NCI Cancer Prevention-Interception Targeted Agent Discovery Program (CAP-IT)

New Program for Precision Cancer Prevention

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**Working Definition of Cancer Prevention – Interception by CAP-IT**

- Normal
- Initiated
  - Mild dysplasia
  - Moderate dysplasia
  - Severe dysplasia
  - Carcinoma in situ
- Invasive cancer

(Adapted from Nat Rev Cancer 2012, 12:835)

**Precancerous Abnormalities**

**Prevention**

**Interception**
Precision Cancer Prevention for High-risk Groups

Cancer Patients: Efficacious therapeutics

High Risk Cohorts: Preventive Strategies Tailored for Each High-risk Group

Individuals with heritable cancer syndromes (HCS) with/without precancerous abnormalities (precancer)

Individuals exposed to carcinogens without HCS with/wo precancer

Individuals with precancer without HCS & carcinogen exposure

General Population: Avoid/Reduce Cancer Risks
(e.g. Smoking cessation, Healthy lifestyle, HBV vaccine, HPV vaccine, HCV Rx, etc)

Precision Cancer Prevention-Interception

Shizuko Sei, M.D., DCP
**CAP-IT: Presentation Overview**

- **Problem:** Cancer prevention/interception modalities for high-risk cohorts are centered on surgery; Very few risk-tailored intervention options available

- **Solution:** CAP-IT = Targeted agent discovery pipeline for cancer prevention and interception, focusing on high-risk cohorts

- CAP-IT is **NOT** about:
  - Discovering preventive agents for general population
  - Discovering agents for adjuvant therapy
  - Determining whether FDA-approved cancer therapeutics can be efficacious in cancer interception – Those ideas can be examined by the existing DCP PREVENT program
  - Screening large chemical libraries with lead optimization
Preventive Interventions for High-Risk Groups

- **Tailored Interventions for High-Risk Cohorts?**
  - Why very few preventive interventions available beyond surgery?
  - *Lack of validated intervention targets for precision prevention* is a major roadblock to *new agent discovery and development*; Industry mostly not interested

- **Opportunities and Program Gap**
  - Genomic and molecular analyses of precancer and cancer, when examined together, can *identify potentially useful targets for preventive interventions*
  - *There are no NCI programs* to facilitate external PIs’ intellectual commitment on discovery of cancer preventive agents directed against those targets
CAP-IT Overarching Goal & Objectives

Develop a pipeline for discovery of target-specific agents for precision cancer prevention through:

- **Validate Targets for Intervention**
  - Potential target leads are already available from molecular databases of precancer/cancer generated by NCI big data science initiatives
  - Validate as intervention targets focusing on high-risk cohorts

- **Discover New Cancer Prevention/Interception Agents**
  - Identify compounds (i.e. target-specific agents) and immunological agents (i.e. cancer vaccines) that prevent or intercept/eliminate precancerous abnormalities before progressing to cancer
**PREVENT Program Has No Discovery Function**

**NExT**
- Early Discovery Research for Cancer Prevention Agents Is Not Part of PREVENT, Nor Is It a Major Focus of Big Pharma R&D

**DCP**
- PREVENT Cancer Preclinical Drug Development Program
- EDRN: Early Detection Research Network
- CP-CTNet: Cancer Prevention Clinical Trials Network
- NCORP: NCI Community Oncology Research Program

Diagram:
- **Discovery**
  - Target Validation
  - Screening/Hit-to-Lead
  - Lead Development
  - Preclinical Evaluation
- **Preclinical**
- **Clinical Development**
  - Phase 0
  - Phase I
  - Phase II
  - Phase III

**Academic/Biotech Collaborations**

**Biotech/Pharma Collaborations**
PREVENT Program Has No Discovery Function

CAP-IT inventors will retain IP

Projects can start at any point as appropriate
Example of Cancer Preventive Agents Targeting Oncogenic Pathways:

**Hedgehog Pathway Inhibition in Patients with Gorlin Syndrome (Basal Cell Nevus Syndrome)**

- **Phase 3 (Underway with 2% patidegib topical gel)** (NCT02762084)
  - Based on the Phase 2 study data, FDA granted Orphan Drug and Breakthrough Therapy Designation for topical patidegib in the treatment of Gorlin syndrome in 2017.

**ClinicalTrials.gov**

- **Trial of Patidegib Gel 2%, 4%, and Vehicle to Decrease the Number of Surgically Eligible Basal Cell Carcinomas in Gorlin Syndrome Patients** (NCT02762084)

Daily oral vismodegib (Erivedge™) @150 mg not only reduces tumor burden, but also prevents new BCC growth (NEJM 2012, 366: 2180 and Lancet Oncol 2016, 17: 1720)

This is the type of target-specific agents CAP-IT investigators will hopefully discover!
CAP-IT will establish a foundational infrastructure and scientific roadmap for fast-tracking agent discovery research for cancer prevention and interception.

**CAP-IT Center Components**

**CAP-IT Specialized Centers (U54): Multi-PI & Integrated and Streamlined Projects**

- **Target Validation & Agent Discovery Unit (TAU)**
  - TAU Validation group: Functional validation and prioritization of precancer intervention targets
  - TAU Informatics Group: Informatics analysis of validated targets
  - TAU Agent Discovery Group: Agent screen and selection

- **Efficacy Testing Unit (ETU)**
  - Pilot in vivo efficacy evaluations of agents

**Data and Resource Coordination Center (DRCC) (U24)**

- Establish a central CAP-IT database and SOPs for in-network sharing
- Coordinate and facilitate in-network sharing of unique tools, novel technologies and resources
- Provide program/project management support and administrative & logistical assistance
None of these premalignant genome-based projects are focused on undertaking all elements of the CAP-IT research objectives, from the validation of molecular or immune targets to the discovery of potentially efficacious agents for cancer prevention-interception.
## CAP-IT Proposed Budget

<table>
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<th>CAP-IT Centers</th>
<th>FY2022</th>
<th>FY2023</th>
<th>FY2024</th>
<th>FY2025</th>
<th>FY2026</th>
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<td>Specialized Centers (U54) (n~4)</td>
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- Each CAP-IT Specialized Center will carry out 3 ~ 4 specific organ site projects over the period of 5 years.
- DRCC will establish a central CAP-IT database and coordinate in-network sharing of unique technologies (e.g. assay tools, new models, etc.) and other resources; will also provide project management, administrative & logistical assistance.
- In addition, $0.5M/year will be set aside from year 2 to year 4 to support administrative supplements for new collaborations with non-CAP-IT investigators.
Justification for RFA & Cooperative Agreement

- **RFA:**
  - The proposed research network endeavor will require a high degree of scientific and technical coordination
  - Set-aside funding will ensure sufficient support for innovative discovery research projects without disruption

- **Cooperative Agreement:**
  - Substantial programmatic involvement by NCI (e.g. a liaison and facilitator for coordination and collaboration across the NCI programs to ensure orchestrated handoff of lead targets and agents; Members of Steering Committee and Team Lead)
  - Allow collaborative flexibility and coordination of scientific framework between CAP-IT members and NCI
Reviewers Comments (Drs. Knudsen, Sidransky, & Counter) & Responses

- **Allow more flexibility for project entry points**
  - ✓ FOA language will clarify flexible entry points to the CAP-IT discovery pipeline; FOA will also include existing resources available outside of CAP-IT for project needs (e.g. PREVENT and CP-CTNet)
  - ✓ Target Validation and Agent Discovery Units will be combined into one, so CAP-IT Specialized Centers will have flexibility to determine project starting points based on the discovery stage

- **Provide mechanisms for non-CAP-IT PIs to join the CAP-IT research**
  - ✓ Administrative supplements proposed from year 2 to year 4 are intended for new collaborations with non-CAP-IT investigators
  - ✓ DCP will engage R01 investigators after the network is established

- **Cite examples of targeted agent discovery projects for cancer prevention/interception**
  - ✓ FOA will include examples of potential targets and projects for different high-risk cohorts

- **Target validation for cancer prevention is different from cancer treatment target validation; Higher bars for prevention interventions**
  - ✓ FOA language will clarify project prioritization criteria to include risk-benefit considerations for different high-risk cohorts