### Morphology

- **Flow cytometry**
- **Cytogenetics**

### Acute Myeloid Leukemia with Defining Genetic Abnormalities

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AML with CBFB::MYH11 fusion</strong></td>
<td>Good prognosis; m(16);(p13.1;q22) or t(16;16)(p13.1;q22) - likely need FISH/RT-PCR – subtle rearrangement</td>
</tr>
<tr>
<td><strong>AML with DEK::NUP214 fusion</strong></td>
<td>Poor prognosis; t(6;9)(p23;q34.1); mostly sole karyotypic abnormality</td>
</tr>
<tr>
<td><strong>AML with KMT2A rearrangement</strong></td>
<td>Poor prognosis; ≥80 KMT2A fusion partners described, with MLLT3, AFDN, ELL, and MLLT10 being most common; most poor prognosis</td>
</tr>
<tr>
<td><strong>AML with RUNX1::RUNX1T1 fusion</strong></td>
<td>Good prognosis; ≥70% have additional karyotypic abnormality: X, del(9q)</td>
</tr>
<tr>
<td><strong>AML with KMT2A::MLLT3</strong></td>
<td>Adults often have high blast counts at presentation, usually with monocyctic differentiation</td>
</tr>
<tr>
<td><strong>AML with RUNX1:RUNX1T1</strong></td>
<td>Presence of Kit mutation and CD56 expression associated with worse prognosis; ASXL1/2, KRAS, NRAS mutations may also be seen</td>
</tr>
</tbody>
</table>

### Acute myeloid leukemia

- **Good prognosis**
- **Poor prognosis**

### Work-up

- Suspected acute leukemia
- Molecular In My Pocket™...
**Acute Myeloid Leukemia with Defining Genetic Abnormalities (cont’d)**

<table>
<thead>
<tr>
<th>AML with NUP98 rearrangement</th>
<th>AML with other defined genetic alterations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• &gt;30 fusion partners</td>
<td>• &quot;Landing spot&quot; for emerging or rare entities</td>
</tr>
<tr>
<td>• Rearrangement may be cryptic</td>
<td>Diagnosis requires:</td>
</tr>
<tr>
<td>• Many associated with overexpression of HOXA9; poor prognosis</td>
<td>• &gt;20% blasts required by WHO; 10% blasts by ICC</td>
</tr>
<tr>
<td></td>
<td>• Either: history of MDS or MDS/MPN, or MDS-related cytogenetic abnormality or somatic mutation</td>
</tr>
<tr>
<td></td>
<td>• Absence of prior cytotoxic or radiation therapy for unrelated disease or AML-defining recurrent genetic abnormality</td>
</tr>
</tbody>
</table>

**AML with NPM1 mutation**

- Overall good prognosis; poorer prognosis with presence of FLT3-ITD +/- DNMT3A
- Blasts often show monocytic features
- Multilineage dysplasia seen in up to 25% of cases
- Usually associated with normal karyotype
del(9q), +8 seen in 5-15% of cases
- Secondary mutations include FLT3, DNMT3A, IDH1/2, KRAS, NRAS
- Up-regulation of HOX gene

**AML with mutated TP53**

- Very poor prognosis
- Typically associated with complex karyotype
- Although multi-hit TP53 is required for MDS with mutated TP53, in AML and MDS/AML with mutated TP53, any pathogenic TP53 mutation VAF >10% is sufficient.

**Myeloid/Lymphoid Neoplasms with eosinophilia and tyrosine kinase gene fusions (MLN-TK)**

- Broad range of histologic types – MPN, MDS, MDS/MPN, AML, MPAL, B-ALL, T-ALL
- Eosinophilia common feature but may be absent in some cases
- Sensitive to tyrosine kinase inhibitor (TKI) therapy
- Defining genetic abnormalities
  - PDGFRα rearrangement (often del[4](q12;q12); FIP1L1:PDGFRα)
  - PDGFRβ rearrangement (often t(5;12)(q22;p12); ETV6:PDGFRβ)
  - FGFR1 rearrangement
  - JAK2 rearrangement (often t(8;9)(p22;p24.1);PMCL1::JAK2
  - FLT3 rearrangement
  - ET6:ABL1 fusion (separate from B-ALL with ET6:ABL1) and other ET6 rearrangement (ET6::FGFR2; ET6::LYN; ET6::NTRK3; RANBP2::ALK)
  - Other MLN-TK (more is accrued): BCR::RET; FGFR1OP::RET
- Mostly, long-term survival option is bone marrow transplant

**Myeloid neoplasms post cytotoxic therapy (MN-pCT)**

- Poor prognosis
- Requires a documented history of chemotherapy (e.g. alkylating agents, topoisomerase II inhibitors, antimitabolites, antitubulin agents) or large-field radiation therapy for an unrelated condition
- De novo AML with defining genetic abnormality, such as NPM1 mutation and CBF AML, post cytotoxic therapy should be assigned to this category based on medical history
- Majority AML-pCT and MDS-pCT associated with TP53 mutations; worse outcomes with biallelic (multi-hit) TP53 alterations
- Less frequent mutations involving genes such as PPM1D or DNA-damage response genes require consideration of a germline predisposition

**Myeloid neoplasms with germline predisposition**

- Myeloid neoplasms with germline predisposition without a pre-existing platelet disorder or organ dysfunction
  - Germline CEBPA P/LP variant (CEBPA-associated familial AML)
  - Germline DDX41 P/LP variant
  - Germline TP53 P/LP variant (Li-Fraumeni syndrome)
- Myeloid neoplasms with germline predisposition and pre-existing platelet disorder
  - Germline RUNX1 P/LP variant (familial platelet disorder with associated myeloid malignancy, FPD-MM)
  - Germline ANKRD26 P/LP variant (Thrombocytopenia 2)
  - Germline ET6V P/LP variant (Thrombocytopenia 5)

**Myeloid neoplasms with germline predisposition and potential organ dysfunction**

- Germline GATA2 P/LP variant (GATA2-deficiency)
- Bone marrow failure syndromes
  - Severe congenital neutropenia (SCN)
  - Shwachman-Diamond syndrome (SDS)
  - Fanconi anemia (FA)
- Telomere biology disorders
- Rasopathies (Neurofibromatosis type 1, CBL syndrome, Noonan syndrome or Noonan syndrome-like disorders)
- Down Syndrome
- Germline SMAD9 P/LP variant (MIRAGE syndrome)
- Germline SAMD9L P/LP variant (SAMD9L-related ataxia pancytopenia syndrome)
- Biallelic germline BLM P/LP variant (Bloom syndrome)