Myelodysplastic Syndrome: What is Driving the Abnormal Cells

- Chromosome abnormalities are present in 50-60% of cases and may contribute to defective cell maturation.
- Excessive methylation of certain genes may turn off the production of proteins that regulate cell growth, maturation and survival.
- Genes involved in cell growth and survival are mutated or activated.
- Immune cells may suppress blood cell production by directly killing blood-forming cells or by producing inflammatory factors.

Gene Mutations in MDS

<table>
<thead>
<tr>
<th>Mutated Gene</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>TET2</td>
<td>Converts methylcytosine to 5-hydroxymethylcytosine, affects chromatin structure</td>
</tr>
<tr>
<td>ASXL1</td>
<td>Chromatin remodeling</td>
</tr>
<tr>
<td>RUNX1</td>
<td>Transcription factor required for hematopoiesis</td>
</tr>
<tr>
<td>EZH2</td>
<td>Transcription factor, regulates cell cycle, mediates response to DNA damage</td>
</tr>
<tr>
<td>NARAS, KRAS</td>
<td>Histone H3 lysine 27 methyltransferase (on 7q)</td>
</tr>
<tr>
<td>JAK2</td>
<td>Signaling protein downstream of growth factor receptors with tyrosine kinase activity</td>
</tr>
<tr>
<td>ETB</td>
<td>Signaling protein downstream of growth factor receptors with tyrosine kinase activity</td>
</tr>
<tr>
<td>IDH1, IDH2</td>
<td>Mutated enzymes that prevent oxidative damage (dehydrogenate isocitrate to α-ketoglutarate)</td>
</tr>
<tr>
<td>NPM1</td>
<td>Nuclear-cytoplasmic shuttling phosphoprotein</td>
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</tbody>
</table>
Gene Mutations in MDS

<table>
<thead>
<tr>
<th>Mutated Gene</th>
<th>No. of Samples (%)</th>
<th>Median Survival in Yrs (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All samples</td>
<td>439 (100)</td>
<td>1.86 (1.60–2.14)</td>
<td></td>
</tr>
<tr>
<td>TET2</td>
<td>90 (20.5)</td>
<td>1.88 (1.26–2.55)</td>
<td>0.48</td>
</tr>
<tr>
<td>ASXL1</td>
<td>63 (14.4)</td>
<td>1.33 (0.96–1.88)</td>
<td>0.003</td>
</tr>
<tr>
<td>RUNX1</td>
<td>38 (8.7)</td>
<td>1.16 (0.77–1.53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TP53</td>
<td>33 (7.5)</td>
<td>0.80 (0.44–1.50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EZH2</td>
<td>28 (6.4)</td>
<td>0.79 (0.47–1.30)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NRAS</td>
<td>16 (3.6)</td>
<td>1.16 (0.91–1.41)</td>
<td>0.006</td>
</tr>
<tr>
<td>JAK2</td>
<td>13 (3.3)</td>
<td>1.94 (1.42–2.63)</td>
<td>0.04</td>
</tr>
<tr>
<td>FLT3</td>
<td>12 (2.7)</td>
<td>0.83 (0.42–1.29)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CEB1</td>
<td>10 (2.3)</td>
<td>1.52 (1.14–1.71)</td>
<td>0.02</td>
</tr>
<tr>
<td>SFP1</td>
<td>9 (2.1)</td>
<td>0.88 (0.59–1.34)</td>
<td>0.33</td>
</tr>
<tr>
<td>BCL2</td>
<td>9 (2.1)</td>
<td>0.55 (0.39–0.72)</td>
<td>0.03</td>
</tr>
<tr>
<td>SUZ12</td>
<td>6 (1.4)</td>
<td>3.26 (1.09–9.43)</td>
<td>0.02</td>
</tr>
<tr>
<td>AKBG</td>
<td>4 (0.9)</td>
<td>0.80 (0.36–1.74)</td>
<td>0.64</td>
</tr>
<tr>
<td>IDH2</td>
<td>3 (0.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDH1</td>
<td>2 (0.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTEN</td>
<td>1 (0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDKN1A</td>
<td>1 (0.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Mutations of RNA Splicing Proteins in MDS

- RNA molecules serve as templates for proteins in cells
- A single immature RNA can be spliced in several ways to encode several different proteins
- Recently, mutations in the gene encoding RNA splicing factor 3B, subunit 1 (SF3B1) were found in 20% of MDS patients including 65% of MDS with ringed sideroblasts
- Mutations in other genes encoding RNA splicing factors have since been identified in MDS including U2AF35, SRSF2, ZRSR2, SF3A1, PRPF40B, U2AF65 and SF


Therapeutic Approaches in MDS

- Hematopoietic growth factors
- Immunomodulatory drugs
- DNA methylation inhibitors
- Histone deacetylase inhibitors
- Immunosuppressive therapy
- Transplantation
Romiplostim (Nplate) in MDS

- Romiplostim is a peptibody that mimics the activity of thrombopoietin (platelet growth factor)
- It is approved by the FDA for treatment of an immune platelet disorder (ITP)
- In a small study, Romiplostim at doses of 500 mcg or 750 mcg/week by SQ injection reduced the frequency of platelet counts <50,000/uL (but not significantly) in MDS patients receiving Vidaza
- Romiplostim was well tolerated

Wijermans et al. Blood 2008;112:91(abstract 227)

Randomized, Double-Blind, Placebo-Controlled Study of Romiplostim in Low or Int-1 Risk MDS

- 250 pts with low/int-1 risk MDS randomized 2:1 to romiplostin:placebo
- Romiplostim 750 mcg or placebo per week for 26 weeks
- Primary endpoint was number of clinically relevant bleeding events
- From week 4, platelets on romiplostim were significantly higher than placebo
- Serious adverse events on romiplostim 40%, placebo 27%
- Peripheral blood blasts >10% occurred in 15% romiplostim, 3.6% placebo
- AML occurred in 6% of romiplostim, 2.4% placebo
- Survival was the same on both arms (romiplostim 80%, placebo 78%)
  - Romiplostim deaths: 3% from AML/MDS progression, 0% from bleeding
  - Placebo deaths: 3.6% from AML/MDS progression, 4.8% from bleeding
- Study was terminated early over concern for risk for AML progression


Lenalidomide (Revlimid) in 5q- MDS

- Thalidomide analog without neurotoxicity
- Apoptosis sensitizer, anti-VEGF activity, suppressor of inflammatory cytokine production
- 148 transfusion-dependent MDS patients with low or intermediate-1 IPSS score, and 5q31 deletion
- Lenalidomide 10 mg/d for 21 days every 4 weeks
- Results
  - 67% became transfusion independent
  - 9% had transfusion reduced by 50%
  - Median time to response was 4.6 weeks
  - Median duration of response was >104 weeks
  - 73% had a cytogenetic response, 61% complete
- Side effects: neutropenia, thrombocytopenia, rash
- FDA approved for MDS (low or int-1 IPSS risk) with transfusion-dependent anemia and 5q deletion

List et al. NEJM 2006;355:14
**Revlimid in MDS without 5q Deletion**

- 214 transfusion-dependent MDS patients without 5q deletion received Revlimid 10 mg/d for 21 of 28 days
- 26% became transfusion independent (compared to 67% for 5q-)
- 17% had transfusion requirement reduced in half or more
- Median time to response was 4.8 weeks, and median duration of response was 41 weeks
- 19% of patients with cytogenetic abnormalities had a >50% reduction in cells with abnormalities (compared to 73% for 5q-)
- Side effects included neutropenia, thrombocytopenia, rash

Raza et al, Blood 2008;111:86-93

**5-Azacytidine (Vidaza) in MDS**

- DNA methyltransferase inhibitor
- Phase III randomized trial of Vidaza 75 mg/m²/d SQ x 7 days every 28 days for 4 cycles, versus supportive care
- Additional cycles permitted if response observed
- Cross-over permitted after 4 months for disease progression
- Response: CR, PR, Improved, Total
- 5-Aza: 7% 16% 37% 60%
- Control: 0% 0% 5% 5%
- Crossover: 10% 4% 33% 47%
- Landmark analysis suggested that 5-Aza prolonged survival
- Time to progression or death was longer for 5-Aza arm (21 mos) than the control arm (12 months); p = 0.007
- QOL measures improved for 5-Aza patients but not controls


**Vidaza is Superior to Conventional Care in Higher-Risk MDS**

- Phase III trial randomized 358 patients with Int-2 or High risk MDS to
  - 5-Aza 75 mg/m²/d x 7 days every 28 days (n =179), or
  - Conventional care including supportive care (n =105), low dose cytarabine (n =49) or intensive chemotherapy (n = 25)
  - No cross-over to Vidaza was permitted
- Median survival was superior for patients receiving Vidaza (24 months) compared to conventional care (15 months)
- Survival at 2 years favored Vidaza (91%) over conventional care (26%)
- Survival benefit was pronounced for patients with chromosome 7/7q deletion (13 vs 5 months median survival)
- Time to AML was significantly longer for Vidaza treated patients
- Time to first Vidaza response: 3 cycles (50%), 6 cycles (81%), 9 cycles (91%)

Fenaux et al Lancet Oncol 2009;10:223
**Phase I Trial of Vidaza Plus Revlimid in Higher Risk MDS**

- 18 patients with higher risk MDS (RAEB, RAEB-T, CMML with >2% blasts) were treated in phase I, an additional 18 in phase II.
- A range of revlimid doses and schedules were evaluated.
- These drugs were well tolerated in combination.
- The best regimen was:
  - Vidaza 75 mg/m² days 1-5
  - Revlimid 10 mg days 1-21
  - Repeat every 28 days
- Overall response rate was 71%:
  - 40% CR
  - 31% hematologic improvement


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**Phase II Trial of Vidaza Plus Revlimid Response Results**

- ORR (n=36): 26/36 (72%)
  - 15 CR (42%)
  - 10 HI (28%)
  - 1 BM CR (3%)
- Median CR duration: 16+ months (range, 3-36+)
- Median OS among CR pts: 27+ months (range, 7-55+)


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**Phase II Study of Vidaza and Vorinostat in Newly Diagnosed MDS or AML**

- Vorinostat activates genes by preventing deacetylation of histone proteins that are physically associated with the DNA.
- Vorinostat is FDA approved for treating T cell lymphoma.
- Vidaza is a hypomethylating agent.
- Laboratory studies suggest that combining these drugs may be more effective than using either one alone.
- Treatment:
  - Vidaza 75 mg/m² days 1-5
  - Vorinostat 200 mg po TID days 1-5
  - Repeat every 28 days
- Complete response rates for 30 patients was 26%

North American Intergroup Randomized Phase II MDS Proposal

Higher-risk MDS (IPSS >1.5)

- AZA
  - N=80
- AZA + LEN
  - N=80
- AZA + Vorin
  - N=80

Groups: SWOG, ECOG, CALGB, NCIC

Total Sample Size: 240

Primary Objective: 30% improvement of RR based on 2006 IWG Criteria

Secondary Objectives: OS, SFS, LFS

Power 91%, alpha 0.05 for each combo arm vs. AZA

Anticipated time: 2.5 years

Sekeres et al. Blood 2011;118:607a

Oral Azacytidine: Preliminary Activity in MDS/CML

<table>
<thead>
<tr>
<th>Response</th>
<th>Treatment Schedule, Responders/Evaluable Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total 300 mg 200 mg</td>
</tr>
<tr>
<td></td>
<td>14-day qd 21-day qd 14-day bid 21-day bid</td>
</tr>
<tr>
<td>CR</td>
<td>10/15 (67)</td>
</tr>
<tr>
<td>14-day qd</td>
<td>0/6 2/3 0/3 0/3</td>
</tr>
<tr>
<td>21-day qd</td>
<td>4/6 3/3 0/3 0/3</td>
</tr>
<tr>
<td>HI-E</td>
<td>2/5 1/2 0 0</td>
</tr>
<tr>
<td>HI-P</td>
<td>2/6 3/3 0/3 0/3</td>
</tr>
<tr>
<td>HI-N</td>
<td>1/5 1/5 0/3 0/3</td>
</tr>
<tr>
<td>HI-E</td>
<td>6/14 3/3 0/3 0/3</td>
</tr>
<tr>
<td>HI-P</td>
<td>2/6 1/2 0 0</td>
</tr>
<tr>
<td>HI-N</td>
<td>1/5 1/5 0/3 0/3</td>
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<tr>
<td>TI</td>
<td>7/10 3/3 2/3 0</td>
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<tr>
<td>RBC</td>
<td>3/3 1/3 1/1 1/1</td>
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<tr>
<td>Platelet</td>
<td>4/5 2/2 1/1 1/2</td>
</tr>
<tr>
<td>mCR</td>
<td>0/3 0/1 0/1 0/1</td>
</tr>
</tbody>
</table>

Ohno-Higa et al, ASH 2010, 487a

Dacogen Versus Supportive Care in Higher-Risk MDS

- DNA methyltransferase inhibitor
- Phase III trial randomized 233 patients with higher-risk MDS to
  - Dacogen 15 mg/m²/q8h x 3 days every 6 wks for up to 8 cycles, or
  - supportive care
- Responses
  - Dacogen: 13% complete, 6% partial, 15% hematologic improvement
  - Supportive care: 0% complete, 0% partial, 2% hematologic improvement
- Survival or time to AML was not significantly longer in Dacogen arm (338 days) than in supportive care arm (263 days)
- Dacogen is now given most frequently at 20 mg/m²/d x 5 days, which yields a complete remission rate of approximately 39%

Wyermans et al, Blood 2008;112(11):30 (abstract 226)
Dacogen Plus Valproic Acid in MDS and AML

- Dacogen activates genes by inhibiting DNA methylation
- Valproic acid activates genes by preventing deacetylation of histone proteins that are physically associated with the DNA
- Laboratory evidence suggests that these activities are complementary
- Phase II trial randomized of 76 patients with MDS (43), CMML (8) or AML (23)
  - Dacogen 20 mg/m²/d x 5 days every 4 wks, or
  - Dacogen plus Valproic acid 50 mg/kg/d x 7 days every 4 wks
- Responses
  - Dacogen: 43%
  - Dacogen + Valproic acid: 52% (difference not significant)
- Survival at one year was not significantly different
- Valproic acid caused sleepiness and confusion

Issa et al. Blood 2008;112(11):91 (abstract 228)

Clofarabine in MDS

- DNA synthesis inhibitor
- FDA approved for acute lymphoblastic leukemia
- 32 MDS patients with >5% bone marrow blasts were treated
  - Clofarabine 20, 30, or 40 mg/m² IV x5d every 4-6 weeks
- Most pts (69%) had received prior Vidaza or Dacogen
- Responses: CR 25%, HI 9%, Clinical Benefit 9% (ORR 43%)
- Side effects included neutropenia, infections, nausea, vomiting, rash, and abnormal liver function tests. The mortality rate was 10%.
- These results are not better than prior trials using standard chemotherapy
- Lower doses and alternate schedules are being explored

Faderl et al. Blood 2008;112;89(abstract 222)
Faderl et al. J Clin Oncol 2010

Reduced-Intensity Conditioning Transplants for Older MDS Patients

- 535 MDS pts aged ≥40 yrs (range 40-78) from CIBMTR registry had RIC transplants using related (40%) or unrelated (60%) donors
- Recipient age did not affect any outcome measure
- Greater HLA disparity with donor and high risk cytogenetics were associated with decreased DFS and OS in multivariate analysis
- 2 year survival ranged from 35-45% across all age groups

McClune, B. L. et al. J Clin Oncol 2010;28;1876-1887
### Clinical Trials: Why Participate?

- Patients can gain access to new treatments that may not be otherwise available.
- Patients can help others by contributing to medical research and helping establish new and better treatments for future patients.
- Clinical researchers are experts in the disease being studied and provide state-of-the-art care.

### Conclusions

- Current medical treatments can be effective for managing MDS, but none are curative.
- Advances in understanding of the molecular abnormalities involved in MDS will lead to novel therapies.
- Clinical trials will continue to advance treatment over the next few years.
- Stem cell transplantation is likely to play an increasing role in the management of MDS patients.