Phase II Prevention Trials

The Translational Bridge Between Prevention Science and Clinical Benefits

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Division of Cancer Prevention

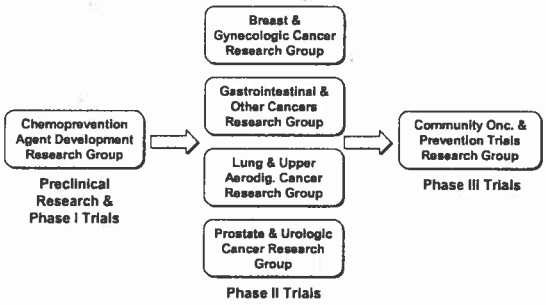
Forces Driving Phase II Trials

- Growing biological understanding of
  - Carcinogenesis & cancer risk
  - Molecular targeting
  - Responses to interventions
- Opportunity to extend translational insights
- Wealth of reasonable preventive targets & agents
- Urgent need to efficiently prioritize candidates for definitive clinical trials
  - Time
  - Participants
  - Funding

Phase II Programmatic Objectives

- Identify and prioritize the most promising compounds for definitive phase III trials
- Improve mechanistic insights into carcinogenesis and chemopreventive efficacy
- Standardize and validate surrogate endpoint biomarkers

NCI's Chemoprevention Program

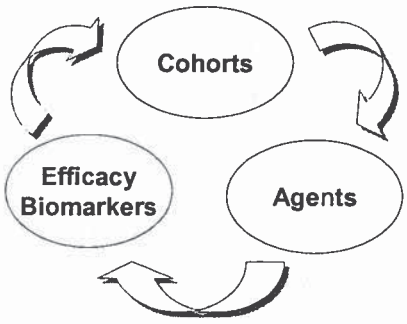


Scope of the Phase II Program

Over 40 ongoing Phase II trials

- **49 investigators**
- **25 primary clinical sites**
  - Baylor University
  - British Columbia Cancer Agency
  - Cleveland Clinic
  - Columbia University
  - Duke University
  - European Institute of Oncology
  - Fox Chase Cancer Center
  - Johns Hopkins University
  - Mayo Clinic
  - Northwestern University
  - Strang Cancer Prevention Center
  - University of Alabama
  - University of Arizona
  - University of California – Irvine
  - University of California – San Francisco
  - University of Illinois – Chicago
  - University of Kansas
  - University of Michigan
  - University of Minnesota
  - University of North Carolina
  - University of Pittsburgh
  - University of Texas – MD Anderson
  - University of Texas – Southwestern
  - University of Wisconsin
  - Wayne State University

Cardinal Elements of Clinical Trials



Pharmacodynamic Endpoints: Importance of the Biologic Continuum in Phase II Trials

Clinical
- Intraepithelial lesions
  - Number
  - Size
  - Cumulative burden

Pathologic
- Dysplasia regression
- Dysplasia grade
- Nuclear morphometry

Cellular
- Proliferation
- Apoptosis

Molecular
- Mutations
- Epigenetic alterations
- LOH
- Genomic microarrays
- Proteomics

Biochemical
- Prostanoids
- Polyamines
- Cytokines

Molecular Targets for Colorectal Cancer Chemoprevention

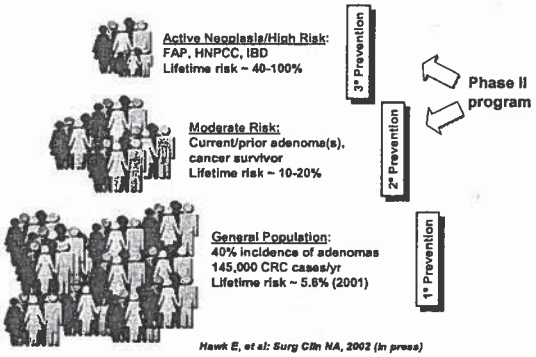
- **Genetic Mutations**
  - *APC*
  - *p53*
- **Growth Factors & Critical Receptors**
  - VEGF
  - Vitamin D receptor
  - EGFR
  - Retinoid receptors
    - RARs/RXRs/both
  - Estrogen receptor
  - PPAR-gamma or -delta
- **Key Enzymes**
  - COX-2
  - Ornithine decarboxylase
  - Farnysyl transferase
  - Matrix metalloproteinase
  - Raf kinase
  - SAM decarboxylase
  - Cyclin-dependent kinases
  - Inducible nitric oxide synthetase (INOS)

Hawk E, et al: Surg Clin NA, 2002 (in press)

Chemopreventive Agents in Phase II Trials

Target	Agent
Estrogen pathway	Tamoxifen, raloxifene
COX-1 and/or COX-2	NSAIDs, celecoxib
Steroid receptor	Budesonide
5-Lipoxygenase	Zileuton
Reactive oxygen species	Selenium
EGFR pathway	EGFR antagonists
Farnesyl transferase, ras	Farnesyl transferase inhibitors

Cohorts at Risk for Colorectal Cancer



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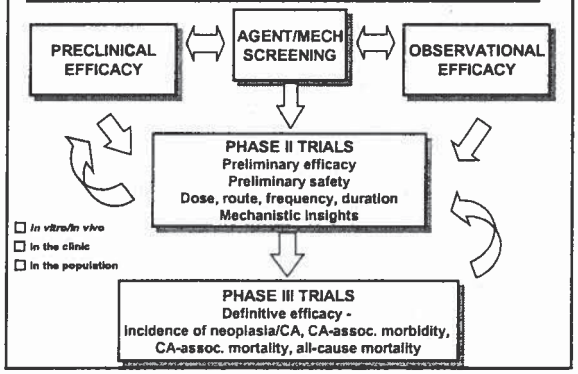
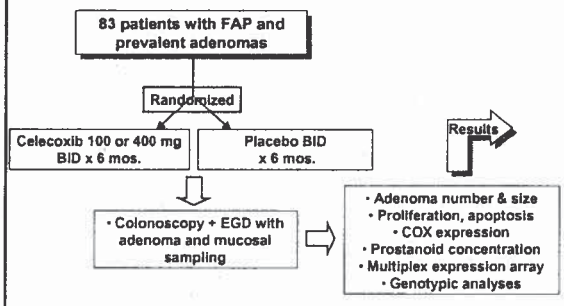
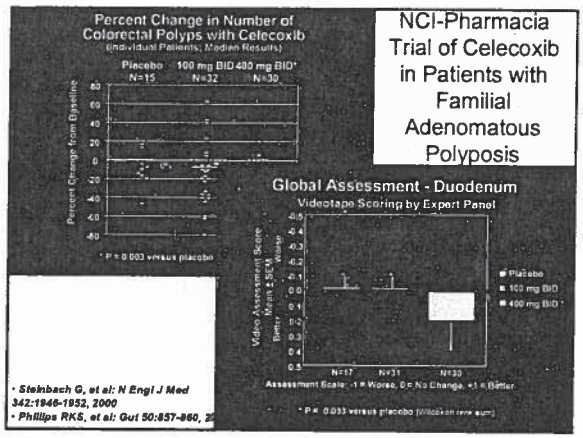
Trials Emerge from Multidisciplinary Data



Celecoxib Reduces Adenomas in Patients with Familial Adenomatous Polyposis





Phase II Trial in Lung Cancer Chemoprevention

Anethole dithiolthione (Sialor®) Reduces Bronchial Dysplasia

112 current or former smokers with bronchial dysplasia on LIFE bronchoscopy

Randomized

ADT 25 mg TID x 6 mos.

Placebo TID x 6 mos.

• LIFE bronchoscopy with re-biopsy of pre-treatment sites and new lesions

• Histopathologic grade
• Nuclear morphometric index

Results:

	Persons	Lesions
• CR	↑68.8%	↑29.3%
• PD	↓45.8 %*	↓52.9%*

Key: *Statistically significant p<0.05; CR – complete regression of all dysplastic lesions AND no new dysplastic lesions; PD – progression of dysplastic lesions by ≥1 grades OR any new dysplastic lesion

Lam S, MacAulay C, le Riche JC, et al: J Natl Cancer Inst 94:1001-1009, 2002

Phase II Trial in Prostate Cancer Chemoprevention

Selenomethionine Accumulates in Prostate Tissues after Short-term Administration

68 men with prostate cancer preprostatectomy

Randomized

Selenomethionine 200 mcg/d x 14-31 days

No intervention x 14-31 days

•Blood
• Prostate tissue (*via* needle/punch bx)
• Seminal vesicle tissue

Results:
Mean serum Se = ↑ 15%*
Mean prostatic Se = ↑ 22%*
Mean SV Se = no change

Sabichi, et al: PAACR 43:94993, 2002

Phase II Trial in Breast Cancer Chemoprevention

Design Validation with Tamoxifen as a Positive Control

100 women at ≥1.66% 5-year risk for breast cancer

Randomized

Tamoxifen 10 mg BID x 3 months

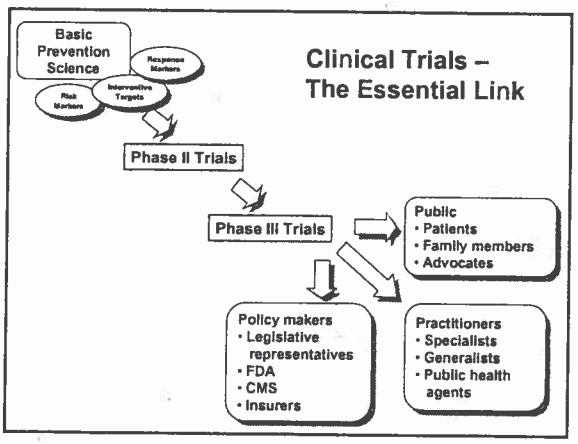
Placebo x 3 months

• Bilateral random FNA's and a unilateral random core biopsy

• Histopathology
• Proliferative & apoptotic rates
•Fractional allelic loss
• IGF and EGFR-related markers

Open to accrual:
University of Texas-Southwestern
University of Texas – MD Anderson
Baylor University Medical Center

Innovations in NCI's Phase II Program

- **New Agents**
  - Curcumin
  - EGFR inhibitors
  - T4NV endonuclease
  - HSP E-7 HPV vaccine
- **New Methods of Agent Delivery**
  - Aerosolized inhalation
  - Topical
- **New Cohorts**
  - HNPCC
  - MGUS
  - Squamous esophageal dysplasia
  - Solid organ transplant recipients
- **New Technologies for Efficacy Assessment**
  - High-resolution endoscopy
  - Digital imaging of skin lesions
  - LIFE bronchoscopy
  - Spiral CT
  - Ductal lavage
  - Expression microarrays
  - Proteomics
- **New Pharma Collaborators**
  - AGI Dermatics
  - Pharmascience
  - StressGen Biotechnologies
- **New Concepts**
  - Preventive combinations
  - Nested prevention endpoints

Clinical Trials – The Essential Link