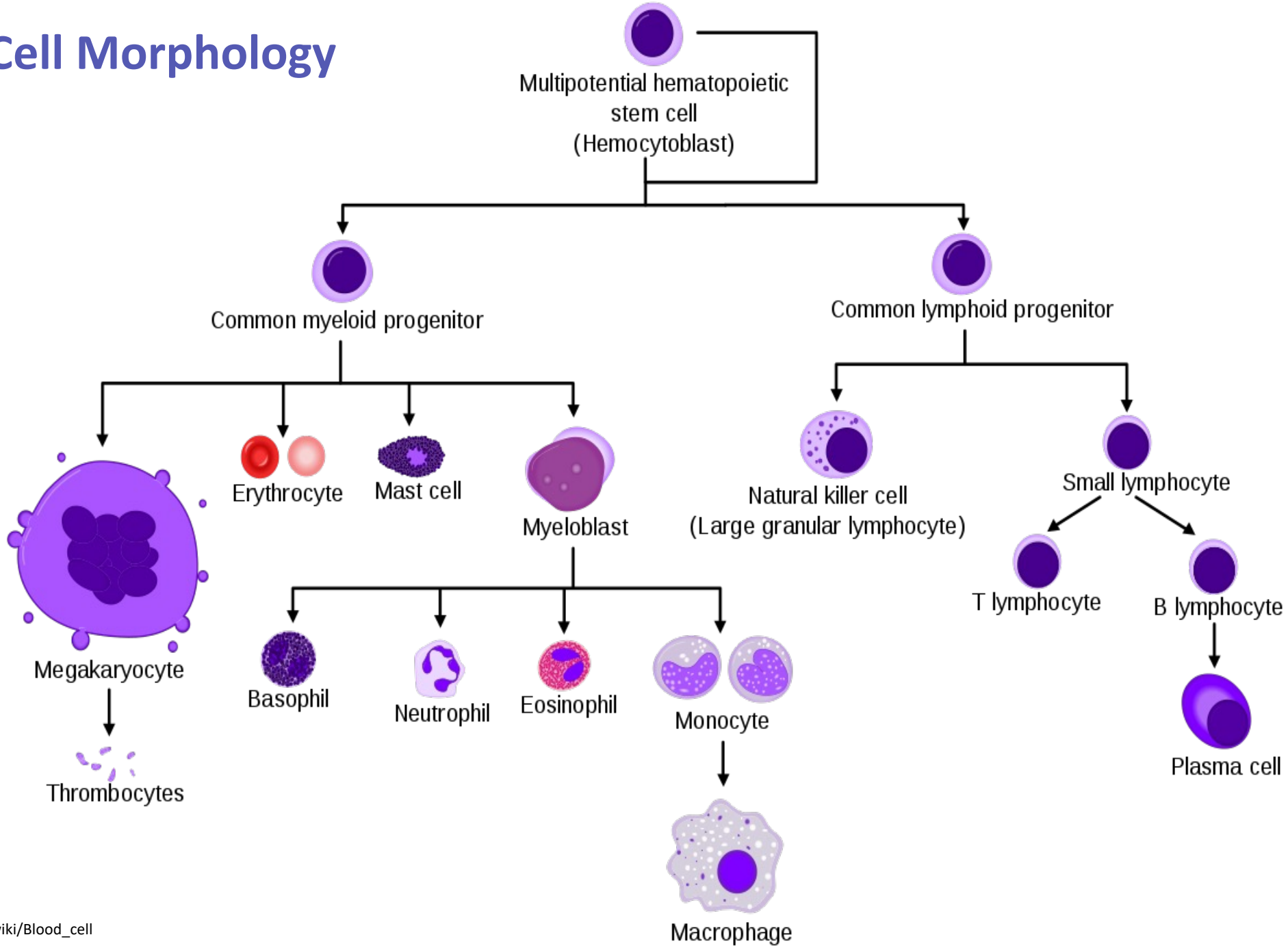
ACUTE MYELOID LEUKEMIA
& ACUTE PROMYELOCYTIC LEUKEMIA
Introductory Lecture

OVERVIEW

- Blood Cell Morphology
- Lab Techniques
- AML
- APML
- Review Handout

Blood Cell Morphology

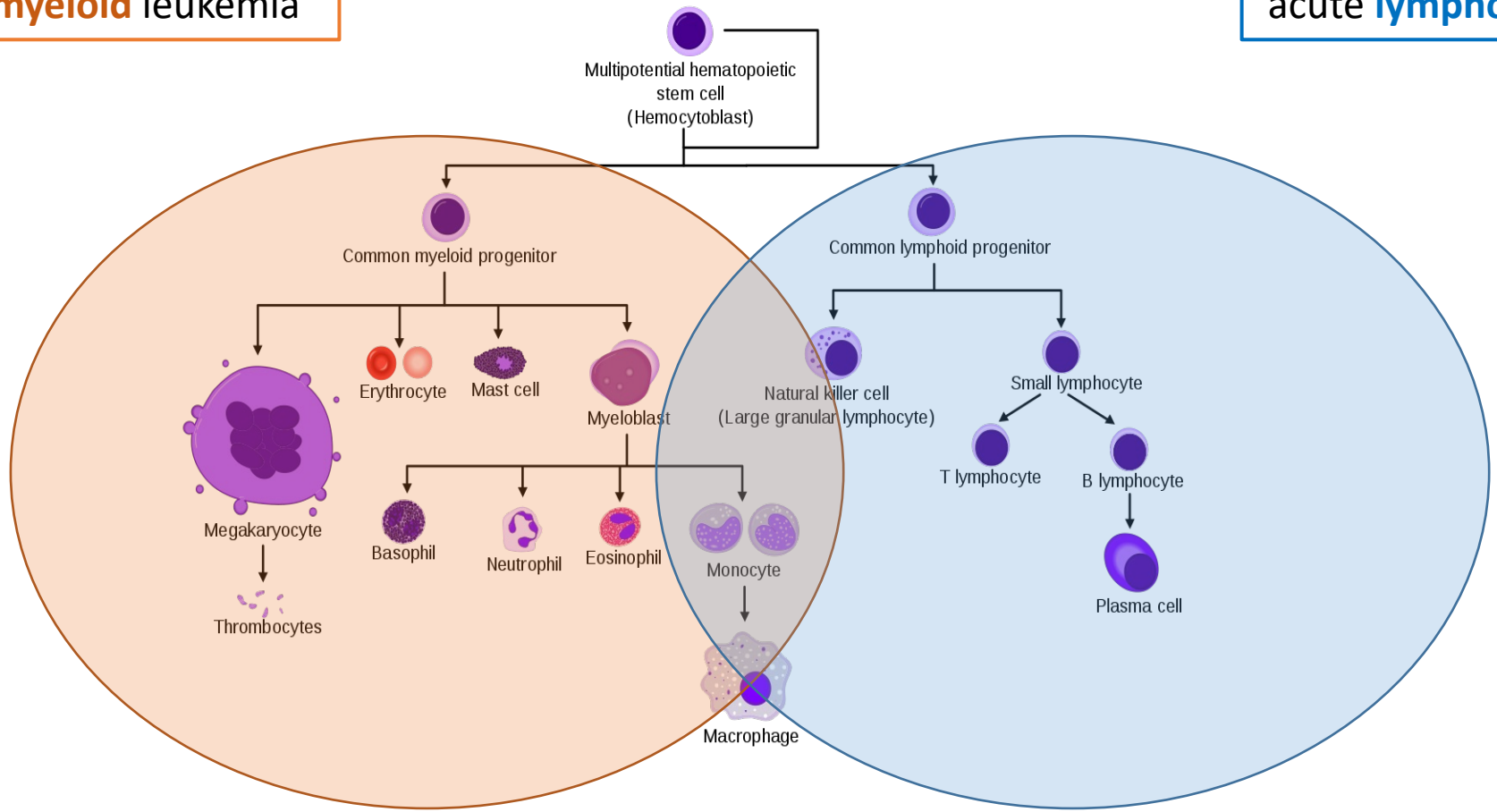


https://en.wikipedia.org/wiki/Blood_cell

Types of Acute Leukemia

acute **myeloid** leukemia

acute **lymphoid** leukemia



Types of Acute Leukemia

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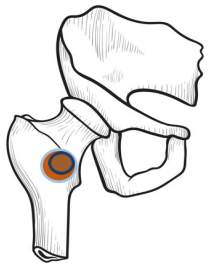
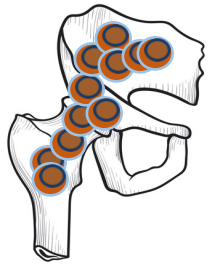
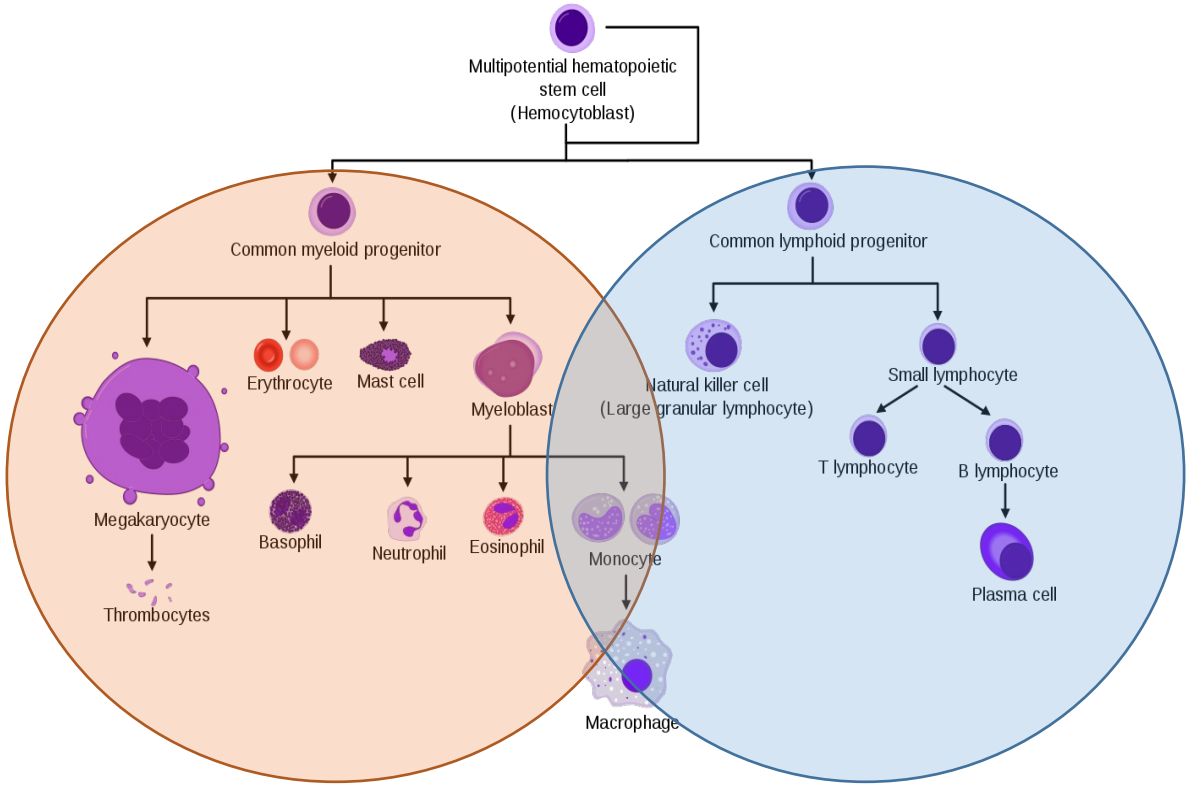


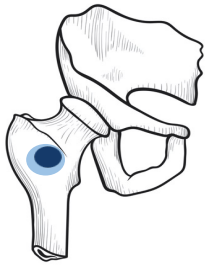
normal bone marrow



excess proliferation of myeloid cells



acute **lymphoid** leukemia



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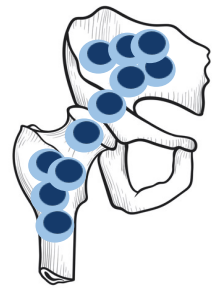
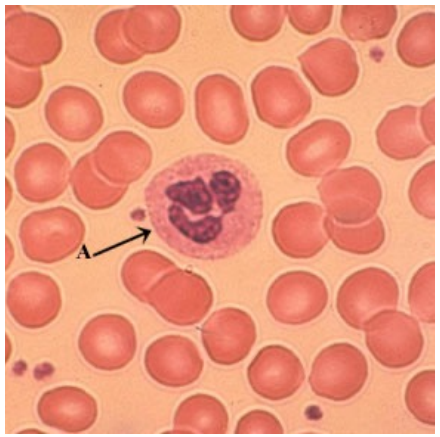


excess proliferation of lymphoid cells

PERIPHERAL BLOOD SMEARS

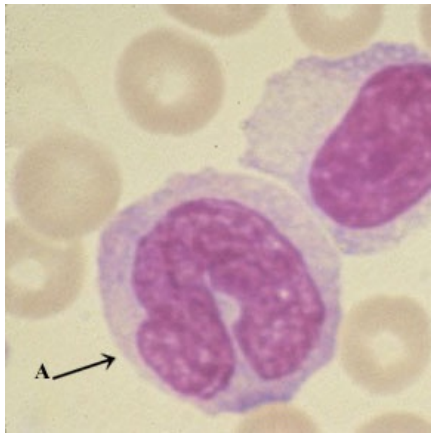
Mature Myeloid Cells

(A) Neutrophil

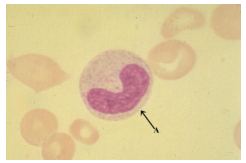


- Most common WBC
- Average 3-lobed nucleus
- > 6 lobes = hyper-segmented
- Thin chromatin strand between lobes

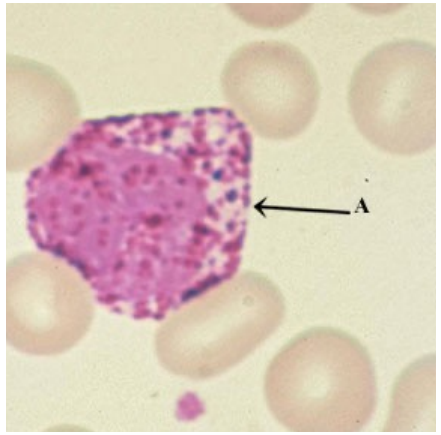
(A) Monocyte



- Horse-shoe or kidney-shaped nucleus
- Gray-blue cytoplasm
- Sometimes vacuoles
- Can look like a band

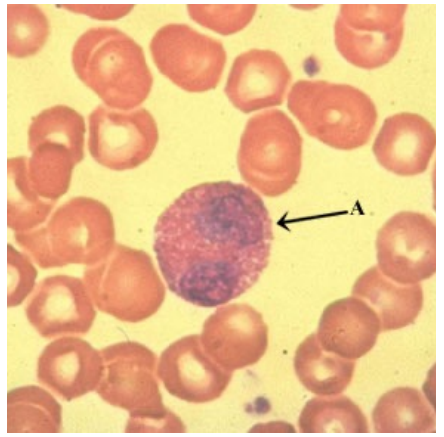


(A) Basophil



- Bi-lobed nucleus
- Large purple/black granules

(A) Eosinophil

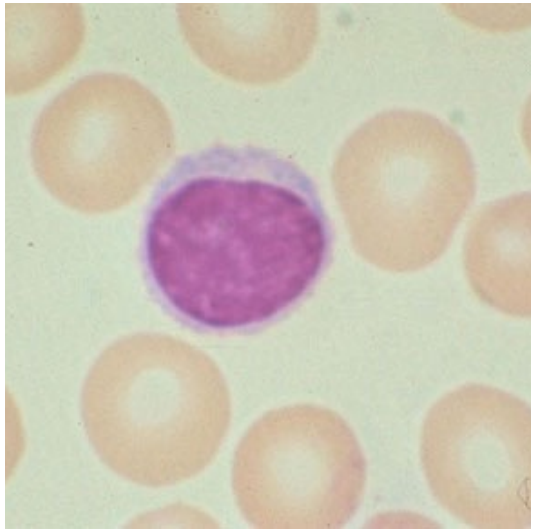


- Bi-lobed nucleus
- Red/orange cytoplasmic granules

Courtesy of Dr. Scigliano's Online Morphology Tutorial

Mature Lymphoid Cells

Mature Lymphocyte

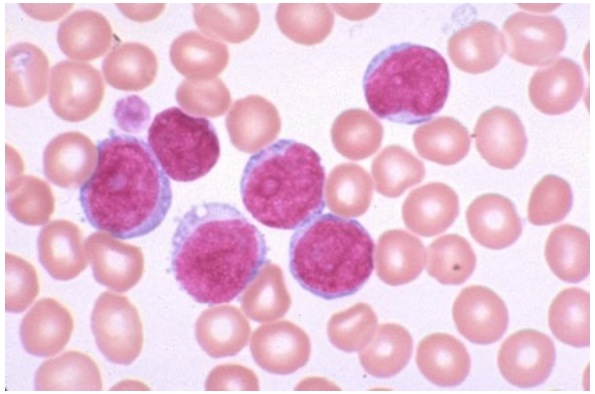


- Size slightly bigger than surrounding RBCs
- Large round/oval nucleus
- Slightly eccentric nucleus
- Thin rim of blue cytoplasm

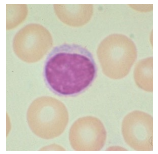
Courtesy of Dr. Scigliano's Online Morphology Tutorial

Immature Blasts

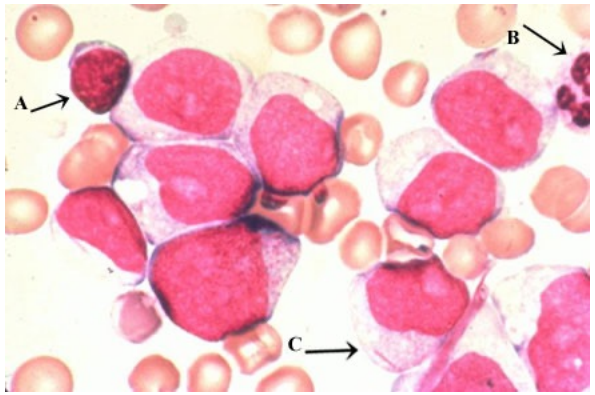
Blasts (AML or ALL)



- Larger than mature lymphocyte/RBC
- High nuclear:cytoplasmic ratio
- Nucleoli
- Fine chromatin
- Basophilic cytoplasm

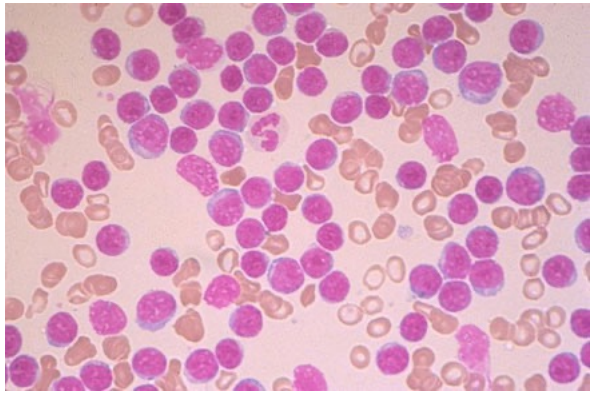


Myeloblasts (APML)



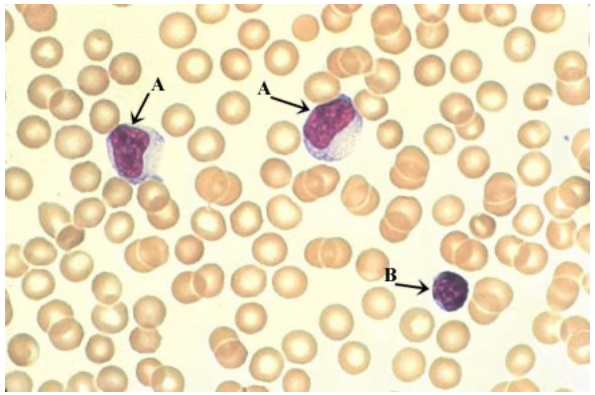
- (c) = auer rods
- Linear granules in cytoplasm of myeloblasts
- NOT seen in lymphoblasts
- Cannot distinguish between ALL and AML on peripheral smear UNLESS auer rods present

Mature Lymphocytes (CLL)



- Increased number of mature, small lymphocytes
- "Soccer ball" nuclear pattern

Atypical Lymphocytes (viral infection)



- Larger than mature lymphocyte/RBC
- Cytoplasm appears idented by RBCs
- Nucleus immature, large, convoluted
- Sometimes azurophilic granules

Courtesy of Dr. Scigliano's Online Morphology Tutorial

LABORATORY TESTS

Lab Techniques

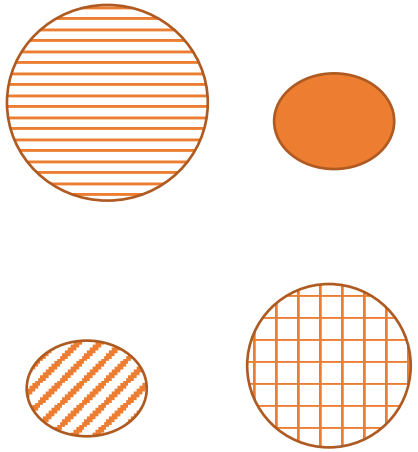
Flow Cytometry

Karyotyping

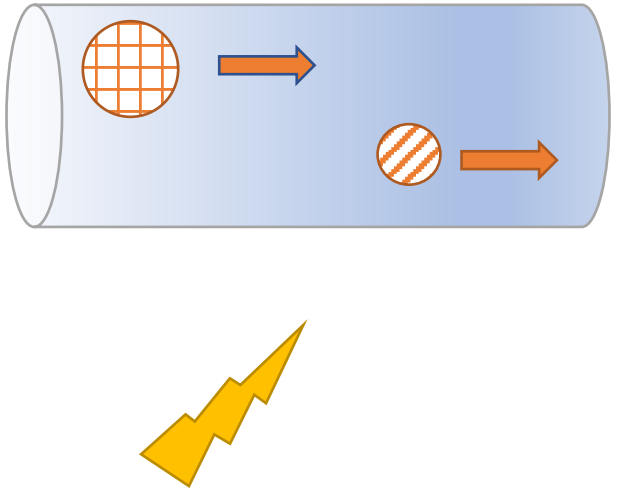
FISH

Genetic Sequencing

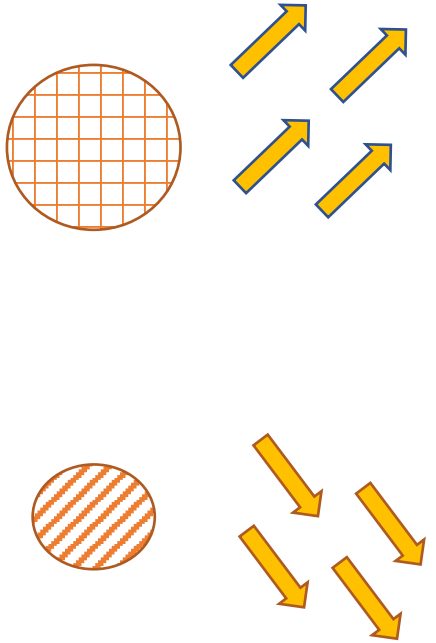
Flow Cytometry



Different blood cell types have unique sizes and granularities

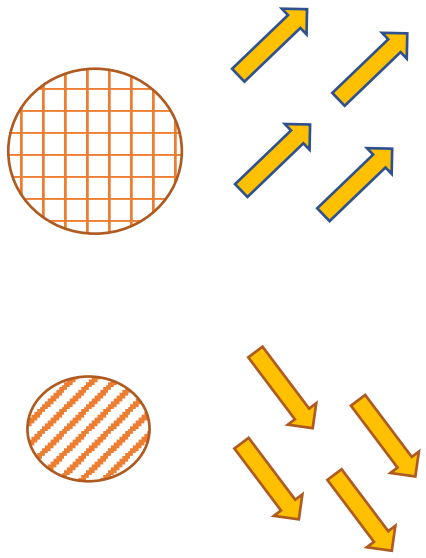


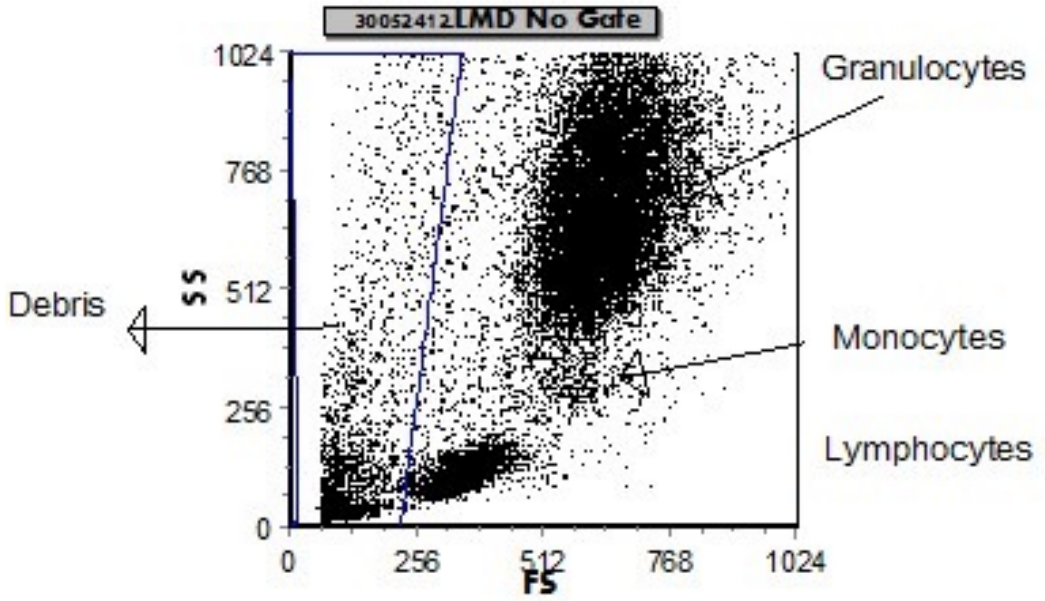
these cells travel through a flow cytometry machine which shoots a laser beam at the cells



Unique cell sizes and granularities causes unique patterns of light scatter from the laser beam

Flow Cytometry



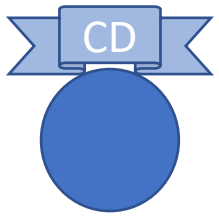


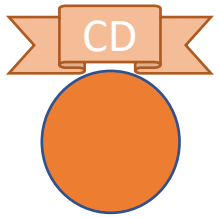
flow cytometry scatter data output is mapped by:

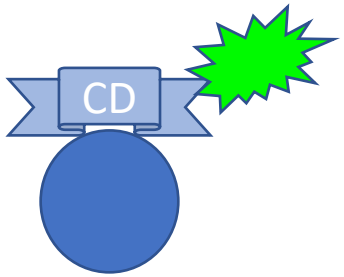
FS “forward light scatter”
SS “side light scatter”

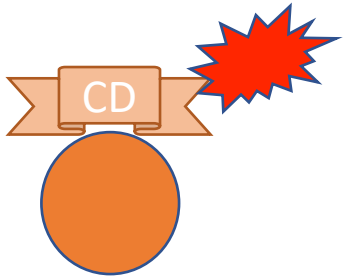
FS and SS data can be graphed to identify different cell populations

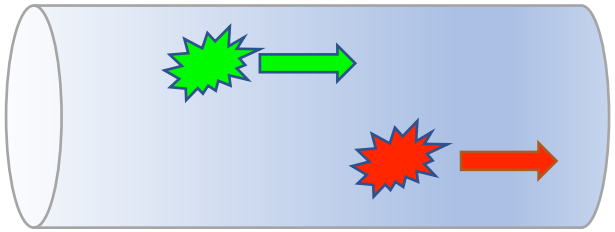
Flow Cytometry









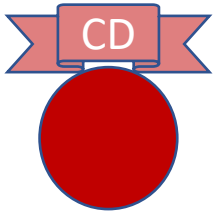


blood cells have identifying markers on their cell surface = CD “cluster of differentiation”

these CD markers can be tagged with fluorescently labeled monoclonal antibodies

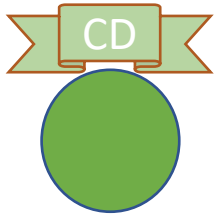
These fluorescent tags can be picked up on flow cytometry

Flow Cytometry



some Myeloid CD Markers

- CD11
- CD13
- CD14
- CD33
- CD64



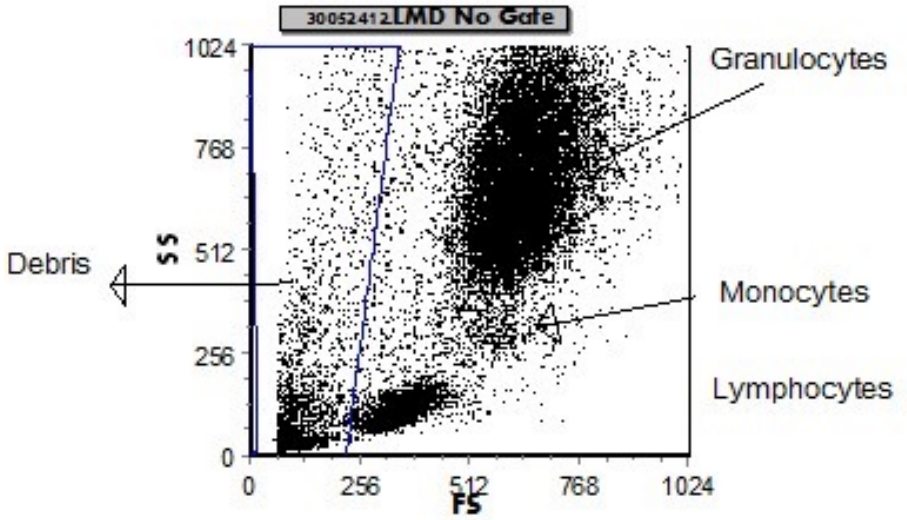
some B Lymphoid CD Markers

- CD10
- CD19
- CD20
- CD22

some T Lymphoid CD Markers

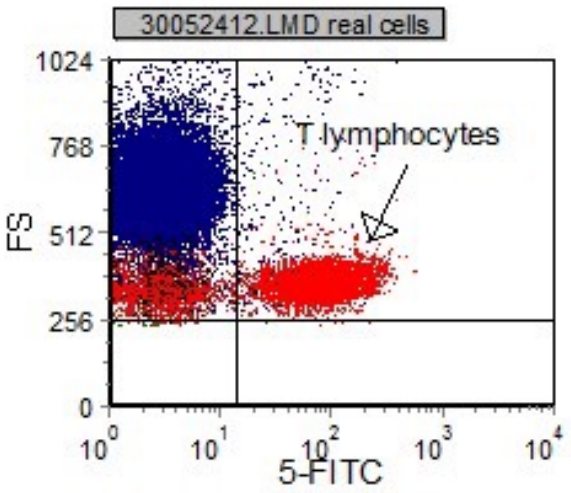
- CD3
- CD4
- CD7
- CD8

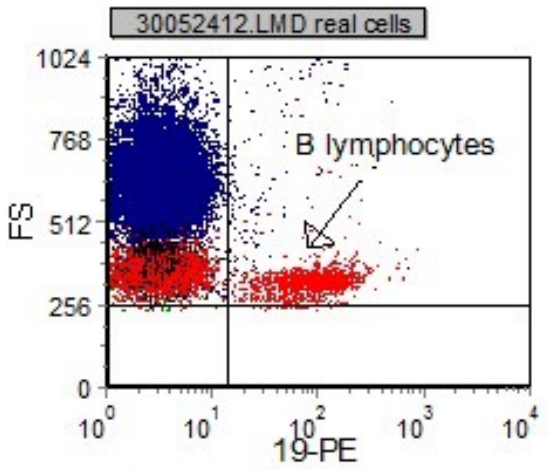
Flow Cytometry



CD5+ T cells

CD19+ B cells





Flow cytometry data tells you what cell type you are looking at: granulocyte, monocyte, lymphocyte…

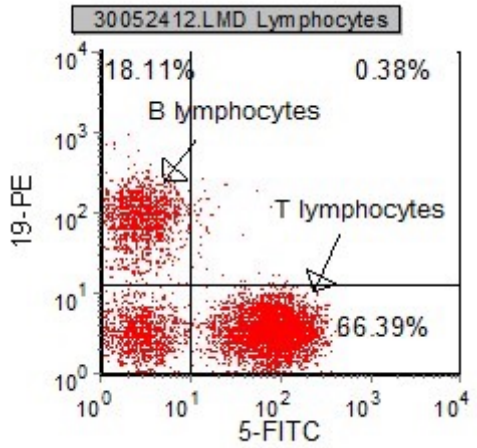
As well as what CD markers each cell type has: B cell markers, T cell markers, myeloid cell markers…

Taken together, can tell you what percentage of lymphocytes are B cells and identify monoclonal cell populations

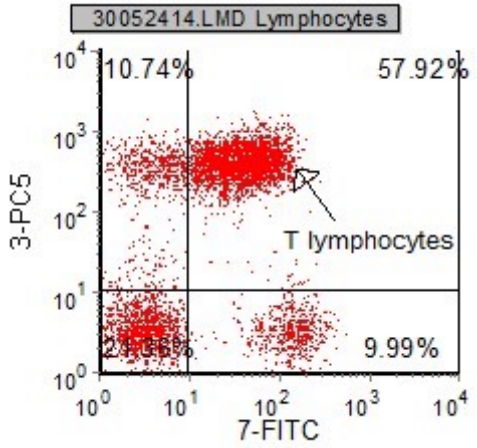
https://wiki.clinicalflow.com/introduction-flow-cytometric-analysis

Flow Cytometry

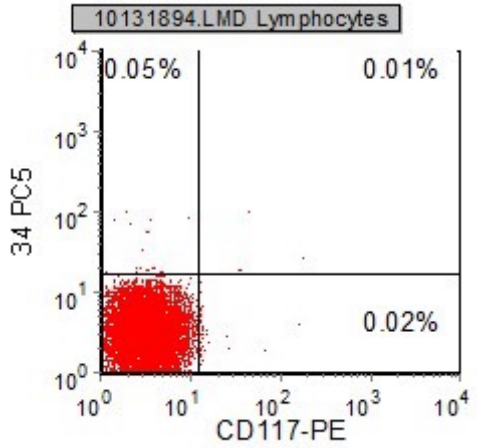
Multiple CD markers can be tagged and analyzed at one time



Mutually Exclusive Markers
CD5 and CD19 stain different populations



Co-Expression Markers
CD7 and CD3 stain the same population

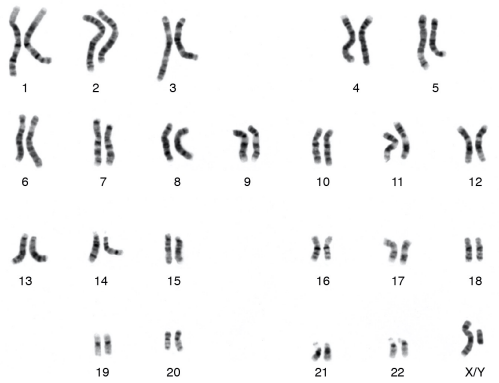


Non-Expression Markers
CD117 and CD34 stain neither population

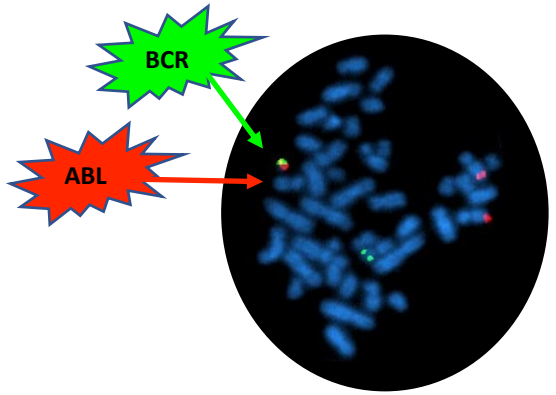
https://wiki.clinicalflow.com/introduction-flow-cytometric-analysis

Cytogenomics

1. Karyotyping

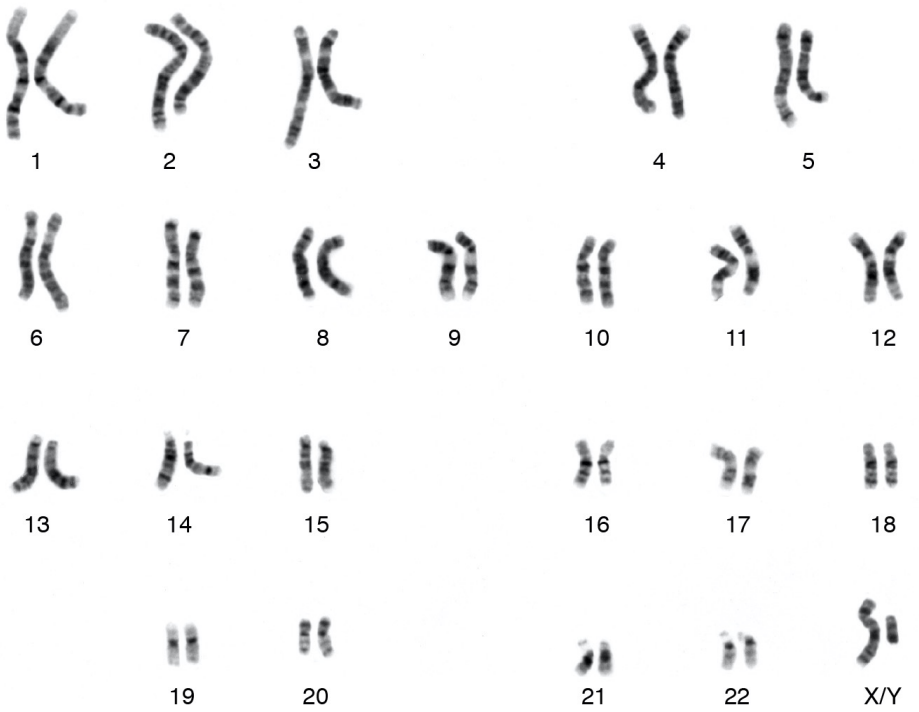


2. FISH



https://www.genome.gov/genetics-glossary/Karyotype

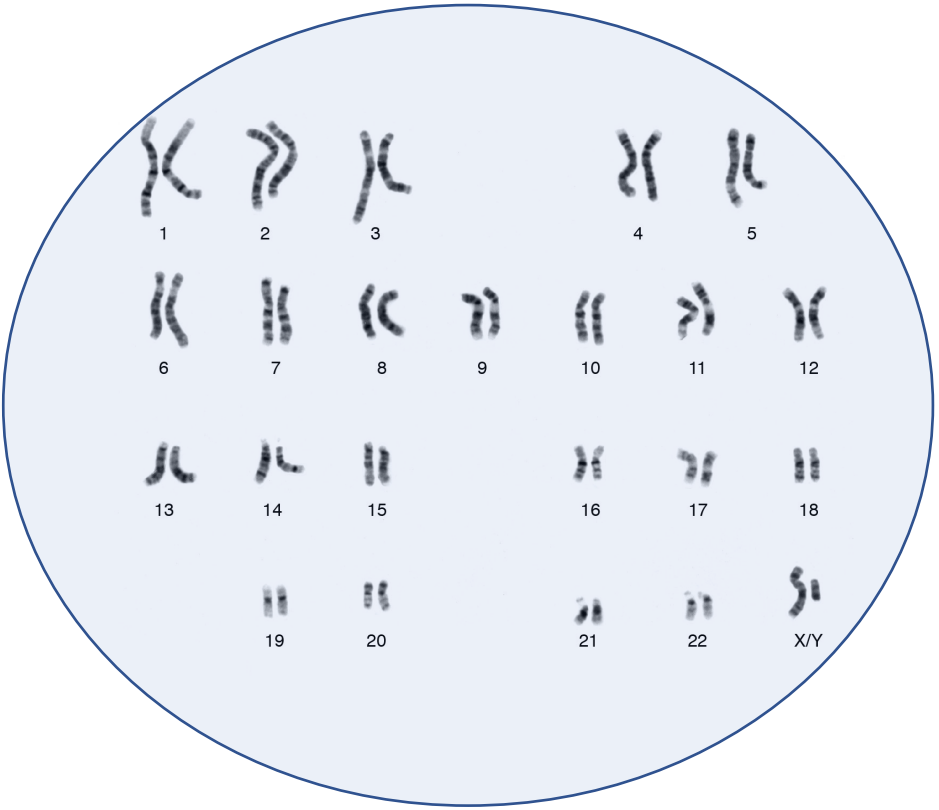
Karyotyping



Karyotyping = visual inspection of metaphase (condensed) chromosomes

https://www.genome.gov/genetics-glossary/Karyotype

Karyotyping

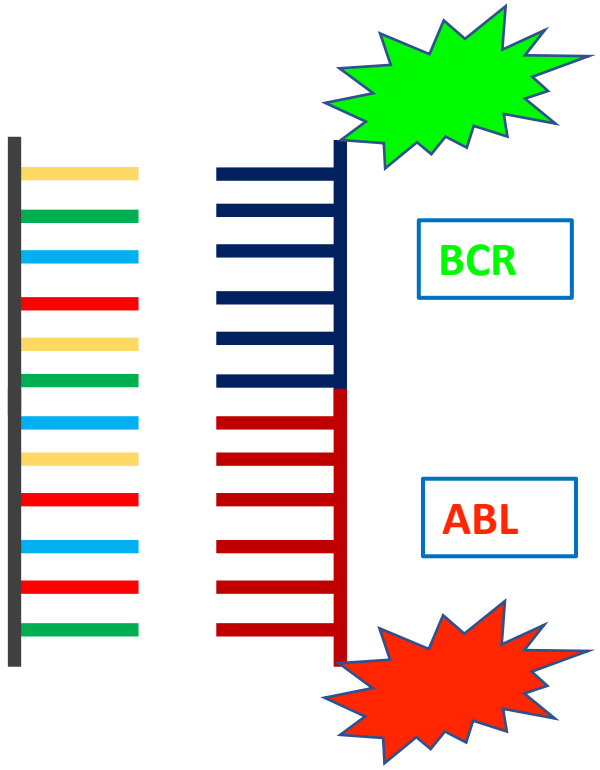


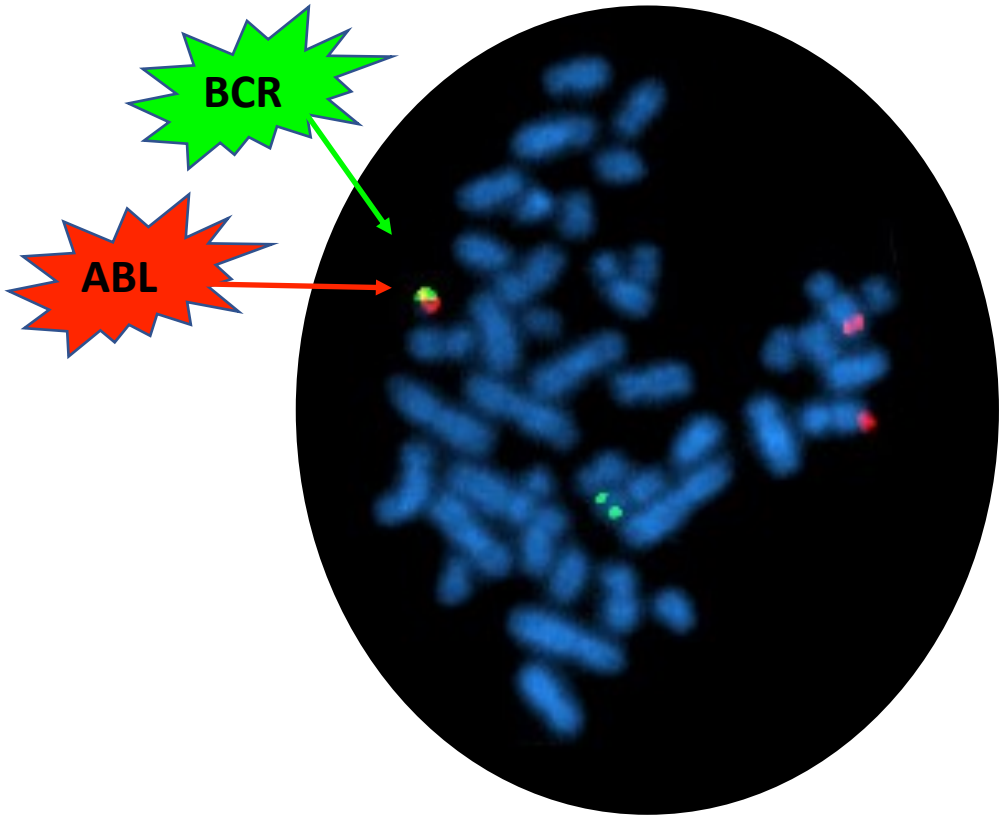
Monosomy	Absence of a single chromosome
Trisomy	Gain of a single chromosome
Deletions	Deletion of part of a chromosome
Duplications	Duplication of a piece of a chromosome
Translocation	Movement of a piece of a chromosome to another area

46 Chromosomes:
22 autosomal chromosome pairs
1 sex chromosome pair (XX or XY)

https://www.genome.gov/genetics-glossary/Karyotype

Fluorescence In-Situ Hybridization = FISH

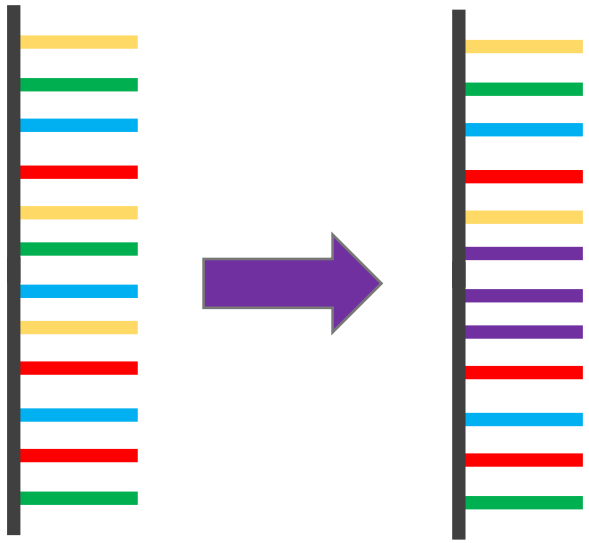




Fluorescently tagged DNA probes can detect targeted DNA sequences

FISH can only detect KNOWN targets with KNOWN DNA probes

Next Generation Sequencing = NGS



Gene X

Substitution in Gene X

Gene Sequencing sequences specific genes and detects ANY gene mutations

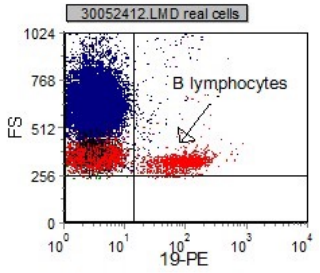
TCGACTA → CGTCCTA

Substitution	Substitution of one nucleotide for another
Insertion	Insertion of additional nucleotide
Deletion	Deletion of additional nucleotide

** **Germline mutation = INHERITED:** present at birth, present in gametes
** **Somatic mutation = NOT INHERITED:** acquired during lifetime, present in certain cells

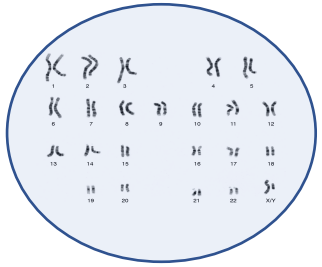
Lab Technique Review

Flow Cytometry



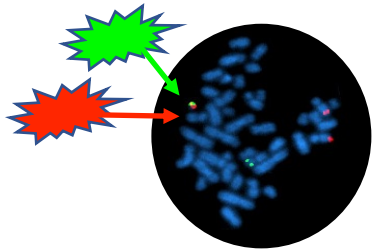
Cell shape/size and CD marker identifies the cell population

Karyotyping



Visual inspection of metaphase chromosomes reveals large gene changes

FISH



Fluorescently tagged DNA probes can detect target DNA sequences

Genetic Sequencing

GGCCTAA → GGTCCAA

NGS sequences specific genes and detects ANY gene mutations

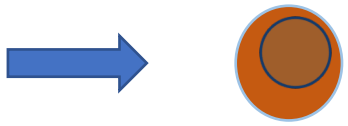
ACUTE MYELOID LEUKEMIA

AML Pathology & Presentation

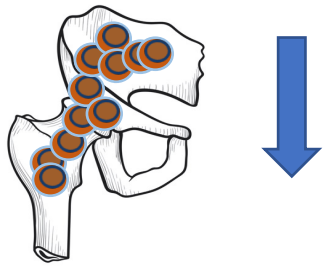
(1) RISK FACTORS

De Novo
- Congenital
- Age
- Radiation Exposure
- Chemical Exposures (topoisomerase, alkylating agents)

Secondary
- MDS/MPN
- PNH
- Aplastic Anemia



(2) GENETIC MUTATION
a genetic abnormality causes proliferation of myeloid progenitor cells



(3) ABNORMAL PROLIFERATION & MYELOPHTHISIS
These myeloid progenitor cells take over the bone marrow, crowding it and inhibit production of other BM produced cells (RBCs, platelets)

EPIDEMIOLOGY

- Most common adult leukemia
- Average age 67

PROGNOSIS

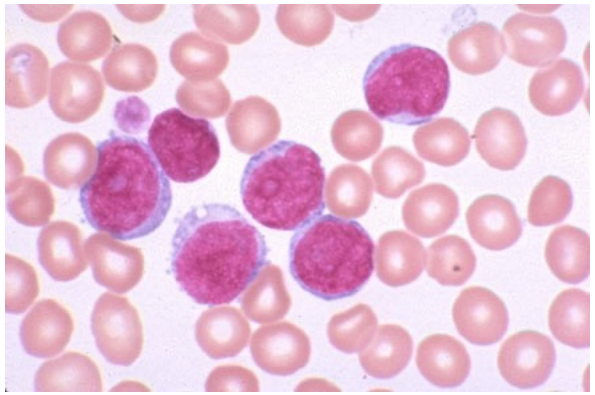
- 5-year OS 25%

AML Presentation

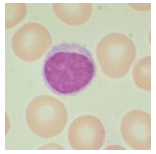
PRIMARY DISORDER	SYMPTOM/LAB FINDING
Leukocytosis/Leukopenia	**Infections/Fever** **Fatigue** **Peripheral blasts**
Anemia Myelophthisic	**Fatigue** **Pallor** **SOB** **Peripheral teardrop RBCs**
Thrombocytopenia Myelophthisic	**Petechiae** **Mucocutaneous bleeding**
Leukemic Cell Organ Infiltration	**Bone infiltration → Pain** **Skin infiltration → Rash/Leukemia cutis** **Liver/Kidney → liver/kidney dysfunction** **CNS → HA, neuropathy**
DIC Activation of the clotting cascade	**INR/PTT, D-dimer elevation** **Thrombocytopenia, Low fibrinogen** **Low Factor levels (including F8)** **Increased bleeding/clotting**
TLS Increased leukemic cell turnover	**Hyperkalemia** **Hyperuricemia** **Hyperphosphatemia** **Hypocalcemia**
Leukostasis Increased viscosity, endothelial damage, cytokine release	**HA, neuropathy, visual changes, tinnitus** **SOB/respiratory failure, MI**

AML Peripheral Smear

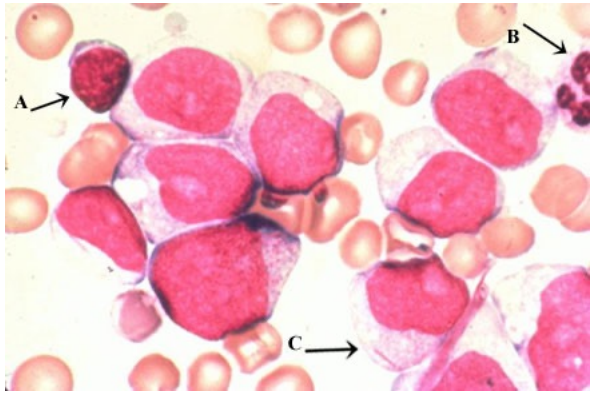
Blasts
(AML or ALL)



- Larger than mature lymphocyte/RBC
- High nuclear:cytoplasmic ratio
- Nucleoli
- Fine chromatin
- Basophilic cytoplasm



Myeloblasts
(APML)



- (c) = auer rods
- Linear granules in cytoplasm of myeloblasts
- NOT seen in lymphoblasts
- Cannot distinguish between ALL and AML on peripheral smear UNLESS auer rods present

CBC DIFF on PERIPHERAL BLOOD:

(1) Peripheral blasts
* may be read as “other” on initial read

(2) Variety of myeloid cells
* neutrophils, eosinophils, basophils…

AML Work Up

Flow Cytometry

Karyotyping

FISH

NGS

Peripheral Labs:

- 2 green top tubes (Peripheral Flow & Cytogenetics)
- In-house NGS (FLT3, CEBPA, NPM1, C-Kit, BCR-ABL, TP53, JAK2)
- CBC w/ diff, CMP BID-TID
- DIC labs (INR, PTT, fibrinogen) BID-TID
- TLS labs (uric acid, LDH, K, Ca, PO4) BID-TID
- G6PD
- HIV, hepatitis, CMV
- Fe studies
- Type & Cross
- Blood cultures

Other Tests

- EKG
- TTE
- CXR or CT if symptoms

Start

- IVF
- Consider starting allopurinol, acyclovir, posaconazole ppx
- Pseudomonal AB coverage if fever

AML Work Up

Is there an abnormal myeloblastic cell population?

Flow Cytometry

CD34, TdT, CD117, MPO

Is there a cytogenetic abnormality?

Karyotyping

FISH

t(15;17)	inv(16)
t(8;21)	t(16;16)

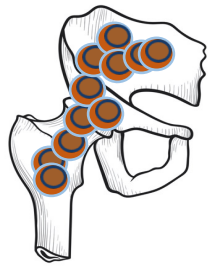
Is there a known AML associated mutation?

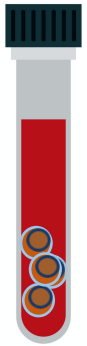
NGS

FLT3	CEBPA	p53
NPM1	C-kit	

AML Diagnosis

#1 20% leukemia cells in the bone marrow or blood





Flow Cytometry

#2 <20% leukemia cells in blood/bone marrow BUT AML defining cytogenetic mutation

Karyotyping

FISH

NGS

t(15;17)	inv(16)
t(8;21)	t(16;16)

AML Risk Stratification

AML can be risk-stratified based on genetic profile. This DEFINES what treatment patients will receive

Good Risk
t(15;17); PML-RARA
t(8;21)
Inv(16)
t(16;6)
Biallelic mutated CEBPA
FLT3 negative
NPM1 mutation With FLT3 negative/low
IDH2

Intermediate Risk
FLT3 Low, NPM1 negative
FLT3 High, NPM1 positive

High Risk
t(6;9)
inv3
t(9;22); BCR-ABL1
FLT3 positive
ASXL1
RUNX1
TP53
MLL (11q23)
Complex or monosomal karyotype

** Intermediate & high risk usually need stem cell transplant if they are candidates

AML Treatment

INDUCTION

Goal = achieve **remission**

remission = no leukemia cells in bone marrow

chemotherapy

CONSOLIDATION

Goal = maintain **remission**

Low Risk

Chemo (HiDAC)

Intermediate/High Risk

Allogeneic SCT

AML Induction: Age < 60 or Good Performance Status

7 **CYTARABINE**

Continuous infusion D1-7
100-200 mg

&

3 **ANTHRACYCLINE**

IV Push D1-3
Idarubicin = 12 mg/m2
Daunorubicin = 60-90 mg/m2

---

add ons:

FLT3+ = Midostaurin 50 mg PO BID (D8-21)

CD33+ = Gemtuzumab 3 mg/m2 (D1, 2, or 3)
*Risk of VOD/SOS

t(9,22) = TKI

AML Induction: Age > 60 or Poor Performance Status

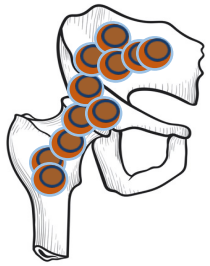
HMA = Hypomethylating Agent

Azacitidine or Decitabine

+/-

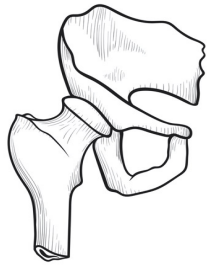
VENETOCLAX

AML Monitoring



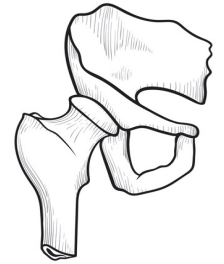
Diagnostic BMB

Pre-treatment assessment
Send Cytogenetics, NGS



D14 Bone Marrow Biopsy

Goal = < 5% blasts
Expect hypocellular
Don’t Send Cyto, NGS



D28 Bone Marrow Biopsy

Goal = < 5% blasts
Expect count recovery
Repeat Cyto, NGS

* If D14 marrow is positive, consider repeat 7&3 or 5&2

AML Consolidation

Low Risk → CHEMO

Commonly: HiDac = high dose cytarabine

Intermediate & High Risk → BMT

 # 1 Conditioning Chemotherapy

* myeloablative (MAC) >> Reduced Intensity (RIC) if young/fit

 # 2 Allogeneic Stem Cell Transplant

* from umbilical cord, peripheral blood, bone marrow

* Can only get BMT if in remission

AML Relapsed/Refractory

Targeted Agents

IDH1 Inhibitors: ivosidenib

IDH2 Inhibitor: enasidenib

FLT 3 Inhibitor: gilteritinib

CD33: gemtuzumab

Non-Targeted Agents

7 & 3 Cytarabine + Anthracycline

HMA +/- venetoclax

FLAG +/- IDA Fludarabine, cytarabine, G-CSF +/- Idarubicin

CLAG +/- IDA Cladribine, cyarabine, G-CSF +/- Idarubicin

AML Prophylaxis

PROPHYLAXIS TARGET	PROPHYLAXIS MEDICATION
Bacterial	**Levofloxacin 750 mg QD** * Can defer inpatient until patient has fever, however if fever consider broad spectrum AB
Viral	**Acyclovir 400 mg BID**
Fungal	**Posaconazole 300 mg QD (load 300 mg BID x1)** * Can cause LFT abnormalities * Covers mucor, aspergillus
TLS	**Allopurinol 300 mg QD** * Renally dose if AKI
Neutropenia	**GSCF** * used in consolidation, not often used for induction (consider in neutropenic fever)

AML Complications

COMPLICATIONS	MANAGEMENT
Neutropenic Fever	**Cefepime +/- vancomycin +/- flagyl** * Pan-culture (peripheral & central line if present) * Consider CT scan of chest or abdomen
Anemia/Thrombocytopenia	**Hb > 7** **Plts >10 (>30 if fever, >50 if bleeding/procedure)** **If not responsive to plts, run slowly over 4H** * Check 1 hour post-transfusion CBC * TBW blood bank re: matched plts * Consider sending platelet AB
TLS	**IVF** **Allopurinol** **Rasburicase 0.1 mg/kg if uric acid > 10** * If G6PD negative * Up to 4.5 mg max
DIC	**FFP or Cryo for goal INR < 1.5, fibrinogen >100** * Confirm no suspicion for APML, consider ATRA
CNS/CSF Disease	**IT Methotrexate**
Leukocytosis/Leukostasis	**Cytoreduction (chemotherapy or hydroxyurea)** **Leukopheresis** * Usually only if WBC >50 -100 * Consider avoiding transfusions, can increase viscosity

ACUTE PROMYELOCYTIC LEUKEMIA

APML Pathology

APML is a sub-set of AML

(mostly) defined by the **t(15;17)** translocation of **PML-RARA**

Good Risk
t(15;17); PML-RARA
t(8;21)
Inv(16)
t(16;6)
Biallelic mutated CEBPA
FLT3 negative
NPM1 mutation With FLT3 negative/low

Good Overall Prognosis for APML:

complete remission = 80-90%

however

Poor Early Survival for APML:

30-day mortality = 20%

APML Treatment

RISK CATEGORY	WBC	Platelet
LOW	< 10	> 40
INTERMEDIATE	< 10	< 40
HIGH	> 10	

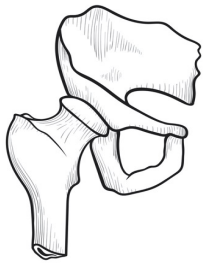
LOW RISK TREATMENT

ATRA (all-trans-retinoic acid) + ARSENIC

* ATRA causes APML blasts to differentiate into mature myeloid cells

HIGH RISK TREATMENT

ATRA + ARSENIC + ADDITIONAL AGENT
(1) with **Anthracycline**
(2) with **Gemtuzumab**



BMB Monitoring occurs at 4-6 weeks
* Delayed because of differentiation

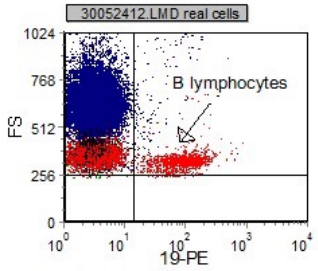
APML Complications

COMPLICATIONS of APML	
DIC	• Activation of clotting cascade • Symptoms = bleeding/clotting • Treatment = FFP/Cryoglobulin
DIFFERENTIATION SYNDROME	• Maturing myeloid cells → cytokine release • Occurs in 25% of patients that get ATRA • Symptoms = fever, hypotension, weight gain, effusions, hypoxia, renal/hepatic dysfunction • Treatment = Steroids (dexamethasone 10 mg BID)
PSEUDOTUMOR CEREBRI	• Caused by ATRA • Discontinue ATRA
QTC Prolongation	• Caused by arsenic • Daily EKG

AML & APML Reference Handout

Lab Techniques

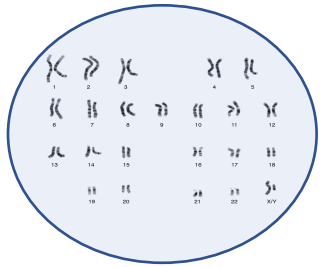
Flow Cytometry



Cell shape/size and CD marker identifies the cell population

Blood or Bone Marrow Flow Cytometry Result:
There is a 20% abnormal CD20+ population

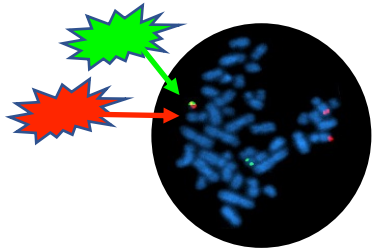
Karyotyping



Visual inspection of metaphase chromosomes reveals large gene changes

Karyotype result:
There is trisomy 21

FISH



Fluorescently tagged DNA probes can detect target DNA sequences

FISH result:
There are X copies of a BCR-ABL translocation

NGS

GGCCTAA → GGTCCAA

Gene Sequencing sequences specific genes and detects ANY gene mutations

NGS result:
There is a FLT3 mutation

AML Diagnosis

Peripheral Labs:

- 2 green top tubes (Peripheral Flow & Cytogenetics)
- In-house NGS (FLT3, CEBPA, NPM1, C-Kit, BCR-ABL, TP53, JAK2)
- CBC w/ diff, CMP BID-TID
- DIC labs (INR, PTT, fibrinogen) BID-TID
- TLS labs (uric acid, LDH, K, Ca, PO4) BID-TID, G6PD
- HIV, hepatitis, CMV
- Type & Cross, Fe studies
- Blood cultures

Other Tests

- EKG
- TTE
- CXR or CT if symptoms
- IVF
- Consider TLS/ID ppx
- Pseudomonal AB coverage if fever

Flow Cytometry

#1) 20% leukemia cells in the marrow or blood

Karyotyping | FISH | NGS

#2) AML defining cytogenetic mutation

t(15,17)	inv(16)
t(8,21)	t(16,16)

AML Presentation

PRIMARY DISORDER	SYMPTOM/LAB FINDING
Leukocytosis/Leukopenia	**Infections/Fever** **Fatigue** **Peripheral blasts**
Anemia Myelophthisic	**Fatigue** **Pallor** **SOB** **Peripheral teardrop RBCs**
Thrombocytopenia Myelophthisic	**Petechiae** **Mucocutaneous bleeding**
Leukemic Cell Organ Infiltration	**Bone infiltration → Pain** **Skin infiltration → Rash/Leukemia cutis** **Liver/Kidney → liver/kidney dysfunction** **CNS → HA, neuropathy**
DIC Activation of the clotting cascade	**INR/PTT, D-dimer elevation** **Thrombocytopenia, Low fibrinogen** **Low Factor levels (including F8)** **Increased bleeding/clotting**
TLS Increased leukemic cell turnover	**Hyperkalemia** **Hyperuricemia** **Hyperphosphatemia** **Hypocalcemia**
Leukostasis Increased viscosity, endothelial damage, cytokine release	**HA, neuropathy, visual changes, tinnitus** **SOB/respiratory failure, MI**

AML Risk Assessment

Good Risk	High Risk
t(15;17); PML-RARA	t(6;9)
t(8;21)	inv3
Inv(16)	t(9;22); BCR-ABL1
t(16;6)	FLT3 positive
Biallelic mutated CEBPA	ASXL1
FLT3 negative	RUNX1
NPM1 mutation With FLT3 negative/low	TP53
IDH2	MLL (11q23)
	Complex or monosomal karyotype

AML Induction Therapy

7 = CYTARABINE

Continuous infusion D1-7
100-200 mg

3 = ANTHRACYCLINE

IV Push D1-3
Idarubicin = 12 mg/m2
Daunorubicin = 60-90 mg/m2

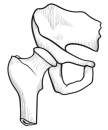
FLT3+ = Midostaurin

CD33+ = Gemtuzumab
*Risk of VOD/SOS

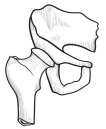
Age > 60 or Poor PS

HMA (AZA/decitabine) +/- Venetoclax

Monitor BMB:
Goal < 5% blasts



D14



D28
*** Send Cytogenetics, NGS**

Treatment Paradigm

INDUCTION
achieve remission

→ **Chemotherapy**

CONSOLIDATION
maintain remission

→ Low Risk **Chemotherapy**

→ Intermediate/High Risk **BMT**

AML Consolidation Therapy

Low Risk

Intermediate & High Risk

Relapsed/Refractory

HiDac = high dose cytarabine

1 Conditioning Chemotherapy
* myeloablative (MAC) >> Reduced Intensity (RIC)

2 Allogeneic Stem Cell Transplant
* from umbilical cord, peripheral blood, bone marrow

- Targeted agent (ex: IDH inhibitor)
- HMA +/- venetoclax
- FLAG +/- IDA, CLAG +/- IDA
- 7 & 3

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Defined by the **t(15,17)** translocation of **PML-RARA** (mostly)

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LOW RISK TREATMENT

ATRA + ARSENIC

HIGH RISK TREATMENT

ATRA + ARSENIC with Anthracycline or Gemtuzumab

* ATRA causes differentiation of APML → mature myeloid cells

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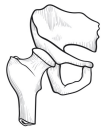

BMB @ 4-6 weeks
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