Improving Treatment Options for Myelodysplastic Syndromes (MDS) and Myeloid Leukemias

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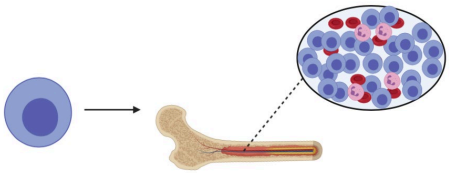
Myelodysplastic Syndrome (MDS) is a blood disorder that mostly affects older patients

2500 new cases per year

In patients with MDS, leukemia starts in the blood stem cells



MDS Cell

MDS cells multiply uncontrollably, eventually crowding out normal cells in the bone marrow and in the bloodstream **INHIBITING** healthy blood development

Symptoms vary and may take **YEARS** to manifest

There is **NO CURE**

Azacytidine (AZA) is the **FRONT-LINE** therapy for MDS. **UNFORTUNATELY,** only 50% of MDS patients respond with most relapsing within **2 YEARS.**

If AZA fails, patients are placed on supportive therapy until they inevitably succumb to MDS.

Can we make AZA therapy **MORE EFFECTIVE?**

Combination therapies can improve treatment outcomes, but this needs knowledge about **novel drug targets**. Large scale screens can identify targets which then need to be validated.

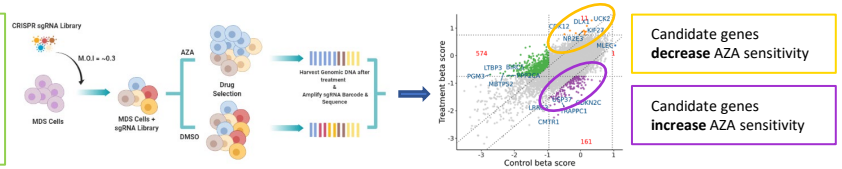
We know that leukemic cells from patients with primary resistance to AZA are more likely to be quiescent. If we can push cells back into the cell cycle they might **become more responsive** to AZA therapy.

Techniques

Cell culture, molecular biology, PCR, western blotting, proliferation assays, colony assays

Project 1: Validation of novel drug targets identified by CRISPR/Cas9 in leukemic cells

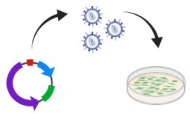
Genome wide CRISPR/Cas 9 screen to identify novel gene targets



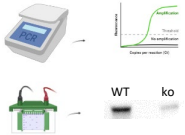
Candidate genes **decrease** AZA sensitivity

Candidate genes **increase** AZA sensitivity

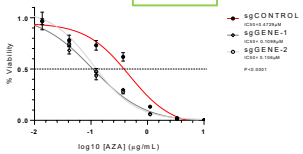
Aim 1



Aim 2



Aim 3

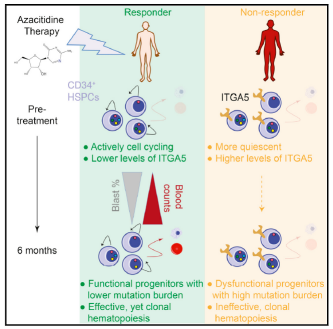


Hypothesis: The DNA damage response induced by AZA incorporation into replicating cells is enhanced or obstructed by interference of specific genes.

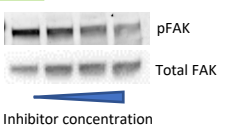
Aims:

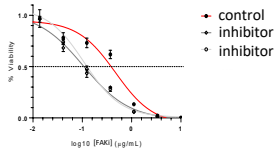
1. Generate lentiviral constructs to deliver guide RNAs to leukemic cells;
2. Validate on-target activity;
3. Assess relative resistance of targeted MDS/AML cells to AZA and explore mechanisms of action by which the gene target alters AZA sensitivity.

Project 2: Pre-clinical evaluation of a kinase inhibitor to overcome chemotherapy resistance in leukemic cells

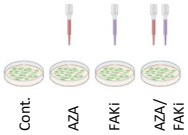


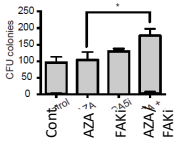
Aim 1





Aim 2





Hypothesis: Primary AZA resistance in leukemic cells is a result of altered adhesion and cell cycle exit and can be overcome by inhibiting integrins and their downstream signaling pathways.

Aims:

1. Determine the optimal concentration for in vitro use of small molecule focal adhesion kinase inhibitors (FAKi) in leukemic cell lines;
2. Test the effect of FAKi alone, and in combination with AZA, on growth kinetics and colony formation in leukemic cell lines, primary blood stem cells, and primary leukemic cells.

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