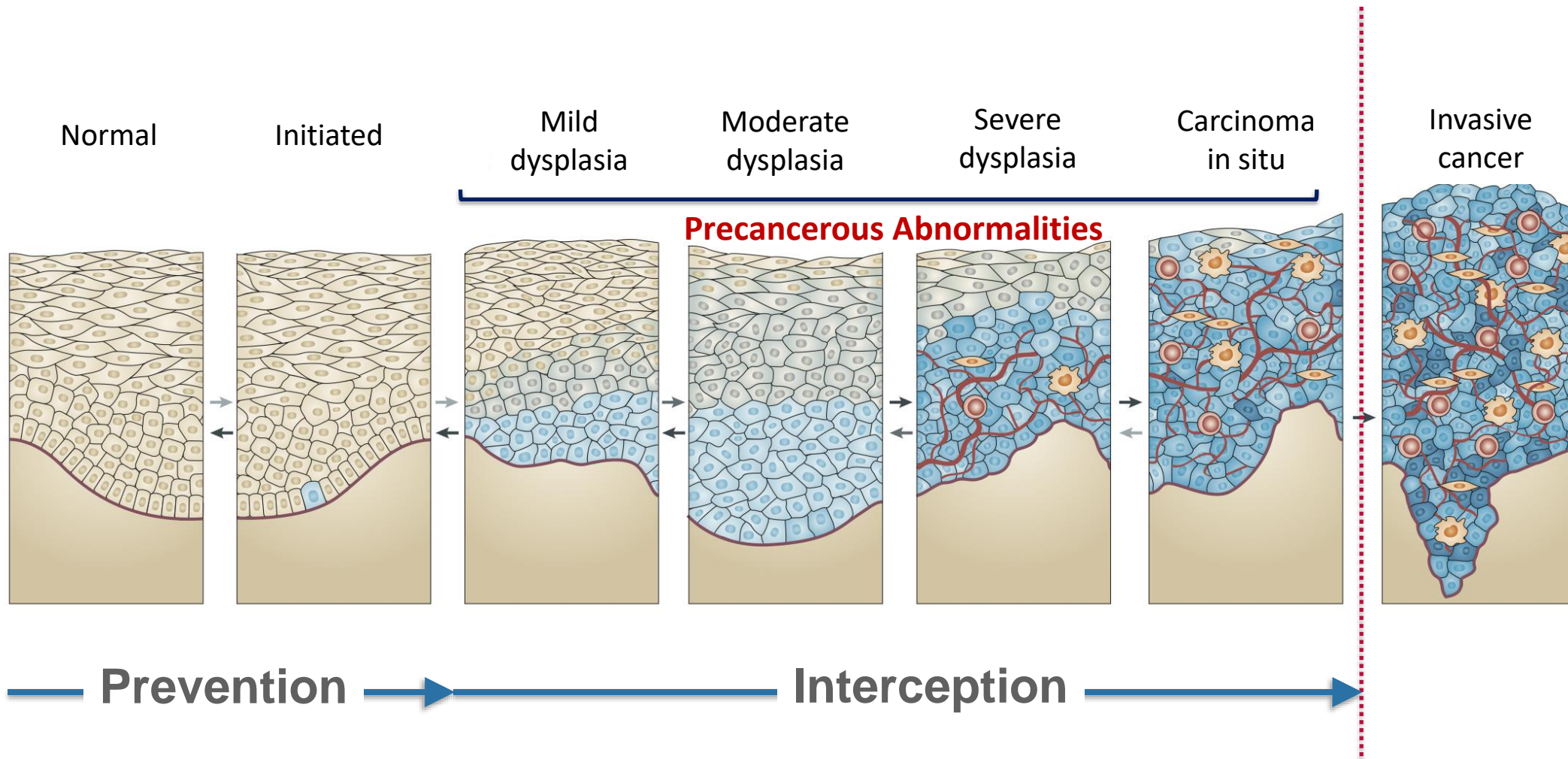# *NCI Cancer Prevention-Interception Targeted Agent Discovery Program (CAP-IT)*

New Program for Precision Cancer Prevention
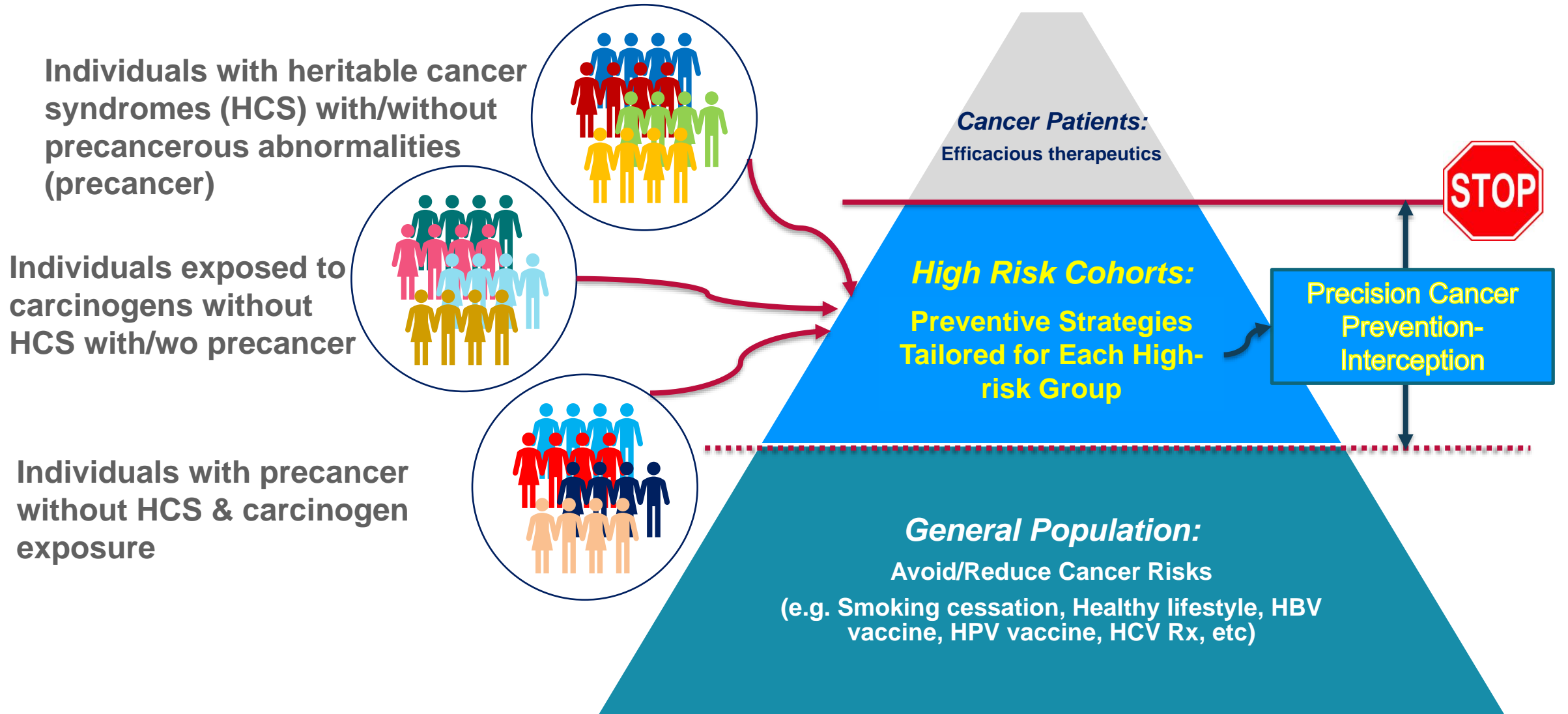
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Working Definition of Cancer Prevention – Interception by CAP-IT

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

Precancerous Abnormalities

Prevention → Interception →

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

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Precision Cancer Prevention for High-risk Groups

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

Cancer Patients:
Efficacious therapeutics

STOP

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

Precision Cancer Prevention-Interception

General Population:
Avoid/Reduce Cancer Risks

(e.g. Smoking cessation, Healthy lifestyle, HBV vaccine, HPV vaccine, HCV Rx, etc)

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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 <u>new agent discovery and development</u>; 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
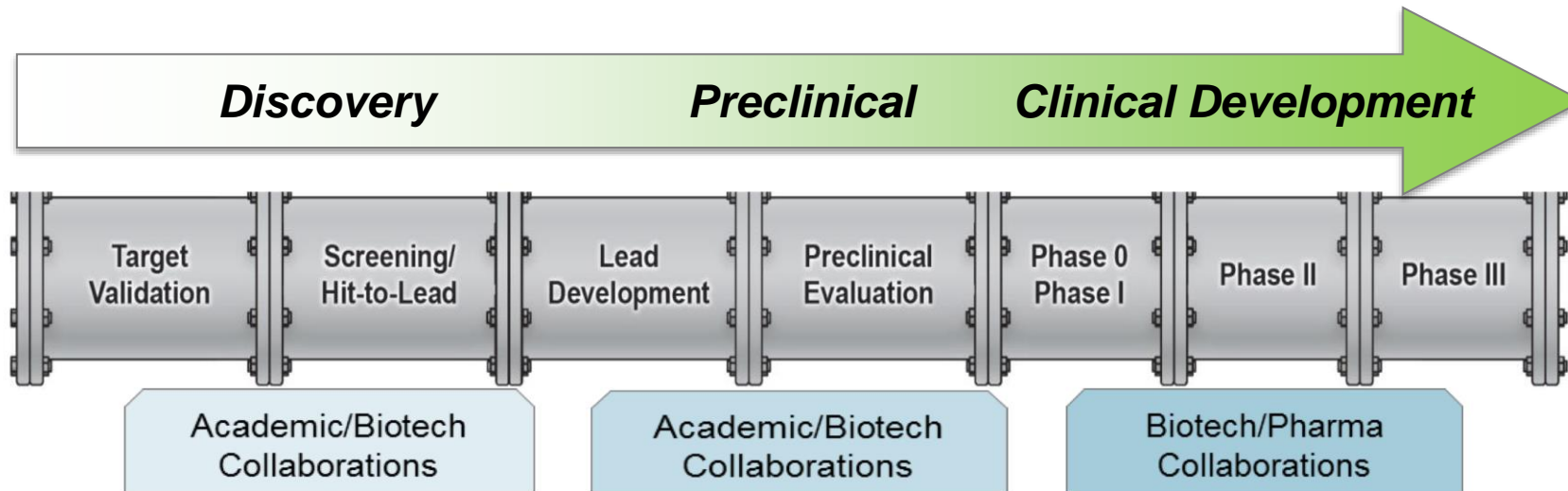 - Validate as intervention targets focusing on **high-risk cohorts**

- **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
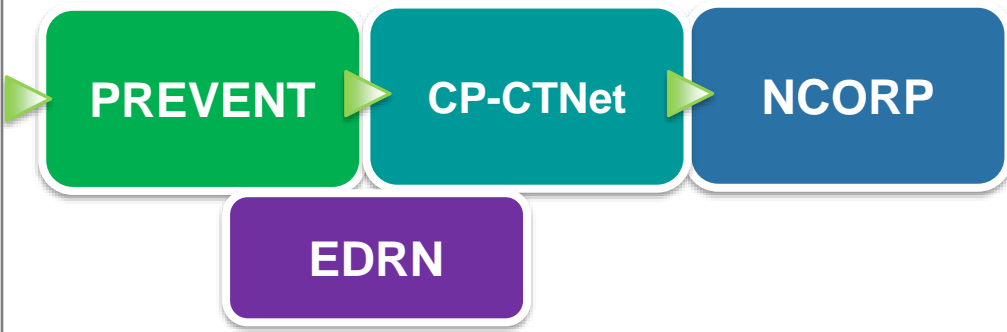
PREVENT Program Has No Discovery Function

NExT

Discovery | Preclinical | Clinical Development

| Target Validation | Screening/Hit-to-Lead | Lead Development | Preclinical Evaluation | Phase 0 Phase I | Phase II | Phase III |

Academic/Biotech Collaborations | Academic/Biotech Collaborations | Biotech/Pharma Collaborations

DCP

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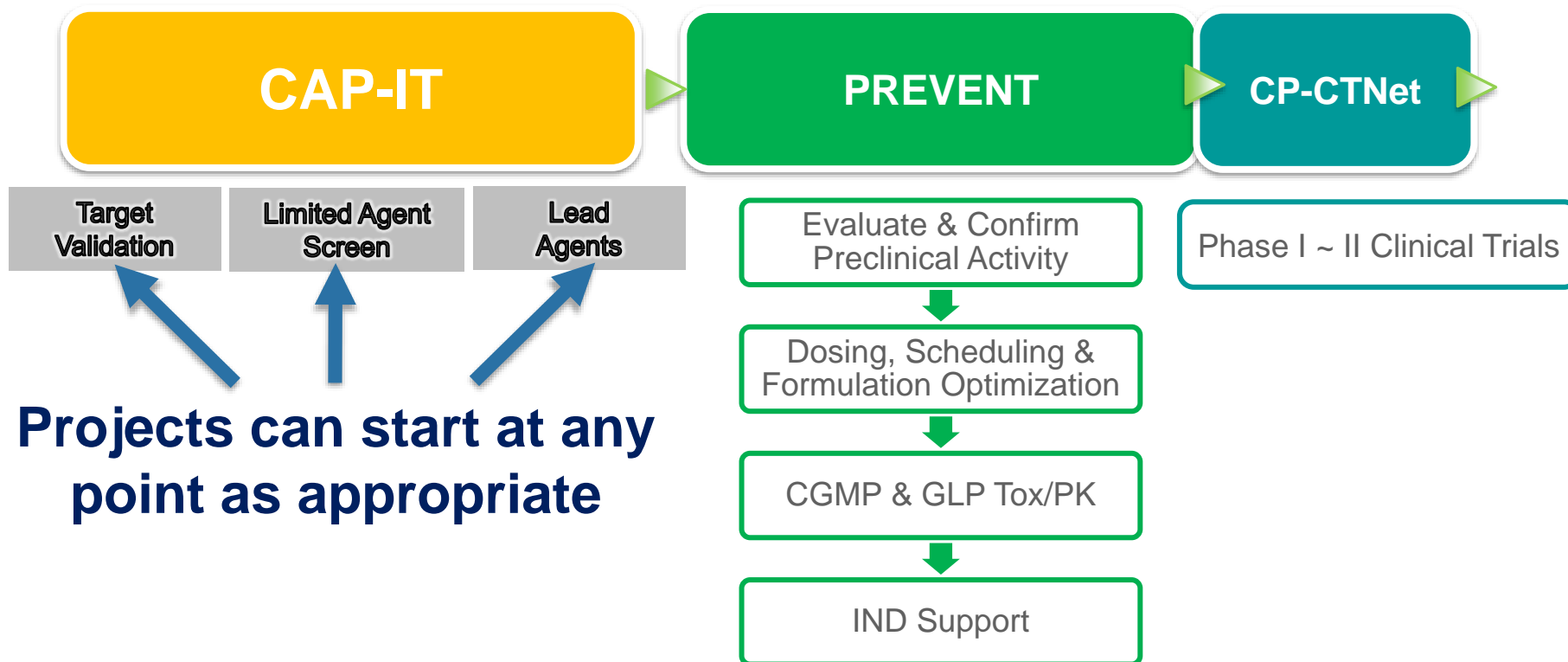
PREVENT → CP-CTNet → NCORP

EDRN

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

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PREVENT Program Has No Discovery Function

Discovery → Preclinical → Clinical Development

CAP-IT inventors will retain IP

DCP

CAP-IT	PREVENT	CP-CTNet

Target Validation	Limited Agent Screen	Lead Agents

Projects can start at any point as appropriate

Evaluate & Confirm Preclinical Activity

↓

Dosing, Scheduling & Formulation Optimization

↓

CGMP & GLP Tox/PK

↓

IND Support

Phase I ~ II Clinical Trials

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Example of Cancer Preventive Agents Targeting Oncogenic Pathways:

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

Baseline Month 5

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)

increased risk of developing various cancers.

NIH U.S. National Library of Medicine
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)

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.

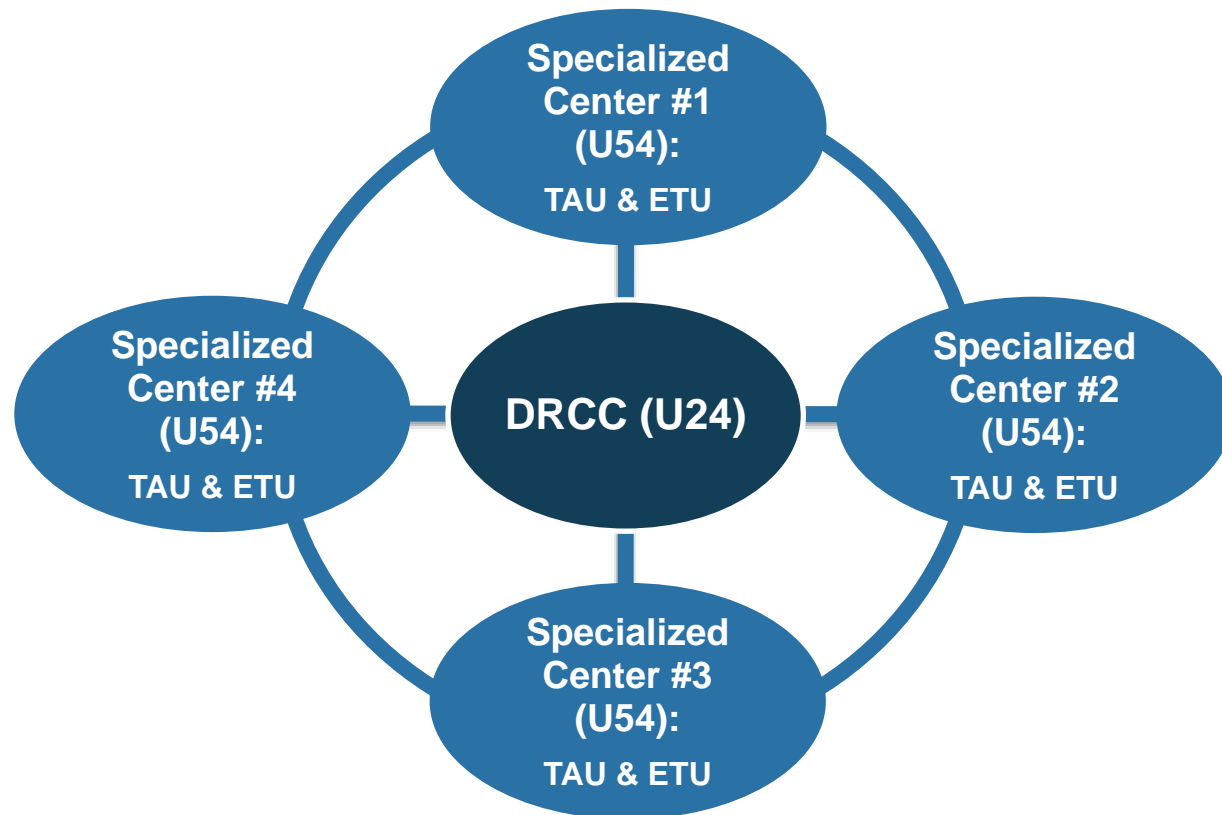**Phase 3 (Underway with 2% patidegib topical gel)**

This is the type of target-specific agents CAP-IT investigators will hopefully discover!

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CAP-IT Center Components

CAP-IT will establish a foundational infrastructure and scientific roadmap for fast-tracking agent discovery research for cancer prevention and interception

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

Portfolio Analysis

NIH RePORTER Query Focused on Identifying Projects Aimed for Drug or Vaccine Discovery Based on Cancer Genome or Premalignant Lesions Genomic Profiles

Genomic Profiles of Cancer or Premalignant Lesions with:	Cancer Genome	Premalignant Genome
	(FY2011 through FY2020: Number of Unique Project Hits)	
Drug discovery	636	1
Novel targets	297	1
Immunotherapy	1335	-
Immunoprevention	-	3
Cancer vaccine	156	2

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

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CAP-IT Proposed Budget

CAP-IT Centers	FY2022	FY2023	FY2024	FY2025	FY2026	Total
Specialized Centers (U54) (n=~4)	$6M	$6M	$6M	$6M	$6M	$30M
DRCC (U24) (n=1)	$0.5M	$0.5M	$0.5M	$0.5M	$0.5M	$2.5M
Administrative Supplements (Yr 2 - 4)	-	$0.5M	$0.5M	$0.5M	-	$1.5M
Total (Direct + Indirect)	$6.5M	$7M	$7M	$7M	$6.5M	**$34M**

- 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

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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

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