Preclinical Chemopreventive Agent Development Research

Peter Greenwald, MD, DrPH
Director

Vernon E. Steele, PhD, MPH
Acting Group Leader, CADRG

Division of Cancer Prevention
Chemoprevention Agent Development Program (CADP)

Cancer Prevention Drug Development Program
Preclinical Chemoprevention Agent Development Research

Preclinical Program

Preclinical Efficacy
Molecular Targets
Toxicology & PD/PK

Early Phase Trial Consortia

Phase I/II Trials
Safety
Preliminary Efficacy

CCOPs/MB-CCOPs

Phase III Trials
Chemoprevention Agent Development Program (CADP)

External Review Panel

December, 2009

• **Ming You, MD, PhD (Chair)** – Mary Culver Distinguished Professor of Surgery, School of Medicine, Washington University

• **Monica Bertagnolli, MD** – Professor & Chief of Surgical Oncology, Brigham and Women’s Hospital, Harvard Medical School

• **Dean Brenner, MD** – Professor of Internal Medicine, Professor of Pharmacology, Department of Internal Medicine & Pharmacology, University of Michigan Medical Center

• **Andrew Dannenberg, MD** – Professor of Medicine & Director of the Weill Cornell Cancer Center
Consistent with the priorities of the NCI to accelerate progress in cancer prevention

The Program has performed in an outstanding manner

Endorses the continued and increased financial and staffing support

Contract funding mechanism is the most efficient way to support applied agent development.
Chemoprevention Agent Development Program (CADP)

External Review Panel
May, 2010

• **J. Carl Barrett, PhD** (Co-Chair) – VP, Global Head, Oncology Biomarkers, Novartis

• **Chris H. Takimoto, MD, PhD** (Co-Chair) – Senior Director Oncology R&D, Ortho Biotechnology

• **Greg A. Curt, MD** – US Medical Lead, Astra Zeneca Oncology

• **Ethan Dmitrovsky, MD** – Professor of Medicine and Pharmacology, Dartmouth University

• **Carlo C. Maley, PhD** – Associate Professor, Division of Adult Cardiothoracic Surgery, Helen Diller Family Comprehensive Cancer Center, UCSF

• **William G. Nelson, MD, PhD** – Professor of Oncology and Director Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University

• **David Parkinson, MD** – President and CEO, Nodality Biotech
**** CADRG’s Preclinical Agent Development Program should **continue its contract program** to qualify agents for clinical trials

• **Expand the Program’s sphere of influence** within NCI and scientific community in general

• **Optimize the preclinical testing program** for drug development

• Develop a better **prioritization process**

• Develop a **research business, educational and communication plan for the Program**
Preclinical Chemopreventive Agent Development Research

Vernon E. Steele, PhD, MPH
Acting Group Leader
Chemoprevention Agent Development Research Group

Division of Cancer Prevention
Chemoprevention Agent Development Research Group (CADRГ)
PREVENT Cancer Program

**Future Directions (2011-2015)**

- Optimize agent *development process*
- Implement *new prioritization and decision gate process*
- Further explore *immunologic interventions*
- Use additional *new animal models* that optimally reflect the human cancer being modeled
- Optimize *alternate dosing schedules, regional drug delivery*, and develop *new drug combinations* to lower drug toxicities:
- Increase *communications and working partnerships*
Chemoprevention Agent Development Research Group (CADRG)

Cancer PREVentative development (PREVENT Cancer) Program

Discovery, Development & Prioritization Process

Chemoprevention Agent Development Program

- Redirect Research Efforts Elsewhere
- Published Literature, Meetings, Class Studies, RAPID, Industry, & Other Sources
- In Vitro & In Vivo Screening
- Efficacy Testing & Biomarker Evaluation
- Toxicology Studies
- Submit IND
- Phase I/II Clinical Trials

Cancer PREVentative development Program

- Discovery, Development, & Prioritization Special Emphasis Panel (SEP)
- Discovery, Development, & Prioritization Management & Administrative Committee (MAC)
- Discovery, Development, & Prioritization External Oversight/Steering Committee (EOC)

APPLICATIONS

- Outside Members
- Federal Employees
- Contractors
- In vitro & In vivo Testing
- Efficacy Testing
- Toxicology & Pharmacology
- IND Application

IND Application
Chemoprevention Agent Development Research Group (CADRG)

**Cancer PREVENTative development (PREVENT Cancer) Program**

**Discovery, Development & Prioritization Process**

- **Discovery, Development, & Prioritization**
  - Special Emphasis Panel (SEP)
  - Management & Admin. Committee (MAC)
  - External Oversight/Steering Committee (EOC)

**External Members**
- Outside Members
- Federal Employees
- Contractors

**Portfolio Managers**

**In vitro & In vivo Testing**
- Efficacy Testing
- Toxicology & Pharmacology

**IND Application**

**PREVENT Cancer Program Applications**
Discovery, Development, & Prioritization
Special Emphasis Panel (SEP)

Experts in Various Areas of Chemoprevention Drug Development (15-20)

Perform & Facilitate Reviews for:

- Agent selection
- Agent Prioritization
- Biomarkers/target selection
- Preclinical models
- Review/score/rank proposals
Chemoprevention Agent Development Research Group (CADRГ)

PREVENT Cancer Program Processes
External Oversight/Steering Committee (EOC)

Discovery, Development, & Prioritization
External Oversight/Steering Committee (EOC)

Distinguished Leaders in Drug Development from Industry & Academia (10-12)

Recommends/Advises on:
- Areas of focus
- Selection of Agents
- Development process
- Prioritization plans
- Project progress
- Strategic objectives
Chemoprevention Agent Development Research Group (CADRG)

PREVENT Cancer Program Processes
Management & Administrative Committee (MAC)

Discovery, Development, & Prioritization
Management & Administrative Committee (MAC)

Members, including DCP, DCTD, & CCR (Intramural NCI) (15-20)

Internal Management and Administration of:
- Program Resource allocation
- Managing individual projects
- Making Go/No Go decisions
- Presentations to EOC
- Oversee Projects
- Project progress
- Strategic objectives
A. Scientific Merit _____

B. Efficacy _______ 1 = Exceptional

C. Toxicity/PK _______ 3 = Excellent

D. Feasibility _______ 6 = Satisfactory

E. Clinical Need/Opportunity _____ 9 = Poor
Preclinical Cancer Preventative Development Decision Gates

• Prepare a product profile
• Conduct a technology overview
• Develop a screening strategy
• Identify potential biomarkers (efficacy/surrogate)
• Develop a strategy for “clinical readiness”
• Prepare medical needs assessment
• Prepare project operational plan

• Run screen(s)
• Assess mechanism of action for link to disease
• Determine desirable potency
• Determine evidence of structure–activity relationship
• Evaluate functional activity in vitro
• Determine selectivity for target
• Evaluate PK, PD, and physiochemistry using best available tools/in silico modeling
• Assess amenability to synthesis
• Evaluate stability

• Establish laboratory objectives for clinical efficacy
• Resolve IP issues
• Evaluate activity in validated animal models
• Evaluate physiochemistry
• Differentiate Leads from current therapies
• Evaluate preliminary safety issues
• Develop PD and toxicology biomarker assays(s)
• Assess achievability of human PK/PD profile
• Assess feasibility of scale-up and bulk synthesis

• Evaluate synthesis and proposed clinical formulation
• Evaluate biopharmaceutical properties
• Assess potency against clinical efficacy
• Evaluate biodistribution
• Evaluate clinical readiness of PK/PD assay(s) and specimen handling SOPs
• Assess amenability to imaging
• Evaluate safety issues (most sensitive species) in range finding toxicology studies

• Manufacture GMP-grade bulk drug
• Conduct IND-directed toxicology studies
• Define / toxicokinetics
• Determine preclinical MTD and DLTs
• Validate PK/PD assay(s) and specimen handling SOPs
• Develop and validate product characterization and release assays
• Characterize clinical product
• Prepare CMC package and toxicology summary report
• Prepare and review clinical development plan
• Prepare and file IND

Preclinical data required for “go/no go” decision-making gates throughout drug discovery and development and for IND filing for clinical trials
Chemoprevention Agent Development Research Group (CADRG)

PREVENT Cancer Program Processes/Deliverables

Contract Mechanism is Best Suited for Cancer Prevention Drug Development

- Ability to move drugs seamlessly through the cancer prevention drug development pipeline

- Need for **stable, reliable pool of PIs** to perform standard protocols & statistical analyses for IND submission

- **Direct ownership of these study data by NCI**
  - Facilitates collaboration with the pharmaceutical industry

- **Protection of Intellectual Property**
  - Academic institutions – Pharmaceutical industry
  - Principal Investigators – Small Business

- The contracts have **scheduled deliverables and milestones**
  - Greater flexibility to implement go/no go decision
  - Prioritization & reassignment of the funds toward more promising areas
Greater control over timelines and costs
- Limit payment to services rendered
- Allowing cost reimbursement to be directly tied to performance

FDA requirement for IND-application and Tox/Pharm testing
- The Toxicology and Pharmacology testing is rigorously defined by the FDA for an IND application and must be performed in GLP facilities (Good Laboratory Practice) approved laboratories and under strict GLP conditions

Mandate specific SOP for data and specimen collection protocols
- The data is meaningful and consist throughout the cancer prevention drug development continuum

The use of subcontracts allows the program to reach out to the widest range of investigators in a timely and focused manner to incorporate new methodologies or new models.
Chemoprevention Agent Development Research Group (CADRG)

PREVENT Cancer Program Major Areas of Activity:
In Vitro & In Vivo Testing

- **Identification & Prioritization** of Candidate Agents
- **Molecular Target or Pathway Assessment**
- **Data for Decision Gate Process** for Further Efficacy Testing
Chemoprevention Agent Development Research Group (CADDRG)
PREVENT Cancer Program Major Areas of Activity:
Animal Efficacy Testing

- Efficacy Measurement
- Exploration of Dose Response
- Blood Levels
- Altered Dosing Methods
- Combinations of Agents
- Age & Dietary Effects
- Pharmacodynamic Drug Effect Markers
- Data for Decision Gates (Go/No Go) to Next Step
PREVENT Cancer Program Major Areas of Activity:
Preclinical Toxicology & Pharmacology Testing

- Evaluate Potential for Toxicity
- Identify Target Organs for Toxicity
- Characterize Dose Dependence, Relationship to Exposure, and Potential Reversibility
- Identify Parameters for Clinical Monitoring Potential Adverse Effects
- Obtain Pharmacokinetic and ADME Data
- Estimate Initial Human Dosing
- Satisfy FDA Requirements for IND
Different NSAIDs (Piroxicam, Aspirin, Celecoxib & Sulindac) were used by different groups.

Difluoromethylornithine (DFMO) is a suicide inhibitor of Ornithine decarboxylase (ODC).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Placebo</th>
<th>NSAIDs¹</th>
<th>DFMO²</th>
<th>Combination†</th>
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</thead>
<tbody>
<tr>
<td>Nigro, 1986</td>
<td>3.4</td>
<td>3.2 (6%) P</td>
<td>2.1 (38%)*</td>
<td>1.0 (71%)*</td>
</tr>
<tr>
<td>Reddy, 1990</td>
<td>0.73</td>
<td>0.37 (49%)* P</td>
<td>0.3 (59%)*</td>
<td>0.17 (77%)*</td>
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<tr>
<td>Rao, 1991</td>
<td>1.14</td>
<td>0.31 (73%)* P</td>
<td>0.22 (81%)*</td>
<td>0.08 (93%)*</td>
</tr>
<tr>
<td>Li, 1999</td>
<td>1.6</td>
<td>1.5 (6%) A</td>
<td>0.5 (69%)*</td>
<td>0.3 (81%)*</td>
</tr>
<tr>
<td>Jacoby, 2000</td>
<td>10.4</td>
<td>2.5 (76%)* C</td>
<td>3.7 (64%)*</td>
<td>0.8 (92%)*</td>
</tr>
<tr>
<td>Ignatenko, 2008</td>
<td>35</td>
<td>13 (63%)* S</td>
<td>19 (46%)*</td>
<td>14 (86%)*</td>
</tr>
</tbody>
</table>

Typically testing each compound at ~50% of the single-agent dose

Statistically significant vs. placebo, p<0.05
### Difluoromethylornithine Plus Sulindac for the Prevention of Sporadic Colorectal Adenomas: A Randomized Placebo-Controlled, Double-Blind Trial

<table>
<thead>
<tr>
<th>Study Group</th>
<th>N</th>
<th>Adenoma (2-39 mo) Number</th>
<th>Adenoma (2-39 mo) Percent</th>
<th>Advanced Adenoma (2-39 mo) Number</th>
<th>Advanced Adenoma (2-39 mo) Percent</th>
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</thead>
<tbody>
<tr>
<td>Placebo Control</td>
<td>129</td>
<td>53</td>
<td>41.1</td>
<td>11</td>
<td>8.5</td>
</tr>
<tr>
<td>150 mg Sulindac+ 500 mg DFMO/day</td>
<td>138</td>
<td>17 (70% ↓)</td>
<td>12.3</td>
<td>1 (92% ↓)</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Chemoprevention Agent Development Research Group (CADRG)

Chemoprevention Agent Development Program
Progress 2004-2010

- 20 new INDs
- 34 new collaborative drug development agreements
- Supported DCP clinical trials (90%)
- New classes of chemopreventive agents
- 200 new agents screened/ 67 advanced to efficacy testing/ 30 to toxicology/pharmacology testing
- Expanded use of new animal models
- Published positive and negative findings (250)
- RAPID program
## Chemopreventive Agent Development Program

Examples of Current Agents in the Development Pipeline

<table>
<thead>
<tr>
<th>Agent</th>
<th>Class</th>
<th>Animal Efficacy</th>
<th>Preclinical Toxicology</th>
<th>Phase 1</th>
<th>Phase 2</th>
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</thead>
<tbody>
<tr>
<td>Sirolimus (Rapamycin)</td>
<td>mTOR Inhibition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SR13668*</td>
<td>PI3K/AKT Inhibition</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Eflornithine (DFMO) + Sulindac</td>
<td>ODC/COX-1 and -2 Inhibition</td>
<td></td>
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<tr>
<td>myo-Inositol</td>
<td>Antioxidant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pioglitizone</td>
<td>PPAR gamma agonist</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erlotinib (Tarceva)</td>
<td>EGFR Inhibition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9-cis-UAB30</td>
<td>RXR Agonist</td>
<td></td>
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<tr>
<td>Vorinostat (SAHA)</td>
<td>HDAC Inhibition</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Atorvastatin (Lipitor)</td>
<td>HMG-CoA Reductase Inhibition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CP31398</td>
<td>Rescues Mutant P53</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
EFFECT OF TARCEVA (VARIOUS DOSING REGIMENS) ON METHYLNITROSOUREA (MNU)-INDUCED MAMMARY CANCERS IN FEMALE SPRAGUE-DAWLEY RATS

Example: New Dosing Regimens to Reduce Toxicity While Maintaining Efficacy

Clinton Grubbs lab, Univ. of Alabama at Birmingham (unpublished data)
Chemoprevention Agent Development Research Group (CADRG)

Chemopreventive Agent Development Program

**Example:** New Molecular Endpoints for Efficacy Testing

Prevention of Cigarette Smoke-induced miRNA changes in rats with Chemopreventive Agents

Hierarchical cluster analysis linking the expression profiles of 484 miRNAs
Chemoprevention Agent Development Research Group (CADRG)

Chemopreventive Agent Development Program

Example: Combination Vaccine/ Targretin (Bexarotene)

Animals: FVB/N-TgN (MMTVneu) mice
Multivalent Vaccine: neu, IGFBP2, IGF1R
Targretin: retinoid X receptor agonist

Nora Disis lab. Washington University Seattle, WA (Unpublished data)
Chemoprevention Agent Development Research Group (CADRG)  
PREVENT Cancer Program  
Proposed Budget (FY2011-2015)

<table>
<thead>
<tr>
<th>Year</th>
<th>$M</th>
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<tbody>
<tr>
<td>2011</td>
<td>16.0</td>
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<tr>
<td>2012</td>
<td>16.5</td>
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<tr>
<td>2013</td>
<td>17.0</td>
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<tr>
<td>2014</td>
<td>17.5</td>
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<tr>
<td>2015</td>
<td>18.0</td>
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<tr>
<td>Total</td>
<td>84.9</td>
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Acknowledgements: Staff

Martha Basinger
Dan Boring Ph.D., RPh.
Izet Kapetanovic, Ph.D.
Levy Kopelovich, Ph.D.
Ron Lubet, Ph.D.
Winfred Malone, Ph.D., M.P.H.
Marjorie Perloff, M.D.
Vernon Steele, Ph.D., M.P.H.
THANK YOU!
Targretin (Bexarotene)

Dendritic cell

TAA-specific T-cell & B-cell Stimulation & Expansion

Tumor cell

IGFBP

IGF1R

neu
Epidermal Growth Factor Receptor

EGFR Inhibitor
[Erlotinib (Tarceva)]

Translation
mRNA

Proliferation

ELK1

SRF

PTEN

PI3K

SHP2

SHC

GRB2

SOS1

RAS-GTP

GAP

RAS-GDP

Akt

mTOR

4EBP1

S6K

40S

60S

eIF4E

Epidermal Growth Factor Receptor
Factors and Criteria for Agent Prioritization for Preclinical Chemopreventive Agent Development: (agent)

A. Scientific Merit SCORE
1. Mechanism of Action Directly Relevant to Inhibition of Carcinogenesis (Most Class Study Drugs)
2. Relevance of Mechanism to Chemopreventive Efficacy Unknown, But Suspected to be Positive
3. Relevance Unknown

B. Efficacy SCORE
1. Animal Chemopreventive Efficacy >75% inhibition
2. Animal Chemopreventive Efficacy 50 -75% inhibition
3. Animal Chemopreventive Efficacy 25-50% inhibition
4. In Vitro Inhibition of Carcinogenesis
5. In Vivo or In Vitro Inhibition of Tumor Cell Growth
6. Structural Relationship to Agent with Known In Vivo Efficacy
7. No Known Activity Relevant to Carcinogenesis
Factors and Criteria for Agent Prioritization for Preclinical Chemopreventive Agent Development: ____ (agent) ______

C. Toxicity SCORE
1. Tested Clinically, MTD > Effective Chemopreventive Dose in Animals
2. Tested in Animals, MTD > Effective Chemopreventive Dose in Animals
3. No Significant Toxicity; Chemopreventive Dose Not Established
4. Mild Clinical/Animal Toxicity, Chemopreventive Dose Not Established
5. No or Little Toxicity Data, No Indication of Significant Toxicity
6. No or Little Toxicity Data, Suspected of Having Significant Toxicity
7. Evidence of Significant Clinical/Animal Toxicity, Chemopreventive Dose Not Established
8. Evidence of Clinical/Animal Toxicity at Doses Lower Than Chemopreventive Dose
9. Evidence of Clinical/Animal Toxicity That is Significant and Supersedes Interest Based on Efficacy

D. Feasibility / Availability (Source and Supply) SCORE
1. Commercially Available: Supplier with CTA or Purchase Off the Shelf
2. Commercially Available, Expected High Cost
3. Not Commercially Available, Synthesis or Extraction Possible, Well-Defined Methods
4. Synthesis or Extraction Possible, Methods May Require Limited Developmental Effort
5. Complex Synthesis or Extraction
6. Experimental Compound, Proprietary Synthesis or Extraction Methods, No or Unlikely CTA

E. Clinical Need/Opportunity
1. Great Unmet need and prime opportunity
9. No need/little opportunity

TOTAL SCORE ____ (5-45) _________________________
<table>
<thead>
<tr>
<th>CLASS STUDY</th>
<th>SUGGESTED AGENTS</th>
<th>SELECTED AGENTS</th>
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</thead>
<tbody>
<tr>
<td>HDAC Inhibitors</td>
<td>SAHA, Valproic acid, Trichostatin A, Oxamflatin</td>
<td>SAHA (Vorinostat)</td>
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<tr>
<td>mTOR Pathway</td>
<td>Rapamycin, CCI-779, RAD-001, AP23573</td>
<td>Rapamycin</td>
</tr>
<tr>
<td>P53 Modulators</td>
<td>CP31398, PRIMA-1</td>
<td>CP31398</td>
</tr>
<tr>
<td>PI3Kinase Inhibitors</td>
<td>XL147, XL765, TGX221, Myo-inositol</td>
<td>Myo-inositol</td>
</tr>
<tr>
<td>AMPK enhancers</td>
<td>Metformin</td>
<td>Metformin</td>
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<tr>
<td>AKT Protein Kinase</td>
<td>DIM, SR13668</td>
<td>DIM, SR13668</td>
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<tr>
<td>EGFR Antagonists</td>
<td>Tarceva, Lapatinib</td>
<td>Tarceva, Lapatinib</td>
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<td>Target Organ</td>
<td>Classes Highly Effective</td>
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<tr>
<td>--------------</td>
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</tr>
<tr>
<td>Colon</td>
<td>NSAIDs, ODC inhibitors</td>
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<tr>
<td>Lung</td>
<td>Glucocorticoids, rexinoids, PI3K inhibitors</td>
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<tr>
<td>Breast</td>
<td>SERMs, aromatase &amp; EGFR inhibitors, rexinoids</td>
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<td>Bladder</td>
<td>NSAIDs, ODC inhibitors, EGFR inhibitors</td>
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<td>Prostate</td>
<td>DHT inhibitors, retinoids</td>
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<td>Skin</td>
<td>NSAIDs, ODC inhibitors, retinoids</td>
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<tr>
<td>Oral</td>
<td>NSAIDs, antioxidants</td>
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<tr>
<td>Pancreas</td>
<td>k-ras inhibitors, NSAIDs</td>
<td></td>
</tr>
<tr>
<td>Esophagus</td>
<td>NSAIDs/COX and LOX inhibitors</td>
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</tbody>
</table>
Progress to Date

• Activated **20 new INDs** since 2004 (32 INDs now active)

• Negotiated **34** new collaborative drug development agreements

• Supported **DCP clinical trials**:
  
  - **Primary Source**: 38/54 (70%)
  - **Supplemented**: 11/54 (20%)

• Developing 75 single agents and 26 combinations currently
Progress to Date (continued)

• Identified **new classes of chemopreventive agents** including: Statins, HDAC inhibitors, NO-NSAIDs, p53 modulators and vaccines

• Employed **new animal models**, including ER-breast, squamous and small cell lung, squamous and basal cell skin, colon and a pancreas model

• Published 220+ **peer-reviewed manuscripts**

• Supported nine new agents under the **RAPID program** since 2004 leading to 3 INDs for DCP clinical trials
Promising Agents Effective Against ER negative Breast Cancers

• Tyrosine Kinase Inhibitors – Lapatinib
• Rexanoids – Bexarotene/ UAB30
• NSAIDS – Celecoxib
• Polyamine synthesis inhibitors – DFMO
• PARP-1 Inhibitors – ABT888
• Combinations – Bexarotene+Celecoxib
Examples of Preclinical GEM Models Directly Relevant to Humans at High Risk

• **Min/+ mice**: Mice with a mutation in the APC Gene is directly relevant to Human FAP and also sporadic colon cancer. Data supported Sulindac, DFMO and Celecoxib (FDA Approved for FAP) clinical trials.

• **MLH or MSH2 deficient mice**: Mice with such repair deficiencies relate to humans with HNPCC. NSAIDS (Aspirin) and DFMO active and plan to test PARP inhibitors.

• **BRCA-1 conditional KO/p53 heterozygous KO mice**: Have alterations in both BRCA-1 and p53 which is typically seen in human BRCA-1 tumors. Tamoxifen and Ovx tested

• **PTCH Mice**: Mice deficient in PTCH gene have similarities to humans with basal cell nevus syndrome. Supported 2 successful FDA approved trials with Celecoxib to control BCC and squamous cell cancers
## INDs Approved – 2004-2010

<table>
<thead>
<tr>
<th>First Column</th>
<th>Second Column</th>
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<tbody>
<tr>
<td>• Diindole Methane</td>
<td>• NCX 4016</td>
</tr>
<tr>
<td>• 9-cis-UAB30</td>
<td>• Polyethylene glycol</td>
</tr>
<tr>
<td>• ALA PDT</td>
<td>• Pioglitizone</td>
</tr>
<tr>
<td>• Curcumin (Purified)</td>
<td>• Resiquimod topical</td>
</tr>
<tr>
<td>• Esomeprazole + Aspirin</td>
<td>• Resveratrol</td>
</tr>
<tr>
<td>• Nexium + Aspirin</td>
<td>• Sirolimus</td>
</tr>
<tr>
<td>• Lapatinib</td>
<td>• SR13668</td>
</tr>
<tr>
<td>• Letrozole</td>
<td>• Sulindac</td>
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<tr>
<td>• Letrozole</td>
<td>• SR13668</td>
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<tr>
<td>• Lovastatin</td>
<td>• Sulindac</td>
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<tr>
<td>• L-Se-Me-selenocysteine</td>
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Prime Contractors for Chemoprevention
Agent Development

In Vitro/animal Screening
• University of Alabama at Birmingham
• University of Toledo
• Cornell (Weill) University
• IIT Research Institute

Efficacy Testing
• Ohio State University
• Fox Chase Cancer Center
• University of Washington St. Louis
• University of Oklahoma

Toxicology/Pharmacology
• SRI International
• Southern Research Institute
• University of Illinois at Chicago
• IIT Research Institute