National Cancer Institute

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

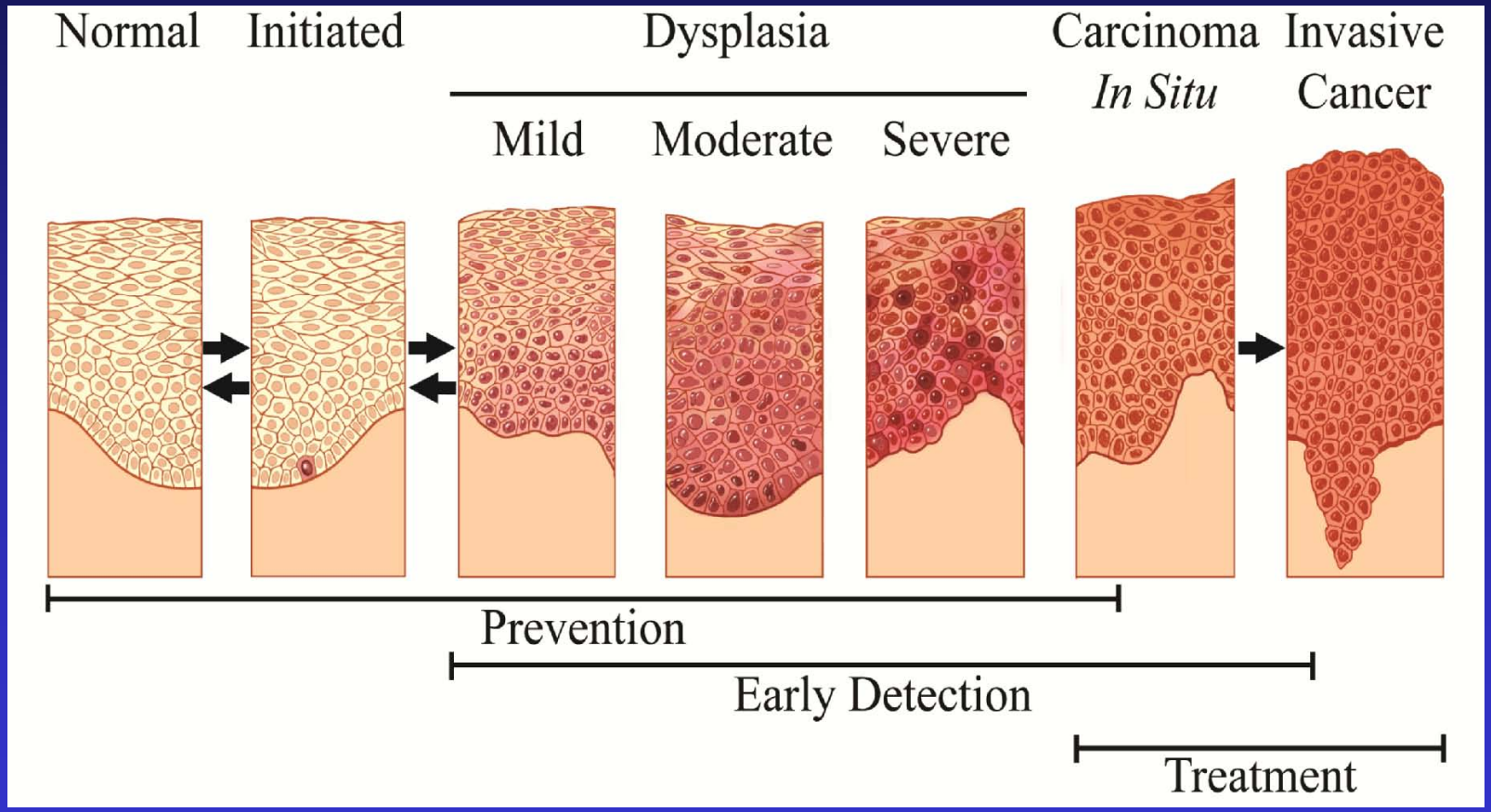
National Institutes of Health

NCI's Consortia for Early Phase Prevention Trials

CTAC March 2012

Eva Szabo, MD
Chief, LUACRG
Division of Cancer Prevention, NCI

Development of Cancer: Opportunities for Intervention



Challenges for Cancer Prevention Drug Development - Scientific

- Targets/agent selection
- Risk-benefit balance
- Cohort selection
- Recognizing efficacy during early clinical development

Challenges for Cancer Prevention Drug Development - Logistical

- Expense and difficulty of biomarker trials requiring tissue acquisition
- Limited funding opportunities to conduct early phase clinical trials (grants, pharma)
- Magnitude and duration of definitive phase III trials, funding issues

Minimal Requirements for Preventive Strategies

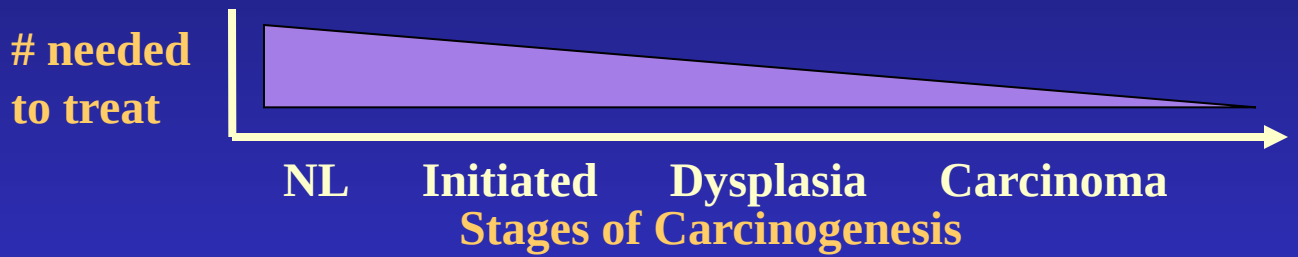
- **Benefit**
  - **Efficacy in preventing cancer and associated morbidity/mortality**
- **Risk**
  - **Lack of adverse side effects that increase morbidity/mortality from other diseases, short- and long-term (major side effects)**
  - **Tolerability of intervention (minor side effects affecting compliance)**

Efficacy: How Do We Identify New Agents?
Areas for Investment

- **Knowledge of mechanism**
  - **Example: HPV vaccine and cervical cancer**
  - **Need: understanding molecular pathogenesis**
- **Preclinical (*in vitro* and animal models)**
  - **Example: NSAID treated carcinogenesis and transgenic models**
  - **Need: models reflective of complexity of human disease**
- **Observational epidemiology (cohort and case-control studies)**
  - **Example: NSAIDs and colon cancer incidence/mortality**
- **Secondary endpoints from clinical trials (including non-malignant diseases)**
  - **Example: Tamoxifen/raloxifene and breast cancer**

Optimizing the Risk-Benefit Balance

- Identify individuals most likely to develop cancer in short time frame
  - Highest risk (e.g., presence of high-risk preneoplasia)
  - Homogeneous cohorts (current vs. former smokers, FAP vs. HNPCC vs. sporadic colorectal adenomas)
  - Pharmacogenetic considerations

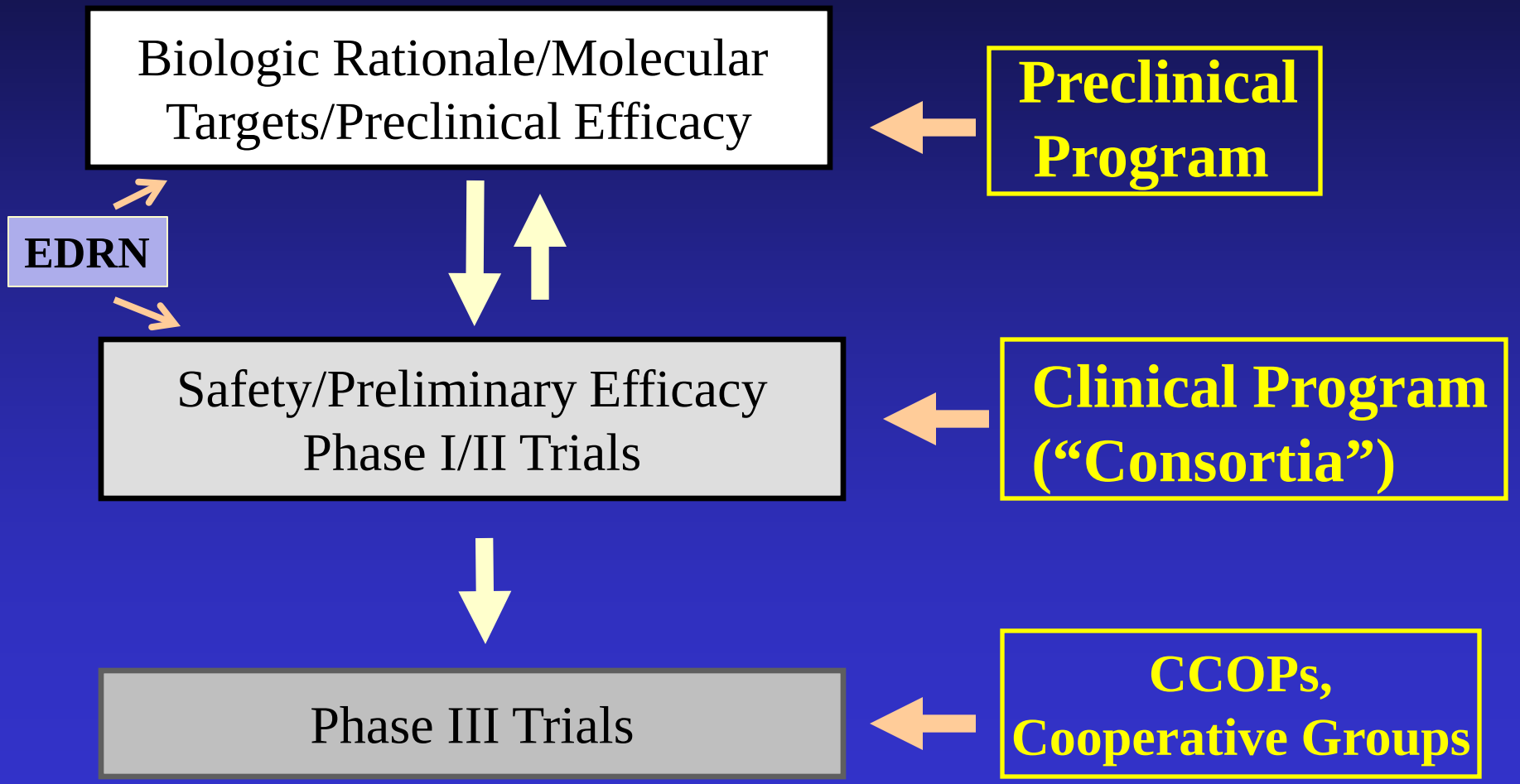


- Minimize toxicities from drug (e.g., route, schedule, modulators of toxicity)

Barriers:

- Lack of adequate risk assessment models for most cancers
- Incomplete understanding of carcinogenesis at different target organs

NCI-DCP Consortia for Early Phase Clinical Trials

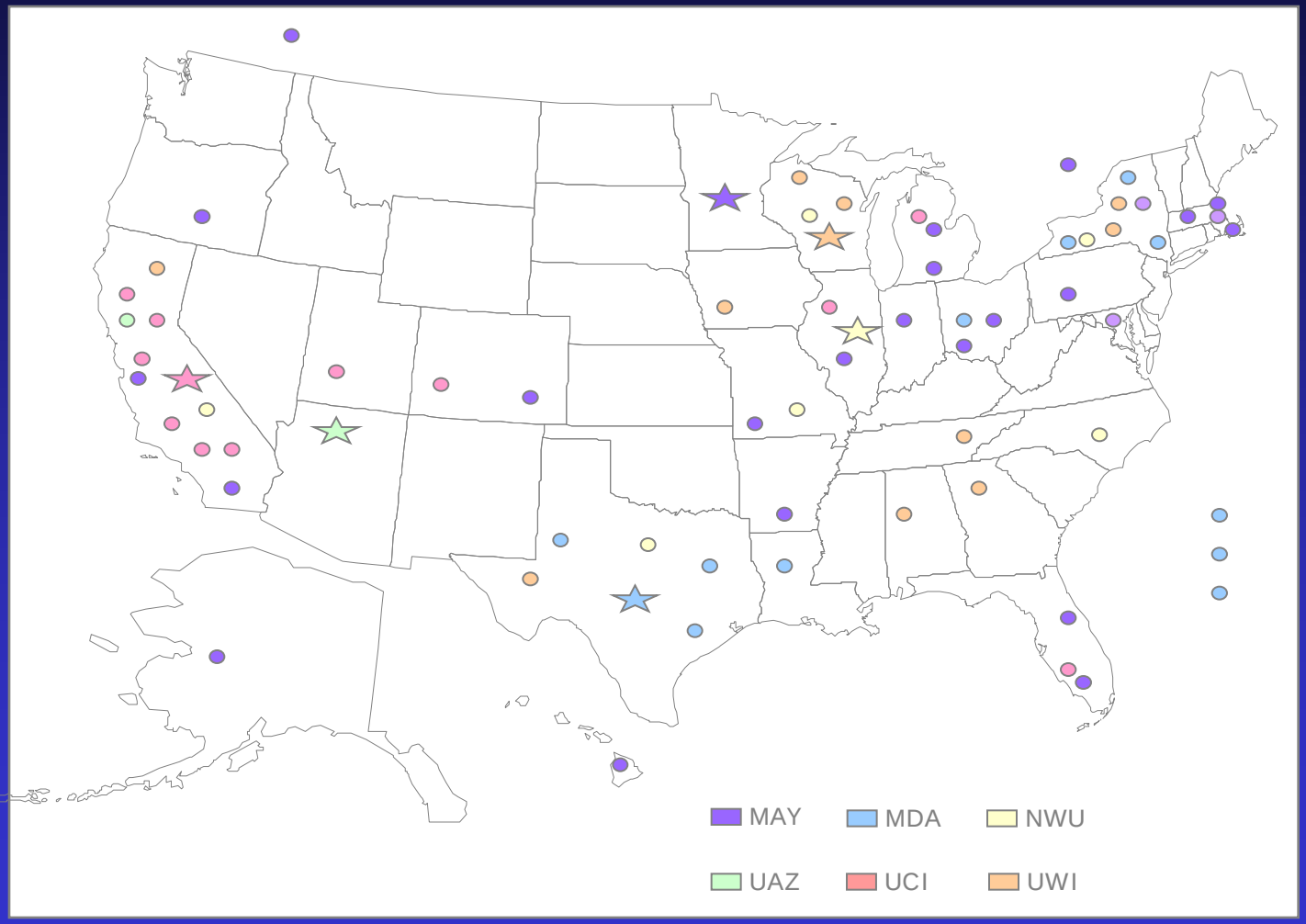


NCI-DCP Consortia for Early Phase Clinical Trials
Objectives

- To qualify cancer preventive agents for further clinical development via the conduct of phase 0, I, & II clinical trials assessing preliminary efficacy and safety

- 2^{o} goals:
  - Optimize clinical trial designs
  - Investigate intermediate endpoint biomarkers

NCI-DCP Consortia for Early Phase Clinical Trials 2003-2011

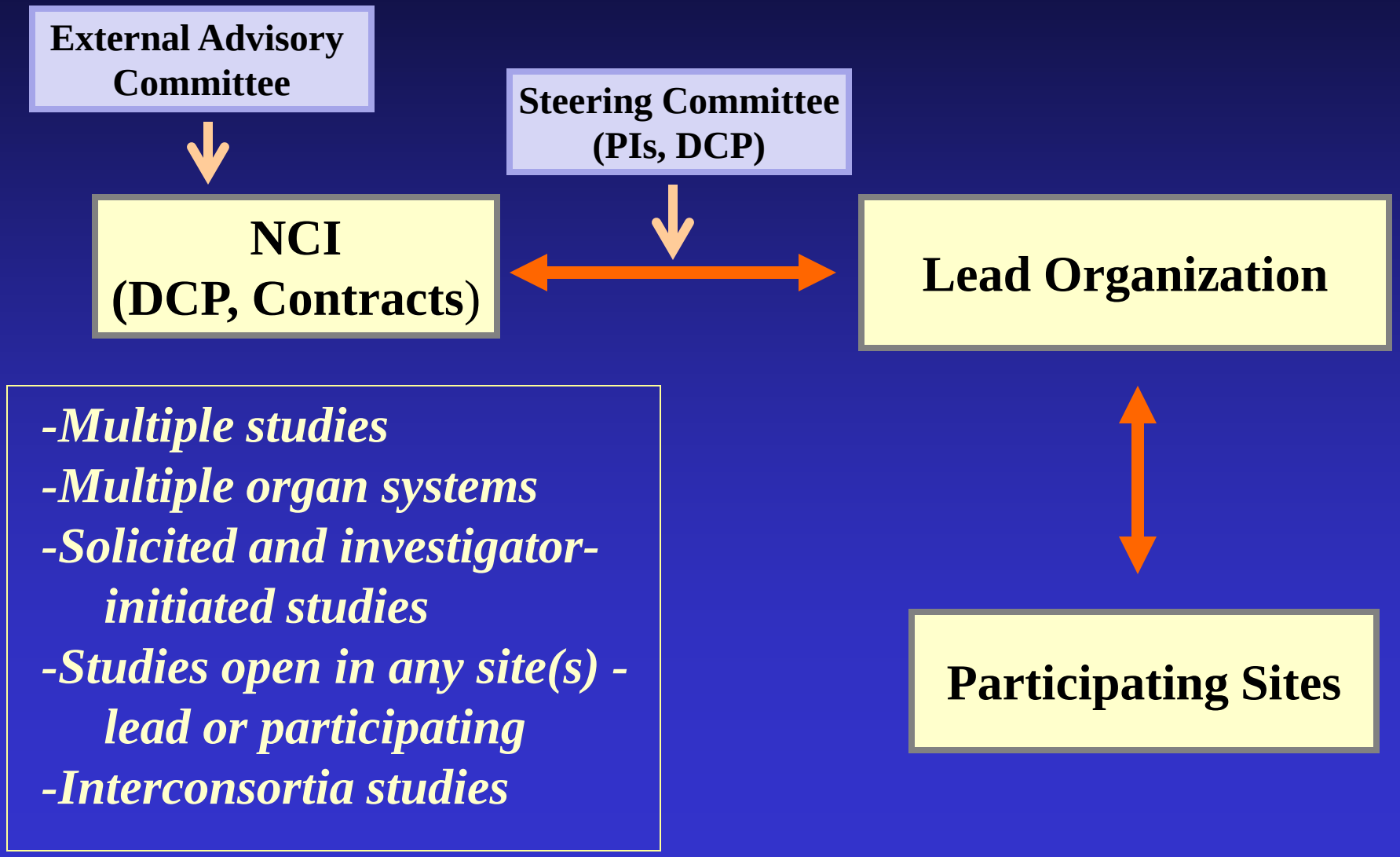


6 contractors
->90 member sites
-perform phase 0, I & II studies

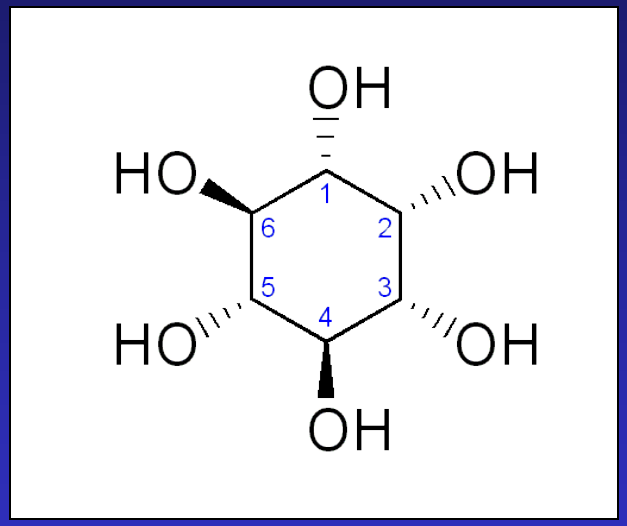
<u>Goals:</u>
-agent testing
-biomarker identification
-clinical trial design optimization

NCI-DCP Consortia for Early Phase Clinical Trials

Structure



myo-Inositol



- Glucose isomer
- Source of several second messengers & signaling molecules
- Dietary sources (grains, beans, fruits, rice)
- Studied in psychiatric conditions (+/-), diabetic neuropathy(+/-), polycystic ovary syndrome (+)

Rationale for *myo*-Inositol in Lung Cancer Prevention

- **Efficacy**
  - **Multiple animal studies show inhibition of carcinogen induced tumors in mice (40-50%)**
    - **Estensen and Wattenberg, Carcinogenesis 1993;14:1975**
    - **Hecht et al., Carcinogenesis 2002;23:1455**
  - **Inhibits carcinogenesis in mainstream/sidestream smoke-exposed A/J mice by 53%**
    - **Witschi H et al., Carcinogenesis 1999;20:1375**
  - **Combination with budesonide ↑↑ efficacy up to 80%**
    - **Estensen and Wattenberg, Carcinogenesis 1993;14:1975**
    - **Witschi et al. Carcinogenesis 1999;20:1375**
    - **Wattenberg et al. Carcinogenesis 2000;21:179**
- **Safety**
  - **Used in multiple short term trials for psychiatric and diabetic neuropathy indications – no toxicity reported**
  - **Generally Regarded as Safe (GRAS) by US FDA terminology**

Phase I Study of *myo*-Inositol in Bronchial Dysplasia

-Lam et al., CEBP 2006;15:1526

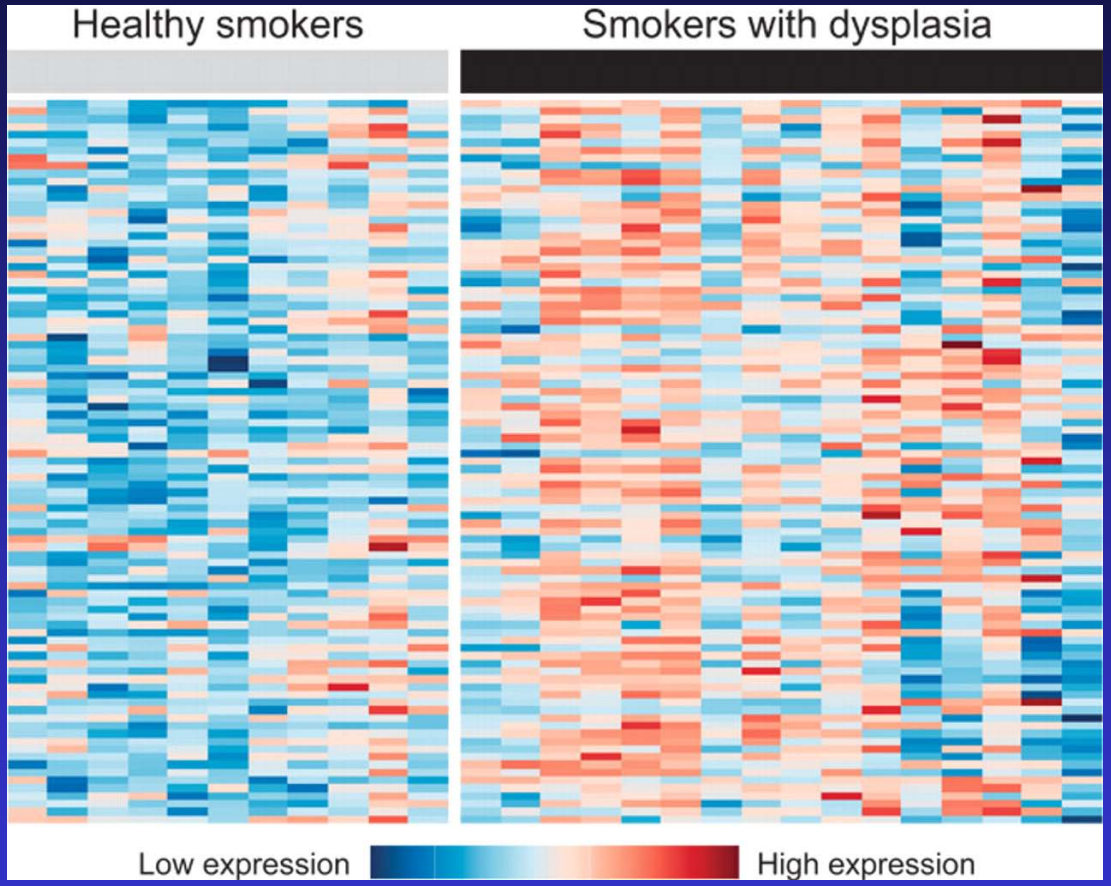
- **Phase I study (26 participants)**
  - **tolerable 18 g/d**
  - **91% vs. 48% regression dysplasia, P=0.014 (10 participants)**
  - BP↓ ~14 mm Hg, independent of meds

Table 5. Changes in pathologic grades of bronchial biopsy samples at baseline and after 3 months of *myo*-inositol (18 g): Lesion-specific analysis

Pathologic grades of bronchial biopsies at baseline	Status after 3 months of treatment			
	N	Stable	Regression*	Progression†
Placebo group (from ref. 18)				
Normal/hyperplasia/metaplasia	256	219	0	37
Mild dysplasia	134	72	62	0
Moderate/severe dysplasia	13	5	8	0
myo-Inositol group				
Normal/hyperplasia/metaplasia	38	36	0	2
Mild dysplasia	10	1	9	0
Moderate/severe dysplasia	1	0	1	0

PI3K pathway activation in the airways of smokers with dysplasia

Gustafson A M et al. Sci Transl Med 2010;2:26ra25



-PI3K pathway is activated in smokers with dysplasia in airway $p<0.001$

-Myo-inositol inhibited PI3K activation in normal bronchial airways in smokers with regression of dysplasia ($p=0.04$)

Why is this study so important?

- **Does PI3K activation truly identify smokers at risk for cancer?**
  - **Easier to get normal brushings than to identify dysplasia (sampling bias); do not remove biomarker with procedure**
  - **Potential to identify "the right" cohort**
- **New potential clinical trial model – pathway analysis pre- and post-treatment, smaller # participants, shorter interventions**
  - **Identify mechanisms of interventions**
  - **Needs validation!**

Potential for Personalized Chemoprevention

Phase IIb *myo*-Inositol Chemoprevention Trial

PI: Stephen Lam, British Columbia Cancer Agency

30+ pack yr. smokers with dysplasia, age ≥45-79
N=110

↓ (Bronch, Spiral CT)

myo-inositol 9g bid vs. placebo x 6 mths

↓ (Bronch, Spiral CT)

1º Endpoint: bronchial dysplasia (# sites/grade)
2º Endpoints: multiple biomarkers (gene expression)

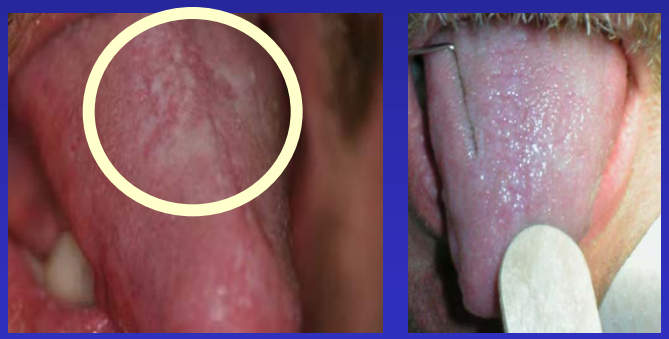
Clinical sites: BCCA, Mayo Clinic, New Mexico VA

Peroxisome Proliferator-Activated Receptor γ (PPAR γ) as a Target for Prevention of Aerodigestive Carcinogenesis

- Pioglitazone – PPARγ agonist approved for type II DM
- Rationale:
  - Cell lines – induces growth arrest, differentiation (NSCLC)
  - Animal carcinogenesis models
    - 4-NQO rat tongue model; incidence and multiplicity ↓ 10-fold
      - Yoshida et al., Cancer Sci 94:365, 2003
  - Epidemiology
    - 33% ↓ lung cancer in diabetics using TZDs (RR=0.67; 95% CI, 0.51-0.87); Nonsignificant decrease in colon and prostate cancer
      - Govindarajan et al. JCO 2007;25:1476-81
    - 41-55%↓ HNSCC in diabetics using TZDs
      - Govindarajan R et al. JCO 2007;25:63s

Pioglitazone in Oral Leukoplakia

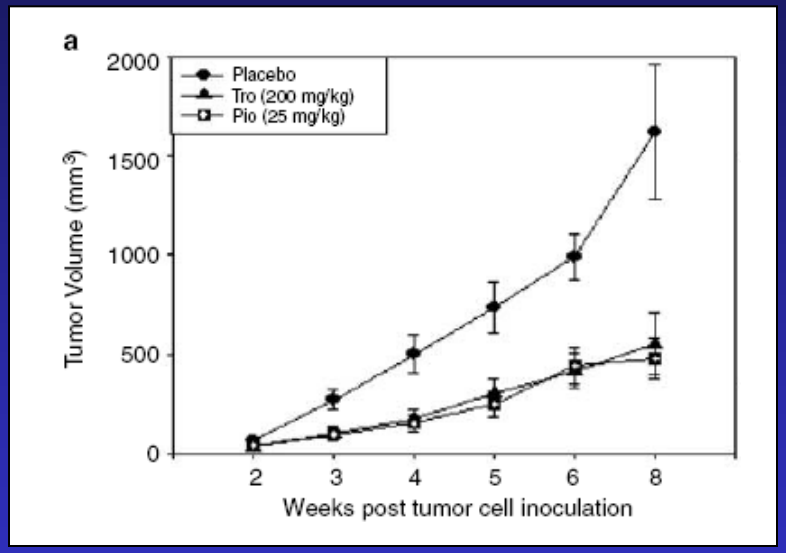
- DCP phase IIa clinical trial - 22 pts., 81% clinical response rate, 79% average ↓size
  - F. Ondrey, U Minn
    - AACR Frontiers Cancer Prev Res, 2007



pre post

Effect of PPARγ Agonists on NSCLC: Animal Models

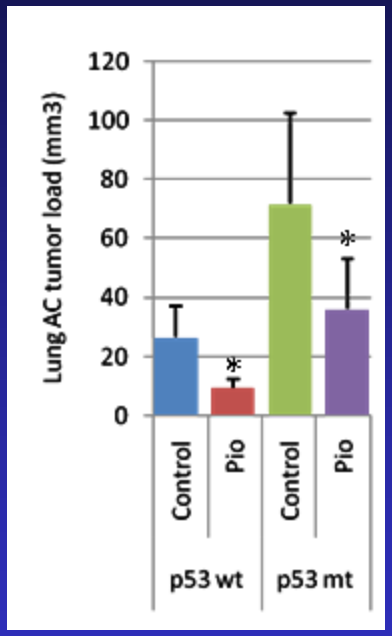
Treatment



-tumor volume ↓ 66.7%
-growth delay 104 days

-Keshamouni et al. Oncogene 2004;23:100-8

Prevention



- Vinyl carbamate-treated mice
  - 56-64% ↓ in tumor burden in wildtype and p53 mutant animals
  - Wang Y et al. Mol Cancer Ther 2010;9:3074-82

Current Pioglitazone Clinical Trials (NCI sponsored)

- Phase IIb oral leukoplakia
  - Pioglitazone 45 mg qd vs placebo x6 months
  - 100 participants; 11 sites
  - 1^{o} Endpoint: clinical and pathologic response
  - PIs: Jay Boyle, MSKCC and Frank Ondrey, UMinn
- Pilot trial presurgical NSCLC trial
  - Pioglitazone 45 mg qd for 2-6 weeks prior to definitive surgery
  - 20 participants; biomarker endpoints
  - PI: Dennis Wigle, Mayo

Novel Agents in Prevention Clinical Trials

Examples

Agent/Agent Class	Target	Organ
metformin	LKB/AMPK	colon, Barrett's, prostate
SR13688	Akt	phase I
UAB30 (rexinoid)	RXRs	phase I
EGF receptor inhibitors	EGFR	lung, colon ACF (dose de-escalation)
myo-inositol	PI3K	lung, colon

Areas of Emphasis for New Consortia

- **Emphasis on:**
  - **Understanding biology of carcinogenesis**
    - **Pilot studies integrating high throughput technologies to understand mechanisms of carcinogenesis and drug action**
    - **New scientific areas – e.g., immunoprevention**
  - **Re-purposing old drugs for prevention; emphasis on drugs affecting multiple chronic diseases**
  - **Intermediate endpoint biomarkers as surrogates for cancer incidence (EDRN)**
  - **Develop and integrate existing risk assessment strategies into trials to identify highest risk populations**
  - **Minimizing toxicity – combinations, alternative delivery schedules (e.g., pulsatile treatment), regional drug delivery**
  - **Biorepository**