Tumor intrinsic and microenvironmental mechanisms driving drug combination efficacy and resistance in AML
Our Motivation

Stromal Cell

Cell Contact Signals

Cytokines Growth Factors

Tumor-Associated Macrophage

CD8+ T Cell

AML Cell

Oncogenic Signaling

Protein C

Actionable Target

Drug Combinations

Protein B

Protein A

Mutation

Immune Checkpoints
Long-Standing Collaborative Team Focused on Targeted Therapies for AML

900 AML Patient Samples

Genomics → Functional Screens

Computational Modeling → Target Validation

Clinical Trials

Immune Microenvironment

Our Beat AML Consortium
Drug Combinations to Circumvent Resistance (D2RC)-DSRC

Project 1: Genetics & Signaling


Project 2: Inflammatory, Immune & Stromal Microenvironment

Project 3: Drug Combinations
Project 1 Concept & Workflow

CRISPR/Cas Screens on Cell Lines
Identification of Gene Targets for Drug Sensitization and Resistance

Analysis of Beat AML Functional/Genomic Data
Nomination of Prioritized Drug Targets

Gene Editing to Produce Cell Line Models
Identification of Gene Targets in Mutational Subsets

Design of Custom CRISPR/Cas Panel & Testing on Primary AML Patient Samples

Nomination of Gene Targets, Drugs for Combination Testing in Project 3
Project 2 Concept & Workflow

Patient Sample Cytokine Profiling

- Cytokine Pathways Driving Drug Response/Resistance

Patient Stroma Profiling

- Stromal-Mediated Resistance Pathways

Immune Phenotyping, Functional Studies

- Identification of Patient Subsets for Immune Checkpoint Blockade

Nomination of Gene Targets, Drugs for Combination Testing in Project 3
Project 3 Concept & Workflow

Small-Molecule Pair Testing on AML Patient Samples
Prioritization of Most Active Small-Molecule Pairs

Small-Molecule Pair Testing with Single-Cell Resolution
Prioritization of Pairs with Efficacy in Sub-Populations

Small-Molecule/Immune Checkpoint Testing
Prioritization of Best Small-Molecule/Immune Checkpoint Pairs

Nominate 3-5 Combinations for 7x7 Matrix Testing to Optimize Dosing

Test Optimal Doses of Drug Combinations in AML Patient-Derived Xenografts for Efficacy and Pharmacokinetics
Center Resources & Collaborative Opportunities

**Biospecimen Resources**
- Primary AML patient samples (prospective and banked)
- Xenografted AML patient sample material
- Novel drug-resistant cell lines

**Cutting-Edge Technical Expertise**
- CRISPR-Cas screening capabilities (genome-wide and custom sgRNA panels)
- CyTOF panels as well as technical and computational expertise with CyTOF data
- Small-molecule libraries and drug screening capabilities
- Imaging-based assay for synergy of small-molecule + immune checkpoint drug pairs

**Problem Driven Methodology**
- HitWalker2 Prioritization Framework
- Cancer Targetome
- Modeling Tools integrated w/ Reactome Knowledgebase