U54 NCI Drug Resistance and Sensitivity Center (DRSC):
MSKCC-UW / Fred Hutch Prostate Cancer Drug Resistance and Sensitivity Center

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: MSKCC-UW/Fred Hutch Prostate Cancer Drug Resistance and Sensitivity Center: Current DRSN-related research projects

Overarching DRSC Study Title:

Mechanisms of Cancer Drug Resistance and Sensitivity (U54), RFA-CA-17-009

Primary Contact for Collaborative Supplement Inquiries

Name/Title: Cynthia Jung, PhD; Sr. Editor/Grant Writer, Human Oncology and Pathogenesis Program

Institution: Memorial Sloan Kettering Cancer Center

Email: jungc@mskcc.org

Phone: (646) 888-2774

Research Project 1 Title: Resistance caused by AR pathway reactivation

Project 1 Summary: We will address resistance caused by restored androgen receptor (AR) pathway function, which occurs in over ~50% of castrate-resistant prostate cancer (CRPC) patients. Analysis of preclinical models and patient samples has revealed two primary mechanisms responsible for restored AR function. One involves a bypass mechanism, whereby a related nuclear hormone receptor, the glucocorticoid receptor (GR), is upregulated and substitutes for AR (1). The second mechanism involves AR directly -- through gene amplification, mutation or the generation of alternative splice variants (2). Both mechanisms will be addressed in this project using a range of approaches, including epigenetic modulation of GR or AR using inhibitors of relevant chromatin modifying enzymes (BET, CBP/p300), direct inhibition of GR using a novel antagonist, and "synthetic" inhibition using targets emerging from shRNA and CRISPR screens conducted with enzalutamide.

Project 1 scientific assays and models used:

We possess a unique panel of human CRPC cell lines, organoids, and patient-derived xenografts that have been genomically annotated through whole exome sequencing and RNA-seq, and characterized for growth sensitivity to castration and enzalutamide. We will identify possible mechanisms of sensitivity and evaluate potential biomarkers through functional genomics approaches (e.g. ChIPSeq, ATACseq, RNAseq, and CRISPR or inducible shRNA library screens). The MSK-Fred-Hutch DRSC will collaborate with in-house biostatisticians and computational biologists to collect and analyze these data-intensive results.

Project 1 Lead

Name/Title: Charles Sawyers, MD; Chair, Human Oncology and Pathogenesis Program

Institution: Memorial Sloan Kettering Cancer Center

Email: sawyersc@mskcc.org

Research Project 2 Title: Reversing resistance caused by lineage plasticity through epigenetic therapy

Project 2 Summary: This project will address a distinct clinical context where resistance occurs in the absence of any evidence of restored androgen receptor (AR) pathway activity. In contrast to drugs that directly target oncogenes selectively expressed in tumor cells, AR pathway therapy is effective in prostate cancer because AR is required for survival of normal (and malignant) luminal epithelial cells. Therefore, one mechanism of escape is through transition to a non-luminal state (e.g. basal-like or neuroendocrine-like prostate cancer) in which tumor cells are no longer dependent on AR for survival. We recently reported that the reprogramming factor SOX2 can cause this lineage transition in prostate, particularly in tumors that have mutations in TP53 and RB1 (3). We also have evidence that aberrant expression of a different master regulator transcription factor HNF4G, which specifies gastrointestinal lineage development, confers resistance to AR therapy due to similar changes in luminal identity (4). Conceptually we refer to these mechanisms as examples of lineage plasticity, which we postulate are driven by epigenetic reprogramming of luminal epithelial cells. This project will evaluate the role of three chromatin modifying enzymes in this process (EZH2, BET, CBP/p300) through preclinical studies of relevant inhibitors in organoid and PDX models, in association with mechanistic studies of their genome-wide effects on chromatin structure.

Project 2 scientific assays and models used: We will assay human castration-resistant prostate cancer (CRPC) cell lines, organoids, and patient-derived xenografts for growth sensitivity to inhibitors of EZH2, BET, and CBP/p300. We will evaluate lineage plasticity, mechanisms of sensitivity and potential biomarkers in this context through functional genomics approaches (e.g. ChIPSeq, Chemseq, RNAseq, CRISPR or inducible shRNA library screens, immunohistochemistry, tissue microarrays, gene set enrichment analysis, quantitative RT-PCR). The MSK-Fred-Hutch DRSC will collaborate with in-house biostatisticians and computational biologists to collect and analyze these data-intensive results.

Project 2 Lead

Name/Title: Yu Chen, MD PhD; Assistant Member, Human Oncology and Pathogenesis Program; Assistant Attending, Medicine

Institution: Memorial Sloan Kettering Cancer Center

Email: cheny1@mskcc.org

Research Project 3 Title: Combination trials with kinase inhibitors to prolong response to AR therapy

Project 3 Summary: Project 3 focuses on the role of kinase inhibitors as an adjunct to androgen receptor (AR) pathway therapy in two distinct contexts – PI3K/AKT activation in tumors with PTEN loss and FGFR activation in tumors with autocrine FGF8/FGF9 production. Our preliminary studies have identified key roles for signal transduction pathways involving kinases that mediate resistance via restored AR pathway function, or alternatively in the absence of AR activity. A recent randomized phase 2 clinical study showed improved time to progression in CRPC patients treated with abiraterone plus an AKT kinase inhibitor (ipatasertib) versus abiraterone alone, with the clinical benefit restricted to those with PTEN null tumors (ASCO, 2016). This clinical result confirms predictions from earlier preclinical studies by our group that combined inhibition of both AR and PI3K/AKT pathways would be necessary in PTEN null cancers due to reciprocal negative feedback between the pathways (5). Based on this clinical success, we will evaluate the activity of this combination regimen in our organoid and patient-derived xenograft (PDX) models. We will also evaluate combination regimens involving isoform-selective PI3K inhibitors and inhibitors of HER2/HER3 feedback. In parallel, we will study inhibitors of FGFR kinase signaling in tumors with elevated expression of FGF8/FGF9, which define a subset of basal epithelial cancers with low or absent AR expression (that are also negative for neuroendocrine markers)

Project 3 scientific assays and models used: We will perform co-clinical trials in PDX models, focusing on AR combination therapy regimens with PI3K and FGFR inhibitors, and will assay sensitivity by measuring serum PSA (ELISA), tumor volume, and AR target gene expression using standard molecular and pathologic assays (e.g. DNA, RNA, western blots; immunohistochemistry, PTEN genomic loss/mutation). To investigate mechanisms of sensitivity and resistance, we will employ genomics and transcriptomics approaches (exome sequencing, RNAseq, CRISPR, shRNA knock-down, cDNA overexpression) to identify and interrogate the involvement of potential pathways in PDX models, as well as human CRPC cell lines and organoids. The MSK-Fred-Hutch DRSC will collaborate with in-house biostatisticians and computational biologists to collect and analyze these data-intensive results.

Project 3 Lead

Name/Title: Brett Carver, MD; Associate Attending, Surgery

Institution: Memorial Sloan Kettering Cancer Center

Email: carverb@mskcc.org

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:

The common theme linking projects in our DRSC is resistance to androgen receptor pathway therapy and pre-clinical evaluation of promising, rationally-designed combination therapy regimens to overcome resistance to AR therapy, using compounds that have progressed to human studies. While each project addresses a distinct molecular mechanism and its role in resistance to AR therapy, the experimental framework of every project incorporates rapid preclinical assessment of candidate therapeutics using a panel of genomically annotated CPRC human cell lines, organoids and PDX models, a collection of model systems that is unique to our center.

Potential areas of synergy with supplement awardees may include:

- testing novel, alternative inhibitors of EZH2, BET, AKT, FGFR, glucocorticoid receptor and CBP/P300, that have demonstrated preclinical efficacy in other model systems (e.g. hormone driven cancers, kinase-targeted combination therapies)
- genomic and clinical data sharing to help evaluate potential biomarkers of treatment response in CRPC prostate cancer
- genomic and clinical data sharing provided to others for comparative evaluation of biomarkers among different cancers
- novel reagents including prostate organoid lines, engineered cell lines, plasmids, and genetically engineered mouse models

Our DRSC limits to collaborative interactions or assistance to supplement awardees:

Some inhibitors being tested in this grant are proprietary compounds made available to us under Material Transfer Agreements directly with the sponsor under typical terms acceptable to our academic centers and HHMI. These terms may affect where experiments may be conducted and which materials may be shared. However, we can facilitate other DRSC members by providing contact information to obtain MTA for proprietary reagents.

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

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

Any year.

Suggestions to potential supplement applicants:

Potential supplement applicants who are interested in collaborating with the MSK/UW Prostate Cancer DRSC should provide a one-page summary that mentions their research interests, how their research would integrate with a specific project and the overall goals of the Prostate Cancer DRSC, and how a DRSC supplement award might benefit the awardee and/or our center.

1. Arora VK, Schenkein E, Murali R, Subudhi SK, Wongvipat J, Balbas MD, Shah N, Cai L, Efstathiou E, Logothetis C, Zheng D, Sawyers CL. Glucocorticoid receptor confers resistance to antiandrogens by bypassing androgen receptor blockade. Cell. 2013;155(6):1309-22. Epub 2013/12/10. doi: 10.1016/j.cell.2013.11.012. PubMed PMID: 24315100; PMCID: PMC3932525.

2. Watson PA, Arora VK, Sawyers CL. Emerging mechanisms of resistance to androgen receptor inhibitors in prostate cancer. Nat Rev Cancer. 2015;15(12):701-11. doi: 10.1038/nrc4016. PubMed PMID: 26563462; PMCID: PMC4771416.

3. Fujiki Y, Miyata N, Mukai S, Okumoto K, Cheng EH. BAK regulates catalase release from peroxisomes. Molecular & cellular oncology. 2017;4(3):e1306610. Epub 2017/06/16. doi: 10.1080/23723556.2017.1306610. PubMed PMID: 28616584; PMCID: PMC5462519.

4. Shukla S, Cyrta J, Murphy DA, Walczak EG, Ran L, Agrawal P, Xie Y, Chen Y, Wang S, Zhan Y, Wong WPE, Sboner A, Beltran H, Mosquera JM, Sher J, Cao Z, Wongvipat J, Koche RP, Gopalan A, Zheng D, Rubin MA, Scher HI, Chi P, Chen Y. Aberrant activation of a gastrointestinal transcriptional circuit in prostate cancer mediates castration resistance. Cancer Cell. 2017, in press.

5. Carver BS, Chapinski C, Wongvipat J, Hieronymus H, Chen Y, Chandarlapaty S, Arora VK, Le C, Koutcher J, Scher H, Scardino PT, Rosen N, Sawyers CL. Reciprocal feedback regulation of PI3K and androgen receptor signaling in PTEN-deficient prostate cancer. Cancer Cell. 2011;19(5):575-86. doi: 10.1016/j.ccr.2011.04.008. PubMed PMID: 21575859; PMCID: PMC3142785.