Critical Components of Systematic Preventive Agent Development
DCP Drug Development Programs

Biologic Rationale/Molecular Targets/Preclinical Efficacy

Preclinical Program (PREVENT)

Safety/Preliminary Efficacy Phase 0/I/II Trials

Clinical Program ("Consortia")

Phase III Trials

EDRN

NCORP
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:

  ![Accrual chart]

• 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 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

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

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.**

|---------|---------|---------|---------|---------|---------|

– 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

<table>
<thead>
<tr>
<th></th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coordinating Center</td>
<td>$2M</td>
<td>$3M</td>
<td>$3M</td>
<td>$3M</td>
<td>$3M</td>
</tr>
<tr>
<td>CLO #1</td>
<td>$1M</td>
<td>$2M</td>
<td>$2M</td>
<td>$2M</td>
<td>$2M</td>
</tr>
<tr>
<td>CLO #2</td>
<td>$1M</td>
<td>$2M</td>
<td>$2M</td>
<td>$2M</td>
<td>$2M</td>
</tr>
<tr>
<td>CLO #3</td>
<td>$1M</td>
<td>$2M</td>
<td>$2M</td>
<td>$2M</td>
<td>$2M</td>
</tr>
<tr>
<td>CLO #4</td>
<td>$1M</td>
<td>$2M</td>
<td>$2M</td>
<td>$2M</td>
<td>$2M</td>
</tr>
<tr>
<td>CLO #5</td>
<td>$1M</td>
<td>$2M</td>
<td>$2M</td>
<td>$2M</td>
<td>$2M</td>
</tr>
<tr>
<td>Total/yr.</td>
<td>$7M</td>
<td>$13M</td>
<td>$13M</td>
<td>$13M</td>
<td>$13M</td>
</tr>
</tbody>
</table>

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