupation, „immunosuppression“ established -> malignant B-Ly with leucocytosis
   - Asymptomatic for a long time -> MBLy in peripheral blood, „smudge/basket“ cells, hypogammaglobulinemia

CLL MANIFESTATIONS

- Long-term asymptomatic
- Decresed functional leukocytes + hypogammaglobulinemia – frequent infections
- Inflammatory cytokines production -> fever, „night chills“, weight loss, appetite loss
- Splenomegaly, lymphadenopathy
- ↓Ery -> normocytic normochromic anaemia
- ↓Tr – bleeding manifestations

CLL TREATMENT AND PROGNOSIS

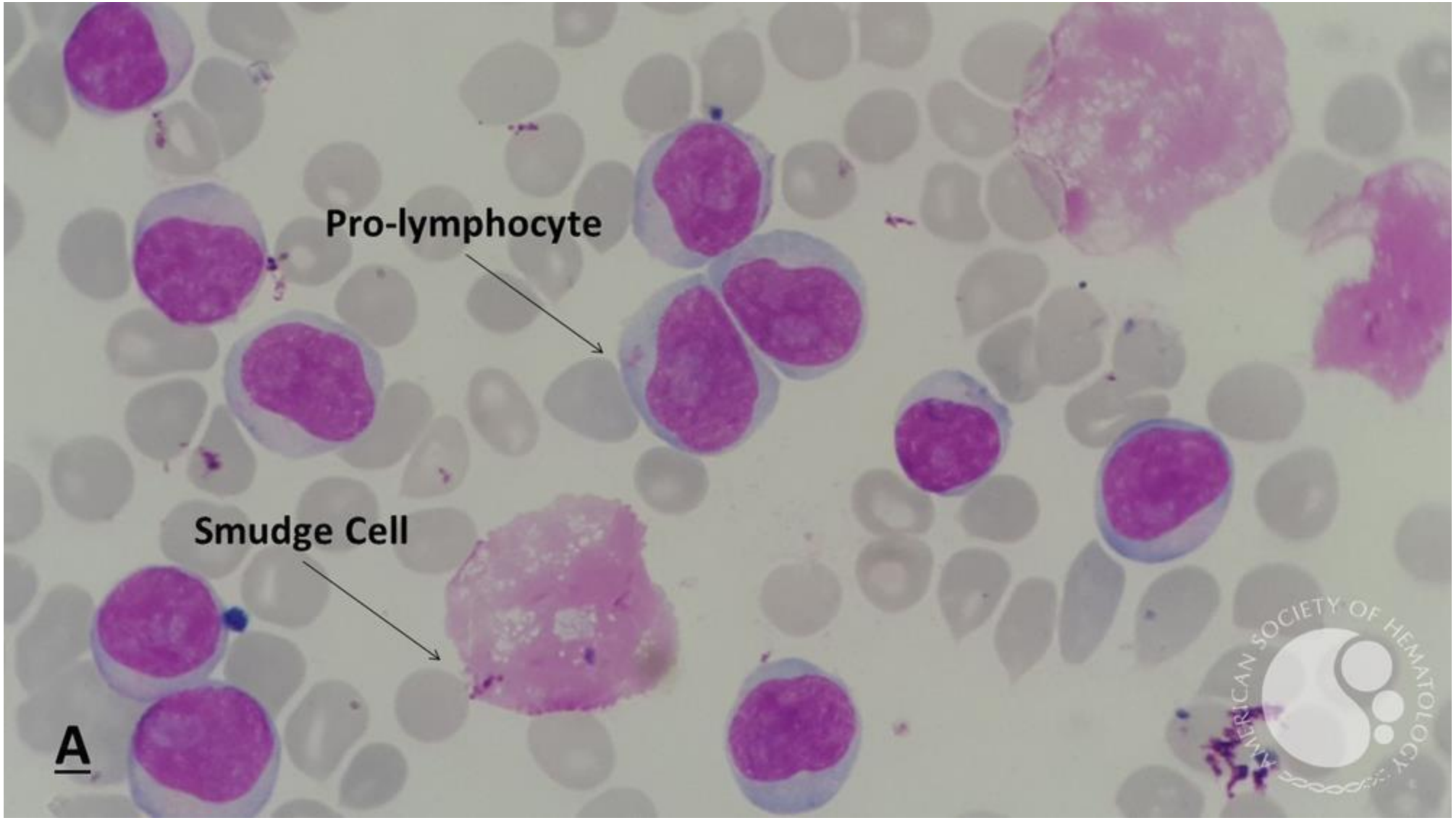
Treatment

1. Bruton kinase inhibitors – e.g. ibrutinib, zanubrutinib
2. Bcl-2 inhibitors – venetoclax + obinutuzumab (anti-CD20)
3. Bruton kinase inhibitors + Bcl-2 inhibitors

Prognosis and risks

- Prognosis
  - 5-year survival – 87 % patients
  - Remission - ? % (complete, partial), relapse – 20+ % (relapse within 6 months, but may even after 7 yrs)
- Risks
  - Autoimmune disease trigger – haemolytic anaemia (5–10 %), thrombocytopenia
  - Richter transformation -> diffuse large-B-cell lymphoma, Hodgkin lymphoma (rare)
  - Aggressive leukemic transformation – lymphoblastic lymphoma, „hairy cell“ leukaemia, T-cell lymphoma , AML, etc.

Bcl-2 – B-cell lymphoma 2



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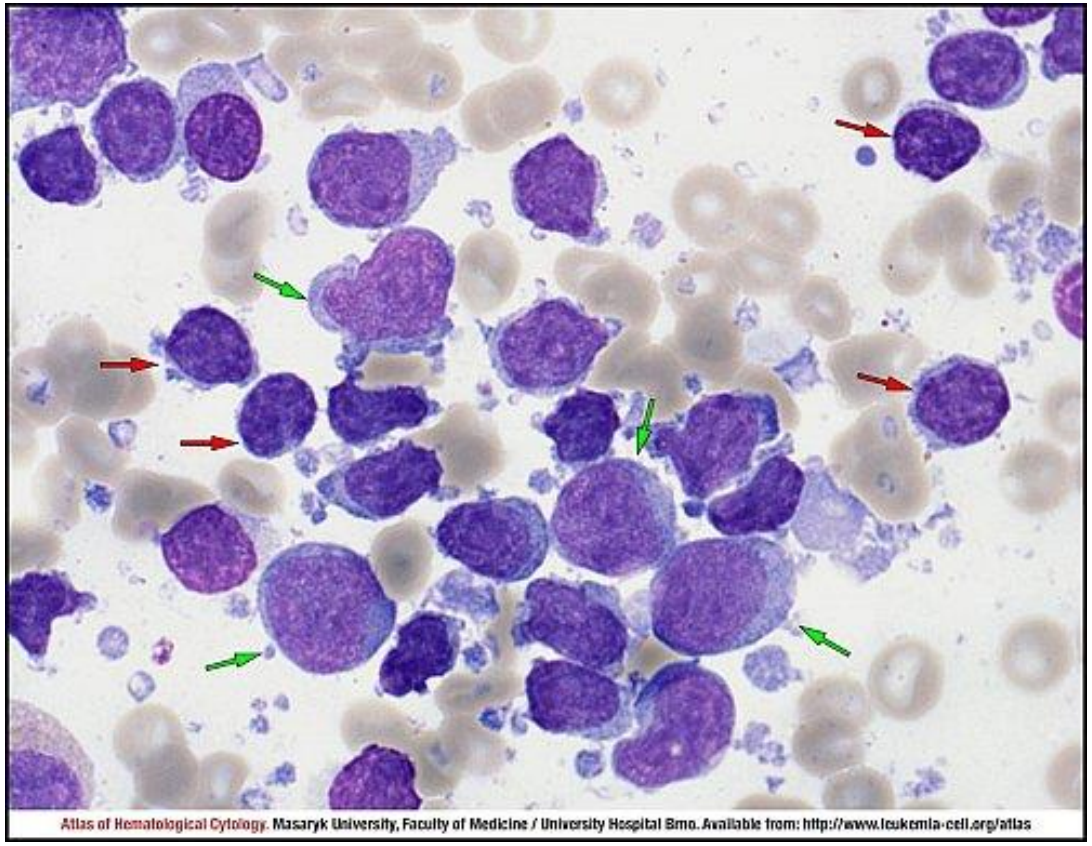
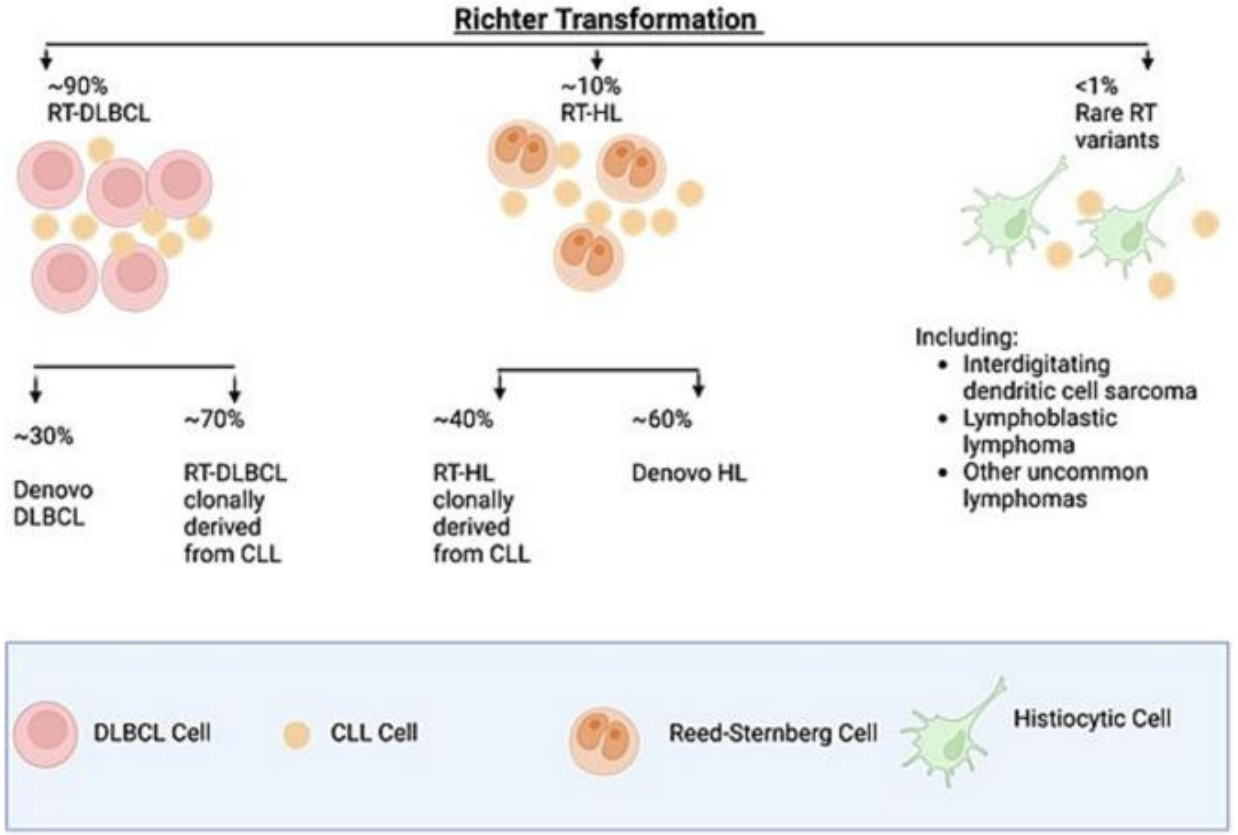
RICHTER TRANSFORMATION (RT) – B-CELL-CLL TO DIFFUSE LARGE B-CELL LYMPHOMA



Red arrows - monoclonal B-cells, green - blasts

https://www.leukemia-cell.org/atlas/res/photogallery/th-richter1.jpg



RT may include also Hodgkin lymphoma a other, mainly mutation in monoclonal B-Ly (Bcl-2 susp.)

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LYMPHOMAS

- Oncohematological diseases from peripheral lymphocytes of various maturation degrees (B-, T-, NK-cells)
- Heterogenic disease groups (progression and malignancy degree varying)
- Possible start both in bone marrow and peripheries
  - Leukemic transformation possible -> ALL mostly
- Classification
  - Hodgkin lymphomas
    - Nodular sclerosis Hodgkin lymphoma, mixed-cellularity HL, lymphocyte-rich HL, lymphocyte-depleted HL
    - Nodular lymphocyte-predominant Hodgkin lymphoma -> different pathomechanism, to be treated as a separate entity
  - Non-Hodgkin lymphomas

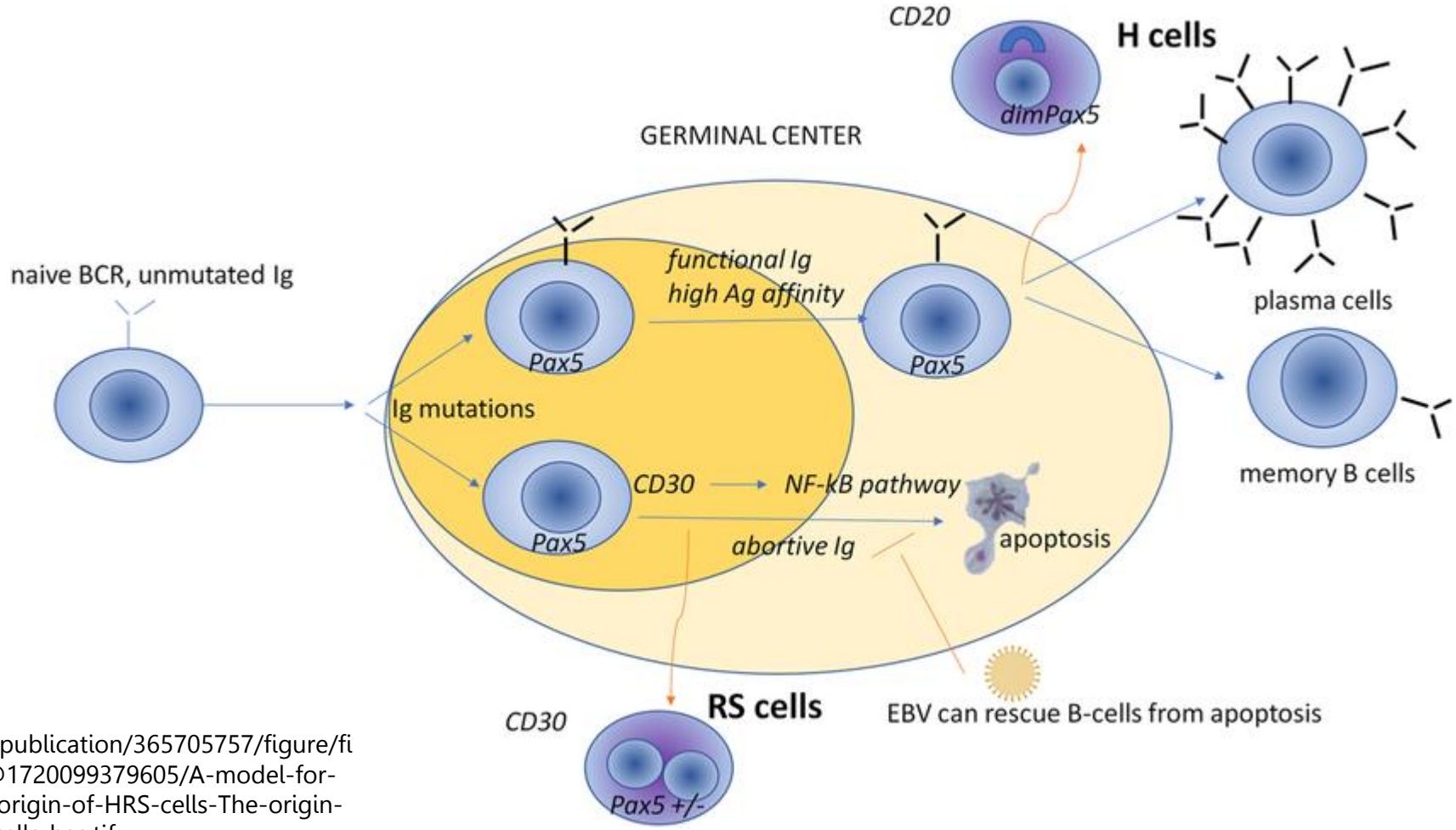
LYMPHOMAS

- Epidemiology and statistics (cca. 5 % of all malignancies)
  - Hodgkin lymphoma
    - USA 2025 estimate – incidence 8 700 cases, mortality 1 150 cases
    - Peak (age groups) – 15–19 years of age and 55+ years of age
  - Non-Hodgkin lymphomas
    - USA 2025 estimate – incidence 80 400 cases, mortality 19 400 cases
    - Peak (age groups) – risk increasing with age, 50 % case in 65+years of age

LYMPHOMAS PATHOMECHANISM

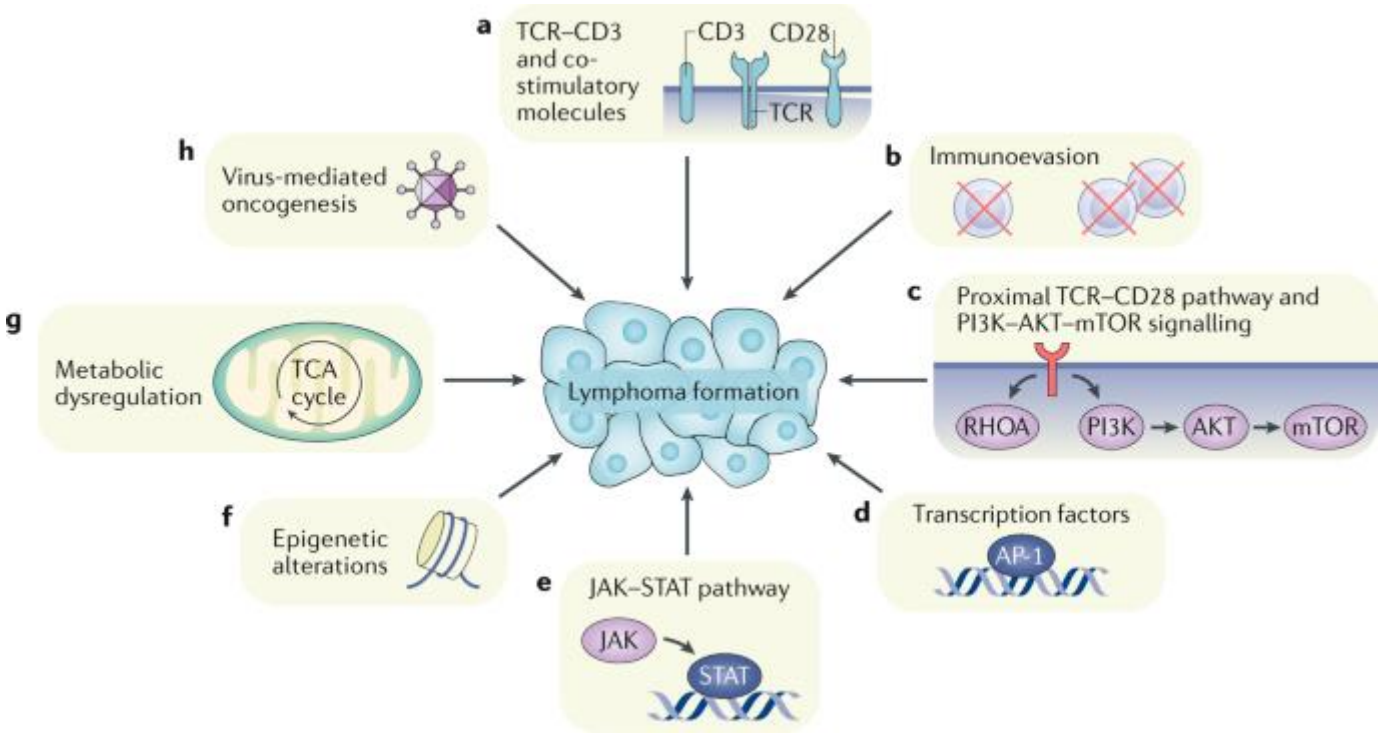
- Hodgkin lymphoma
  - B-cell to plasmocyte transformation failure -> Ig genes mutations and apoptosis escape
  - Genetic factors unknown – even monozygotic twins do not have increased risk
  - EBV viral effect -> apoptosis escape („cell dame fortune")
- Non-Hodgkin lymphomas
  - Genetics – various anomalies
    - B – t(14;18)/Bcl2, t(11,14)/Cyclin D1, t(8;14)/c-MYC, Bcl6
    - T – RASopathies, mutations in PIK3R1, PIK3CA, PTEN, monosomies (45, X0; m-del-3p, Y-deletion, aneuploidies +3, +7, +21, +X, +Y), TCRδ genes translocation (14q32) and TCRα translocation (14q11)
  - Environmental influence – oncogenic viruses (HTLV-1, EBV, HIV), chemical (benzene, chemotherapy), physical (radiation), etc.
  - „Two" to „three" hypothesis theory – according to lymphoma type
  - Frequent „bystander" cells role -> lymphocytes activated without Ag stimulation (intercellular communication)

HODGKIN LYMPHOMA



https://www.researchgate.net/publication/365705757/figure/fig1/AS:11431281258505454@1720099379605/A-model-for-the-cellular-germinal-center-origin-of-HRS-cells-The-origin-of-HRS-cells-has.tif

NON-HODGKIN LYMPHOMAS



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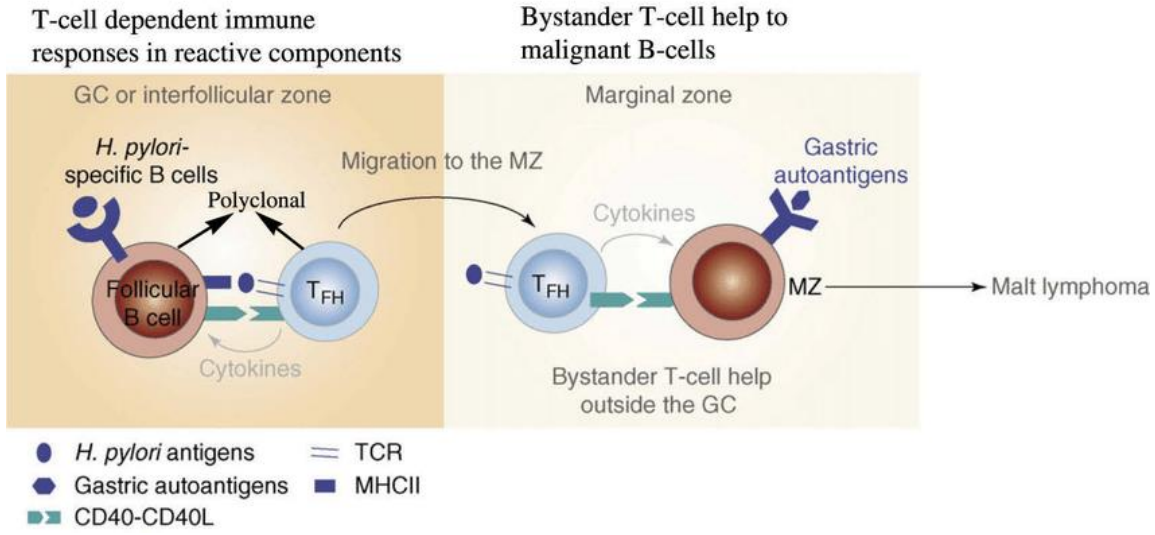
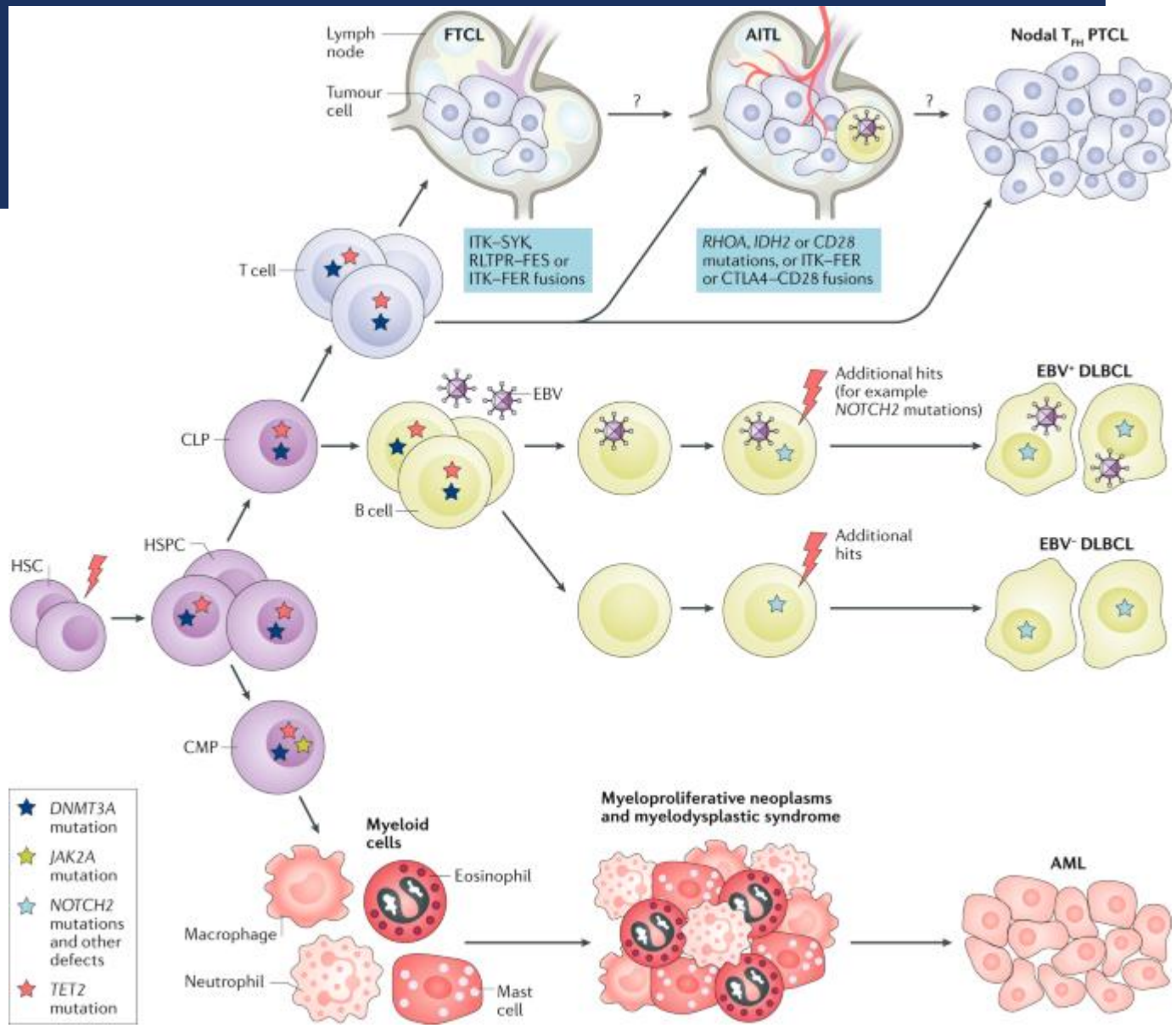
NON-HODGKIN LYMPHOMAS





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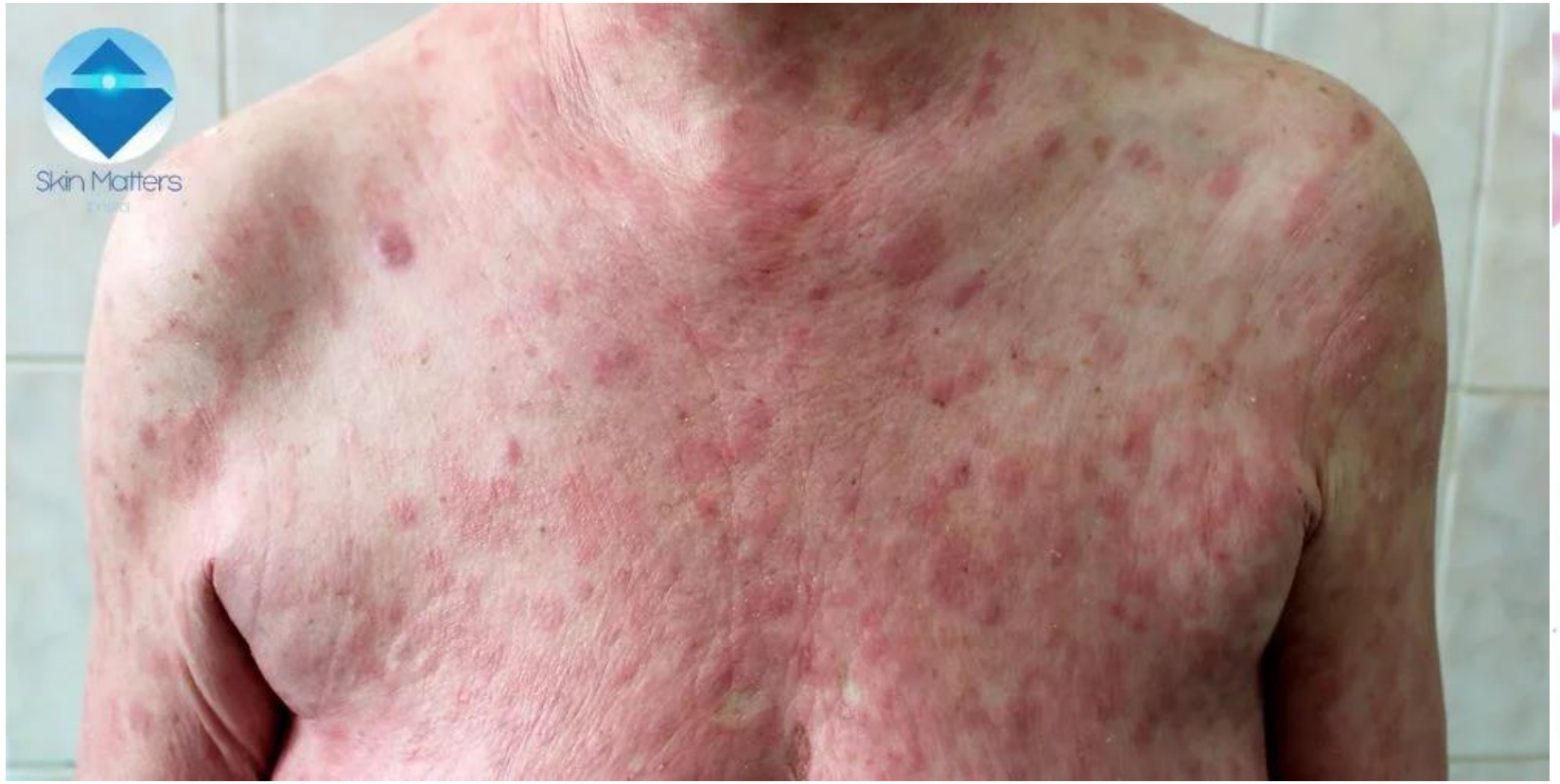
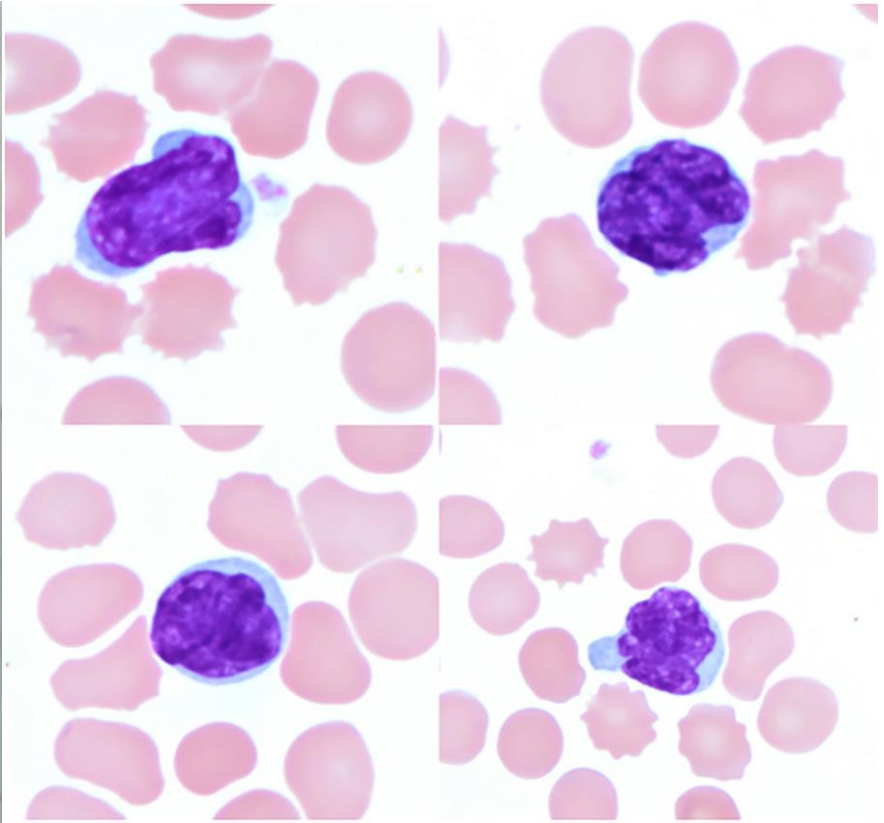
https://www.researchgate.net/publication/303388820/figure/fig2/AS:651522887143450@1532346569265/The-role-of-T-and-B-cell-interaction-in-the-development-of-MALT-lymphoma-FH-Follicular.png

T-LYMPHOMA – MYCOSIS FUNGOIDES



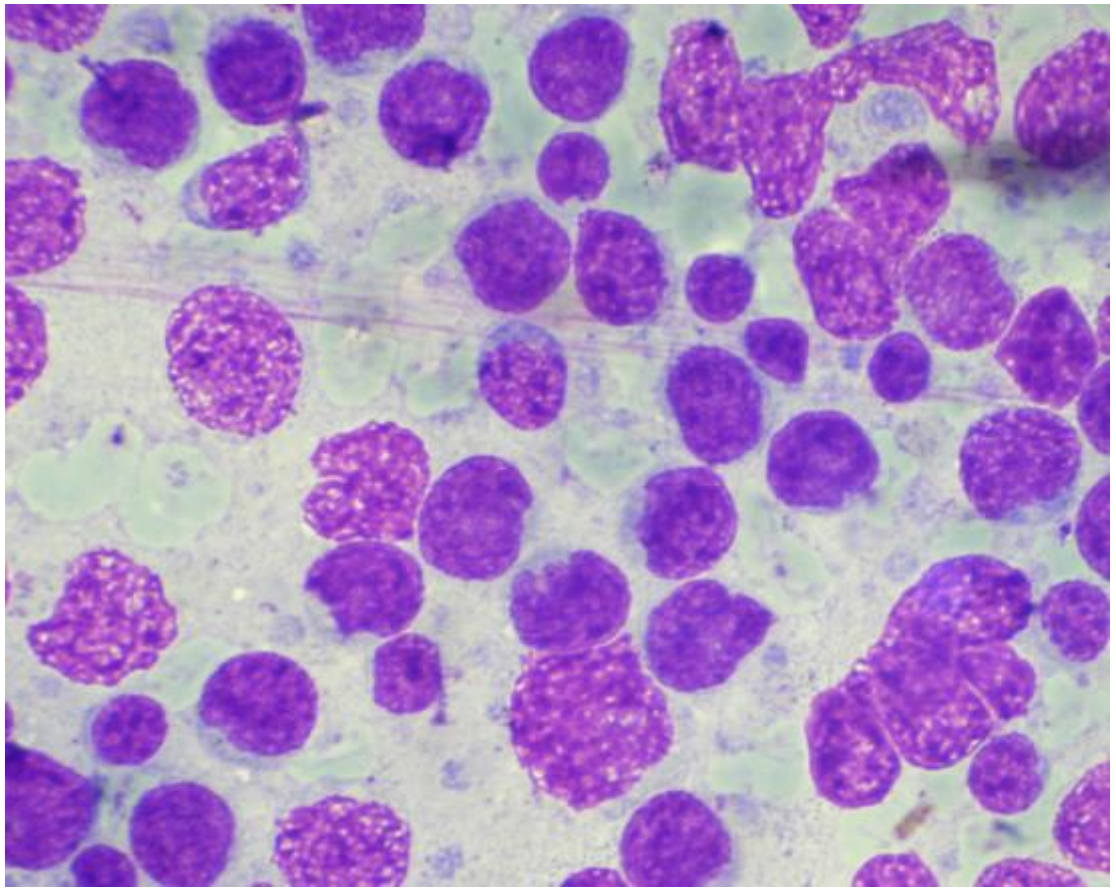
https://www.skinmattersbristol.com/wp-content/uploads/2025/01/Understanding-Mycosis-Fungoides-How-UVB-Light-Can-Slow-Disease-Progression.jpg.webp



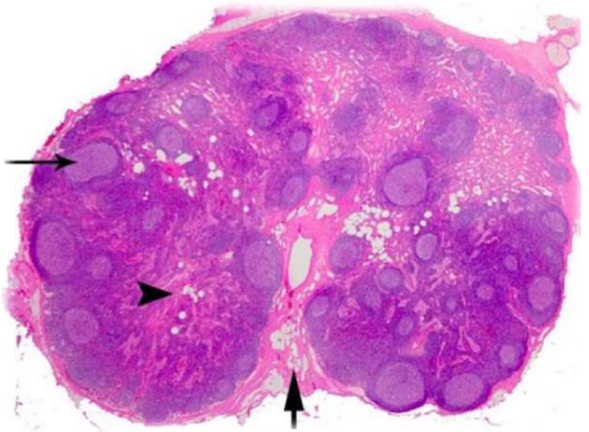
https://www.pathologyoutlines.com/imgau/lymphomanonBsezaryMirandamicro1.jpg

Sézary cells in circulation („hemispheric“ nuclei)

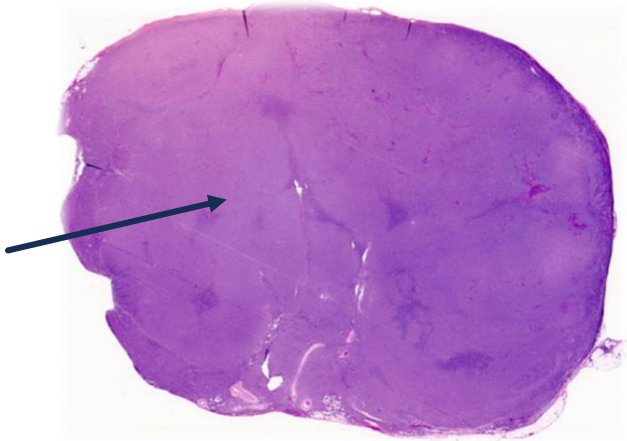
DIFFUSE LARGE B-CELL LYMPHOMA



Physiological lymphatic node (arrows marking germinal centres)



Lymphoma affected lymphatic node Germinal centres destroyed, dif. blasts spreading, rarely invades bone marrow (compared to Richter transformation)



https://wiki.clinicalflow.com/sites/default/files/DLBCLimage.jpg
https://media.springernature.com/full/springer-static/image/art%3A10.1038%2Fs41408-020-00389-w/MediaObjects/41408_2020_389_Fig1_HTML.png

LYMPHOMA MANIFESTATION

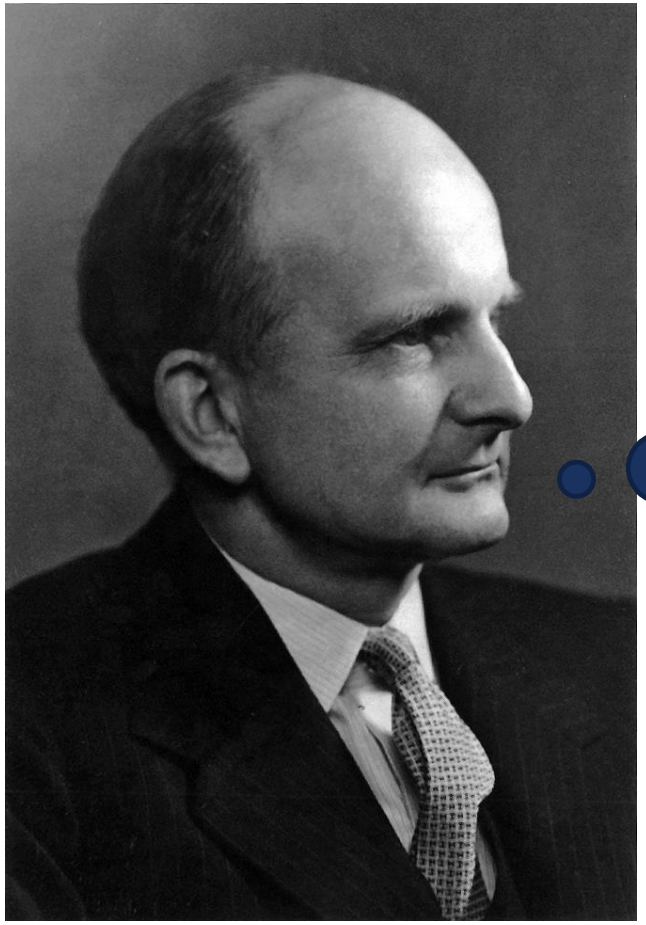
Hodgkin lymphoma

- Lymphadenopathy
  - Sole lymphatic nodes group, upper body, painless
- Systemic signs
  - Pruritus, night sweats, weight loss, mild fever, fatigue
  - Hepato- and/or splenomegaly
  - Pulmonary, cardiovascular, bone marrow invasion
- Pel-Ebstein fever?

Non-Hodgkin lymphoma

- Lymphadenopathies
  - Multiple groups – skin, neck, armpit
- Systemic signs
  - Fever and chills
  - Fatigue, abdominal „mass“ perception
  - Chest pain, chest pressure

DOES PEL-EBSTEIN FEVER EXIST? (A PHENOMENON THAT SOMEBODY NAME)



"Every student and every doctor knows that cases of Hodgkin's disease may show a fever that is high for one week and low for the next week and so on. Does this phenomenon really exist at all?..."

Richard Asher (GBR, endocrinologist and haematologist, 1912-1969)

https://en.wikipedia.org/wiki/Richard_Asher#/media/File:Richard_Asher_for_Wikipedia.jpg

LYMPHOMAS PROGNOSIS

Hodgkin lymphomas

- Prognosis
  - 87 % survive 5 years
  - 25 % cases turn out to be refractory

Non-Hodgkin lymphomas

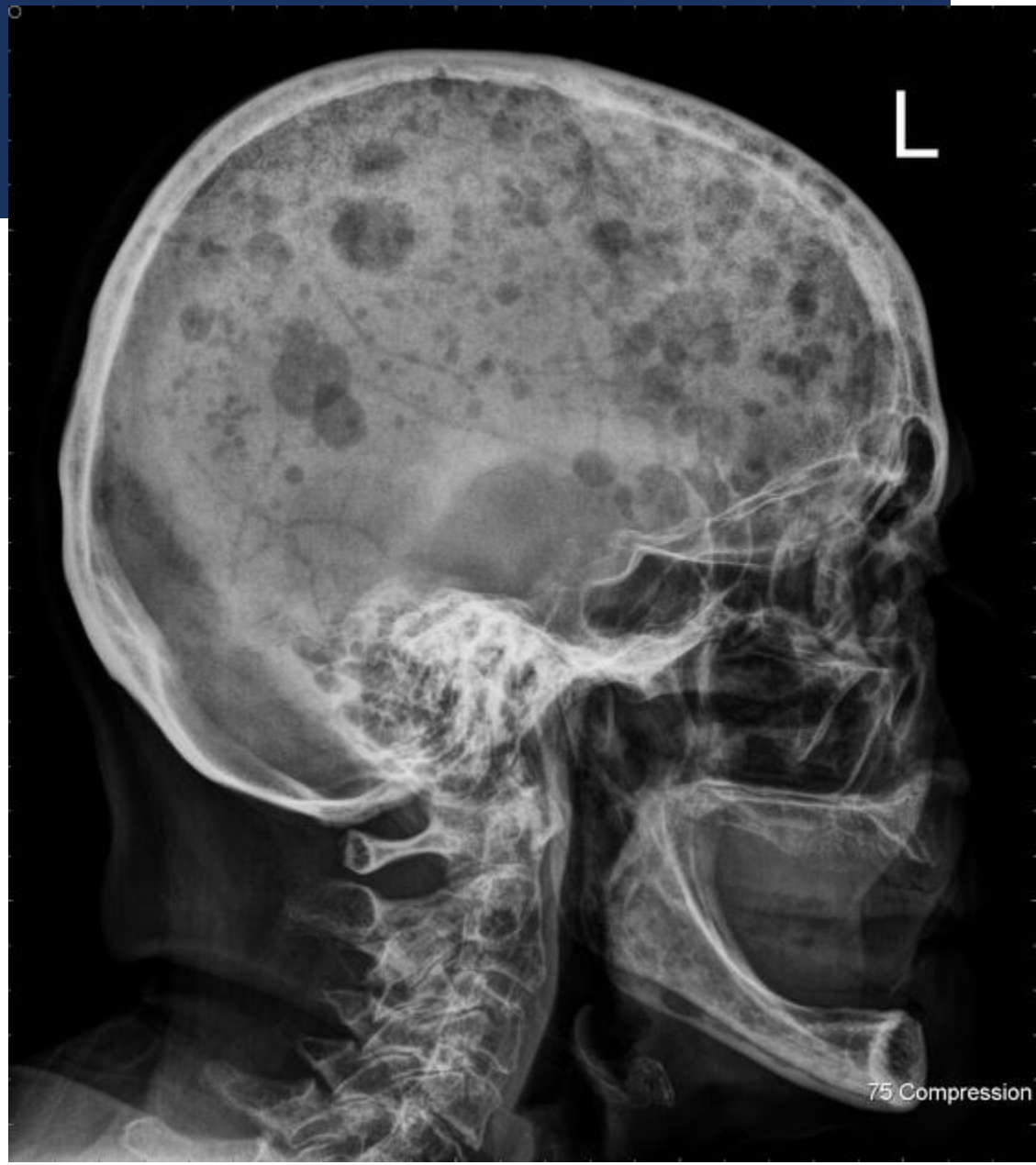
- Prognosis
  - High relapse percentage
  - 4–40 % (worst prognosis for diffuse large B-cell lymphoma)

MYELOMAS

- Oncohematological disease derived from plasmoblasts (plasmocytes precursors) or activated B-memory cells
- Multiple myeloma (MM)
  - Genetic abnormalities – heavy chain gene (14q32) and oncogene (e.g. 11q13, 4p16.3, 6p21, 16q23 a 20q11) translocation
  - Translocation of Ch14 -> plasmoblasts group emerge -> monoclonal gamapathy of uncertain significance (MGUS) -> „smouldering“ MM -> MM -> plasmoblastic leukaemia
  - IL-6 -> decisive factor
  - Manifestations – CRAB (hyperCalcemia, Renal insufficiency , Anaemia, Bone lesions -> pathologic fractures)
  - Bence-Jones protein filtrated to urine

MYELOMAS

- Other important myelomas and monoclonal gamapathies
  - Waldenström macroglobulinemia
  - Primary amyloidosis
  - Heavy-chain disease
- Statistics
  - Risk 3–5 % >50 years of age
  - Remissions and relapses according to types
    - MM relapsing in almost all patients after them being „cured“



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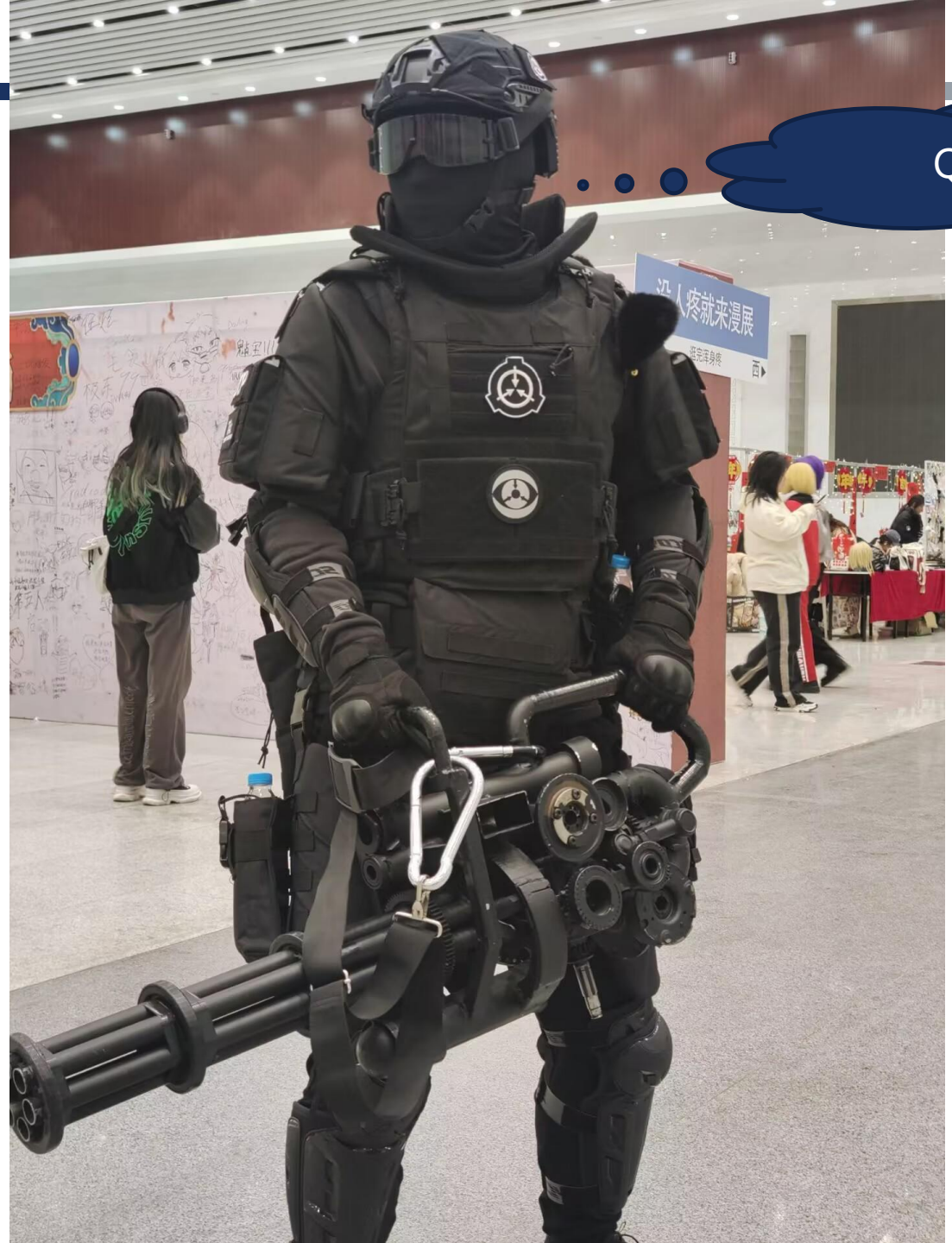
OTHER IMPORTANT ONCOHEMATOLOGIC DISORDERS AND CONDITIONS – MYELOID PRECURSOR

- Pre-leukemic states or leukaemia development risk factors

- Myelodysplastic sy.
- Polycytemia vera rubra
- Essential (primary) thrombocytemia
- Myelofibrosis
- Mastocytosis



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