Cancer Prevention Clinical Trials Network (CP-CTNet)

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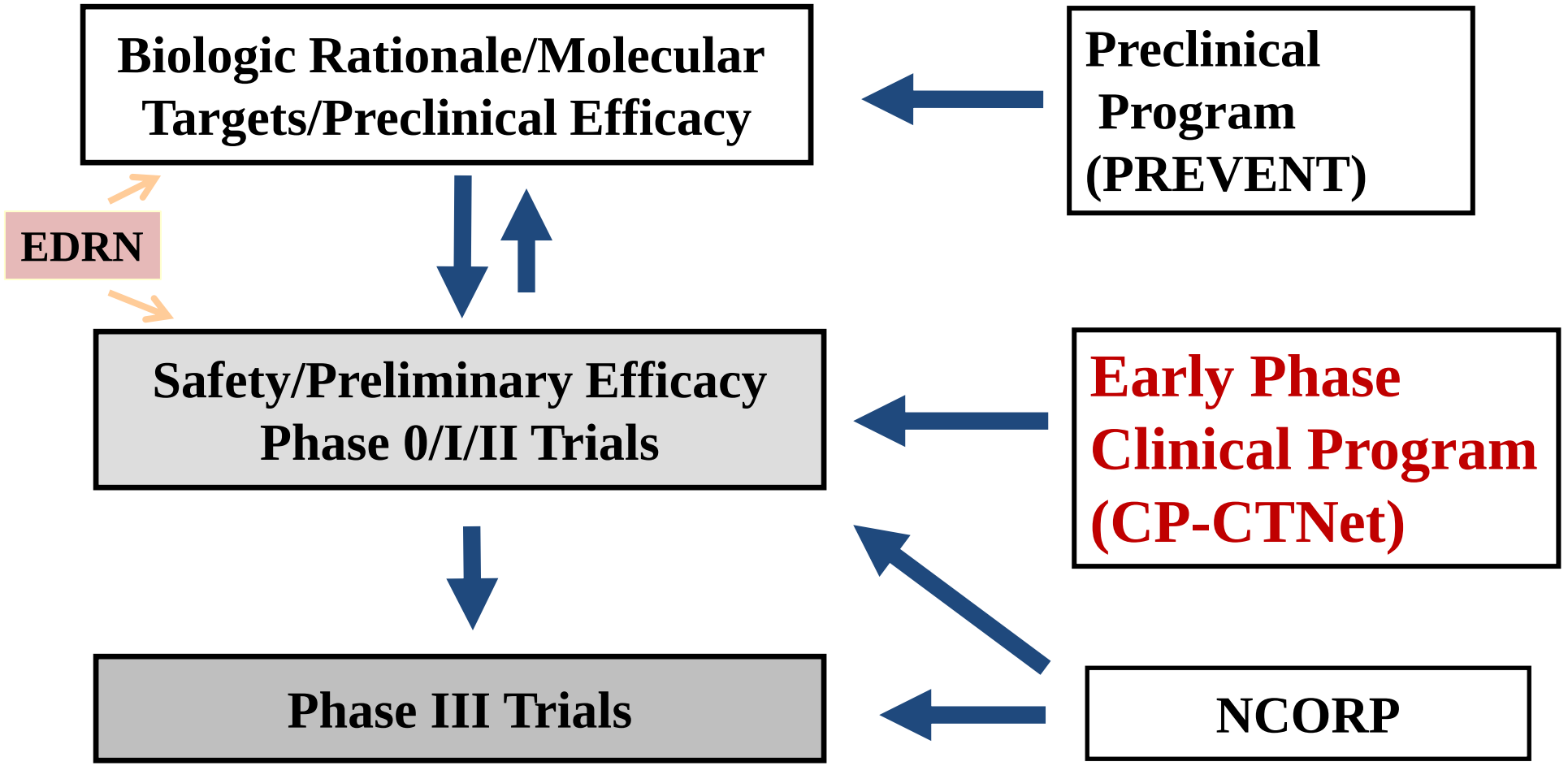
NIH NATIONAL CANCER INSTITUTE

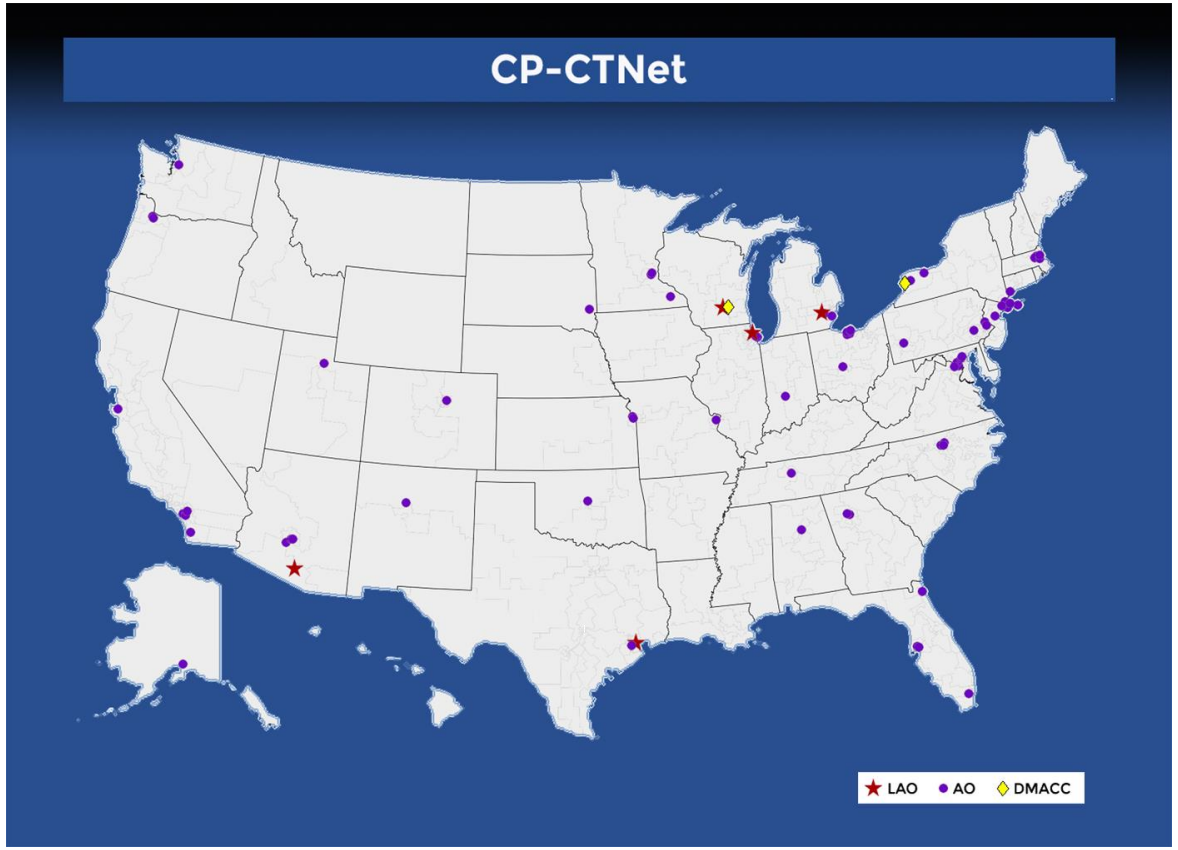
Concept Renewal
BSA 3/20/24

Early Phase Clinical Trials are a Critical Component of DCP's Drug Development Pipeline



- *Specimen biorepositories*

Cancer Prevention Clinical Trials Network: Objectives



Lead Academic Orgs
MD Anderson
Northwestern
Univ Arizona
Univ Michigan
Univ Wisconsin

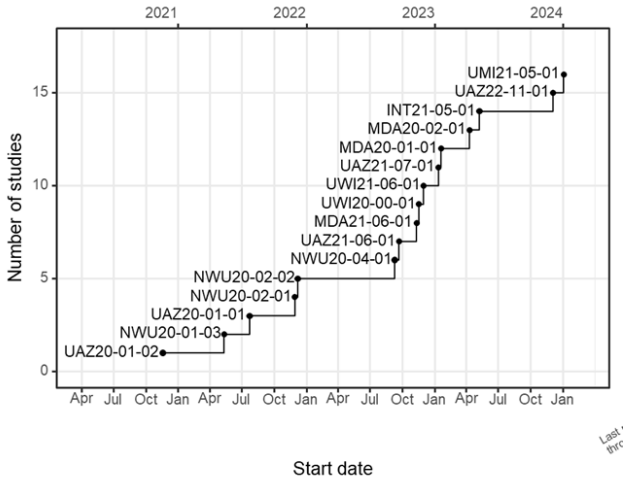
Coordinating Center
Univ Wisconsin

- **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**

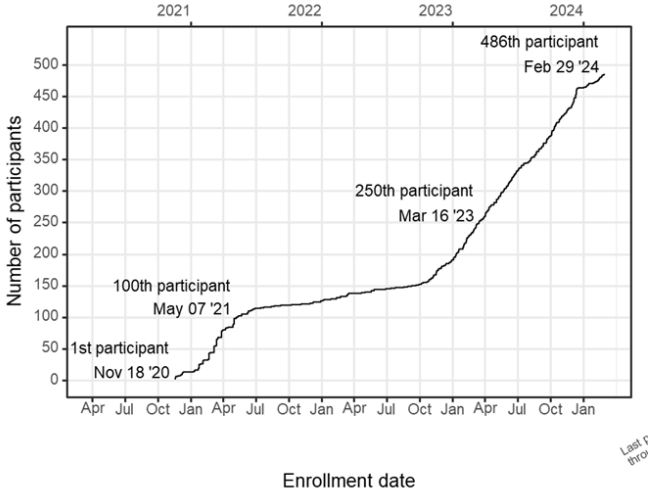
Programmatic Accomplishments FY2019-FY2024

- **59 concepts received (49% approved); 16 studies open to accrual, 1 closed, 12 in development**
  - **3 cross-network trials**
- **24 different agents/combinations; 4 experimental vaccines**

Study Activation



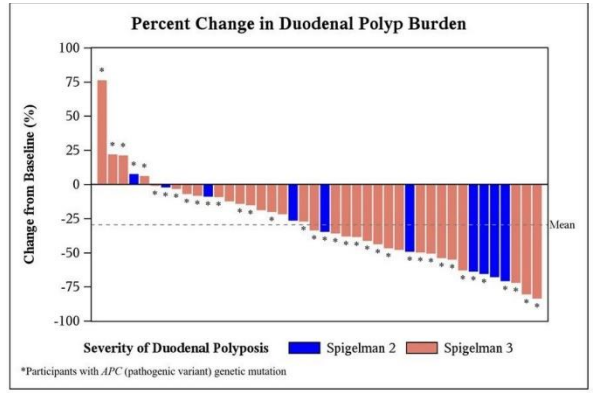
Accrual



- **3,093 individuals were pre-screened; 647 were screened; 491 enrolled (as of 3/11/24)**
  - **63% female; 15% Hispanic/Latino; 21% age >65 yrs**
  - **78% White; 7.4% Black; 5.6% Asian; 4.7% more than 1 race**
- **Rate of accrual since Oct 2022 meets expectations (~250/year)**

Scientific Accomplishments: Alternative Dosing Schedule

- ***Weekly*** **Erlotinib in Familial Adenomatous Polyposis**
  - **Erlotinib 350 mg qweek x 6 months (n=46)**
  - **Results:**
    - **29.6% ↓ in duodenal polyp burden**
    - **AEs: grade 2-3 in 72% (grade 3 in 4%), tolerable**
  - **Next step: under discussion, ph III +/- sulindac vs. other TKI**



- **Alternative dosing of exemestane in ER+ Stage 0-II Breast Cancer**
  - **Exemestane 25 mg qd vs. 3x/week vs. 1x/week x 4-6 weeks prior to surgery (n=180)**
  - **Results (1º endpoint):**
    - **3x/wk noninferior to QD in compliant patients**
    - **Secondary endpoint biomarkers consistent**
    - **AEs mild (but short intervention)**
  - **Next step: Longer study to better assess toxicity**
    - **Funding from Breast Cancer Research Foundation**

	% Change Estradiol
25 mg QD	-89%
25 mg 3x/week	-85%
25 mg 1x/week	-60%

N Jewel Samadder et al. Gut doi:10.1136/gutjnl-2021-326532
Serrano D et al. JAMA Oncol 2023;9(5):664–672. doi:10.1001/jamaoncol.2023.0089

Ongoing Studies: Precision Cancer Interception - Lynch Syndrome

- 1-3% colorectal cancers, 0.8-1.4% endometrial cancers, others
- Caused by mutations in MMR genes (*MLH1*, *MSH2/EPCAM*, *MSH6*, *PMS2*)
- Coding errors that lead to frameshift mutations generate novel peptides (neoantigens)

Study #1: Phase Ib/II Clinical Trial of Nous-209 (n=45)

- Off the shelf, frameshift peptide vaccine, 1º endpoint of safety/immunogenicity
- Preliminary data – positive T-cell (CD8+, CD4+) responses (n=10), against multiple peptide pools

Study #2: Multi-Targeted Adenoviral Vaccines (TriAd5) + N-803 (n=158)

- TriAd5: Combination of 3 vaccines targeting tumor-associated antigens CEA, MUC1, and brachyury
- N-803: IL-15 superagonist, stimulates activation, proliferation, survival, and cytotoxicity of NK and CD8+ T cells
- 1º Endpoint: Cumulative incidence of colorectal neoplasms on two follow-up yearly colonoscopies
  - Collaboration with NCI Intramural CIO: Jeff Schlom and James Gulley

NCT05078866, NCT05419011

D'Alise et al, LBA#1526, SITC 2023

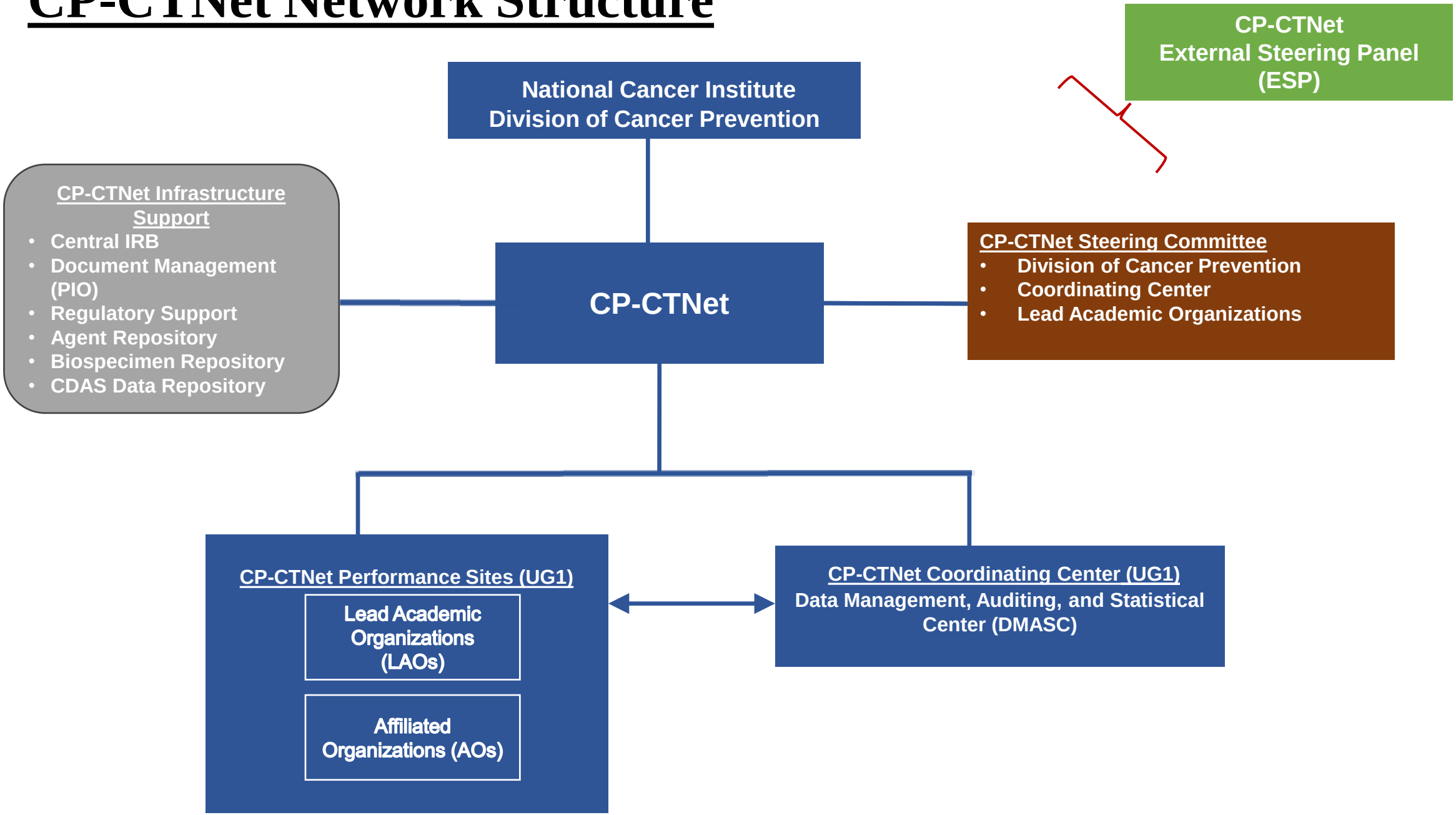
Purpose of RFA: Program Objectives

- **Continue to design and conduct early phase clinical trials to assess the cancer preventive potential of various interventions**
- **To characterize the effects of these agents on molecular targets, immune function, and other biological events associated with cancer development and correlate these effects with clinical endpoints**
- **To develop further scientific insights into the mechanism of cancer prevention by the agent examined and continue to develop novel potential markers as determinants of response**
- **Facilitate the development and conduct of cross-network trials**

Scope

- **Multiple organ sites to be explored**
- **Broad range of agents/interventions and clinical trial models**
- **Emphasis on risk/benefit**
- **Solicited and unsolicited proposals for study development**

CP-CTNet Network Structure



Scientific Areas of Emphasis

Overall Goal: move agents/strategies along the agent development pipeline

- **Targeting the biology of carcinogenesis**
  - Immunoprevention
  - Focus on high-risk populations
  - Pilot studies integrating high throughput technologies to understand mechanisms of carcinogenesis and drug action
- **Strategies to optimize risk/benefit**
  - Regional drug delivery (e.g., topical-breast; inhaled-lung)
  - Alternative dosing schedules (e.g., intermittent)
  - Combinations
- **Re-purposing ‘old’ drugs for prevention**
  - Emphasis on drugs affecting multiple chronic diseases (e.g., ASA, NSAIDs, metformin)

Key Program Changes

- **Coordinating Center (DMASC) mechanism change from U24 to UG1**
  - **responsible for the integrity of the trials (randomization, blinding, establishing interim analyses and early stopping rules for safety and futility) and must ensure compliance with all federal and international standards for clinical research**
  - **Statistical expertise to all trials, statisticians of record to cross-network trials**
- **Emphasis on young investigators**
  - **$125K/yr restricted funds for professional development of young/emerging investigators (faculty, fellows, post-docs)- $25K/person/yr**
- **Patient advocate or community engagement board for each LAO to bring in patient perspective, with funding**
- **Quality of Life – e.g., PROs; impact of high-risk status on QOL , inc. within context of interventions**
- **Develop supplement programs for tools for diverse recruitment and for biomarker analyses**

Future Directions-Scientific

- **Novel agents and optimizing risk-benefit**
  - **Inhaled bexarotene for lung cancer prevention (from PREVENT)**
  - **Build on low-dose tamoxifen (2 studies in development) and alternate dosing of exemestane for breast cancer prevention**
  - **Vaccine trials next steps**
    - **WOKVAC breast cancer vaccine (targeting IGFBP-2, HER2, and IGF-IR) immunogenic, further development under discussion**
    - **Nous-209 neoantigen vaccine (Lynch) potential phase II trial**
    - **TriAd5+N-803 has potential use in prevention of lung and breast cancers**
    - **FSP vaccine for Lynch syndrome developed by PREVENT**
  - **Awaiting results of multiple ongoing and recently completed trials to determine if any ready for next phase of development (inc. hand-off to NCORP)**
  - **PREVENT agents prioritized**

External Review, June 2023

External Steering Panel, Chair: Michael J. Birrer, MD, PhD (Univ. Arkansas)

- **Recommended program continuation, 6 years of funding with increase to do more translational work**
- **Program strengths**
  - **Unique and valuable, "serving a critical function in cancer preventive agent development", "the only program (private or public) doing this type of cancer prevention work in the US"**
  - **Successful in achieving goals, esp. in view of its start during COVID pandemic**
  - **Key scientific successes: moving agents forward, expansion into immunoprevention**
- **Recommendations:**
  - **Increase emphasis on mechanistic work, engage dedicated immunologist(s) and translational scientists**
  - **Optimize accrual and timelines; increase staffing and resources at sites (e.g., navigators)**
  - **Fund more fellows and early career investigators**
  - **Consider utilizing research supplement funds to leverage the program**

Portfolio Analysis

- **Portfolio analysis of clinical trials using term "cancer prevention" identified 664 grants, of which 38 grants met criteria for trials similar to CP-CTNet (since summer 2019)**
  - **18 were dietary and/or exercise, ablative interventions (e.g., cervix), biomarker analysis, or cancer treatment**
  - **21 trials in 20 grants were true cancer prevention interventions**
    - **majority are early phase, endpoints such as inflammation or signaling pathways**
- **Comparison is to 29 CP-CTNet studies**
  - **Range of target organs, more studies with premalignancy endpoints**
  - **Continued development for positive studies**

Justification for RFA and Cooperative Agreement

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

Budget

- **Program pays for:**
  - Core infrastructure (5 performance sites and coordinating center)
  - Screening procedures (e.g., to identify participants with high-risk premalignant lesions when not standard of care) and research biopsies
  - Clinical costs not covered by insurance (inc. history, physical exam, labs, procedures to obtain tissue, etc. that are frequently not standard of care)
  - Partial salary support for main PI and one site coordinator per trial
  - Tissue collection and biomarker endpoint analysis costs

- **Current program budget (FY2019-FY2024)**
  - Staggered funding – FY2019 funded 3 LAOs and DMACC; full program (5 LAOs) since FY2020; restructured to provide 6th year for the initially funded LAOs
  - RFA budget ~$10M/yr since FY2020 (range $8M - $11.5M); total $54.5M over 6 yrs
  - Support contract costs ~$1.4M/yr (range $1.3M - $1.6M); total $8.5M over 6 yrs
  - Total FY2019-FY2024 = $63.0M

Budget - New Program (FY2025-FY2030)

- **Program request for 6 years of funding:**
  - **RFA Request for UG1s (LAOs, DMASC): $12.0M year 1; total $72.0M over 6 years**
  - **Support Contracts: $1.7M year 1; total $11.35M over 6 years**
  - **Total budget: $13.7M year 1; $83.35M over 6 years**

CP-CTNet Component	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Total
Coordinating Center	$3.25M	$3.25M	$3.25M	$3.25M	$3.25M	$3.25M	$19.5M
LAOs (5)	$8.75M	$8.75M	$8.75M	$8.75M	$8.75M	$8.75M	$52.5M
Total RFA Request	**$12.0M**	**$12.0M**	**$12.0M**	**$12.0M**	**$12.0M**	**$12.0M**	**$72.0M**
Contracts							
Rave/CIRB/ CDAS/ Biorepository	$1.7M	$1.8M	$1.85M	$1.9M	$2.0M	$2.1M	$11.35M
Total CP-CTNet Funding	**$13.7M**	**$13.8M**	**$13.85M**	**$13.9M**	**$14.0M**	**$14.1M**	**$83.35M**

Budget Justification

- **Trials ongoing, Network at full function**
  - **Open competition, may need to ramp up new LAOs and transition studies from current program**
  - **Transition to UG1 funding by current or new DMASC**

- **Coordinating Center (DMASC):**
  - **Statistical center, centralized data management and database, DSMB coordination, ↑auditing, administer young/emerging investigator restricted funds**
- **LAOs:**
  - **↑Patient care costs, ↑vaccine monitoring costs, ↑translational endpoints, anticipate 2-3 additional studies per year, reserve $0.5M/yr for cross-network trials and emerging new ideas**

BSA Subcommittee Questions

- **How will the RFA address mentoring of junior investigators, in addition to requiring set aside funding?**
  - **A specific plan for mentoring and professional development of young investigators will be required, including criteria for selection of investigators, activities to prepare investigators for independent careers, and mentor requirements ($25K/yr/LAO restricted funds)**
  - **Proposals to access funds for specific investigators will be reviewed by Steering Committee**
- **How will the RFA address diverse recruitment?**
  - **LAOs will need to form teams capable of diverse enrollment, including AOs with access to diverse populations. Strength of the plan will be included in the review criteria**
  - **Specific strategies to ensure diverse enrollment will need to be outlined**
- **How will the inclusion of patient advocates be incorporated into the RFA?**
  - **Each LAO will propose a plan to include patient advocates in network activities, ranging from concept development through trial conduct. Funds should be allocated within the grant**

Acknowledgments

- CP-CTNet Program – grantees, DCP staff, DCP contractors
- Jeff Schlom and James Gulley, NCI CIO
- Pharmaceutical and biotech collaborators
- Participants in early phase prevention trials
- BSA Subcommittee

NCI Cancer Prevention Clinical Trials Network

A program of the National Cancer Institute of the National Institutes of Health