

## Identification & Early Development of Potential Cancer Preventive Agents

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## Objectives of Presentation

- Provide an overview of the cancer preventive agent development program in the Division of Cancer Prevention
- Present examples of ongoing projects and accomplishments in various program areas of agent development

## Preclinical & Early Clinical Agent Development

- *In Vitro* Mechanistic Screening
- Short-term *In Vivo* Screening
- *In Vivo* Efficacy Studies
- Intermediate Endpoint Studies
- Pharmacokinetic & Toxicology Studies
- Chemistry, Manufacturing, & Control
- Phase 1 Clinical Pharmacokinetic & Safety

## Chemopreventive Agent Development Program Organization

- Agent Identification
  - RAPID, PA Cancer Prevention Small Grants R03
- *In Vitro* and Short-Term *In Vivo* Screening
  - PA Molecular Targets of Drug Discovery R21 & SBIR
- *In Vivo* Efficacy & Intermediate Endpoints
  - RFAs Preclinical models of former smokers and of nonhormonally responsive breast cancer R01
- Pharmacology and Toxicology
  - PAR Innovative Toxicology Models R21/R33
- Phase 1 and 2 Clinical Trials
  - RFA Phase 2 prevention studies in former smokers R01

## Identification of Agents

- Experimental Carcinogenesis and Epidemiological Literature
- Pharmaceutical and Biotechnology Collaborations
- RAPID

## Pharmaceutical Collaborations

- Proprietary Agents (>45 Collaborations)
  - COX-2 Inhibitors, Aerosolized Glucocorticoid, Farnesyl Transferase & EGFR antagonists, etc.
  - First generation agents in mechanistic classes:  
e.g., 4-HPR, DFMO, & Oltipraz
- Development of Natural Products
  - Isoflavones, catechins, lycopene, resveratrol, DIM
- Development of Nonpatentable Agents
  - Indole-3-carbinol, curcumin, PEITC, Se Cmpds.

### RAPID: Rapid Access to Preventive Agent Development

- Lipoxygenase inhibitors
- Steroid hormone analogs
- Phase II enzyme modulators
- Intermediary metabolites
- Flavonoid compounds
- Natural products / extracts
- HPV vaccines

### Chemopreventive Agent Development: Efficacy Testing

Intervention using various regimens:  True Clinical Response

Early  
Continuous  
Late  
Combinations

*i.e., ↓ incidence and multiplicity of adenomas / cancers, ↑ latency*

### In Vivo Efficacy Studies: Carcinogen-Induced Models

- Prevention of Mammary Cancer in Rats
  - Administer methyl nitrosourea (MNU) to 100 day-old rats then admix preventive agent in diet from day 7 to day 150 post MNU
  - endpoints: tumor incidence, multiplicity, latency, histopathology
- Established models for prostate, colon, lung, skin, esophagus, bladder
- Additional models for pancreas, head & neck, ovary, and melanoma

### In Vivo Efficacy Studies: Genetically Engineered Models

- Tumor Suppressor Genes
  - APC in colon, P53 in lung, & BRCA 1 in breast
- Oncogenes
  - KiRas in lung and Ptc in skin
- DNA Repair Genes
  - MLH1 and MSH2 in colon
- Other Models: *e.g. breast*, retrovirally mediated HaRas or Neu oncogene, BRCA1 x P53 knockouts, BRCA1 conditional knock-outs, and SV40 T-antigen oncogene combined with hormonally responsive promotor

### Celecoxib: Colon Tumor Incidence & Multiplicity in AOM-Treated Rats

Treatment	Incidence (animals w/tumor)	Multiplicity (adenocarcinomas)
Control	74 %	1.26 ± 1.11
Celecoxib (1500 ppm; week 5-58)	17	0.22 ± 0.59
Celecoxib (1500 ppm; week 22-58)	39	0.50 ± 0.77

Reddy, B.S., Hirose, Y., Lubet, R. et al. *Cancer Research* 60: 293-297, 2000.

### Celecoxib: Bladder Tumor Incidence & Multiplicity in BBN-Treated Mice

Treatment (ppm)	Incidence (%)	Multiplicity
0	51	0.56
200	29	0.32
500	24	0.24
1250	12	0.13

Adapted from Grubbs et al. *Cancer Res.* 60: 5599, 2000.

### NSAID + DFMO: Tumor Multiplicity in Small Intestine of MIN Mouse

Treatment	Middle	Distal
Control	23.75 ± 2.23	10.38 ± 1.56
Piroxicam (25 ppm)	10.93 ± 3.27**	2.50 ± 0.69**
DFMO (0.5%)	19.80 ± 2.43	3.67 ± 1.05**
PX + DFMO	7.21 ± 1.93**	0.80 ± 0.29**

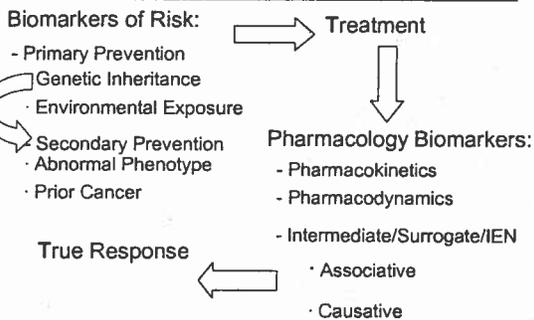
Jacoby, R.F., Cole, C.E., Tutsch, K. et al. *Cancer Research* 60: 1864-1870, 2000.

### Aerosolized Glucocorticoids: Lung Tumor Incidence & Multiplicity in B[a]P-Treated Rats

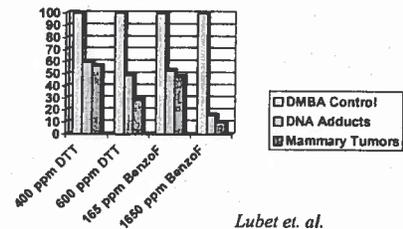
Treatment	Incidence (animals w/tumor)	% Inhibition
Control	6.1 ± 2.3	0
Budesonide (23 µg / kg bwt)	1.1 ± 1.0	82
Budesonide (72 µg / kg bwt)	0.6 ± 1.1	90

Wattenberg, et al. *Carcinogenesis* 2: 179, 2000.

### Biomarkers and Efficacy Testing



### Environmental Exposure: Effect of Blocking Agents on DNA Adducts and Tumor Multiplicity

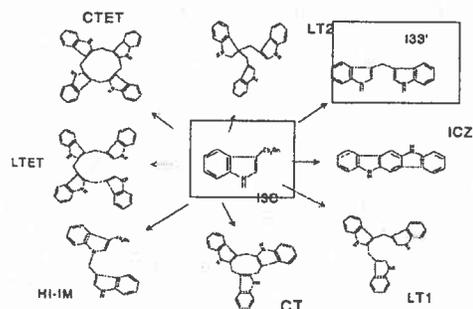


Lubet et al.

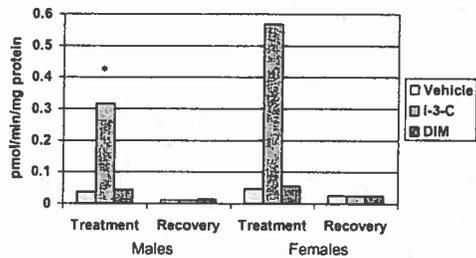
### Autosomal Dominant Syndromes: Early Molecular Changes in Cancer

- Molecular genetic pathways are relatively well understood in many instances of autosomal dominant forms of cancer
- Genetic changes occurring in autosomal dominant forms of cancer are also present in intraepithelial neoplasia and sporadic forms of cancer
- Characterization of phenotypically normal cells from autosomal dominant forms of cancer will facilitate discovery of early molecular genetic changes in IEN and sporadic cancers
- Ongoing projects in BRCA 1 & 2, P53, Rb, TSC2, VHL, FAP, and MLH1

### Metabolism of Indole-3-Carbinol



### CYP 1A1/2 Activity in Liver



\*  $p < 0.05$

Induction can be elimination of acetaminophen, theophylline, estradiol, etc.

### Examples of Agents in Development

- **Colon**
  - NO-releasing NSAIDs, lipoxygenase inhibitors, curcumin, resveratrol
- **Breast**
  - EGFR & Aromatase inhibitors, RXR agonists, I-3-C / DIM
- **Prostate**
  - EGCG, Lycopene, isoflavones, DHEA analog, Se cmpds
- **Lung**
  - PPARs, PEITC, FTI, EGCG, glucocorticoids

*Combinations of agents that have different mechanisms of action*

### Chemopreventive Agent Development : Summary

- The use of pharmacologic, nutritional, endocrinologic, & immunologic interventions to block, reverse, or delay the process of carcinogenesis is a novel approach to risk reduction and cancer control
- Techniques in molecular biology will continue to identify novel molecular targets for intervention with single & combinations of agents
- Many early intraepithelial neoplasias are currently recognized as pre-invasive cancers and amenable to pharmaceutical interventions