NCI’s Consortia for Early Phase Prevention Trials
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Development of Cancer: Opportunities for Intervention

- Normal
- Initiated
- Dysplasia: Mild, Moderate, Severe
- Carcinoma In Situ
- Invasive Cancer

Prevention
Early Detection
Treatment
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

Stages of Carcinogenesis

<table>
<thead>
<tr>
<th>Stages of Carcinogenesis</th>
<th># needed to treat</th>
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<tbody>
<tr>
<td>NL</td>
<td></td>
</tr>
<tr>
<td>Initiated</td>
<td></td>
</tr>
<tr>
<td>Dysplasia</td>
<td></td>
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<tr>
<td>Carcinoma</td>
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NCI-DCP Consortia for Early Phase Clinical Trials

Biologic Rationale/Molecular Targets/Preclinical Efficacy

Preclinical Program

Safety/Preliminary Efficacy
Phase I/II Trials

Clinical Program ("Consortia")

Phase III Trials

CCOPs, Cooperative Groups

EDRN
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° 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

Goals:
-agent testing
-biomarker identification
-clinical trial design optimization
NCI-DCP Consortia for Early Phase Clinical Trials
Structure

- Multiple studies
- Multiple organ systems
- Solicited and investigator-initiated studies
- Studies open in any site(s) - lead or participating
- Interconsortia studies

- Lead Organization
- Participating Sites

NCI (DCP, Contracts)

Steering Committee (PIs, DCP)

External Advisory Committee
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

**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>
<thead>
<tr>
<th>Pathologic grades of bronchial biopsies at baseline</th>
<th>Status after 3 months of treatment</th>
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<tr>
<td></td>
<td>N</td>
</tr>
<tr>
<td>Placebo group (from ref. 18)</td>
<td></td>
</tr>
<tr>
<td>Normal/hyperplasia/metaplasia</td>
<td>256</td>
</tr>
<tr>
<td>Mild dysplasia</td>
<td>134</td>
</tr>
<tr>
<td>Moderate/severe dysplasia</td>
<td>13</td>
</tr>
<tr>
<td><em>myo</em>-Inositol group</td>
<td></td>
</tr>
<tr>
<td>Normal/hyperplasia/metaplasia</td>
<td>38</td>
</tr>
<tr>
<td>Mild dysplasia</td>
<td>10</td>
</tr>
<tr>
<td>Moderate/severe dysplasia</td>
<td>1</td>
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</table>
PI3K pathway activation in the airways of smokers with dysplasia


- 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)

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

Clinical sites: BCCA, Mayo Clinic, New Mexico VA
Peroxisome Proliferator-Activated Receptor γ (PPARγ) 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
  – 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


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 carbamamate-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
  - 1st 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

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<thead>
<tr>
<th>Agent/Agent Class</th>
<th>Target</th>
<th>Organ</th>
</tr>
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<tbody>
<tr>
<td>metformin</td>
<td>LKB/AMPK</td>
<td>colon, Barrett’s, prostate</td>
</tr>
<tr>
<td>SR13688</td>
<td>Akt</td>
<td>phase I</td>
</tr>
<tr>
<td>UAB30 (rexinoid)</td>
<td>RXRs</td>
<td>phase I</td>
</tr>
<tr>
<td>EGF receptor inhibitors</td>
<td>EGFR</td>
<td>lung, colon ACF (dose de-escalation)</td>
</tr>
<tr>
<td>myo-inositol</td>
<td>PI3K</td>
<td>lung, colon</td>
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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