Cancer Preventive Agent Development Program: The Early Phase Pipeline

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Development of Cancer Opportunities for Intervention

DCP Early Phase Clinical Trials Program
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
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
DCP Early Phase Clinical Trials Consortia

Current:
5 contractors
->100 member sites
-perform phase 0, I & II studies
-43 approved trials, 2013-now

Future:
Cancer Prevention Clinical Trials Network (CP-CTNet)- funded by cooperative agreements
-RFA-CA-18-029 (CP-CTNet Sites)-UG1
-RFA-CA-18-030 (Coordinating Center)-U24
Areas of Emphasis for 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)
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
Immunoprevention

**Pathogen-associated cancers**
- Cervical cancer: deferred booster nonavalent HPV vaccine
- Multivalent broadly protective HPV vaccine (RG1-VLP, developed by PREVENT program)
- Therapeutics of HPV IEN - 5-FU/imiquimod (TLR7 agonist), Phase 1
- Liver cancer: HCV vaccine, Phase 1

**Tumor-associated antigens**
- MUC1 vaccine (MUC1 aberrantly glycosylated in adenocas, expressed in many premalignancies)
  - Colorectal adenoma (immunogenicity)
  - Current/former smokers undergoing CT screening (immunogenicity)
- Multi-peptide (WOKVAC-HER2/IGFBP2/IGFR1) and HER2 vaccines in breast cancer - immunogenicity endpoints
- PSA vaccine (PROSTVAC) in prostate cancer active surveillance cohort – immunologic response in tissue (CD8+, CD4+ cells)
Rationale for Topical Approaches to Breast Cancer Prevention

1) The mammary gland is derived from the skin

2) There is well-developed internal lymphatic circulation

3) Drugs applied to the breast skin reach higher concentrations in the breast than when applied to the skin elsewhere.

Hiroo Suami Annals Surg Oncol
Pujol H 1995 Cancer Chemother Pharmacol
Lee O 2015 Cancer Chemother Pharmacol
Minimizing Toxicity – Topical Approaches for Breast Cancer Prevention

• 4-hydroxytamoxifen- tamoxifen metabolite
  – Phase II topical 4-hydroxytamoxifen (4-OHT) vs. oral tamoxifen (T) in women with DCIS, 6-10 wks pre surgery (Consortia 2003) – n=27 (loss of drug supply)
    • ↓ Ki-67 post Rx in DCIS; 3.4% 4-OHT vs. 5.1% T (P<0.03 in both, between-group P=0.99)
    • Tissue concentrations of 4-OHT equivalent
    • Endocrine/coagulation biomarker effects reduced by 4-OHT; no difference in hot flashes

• Ongoing topical 4-OHT studies (n=2)
  – presurgical DCIS, topical vs. oral (n=100), 8 wks Rx, 1º endpoint-Ki-67, 2º include breast tissue levels (multiple sites if mastectomy)
  – Phase IIb, placebo controlled (n=152), mammographically dense breasts, 12 mths Rx, 1º endpoint- breast density
Minimizing Toxicity – Topical Approaches for Breast Cancer Prevention: Other Agents

- **Telapristone - anti-progestin**
  - Phase II trial topical vs. oral telapristone x 4 wks in women with Stage I-III breast ca., undergoing mastectomy;
  - 1° endpoint: tissue concentration
  - n=65 completed, analysis in progress

- **Endoxifen (tamoxifen metabolite)**
  - Phase I: 2 dose levels and MTD expansion; 3-5 week Rx, women scheduled for mastectomy, 1° endpoint- safety/toxicity

- **Bexarotene (rexinoid), potentially effective in ER-negative breast cancer**
  - Phase I: 3 dose levels and MTD dose expansion, 4 wk Rx, women at risk for breast cancer (various criteria); 1° endpoint- safety/toxicity

*Wiehle R et. al. CAPR 2011*
Repurposing Old Drugs for Chemoprevention

- Metformin-cancer incidence literature mixed and affected by multiple confounders and time-related biases
  - DCP meta-analysis, RR=0.69, 95%CI, 0.52-0.90
  - Correction for BMI or time-related biases reduced RR to 0.82 and 0.90, respectively

- Awaiting long-term f/u of Diabetes Prevention Program

- 3 prior DCP phase II trials measuring metformin impact on biomarkers negative (Barrett’s, prostate, colorectal aberrant crypt foci)
  - Metformin accumulated in prostate

- Ph IIa in oral leukoplakia
  - Clinical PR – 18%
  - Histologic CR/PR- 59%

Next Steps for Metformin

- *Thus far insufficient data for phase III trials across multiple organ systems*

- Biomarker analysis and sequencing of oral leukoplakia lesions
# Potential Future Trials: PREVENT and Follow-up Studies

## Immunoprevention Agents

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

PREVENT  CP-CTNet  NCORP