An Integrated Translational Approach to Overcome Drug Resistance

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Overview

• Bypass resistance mechanisms
  • (genetic and adaptive)

• 3 drug classes
  • MAPK, RTK, Immune checkpoint inhibitors

• Each project covers 2 cancer types
  • GI, lung, melanoma

• Highly integrated translational platforms:
  • Liquid biopsy, patient-derived tumor models, rapid autopsy, WES/RNAseq, functional genomic screens, preclinical mouse models, high-throughput drug screen covering CTEP portfolio
Project 1: Overcoming adaptive resistance in cancers with RAS pathway activation

• **Rationale:** complex feedback networks leading to MAPK reactivation limit clinical efficacy

• Aim 1: Establish and characterize a large collection of patient-derived tumor models with RAS pathway activating mutations.

• Aim 2: Define and target critical adaptive feedback networks driving MAPK reactivation.

• Aim 3: Elucidate target pathways that are synthetically lethal with optimal MAPK inhibition.

• Aim 4: Evaluate novel therapeutic strategies in innovative patient organoid-derived in vivo models.
Project 2: Surmounting the heterogeneity of acquired resistance to RTK inhibition

• **Rationale:** acquired resistance involves emergence of heterogeneous resistant subclones, complicating strategies to overcome

• Aim 1: Define the molecular landscape and heterogeneity of acquired resistance to MET inhibition.
  • Serial liquid biopsy, paired tumor biopsies, rapid autopsy

• Aim 2: Elucidate molecular mechanisms of resistance and identify convergent signaling nodes.

• Aim 3: Evaluate novel convergent and sequential therapeutic strategies to overcome heterogeneity.
Project 3: Identifying and overcoming mechanisms of acquired resistance to immune checkpoint inhibition

- **Rationale:** understanding mechanisms of acquired resistance to immunotherapy will help guide future strategies

- **Aim 1:** Identify and monitor the emergence of \(B2M\) mutations in tumors and circulating free DNA (cfDNA) in patients with solid tumors treated with anti-PD-1 therapy.

- **Aim 2:** Elucidate the influence of epigenetic silencing of \(B2M\) in patients with solid tumors treated with anti-PD-1 therapy.

- **Aim 3:** Develop strategies to overcome PD-1 inhibitor resistance mediated by \(B2M\) loss utilizing preclinical models and agents within and outside the CTEP portfolio.
Team members

MAPK

Project 1:
- Ryan Corcoran
- Ryan Sullivan
- Keith Flaherty
- Cyril Benes
- Wilhelm Haas
- Gad Getz
- Cory Johannessen (Broad)
- Omer Yilmaz (MIT)

RTK

Project 2:
- Ryan Corcoran
- Cyril Benes
- Gad Getz
- Cory Johannessen (Broad)
- Victor Adalsteinsson (Broad)
- Alice Shaw
- Aaron Hata
- Rebecca Heist
- Dejan Juric

Immune checkpoint

Project 3:
- Keith Flaherty
- Ryan Sullivan
- Victor Adalsteinsson (Broad)
- Alice Shaw
- Ryan Corcoran
- Nir Hacohen
- Genevieve Boland
Shared resources for DRSC network

--A large clinically-annotated database of genomic data from whole-exome sequencing and RNAseq, which can be mined to address key questions related to drug resistance.

--A large repertoire of patient-derived tumor models and organoid lines. Most will have comprehensive genomic characterization. Many will be from resistant tumor biopsies or paired pre- and post-progression biopsies.