# Molecular in My Pocket…

## Hematopathology

Prepared by the Association for Molecular Pathology Training and Education Committee

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## Acute Myeloid Leukemia (AML)

Good Prognosis
- Core Binding Factor (CBF) AML
  - t(8;21)(q22;q22); *RUNX1-RUNX1T1*
    - Blasts with salmon/pink granules
  - inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
    - Abnormal eosinophils
  - Worse prognosis in CBF AMLs when *KIT* is mutated
- Acute Promyelocytic Leukemia (APL)
  - t(15;17)(q22;q12); *PML-RARA*
    - Bilobed blasts with granules +/- Auer rods
- t(1;22)(p13;q13); *RBM15-MKL1*
  - Megakaryoblastic
- *NPM1* mutation
- Biallelic mutations of *CEBPA*

Intermediate Prognosis
- t(9;11)(p22;q23); *MLLT3-KMT2A*
  - Blasts with monocytic differentiation and fine azurophilic granules
  - Associated with gingival myeloid sarcoma
- Normal Karyotype, mutation status unknown (or rarely negative)

Poor Prognosis
- t(6;9)(p23;q34); *DEK-NUP214*
  - Basophilia, multilineage dysplasia
- inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
  - Abnormal megakaryocytes
  - Multilineage dysplasia
- AML with myelodysplasia related changes (AML-MRC)
  - ≥50% dysplasia in ≥2 lineages
  - History of MDS
  - MDS defining cytogenetic abnormality (see MDS section)
- 11q23 (non t(9;11), many partners)
- t(9;22) (q34;q11.2 ); *BCR-ABL1*
- *FLT3*-ITD mutation
- *ASXL1, TP53, RUNX1, DNMT3A, WT1* mutation

## Myelodysplastic Syndromes (MDS)

Cytogenetics
Very Good Prognosis
- del(11q)* or -Y

Good Prognosis
- Normal
- del(5q)*, del(12p)*, del(20q)

Intermediate Prognosis
- del(7q)
- Monosomy 5*
- Trisomy 8, trisomy 19
- i(17q)*
- Monosomy 13* or del(13q)*

Poor Prognosis
- Monosomy 7*
- inv(3), t(3;3), del(3q)

Very Poor Prognosis
- Complex (≥3 abnormalities)*

*MDS defining abnormality

Mutations
Good Prognosis
- *SF3B1* mutation (strongly correlated with ring sideroblasts)
  - With *SF3B1* mutation can diagnose MDS with ring sideroblasts (MDS-RS) with only 5% ring sideroblasts rather than 15% without the mutation

Poor Prognosis
- *ASXL1*, *SRSF2*, *STAG2*, *EZH2*, *DNMT3A*, *TET2*, *TP53* mutation

Progression mutations
- *RAS, FLT3, JAK2, NF1, RUNX1, ETV6, SETBP1*

## Myeloproliferative Neoplasms (MPN) and Mastocytosis

Chronic Myelogenous Leukemia (CML)
- t(9;22)(q34;q11.2 );*BCR-ABL1*
  - Usually M-BCR (p210) breakpoint
  - Rarely m-BCR (p190) or µ-BCR (p230) breakpoints
  - *ABL1* kinase mutations confer TKI resistance
    - Particularly T315I

Polycythemia Vera (PV)
- *JAK2* V617F (~95% of cases)
- *JAK2* exon 12 mutation (~5% of cases)

Essential Thrombocythemia (ET) and Primary Myelofibrosis (PMF)
- *JAK2* V617F (~50% of cases)
- *CALR* exon 9 indel mutations (~30% of cases)
- *MPL* W515K/L (~5% of cases)

Chronic Neutrophilic Leukemia (CNL)
- *CSF3R* mutation, especially T618I

Mastocytosis
*KIT* D816V (~95% of cases)

## Other Entities

Chronic Myelomonocytic Leukemia (CMML)
- Frequent *TET2*, *SRSF2*, *ASXL1* mutation

Juvenile Myelomonocytic Leukemia (JMML)
- Somatic *PTPN11*, *KRAS*, *NRAS* mutation
- Clinical *NF1* disease or *NF1* mutation
  Germline *CBL* mutation

Myeloid/Lymphoid Neoplasms associated with Eosinophilia
- *PDGFRA* rearrangement (often del(4)(q12q12); *FIP1L1-PDGFRA*)
- *PDGFRB* rearrangement (often t(5;12)(q31~33;p12) ;*ETV6*-PDGFRB)
- *FGFR1* rearrangement (various partners)
- t(8;9)(p22;p24.1);*PCM1-JAK2*

Myeloid Neoplasms with Germline Predisposition
- AML with germline *CEBPA* mutation
- Myeloid neoplasm with germline *DDX41* mutation
- Associated with platelet disorders
  - *RUNX1*, *ANKRD26*, *ETV6* mutation
- Associated with other organ dysfunction
  - *GATA2* mutation
  - *JMML* type mutations

Langerhans cell histiocytosis, histiocytic sarcoma, disseminated juvenile xanthogranuloma, Erdheim-Chester disease, follicular dendritic cell sarcoma
- *BRAF* p.V600E mutation

## T-cell Neoplasms

T Lymphoblastic Leukemia (T-ALL)
- *NOTCH1*, *CDKN1*/2 mutations

Early T-precursor Acute Lymphoblastic Leukemia (ETP ALL)
- *FLT3*, *NRAS*/*KRAS*, *DNMT3A*, *IDH1*/2

Anaplastic Large Cell Lymphoma, ALK-negative (ALCL, ALK-)
- Subset have rearrangement at 6p25 (region with *DUSP22* and *IRF4*) - good prognosis
- *TP63* rearrangement - poor prognosis

Anaplastic Large Cell Lymphoma, ALK-positive (ALCL, ALK+)
- Rearrangements t(2;5)(p23;q35); *ALK-NPM1*
- Other *ALK* rearrangements

T-cell Large Granular Lymphocyte Leukemia (T-LGL)
- *STAT3* mutation
- *STAT5B* mutation - poor prognosis

Peripheral T cell lymphoma, NOS (PTCL)
- *TET2*, *DNMT3A*, *VAV1*

Follicular T cell lymphomas (inc. angioimmunoblastic T cell lymphoma, AILT)
- *RHOA, CD28, TET2, DNMT3A, IDH2*

T Prolymphocytic leukemia (T-PLL; with inv(14) or t(14;14))
- *ATM*, *STAT5B*, *JAK3*

## B-cell Neoplasms

B Lymphoblastic Leukemia (B-ALL)
- Good prognosis
  - Hyperdiploid
  - t(12;21)(p13;q22);*ETV6-RUNX1* - good prognosis
- Interm. prognosis- *t(5;14)*(q31;q32); *IL3-IGH*, associated with eosinophilia
- Poor Prognosis
  - t(9;22)(q34;q11.2 );*BCR-ABL1*
    - Usually m-BCR (p190)
  - t(v;11q23);*KMT2A* rearranged
  - Hypodiploid
  - Intrachromosomal amplification of chromosome 21 (iAMP21)
  - *BCR-ABL1* like B-ALL
    - *CRLF2* or *EPOR* rearrangement
    - *JAK* mutations
    - *CDKN2A/B* or *IKZF1* deletion
    - Numerous other translocations involving tyrosine kinases

Follicular Lymphoma (FL)
- t(14;18)(q32;q21);*IGH-BCL2*
  - Less common in grade 3
- *BCL6* rearrangements

Mantle Cell Lymphoma (MCL)
- t(11;14)(q13;q32);*CCND1-IGH*

Burkitt Lymphoma (BL)
- *MYC* rearrangements
  - t(8;14)(q24;q32);*MYC-IGH*
  - t(2;8)(p12;q24);*IGK-MYC*
  - t(8;22)(q24;q11);*MYC-IGL*

Hairy Cell Leukemia (HCL)
- *BRAF* p.V600E (~95% of cases)
- *MAP2K1* mutations
  - Hairy Cell Leukemia variant (HCL-v)
  - HCL expressing *IGHV*4-34

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)
- Good Prognosis
  - del(13q14.3)
  - Mutated VH
- Intermediate Prognosis
  - Trisomy 12 (a/w *NOTCH1*)
- Poor Prognosis
  - del(17p)
  - del(11q22-23) (a/w *SF3B1*)
  - del(6q)
    Unmutated VH

Extranodal Marginal Zone Lymphoma, MALT type
- t(11;18)(q21;q21) - gastric MALT
- t(14:18)(q32;q21) - orbital and salivary gland MALT
- t(3;14)(p14.1;q32) - thyroid, orbital, skin MALT

Lymphoplasmacytic Lymphoma (LPL) and IgM Monoclonal Gammopathy of Unknown Significance (MGUS)
- *MYD88* p.L265P (~90% of cases)
- *CXCR4* mutation (~30% of LPL, ~20% of IgM MGUS)

Diffuse Large B-Cell Lymphoma (DLBCL)
- ALK-positive large B-cell lymphoma
  - t(2;17)(p23;q23);*CLTC-ALK*
- Double/Triple-Hit Lymphoma
  - *MYC* rearrangement with *BCL2* and/or *BCL6* rearrangement