U54 NCI Drug Resistance and Sensitivity Center (DRSC):

Massachusetts General Hospital Cancer Center / Broad Institute / Koch Institute

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: Massachusetts General Hospital Cancer Center: Current DRSN-related research projects

Overarching DRSC Study Title: "An integrated translational approach to overcome drug resistance"
Primary Contact for Collaborative Supplement Inquiries Name/Title: Ryan B. Corcoran, M.D. Ph.D. Institution: Massachusetts General Hospital Cancer Center Email: RBCORCORAN@PARTNERS.ORG Phone: 617-726-8599 (office)
Research Project 1 Title: Overcoming adaptive resistance in cancers with RAS pathway activation
Project 1 Summary: The goals of this project are to establish a large collection of CRC and melanoma "organoids" in 3D culture for comprehensive in vitro and in vivo characterization of signaling and adaptive feedback to develop novel therapeutic strategies for future clinical trials, compare feedback networks between CRC and melanoma to provide additional therapeutic insight, evaluate newer MAPK inhibitor classes, and perform a comprehensive assessment of adaptive feedback networks in these models using cutting-edge phospho-proteomic and transcriptomic analyses, in parallel with unbiased functional genomic and high-throughput combination drug screens. We will integrate these data to design novel therapeutic approaches to improve efficacy in CRC and melanoma with RAS pathway activation, using innovative patient-derived mouse tumor models.
Project 1 scientific assays and models used: Patient-derived mouse models of colorectal cancer and metastasis
Project 1 Lead Name/Title: Ryan Corcoran, MD PhD; Cyril Benes, PhD Institution: Massachusetts General Hospital Cancer Center Email: rbcorcoran@partners.org; CBENES@mgh.harvard.edu
Research Project 2 Title: Surmounting the heterogeneity of acquired resistance to RTK inhibition
Project 2 Summary: The goals of this project are to perform a comprehensive assessment of acquired resistance to MET inhibition, employ a systematic liquid biopsy platform for circulating tumor DNA analysis, coupled with serial tumor biopsies, and a rapid autopsy program, to define the molecular landscape and heterogeneity of acquired resistance to MET inhibition, attempt to identify common signaling nodes upon which multiple resistance mechanisms converge, and evaluate the potential for sequential inhibition strategies coupled with real-time ctDNA monitoring to overcome multiple resistance mechanisms that do not share a common signaling output.
Project 2 scientific assays and models used: Tumor xenograft models using RAS mutant cell lines

Project 2 Lead

Name/Title: Ryan Corcoran, MD PhD; Rebecca Heist, MD

Institution: Massachusetts General Hospital Cancer Center

Email: rbcorcoran@partners.org; RHEIST@PARTNERS.ORG

Research Project 3 Title: Identifying and overcoming mechanisms of resistance to immune checkpoint inhibition

Project 3 Summary: The goals of this project are to analyze the evolution of B2M mutations in melanoma and NSCLC patients receiving anti-PD1 therapy and thus create a method for real time tracking of resistance to checkpoint blockade therapies, test the role of epigenetic silencing of B2M to explain the loss of its expression in tumors missing one copy of the gene, attempt to restore B2M expression by modulating epigenetic regulators, and activate natural killer (NK) cells in an attempt to kill cells lacking B2M in mouse models of melanoma.

Project 3 scientific assays and models used: Tumor xenograft models to study immune response

Project 3 Lead

Name/Title: Nir Hacohen, Ph.D.; Keith Flaherty MD

Institution: Massachusetts General Hospital Cancer Center

Email: NHACOHEN@mgh.harvard.edu; kflaherty@mgh.harvard.edu

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:

Organoids generated from project 1. Sequencing/genomic data from paired pre-treatment and post-progression biopsies from projects 2 and 3.

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

No definitive limits

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 OK

Suggestions to potential supplement applicants:

Novel technologies to characterize or test organoid models, or studies in unique molecular subtypes of organoid models encouraged.