Objectives

- Understand the factors that may influence a person’s response to MDS therapy

- Discuss how the hypomethylating agents (azacitidine, decitabine) work

- Understand how patient tailored therapy can lead to more successful treatment
69 yo man with RAEB-1 MDS. Bone marrow shows 5% blasts.

Diagnosed after presenting with low blood counts. Treated with azacitidine 75 mg/m² for 7 days each month.

After 3 cycles, blood counts were normal. Bone marrow showed 2% blasts. Sustained response for > 2 years.
Patient B

69 yo man with RAEB-1 MDS, bone marrow shows 5% blasts.

Diagnosed after presenting with low blood counts.

Treated with azacitidine 75 mg/m² for 7 days each month.

After 3 cycles, blood counts are still low. Bone marrow shows 10% blasts.
Why did they respond so differently?

1) MDS or cancer cells are genetically different

2) Each person’s body processes drug differently (and leads to differences in hitting the target)

A key challenge is that we cannot accurately decipher between these possibilities.
What is Patient-Tailored Therapy?

Therapy should be individualized to:

1. Cancer cell genetics
2. How each person’s body processes the drug (Pharmacodynamics)
3. Goals, beliefs, preferences
In 944 MDS patients tested for mutations in 104 genes, 89.5% had at least one mutation.

Each patient had on average 3 mutations (range, 0-12).

47 genes were mutated in >10% of patients: (TET2, SF3B1, ASXL1, SRSF2, DNMT3A, RUNX1).

Genetic Diversity in MDS Cells

Mutation A
Mutation B
Mutation C
Mutation D
Cancer Genomics

Mutation discovery / Clonality

- Cytogenetics
- Candidate gene sequencing

- Whole Genome Sequencing (unbiased comprehensive platform)

Patient care

Slide Courtesy of B. Scott
Tailor therapy based on cancer DNA

- If you have mutation in Gene A, you are likely to respond to Drug A
- If you have mutation in Gene B, you are *not* likely to respond to Drug A

Gene mutations associated with response to HMA:
- $TET2$, $DNMT3A$, $IDH1$, $IDH2$, miR-29b
- $TP53$
What is Patient-Tailored Therapy?

Tailored to:

1. Cancer cell(s) unique to each person

2. Pharmacodynamics: What each person’s body does to the drug
How do HMA's work?

DNA

Gene 1

DNA

De-coder

STOP

DNA

De-coder

STOP

methylated DNA

Gene 1

DNA

FNED HUTFCH
HMAs remove methylation

Azacitidine
Decitabine

DNA De-coder

Gene 1

STOP

DNA De-coder

Gene 1

methylation

STOP
Drug needs to get inside MDS Cell and Target DNMT...

Azacitidine
Decitabine

CDA

UCK 1/2
DCK

DNA

“S-phase” of Cell Cycle

STOP

DNMT
Did the drug get there?

Treatment with HMA

Patient responds

Patient does not respond
If the drug did not reach its intended target, it has little chance of working (regardless of any mutations).
Can we monitor levels of DNMT inside cancer cells to ensure we are reaching the drug target?

Is decreasing DNMT associated with improved response?

Can we individualize dosing and frequency based DNMT levels?

**Goal**: To make treatment more successful and safe.
Flow Cytometry

Uses antibody labeling and laser to detect protein levels in blood cells.

Image from: https://flowcytometry.med.ualberta.ca
Objective: To investigate the association between change in DNMT1 flow assay level pre- and post-azacitidine or decitabine treatment and response

Sample Collection Schedule:

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Cycle 1 Days 5 &amp; 15</th>
<th>Day 1 &amp; 5 of each subsequent cycle</th>
<th>After Cycle 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Marrow</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
By monitoring DNMT levels throughout treatment, we can tailor dose and frequency to each individual and make treatment more effective and safe.
Why a difference in response?

1) MDS or cancer cells are genetically different

2) Each person’s body processes drug differently

Therapy tailored to each individual will lead to more successful treatment.
Thank you

Patients & Families

Fred Hutch
• Bart Scott
• Joachim Deeg
• Brent Wood
• Brenda Sandmaier
• Erlinda Santos

Case Comprehensive Cancer Center
• James Jacobberger
• Phillip Woost
• Marcos de Lima
• Yogen Saunthararajah (Cleveland Clinic)

Conquer Cancer Foundation of ASCO