Reissuance of *D*rug *R*esistance and *S*ensitivity *N*etwork

***A*cquired *R*esistance to *T*herapy *N*etwork** (ARTNet) RFA Concept

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Therapeutic Target Identification to Overcome Drug Resistance

Moonshot Blue Ribbon Panel report recommendation:

C. Develop ways to overcome cancer's resistance to therapy

- Identify therapeutic targets to overcome drug resistance through studies that determine the mechanisms that lead cancer cells to become resistant to previously effective treatments.
- Launch an **interdisciplinary initiative** to determine points of cancer cell weakness, known as vulnerabilities, that can be used as targets for the development of new therapies that **prevent or overcome a tumor's ability to resist or become non-responsive to cancer therapies**.

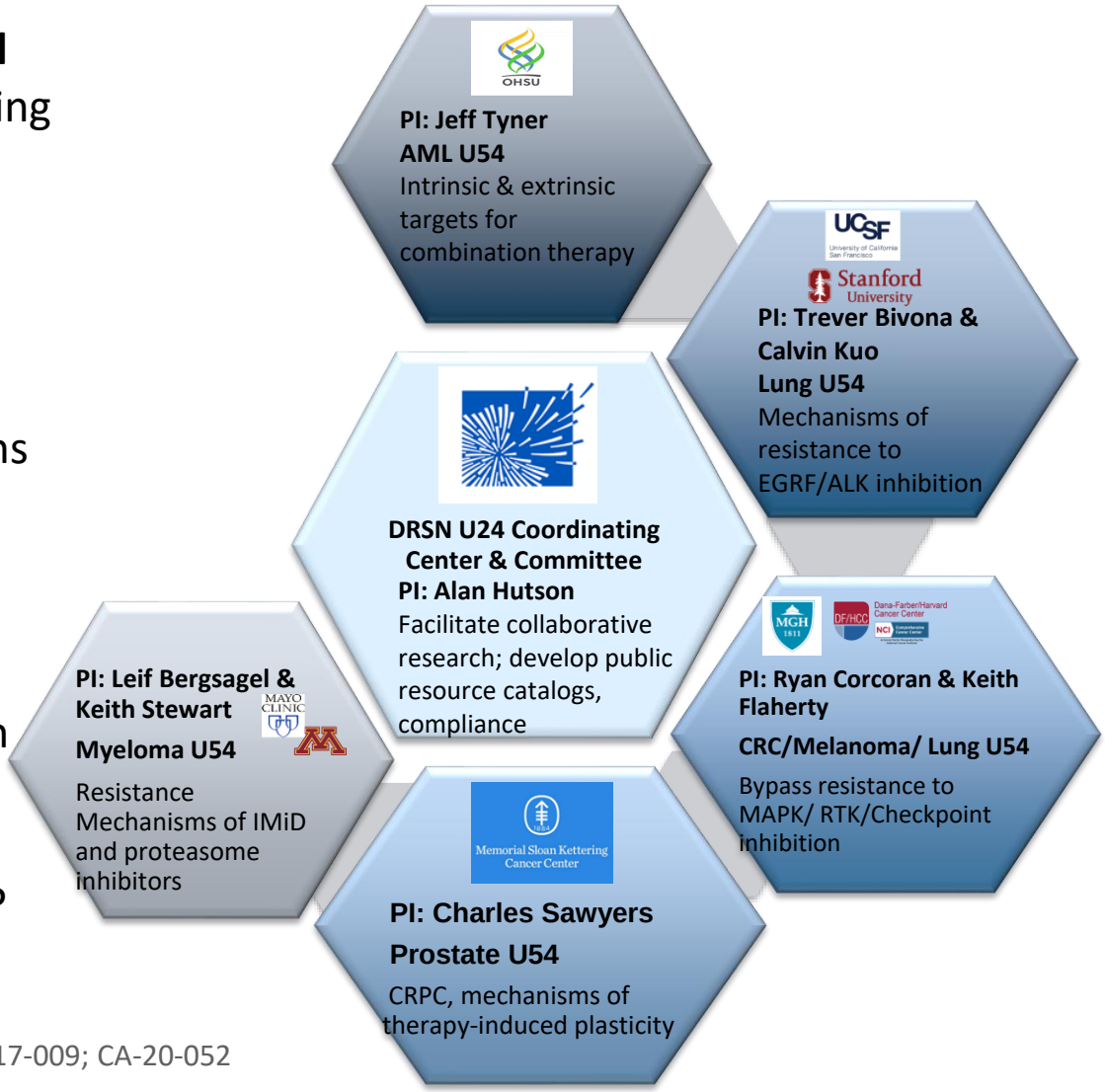
Understanding both the *biological* and *clinical challenges* of resistance to cancer therapy is a priority

- **Acquired resistance** is a major cause of **treatment failure**;
- Understanding the **biology of tumor adaptation**, the underpinnings of acquired resistance, and disease recurrence require urgent attention;
- **Focused, coordinated, and iterative investigations** from both the pre-clinical modeling and clinical perspectives are needed;
- **Bridging the gap** between basic and clinical translational research is the ultimate goal to overcome resistance and improve sensitivity.

Drug Resistance and Sensitivity Network (DRSN)

Overview and accomplishments

- **Programmatic need to provide a better integrated basic-preclinical research arm** focused on developing evidence to inform strategies to overcoming drug resistance
- A **Cancer Moonshot initiative** to break silos and accelerate clinical research of drug combinations
- **High productivity**: 134 publications partly funded by DRSN Moonshot funds and cited 5161 times
- 12 supplements and 2 revision projects initiated
- Recently funded U24 coordination center (funded Q3/4 2020)
- Initiated 25 clinical trials with IND agents, including 2 from NCI/CTEP



CANCER MOONSHOT RESEARCH INITIATIVES

DRSN Drug Resistance and Sensitivity Network

RFA CA-17-009; CA-20-052

DRSN supplement and revision program

RFA CA-18-752; CA-19-049, -050, -051, -052, -053

- DRSN supplement program created the **opportunity for non-DRSN investigators to collaborate** with DRSN laboratories
  - Non-DRSN investigators applied for supplements to other NCI awardees describing collaboration with DRSN;
  - If awarded, the **collaborating DRSN investigator received an additional supplement** to the U54 to fund the collaboration
  - Successful in providing DRSN access to non-DRSN investigators

Supplement/Revision Projects:

PI: Kaufman
AML
Role of NK cell mediating sensitivity & resistance

PI: Boise
Myeloma
Determine chromatin accessibility & CD86 with IMiD-induced changes

PI: McMahon
Lung
Discover how WNT-β–catenin signaling promotes BRAFV600E-induced lung tumorigenesis

PI: Hsieh
Prostate
EZH2 suppression of Arhi and ARIo CRPC; epigenetic vulnerabilities unique to ARIo or ARhi CRPC

PI: Roth
Lung
EGFR-mut. LunPDX model to explore TAMs; response to EGFR pathway- targeted and cognate resistance –assoc. targets

PI: Goodrich
Prostate
EZH2 suppression on Arhi and ARIo CRPC; epigenetic vulnerabilities unique to ARIo or Arhi CRPC

PI: Gillespie &
Hjelmeland
GBM
GBM models, TME influence on acquired and intrinsic resistance

PI: Alumkal &
Chinnaiyan
Neuroendo-Prostate
Targeting LSD1 histone demethylase and differentiation in stem cells

DRSN External Evaluation:

Areas needing optimization

- Individual sites are productive in new drug development and systematic testing of drug combinations; yet need a more specific focus, increase in hypothesis testing and further consideration and evaluation prior to validation in clinical trials.

- DRSN organizationally needs to increase Network functionality

Path forward

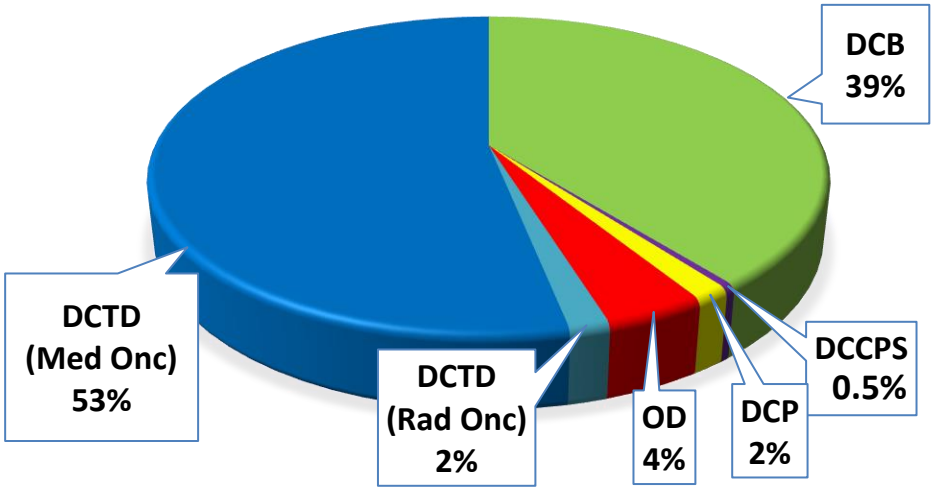
- Make the range of existing treatments better - not new target discovery

- Prioritize focus on acquired resistance
  - Need models of recurrence (in contrast to treatment naïve, intrinsic mutations)
  - Place emphasis on mechanisms of adaptive response to therapies
  - Strengthen ways to connect pre-clinical findings with clinical validation

- Tying basic and translational research through hypothesis testing approaches

Portfolio Analysis

DISTRIBUTION OF THERAPY RESISTANCE AWARDS BY NCI DOC



Criteria:

- RCDC terms related to "therapy or drug resistance"
- N = 479 active awards (as of Jan 2021)
- Mechanisms = R01, R00, R35, R37, P01, U01, U54, UM1

- DCB and DCTD respectively *manage approx. 40% and 55% of the "resistance portfolio;"* however, there are **no jointly held Programs that connect & integrate across the basic-preclinical-clinical spectrum**;

- Vast majority of current awards evaluate cancer cell intrinsic resistance processes leaving a **paucity of research focused on acquired resistance and disease recurrence**; and,

- Current portfolio is **underweighted on research** that incorporates the **cellular constituents and complexities of the tumor microenvironment relative to cancer cell autonomous processes**.

Proposed Program:
*A*cquired *R*esistance to *T*herapy *Net*work (ARTNet)

- Build upon and **expand the scope** of the original DRSN
- Focused on **acquired resistance/sensitivity** and **modeling cancer recurrence**
- Incorporate a wider range of treatment modalities:
  - Chemotherapeutics, radiation, targeted agents, immuno-onc., etc.
- Establish an **iterative bridge between basic-mechanistic, preclinical and clinical-translational science**

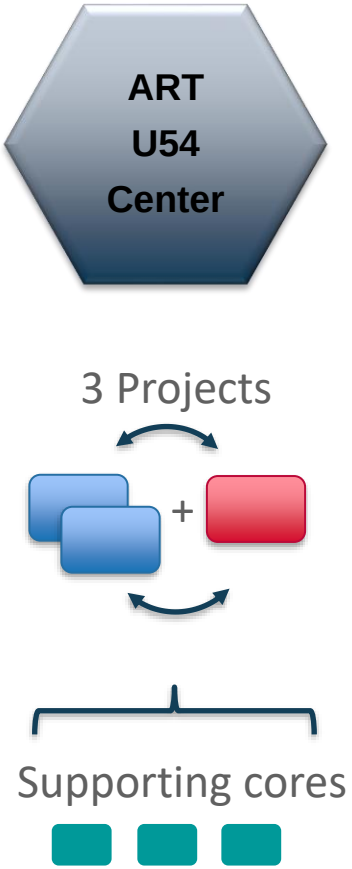
- **Translation of acquired resistance mechanisms and associated therapeutics, combinations or treatment modalities into clinically-feasible trials**

Understanding Therapy Resistance and Sensitivity:

Understudied and Underdeveloped Areas

- Acquired resistance pathways – including regulatory nodes involved in **varying cell state dynamics** (senescence, quiescence, dormancy, stemness) and other adaptive mechanisms – in resistance and recurrence;
- Role of the **tumor microenvironmental response (originating in stromal cells, ECM)** in driving therapy resistance;
- Understanding the **rewiring of multiple cell death and therapy survival pathways** involving organelle networks and adaptive cell-cell cooperation;
- Defining the role of **host context** and microbiota informing the trajectory of acquired resistance and therapeutic outcome;
- **Adaptive dose & timing regimens** of combined modality treatments (e.g., chemoradiation, synthetic lethal combinations); and,
- Greater emphasis on **disparities research.**

ARTNet U54 Center Organizational Requirements:



Required Structure 3 Projects

- Minimum of 2 **Basic - Mechanistic** Projects and
  1 **Pre-Clinical - Clinical** Project;

  OR

- Minimum of 2 **Pre-Clinical - Clinical** Projects and
  1 **Basic - Mechanistic** Project;
- Relevant Cores (e.g., models, -omics, biospecimen);

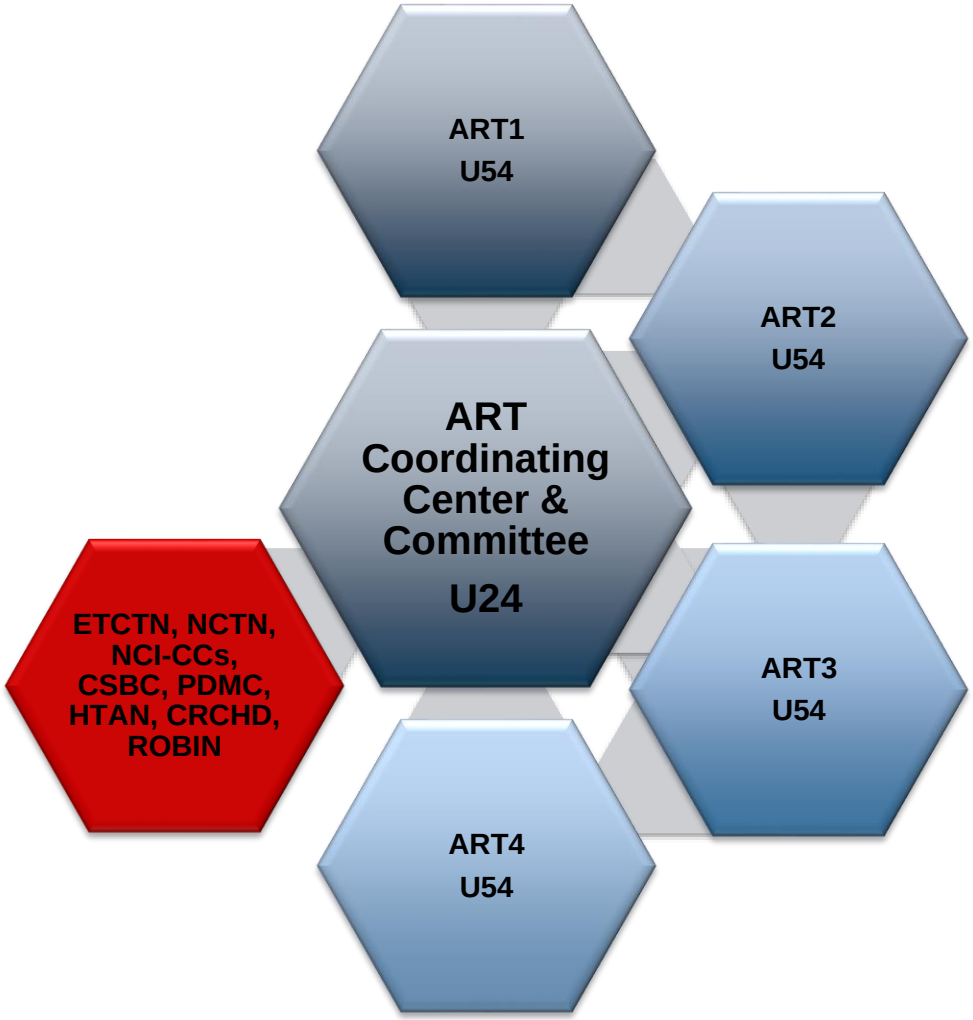
Thematic Focus

- Center is defined by a central hypothesis related to the mechanistic basis of acquired resistance;

Special Review Criteria

- Rationale and significance for chosen cancer and treatment types;
- Degree of innovation in predicting and thwarting acquired resistance; and,
- Level of iteration (=) between basic, preclinical, and clinical components;

ARTNet Structure and Networking



Structure

- **4-5 U54 research programs**
  - Complementary Multi-PI & integrated basic and translational research areas
  - Access to clinical specimens/derivatives (PDMx, organoids, cell lines) with computational/systems biology-based infrastructure
- **1 U24 Coordinating and data management center**

Networking and collaboration

- **Restricted funds** (~15%) for inter- and extra-U54 collaborations
- **Working groups** to address common goals, **challenges and opportunities**
  - Identify collaborative projects to support the basic-translational pipeline, including clinical drug development
  - Enhance and amplify the pre-clinical and pre-analytical basic understanding of resistance and sensitivity
- **Sharing** of tools, reagents and resources (facilitated by the coordinating center)
- **Leadership**, Steering Committee and Coordinating Center led meetings to **address clinical challenges and opportunities** with other basic and clinical research networks, e.g., ETCTN, NCTN, NCI-CCs, CSBC, PDMC, HTAN, CRCHD, ROBIN

Requested Funding for ARTNet	
Number of awards	4-5 U54s and 1 U24
Funding	**$7.6M TC per fiscal year**
Project Period	5 years
Restricted Fund (years 2-5)	15% Total Cost per award
Estimated Total Cost Requested	**$ 7.6M TC per fiscal year** **$ 38M TC for 5 years**

ARTNet Evaluation Criteria

- Collaborations and participation in new basic, preclinical and clinical pilot studies with clinical research networks (e.g., ETCTN, NCTN, CSBC, PDXNet, PDMC)
- Collection and sharing of curated human specimens for the development of advanced preclinical models for collaborative research in new directions
- Development, sharing and maintenance of catalogs for data sharing, software programs and preclinical models
- Degree of integration and synergy between the U54 sites and investigators
- Effectiveness in expanding original aims to include new aims using restricted
- Development, implementation and coordination of working groups to leverage common expertise, challenges and translational projects
- Publication of Center and collaborative research findings

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