### Hematopathology

**Prepared by the Association for Molecular Pathology Training and Education Committee**

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**Molecular in My Pocket…**

#### Acute Myeloid Leukemia (AML)

<table>
<thead>
<tr>
<th>Good Prognosis</th>
<th>Intermediate Prognosis</th>
<th>Poor Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core Binding Factor (CBF) AML</td>
<td>Blasts with monocytic differentiation and fine azurophilic granules</td>
<td>With or without monocytic features, often associated with basophilia and multilineage dysplasia</td>
</tr>
<tr>
<td>t(8;21)(q22;q22); RUNX1-RUNX1T1</td>
<td>Associated with gingival myeloid sarcoma</td>
<td>inv(3)(q21q26.2) or t(3;3)(q21;q26.2); GATA2, MECOM</td>
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<tr>
<td>-</td>
<td>More common in children (10% pediatric AML)</td>
<td>Abnormal megakaryocytes</td>
</tr>
<tr>
<td>-</td>
<td>Normal Karyotype, mutation status unknown (or rarely negative)</td>
<td>Multilineage dysplasia</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>Common secondary karyotypic abnormalities include -7 (50% cases), del(5q) and complex karyotypes</td>
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<tr>
<td>-</td>
<td>-</td>
<td>AML with myelodysplasia related changes (AML-MRC)</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>≥50% dysplasia in ≥2 lineages (if no NPM1 mutation)</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>History of MDS</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>MDS-defining cytogenetic abnormality (see MDS section)</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>11q23 (non t(9;11), many partners)</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>t(9;22) (q34;q11.2) bcr-abl1</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>FLT3-ITD mutation</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>~20% AML cases</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>ASXL1, TP53, RUNX1 mutation</td>
</tr>
</tbody>
</table>

#### Myelodysplastic Syndromes (MDS)

<table>
<thead>
<tr>
<th>Cytogenetics</th>
<th>Mutations</th>
<th>Other Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Good Prognosis</td>
<td>Good Prognosis</td>
<td>Poor Prognosis</td>
</tr>
<tr>
<td>- del(11q)* or -Y</td>
<td>SF3B1 mutation (strongly correlated with ring sideroblasts)</td>
<td>TPS3</td>
</tr>
<tr>
<td>Good Prognosis</td>
<td>With SF3B1 mutation can diagnose MDS with ring sideroblasts (MDS-RS) with only 5% ring sideroblasts rather than 15% without the mutation</td>
<td></td>
</tr>
<tr>
<td>- del(5q)<em>, del(12p)</em>, del(20q), double del(5q)</td>
<td>Poor Prognosis</td>
<td></td>
</tr>
<tr>
<td>Intermediate Prognosis</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>- del(7q)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>- Monosomy 5*</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>- Trisomy 8, trisomy 19</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>- i(17)(q10)*</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>- Monosomy 13* or del(13q)*</td>
<td>-</td>
<td></td>
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<tr>
<td>- 2+ independent clones</td>
<td>-</td>
<td></td>
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<tr>
<td>- Double any other abnormality</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Poor Prognosis</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>- Monosomy 7*</td>
<td>Other mutations may impart worse prognosis: ASXL1, SRSF2, STAG2, EZH2, U2AF1, RUNX1, NRRAS</td>
<td></td>
</tr>
<tr>
<td>Very Poor Prognosis</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>- Complex (≥3 abnormalities)*</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>MDS-defining abnormality</td>
<td>-</td>
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<tr>
<td>MDS-associated mutations may also occur in clonal hematopoiesis of indeterminate potential— particularly DNMT3a, TET2, ASXL1. Mutational findings alone are not diagnostic of MDS.</td>
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<tr>
<td>Chronic Myelogenous Leukemia (CML)</td>
<td></td>
<td>Chronic Neutrophilic Leukemia (CNL)</td>
</tr>
<tr>
<td>t(9;22)(q34;q11.2)BCR-ABL1</td>
<td>-</td>
<td>Activating membrane proximal mutations in CSF3R at exon 14, especially T618I and T615A; present in 50-80% of CNL</td>
</tr>
<tr>
<td>- Usually M-BCR (p210) breakpoint</td>
<td>-</td>
<td>Mastocytosis</td>
</tr>
<tr>
<td>Rarely m-BCR (p190) or ι-BCR (p230) breakpoints</td>
<td>ABL1 kinase mutations confer TKI resistance</td>
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<td>Particularly T315I</td>
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<td>Transformation to accelerated phase (AP) or blast phase (BP) often accompanied by extra Ph chromosome, +8, +19, or i(17)(q10)</td>
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<td>Polycythemia Vera (PV)</td>
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<td>-</td>
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</tr>
<tr>
<td>- JAK2 V617F (~95% of cases)</td>
<td>-</td>
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</tr>
<tr>
<td>- JAK2 exon 12 mutation (~5% of cases)</td>
<td>-</td>
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<tr>
<td>Essential Thrombocythemia (ET) and Primary Myelofibrosis (PMF)</td>
<td>Chronic Thrombocytopenia (ET) and Primary Myelofibrosis (PMF)</td>
<td></td>
</tr>
<tr>
<td>JAK2 V617F (~50% of cases)</td>
<td>-</td>
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<tr>
<td>CALR exon 9 indel mutations (~30% of cases)</td>
<td>-</td>
<td></td>
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<tr>
<td>MPL W515K/L (~5% of cases)</td>
<td>-</td>
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</tr>
<tr>
<td>Myeloproliferative Neoplasms (MPN) and Mastocytosis</td>
<td>Myelofibrosis (PMF)</td>
<td>Mastocytosis</td>
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<td>-</td>
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### B-cell Neoplasms

#### B Lymphoblastic Leukemia (B-ALL)
- **Good prognosis**
  - Hyperdiploid (extra chromosome copies are not random: X, 4, 14, 21 most common)
  - Intermediate prognosis - t(5;14)(q31;q32); IGHL/JJI, associated with eosinophilia
  - Poor Prognosis
    - t(9;22)(q34;q11.2); BCR-ABL1
    - Usually m-BCR (Most pediatric cases have p190; in adults, 50% is p190 and 50% is p210)
    - (t;11q23); M2TA2 rearranged
    - Most common leukemia in infants <1 year old; may occur in utero
    - Common translocation partners AF11 (q421) and MLT1 (19p13)
    - Hydroploid
    - Most commonly lost chromosomes include 3, 4, 7, 9, 13, 17, and 20
    - Worse prognosis: near haploid (25-29 chromosomes) and low hypoploid (33-39 chromosomes)
    - Intrachromosomal amplification of chromosome 21 (iAMP21)
    - Defined by multiple copies of RUNXI, not detectable by standard karyotyping
    - BCR-ABL1 like B-ALL
      - Lacks BCR-ABL1 translocation
      - IS-20 pediatric ALL
      - CRLF2 or EPOR rearrangement
      - JAK mutations
      - CDKN2A/B or IKZF1 deletion/mutation
      - Other translocations involving tyrosine kinases

#### T-cell Neoplasms

#### T Lymphoblastic Leukemia/Lymphoma (T-ALL)
- Translocations involving T-cell receptor (TCR) error during TCR gene rearrangements
- NUP214-ABL1 strictly associated with T-ALL <6% cases
- MYC rearrangements (~6% cases)
- NOTCH1 (70% cases), CDKN2A/B (cryptic deletions >70% cases)

#### T-cell Large Granular Lymphocyte Leukemia (T-LGL)
- STAT3 mutation
- STAT5B mutation

#### Peripheral T cell lymphoma, NOS (PTCL-NOS)
- TET2, DNMT3A, VAV1
- GATA3 vs. TBX21 profiles

#### Complex cytogenetic abnormalities common:
- t(5;9)(q33;q32)/TIR-SYK in follicular variant

#### Clonal rearrangements of TRB and TRG, IGH rearrangements in ~30% cases

#### Angioimmunoblastic T-cell lymphoma (AITL)
- RHOD, CD26, TET2, DNMT3A, IDH2

#### T-cell Prolymphocytic lymphoma (T-PDLL; with inv(14) or t(14;14))
- STAT5B, JAK1, JAK3

#### Complex karyotypes common with numerical and structural abnormalities including inv(14), t(14;14), i(8)(q10), -11, del11q, -22, -13.

#### TCL1A (TCL1) rearrangements at 14q32.

#### Multiple submicroscopic abnormalities.

### Myeloid/Lymphoid Neoplasms associated with Eosinophilia
- **PDGFRα rearrangement** (often del(11)(q22); FGFR1-PDGFRα)
- **PDGFRβ rearrangement** (often t(5;12)(q31–33;p12);ETV6-PDGFRB)
- **FGFR1 rearrangement** (various partners)
- **t(8;9)(p22;p24.1); PCM1-JAK2**
- **ETV6-FLT3 fusion**

### Myeloid Neoplasms with Germline Predisposition
- **AML with germline CEBSA mutation**
- **Myeloid neoplasm with germline DDX41 mutation**
- Associated with platelet disorders
  - RUNX1, ANKRD26, ET6V mutation
  - Associated with other organ dysfunction
    - GATA2 mutation
    - JMML-type mutations

#### Juvenile Myelomonocytic Leukemia (JMML)
- **Somatic PTPN11 (20-30%); KRAS, NRAS, EZH2, ETNK1, CBL, JAK2; (~10-30%)**, SF3B1 (~1%, T618I most common), CALR (rarely or never present)

#### Atypical Chronic Myeloid Leukemia (aCML)
- Overlap MDS/MPN neoplasm
- **BCR-ABL1 negative**
- Cytogenetics: 48, i(17q), -7, del(7q), del(20q), +9, del(13q)
- Molecular genetics: SETBP1 mutation (~20-30%), exon 4 mutations with DIS6N most common, associated with -7 and i(17q). ASXL1 (65%), SF3B1, TET2 (~40%). KRAS, NRAS, EZH2, ETNK1, CBL, JAK2, (~10-30%), SF3B1 (~1%, T618I most common), CALR (rarely or never present)

#### KRAS prognosis if missense mutations are excluded), Poor Prognosis most common, associated with -7 and i(17q), ASXL1 (65%), SF3B1, TET2 (~40%). KRAS, NRAS, EZH2, ETNK1, CBL, JAK2, (~10-30%), SF3B1 (~1%, T618I most common), CALR (rarely or never present)

#### SetBP1 mutation (~20-30%), exon 4 mutations with DIS6N most common, associated with -7 and i(17q), ASXL1 (65%), SF3B1, TET2 (~40%). KRAS, NRAS, EZH2, ETNK1, CBL, JAK2, (~10-30%), SF3B1 (~1%, T618I most common), CALR (rarely or never present)

#### 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 IRF6) - good prognosis**
- TP53 rearrangement - poor prognosis

#### Anaplastic Large Cell Lymphoma, ALK-positive (ALCL, ALK+)
- ** Chromosome translocations involving ALK gene at 2p23**
  - t(2;5)(p23;q35); ALK-STAT5A
  - Other ALK rearrangements

### Other Entities

#### Chronic Myelomonocytic Leukemia (CMML) (MDS/MPN "bridging" category)
- Frequent mutations: TET2 (~50%), SRSF2 (~30-50%), ASXL1 (~90-50%), poor prognosis if missense mutations are excluded, KRAS and NRAS (myeloproliferative phenotype), SETBP1 (poor prognosis), JAK2 (not specific)

#### Myeloid/Lymphoid Neoplasms with Germline Predisposition
- **AML with germline CEBSA mutation**
- **Myeloid neoplasm with germline DDX41 mutation**
  - Associated with platelet disorders
  - RUNX1, ANKRD26, ET6V mutation
  - Associated with other organ dysfunction
    - GATA2 mutation
    - JMML-type mutations

#### Intrachromosomal amplification of chromosome 21 (iAMP21)
- **Most common leukemia in infants <1 year old; may occur in utero**
- **Common secondary abnormalities: loss of 1p, 13q, 17p, gains**
- **Worse prognosis: near haploid (25-29 chromosomes) and low hypoploid (33-39 chromosomes)**
- **BCL6 rearrangements more common in grade 3B tumors**

#### Mantle Cell Lymphoma (MCL)
- **t(11;14)(q13;q32); IGH/CCND1**
  - Common secondary abnormalities: loss of 1p, 13q, 17p, gains in 3q. Numerical abnormalities include +3, +12, -8, -9, -Y, -Y
  - (t;8;14)(q24;q32) occurs rarely and has worse prognosis; (t;8;14) and CCND1 rearrangement is called a “double hit” MCL

#### Burkitt Lymphoma (BL)
- **MYC rearrangements**
  - t(8;14)(q24;q32); IGH/MYC
  - t(2;8)(p12;q24); IKG/MYC
  - t(8;22)(q11;11); IGL/MYC

#### hairy cell leukemia (HCL)
- **BRF; pV600E (~95% of cases)**
  - >85% HCL cases demonstrate somatic hypermutation in VH genes
  - **MAP2K1 mutations = hairy cell leukemia variant (HCL-v)**

#### Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)
- **Good Prognosis**
  - del(13q) (14%) most common cytogenetic abnormality
  - **Mutated IGHV**
  - **Intermediate Prognosis**
    - Trisomy 12 (a/w ALK-)
  - **Poor Prognosis**
    - del(13q)
    - del(11)(q22-23) (a/w SF3B1)

#### Extranodal Marginal Zone Lymphoma, MALT type
- **t(11;18)(q21;q21) – pulmonary and gastric MALT**
  - t(14;18)(q32;q21) – orbital and salivary gland MALT
  - t(13;14)(q14;q32) - thyroid, orbital, skin MALT
  - t(1;14)(p23;q22)

#### Diffuse large B-cell lymphoma, NOs
- **Activated B cell type**
  - BCL6 rearrangements/NOTCH2 mutations
  - MYD88, CD79B mutations
  - NOTCH1 mutations
  - Germinal center B cell type
  - IGH/BCL2 and EZH2 mutations

#### Lymphoplasmacytic Lymphoma (LPL) and IgM monoclonal gammopathy of unknown significance (MUGS)
- 6q23 deletion most common cytogenetic finding in LPL
  - MYD88 p.L265P (~90% of cases)
  - CXCR4 mutation (~30% of LPL, ~20% of IgM MUGS)
  - ALK-positive large B-cell lymphoma
    - t(1;14)(p23;q23); CLTC-ALK
  - High-grade B-cell lymphoma
    - MYC rearrangement with BCL2 and/or BCL6 rearrangement