

Drug Resistance and Sensitivity RFA Concept Presentation to Board of Scientific Advisors

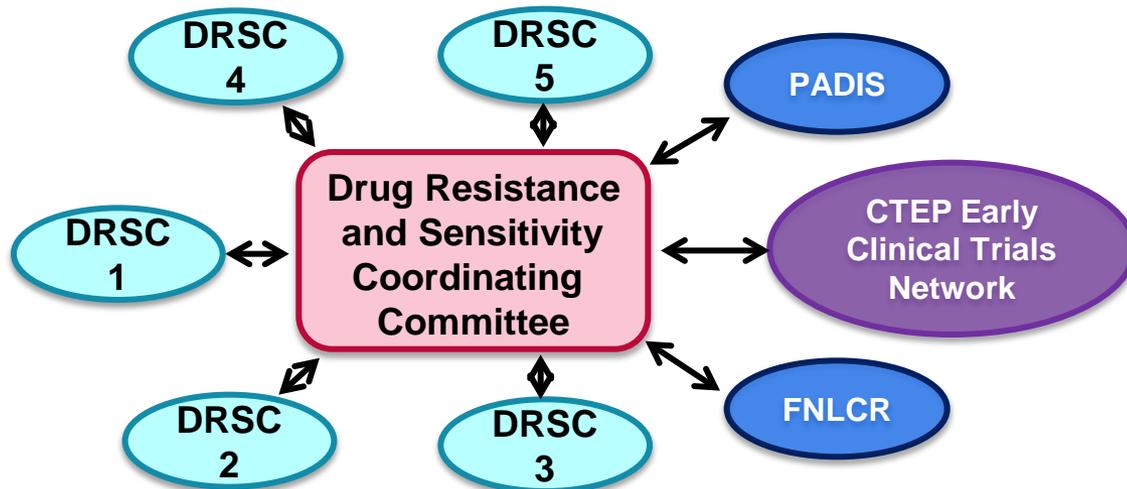
Austin Doyle, M.D

IDB/CTEP/DCTD

*For the NCI Drug Resistance Working Group: Naoko Takebe,
William Timmer, Beverly Teicher, Lyndsay Harris, Shannon Hughes,
and Daniel Gallahan*

Intent of RFA for Studies of Mechanisms of Cancer Resistance or Sensitivity to Therapy

- Create a specialized Drug Resistance/Sensitivity Network (DRSN) formed by up to 5 sites. Each U54 project team will be asked to focus on a unique broad area of drug resistance/sensitivity research and to provide NCI with expertise in new drug development.



- Each U54 response will include several linked projects in that area of drug resistance/sensitivity.
- This effort will be part of an integrated NCI Precision Medicine Initiative to improve cancer treatment that also includes networked laboratory efforts in immunotherapeutic biomarkers and patient derived xenograft models

Focus of a Drug Resistance/Sensitivity Network (DRSN)

- The DRSN will focus on new models and diagnostic techniques, and use human tumor samples whenever possible
- Applicants should have components of their proposed research involve druggable targets, and use an iterative approach between bench and bedside
- While studies involving NCI IND agents* (or other agents that target the same pathway as NCI IND agents) are preferred, applications that propose strategies for understanding resistance/sensitivity to other agents are permitted

**Note: The NCI-IND agents (>60) include a wide variety of small molecule and antibody inhibitors impacting cancer growth and survival, and modulating DNA repair, epigenetic regulation of gene expression, control of immune checkpoints, tumor angiogenesis and hypoxia (<https://ctep.cancer.gov>)*

NCI Supplements for Resistance and Sensitivity

- DCTD recently issued a 1 year supplement to NCI cancer centers and other grantees to accelerate research in drug resistance/sensitivity.
- 38 Applications were received and 11 applications will be funded
- Themes in these 1 year projects include:
 - Determination of genetic alterations associated with Her-2 resistance in breast cancer using paired specimens in neoadjuvant studies
 - Examination of AML patients treated with FLT3 inhibitors to determine secondary mutations related to the short clinical remissions to these agents.
 - The use of WES to determine the mutational profile that may predict EFS in DLBCL patients treated with lenalidomide/RCHOP.
 - Deep proteogenomic analysis, coupled to drug distribution profiling and imaging, to examine adaptive resistance to WEE1 inhibition in GBM.

Representative Example of a Proposal for this RFA

- An RFA response could propose to study the various DNA repair gene defects, which are common and indicate aggressive clinical behavior in prostate cancer (Mateo et al, NEJM 2015).
- The work could involve CRISPR-Cas9 knockout of various DNA repair genes in prostate cancer cells to examine whether this deficiency led to increased dependency on compensatory DNA repair pathways.
- In vivo studies using prostate cancer PDX models, with the DNA repair defect of interest, could study sensitivity to anticancer therapy, with or without addition of DNA Damage Response (DDR) inhibitors,
- PK/PD studies could determine whether the compensatory DDR proteins targeted were inhibited at tolerable concentrations in mice.

Applicants should consider whether their proposal answers important questions in cancer drug resistance/sensitivity, such as:

- What are the various patterns of cellular evolution that lead to resistant cancer cells emerging following treatment?
- Do resistant tumors always arise from cells that pre-exist in tumors prior to treatment?
- Can new methods or approaches be applied to sample solid tumors during the process of treatment?
- How early in a treatment cycle can markers of resistance be optimally detected?
- What strategies can be developed to test for therapeutic drug combinations that are effective in delaying the appearance of resistance?

Review Considerations for Drug Resistance and Sensitivity Applicants

- Demonstrate preliminary data with potential for making clinical advances to overcome cancer resistance.
- Expertise in patient-derived models for in vivo studies of drug resistance/sensitivity.
- Ability of laboratory to confirm presence of putative resistance mechanisms in cancer patient biospecimens.
- Access to patient specimens appropriate for the mechanism or drug target being proposed.
- Ability to conduct pharmacodynamic and pharmacokinetic studies in animal models to demonstrate inhibition of cancer targets *in vivo*.
- Multidisciplinary expertise of team for proposed studies in cancer drug resistance or sensitivity to therapy.

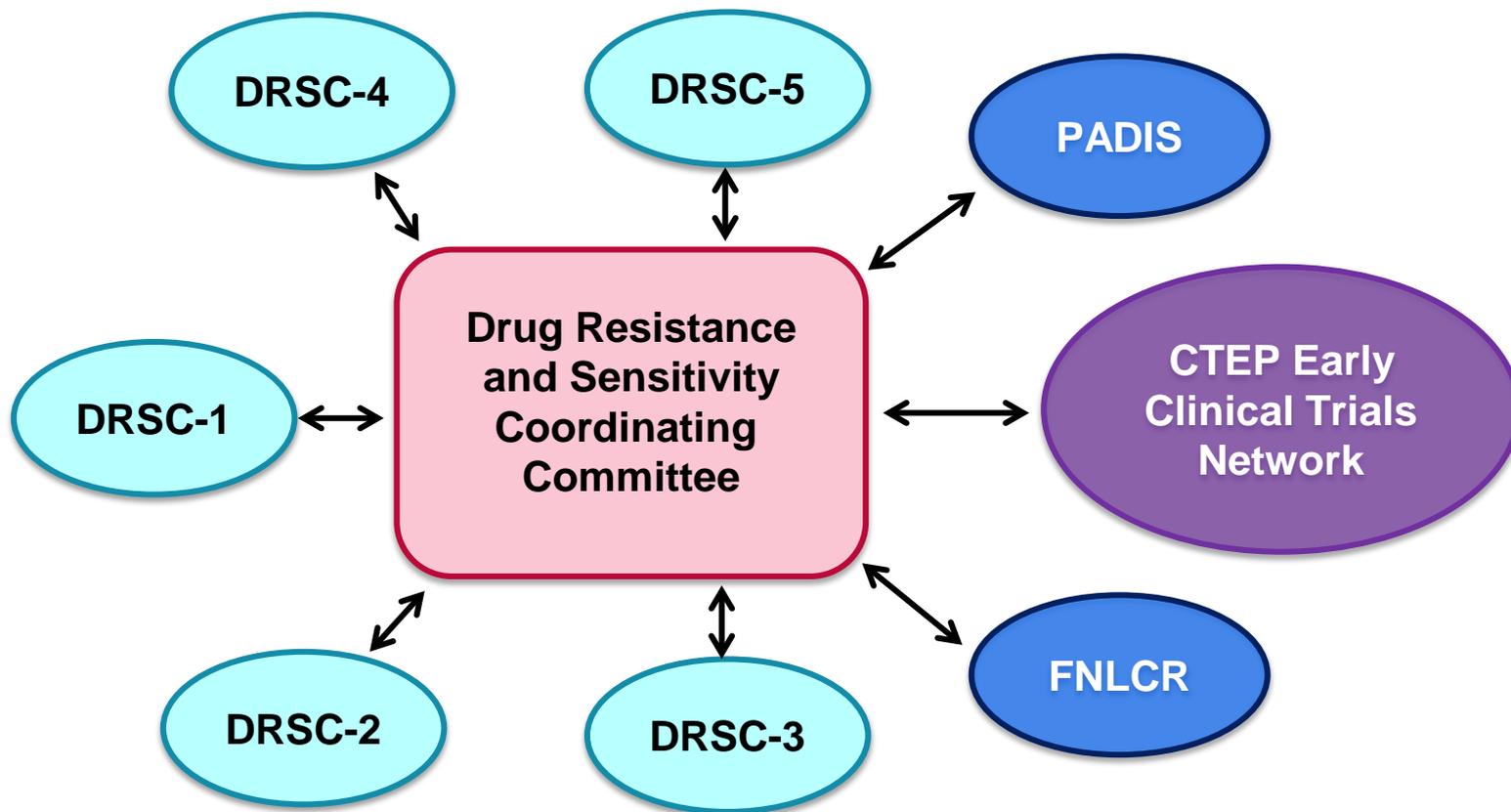
Development of a Drug Resistance and Sensitivity Coordinating Committee (DRSCC)

- The DRSCC will facilitate the network activities to encourage interaction and utilization of resources.
- The DRSCC will be composed of
 - The Principal Investigators of each U54
 - NCI members from DCTD and DCB program staff
 - Ad hoc participants from other NCI Divisions and extramural experts.
- DRSCC will promote exchange of scientific findings and facilitate potential collaborations between the investigator teams and the NCI.
- Formal meetings of the DRSCC will be held twice each year
 - To engage the greater community, one DRSCC meeting each year will invite non-U54 holders to have the opportunity to present new proposals in cancer drug resistance or sensitivity.

Available NCI Resources in Support of Drug Resistance and Sensitivity Center Projects

- Access to patient-derived specimens (tumor biopsies or blood samples) from NCI-sponsored trial networks.
- Collaboration with Frederick National Laboratory for Cancer Research (FNLCR) staff for pre-clinical combination studies of targeted anticancer agents.
- Access to the Patient-Derived Models Repository (PDMR) - national repository of PDMs.
- Potential collaboration with the Pharmacodynamic Assay Development & Implementation Section (PADIS) Laboratory - validated PD assays for critical tumor pathways.
- Facilitated entry of genomic and clinical data into the Genomic Data Commons repository, to utilize databases and analytic tools within the GDC.

Interactions between Drug Resistance and Sensitivity Centers (DRSC) and NCI Resources



PADIS = PD Assay Development & Implementation Section

FNLCR = Frederick National Laboratory for Cancer Research

Funding Decisions and Importance of Drug Resistance/Sensitivity to DCTD Programmatic Goals

- A Special Emphasis Panel will select the 5 best scores from applications that focus on separate areas of drug resistance/sensitivity, to have a well rounded network.
- The selected teams will be requested to serve as “experts” in their chosen area of cancer drug resistance/sensitivity to advise NCI about implications of their research on drug development and biomarker planning by the Division.
- Meetings will be conducted between NCI staff, the five Drug Resistance/Sensitivity research groups, and NCI early phase trial investigators to discuss future design of NCI clinical trials and to evaluate other breaking discoveries in cancer drug resistance.
- This program of specialized centers will contribute a critical preclinical component to NCI’s clinical drug development. It will be evaluated by how well the network can bring drugs, biomarkers and advanced preclinical models to anticipate and overcome the compelling problem of clinical drug resistance.

Requested Funding

Number of awards:	five U54 awards
Funding:	\$1.25 M / year total costs per award
Project period:	five years; each award
Estimated total cost:	\$31.25 M

- From review of the recent drug resistance supplement requests, a likely breakdown of yearly costs per award would be expected:
 - Personnel \$280K
 - Animals and supplies \$130K
 - Sequencing and core facilities \$415K
 - Indirect costs \$425K

Additional supplement awards over course of U54 awards

- As part of DCTD's precision medicine initiative, the division will fund additional supplement awards for proposals over years 1 through 5 of the award period.
- These supplement awards will be given to non-U54 awardees, to support new breaking discoveries in drug resistance/sensitivity.
- The awards would be given out after evaluation and prioritization of proposals by a Special Emphasis Panel, created by NCI for this purpose.
- Recipients could receive funding for either 1 or 2 years by this mechanism, with the second year contingent on a successful review of progress by the SEP.
- Two awards/year for 5 years at up to \$780,000 per award per supplement would come to a total of \$7.8 million dollars for supplements.
- The \$7.8 million for supplements, plus the \$31.25 million for the five awarded U54 grants totals approximately \$39 million.
- These supplements will allow additional investigators studying drug resistance/sensitivity to engage with NCI's drug development program.