Patient-Tailored Therapy

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Educational Patient-Caregiver Forum

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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

Patient A

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

Diagnosed after presenting with low blood counts.

Treated with azacitidine 75 mg/m^2 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/m^2 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

Genetic mutations in MDS – Example

In 944 MDS patients tested for a mutations in 104 genes, **89.5%** had at least one mutation

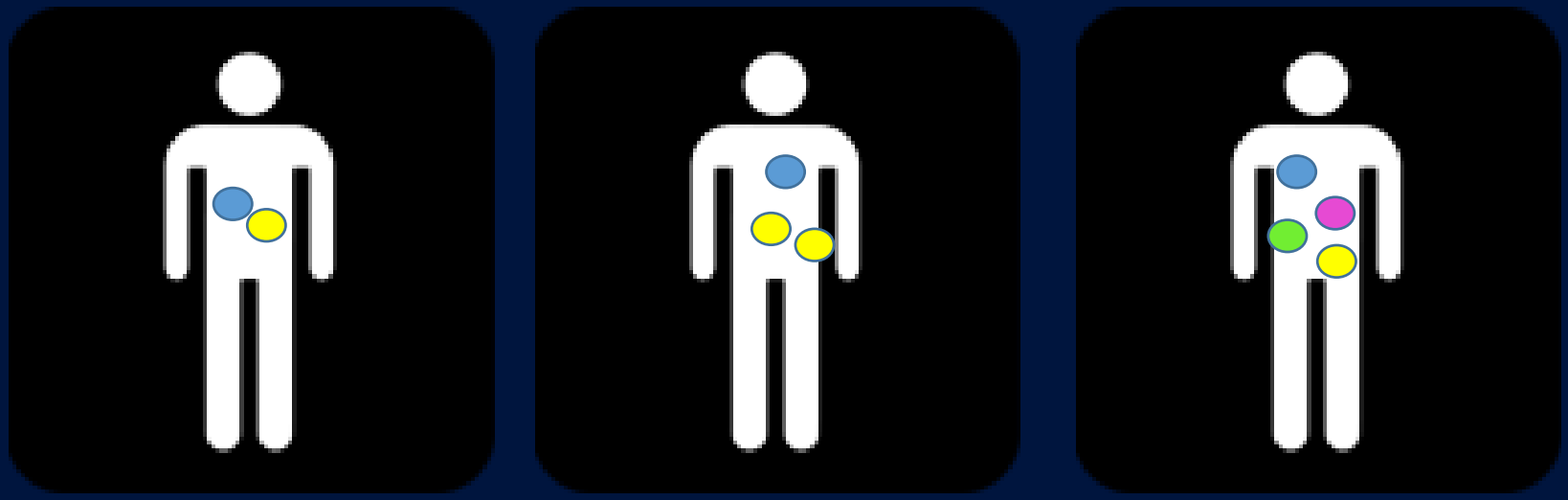
Each patient had on average 3 mutations (range, 0-12)

47 genes were mutated in >10% of patients

(*TET2*, *SF3B1*, *ASXL1*, *SRSF2*, *DNMT3A*, *RUNX1*)

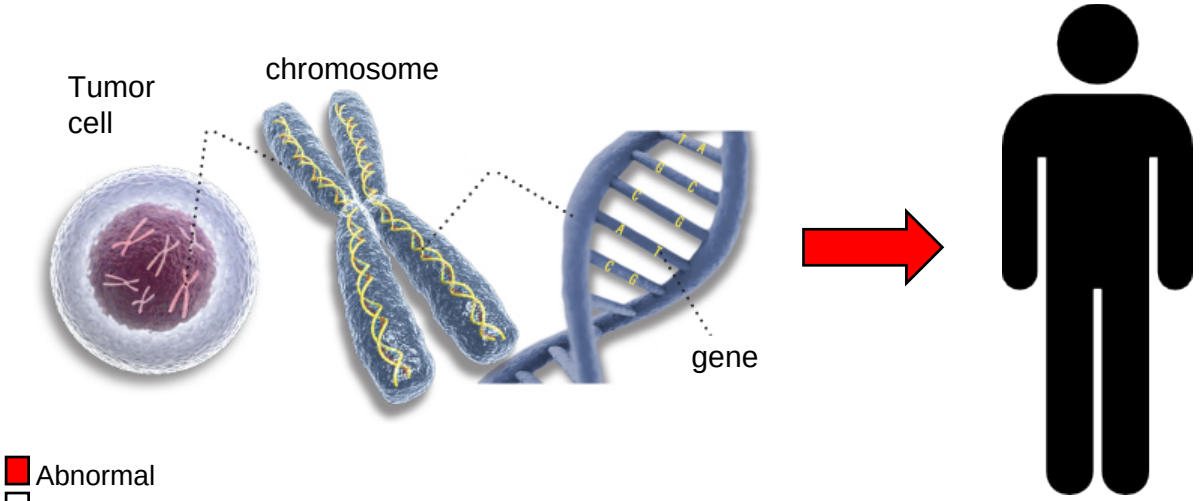
Haferlach T et al. *Leukemia* 2014;28:241-247

Genetic Diversity in MDS Cells



Mutation A
Mutation B
Mutation C
Mutation D

Cancer Genomics



Mutation discovery /Clonality Patient care

- •Cytogenetics
- •Candidate gene sequencing
- •Whole Genome Sequencing (unbiased comprehensive platform)

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*

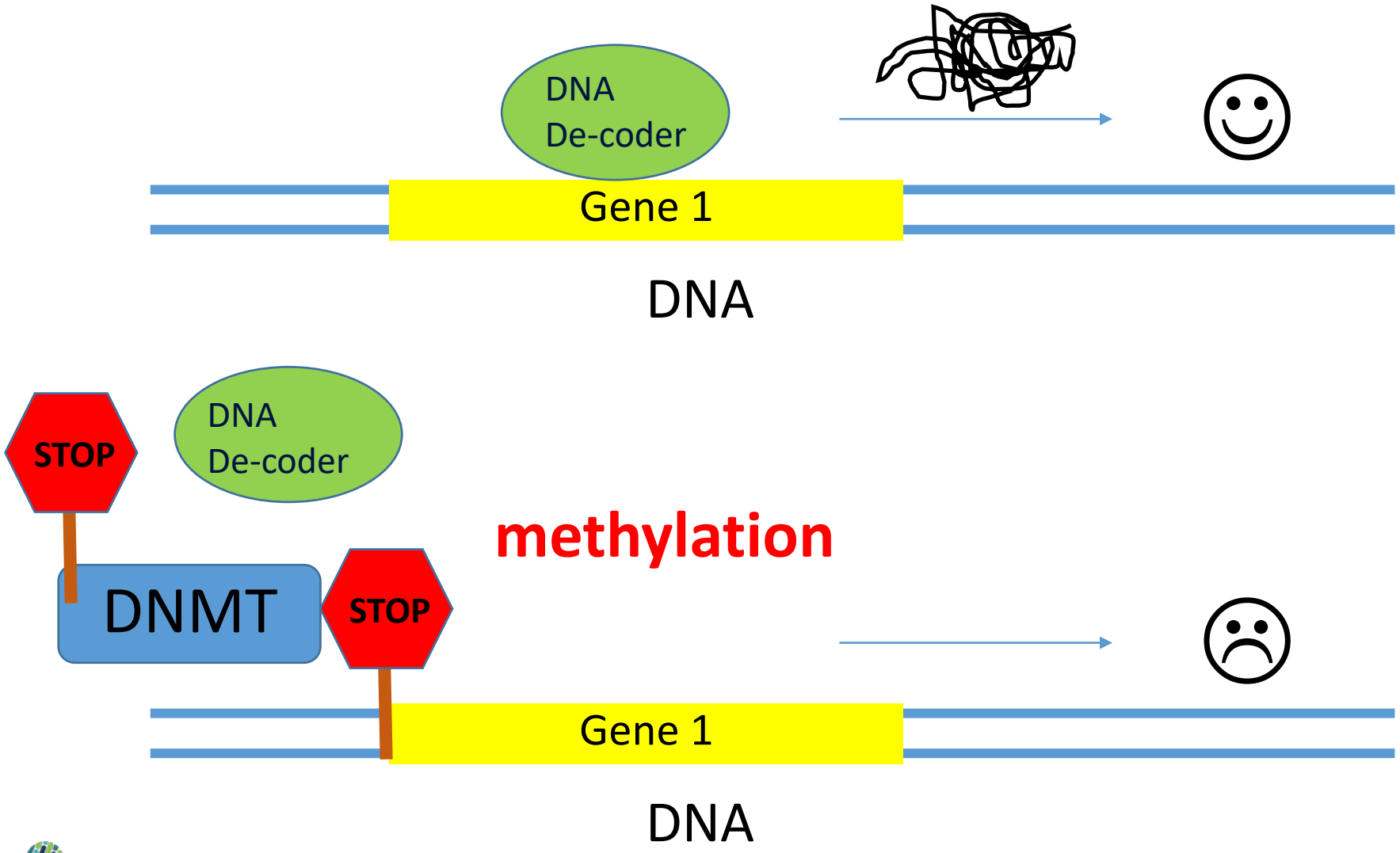
What is Patient-Tailored Therapy?

Tailored to:

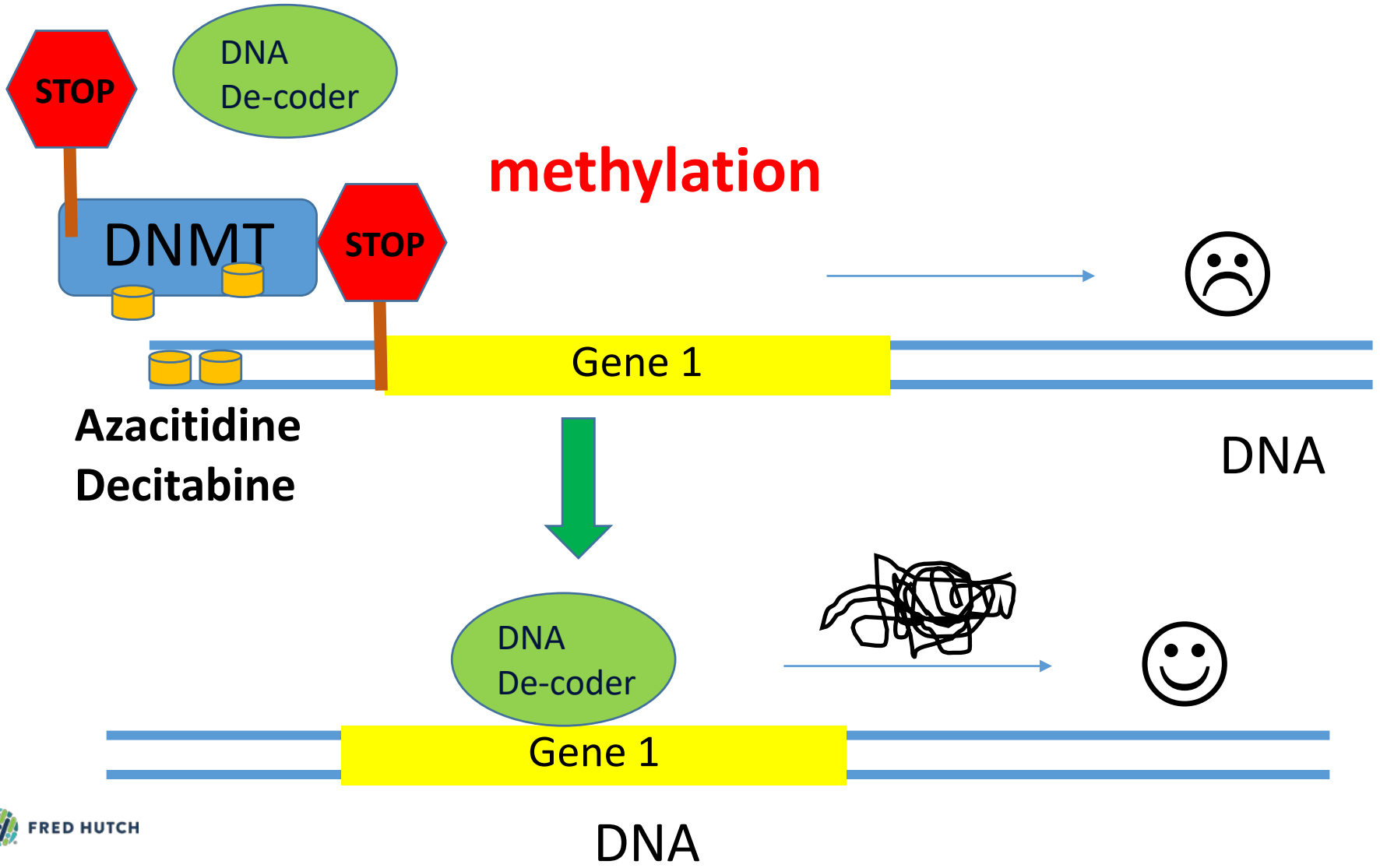
1. Cancer cell(s) unique to each person

2. Pharmacodynamics: What each person's body does to the drug

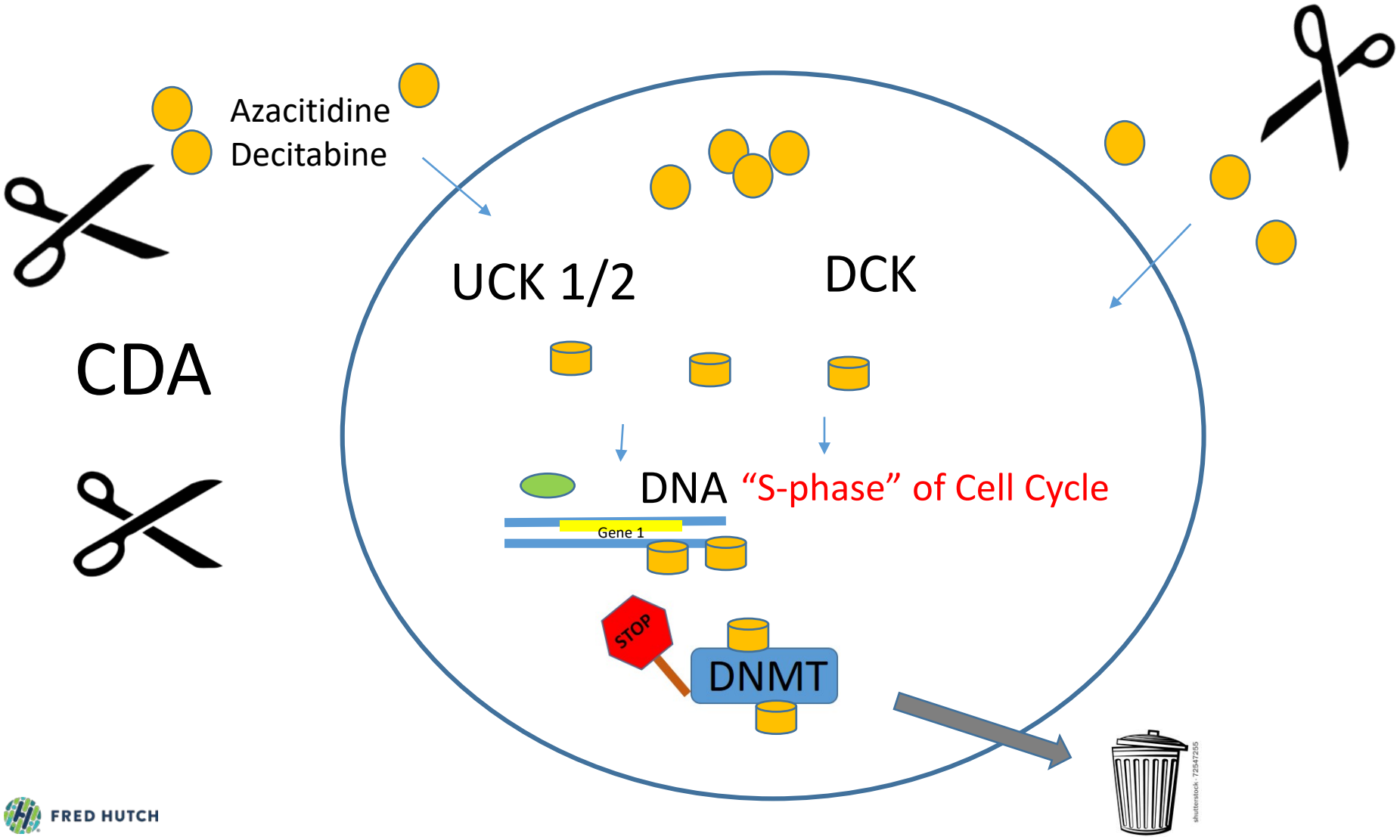
How do HMAs work?



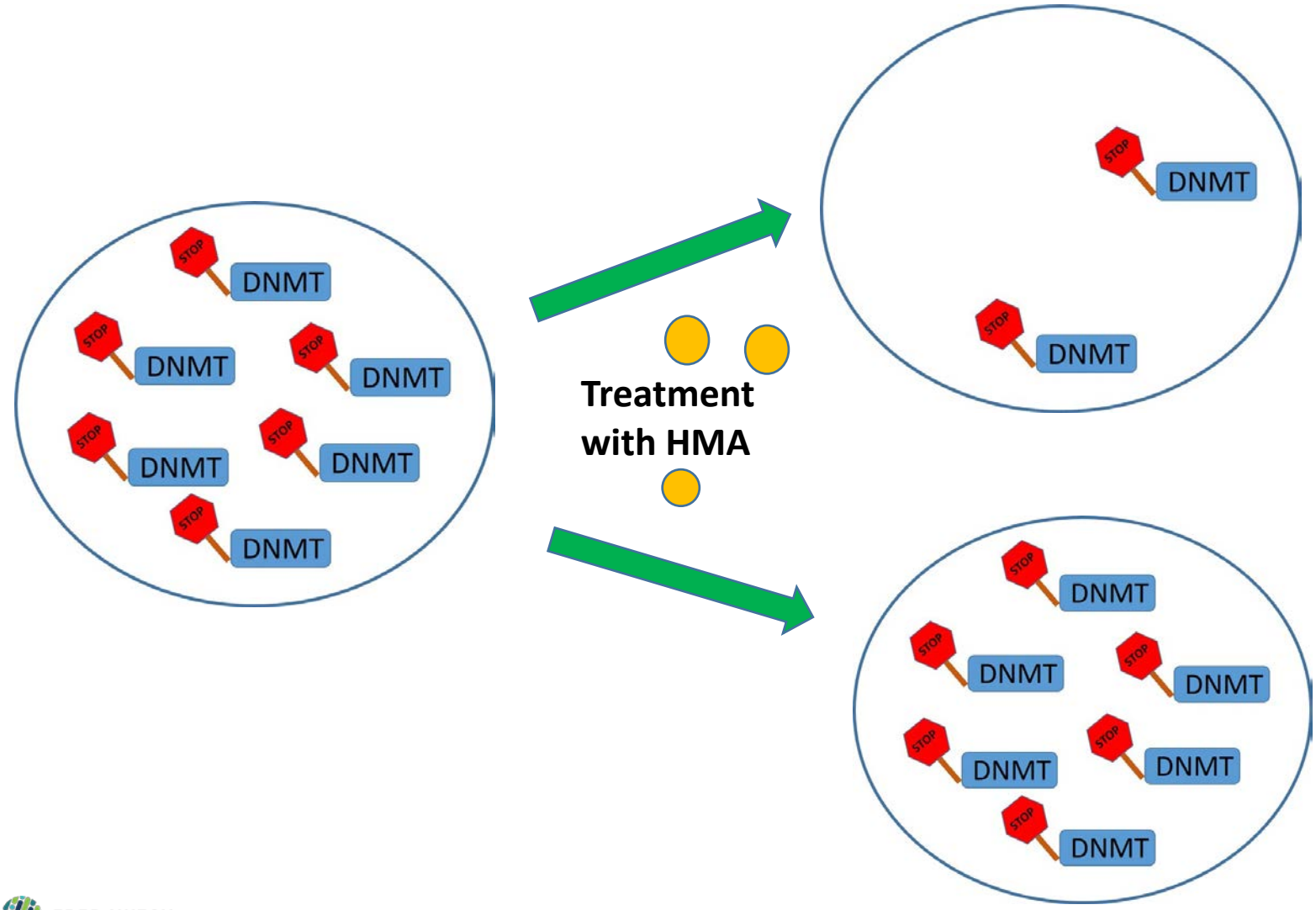
HMAs remove methylation



Drug needs to get inside MDS Cell and Target DNMT…



Did the drug get there?



Predicting Response to Therapy

If the drug did not reach its intended target, it has little chance of working (regardless of any mutations).

Research Questions

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.

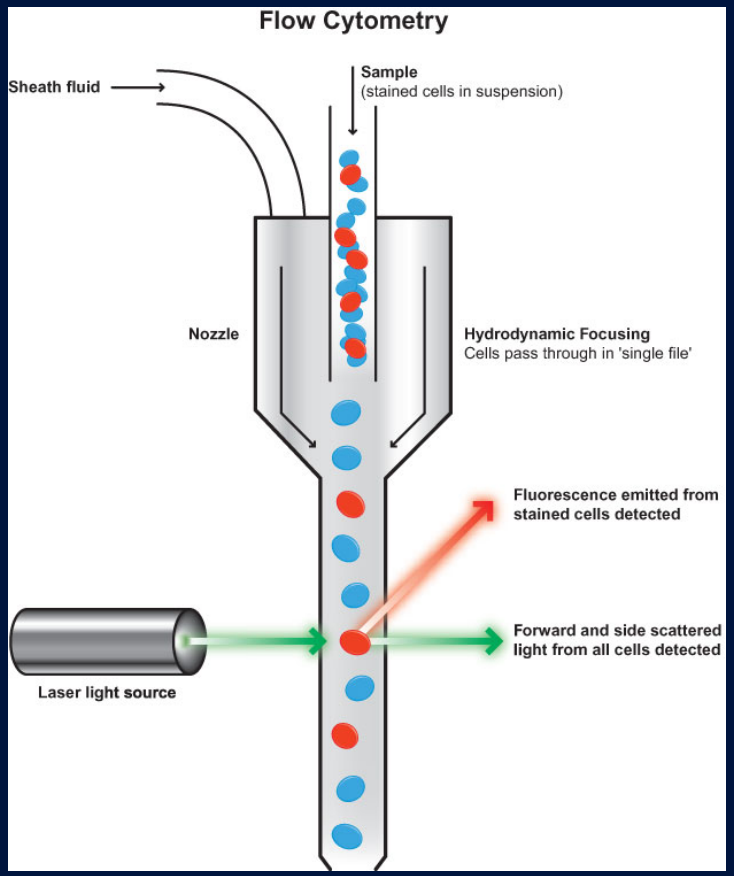


Image from: https:// flowcytometry.med.ualberta.ca

Protocol FH9783

Objective: To investigate the association between change in DNMT1 flow assay level pre- and post-azacitidine or decitabine treatment and response

Sample Collection Schedule:

	Baseline	Cycle 1 Days 5 & 15	Day 1 & 5 of each subsequent cycle	After Cycle 3
Blood	X	X	X	X
Marrow	X			X

Patient Tailored Drug Dosing

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

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- Bart Scott
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Conquer Cancer Foundation of ASCO

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