An Integrated Translational Approach to Overcome Drug Resistance

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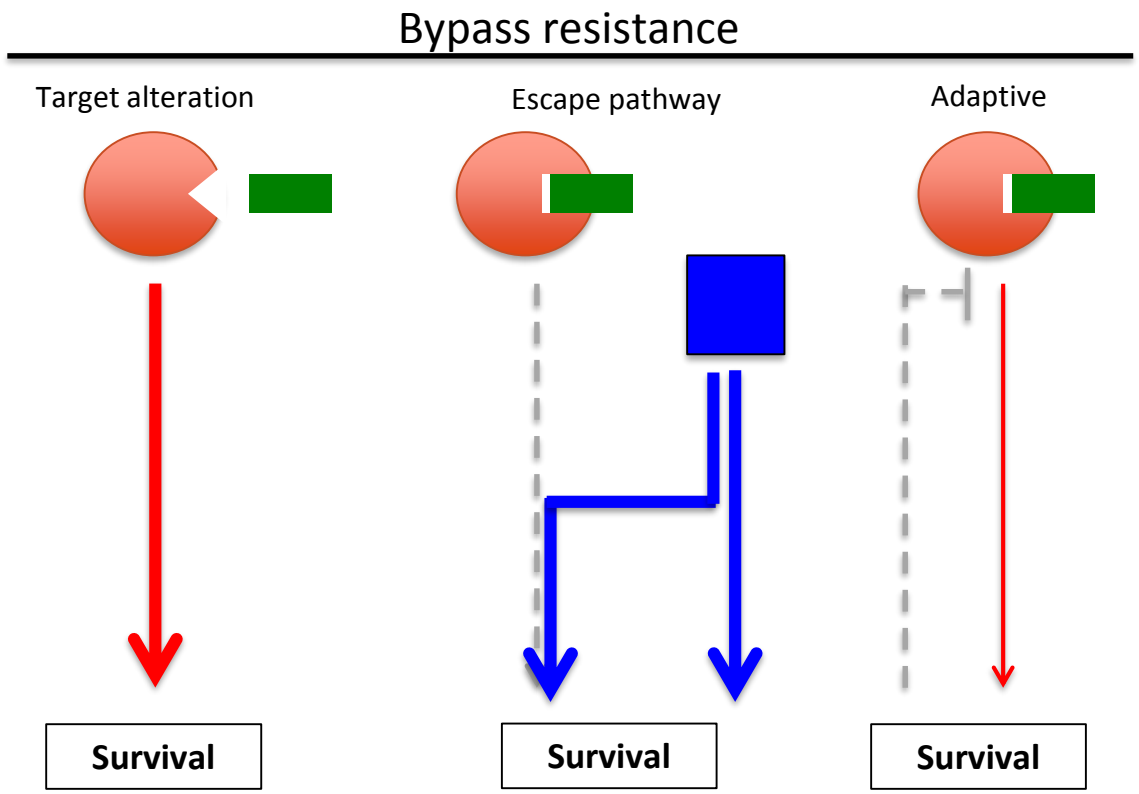
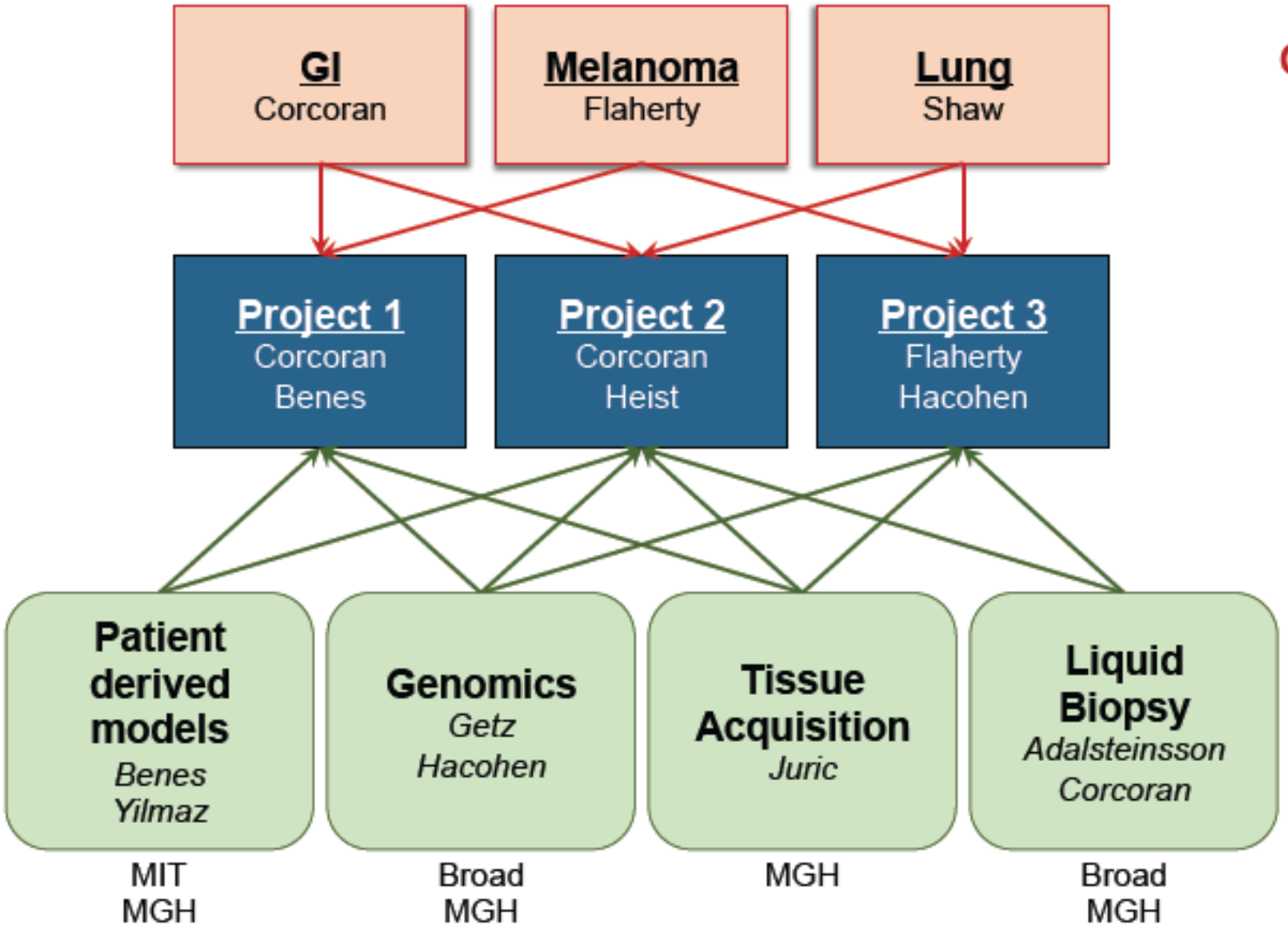
U54 DRSC

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



Team Structure and Integration



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 sublcones, 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.