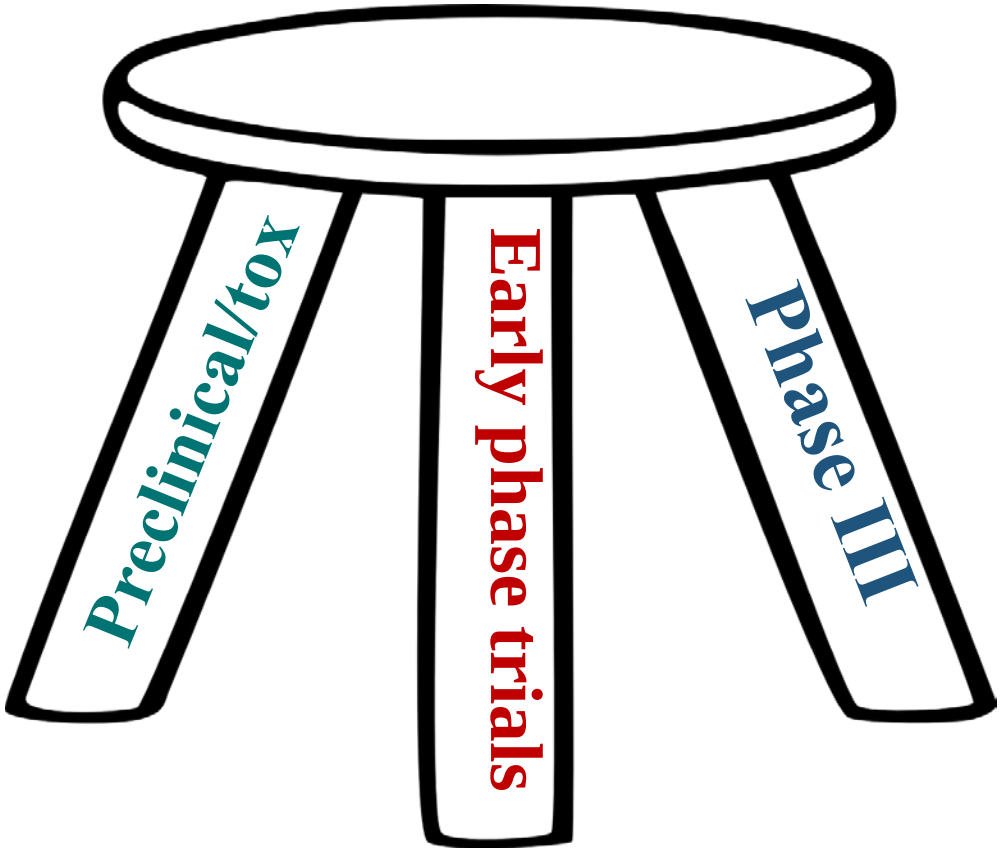
NCI, DCP Cancer Preventive Agent Development Program: Early Phase Clinical Research

Eva Szabo, MD
Chief, Lung and Upper Aerodigestive Cancer Research Group
Division of Cancer Prevention, National Cancer Institute

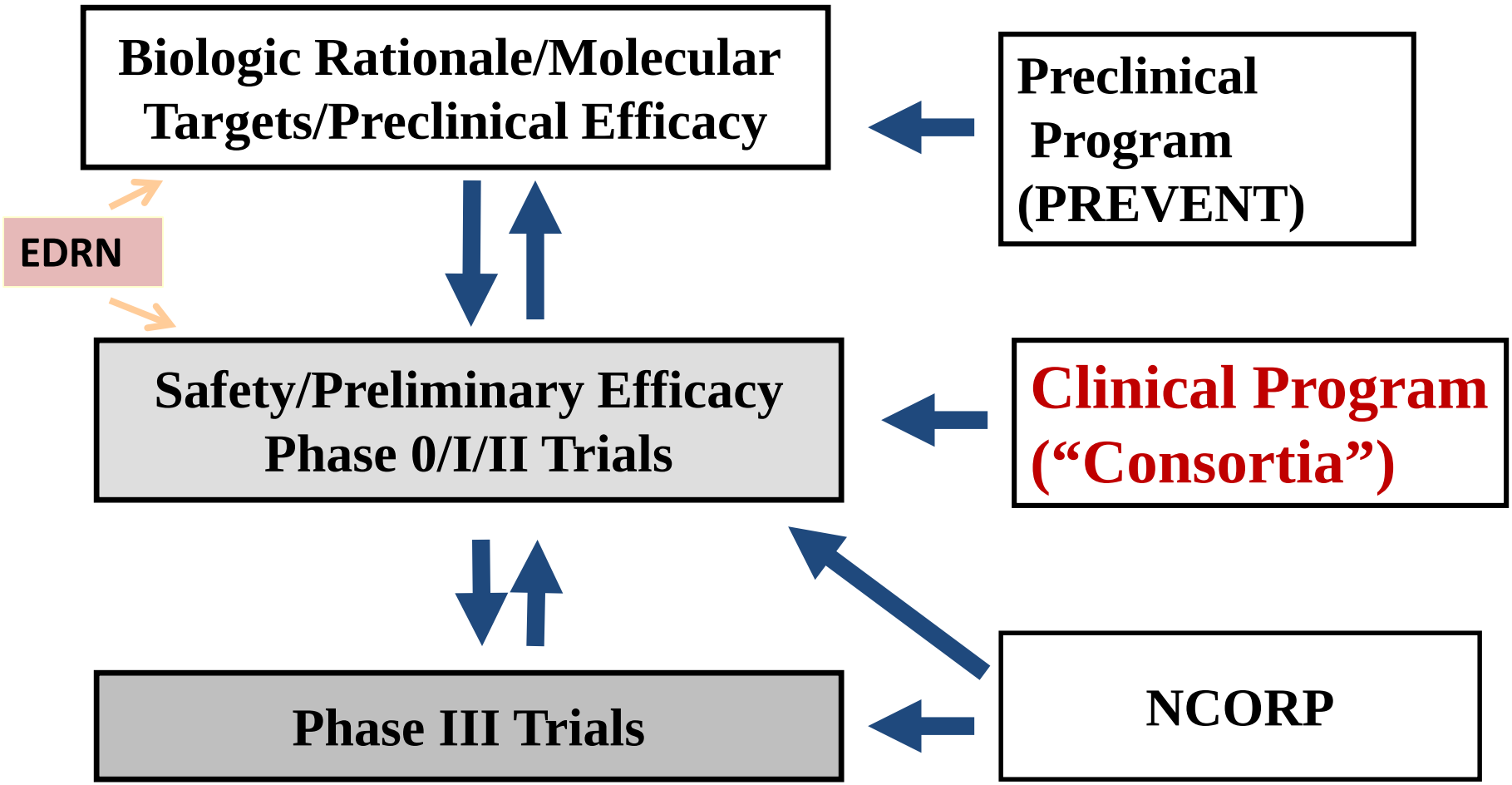
NIH NATIONAL CANCER INSTITUTE

BSA
March 20, 2018

Critical Components of Systematic Preventive Agent Development



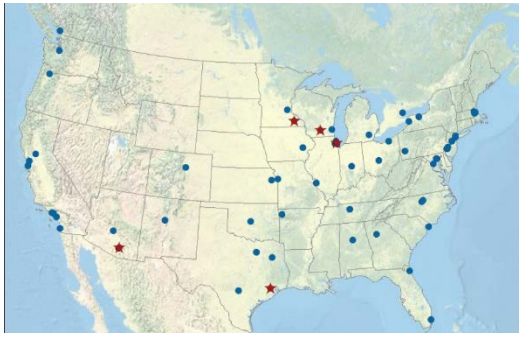
DCP Drug Development Programs



DCP Early Phase Clinical Trials Consortia

Program Objectives

- **To qualify cancer preventive agents for further clinical development via the conduct of phase 0, I, & II clinical trials assessing preliminary efficacy and safety**
- **Additional goals:**
  - **Optimize clinical trial designs**
  - **Develop surrogate and intermediate endpoint biomarkers**
  - **Test novel imaging technologies**
  - **Develop further insights into mechanisms of cancer prevention by agents**



Current Program

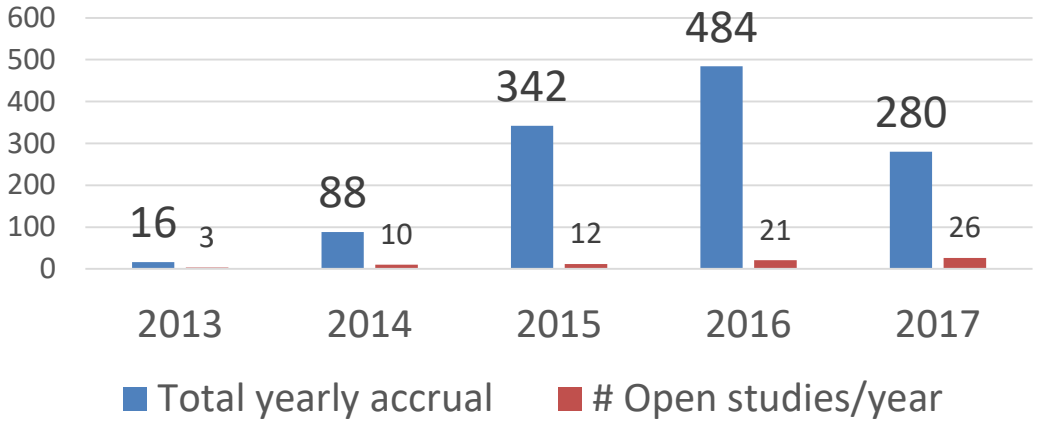
- **5 contractors**
- **>100 member sites**

Types of Studies

- **Phase 0 microdosing, biomarker modulation trials**
- **Phase I pharmacokinetic, safety trials**
- **Phase II preliminary efficacy trials (usually placebo-controlled)**
  - **Premalignancy endpoint trials - require screening/biopsy to identify individuals with lesions**
  - **Molecular endpoint trials**
  - **Presurgical (window-of-opportunity) trials**

Programmatic Accomplishments
FY13-FY17

- **67 concepts received (58% approved); 43 protocols approved (~8-9/yr)**
- **30 different agents/combinations**
  - **8 vaccines (1 FDA approved; 7 experimental)**
- **31 studies opened; 9 closed to accrual; 3 completed**
- **Accrual:**



- **Central IRB since 2015**
- **Accrual Quality Improvement Program (AQuIP)**
- **Biospecimen Repository**

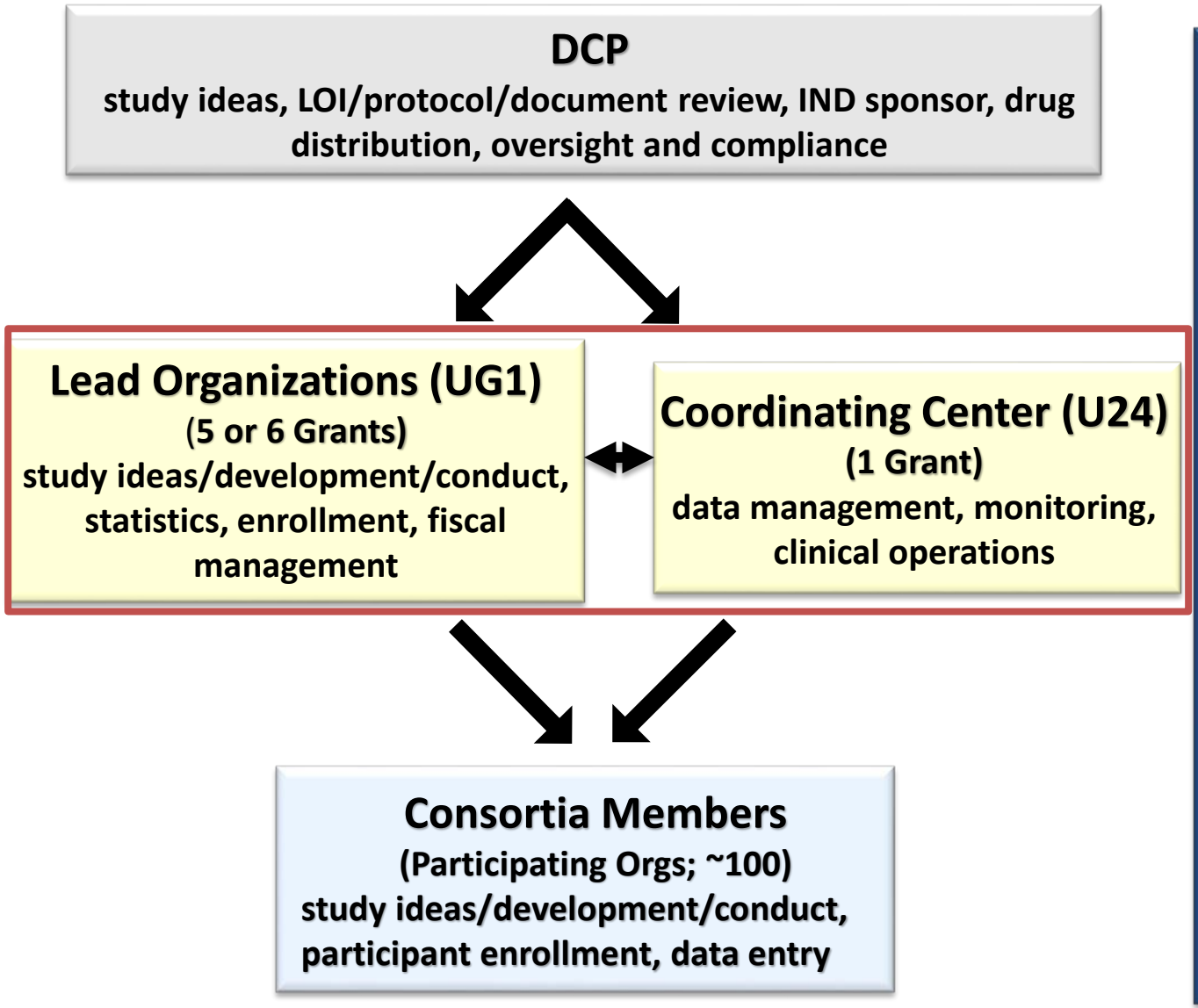
Scientific Accomplishments

- **Expanded new portfolio in immunoprevention**
  - **Pathogen-associated cancers-prophylactic and therapeutic HPV; HCV**
  - **Tumor-associated antigens (MUC1, WOKVAC (HER2/IGFBP2/IGFR1), PROSTVAC (PSA) vaccines)**
- **Agents moving through different phase of drug development**
  - **9cUAB30 (rexinoid), from PREVENT→Ph 1 (single/multi-dose)→phase Ib (effect on tissue biomarkers)**
- **Optimizing risk/benefit**
  - **Topical approaches to breast cancer prevention (4 agents)**
  - **Alternative dosing regimens (intermittent dosing)**

Minimizing Toxicity – Topical Approaches for Breast Cancer Prevention

- **Phase II topical 4-hydroxytamoxifen (4-OHT) vs. oral tamoxifen (T) in women with DCIS, 6-10 wks pre surgery**
  - **Equivalent ↓ Ki-67 in DCIS with topical vs. oral agent**
    - ***Lee et al. Clin Cancer Res 2014;20:3672***
- **Ongoing 4-OHT studies (n=2) – presurgical; mammographically dense breasts (12 mth duration)**
- **Other topical breast cancer trials (inc. analysis of intramammary distribution):**
  - **Telapristone (anti-progestin) – oral vs. topical Rx, presurgical trial**
  - **Endoxifen (tamoxifen metabolite)**
  - **Bexarotene (rexinoid), potentially effective in ER-negative breast cancer**

RFA Purpose: Proposed New Consortia Structure



Key Program Changes

- Funding – grant mechanism (UG1, U24)
- Centralized coordination
- One data management system
- Restricted funds for inter-consortia & high priority new studies

Areas of Emphasis for Consortia Program

- **New scientific areas**
  - **Immunoprevention**
- **Strategies to Optimize Risk/Benefit**
  - **Regional drug delivery (topical-topical breast; inhaled-lung)**
  - **Alternative dosing schedules (e.g., intermittent)**
  - **Combinations**
- **Repurposing old drugs for prevention**
  - **Emphasis on drugs affecting multiple chronic diseases (e.g., ASA, NSAIDs, metformin)**
- **Leverage Cancer Moonshot℠ and NCI activities**
  - **Pre-Cancer Atlas**
  - **Immuno-Oncology Translation Network (IOTN)**
  - **Grants portfolio**
    - **Provocative Questions – e.g., addressing premalignancy, etc.**
    - **PA-17-459/460 (Biology Lung/H&N Premalignancy)**

Potential Future Trials:
PREVENT and Follow-up Studies

Agents (Target Cancers)	Next steps
Immunoprevention Agents	
MUC1 vaccine (colon and lung)	Combination MUC1/ASA or metformin (colon); Phase IIB (+/- combination) (lung)
WOKVAC-HER2/IGFBP2/IGFR1 vaccine (breast)	Phase II (combination WOKVAK and 9cUAB30 in PREVENT now)
PROSTVAC-PSA vaccine (prostate)	Prevention of histologic progression in active surveillance cohort
HPV16L1-16RG1 VLP prophylactic vaccine (Cervix)	(CGMP Production & GLP Toxicology in PREVENT now) - Phase I in development
Frame shift peptide (FSP) vaccines + naproxen (Lynch syndrome-associated cancers)	(Proof of Concept in PREVENT now) – Phase I
Chemoprevention Agents	
4-hydroxytamoxifen, topical (breast)	Potential phase III
9cUAB30 (breast)	Phase II; combination with WOKVAK phase I; possible phase I/II in other organs (e.g., lung)
Bexarotene, topical (breast); Aerosolized (lung)	Phase II for breast; phase I for lung
Iloprost, inhaled (lung)	Phase IIb
Endoxifen, topical (Breast)	Phase II
SHetA2 (Ovarian)	(CGMP in PREVENT now) – Phase I

Red= agent developed in PREVENT

External Review

Chair: Kenneth Cowan, MD, PhD (Univ. Nebraska)

- **Recommended program continuation and increased funding**
- **Program strengths**
  - **Unique and valuable, "necessary entity filling the niche between preclinical conception and Phase III trials"**
  - **Successful in achieving goals**
  - **Key scientific successes: movement of agents from early to mid-phase clinical trials, expansion into immunoprevention**
  - **Key programmatic successes – Central IRB, accrual monitoring program (AQuIP)**
- **Recommendations:**
  - **Concurred with shift from contract to cooperative agreement grant mechanism**
  - **Include non-consortia staff in yearly PI meetings (cooperative group leaders, RO1-funded investigators, pharma)**
  - **Focus on enrolling diverse populations**

Portfolio Analysis

- **14 investigator-initiated in DCP grants portfolio were funded (1 phase 0, no phase I trials) from 1/12-11/17**
- **FY2017 – NIH RePORTER query ("cancer prevention" and "clinical trials") identified 119 grants**
  - **Only 8 were phase 0-II clinical trials**
  - **Only 2 were newly funded in 2017**

Justification for RFA

- **High degree of coordination is needed to implement research network**
  - **Coordinated submission and specialized review process**
  - **Set-aside funding to ensure adequate support for multiple clinical trials**

Justification for Cooperative Agreement

- **Substantial programmatic involvement by NCI**
  - **IND sponsor**
  - **Review of LOIs, protocols, clinical oversight**
  - **Identification of new agents/strategies for LOI solicitation**
  - **Liaison with pharmaceutical partners and DCP agent repository for agent acquisition**
  - **Ensuring compliance with FDA and OHRP requirements**
  - **Meetings with investigators, teleconferences**

Budget - Current Program

- **Approved in 2010 for $11M/yr.**

FY2012	FY2013	FY2014	FY2015	FY2016	FY2017
$2.241M	$7.765M	$9.127M	$9.586M	$13.265M	$9.928M

  - **Total FY12-17 = $51.9**

- ***Program pays for:***
  - ***Core infrastructure (5 prime sites)***
  - ***Screening costs (e.g., to identify participants with high risk premalignant lesions)***
  - ***Participant accrual clinical costs (including physical exams, labs, biopsies, etc. – costs usually not covered by insurance)***
  - ***Partial salary support for main PI and one site coordinator per trial***
  - ***Tissue collection and biomarker analysis costs***

Budget - New Program

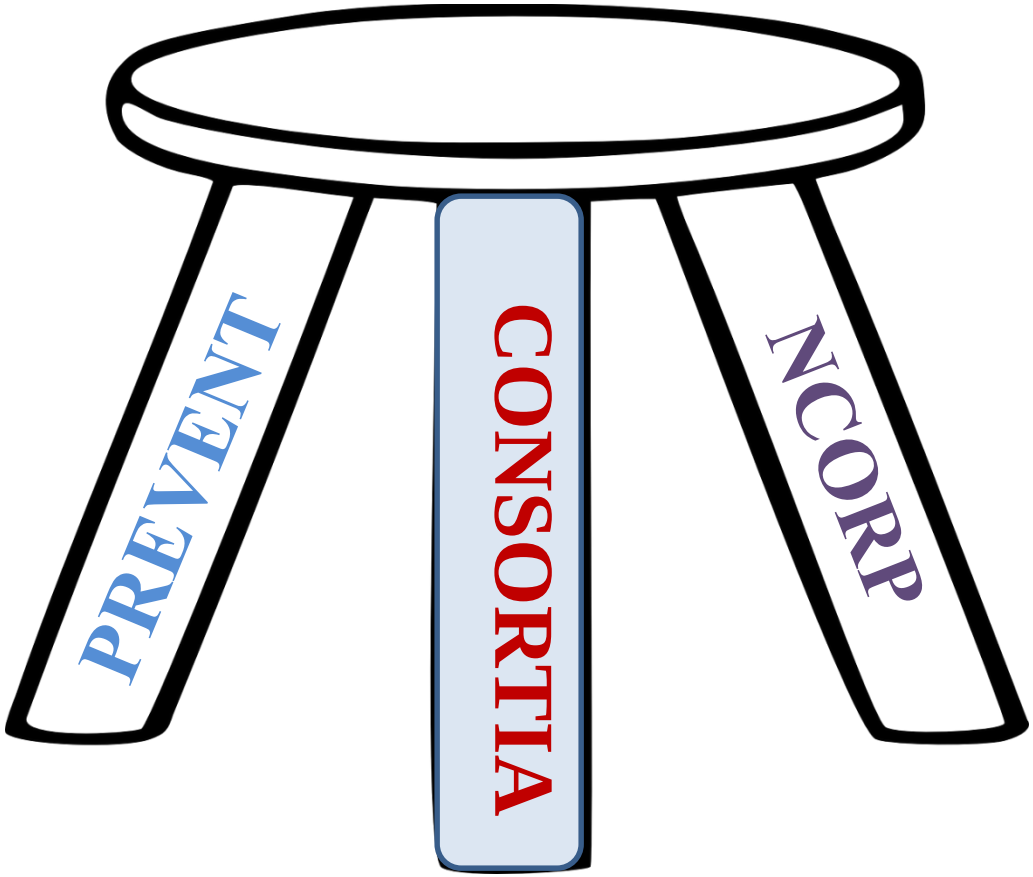
- **Program request: $2M/yr increase ($7M Yr 1, then $13M/yr)**
  - **Total =$59M**

	Year 1	Year 2	Year 3	Year 4	Year 5
Coordinating Center	$2M	$3M	$3M	$3M	$3M
CLO #1	$1M	$2M	$2M	$2M	$2M
CLO #2	$1M	$2M	$2M	$2M	$2M
CLO #3	$1M	$2M	$2M	$2M	$2M
CLO #4	$1M	$2M	$2M	$2M	$2M
CLO #5	$1M	$2M	$2M	$2M	$2M
Total/yr.	$7M	$13M	$13M	$13M	$13M

CLO= Consortia Lead Organization (UG1)

  - **Justification:**
    - **Coordinating Center: $1M for monitoring (transfer from legacy monitoring contract), centralized data management and database**
    - **Consortia Lead Organizations: ↑patient care costs, ↑vaccine monitoring costs, anticipate 3-4 additional larger phase IIb trials, reserve $0.5M/yr for interconsortia trials and emerging new ideas**

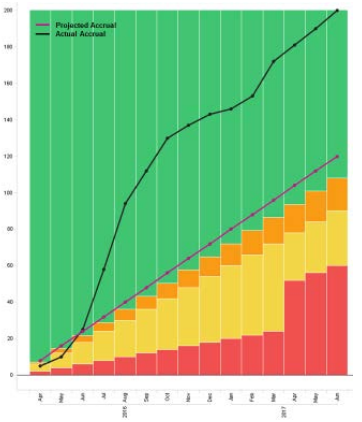
The Three Critical Components of DCP Preventive Agent Development



Back-up Slides

Immunoprevention

- **Pathogen-associated cancers**
  - **Cervical cancer: deferred booster nonavalent HPV vaccine (U Arizona); multivalent broadly protective HPV vaccine (RG1-VLP, developed by PREVENT program); also moving to therapeutics of HPV IEN - 5-FU/imiquimod (TLR7 agonist) ph I trial**
  - **Liver cancer: HCV vaccine (Mayo)**



- **Tumor-associated antigens**
  - **MUC1 vaccine in colorectal adenoma (Mayo)**
    - **Preliminary data: vaccine response in 25% participants (vs. 0% in placebo), correlated with low baseline levels of polymorphonuclear myeloid-derived suppressor cells (PMN-MDSC); f/u for adenoma recurrence ongoing**
    - **New study in current/former smokers undergoing CT screening**
  - **Multi-peptide (WOKVAC-HER2/IGFBP2/IGFR1) and HER2 vaccines in breast cancer (U Wisconsin, MD Anderson) - immunogenicity endpoints**
  - **PSA vaccine (PROSTVAC) in prostate cancer active surveillance cohort (U Arizona) – immunologic response in tissue (CD8+, CD4+ cells)**

Trials Moving through Different Phases of Drug Development

- **9cUAB30: RXR-specific retinoid (rexinoid), no liver agonist function**
  - **Preclinical data: effective in ER+ and ER- mouse models**
  - **Developed under DCP RAPID program (precursor of PREVENT)**
    - **Phase I, first in human (5-20 mg), then 28-day multiple doses (0, 20, 40, 80, 160, 240 mg qd) performed in Consortia programs**
      - **240 mg/d tolerable, no triglyceride elevation**
  - **Current trial- phase IB breast cancer presurgical trial – 14-28 d exposure; Ki-67 tissue primary endpoint**
    - **Current trial waited for results of phase I multi-dose trial to complete**