National Cancer Institute

Preclinical Chemopreventive Agent Development Research

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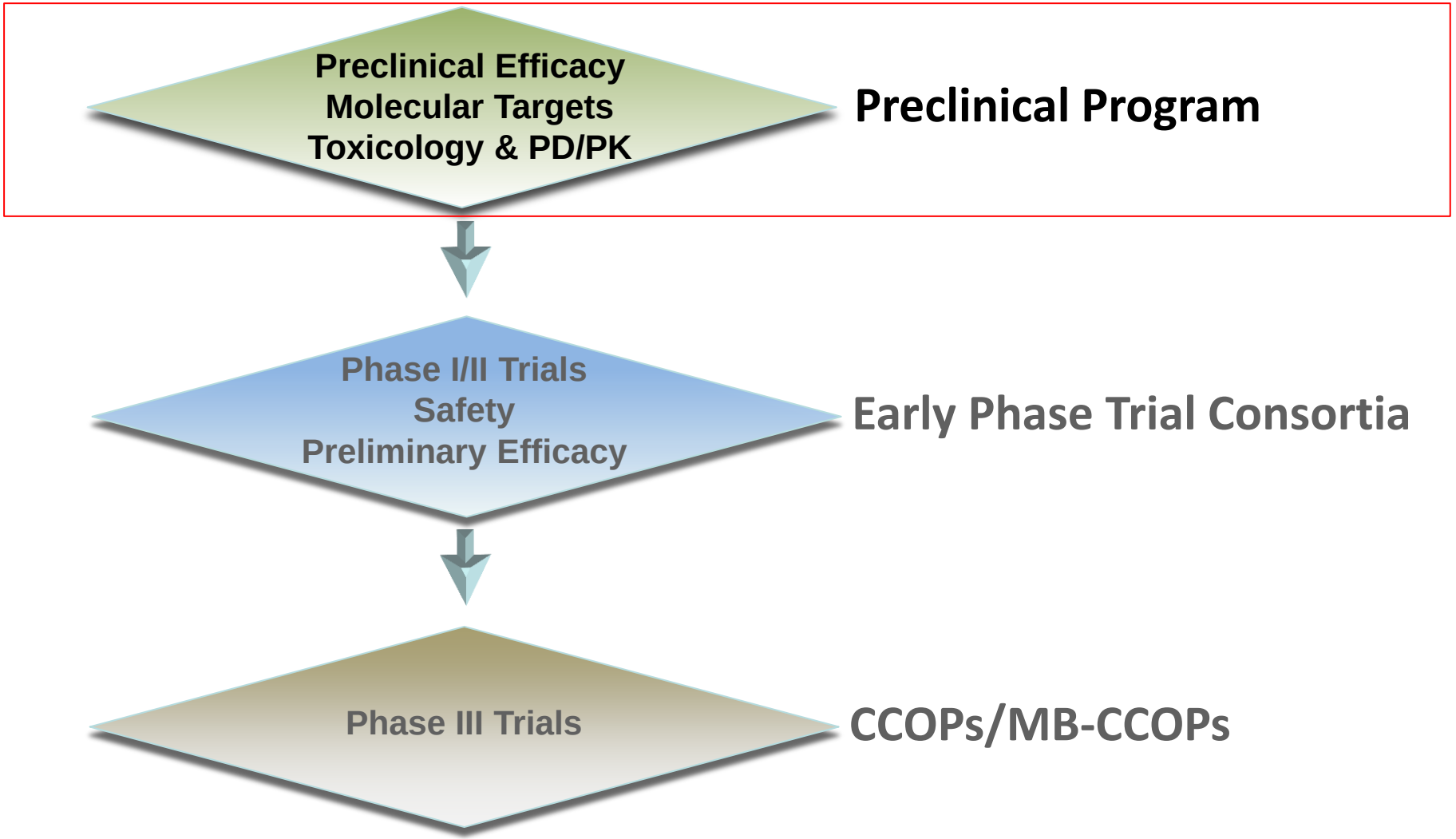
Division of Cancer Prevention

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Insitiutes of Health

Chemoprevention Agent Development Program (CADP)

Cancer Prevention Drug Development Program

Preclinical Chemoprevention Agent Development Research



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

Chemoprevention Agent Development Program (CADP)

Conclusions of the External Review Panel

December, 2009

- **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

Chemoprevention Agent Development Program (CADP)

Recommendations of the External Review Panel

May, 2010

- 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**

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Future Directions (2011-2015)

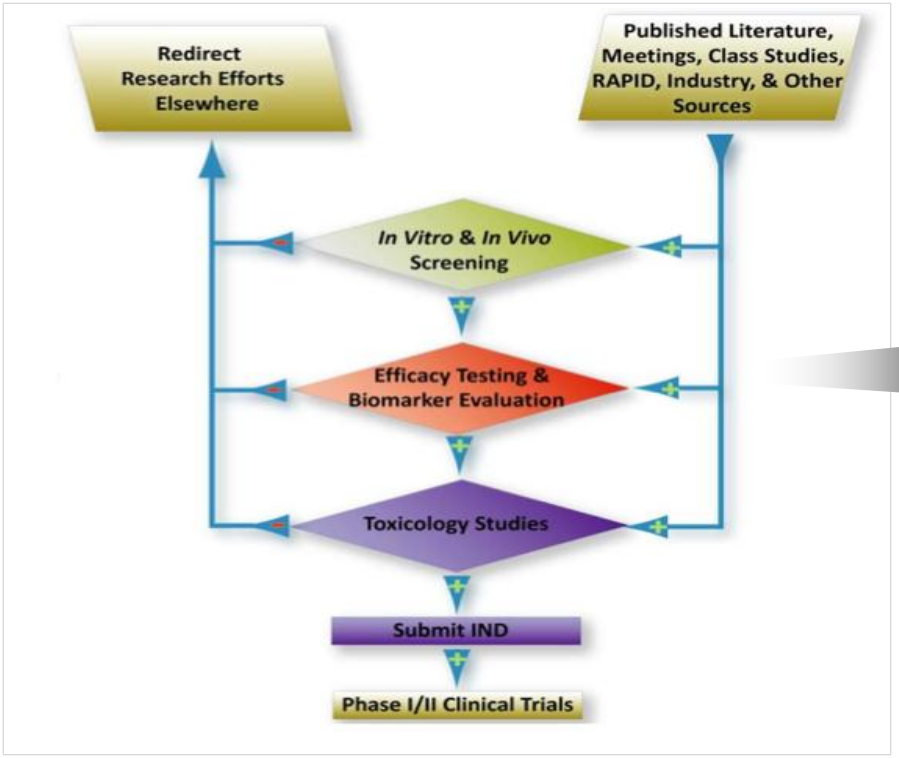
- Optimize agent **development process**
- Implement **new prioritization** and **decision gate process**
- Further explore **immunologic** interventions
- Use additional **new animal models** that optimally reflect the human cancer being modeled
- Optimize **alternate dosing schedules**, **regional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

Chemoprevention Agent Development Research Group (CADRG)

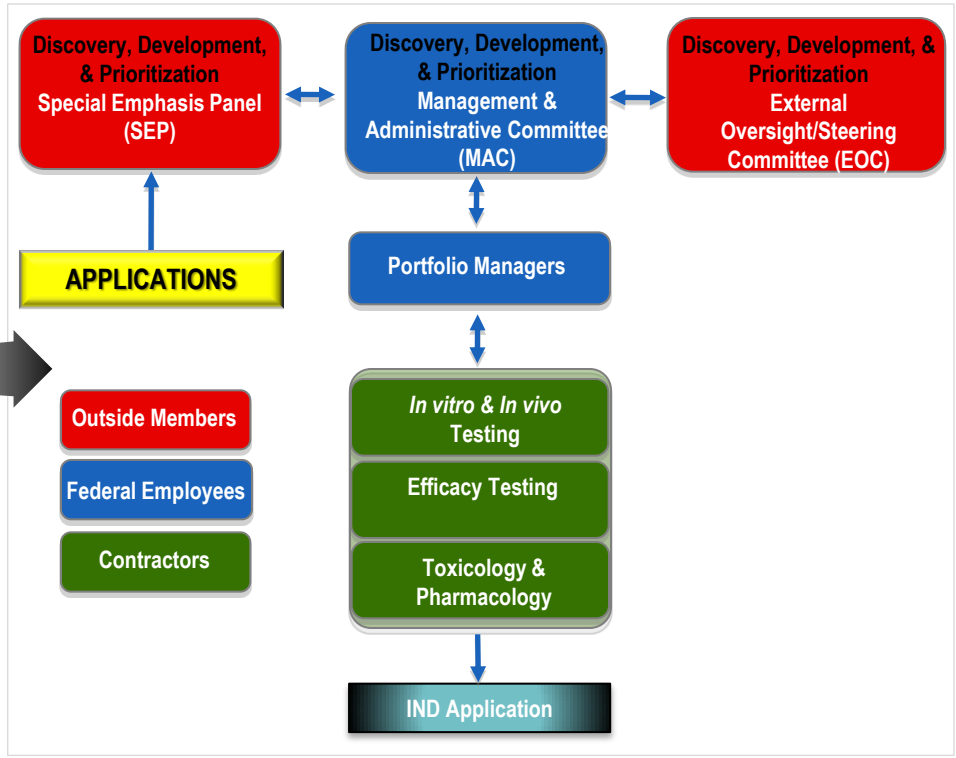
Cancer PREVentative developm**ENT (PREVENT Cancer)** Program

Discovery, Development & Prioritization Process

Chemoprevention Agent Development Program



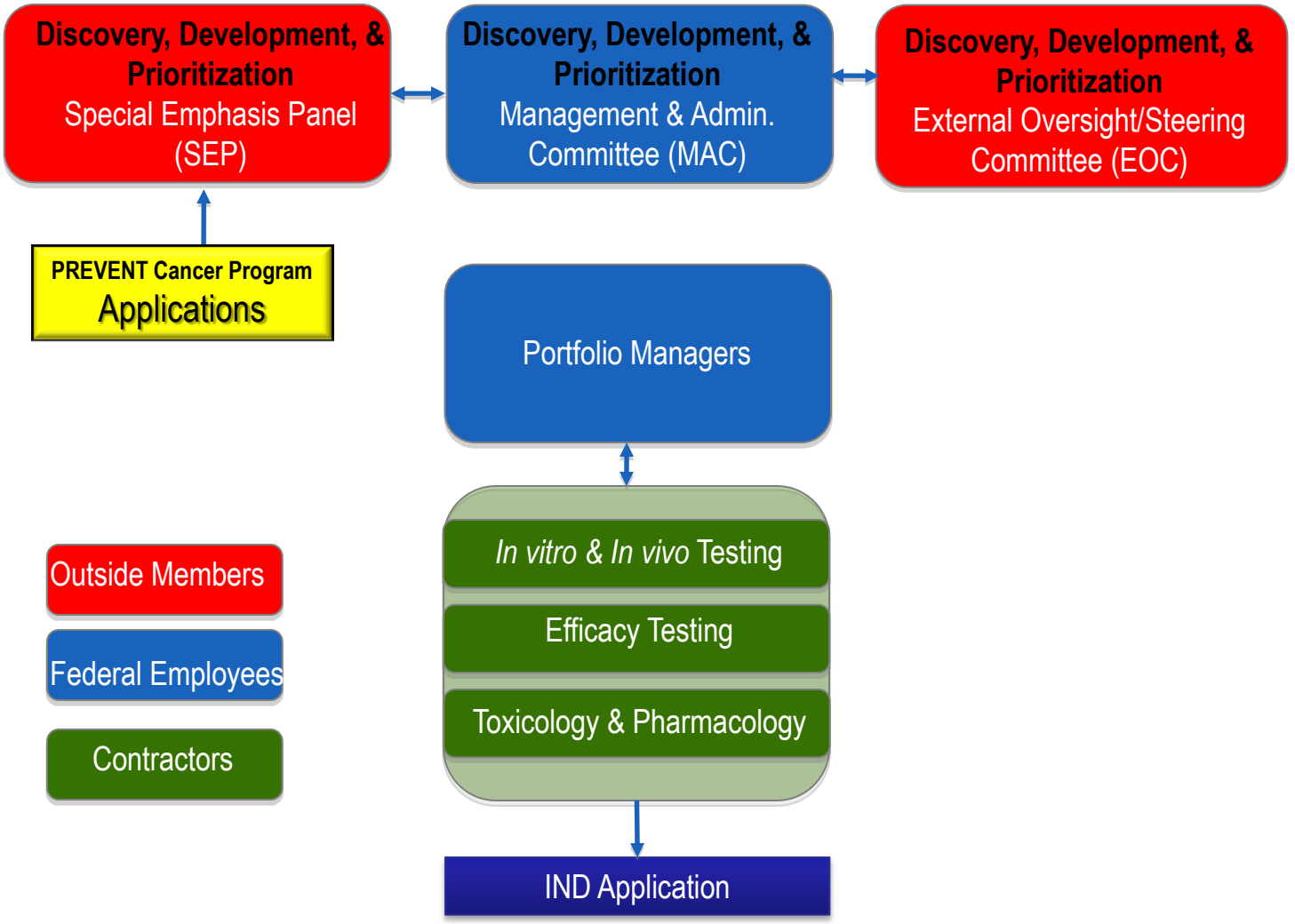
Cancer PREVentative developmENT Program



Chemoprevention Agent Development Research Group (CADRG)

Cancer PREVentative developm**ENT (PREVENT Cancer)** Program

Discovery, Development & Prioritization Process



Chemoprevention Agent Development Research Group (CADRG)

PREVENT Cancer Program Processes

Projects/Compounds Selections through Special Emphasis Panel (SEP)

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

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

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

Chemoprevention Agent Development Research Group (CADRG)

PREVENT Cancer Program Processes

Projects/Compounds Scoring through Special Emphasis Panel (SEP)

A. Scientific Merit ____

B. Efficacy _____

C. Toxicity/PK _____

D. Feasibility _____

E. Clinical Need/Opportunity ____

SCORING

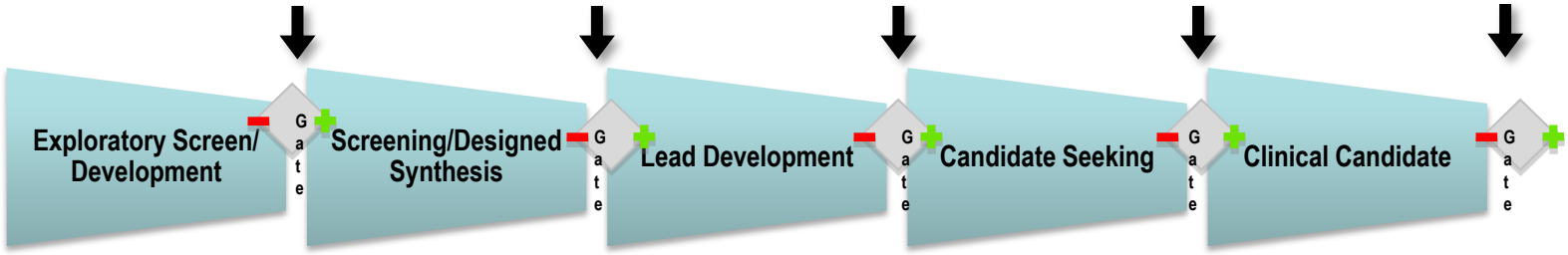
1 = Exceptional

3 = Excellent

6 = Satisfactory

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

Chemoprevention Agent Development Research Group (CADRG)

PREVENT Cancer Program Processes/Deliverables

Contract Mechanism is Best Suited for Cancer Prevention Drug Development

- **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.**

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

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**

Chemoprevention Agent Development Research Group (CADRG)

Chemoprevention Agent Development Program

Example of Combination Strategy – NSAIDs & ODCi

Reference	Placebo	NSAIDs[1]	DFMO[2]	Combination[†]
Nigro, 1986	3.4	3.2 (6%) P	2.1 (38%)*	**1.0 (71%)***
Reddy, 1990	0.73	0.37 (49%)* P	0.3 (59%)*	**0.17 (77%)***
Rao, 1991	1.14	0.31 (73%)* P	0.22 (81%)*	**0.08 (93%)***
Li, 1999	1.6	1.5 (6%) A	0.5 (69%)*	**0.3 (81%)***
Jacoby, 2000	10.4	2.5 (76%)* C	3.7 (64%)*	**0.8 (92%)***
Ignatenko, 2008	35	13 (63%)* S	19 (46%)*	**14 (86%)***

1. *Different NSAIDs (Piroxicam, Aspirin ,Celecoxib & Sulindac) were used by different groups.*
2. *Diflouromethylornithine (DFMO) is a suicide inhibitor of Ornithine decarboxylase (ODC)*
   Absolute incidence or multiplicity (and % reduction) in Colorectal neoplasia (AOM rats or $Apc^{MIN/-}$ mice at study termination

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

**Statistically significant vs. placebo, $p<0.05$*

Clinical Development in DCP Phase II/III

Example of Combination Strategy – NSAIDs & ODCi

Difluoromethylornithine Plus Sulindac for the Prevention of Sporadic Colorectal Adenomas: A Randomized Placebo-Controlled, Double-Blind Trial

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

Meyskens *et al.,* Cancer Prevention Research (2008) 1:32-8.

Chemoprevention Agent Development Program

Progress 2004-2010

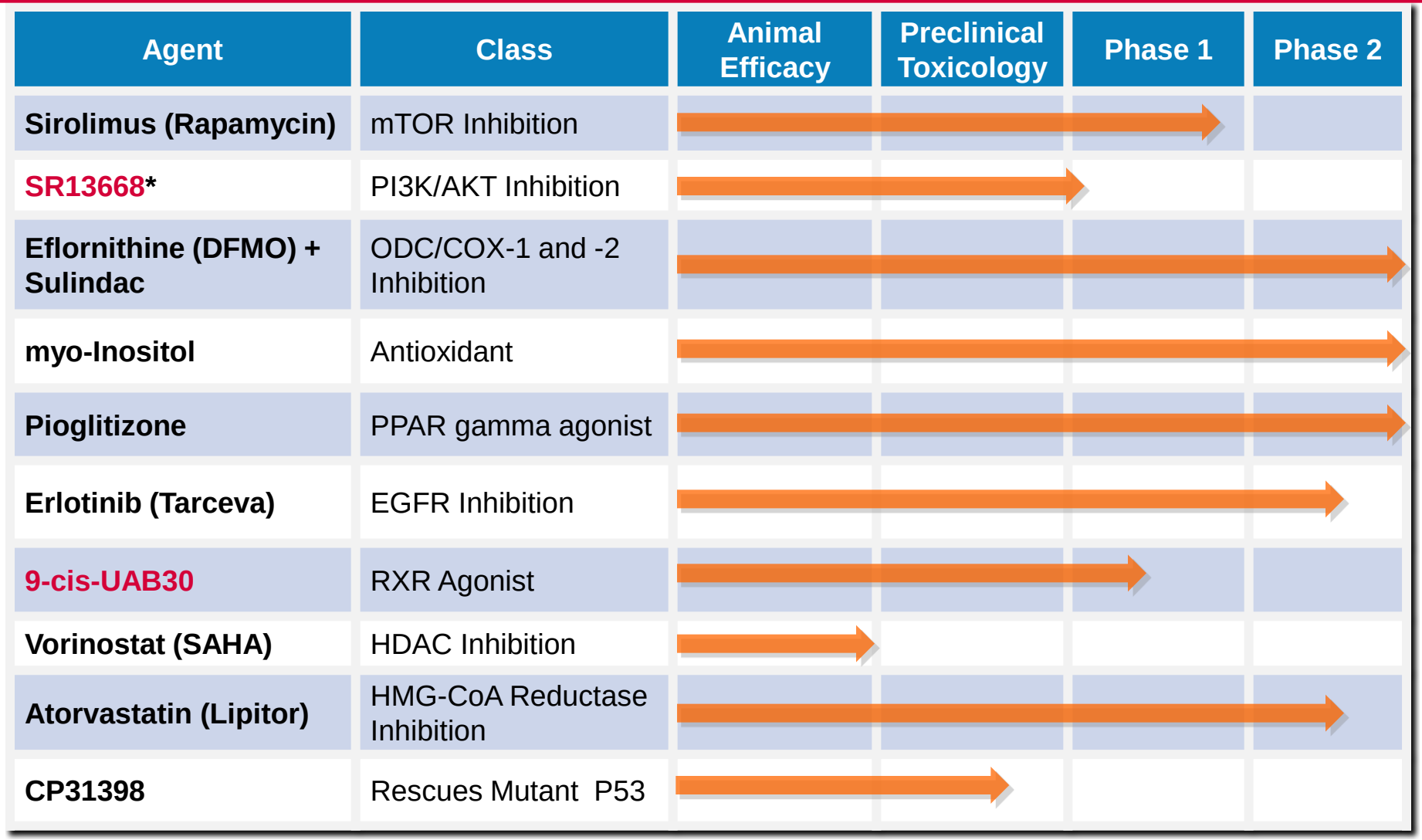
- 20 new INDs
- 34 new collaborative drug development agreements
- Supported DCP clinical trials (90%)
- New classes of chemopreventive agents
- 200 new agents screened/ 67 advanced to efficacy testing/ 30 to toxicology/pharmacology testing
- Expanded use of new animal models
- Published positive and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

Chemoprevention Agent Development Research Group (CADRG)

Chemopreventive Agent Development Program

Examples of Current Agents in the Development Pipeline

Agent	Class	Animal Efficacy	Preclinical Toxicology	Phase 1	Phase 2
Sirolimus (Rapamycin)	mTOR Inhibition				
SR13668*	PI3K/AKT Inhibition				
Eflornithine (DFMO) + Sulindac	ODC/COX-1 and -2 Inhibition				
myo-Inositol	Antioxidant				
Pioglitizone	PPAR gamma agonist				
Erlotinib (Tarceva)	EGFR Inhibition				
9-cis-UAB30	RXR Agonist				
Vorinostat (SAHA)	HDAC Inhibition				
Atorvastatin (Lipitor)	HMG-CoA Reductase Inhibition				
CP31398	Rescues Mutant P53				

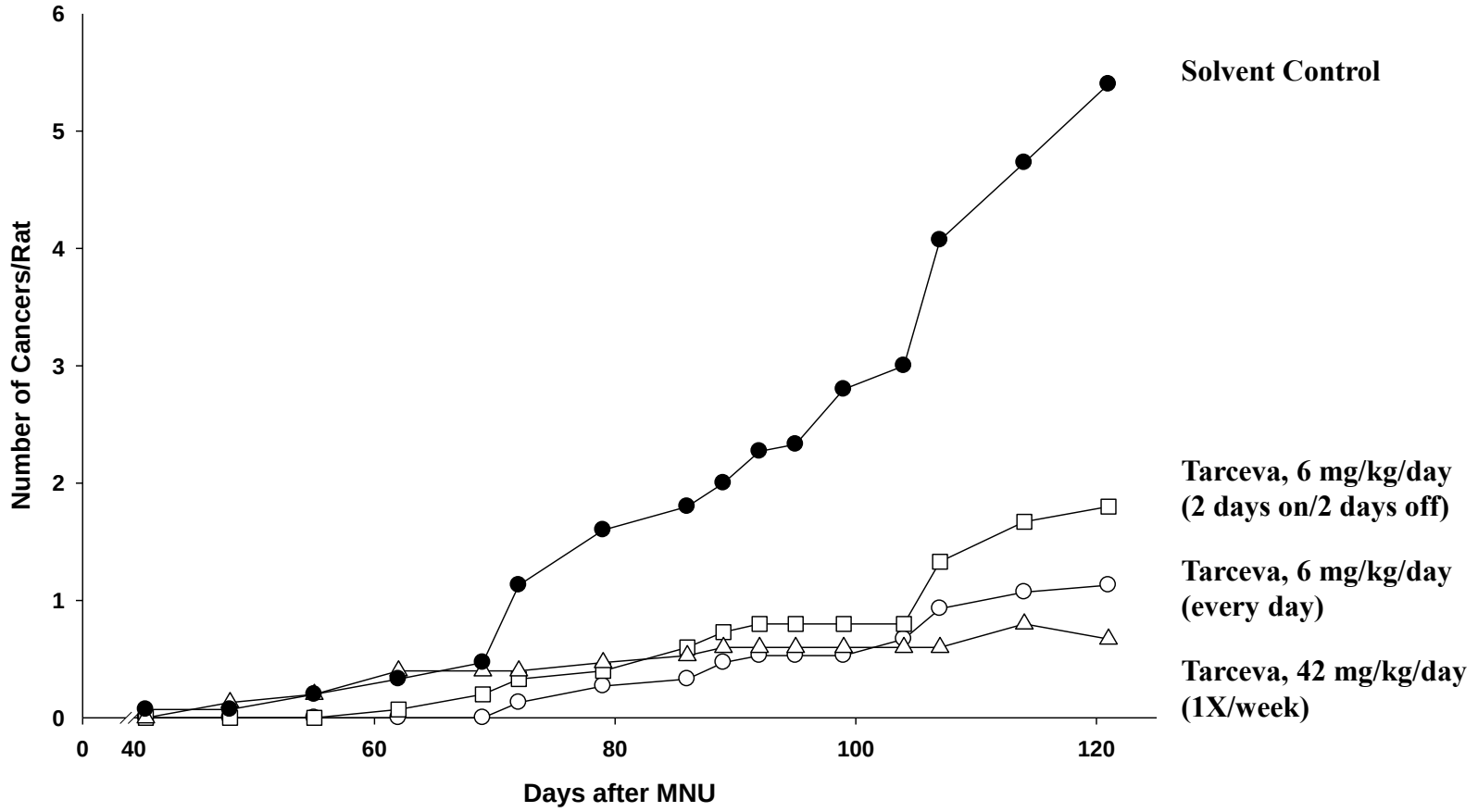


Chemoprevention Agent Development Research Group (CADRG)

Chemopreventive Agent Development Program

Example: New Dosing Regimens to Reduce Toxicity While Maintaining Efficacy

EFFECT OF TARCEVA (VARIOUS DOSING REGIMENS) ON METHYLNITROSOUREA(MNU)-INDUCED MAMMARY CANCERS IN FEMALE SPRAGUE-DAWLEY RATS



Clinton Grubbs lab, Univ. of Alabama at Birmingham (unpublished data)

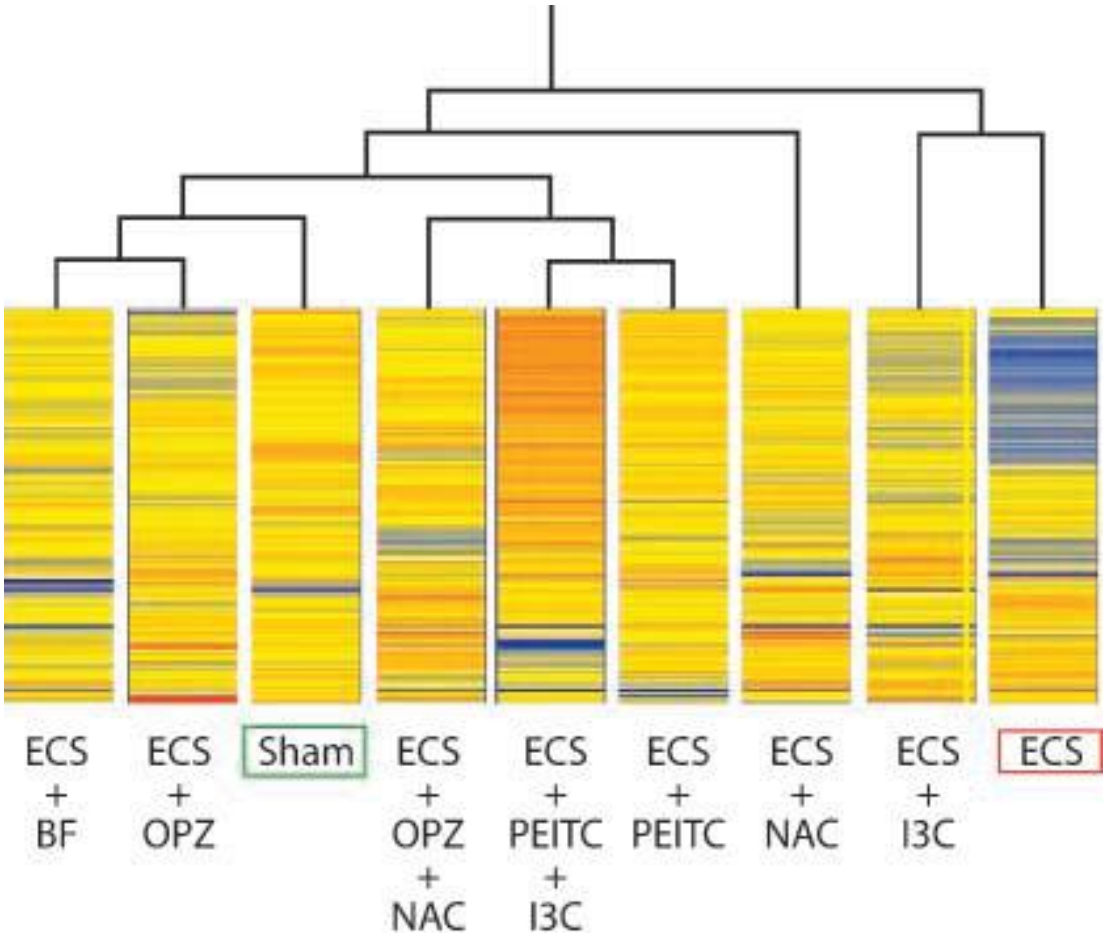
Chemoprevention Agent Development Research Group (CADRG)

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

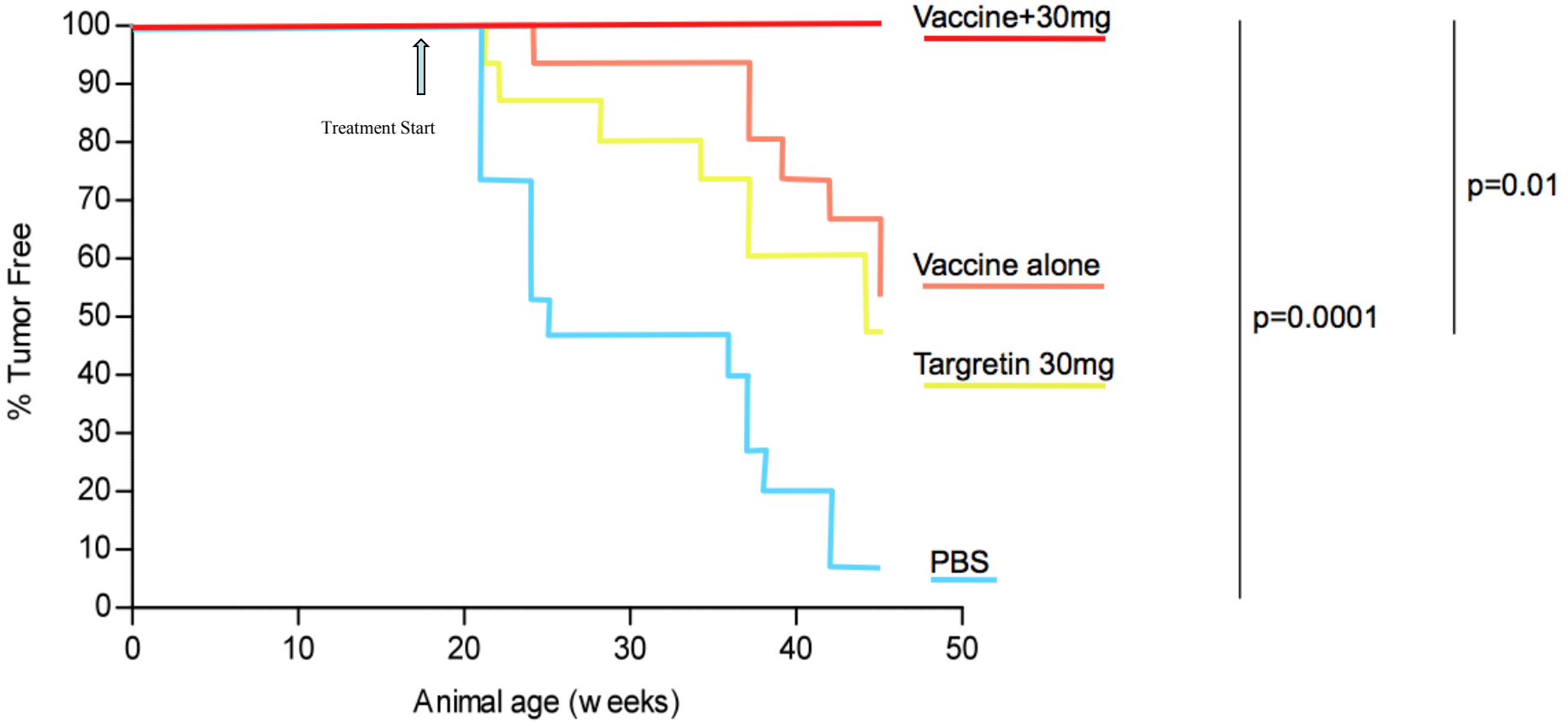


Carlo Croce Lab, OSU (Izzotti *et al.*, Cancer Prev. Res. 2010, 3: 62-72)

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)

Year	$M
2011	16.0
2012	16.5
2013	17.0
2014	17.5
2015	18.0
Total	84.9

Acknowledgements: Staff

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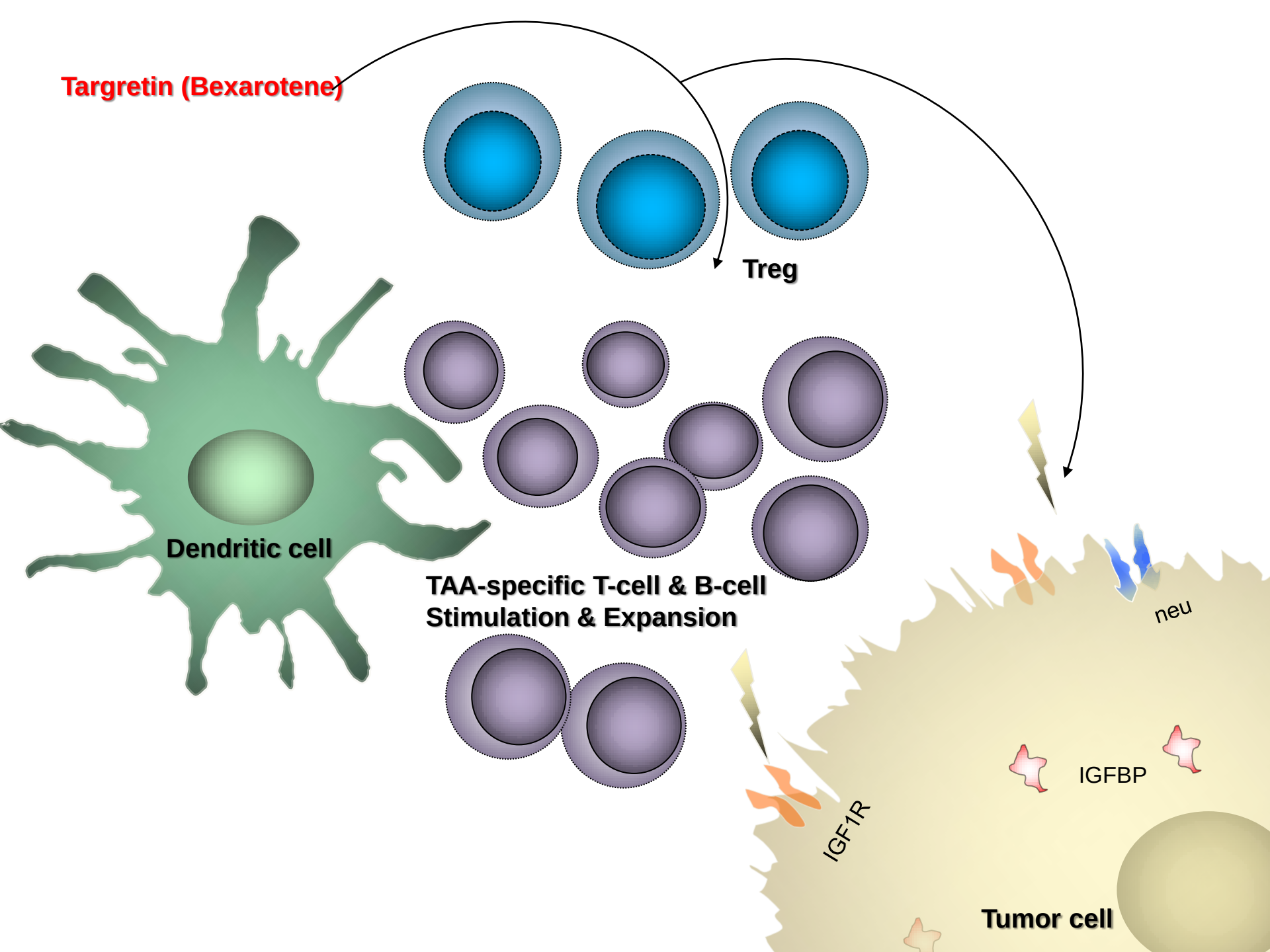
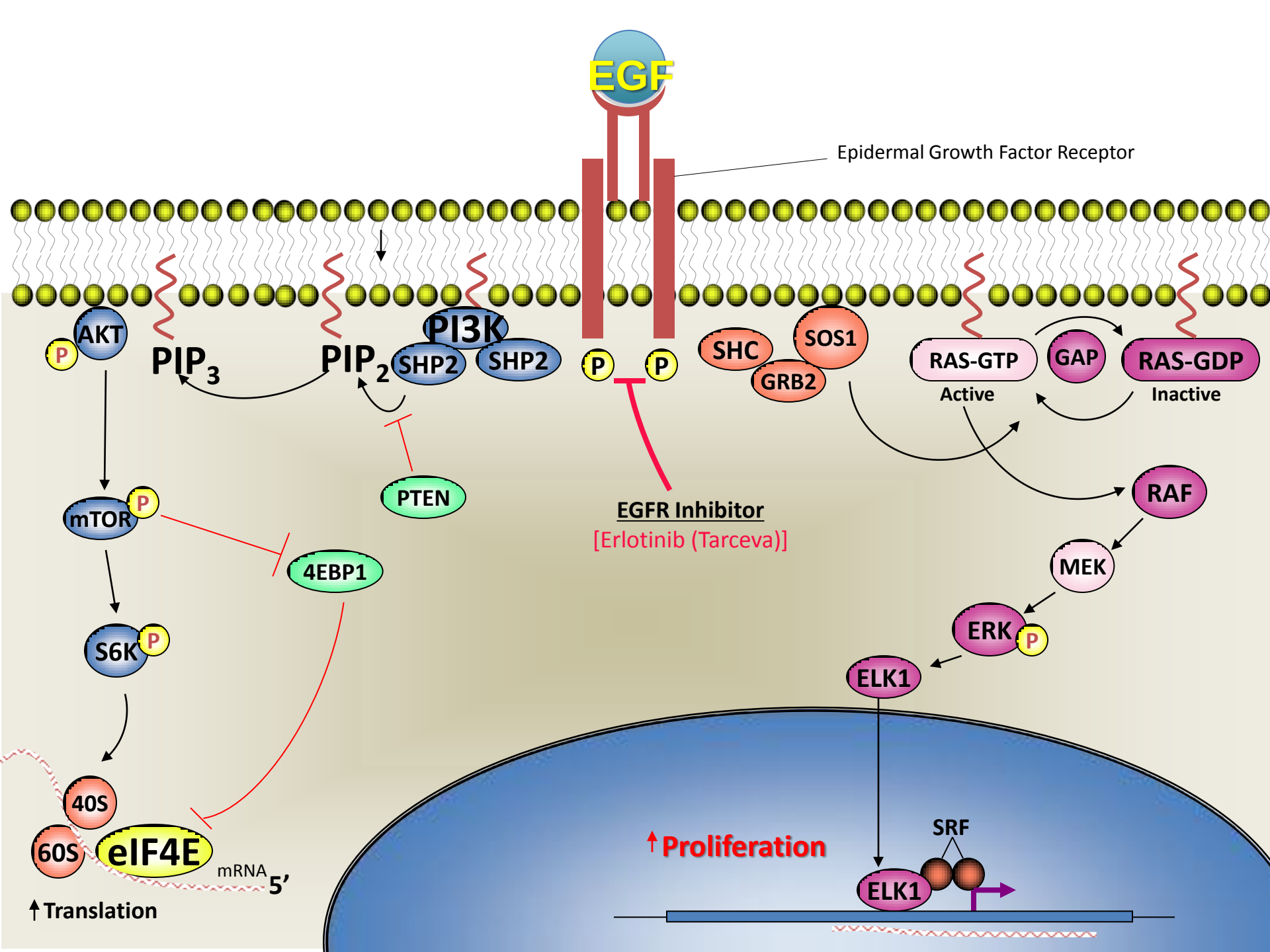
Marjorie Perloff, M.D.
Vernon Steele, Ph.D., M.P.H.

THANK YOU!


Targretin (Bexarotene)
Treg
Dendritic cell
TAA-specific T-cell & B-cell
Stimulation & Expansion
neu
IGFBP
IGF1R
Tumor cell


EGF
Epidermal Growth Factor Receptor
AKT
P
PIP3
PIP2
PI3K
SHP2
SHP2
P
P
SHC
SOS1
GRB2
RAS-GTP
Active
GAP
RAS-GDP
Inactive
PTEN
EGFR Inhibitor
[Erlotinib (Tarceva)]
RAF
mTOR
P
4EBP1
MEK
S6K
P
ERK
P
ELK1
40S
60S
eIF4E
mRNA
5'
Translation
Proliferation
SRF
ELK1

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)

Class Studies Examples 2004-2010

CLASS STUDY	SUGGESTED AGENTS	SELECTED AGENTS
HDAC Inhibitors	SAHA, Valproic acid, Trichostatin A, Oxamflatin	SAHA (Vorinostat)
mTOR Pathway	Rapamycin, CCI-779, RAD-001, AP23573	Rapamycin
P53 Modulators	CP31398, PRIMA-1	CP31398
PI3Kinase Inhibitors	XL147, XL765, TGX221, Myo-inositol	Myo-inositol
AMPK enhancers	Metformin	Metformin
AKT Protein Kinase	DIM, SR13668	DIM, SR13668
EGFR Antagonists	Tarceva, Lapatinib	Tarceva, Lapatinib

Target Organ ↔ Mechanism Link

Target Organ	Classes Highly Effective
Colon	NSAIDs, ODC inhibitors
Lung	Glucocorticoids, rexinoids, PI3K inhibitors
Breast	SERMs, aromatase & EGFR inhibitors, rexinoids
Bladder	NSAIDs, ODC inhibitors, EGFR inhibitors
Prostate	DHT inhibitors, retinoids
Skin	NSAIDs, ODC inhibitors, retinoids
Oral	NSAIDs, antioxidants
Pancreas	k-ras inhibitors, NSAIDs
Esophagus	NSAIDs/COX and LOX inhibitors

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 sqaumous cell cancers

INDs Approved – 2004-2010

- Diindole Methane
- 9-cis-UAB30
- ALA PDT
- Curcumin (Purified)
- Esomeprazole +Aspirin
- Nexium+Aspirin
- Lapatinib
- Letrozole
- Lovastatin
- L-Se-Me-selenocysteine
- Lycopene (5%)
- Myo-inositol
- NCX 4016
- Polyehylene glycol
- Pioglitizone
- Resiquimod topical
- Resveratrol
- Sirolimus
- SR13668
- Sulindac

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