U54 NCI Drug Resistance and Sensitivity Center (DRSC):
Oregon Health & Science University

Drug Combinations to Circumvent Resistance (D2CR)

Information for Potential Administrative Supplement Collaborators

Supplement Funding Announcement released April 11, 2018: Administrative Supplements to NCI Grant and Cooperative Agreement Awards to Support Collaborations with the Drug Resistance and Sensitivity Network (DRSN) (PAR-18-752): https://grants.nih.gov/grants/guide/pa-files/PAR-18-752.html.

Section 1: Drug Combinations to Circumvent Resistance (D2CR)-DRSC: Current DRSN-related research projects

Overarching DRSC Study Title:

Tumor Intrinsic and Microenvironmental Mechanisms Driving Drug Combination Efficacy and Resistance in AML

Primary Contact for Collaborative Supplement Inquiries

Name/Title: Jeffrey Tyner, PhD, Associate Professor of Cell, Developmental & Cancer Biology

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Research Project 1 Title: Genetics and Signaling of Drug Resistance and Sensitivity in AML Cell Lines, Xenografts, and Primary Patient Samples

Project 1 Summary: Genome-wide CRISPR/Cas screens on parental and drug-resistant AML cells are being conducted and results integrated with computational analysis of the largest functional genomic AML cohort in the world. The results are being used to nominate genes/pathways for validation in patient samples and cell lines using gene-edited models and to nominate drug combinations for analysis in Project 3.

Project 1 scientific assays and models used: Beat AML functional genomic dataset; Whole genome and custom CRISPR screening; AML patient-derived cell lines as well as drug-resistant and gene-edited versions of these lines; Primary AML patient samples; Cancer Targetome Knowledgebase for modeling of genes associated with drug sensitivity and resistance

Project 1 Lead

Name/Title: Shannon McWeeney and Brian Druker

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Research Project 2 Title: Impact of Leukemia Microenvironment on Response to Targeted Therapies in AML

Project 2 Summary: We are conducting inflammatory cytokine profiling of our large bank of AML patient samples, looking at both patient plasma and AML patient bone marrow stromal cells. We are also studying the reactive signature of these patient stromal cells upon exposure to specific drugs. High-parameter immunophenotyping and T-cell functional assays are being used to define the immune landscape and candidate immune-modulatory drugs are being tested in an immune-competent, spontaneous mouse model of AML. The downstream candidate targets resulting from this cumulative analysis of the AML microenvironment are being used to nominate drugs for combination with AML tumor-intrinsic targets.

Project 2 scientific assays and models used: Luminex testing for cytokine levels; Primary AML patient tumor cells, stromal cells, and plasma; Mass cytometry (CyTOF) panels and expertise; Genetically engineered AML mouse models; Joint pathway computational modeling

Project 2 Lead

Name/Title: Shannon McWeeney and Anupriya Agarwal

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Research Project 3 Title:

Project 3 Summary: Drug combinations, both in the form of small-molecule pairs and small-molecule/immune checkpoint pairs, from targets nominated in Project 1 and 2 are being tested *ex vivo* on primary AML patient samples using both a high-throughput assay for broad combination testing and a miniaturized single-cell imaging assay for testing multiple cell phenotypes in cell type subsets. In addition, we are conducting *in vivo* drug combination testing using AML patient-derived xenografts to evaluate combination efficacy and pharmacokinetic properties of the drug combinations.

Project 3 scientific assays and models used: Panel of single-agent and pairwise small-molecule combinations; Panel of small-molecule/immune checkpoint combinations; Miniaturized assay for functional testing of patient samples with single-cell resolution and multi-parameter readouts; AML patient derived xenografts; Primary AML patient samples; Statistical modeling of drug synergy/additivity/antagonism

Project 3 Lead

Name/Title: Jeff Tyner and Tomi Mori

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Section 2: DRSC information for a potential collaborative supplement study

Types of assays, technologies, or model systems that our DRSC would be willing to utilize and/or share with other researchers in cancer drug resistance, who might be a recipient of a DRSN supplement award: Biobank and prospective primary AML patient samples; AML patient-derived mouse xenograft models; Genetically engineered mouse models of spontaneous AML; AML cell lines as well as drug-resistant and gene-edited versions of these lines; large functional genomic dataset of AML patient samples (currently the largest in the world); multiple modalities of CRISPR and drug screening of primary patient samples; Multiple formats for computational modeling of genes and pathways involved with drug sensitivity and resistance; Multiple formats for modeling drug synergy

Our DRSC limits to collaborative interactions or assistance to supplement awardees: We do not have *a priori* limits on collaboration and would be interested in discussing all collaborative opportunities

Optimal year(s) for a collaborative supplement study with our DRSC (i.e., 2018, 2019, 2020, 2021, 2022): Any

Otherwise, any year would be acceptable with our DRSC, which is preferred by NCI to allow more flexibility for supplement studies:

Suggestions to potential supplement applicants: We would be interested in collaborating on novel analytical approaches to our AML datasets (genomic, drug response, CRISPR, cytokine, etc), experiments that make use of our drug-resistant and/or gene-edited cell lines, sharing of our patient sample and xenograft biobank for novel modeling and analytical approaches, and/or leveraging of our specialized expertise (CRISPR, CyTOF, imaging-based functional assay, computational approaches, etc.) for studies into other disease types.