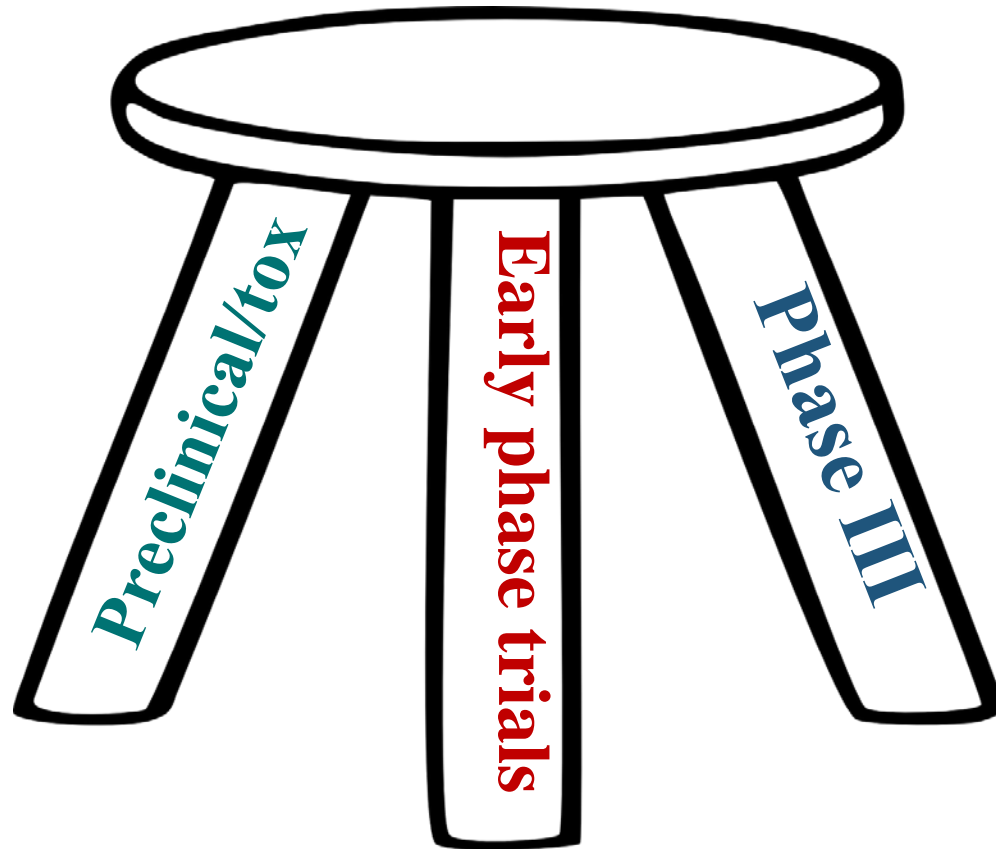


NCI, DCP Cancer Preventive Agent Development Program: Early Phase Clinical Research

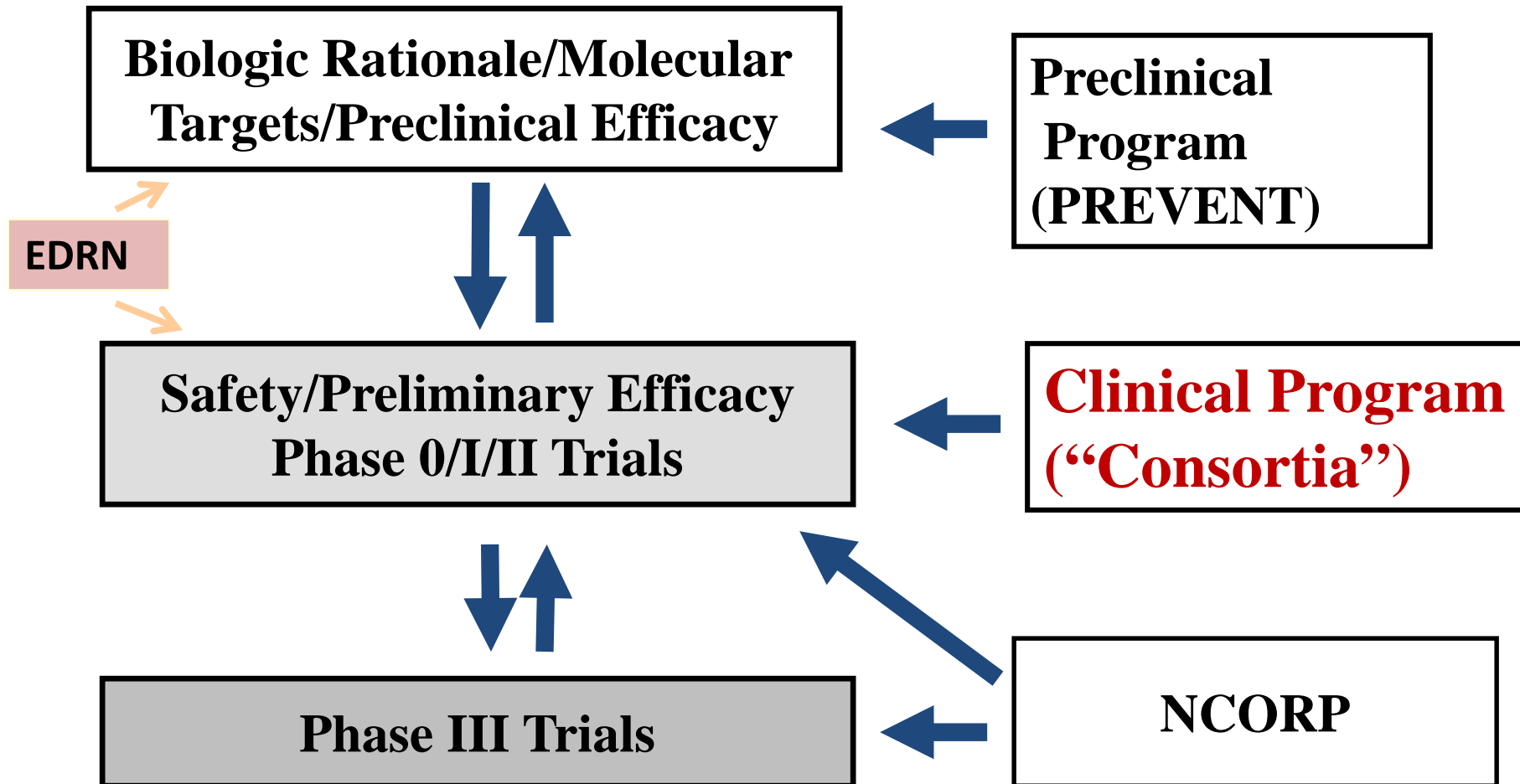
Eva Szabo, MD

*Chief, Lung and Upper Aerodigestive Cancer Research Group
Division of Cancer Prevention, National Cancer Institute*

Critical Components of Systematic Preventive Agent Development



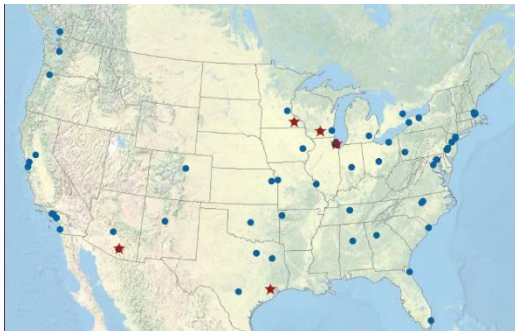
DCP Drug Development Programs



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

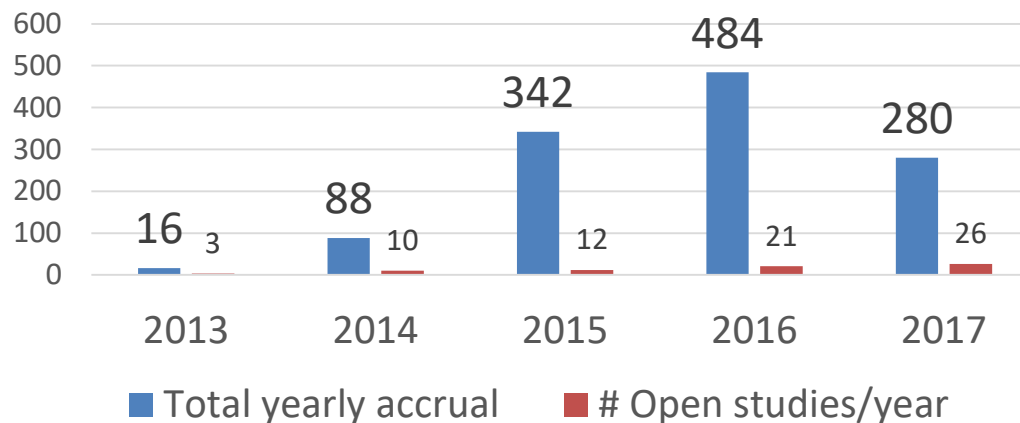
Types of Studies

- **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

DCP

study ideas, LOI/protocol/document review, IND sponsor, drug distribution, oversight and compliance



Lead Organizations (UG1)

(5 or 6 Grants)

study ideas/development/conduct, statistics, enrollment, fiscal management

Coordinating Center (U24)

(1 Grant)

data management, monitoring, clinical operations



Consortia Members

(Participating Orgs; ~100)

study ideas/development/conduct, participant enrollment, data entry

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 MoonshotSM 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**

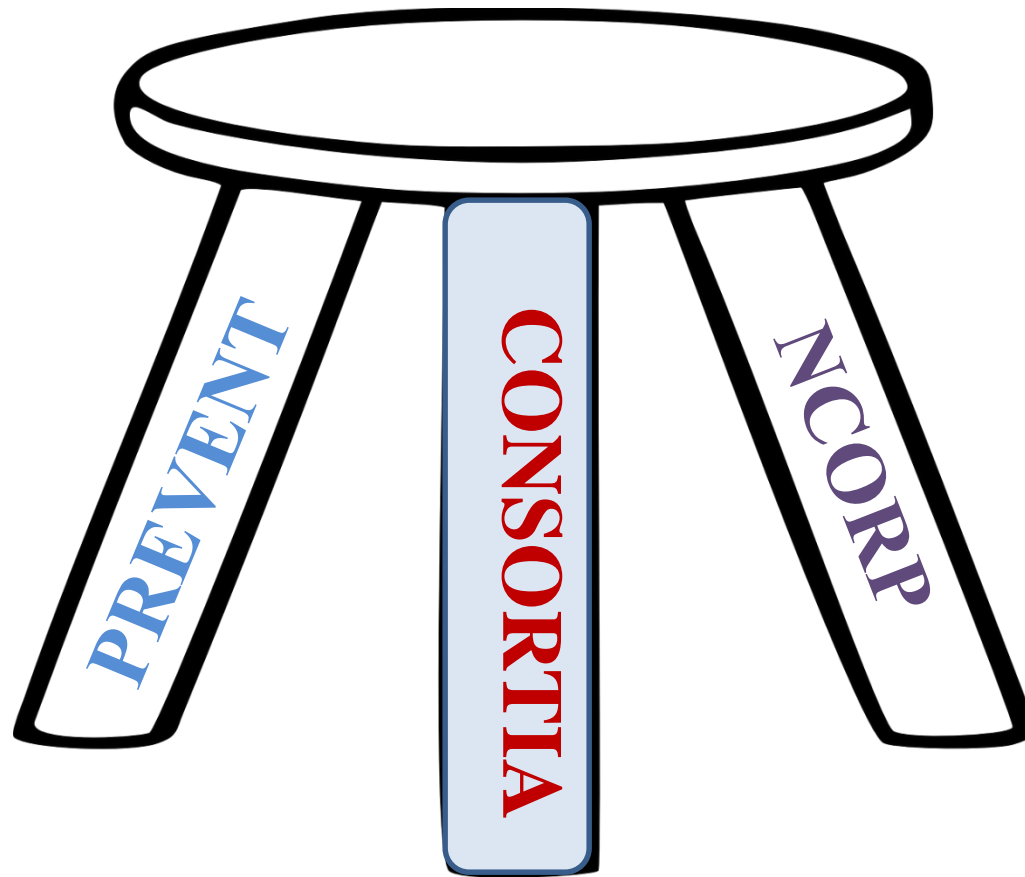
	Year 1	Year 2	Year 3	Year 4	Year 5
Coordinating Center	\$2M	\$3M	\$3M	\$3M	\$3M
CLO #1	\$1M	\$2M	\$2M	\$2M	\$2M
CLO #2	\$1M	\$2M	\$2M	\$2M	\$2M
CLO #3	\$1M	\$2M	\$2M	\$2M	\$2M
CLO #4	\$1M	\$2M	\$2M	\$2M	\$2M
CLO #5	\$1M	\$2M	\$2M	\$2M	\$2M
Total/yr.	\$7M	\$13M	\$13M	\$13M	\$13M

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

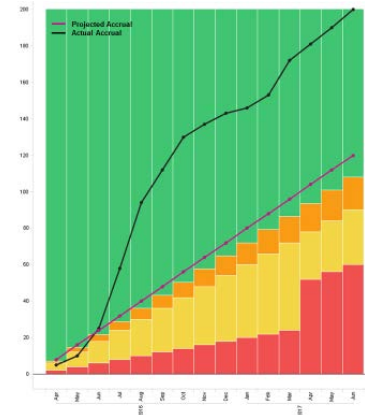


Back-up Slides

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**