Therapeutic Target Identification to Overcome Drug Resistance

Presenter: Michael Graham Espey, PhD, Division of Cancer Biology

*On behalf of the "Therapeutic Resistance" Moonshot Implementation Team**

NCI Board of Scientific Advisors Meeting, March 25, 2019
Concept Proposal: Mechanisms of Cancer Drug Resistance Competing Revisions (RFA)

Moonshot Blue Ribbon Panel report recommendation:
"Launch interdisciplinary studies to delineate the range of genetic, molecular, cellular, and physiological mechanisms that lead cancer cells to become resistant to previously effective treatments, with the goal of informing the development and clinical testing of new therapies…"

Today's RFA Concept presentation:

- Brief overview of the Drug Resistance & Sensitivity Network (DRSN)
  - ✓ Funded under RFA-CA-17-009
  - ✓ Composed of U54 centers
  - ✓ Launched in FY18

- New FY20 initiative: "*Mechanisms of Cancer Drug Resistance Competing Revisions*"
  - ✓ Rationale for a complementary initiative
    - Leverage the wider range of expertise in the NCI portfolio
    - Encourage collaborative projects
    - Incentivize-accelerate ideas not (well) represented in the DRSN
  - ✓ Description of Competing Revision Supplement mechanism

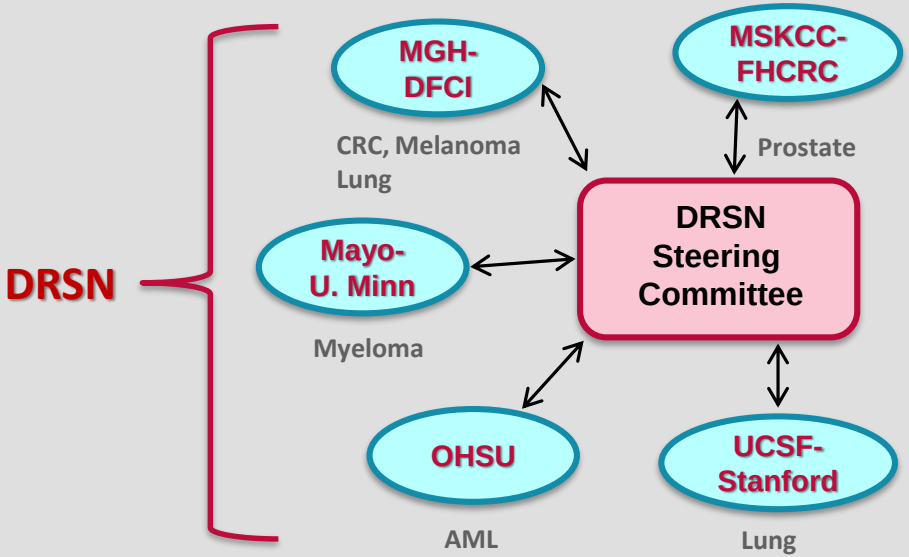
Drug Resistance & Sensitivity Network

(RFA-CA-17-009: U54)

Overarching Focus:

To address the BRP recommendation on establishment of multi-disciplinary research teams to elucidate the complex mechanistic underpinnings of drug resistance and to inform drug development efforts and future clinical trials:

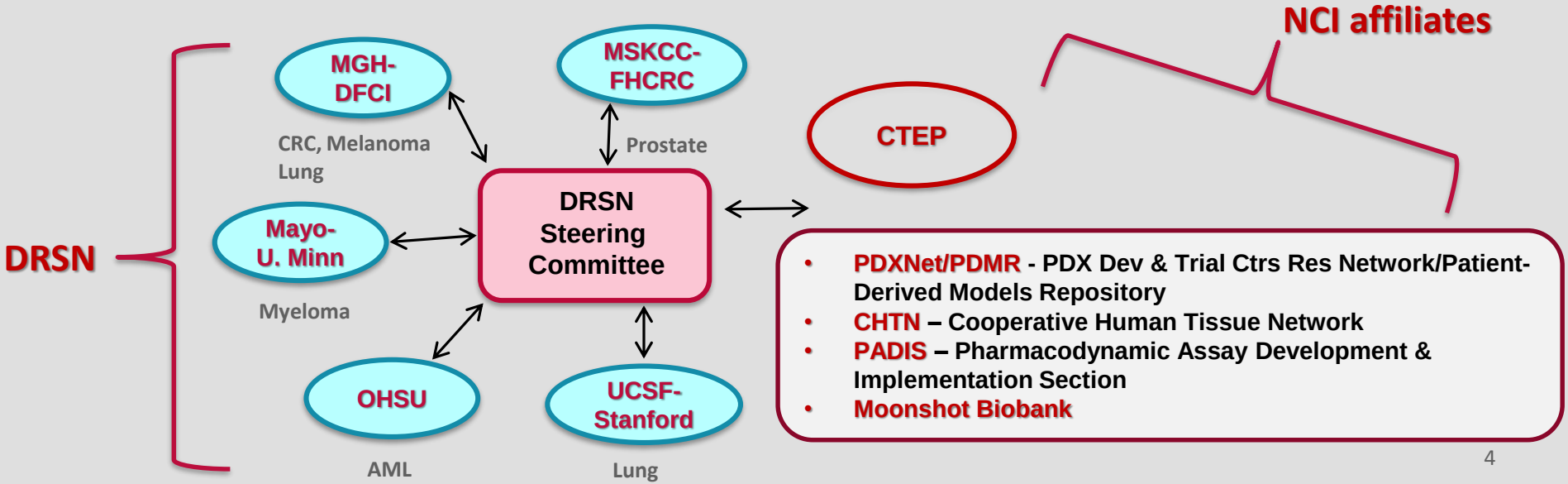
- A Drug Resistance & Sensitivity Network (**DRSN**) composed of 5 x U54s, launched in FY18;
- These U54s are primarily disease-specific.



Drug Resistance & Sensitivity Network

(RFA-CA-17-009: U54)

- Preference given to studies involving NCI CTEP IND agents;
- NCI-IND agents (n= >60) include a wide variety of small molecule and antibody inhibitors that impact classic oncogenic signaling, epigenetic regulators & checkpoint targets (e.g., RTK, MAPK, AR, EZH2, PDL1).



FY20 Moonshot RFA Concept: Mechanisms of Cancer Drug Resistance - Competing Revision Supplements

Overarching Goal:

The goal of the Competing Revision initiative is to accelerate evaluation of: 1) new and/or under-explored mechanisms of drug resistance, 2) new approaches with classical targets, and, 3) promote collaborative efforts that complement on-going DRSN studies.

- Leverage active broad-based NCI research programs that have the capability to incorporate new directions and accompanying know-how/expertise;
- Competing Revision opportunities will incentivize new collaboration, enable testing of new concepts in drug resistance, and accelerate on-going activities represented in the DRSN;
- Identify and characterize new leads for DRSN and other NCI activities;
- Potential to inform and accelerate the development of therapeutic targets in a synergistic manner;
- Opportunity to expand and diversify the current DRSN.

FY20 Moonshot RFA Concept: Mechanisms of Cancer Drug Resistance - Competing Revision Supplements

Clarification points per BSA subcommittee members

Competing Revision vs. Admin. Supplement (defined):

- Competing Revision Supplements are peer reviewed, and support new aims to an existing award;
- Administrative Supplements are programmatically reviewed, and must be within scope of the parent grant;

Portfolio Analysis & Target Audience:

- Approx. 75-100 active NCI awards (R01, U01, P01, U54, P50) query under the term "drug/therapeutic resistance;"
- However, any NCI awards (R01, U01, P01, U54, P50) with ≥ 3 yrs. of time remaining would be eligible for this RFA;
- Moonshot Program Directors will conduct PI outreach to promote and advise on the goals of the RFA concept;

Rationale for use of Competing Revisions mechanism vs. new awards:

- Moonshot Competing Revisions can quickly enable investigation of new leads consistent with the BRP recommendation to accelerate research on cancer drug resistance (e.g., *hit the ground running*);
- Moonshot Competing Revisions would be "in phase" with the time remaining for FY18 funded DRSN U54s, (*strengthening hub-n-spoke character of DRSN*).

FY20 Moonshot RFA Concept: Mechanisms of Cancer Drug Resistance - Competing Revision Supplements

New directions in this Concept to complement DRSN's focus on "classical targets," fall into two broad categories:

- Elucidation of intra-tumoral cellular state diversity and spatiotemporal evolution of resistance;
- Characterization of passenger-driven and organelle-based adaptive responses;
- Identification of intrinsic or acquired mechanisms of age- and ethnicity- related therapy resistance;
- Comprehensive analysis of wide-ranging cell death and survival pathways;
- Defining the role of microbiota in tumor progression and resistance;

Biology

- Testing methodologies and technologies (such as those generated by the Moonshot tech. dev. initiatives) that could accelerate multiplexed monitoring and readouts;
- Development of novel or enhanced disease-relevant models, integration of existing instrumentation or new technology enabled endpoints.

Technology

FY20 Moonshot RFA Concept: Mechanisms of Cancer Drug Resistance - Competing Revision Supplements

Funding Structure & Expectations:

- Variety of mechanisms are eligible (R01, U01, P01, U54, P50);
- Programmatic expectations for responsiveness:
  - involves multi-disciplinary scientific collaborations;
  - brings together complementary expertise;
  - promotes infusion of a new cadre of investigators into DRSN efforts; and
  - accelerates ideas that align and integrate with the overarching objectives of the BRP recommendation;
- Anticipate funding **5 to 10** new competing supplements (4 receipt dates over 2 years);
- Budgetary requests may not exceed **$250,000 D.C./year** for the life of the project;
- Applicants must have a **minimum of 3 years** left of funding on the parent grant (at the time of application);

TOTAL COST = $4.2M/year (12.6M)

FY20 Moonshot RFA Concept: Mechanisms of Cancer Drug Resistance - Competing Revision Supplements (R01, U01, P01, U54, P50)

Review Criteria:

- Extent to which the revision promotes and accelerates research in emerging and underexplored directions in the cancer resistance/sensitivity research arena (not emphasized in current DRSN U54s);
- Novelty of approach and breadth of expertise that will expand, inform and enhance the DRSN and the development of validated therapeutic targets;
- Degree of potential integration and synergy between NCI research programs (including the DRSN); and ability to leverage unique/complementary resources and cores;
- DEA convened SEP panel (e.g., OIA SEP).

FY20 Moonshot RFA Concept: Mechanisms of Cancer Drug Resistance - Competing Revision Supplements

Funding Structure & Expectations:

- Variety of mechanisms are eligible (R01, U01, P01, U54, P50);
- Programmatic expectations for responsiveness:
  - involves multi-disciplinary scientific collaborations;
  - brings together complementary expertise;
  - promotes infusion of a new cadre of investigators into DRSN efforts; and
  - accelerates ideas that align and integrate with the overarching objectives of the BRP recommendation;
- Anticipate funding **5 to 10** new competing supplements (4 receipt dates over 2 years);
- Budgetary requests may not exceed **$250,000 D.C./year** for the life of the project;
- Applicants must have a **minimum of 3 years** left of funding on the parent grant (at the time of application);

TOTAL COST = $4.2M/year (12.6M)

DRSN Centers Areas of Research Focus

The DSRN can currently be characterized as having a primary focus on classic oncogenic signaling & checkpoint targets

- MGH-Broad-MIT "Integrated Approach to Overcome Drug Resistance"
  - Resistance mechanisms to MAPK, RTK and immune checkpoint inhibitors in lung, melanoma and GI cancers;
- MSKCC-FHCRC/UW "Prostate Cancer DRSC"
  - Mechanistic studies on agents that inhibit AR-pathway resistance: nuclear hormone receptors, chromatin modifiers, and kinases;
- Mayo-U Minn "Overcoming Drug Resistance in Multiple Myeloma"
  - Rational therapeutic development of immune modulatory drugs and proteasome inhibitors.
- OHSU "Drug Combination to Circumvent Resistance (D2CR) in AML"
  - Combination therapy evaluation for FLT3, MEK, JAK, BCL2 pathways, inflammatory cytokines, and immune checkpoint targets.
- UCSF-Stanford "Bay Area Team Against Resistance U54 Project (BATAR-UP)"
  - Molecular and cellular dissection of residual EGFR-mutant and ALK-rearranged lung cancers treated with TKIs or anti-PD1 immunotherapy.