Cancer Preventive Agent Development Program: The Early Phase Pipeline

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CTAC
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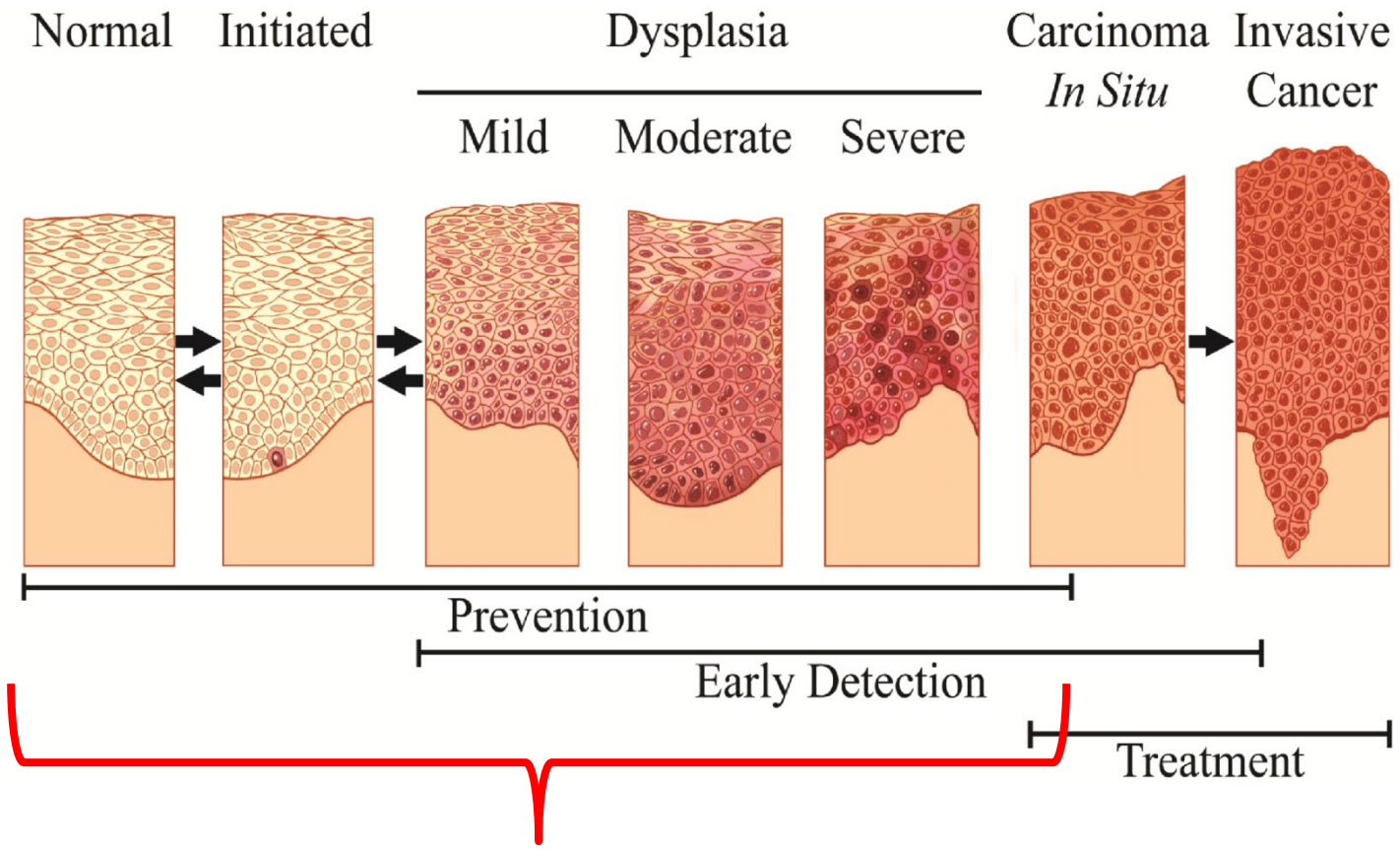
Development of Cancer
Opportunities for Intervention



DCP Early Phase Clinical Trials Program

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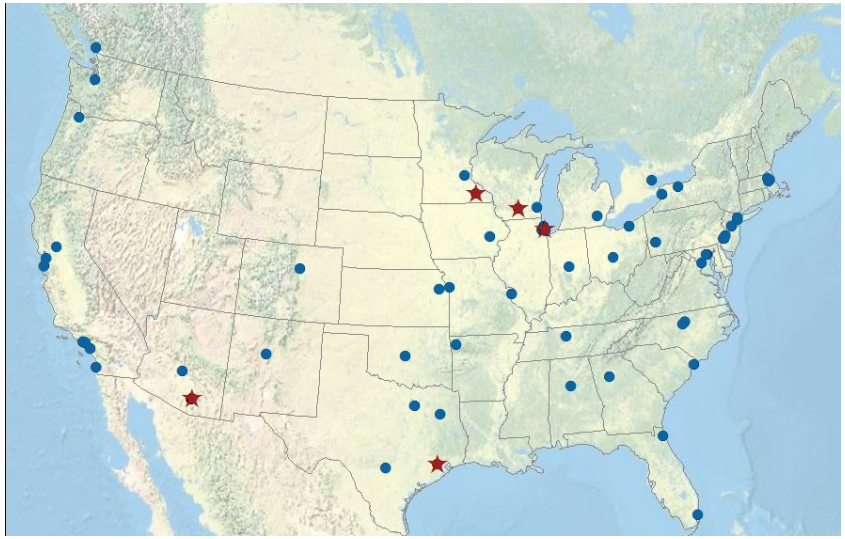
Program Objectives

- **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



★ CLO (Lead Site) ● PO (Participating Site)

<u>Current</u>:

5 contractors

->100 member sites

-perform phase 0, I & II studies

-43 approved trials, 2013-now

<u>Future</u>:

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

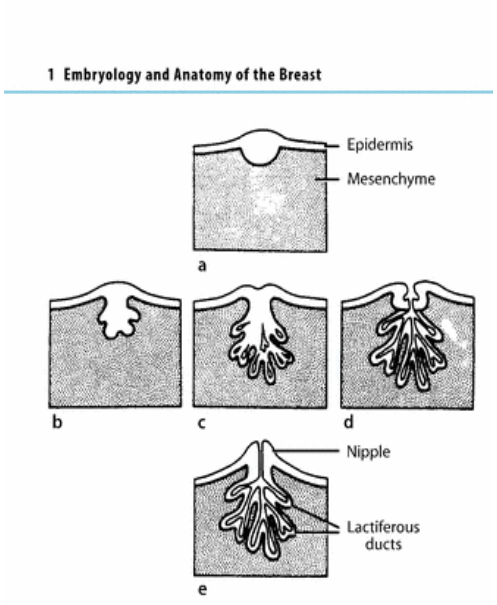
- **9cUAB30: RXR-specific retinoid (rexinoid), no liver agonist function**
  - **Preclinical data: effective in ER+ and ER- mouse models**
  - **Developed under DCP RAPID program (precursor of PREVENT)**
    - **Phase I, first in human (5-20 mg), then 28-day multiple doses (0, 20, 40, 80, 160, 240 mg 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

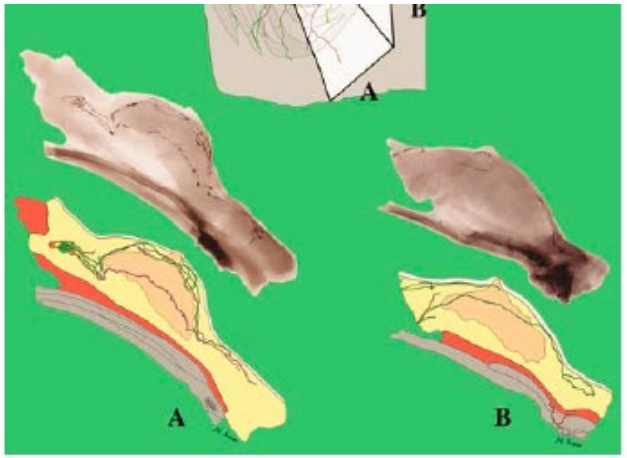
- **Pathogen-associated cancers**
  - **Cervical cancer: deferred booster nonavalent HPV vaccine**
  - **Multivalent broadly protective HPV vaccine (RG1-VLP, developed by PREVENT program)**
  - **Therapeutics of HPV IEN - 5-FU/imiquimod (TLR7 agonist), Phase 1**
  - **Liver cancer: HCV vaccine, Phase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

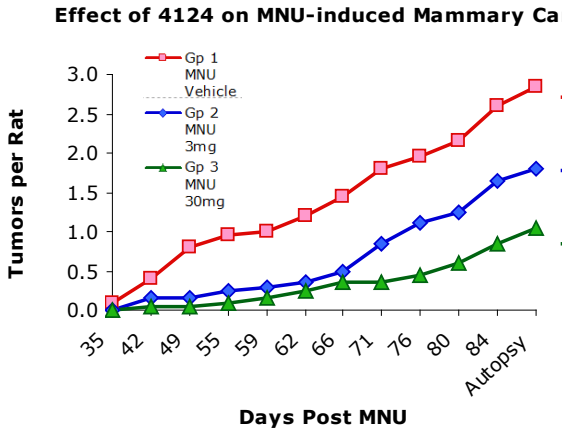
Hiroo Suami Annals Surg Oncol
Pujol H 1995 Cancer Chemother Phamacol
Lee O 2015 Cancer Chemother Phamacol

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**
      - *Lee et al. Clin Cancer Res 2014;20:3672*
- **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;**
    1º endpoint: tissue concentration
    -n=65 completed, analysis in progress



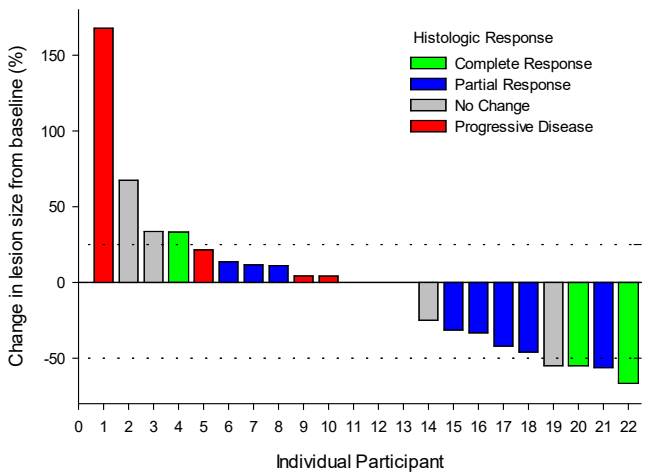
- **Endoxifen (tamoxifen metabolite)**
  - **Phase I: 2 dose levels and MTD expansion; 3-5 week Rx, women scheduled for mastectomy, 1º endpoint- safety/toxicity**

- **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); 1º 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%**



Gandini S et al. Cancer Prev Res 2014;7:867
Chak A et al. Clin Gastroenterol Hepatol 2015;13:665
Nguyen MM et al. Eur J Cancer Prev 2017, Epub

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

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

The Three Critical Components of DCP Preventive Agent Development