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Correlation of In Vitro Chemopreventive Efficacy Data From the Human Epidermal Cell Assay With Animal Efficacy Data and Clinical Trial Plasma Levels

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Abstract The human epidermal cell (HEC) assay, which uses carcinogen exposed normal skin keratinocytes to screen for cancer prevention efficacy, was used to screen possible preventive agents. The endpoints measured were inhibition of carcinogen-induced growth and induction of involucrin, an early marker of differentiation. Sixteen of twenty agents (apigenin, apomine, budesonide, *N*-(2-carboxyphenyl)retinamide, ellagic acid, ibuprofen, indomethacin, melatonin, (−)-2-oxo-4-thiazolidine carboxylic acid, polyphenon E, resveratrol, β-sitosterol, sulfasalazine, vitamin E acetate, and zileuton) were positive in at least one of the two assay endpoints. Four agents (4-methoxyphenol, naringenin, palmitoylcarnitine chloride, and silymarin) were negative in the assay. Nine of the sixteen agents were positive for both endpoints. Agents that showed the greatest response included: ellagic acid > budesonide, ibuprofen > apigenin, and quinicrine dihydrochloride. Fifty-eight of sixty-five agents that have been evaluated in the HEC assay have also been evaluated in one or more rodent bioassays for cancer prevention and several are in clinical trials for cancer prevention. The assay has an overall predictive accuracy of ∼91.4% for efficacy in rodent cancer prevention irrespective of the species used, the tissue model, or the carcinogen used. Comparison of the efficacious concentrations in vitro to plasma levels in clinical trials show that concentrations that produced efficacy in the HEC assay were achieved in clinical studies for 31 of 33 agents for which plasma levels and/or C_{max} levels were available. For two agents, 9-*cis*-retinoic acid (RA) and dehydroepiandrosterone (DHEA), the plasma levels greatly exceeded the highest concentration (HC) found to have efficacy in vitro. Thus, the HEC assay has an excellent predictive potential for animal efficacy and is responsive at clinically achievable concentrations. J. Cell. Biochem. 95: 571–588, 2005. © 2005 Wiley-Liss, Inc.

Key words: cancer prevention efficacy; in vitro/in vivo correlation; human keratinocytes; growth inhibition; involucrin expression; in vitro alternatives; clinical correlation

Highly predictive cancer prevention efficacy assays are needed to screen large numbers of agents with potentially relevant mechanisms. A number of in vitro assays have been developed to prescreen agents [Steele, 1997]. These assays incorporate various cancer-related endpoints including, inhibition of cell transformation, and inhibition of biomarkers associated with carcinogenesis. Extrapolation of in vitro response data to humans has been difficult due to the lack of direct evidence that in vitro assays were responsive at concentrations found in humans and the lack of metabolism in cell culture relative to that found in vivo, and the need for surrogate endpoints that can be modified by clinically achievable agent concentrations.

The human epidermal cell (HEC) assay [Elmore et al., 1997, 1999; Steele et al., 1998] includes multiple exposures to low, non-toxic concentrations of propane sultone (PS), which

Abbreviations used: HEC, human epidermal cell; PS, propane sultone; RA, retinoic acid; KSFM, keratinocyte serum-free medium; HC, highest concentration; CP, chemopreventive; DFMO, difluoromethylornithine; DHEA, dehydroepiandrosterone; EGCG, epigallocatechin gallate.

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induces changes in growth and differentiation in normal skin keratinocytes, and continuous exposure to non-toxic concentrations of potential chemopreventive (CP) agents to inhibit these changes. This model is relevant to human carcinogen exposures, which normally occurs at relatively non-toxic doses, and chemoprevention, where patients are treated with continuous dosing over long periods of time. CP agent efficacy in the HEC assay is determined by the potential to reverse PS-induced growth and/or reduced expression of involucrin, which is a keratin precursor found just inside the cellular membrane in differentiating keratinocytes [Wilke et al., 1998; Okamura et al., 1991]. Our previously published studies [Elmore et al., 1997, 1999; Steele et al., 1998] have shown that activity in the HEC assay has correlated with chemoprevention activity in rodent cancer models [Steele et al., 1996].

This paper presents the response data from 20 agents in the HEC assay. In addition, we present a comparison of the cumulative response data in the HEC assay from the present and previously published studies [Elmore et al., 1999, 2000], to the efficacy found in the rodent bioassays. Also, for the first time, we compare the in vitro agent concentrations showing efficacy in the HEC assay to the plasma concentrations in humans from published data or Final Reports submitted to the National Cancer Institute on chemoprevention clinical trials. While the HEC assay responses for the previous studies have been published, the concentration data presented here have not been published.

MATERIALS AND METHODS

The detailed methods for the HEC assay have been published [Elmore et al., 1997, 2000]. The following is a brief description of the methods for the HEC assay.

HECs and Culture Procedures

Early passage neonatal human foreskin epidermal cells, which were isolated from foreskin tissues obtained from University of California, Irvine Medical Center, were used in these studies. Cultures of neonatal human foreskin epithelial cells were grown and maintained in keratinocyte serum-free medium (KSFM) from Life Technologies (Gaithersburg, MD). The cultures were incubated at 37°C in 5% CO_2 with more than 95% relative humidity. Cell cultures were tested and found to be free of mycoplasma contaminants using the method of Russell et al. [1975].

Preliminary Cytotoxicity Assay

The concentration range for the HEC assay was determined using a preliminary cytotoxicity assay. Cultures were treated over a 2-week period with multiple exposures to CP agents at log dilutions. All other aspects of the culture procedures were identical to that used in the HEC assay (described below) except that PS was not added.

HEC Assay

The concentrations of test agents used in the HEC assay consisted of the highest non-toxic test agent concentration, determined by the cytotoxicity assay, plus four or more half-log dilutions of that concentration. Second passage human keratinocyte cells in complete KSFM were seeded at $3–5 \times 10^3$ cells per well in 24-well culture dishes. Treatment was initiated 1 day after seeding. Negative control cultures received either medium containing solvent or medium only at each treatment. The positive control treatment was PS + retinoic acid (RA) at 0.03 μg/ml. The first day after seeding, all test cultures were exposed to 7.5 μg/ml PS in 0.1% acetone, and the test agent treatment cultures were co-exposed with PS and CP agent at half-log concentrations. On the fourth day after seeding, all cultures were again treated as on the first day except that PS was not included in the culture medium. The cultures were subcultured at the end of the first and second week. Following each subculture, the treatments were repeated as described for the first week. At the third subculture, cells were seeded into two 96-well dishes without additional treatment for a 1-week growth period. The cultures were then stained appropriately to assess the assay endpoints: growth inhibition and involucrin induction.

Growth Inhibition Endpoint

For the assessment of the growth inhibition endpoint, one of the 96-well dishes was stained with methylene blue in a methanol–water solution (4 g/100 ml, 30% methanol). The relative growth was determined using a plate reader (Molecular Devices, Sunnyvale, CA) to determine absorbance at a wavelength of 595 nm. We have previously shown that epidermal

cell numbers can be estimated using this procedure [Elmore et al., 1997].

Involucrin Induction Endpoint

The parallel 96-well culture plate was stained immuno-histochemically to determine the expression of involucrin [Elmore et al., 1997]. Stained cultures were then washed and the precipitate extracted prior to determining the absorbance at 450 nm using a Spectra Max plate reader (Molecular Devices). The absorbance values were then used together with the growth inhibition absorbance values from the parallel plate to normalize the involucrin absorbance values based on the relative number of cells in the each well.

Data Analysis

The percent inhibition of growth and involucrin induction were calculated by the previously published formulas [Elmore et al., 1997]. Valid assay criteria were established and strictly followed. For a valid assay, the following criteria must be met.

- Growth in the PS treated cultures must be at least 40% greater than the growth observed in the solvent control and the positive control, RA, or a preventive agent must inhibit the growth in cultures treated with PS by at least 30%.
- To be considered positive for growth inhibition, a test agent must inhibit the growth observed in the PS treated cultures by 30% or greater at two consecutive concentrations. This criterion was chosen because 30% inhibition of the growth observed in PS treated cultures would result in about the same growth that would occur in the solvent control without PS.
- To be considered positive for involucrin induction, a preventive agent must induce the expression of involucrin relative to that observed in the PS treated cultures by 20% or greater at two consecutive concentrations.
- Agents that do not meet the positive response criteria for at least one endpoint are considered as negative.

The requirement for two consecutive concentrations minimizes the possibility that one false data point could result in a positive call. An agent was considered positive, if it produced a positive response in at least one of the endpoints of the assay.

RESULTS

All 20 agents were evaluated for cytotoxicity in a range-finding assay. Cytotoxicity was assessed after two exposures (1 week) and four exposures (2 weeks). For five agents (indomethacin, methoxyphenol, palmitoylcarnitine chloride, quinicrine, and sulfasalazine), there was a slight increase in toxicity over the 2-week treatment; however, most agents did not show increased toxicity with repeated exposure.

The data presented in Table IA,B summarize the current assay responses for potential CP agents in the HEC assay. The data in Table IA summarize the responses in the growth inhibition endpoint. Table IB summarizes the data from the involucrin induction endpoint. Agents that were considered positive for one or more of the endpoints were considered as positive for the HEC assay. Since the potential for different agents to inhibit growth and/or induce involucrin could vary considerably, the maximum percent inhibition or induction for each agent was included.

Table II summarizes the responses of agents for both endpoints and presents the overall assay response for each agent. Sixteen of the agents were considered positive for inhibiting growth and/or inducing involucrin expression. Of these positive agents, 15 of 16 were active at three or more concentrations. Eight agents were active at five concentrations (two and a half concentration logs). Nine of fifteen positive agents were active for both endpoints. Melatonin and resveratrol were only active for the growth inhibition endpoint and apomine, *N*-(2-carboxyphenyl)retinamide, and (−)-2-oxo-4-thiazolidine carboxylic acid were only active for the involucrin endpoint.

Table III compares the cumulative in vitro data from the present and previous studies with the HEC assay to the in vivo data for those agents that have been evaluated in NCIs in vivo chemoprevention program. Fifty-eight of the sixty-five agents that have been evaluated in the HEC assay have also been screened in one or more of the in vivo organ specific assays with multiple animal species, and with different carcinogens. The columns show the responses of the various agents in vitro and in the various animal tissue model systems. For some agents,

TABLE I. Experimental Summary

Chemical	Concentration range tested[a]	Number of inhibiting concentrations	Maximum percent inhibition	Results[b,c]
A: Growth inhibition endpoint				
Apigenin	0.00296–0.296	2	93	+
Apomine	0.00025–0.025	None	27	NE
Budesonide	0.01–1	5	69	+
N-(2-Carboxyphenyl)retinamide	0.00009–0.009	None	26	NE
Ellagic acid	0.0109–1.09	4	81	+
Ibuprofen	1–100	4	86	+
Indomethacin	0.056–5.59	5	49	+
Melatonin	0.01–1	4	73	+
4-Methoxyphenol	0.01–1	None	28	NE
Naringenin	0.5–50	1	70	NE
(–)-2-Oxo-4-thiazolidine carboxylic acid	10–1,000	1	31	NE
Palmitoylcarnitine chloride	0.002–0.2	None	None	NE
Polyphenon E	10–1,000 μg/ml	4	59	+
Quinacrine dihydrochloride	0.003–0.3	5	84	+
Resveratrol	0.00197–0.197	4	84	+
Silymarin	0.02–2 μg/ml	2	74	NE
β-Sitosterol	0.001–0.1	3	57	+
Sulfasalazine	0.01–1	2	40	NE
Vitamin E succinate	0.0053–0.53	2	90	+
Zileuton	0.423–42.3	2	32	+
B: Involucrin induction endpoint				
Apigenin	0.00296–0.296	2	1,860	+
Apomine	0.00025–0.025	5	888	+
Budesonide	0.01–1	5	980	+
N-(2-Carboxyphenyl)retinamide	0.00009–0.009	5	1,094	+
Ellagic acid	0.0109–1.09	4	349	+
Ibuprofen	1–100	5	698	+
Indomethacin	0.056–5.59	5	748	+
Melatonin	0.01–1	2	284	NE
4-Methoxyphenol	0.01–1	3	39	NE
Naringenin	0.5–50	1	273	NE
(–)-2-Oxo-4-thiazolidine carboxylic acid	10–1,000	4	102	+
Palmitoylcarnitine chloride	0.002–0.2	None	None	NE
Polyphenon E	IC	IC		
Quinacrine dihydrochloride	0.003–0.3	5	796	+
Resveratrol	0.00197–0.197	1	286	NE
Silymarin	0.02–2 μg/ml	2	345	NE
β-Sitosterol	0.001–0.1	5	154	+
Sulfasalazine	0.01–1	4	110	NE
Vitamin E succinate	0.0053–0.53	3	1,274	+
Zileuton	0.423–42.3	5	412	+

[a]Concentrations are in μM except for silymarin, an extract from silybum marianum.
[b]An agent is called positive, if it shows two or more consecutive concentrations with greater than 30% inhibition. NE, not effective. The number of inhibiting concentrations is shown to give an indication of the breadth of activity for each agent. For example, an agent with five inhibiting concentrations would be active over a two-log concentration range.
[c]An agent is called positive, if it shows two or more consecutive concentrations with greater than 20% induction. IC, inconclusive. The number of inducing concentrations is shown to give an indication of the breadth of activity for each agent. For example, an agent with five inducing concentrations would be active over a two-log concentration range.

data were available from more than one species for several of the tissue models.

Table IV shows the correlation of the in vitro and in vivo data. For the comparison of the in vitro data to the in vivo data, an agent that produced a positive response in any animal model was considered as positive in vivo. For an agent to be considered as negative, it must produce a negative response in two or more animal models. Data for agents that produced a negative response in only animal model used were included in Table III but were not used for the comparison to the response in the HEC assay, which is defined as the ability of the in vitro assay response correctly predict the in vivo response. When the data from all animal models were considered, the positive predictivity (the percentage of the positive responses in the in vitro assay that correctly predicted an in vivo positive response) was 94% and the negative predictivity (the percentage of the negative responses in the in vitro assay that correctly

TABLE II. Human Epidermal Cell (HEC) Assay Response Summary

Chemical	Growth inhibition response	Involucrin induction response	Assay response[a]
Apigenin	+	+	+
Apomine	NE	+	+
Budesonide	+	+	+
N-(2-Carboxyphenyl)retinamide	NE	+	+
Ellagic acid	+	+	+
Ibuprofen	+	+	+
Indomethacin	+	+	+
Melatonin	+	NE	+
4-Methoxyphenol	NE	NE	NE
Naringenin	NE	NE	NE
(−)-2-Oxo-4-thiazolidine carboxylic acid	NE	+	+
Palmitoylcarnitine chloride	NE	NE	NE
Polyphenon E	+	IC	+
Quinacrine dihydrochloride	+	+	+
Resveratrol	+	NE	+
Silymarin	NE	NE	NE
β-Sitosterol	+	+	+
Sulfasalazine	NE	+	+
Vitamin E succinate	+	+	+
Zileuton	+	+	+

[a]For an agent to be positive in the assay, it must produce a positive response in either the growth inhibition and/or involucrin induction endpoint. IC, inconclusive.

predicted an in vivo negative response) was 71%. The overall accuracy of the HEC assay for predicting in vivo response was 91.4%.

Table V compares the efficacious concentrations in vitro to the clinical plasma levels. All concentrations shown in the table are in micromolar to facilitate comparison. The in vitro agent concentration data were extracted from the present and previous studies with the HEC assay, which were conducted over the past several years. The effective concentrations in the HEC assay for each endpoint demonstrate the range of effectiveness for each agent in the assay. The range of concentrations and/or C_{max} in plasma and $T_{1/2}$ (half-lives) were obtained from either the published literature or the Final Reports to NCI. Since the presentation of data in the literature varied considerably in the different studies, it was not possible to include all the pharmacokinetic values for each agent. The in vitro vs. in vivo columns compare the plasma and C_{max} concentrations to the concentrations that showed efficacy in vitro. When the in vitro concentration was the same as or similar to concentrations found for either plasma or plasma C_{max}, the in vitro concentration was considered as achieved in vivo. If the concentration predicted to be efficacious in vitro greatly exceeded the concentration in plasma, the in vitro concentrations were considered greater than the achievable in vivo concentration. When the concentration predicted to be efficacious from in vitro data was much less that the concentration found in plasma, the in vitro concentration was considered as achieved in plasma. The data show that the in vitro efficacious concentrations were considered as equal to (21 of 33 agents) or less than (10 of 33 agents) the plasma and/or C_{max} levels from clinical studies. Only two, glucaric acid and polyphenon E, of 33 agents were efficacious only at higher concentrations than the concentrations achieved in vivo. Since glucaric acid was positive at the lowest concentration tested in vitro, it is possible that glucaric acid could have efficacy at lower concentrations.

DISCUSSION

In vitro screening assays that use normal human epithelial cells are the most relevant for use in identifying CP agent efficacy for human clinical trials. The design of the HEC assay, which includes: normal human epithelial cells at early passage levels, multiple exposures to both carcinogen, and CP agent over a 3 weeks, extensive preliminary screens to ensure that non-toxic concentrations of CP agents were used in the assay, and the use of non-toxic concentrations of carcinogen, have permitted the detection of CP agent efficacy at concentrations that are similar to those found in plasma from cancer prevention clinical trials. The two biomarkers, inhibition of carcinogen-induced growth and the induction of involucrin expression have been shown to be independent biomarkers of preventive efficacy. By using two

TABLE III. Summary of Agent Data With the HEC Assay: Comparison to Organ Specific In Vivo Chemoprevention Efficacy Data

Agent	In vitro response	In vivo response							
		Lung	Esophagus	Colon	Mammary	Bladder	Skin	Prostate	Other
N-acetyl-L-cysteine	+[a] (188)	+ (1)		+ (2, 3)	+ (4)	+ (5)	NE[b] (6, 7)		+ Pancreas (9); NE; nasal cavity (8)
S-allylcysteine	+ (189)	NE (10, 11)		+ (12–15)	NE (16–19)				NE; intestine, small (20)
Apigenin	+ (142)						+ (168)		
Anethole trithione	+ (188)	NE (11)		+ (2, 13, 21–25)	+ (26)	NE (5)			
Ascorbyl palmitate	+ (188)	NE (27)		+ (3, 28)	NE (29, 30)	NE (5)	NE (31)		
Aspirin	+ (188)			+ (3, 12, 13, 23–25, 32–34)	NE (29, 35)	+ (36)			+ Intestine, small (24, 32, 33, 37–39); NE; intestine, total (40–42); thymus (lymphoma) (40, 41)
Budesonide	+(142)	+(43–45)							NE; larynx (46)
Carboxyamide amino imidazole (CAI)	+ (188)			+ (12, 13, 47)	+ (48)				+ intestine, small (49)
N-(2-carboxyphenyl)-retinamide	+ (142)			+ (23–25)					
β-Carotene	+ (189)	NE (10, 50, 51)		+ (52, 53)		NE (54)			NE; buccal pouch (55)
Curcumin	+ (189)	NE (10)	+ (56)	+ (14, 15, 24, 25, 57–60)	+ (29, 61)	NE (62)	NE (63, 64)		+ Sebaceous gland (66); NE; GI tract (65); intestine, small (14, 15, 66)
DFMO	+ (189)	+ (10, 67, 68)	+ (56)	+ (24, 57, 58, 67–69)	+ (70–74)	+ (75–77)	+ (6, 78, 79)	NE (80)	+ intestine, small (37–39); intestine, total (40, 41); NE; pancreas (81); thymus (lymphoma) (40, 41); lymphatic system (82, 83)
Dehydroepiandrosterone (DHEA) (prasterone)	+ (189)	NE (84–90)		+ (23–25)	+ (65, 70, 71, 72, 74, 91–98)	NE (99)	NE (100)	+ (80, 101–105)	NE; pancreas (81)
DHEA analog 8354 (fluasterone)	+ (188)			+ (13, 21–25, 69)	+ (96)			+ (80, 105, 106)	
Diphenhydramine, HCl	NE (189)	NE (107)		NE (33)	NE (16, 17)				
1,2-Dithiole-3-thione	+ (189)	NE (10)		+ (14, 15)	+ (16–18)				
Ellagic acid	+ (142)	NE (75, 76, 108)		+ (69)	NE (109, 110)	NE (99)			
Epigallocatechin gallate (EGCG)	+ (189)	NE (21, 111, 112)		+ (13, 21, 22, 113)					NE; intestine, small (21, 114)
Fumaric acid	+ (188)	+ (109)		+ (33)	+ (19)	NE (62)			NE; intestine, small (47)
Genistein	+ (189)			+ (33)	+ (115)				NE; intestine, small (47, 116)
Glucaric acid, Ca salt	+ (189)			+ (12, 13, 33)	+ (19)				NE; sebaceous gland (66)
4-HPR (fenretinide)	+ (188)	+ (117, 118)	NE (56)	+ (23, 119, 120)	+ (61, 71 121–127)	+ (36)	+ (128)	NE (74, 80, 129, 130)	+ Lymphatic system (131); NE; pancreas (9); buccal pouch (55)
Ibuprofen	+ (142)	NE (1)		+ (12, 13, 23, 32, 57, 58, 132)	+ (35)	+ (133)			NE; intestine, small (13, 23, 32)
Indole-3-carbinol	+ (189)	NE (75, 76, 108)		+ (57, 58)	+ (121, 134)	NE (99)	NE (100)		
Indomethacin	+ (142)					+ (57, 58)	NE (135)		
Lycopene	+ (189)	NE (136)		+ (13, 21, 22)	NE (16, 17, 137)				
D-mannitol	NE (189)			NE (57, 58, 138)	NE (135)				
Melatonin	+ (142)			NE (13, 21, 22)	NE (121)		+ (139)		
4-Methoxyphenol	NE (142)			NE (3, 12, 13, 28)	NE (109)				
Naringenin	NE (142)			NE (23–25)	+ (140, 141)				
Nordihydroguaiaretic acid	NE (189)			NE (57, 58)	NE (135)				
Oltipraz	+ (189)	+ (50)	NE (50, 56, 143)	+ (57, 58, 69)	+ (70, 144)	+ (75–77)	+	NE (80, 145)	+ Thymus (40, 41, 146); intestine, total (40, 41); NE; pancreas (9, 81); lymphatic system (131)
L-2-oxothiazolidine-4-carboxylate	+ (142)	NE (1)		NE (13, 21, 22)	NE (4)				
D,L-palmoylcarnitine	NE (142)	NE (107)		+ (53)	NE (121)				
Perillyl alcohol	+ (189)	+ (10, 84–90)	NE (94)	+ (47, 147)	+ (148)				NE; pancreas (9); intestine, small (49)
Phenethyl isothiocyanate	+ (188)	+ (8, 143)	+ (21, 111, 149)	NE (57, 58)	NE (26, 135)				NE; nasal cavity (8)
Phenyl butyrate (sodium)	+ (188)			+ (13, 21, 22)					
Piroxicam	+ (188)	+ (67, 68)		+ (12, 13, 23, 24, 32, 33 , 57, 58, 67–69, 119, 120)	NE (141)	+ (75–77)	+ (31, 63, 64)		+ Intestine, total (40, 41); intestine, small (24, 32, 33, 37–39); NE; pancreas (81); thymus (40, 41); uterus (150)
Propyl gallate	+ (188)			NE (57, 58, 60)	+ (140)		+ (31)		
Quercetin	+ (188)			+ (12, 13, 59)	+ (26, 59)	NE (133)			NE; sebaceous gland (66); intestine, small (66)
Quinacrine dihydrochloride	+ (142)			NE (12, 13)	NE (121)				
Resveratrol	+ (142)		+ (151)	+ (53)					
All-*trans*-retinoic acid (RA)	+ (188)			+ (12, 13, 23–25)			+ (152)		NE; lymphatic system (83)
9-*cis*-RA (alitretinoin)	+ (188)	NE (44)	NE (56)	+ (12, 13, 21, 22–25, 119, 120)	+ (71, 73, 148)			+ (80, 101–105, 130)	NE; larynx (46); lymphatic system (83)

Ro 16-9100	+ (189)			+ (12, 13, 23–25)	+ (153)	NE (62)			
Seleno-L-methionine	+ (188)	+ (136)		+ (156), NE (154, 155[c])				NE (80, 101–105)	
Silymarin	NE (142)			NE (57, 58)	NE (135)	NE (157)			
β-Sitosterol	+ (142)			NE (57, 58, 158)	NE (159)	NE (5)			
Sulfasalazine	+ (142)			NE (57, 58)					
Sulindac sulfone (exisulind)	+ (188)			+ (13–15, 21, 22)					+ intestine, small (20)
Tea (black, extract)	+ (188)	+ (160)		NE (13, 21, 22, 113, 114)			N (63, 64)		NE; intestine, small (161)
Tea (black, polyphenols)	+ (189)		NE (21, 111, 112)	+ (13, 21, 22, 113)					NE; intestine, small (21, 114)
Tea (green, polyphenols)	+ (188)		NE (21, 111, 112)	NE (13, 21, 22, 113, 114)				+ (165)	NE; intestine, small (21, 114)
Thioctic acid	+ (188)				NE (29)				
Ursodiol	+ (189)			NE (23–25); + (166, 167)					
Vitamin E acetate	+ (188)	NE (1)		NE (182, 183)	NE (127)	NE (127)		NE (74)	+ Liver (184); NE trachea (1)
p-Xylylselenocyanate	+ (189)	+ (169)		+ (170)					+ Tongue (171)
Zileuton	+ (142)	+ (172)							

[a]"+", positive response.
[b]NE, not effective.
[c]This paper is for D, L-selenomethionine.
References that cite final reports may be obtained from the Chemopreventive Agent Development Research Group, Division of Cancer Prevention, National Cancer Institute, Bethesda, MD, http://www3.cancer.gov/prevention/cadrg/.

(1) Moon, [1989a]; (2) Reddy et al. [1993a]; (3) Reddy [1992]; (4) Moon [1990c]; (5) Moon, 1992c; (6) McCormick, [1994b]; (7) Moon [1996c]; (8) Chung et al. [1996]; (9) Das Gupta [1995]; (10) Moon [1995]; (11) Moon, 1992a; (12) Wargovich et al. [1995]; (13) Wargovich et al. [2000]; (14) Kawamori et al. [1999]; (15) Reddy et al. [1999b]; (16) Cohen et al. [1999c]; (17) Cohen et al. [1999a]; (18) Moon [1996a]; (19) Moon [1992b]; (20) Reddy [1997]; (21) Steele et al. [2000]; (22) Wargovich et al. [1997]; (23) Zheng et al. [1999]; (24) Li et al. [1999b]; (25) Li et al. [1998]; (26) Lubet et al. [1997]; (27) Moon [1990a]; (28) Rao et al. [1995]; (29) Moon [1990b]; (30) Grubbs [1993a]; (31) Sutherland [1990]; (32) Pereira et al. [1996a]; (33) Pereira et al. [1994]; (34) Reddy et al. [1993b]; (35) Grubbs 1992a; (36) Sharma [1994]; (37) Dove et al. [1997]; (38) Jacoby et al. [1996]; (39) Jacoby et al. [2000]; (40) Liu et al. [1995]; (41) Samaha et al. [1997]; (42) Halberg et al. [2000]; (43) Wattenberg et al. [1997]; (44) Wattenberg et al. [2000]; (45) Pereira et al. [2002]; (46) Wattenberg [2000]; (47) Reddy et al. [1996]; (48) Grubbs [1995a]; (49) Reddy [1995]; (50) Moon et al. [1994b]; (51) Conaway et al. [1998]; (52) Rao et al. [2000b]; (53) Wargovich [1997]; (54) Moon [1986]; (55) Das Gupta [1994]; (56) Stoner [1997]; (57) Wargovich et al. [1992]; (58) Wargovich et al. [1996]; (59) Pereira et al. [1996b]; (60) Tempero [1990]; (61) Grubbs [1995b]; (62) McCormick, [1993b]; (63) Lubet et al. [2000]; (64) Fischer et al. [1999]; (65) Shilkaitis et al. [2000b]; (66) Pereira [1994]; (67) Gunning et al. [2000a]; (68) Gunning et al. [2000b]; (69) Rao et al. [1991]; (70) McCormick et al. [1996b]; (71) Cope et al. [2004]; (72) Green et al. [2001]; (73) Ahnen [1997]; (74) Moon [1997b]; (75) Moon et al., [1994a]; (76) Moon et al., [1992a]; (77) Moon et al. [1993]; (78) Mitsunaga et al. [1997]; (79) Moon, [1996d]; (80) McCormick and Rao [1999]; (81) McCormick [1993c]; (82) McCormick et al. [1996a]; (83) Carter [1997]; (84) Lantry et al. [1997]; (85) Lantry et al. [1999]; (86) Lantry et al. [2000c]; (87) Lantry et al., 2000b; (88) Lantry et al. [2000a]; (89) You and Bergman [1998]; (90) Herzog et al. [1997]; (91) Bednarek et al. [1999]; (92) Shilkaitis et al. [2000a]; (93) Christov et al. [2000]; (94) Liston et al. [2003]; (95) Lubet et al. [1998a]; (96) Ratko et al. [1991]; (97) Pereira, [1995b]; (98) Gould [1996]; (99) Moon, [1987a]; (100) Bresnick [1986]; (101) McCormick et al. [1999]; (102) Rao et al. [1997]; (103) McCormick et al. [1997]; (104) Rao et al. [1999]; (105) Bosland et al. [2000]; (106) Johnson et al. [2000]; (107) McCormick [1993a]; (108) Ratko et al. [1990]; (109) Moon, [1987b]; (110) Moon, 1989c); (111) Boone et al. [2000]; (112) Morse et al. [1997]; (113) Steele et al. [1999]; (114) Weisburger et al. [1998]; (115) Grubbs [1999a]; (116) Rao et al. [1997a]; (117) Moon et al. [1992d]; (118) Moon et al. [1992c]; (119) Zheng et al. [1997]; (120) Li et al. [1999a]; (121) Lubet et al., [1998b]; (122) Rodriguez-Burford et al. [1999]; (123) Weiss et al. [2000]; (124) Moon et al., [1992b]; (125) Cohen et al. [1997b]; (126) Grubbs [1996b]; (127) Grubbs [1991b]; (128) Bresnick [1987]; (129) McCormick et al. [1998]; (130) Christov et al. [2002]; (131) Carter [1995]; (132) Reddy [1990]; (133) Moon [1989b]; (134) Grubbs et al. [1995]; (135) Moon [1991]; (136) Moon [1997a]; (137) Cohen et al. [1999b]; (138) Tempero [1991]; (139) Kumar and Das [2000]; (140) McCormick [1994a]; (141) Grubbs, [1995c]; (142) [this manuscript); (143) Sharma [1997]; (144) Grubbs, [1999b]; (145) Moon [1996b]; (146) Rao et al. [1996]; (147) Reddy et al. [1997]; (148) Gould [2000]; (149) Matzinger et al. [1995]; (150) You [1998]; (151) Li et al. [2002]; (152) McCormick [1995]; (153) Grubbs [1989]; (154) Reddy [1999]; (155) Reddy et al. [2000]; (156) Mukherjee et al. [2001]; (157) Grubbs, [1991a]; (158) Birt [1989]; (159) Grubbs [1992b]; (160) Shukla and Taneja [2002]; (161) Weisburger [1996]; (162) Pereira [1999]; (163) Wargovich [1996]; (164) Jia and Han [2001]; (165) Gupta et al. [2001]; (166) Narisawa et al. [1999]; (167) Momen et al. [2002]; (168) Birt et al. [1997]; (169) Prokopczyk et al. [1997]; (170) Rao et al. [2000a]; (171) Tanaka et al. [1997]; (172) Gunning et al. [2002]; (173) Rao [1999]; (174) Pereira [1993]; (175) Wargovich [1994]; (176) Grubbs [1993b]; (177) Reddy et al., [1999a]; (178) Pereira [1995a]; (179) Pereira, [1997b]; (180) Reddy [1994]; (181) Reddy [1998]; (182) Wargovich [1992]; (183) Pereira [1997a]; (184) Factor et al. [2000]; (185) Lubet et al. [1994]; (186) Grubbs, [1996a]; (187) Grubbs [1997]; (188) Elmore et al. [2000]; (189) Elmore et al. [1999].

TABLE IV. In Vitro Versus In Vivo Results: Predictive Value of the HEC Assay for the In Vivo Result in Animals

In vitro	In vivo[a]		Predictivity
	+	−	
+	48	3	94%
−	2	5	71%
Totals	96% (sensitivity[b])	63% (specificity[c])	91.4% (accuracy[d])

[a]Data taken from Table III.
[b]Sensitivity is defined as the ability to predict positive in vivo responses.
[c]Specificity is defined as the ability to predict negative in vivo responses.
[d]Accuracy is defined as the ability to predict the overall in vivo response.

biomarkers, the HEC assay is able to identify additional agents, which would not have been detectable if only one biomarker was used. Agents that show efficacy for altering both biomarkers may have a greater potential for overall preventive efficacy; however, we do not have any supporting data from in vivo studies to confirm this hypothesis.

Of the 58 agents that have been evaluated in one or more of NCIs animal models for cancer prevention, 51 were positive in the HEC assay. Of the 51 agents, 48 were also positive in vivo (Table III). Only three (quinicrine dihydrochloride, β-sitosterol, and sulfasalazine) of the 51 positive agents (∼6%) were negative in vivo (8). Five of the seven agents that were negative in vitro were also negative in vivo. Two (naringenin and D,L-palmitoylcarnitine) of the seven agents (∼29%) that were identified in vitro as negative were positive in vivo. It is also noteworthy that negative responses in the in vitro assay correctly predicted six of seven negative responses in vivo for both the colon and mammary cancer prevention models. Many of the positive agents were effective over broad concentration ranges of two or more concentration logs in the absence of any observable cytotoxicity. In a number of cases, agents such as budesonide were positive at all concentrations evaluated. Although the HEC assay has provided evidence on the comparative potency of various agents, the correlation to rodent anticarcinogenic activity of individual agents is not possible due to the limited number of doses normally used for animal studies.

While it is unlikely that any one in vitro assay will be responsive to all possible mechanisms of cancer prevention, the data suggest that the HEC assay is responsive to CP agents from various mechanistic classes including: antioxidants, differentiation inducers, retinoids, prostaglandin synthesis inhibitors, and free radical scavengers. Since most agents usually have multiple mechanisms of action and the number of agents evaluated in the HEC assay is limited, additional data will be required to determine the overall sensitivity of the assay for detecting each class of agents.

The high predictive accuracy (Table IV) of the HEC assay (>91%) for in vivo efficacy in animal models, which utilize multiple carcinogens, multiple target organs, and species, would suggest that this in vitro assay has the ability to identify agents with the potential to prevent carcinogen-induced cancer. The overall predictive accuracy (91.4%) of the HEC assay for CP efficacy in vivo is exceptionally high relative to other in vitro assays [Steele et al., 1996]. Since the assay includes CP agent exposure both during and after each carcinogen exposure, it can potentially prevent the initial damage to DNA and/or the induction of early epigenetic changes as well as the subsequent events that follow initiation. While the assay effectively predicts in vivo efficacy in multiple animal models with different carcinogens, it does not yet appear to distinguish between specific target organ systems. Currently, the HEC assay response data correlate best with responses in the in vivo, colon cancer prevention models.

An important goal of our study is to predict in vivo response at physiological concentrations. In fact, the major criticisms of in vitro data include: the in vitro assay cannot adequately reproduce the metabolism found in vivo, and the concentrations tested in vitro are not achievable in vivo. Our data was accumulated using normal human epithelial cells at very early passage levels, which will retain at least some of the metabolism found in vivo. In addition, the HEC assay included a prescreen to prevent testing at overtly toxic agent concentrations. This ensured that the assays were conducted at agent concentrations that would not be expected to

TABLE V. Correlations of Agent Concentrations Showing Efficacy in the HEC Assay and Clinical Plasma Levels*

	HEC assay efficacious concentrations		Clinical concentrations[a]			In vitro versus in vivo[c]	
Agent	Growth inhibition	Involucrin induction	Plasma	C_{max}	$T_{1/2}$ (h)	Plasma	C_{max}
N-acetyl-L-cysteine	61[b]–1,838 (1)	61[b]–1,838 (1)	3.7–61 (4)	10.4–127.5 (4)	1–5 (4)	=	=
S-Allylcysteine	56–1,861 (1)		43–149 (5)	74–149 (5)		=	=
Anethole trithione	0.012[b]–3.64 (2)			0.0042–0.005 (6)			=
Apomine		0.00025–0.025		29.1 (7)	24–192 (7)		<
Aspirin	1.85–5.6 (2)			3.77–28.64 (8); 4.95–5.52 (9)	0.4–0.6 (8); 0.3–0.4 (9)		=
Budesonide	0.01[b]–1 (3)	0.01[b]–1 (3)		0.003–0.008 (10)			=
β-Carotene	0.019–0.056 (2)		6.84–7.53 (11); 0.13–7.45 (12)			<	
Curcumin	0.000008–0.0008	0.000008–0.0008	ND: 1.77 (13)			=	
Difluoromethylornithine (DFMO)		5.5–54.4 (1)	4.97–41.29 (14); 9.8–29.6 (15); 32.7–124.4 (16)		3.17 (16)	=	=
DHEA	0.00005–0.0017 (1)	0.00005–0.0017 (1)	0.85–14.7 (18)	0.031–0.69 (17); 24.3–25.9 (18); 0.02–0.034 (19)	20.8–27.1 (18), 18.7–26.6 (19)		≪
EGCG	0.055–1.64 (1)	0.055–0.164 (1)		0.3–0.85 (20); 0.16–0.96 (21)	2.3–3.05 (20); 1.97–3.06 (21)		=
Genistein	0.093–2.78 (1)	0.093–2.78 (1)		Total: 4.1–27.1 (22)	6.5–13.4 (23)	=	
				Free: 0.02–0.32 (22); 0.47–0.36 (23)	1.67–7.33 (23)	=	=
Glucaric acid, calcium salt	36.3[b]–363 (1)	36.3[b]–362 (1)	1.65–7.25 (24)	5.16–7.25 (24)		>	>
4-HPR	0.0026–0.026 (2)		0.128–1.53 (25); 0.89–1.41 (26)	0.6–12.9 (27)	17–25 (27)	<	<
Ibuprofen	1–100	1–100	Total: 157.6–344.6 (28) Free: 1.2–3.3 (28)	112.5–317.5 (29, 30)		=	=
Indole-3-carbinol	0.05–17 (2)			0.37–2.5 (31)	4.4–4.9 (31)	=	=
Indomethacin	2.79–27.9	0.279–27.9	0.12–3.1 (32)	1.59–2.6 (33)			=
Lycopene		0.047[b]–4.7 (1)	0.63–1.26 (34)	0.075–0.21 (35)	28–61 (35)	=	=
Melatonin	0.01–1.0			0.0097–0.0207 (36)	0.64–0.84 (36)		=
Oltipraz	0.00022[b]–0.022 (1)	0.00022[b]–0.022 (1)	0.0038–0.022 (37)	0.55–21.96 (38); 0.69–2.96 (39)	4.1–11.1 (38); 9.3–22.7 (39)	=	<
Perillyl alcohol		0.95[b]–95 (1)		175–472 (40); 138–493 (41), 433–774 (42)	1–6.4 (40); 0.46–2.5 (41)		<
Phenethyl isothiocyanate	0.0017–0.17 (2)		1.35 (43)	0.4–1.37 (43)	2.4 (43)	<	<
Piroxicam	9.6–30.2 (2)		3.44–6.25 (14)			≅	
Polyphenon E (EGCG)	34.7–1,156 (3)			0.34–0.63 (19); 0.159–0.82 (20)	2.7–4.9 (19); 1.9–3 (20)		>
Quercetin	0.00059–0.197 (2)			0.068–0.266 (44)	15.1–17.7 (44)		=
9-*cis*-RA	0.000008–0.0008 (2)	0.000008–0.00008 (2)		0.082–1.95 (45)			<<
Seleno-L-methionine		0.05–0.51 (2)	0.56–0.82 (46)			<	
All-*trans*-RA	0.1	0.1		0.46–0.93 (47)	0.8 (47)	<	
Sulindac sulfone	0.0064–2.11 (2)		3.49–11.6 (48)	10.1–48.1 (48)	4.9–10.9 (48)	=	<
Thioctic acid	1.21–40.2 (2)			8.2–36.9 (49)	0.12–0.58 (49)		=
Ursodiol		0.127[b]–0.38 (1)		13.1–18.1 (50)			<<
Vitamin E acetate	0.035–105.7 (2)	0.035–105.7 (2)	2–10 (51)			=	
Zileuton	4.2–12.7 (3)	0.42–42.3 (3)		6.09–18.75 (52)	1.85–3.51 (52)		=

*Concentrations in μM.

[a]Concentrations are based on the presence of the agent or one or more of its metabolites or their reactive products. Note that the clinical concentrations were reported in multiple formats and the data presented may be subject to interpretation.

[b]For these agents, the lowest concentration tested was active for the endpoint.

[c]For the in vitro versus in vivo comparisons, agents considered "<" were active at in vitro concentrations at least one half log lower than the lowest plasma concentration. Agents considered ">" were active at in vitro concentrations at least one half log greater than the highest plasma concentration. All other agents considered as having concentrations that were equal to the plasma concentration. Concentrations of agents considered "<" or "=" were considered as achieved in clinical studies.

References that cite final reports may be obtained from the Chemopreventive Agent Development Research Group, Division of Cancer Prevention, National Cancer Institute, Bethesda, MD, http://www3.cancer.gov/prevention/cadrg/.

(1) Elmore et al. [2000]; (2) Elmore et al. [1999]; (3) Redpath and Elmore, [2002]; (4) Pendyala and Creaven [1995]; (5) Kodera et al. [2002]; (6) Nagano and Takeyama [2001]; (7) Alberts et al. [2001]; (8) Ruffin et al. [1997]; (9) Benedek et al. [1995]; (10) As cited in, Spencer and McTavish [1995]; (11) Garewal et al. [1999]; (12) Dimetrov et al. [1986]; (13) Cheng et al. [2001]; (14) Meyskens et al. [1994]; (15) Carbone et al. [1998]; (16) Alberts [1991]; (17) Dyner et al. [1993]; (18) Frye et al. [2000]; (19) Legrain et al. [2000]; (20) Chow et al. [2003]; (21) Chow et al. [2001]; (22) Miltyk et al. [2003]; (23) Bloedon et al. [2002]; (24) Young and Osborne [1995]; (25) Formelli et al. [1993]; (26) Formelli et al. [2003]; (27) Garaventa et al. [2003]; (28) Albert et al. [1984]; (29) Regazzi et al. [1986]; (30) Karttunen et al. [1990]; (31) Hurwitz [2004] (personal communication); (32) Brash et al. [1981]; (33) Friedman et al. [1982]; (34) Chen et al. [2001]; (35) Diwadkar-Navsariwala et al. [2003]; (36) Hoffmann et al. [1998]; (37) Dimitrov et al. [2001]; (38) Gupta et al. [1995]; (39) O'Dwyer et al. [2000]; (40) Ripple et al. [1998]; (41) Ripple et al. [2000]; (42) Hudes et al. [2000]; (43) Liebes et al. [2001]; (44) Erlund et al. [2000]; (45) Weber and Dumont [1997]; (46) Hurwitz [2002]; (47) Mundi et al. [1994]; (48) van Stolk et al. [2000]; (49) Teichert et al. [2003]; (50) Nobilis et al. [2001]; (51) Traber et al. [2001]; (52) Wong et al. [1995].

produce toxicity following repeated exposures. In addition, the endpoints chosen for the assay are directly related to low, non-toxic, carcinogen induced effects that would be relevant to most human exposures. The clinical data comparison, Table V, illustrates the broad concentration ranges for efficacy in vitro as well as the range of concentrations reported in the clinical data. The data show that the clinical plasma and/or C_{max} levels are equal to or greater than effective concentrations identified in the HEC assay for 31 of the 33 agents for which data are available. We have previously shown that changes in polyamine expression that are found in clinical studies with difluoromethylornithine (DFMO) are induced in vitro by the same concentrations that are found in plasma and that the biomarkers used for the HEC assay, growth inhibition, and involucrin induction, are also induced at these same concentrations [Elmore et al., 2001]. For two agents, 9-*cis*-RA, ursodiol, and dehydroepiandrosterone (DHEA), the lowest C_{max} concentration found in clinical studies exceeded the concentrations showing efficacy in vitro by greater than one concentration log, which would suggest that clinical efficacy with these agents could be achieved at lower concentrations and that the clinical toxicity could be reduced. In contrast to the widely held belief that in vitro assay endpoint modification requires higher agent concentrations than are pharmacologically achievable in vivo, the data in Table V clearly show that the HEC assay is responsive at clinically achievable concentrations. The data presented here strongly suggest that the HEC assay provides a valuable tool in prescreening for cancer prevention efficacy and is responsive at clinically relevant concentrations.

REFERENCES

Ahnen D. 1997. Development and characterization a short-term mouse mammary aberrant focus assay for use as a surrogate endpoint biomarker in rodent models of phase II clinical trials of chemopreventive agents for mammary cancer. University of Colorado, Health Sciences Center, Contract no. NO1-CN-55178. Final Report.

Albert KS, Gillespie WR, Wagner JG, Pau A, Lockwood GF. 1984. Effects of age on the clinical pharmacokinetics of ibuprofen. Am J Med 77:47–50.

Alberts DS. 1991. Phase I and pharmacokinetic studies of DFMO. University of Arizona, Contract no. N01-CN-85106-01. Final Report.

Alberts DS, Hallum AV III, Stratton-Custis M, Garcia DJ, Gleason-Guzman M, Salmon SE, Santabarbara P, Niesor EJ, Floret S, Bentzen CL. 2001. Phase I pharmacokinetic trial and correlative in vitro phase II tumor kinetic study of apomine (SR-45023A), a novel oral biphosphonate anticancer drug. Clin Cancer Res 7:1246–1250.

Bednarek A, Shilkaitis A, Green A, Lubet R, Kelloff G, Christov K, Aldaz CM. 1999. Suppression of cell proliferation and telomerase activity in 4-(hydroxyphenyl)retinamide-treated mammary tumors. Carcinogenesis 20: 879–883.

Benedek IH, Joshi AS, Pieniaszek HJ, King S-YP, Kornhauser DM. 1995. Variability in the pharmacokinetics and pharmacodynamics of low dose aspirin in healthy volunteers. J Clin Pharmacol 35:1181–1186.

Birt D. 1989. Chemoprevention of MAM acetate-induced colon cancer in mice with selected chemopreventive agents. Eppley Institute, Contract no. NO1-CN-55451-06. Final Report.

Birt DF, Mitchell D, Gold B, Pour P, Pinch H. 1997. Inhibition of ultraviolet light induced skin carcinogenesis in SKH-1 mice by apigenin, a plant flavonoid. Anticancer Res 17:85–91.

Bloedon LT, Jeffcoat AR, Lopaczynski W, Schell MJ, Black TM, Dix KJ, Thomas BF, Albright C, Busby MG, Crowell JA, Zeisel SH. 2002. Safety and pharmacokinetics of purified soy isoflavones: Single-dose administration to postmenopausal women. Am J Clin Nutr 76:1126–1137.

Boone CW, Stoner GD, Bacus JV, Kagan V, Morse MA, Kelloff GJ, Bacus JW. 2000. Chemoprevention with theaflavins of rat esophageal intraepithelial neoplasia quantitatively monitored by image tile analysis. Cancer Epidemiol Biomarkers Prev 9:1149–1154.

Bosland MC, Johnson WD, Steele VE, Lubet RA, Kelloff GJ, McCormick DL. 2000. Prostate cancer chemoprevention efficacy evaluation of combined administration of L-selenomethionine + vitamin E in a rat model. Proc Am Assoc Cancer Res 41: abstract no. 2154.

Brash AR, Hickey DE, Graham TP, Stahlman MT, Oates JA, Cotton RB. 1981. Pharmacokinetics of indomethacin in the neonate: Relation of plasma indomethacin levels to response of the ductus arteriosus. New Engl J Med 305: 67–72.

Bresnick E. 1986. Evaluation of chemopreventive agents by in vivo screening assays. Eppley Institute, Contract no. NO1-CN-55451-01. Final Report.

Bresnick E. 1987. Chemoprevention of DMBA-induced epidermal tumorigenesis—in vivo. Eppley Institute, Contract no. NO1-CN-55451-03. Final Report.

Carbone PP, Douglas JA, Larson PO, Verma AK, Blair IA, Pomplun M, Tutsch KD. 1998. Phase I chemoprevention study of piroxicam and difluoromethylornithine. Cancer Epidemiol Biomarkers Prev 7:907–912.

Carter C. 1995. Chemoprevention of lymphoma in pim-1 transgenic mice by various chemopreventive agents. Southern Research Institute, Contract no. NO1-CN-25455-01. Final Report.

Carter C. 1997. Chemoprevention of lymphoma in pim-1 transgenic mice by various chemopreventive agents. Southern Research Institute, Contract no. NO1-CN-55149. Final Report.

Chen L, Stacewicz-Sapuntzakis M, Duncan C, Sharifi R, Ghosh L, van Breemen R, Ashton D, Bowen PE. 2001. Oxidative DNA damage in prostate cancer patients consuming tomato sauce-based entrees as a whole-food intervention. J Natl Cancer Inst 93:1872–1879.

Cheng AL, Hsu CH, Lin JK, Hsu MM, Ho YF, Shen TS, Ko JY, Lin JT, Lin BR, Ming-Shiang W, Yu HS, Jee SH,

Chen GS, Chen TM, Chen CA, Lai MK, Pu YS, Pan MH, Wang YJ, Tsai CC, Hsieh CY. 2001. Phase I clinical trial of curcumin, la chemopreventive agent, in patients with high-risk or pre-malignant lesions. Anticancer Res 21: 2895–2900.

Chow H-HS, Cai Y, Alberts DS, Hakim I, Dorr R, Shahi F, Crowell JA, Yang CS, Hara Y. 2001. Phase I pharmacokinetic study of tea polyphenols following single-dose administration of epigallocatechin gallate and polyphenon E. Cancer Epidemiol Biomarkers Prev 10:53–58.

Chow H-HS, Cai Y, Hakim IA, Crowell JA, Shahi F, Brooks CA, Dorr RT, Kara Y, Alberts DS. 2003. Pharmacokinetics and safety of green tea polyphenols after multiple-dose administration of epigallocatechin gallate and polyphenon E in healthy individuals. Clin Cancer Res 9:3312–3319.

Christov K, Shilkaitis A, Green A, Mehta RG, Grubbs C, Kelloff G, Lubet R. 2000. Cellular responses of mammary carcinomas to aromatase inhibitors: Effects of vorozole. Breast Cancer Res Treat 60:117–128.

Christov KT, Moon RC, Lantvit DD, Boone CW, Steele VE, Lubet RA, Kelloff GJ, Pezzuto JM. 2002. 9-*cis*-retinoic acid but not 4-(hydroxyphenyl)retinamide inhibits prostate intraepithelial neoplasia in noble rats. Cancer Res 62:5178–5182.

Chung F-L, Kelloff G, Steele V, Pittman B, Zang E, Jiao D, Rigotty J, Choi C-I, Rivenson A. 1996. Chemopreventive efficacy of arylalkl isothiocyanates and *N*-acetylcysteine for lung tumorigenesis in Fischer rats. Cancer Res 56: 772–778.

Cohen LA, Epstein M, Saa-Pabon V, Meschter C, Zang E. 1994. Interactions between 4-HPR and diet in NMU-induced mammary tumorigenesis. Nutr Cancer 21:271–283.

Cohen LA, Amin S, Marks PA, Rifkind RA, Desai D, Richon VM. 1999a. Chemoprevention of carcinogen-induced mammary tumorigenesis by hybrid polar cytodifferentiation agent, suberanilohydroxamic acid (SAHA). Anticancer Res 19:4999–5005.

Cohen LA, Zhao Z, Pittman B, Khachik F. 1999b. Effect of dietary lycopene on *N*-methylnitrosourea-induced mammary tumorigenesis. Nutr Cancer 34:153–159.

Cohen A, Zhao Z, Pittman B, Lubet R. 1999c. *S*-allycysteine, a garlic constituent, fails to inhibit *N*-methylnitrosourea-induced rat mammary tumorigenesis. Nutr Cancer 35:58–63.

Conaway CC, Jiao D, Kelloff GJ, Steele VE, Rivenson A, Chung F-L. 1998. Chemopreventive potential of fumaric acid, *N*-acetylcysteine, *N*-(4-hydroxyphenyl)retinamide, and β-carotene for tobacco-nitrosamine-induced lung tumors in A/J mice. Cancer Lett 124:85–93.

Cope MB, Steele VE, Lubet RA, Eto I, Juliana MM, Hill DL, Grubbs CJ. 2004. Efficacy of 9-*cis*-retinoic acid and *N*-(4-hydroxyphenyl)retinamide alone and in combination in mammary cancer prevention. Oncol Rep 11:465–469.

Das Gupta TK. 1994. Evaluation of gamma-glutamyltranspeptidase as an intermediate endpoint during 7,12-dimethylbenz(a)anthracene-induced buccal pouch carcinogenesis in hamsters. University of Illinois, Chicago, Contract no. NO1-CN-25492-01. Final Report.

Das Gupta TK. 1995. Evaluation of K-ras activation as an intermediate endpoint during pancreatic carcinogenesis in male hamsters. University of Illinois, Chicago, Contract no. NO1-CN-25492-03. Final Report.

Dimetrov NV, Boone CW, Hay MB, Whetter P, Pins M, Kelloff GJ, Malone W. 1986. Plasma beta-carotene levels—kinetic patterns during administration of various doses of beta-carotene. J Nutr Growth Cancer 3:227–237.

Dimitrov NV, Leece CM, Tompkins ER, Seymour E, Bennink M, Gardiner J, Crowell J, Hawk E, Nashawaty M, Bennett JL. 2001. Oltipraz concentrations in plasma, buccal mucosa cells, and lipids: Pharmacological studies. Cancer Epidemiol Biomarkers Prev 10:201–207.

Diwadkar-Navsariwala V, Novotny JA, Gustin DM, Sosman JA, Rodvold KA, Crowell JA, Stacewicz-Sapuntzakis M, Bowen PE. 2003. A physiological pharmacokinetic model describing the disposition of lycopene in healthy men. J Lipid Res 44:1927–1939.

Dove WF, Clipson L, Gould KA, Luongo C, Marshall DJ, Moser AR, Newton MA, Jacoby RF. 1997. Intestinal neoplasia in the ApcMin mouse: Independence from the microbial and natural killer (beige locus) status. Cancer Res 57:812–814.

Dyner TS, Lang W, Geaga J, Golub A, Stites D, Winger E, Gulmarini M, Masterson J, Jacobsen MA. 1993. An open-label dose-escalation trial of oral dehydroepiandrosterone tolerance and pharmacokinetics in patients with HIV disease. J Acquir Immune Defic Syndr 6:459–465.

Elmore E. 1991. In vitro screening of chemopreventive agents using human epidermal cells and fibroblast cells. ManTech Environmental Technology, Inc., Contract no. N01-CN-95172-04. Final Report.

Elmore E, Sun C, Li H-R, Wyatt GP, Buckmeier JA, Steele VE, Redpath JL. 1997. Human epidermal cell assay for chemopreventive agents. Meth Cell Sci 19:13–18.

Elmore E, Sun C, Li H-R, Wyatt GP, Buckmeier JA, Steele VE, Kelloff GJ, Redpath JL. 1999. In vitro chemopreventive efficacy screening using human keratinocytes and the in vivo data correlation. Anticancer Res 19:909–918.

Elmore E, Luc T-T, Li H-R, Buckmeier JA, Steele VE, Kelloff GJ, Redpath JL. 2000. Correlation of chemopreventive efficacy data from the human epidermal cell assay with in vivo data. Anticancer Res 20:27–32.

Erlund I, Kosonen T, Alfthan G, Maenpaa J, Perttunen K, Kenraali J, Parantainen J, Aro A. 2000. Pharmacokinetics of quercetin from quercetin aglycone and rutin in healthy volunteers. Eur J Clin Pharmacol 56:545–553.

Factor VM, Laskowska D, Jensen MR, Woitach JT, Popescu NC, Thorgeirsson SS. 2000. Vitamin E reduces chromosomal damage and inhibits hepatic tumor formation in a transgenic mouse model. Proc Natl Acad Sci USA 97: 2196–2201.

Fischer SM, Lo H-H, Gordon GB, Seibert K, Kelloff G, Lubet RA, Conti CJ. 1999. Chemopreventive activity of celecoxib, a specific cyclooxygenase-2 inhibitor, and indomethacin against ultraviolet light-induced skin carcinogenesis. Mol Carcinog 25:231–240.

Formelli F, Clerici M, Campa T, Di Mauro MG, Magni A, Mascotti G, Moglia D, De Polo G, Costa A, Veronnesi U. 1993. Five-year administration of fenretinamide: Pharmacokinetics and effects on plasma retinol concentrations. J Clin Oncol 11:2036–2042.

Formelli F, Camerini T, Cavadini E, Appierto V, Villani MG, Costa A, De Palo G, Di Mauro MG, Veronesi U. 2003. Fenretinide breast cancer prevention trial: Drug and retinol plasma levels in relation to age an disease outcome. Cancer Epidemiol Biomark Prev 12:34–41.

Friedman CA, Parks BR, Rawson JE, Serwer GA, Anderson PA. 1982. Indomethacin and the preterm infant with a patent ductus arteriosus: Relationship between plasma concentration and ductus closure. Devel Pharmacol Therapeut 4:37–46.

Frye RF, Kroboth PD, Kroboth FJ, Stone RA, Folan M, Salek FS, Pollock BG, Linares AM, Hakala C. 2000. Sex differences in the pharmacokinetics of dehydroepiandrosterone (DHEA) after single- and multiple-dose administration in healthy older adults. J Clin Pharmacol 40:596–605.

Garaventa A, Luksch R, Piccolo MSL, Cavadini E, Montaldo PG, Pissitola MR, Boni L, Ponzoni M, Decensi A, De Bernardi B, Bellani FF, Formelli F. 2003. Phase I trial and pharmacokinetics of fenretinide in children with neuroblastoma. Clin Cancer Res 9: 2031–2039.

Garewal HS, Katz RV, Meyskens F, Pitcock J, Morse D, Friedman S, Peng Y, Pendrys DG, Mayne S, Alberts D, Kiersch T, Graver E. 1999. β-Carotene produces sustained remissions in patients with oral leukoplakia: Results of a multicenter prospective trial. Arch Otolaryngol Head Neck Surg 125:1305–1310.

Gould M. 1996. Loss or amplification of chromosomal material employing animal models of carcinogenesis. University of Wisconsin, Contract no. NO1-CN-25488-02. Final Report.

Gould M. 2000. Use of a retrovirally mediated rat mammary model for use as a chemopreventive model for hormonally dependent and hormonally independent mammary tumors. University of Wisconsin, Contract no. NO1-CN-85176. Final Report.

Green JE, Shibata M-A, Shibata E, Moon RC, Anver MR, Kelloff G, Lubet R. 2001. 2-Difluoromethylornithine and dehydroepiandrosterone inhibit mammary tumor progression but not mammary or prostate tumor initiation in C3(1)/SV40 T/t-antigen transgenic mice. Cancer Res 61: 7449–7455.

Grubbs CJ. 1989. Chemoprevention of MNU-induced mammary tumors in the rat with five selected retinoids. University of Alabama, Birmingham, Contract no. NO1-CN-75422-01. Final Report.

Grubbs CJ. 1991a. Chemoprevention of MNU-induced mammary tumors in the rat with selected vitamin E analogs. University of Alabama, Birmingham, Contract no. NO1-CN-85062-01. Final Report.

Grubbs CJ. 1991b. Chemoprevention of OH-BBN-induced bladder cancer in mice with selected chemopreventive agents. University of Alabama, Birmingham, Contract no. NO1-CN-95156-01. Final Report.

Grubbs CJ. 1992a. Chemoprevention of MNU-induced mammary tumors in the rat with selected chemopreventive agents. University of Alabama, Birmingham, Contract no. NO1-CN-95156-02. Final Report.

Grubbs CJ. 1992b. Prevention of MNU-induced mammary tumors in the rat with selected prostaglandin synthesis inhibitors. University of Alabama, Birmingham, Contract no. NO1-CN-85062-02. Final Report.

Grubbs CJ. 1993a. Chemoprevention of MNU-induced mammary tumors in the rat with selected chemopreventive agents. University of Alabama, Birmingham, Contract no. NO1-CN-95156-03. Final Report.

Grubbs CJ. 1993b. Chemoprevention of DMBA-induced mammary tumors in the rat with selected chemopreventive agents. University of Alabama, Birmingham, Contract no. NO1-CN-95156-04. Final Report.

Grubbs CJ. 1995a. Chemoprevention of MNU-induced mammary tumors in the rat by combination of chemopreventive agents. University of Alabama, Birmingham, Contract no. NO1-CN-25454-01. Final Report.

Grubbs CJ. 1995b. Chemoprevention of DMBA-induced mammary tumors in the rat with selected chemopreventive agents. University of Alabama, Birmingham, Contract no. NO1-CN-25454-02. Final Report.

Grubbs CJ. 1995c. Chemoprevention of MNU-induced mammary tumors in the rat by combination of chemopreventive agents. University of Alabama, Birmingham, Contract no. NO1-CN-85062-03. Final Report.

Grubbs CJ. 1996a. Chemoprevention of MNU-induced mammary tumors in the rat by combinations of chemopreventive agents. University of Alabama, Birmingham, Contract no. NO1-CN-35571-01. Final Report.

Grubbs CJ. 1996b. Effects of various chemopreventive agents on MNU-induced mammary tumors. University of Alabama, Birmingham, Contract no. NO1-CN-25454-04. Final Report.

Grubbs CJ. 1997. Chemoprevention of MNU-induced mammary tumors in the rat by combinations of chemopreventive agents. University of Alabama, Birmingham, Contract no. NO1-CN-55118. Final Report.

Grubbs CJ. 1999a. Chemoprevention of MNU-induced mammary tumors in the rat by combinations of chemopreventive agents. University of Alabama, Birmingham, Contract no. NO1-CN-75027. Final Report.

Grubbs CJ. 1999b. Effects of various chemopreventive agents on MNU-induced rat mammary tumors. University of Alabama, Birmingham, Contract no. NO1-CN-75101. Final Report.

Grubbs CJ, Steele VE, Casebolt T, Juliana MM, Eto I, Whitaker LM, Dragnev KH, Kelloff GJ, Lubet RA. 1995. Chemoprevention of chemically-induced mammary carcinogenesis by indole-3-carbinol. Anticancer Res 15:709–716.

Gunning WT, Kramer PM, Boone CW, Kelloff GJ, Lubet RA, Steele VE, Pereira MA. 2000a. Prevention of vinyl carbamate-induced mouse lung tumors by dexamethasone, difluoromethylornithine, piroxicam, and green tea. Proc Am Assoc Cancer Res 41: abstract no. 4224.

Gunning WT, Kramer PM, Lubet RA, Steele VE, Pereira MA. 2000b. Chemoprevention of vinyl carbamate-induced lung tumors in strain a mice. Exp Lung Res 26: 757–772.

Gunning WT, Kramer PM, Steele VE, Pereira MA. 2002. Chemoprevention by lipoxygenase and leukotriene pathway inhibitors of vinyl carbamate-induced lung tumors in mice. Cancer Res 62:4199–4201.

Gupta E, Olopade OI, Ratain MJ, Mick R, Baker TM, Berezin FK, Benson AB III, Dolan ME. 1995. Pharmacokinetics and pharmacodynamics of oltipraz as a chemopreventive agent. Clin Cancer Res 1:1133–1138.

Gupta S, Hastak K, Ahmad N, Lewin JS, Mukhtar H. 2001. Inhibition of prostate carcinogenesis in TRAMP mice by oral infusion of green tea polyphenols. Proc Natl Acad Sci USA 98:10350–10355.

Halberg RB, Katzung DS, Hoff PD, Moser AR, Cole CE, Lubet RA, Donehower LA, Jacoby RF, Dove WF. 2000. Tumorigenesis in the multiple intestinal neoplasia mouse: Redundancy of negative regulators and speci-

ficity of modifiers. Proc Natl Acad Sci USA 97:3461–3466.

Herzog CR, Lubet RA, You M. 1997. Genetic alterations in mouse lung tumors: Implications for cancer chemoprevention. J Cell Biochem Suppl 28(29):49–63.

Hoffmann H, Dittgen M, Hoffmann A, Bartsch C, Breitbarth H, Timpe C, Farker K, Schmidt U, Mellinger U, Zimmermann H, Graeser T, Oettel M. 1998. Evaluation of an oral pulsatile delivery system for melatonin in humans. Pharmazie 53:462–466.

Hudes GR, Szarks CE, Adams A, Ranganathan S, McCauley RA, Weiner LM, Langer CJ, Litwin S, Yeslow G, Halberr T, Qian M, Gallo JM. 2000. Phase I pharmacokinetic trial of perillyl alcohol (NSC 641066) in patients with refractory solid malignancies. Clin Cancer Res 6: 3071–3080.

Hurwitz A. 2002. Phase I multiple-dose safety and clinical study of L-selenomethionine and D-alpha-tocopherol in smokers. University of Kansas Medical Center, Contract no. N01-CN-65019. Final Report.

Hurwitz A. 2004. University of Kansas Medical Center. Personal communication.

Jacoby RF, Marshall DJ, Newton MA, Novakovic K, Tutsch K, Cole CE, Lubet RA, Kelloff GJ, Verma A, Moser AR, Dove WF. 1996. Chemoprevention of spontaneous intestinal adenomas in the ApcMin mouse model by the nonsteroidal anti-inflammatory drug piroxicam. Cancer Res 56:710–714.

Jacoby RF, Cole CE, Tutsch K, Newton MA, Kelloff GJ, Hawk ET, Lubet RA. 2000. Chemopreventive efficacy of combined piroxicam and DFMO treatment in the APC mutant Min mouse model of adenomas, and selective toxicity against APC mutant embryos. Cancer Res 60: 1864–1870.

Jia X, Han C. 2001. Effects of green tea on colonic aberrant crypt foci and proliferative indexes in rats. Nutr Cancer 39:239–243.

Johnson WD, Bosland MC, Lubet RA, Steele VE, Kelloff GJ, McCormick DL. 2000. Chemoprevention of rat prostate carcinogenesis by fluasterone, a non-androgenic analog of dehydroepiandrosterone. Proc Am Assoc Cancer Res 41: abstract no. 5408.

Karttunen P, Saano V, Paronen P, Peura P, Vidgren M. 1990. Pharmacokinetics of ibuprofen in man: A single-dose comparison of two over-the-counter, 200 mg preparations. Intl J Clin Pharmacol Ther Toxicol 28:251–255.

Kawamori T, Lubet R, Steele VE, Kelloff GJ, Kaskey RB, Rao CV, Reddy BS. 1999. Chemopreventive effect of curcumin, a naturally occurring anti-inflammatory agent, during the promotion/progression stages of colon cancer. Cancer Res 59:597–601.

Kodera Y, Suzuki A, Imada O, Kasuga S, Sumioka I, Kanezawa A, Taru N, Fujikawa S, Nagae S, Masamoto K, Masshige K, Ono K. 2002. Physical, chemical, and biological properties of *S*-allylcysteine, an amino acid derived from garlic. J Agric Food Chem 50:622–632.

Kumar CA, Das UN. 2000. Effect of melatonin on two stage skin carcinogenesis in Swiss mice. Med Sci Monit 6:471–475.

Lantry LE, Zhang Z, Gao F, Crist KA, Wang Y, Kelloff GJ, Lubet RA, You M. 1997. Chemopreventive effect of perillyl alcohol on 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone induced tumorigenesis in (C3H/HeJ X A/J)F1 mouse lung. J Cell Biochem Suppl 27:20–25.

Lantry LE, Zhang Z, Crist KA, Wang Y, Kelloff GJ, Lubet RA, You M. 1999. 5-Aza-2′-deoxycytidine is chemopreventive in a 4-(methyl-nitrosamino)-1-(3-pyridyl)-1-butanone-induced primary mouse lung tumor model. Carcinogenesis 20:343–346.

Lantry LE, Zhang Z, Crist KA, Wang Y, Hara M, Zeeck A, Lubet RA, You M. 2000a. Chemopreventive efficacy of promising farnesyltransferase inhibitors. Exp Lung Res 26:773–790.

Lantry LE, Zhang Z, Wang Y, Liu G, Hamilton AD, Sebti SM, Kelloff GJ, Lubet RA, You M. 2000b. The farnesyltransferase inhibitor FTI-276 is chemopreventive for 4-(methyl-nitrosamino)-1-(3-pyridyl)-1-butanone induced lung tumorigenesis in A/J mice. Proc Am Assoc Cancer Res 41: abstract no. 2913.

Lantry LE, Zhang Z, Yao R, Crist KA, Wang Y, Ohkanda J, Hamilton AD, Sebti S, Lubet RA, You M. 2000c. Effect of farnesyltransferase inhibitor FTI-276 on established lung adenomas from A/J mice induced by 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone. Carcinogenesis 21: 113–116.

Legrain S, Massien C, Lahlou N, Roger M, Debuire B, Diquet B, Chantellier G, Azizi M, Faucounau V, Porchet H, Forette F, Baulieu E-E. 2000. Dehydroepiandrosterone replacement administration: Pharmacokinetic and pharmacodynamic studies in healthy elderly subjects. J Clin Endrocrin Metabol 85:3208–3217.

Li H, Kramer PM, Lubet RA, Steele VE, Kelloff GJ, Pereira MA. 1998. Effect of calcium on azoxymethane-induced aberrant crypt foci and cell proliferation in the colon of rats. Cancer Lett 124:39–46.

Li H, Kramer PM, Lubet RA, Steele VE, Kelloff GJ, Pereira MA. 1999a. Termination of piroxicam treatment and the occurrence of azoxymethane-induced colon cancer in rats. Cancer Lett 147:187–193.

Li H, Schut HAJ, Conran P, Kramer PM, Lubet RA, Steele VE, Hawk ET, Kelloff GJ, Pereira MA. 1999b. Prevention by aspirin and its combination with α-difluoromethylornithine of azoxymethane-induced tumors, aberrant crypt foci and prostaglandin E(2) levels in rat colon. Carcinogenesis 20:425–430.

Li ZG, Hong T, Shimada Y, Komoto I, Kawabe A, Ding Y, Kaganoi J, Hashimoto Y, Imamura M. 2002. Suppression of *N*-nitrosomethylbenzylamine (NMBA)-induced esophageal tumorigenesis in F344 rats by resveratrol. Carcinogenesis 23:1531–1536.

Liebes L, Conaway CC, Hochster H, Mendoza S, Hecht SS, Crowell J, Chung F-L. 2001. High-performance liquid chromatography-based determination of total isothiocyanate levels in human plasma: Application to studies with 2-phenethyl isothiocyanate. Anal Biochem 291:279–289.

Liston BW, Nines R, Carlton PS, Gupta A, Aziz R, Grankel W, Stoner GD. 2003. Perillyl alcohol as a chemopreventive agent in *n*-nitrosomethyl-benzylamine-induced rat esophageal tumorigenesis. Cancer Res 63:2399–2403.

Liu T, Mokuolu AO, Rao CV, Reddy BS, Holt PR. 1995. Regional chemoprevention of carcinogen-induced tumors in rat colon. Gastroenterology 109:1167–1172.

Lubet RA, Steele VE, Casebolt TL, Eto I, Kelloff GJ, Grubbs CJ. 1994. Chemopreventive effects of the aromatase inhibitors vorozole (R-83842) and 4-hydroxyandrostenedione in the methylnitrosourea (MNU)-induced mammary tumor model in Sprague–Dawley rats. Carcinogenesis 15:2775–2780.

Lubet RA, Steele VE, Eto I, Juliana MM, Kelloff GJ, Grubbs CJ. 1997. Chemopreventive efficacy of anethole trithione, *N*-acetyl-L-cysteine, miconazole, and phenethyl isothiocyanate in the DMBA-induced rat mammary cancer model. Intl J Cancer 72:95–101.

Lubet RA, Gordon GB, Prough RA, Lei X-D, You M, Wang Y, Grubbs CJ, Steele VE, Kelloff GJ, Thomas CF, Moon RD. 1998a. Modulation of methylnitrosourea-induced breast cancer in Sprague–Dawley rats by dehydroepiandrosterone: Dose-dependent inhibition, effects of limited exposure, effects on peroxisomal enzymes, and lack of effects on levels of Ha-Ras mutations. Cancer Res 58: 921–926.

Lubet RA, Steele VE, DeCoster R, Bowden C, You M, Juliana MM, Eto I, Kelloff GJ, Grubbs CJ. 1998b. Chemopreventive effects of the aromatase inhibitor vorozole (R 83842) in the methylnitrosourea-induced mammary cancer model. Carcinogenesis 19:1345–1351.

Lubet RA, Fischer SM, Conti C, Kelloff GJ, Zhang Z, You M. 2000. Chemopreventive efficacy of NSAIDS in tumor models with mutations in the p53 tumor suppressor gene. Proc Am Assoc Cancer Res 41: abstract no. 3153.

Matzinger SA, Crist KA, Stoner GD, Anderson MW, Pereira MA, Steele VE, Kelloff GJ, Lubet RA, You M. 1995. K-ras mutations in lung tumors from A/J and A/J X TSG-p53 F1 mice treated with 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and phenethyl isothiocyanate. Carcinogenesis 16:2487–2492.

McCormick DL. 1993a. Chemoprevention of lung carcinogenesis in hamsters with selected chemopreventive agents. IIT Research Institute, Chicago, Contract no. NO1-CN-95151-06. Final Report.

McCormick DL. 1993b. Chemoprevention of OH-BBN-induced bladder cancer in mice with selected chemopreventive agents. IIT Research Institute, Chicago, Contract no. NO1-CN-95151-07. Final Report.

McCormick DL. 1993c. Chemoprevention of pancreatic carcinogenesis in hamsters with selected chemopreventive agents. IIT Research Institute, Chicago, Contract no. NO1-CN-95151-08. Final Report.

McCormick DL. 1994a. Chemoprevention in a complete carcinogenesis model involving B(a)P induced skin carcinomas in C57BL/6 mice. IIT Research Institute, Chicago, Contract no. NO1-CN-85097-07. Final Report.

McCormick DL. 1994b. Chemoprevention of MNU-induced mammary tumors in the rat with selected chemopreventive agents. IIT Research Institute, Chicago, Contract no. NO1-CN-25449-01. Final Report.

McCormick DL. 1995. Chemoprevention of spontaneous mammary cancer in the oncomouse (c-*neu* oncogene and c-*myc* oncogene) by selected agents and combinations. IIT Research Institute, Chicago, Contract no. NO1-CN-85097-12. Final Report.

McCormick DL, Rao KVN. 1999. Chemoprevention of hormone-dependent prostate cancer in the Wistar–Unilever rat. Eur Urol 35:464–467.

McCormick DL, Johnson WD, Rao KVN, Bowman-Gram T, Steele VE, Lubet RA, Kelloff GJ. 1996a. Comparative activity of *N*-(4-hydroxyphenyl)-all-*trans*-retinamide and α-difluoromethylornithine as inhibitors of lymphoma induction in PIM transgenic mice. Carcinogenesis 17: 2513–2517.

McCormick DL, Rao KVN, Johnson WD, Bowman-Gram TA, Steele VE, Lubet RA, Kelloff GJ. 1996b. Exceptional chemopreventive activity of low-dose dehydroepiandrosterone in the rat mammary gland. Cancer Res 56:1724–1726.

McCormick D, Rao K, Lubet R, Steele V, Kelloff G, Bosland M. 1997. Differential activity of 9-*cis*-retinoic acid, α-tocopherol, and selenomethionine as chemopreventive agents in the rat prostate. Proc Am Assoc Cancer Res 38:261, abstract no. 1754.

McCormick DL, Rao KVN, Dooley L, Steele VE, Lubet RA, Kelloff GJ, Bosland MC. 1998. Influence of *N*-methyl-*N*-nitrosourea, testosterone, and *N*-(4-hydroxyphenyl)-all-*trans*-retinamide on prostate cancer induction in Wistar–Unilever rats. Cancer Res 58:3282–3288.

McCormick DL, Rao KVN, Steele VE, Lubet RA, Kelloff GJ, Bosland MC. 1999. Chemoprevention of rat prostate carcinogenesis by 9-*cis*-retinoic acid. Cancer Res 59:521–524.

Meyskens FL, Emerson SS, Pelot D, Meshkinpour H, Shassetz LR, Einspahr J, Alberts DS, Gerner EW. 1994. Dose de-escalation chemoprevention trial of α-difluoromethylornithine in patients with colon polyps. J Natl Cancer Inst 86:1122–1130.

Miltyk W, Craciunescu CN, Fischer L, Jeffcoat RA, Koch MA, Lopaczynski W, Mahoney C, Jeffcoat RA, Crowell J, Paglieri J, Zeisel SH. 2003. Lack of significant genotoxicity of purified soy isoflavones (genistein, daidzein, and glycitein) in 20 patients with prostate cancer. Am J Clin Nutr 77:875–882.

Mitsunaga S-I, Clapper M, Litwin S, Watts P, Bauer B, Klein-Szanto AJP. 1997. Chemopreventive effect of difluoromethylornithine (DFMO) on mouse skin squamous cell carcinomas induced by benzo(a)pyrene. J Cell Biochem Suppl 28(29):81–89.

Momen MA, Monden Y, Houchi H, Umemoto A. 2002. Effect of ursodeoxycholic acid on azoxymethane-induced aberrant crypt foci formation in rat colon: In vitro potential role of intracellular Ca^{2+}. J Med Invest 49:67–73.

Moon RC. 1986. Chemoprevention of bladder carcinoma by beta-carotene. IIT Research Institute, Chicago, Contract no. NO1-CN-45192-03. Final Report.

Moon RC. 1987a. Chemoprevention of DMBA-induced mammary tumors. IIT Research Institute, Chicago, Contract no. NO1-CN-55448-01. Final Report.

Moon RC. 1987b. Chemoprevention of OH-BBN-induced bladder tumors. IIT Research Institute, Chicago, Contract no. NO1-CN-55448-03. Final Report.

Moon RC. 1989a. Chemoprevention of OH-BBN-induced bladder cancer in mice with selected chemopreventive agents. IIT Research Institute, Chicago, Contract no. NO1-CN-55448-09. Final Report.

Moon RC. 1989b. Chemoprevention of MNU induced lung tumors in hamsters with selected chemopreventive agents. IIT Research Institute, Chicago, Contract no. NO1-CN-55448-07. Final Report.

Moon RC. 1989c. Chemoprevention of MNU-induced mammary tumors in the rat with five selected retinoids. IIT Research Institute, Chicago, Contract no. NO1-CN-45192-14. Final Report.

Moon RC. 1990a. Chemoprevention of MNU induced mammary tumors in the rat with selected chemopreventive agents. IIT Research Institute, Chicago, Contract no. NO1-CN-55448-08. Final Report.

Moon RC. 1990b. Chemoprevention of MNU-induced lung tumors. IIT Research Institute, Chicago, Contract no. NO1-CN-55448-10. Final Report.

Moon RC. 1990c. Chemoprevention of MNU-induced mammary tumors. IIT Research Institute, Chicago, Contract no. NO1-CN-55448-11. Final Report.

Moon RC. 1991. Chemoprevention of MNU-induced mammary tumors in the rat with selected chemopreventive agents. IIT Research Institute, Chicago, Contract no. NO1-CN-95151-02. Final Report.

Moon RC. 1992a. Chemoprevention of lung carcinogenesis in hamsters with selected chemopreventive agents. IIT Research Institute, Chicago, Contract no. NO1-CN-95151-03. Final Report.

Moon RC. 1992b. Chemoprevention of MNU-induced mammary tumors in rats with selected chemopreventive agents. IIT Research Institute, Chicago, Contract no. NO1-CN-95151-04. Final Report.

Moon RC. 1992c. Chemoprevention of OH-BBN-induced bladder cancer in mice with selected chemopreventive agents. IIT Research Institute, Chicago, Contract no. NO1-CN-95151-05. Final Report.

Moon RC. 1995. Chemoprevention of B(a)P-induced lung tumors in strain A mice. University of Illinois, Chicago, Contract no. NO1-CN-35535-01. Final Report.

Moon RC. 1996a. Effect of various chemopreventive agents on MNU-induced rat mammary tumors. University of Illinois, Chicago, Contract no. NO1-CN-35535-04. Final Report.

Moon RC. 1996b. Measurement of prostatic intraepithelial neoplasia (PIN) as an intermediate endpoint for the development of chemopreventive drugs. University of Illinois, Chicago, Contract no. NO1-CN-25492-04. Final Report.

Moon RC. 1996c. Rapid quantitative transgenic mouse skin carcinogenesis assay for chemopreventive agent development. University of Illinois, Chicago, Contract no. NO1-CN-35535-05. Final Report.

Moon RC. 1996d. SENCAR mouse skin model of surrogate endpoint biomarkers (SEB) of neoplasia measured by computer assisted image analysis (CIA): Development of improved algorithms for measurement of DNA ploidy, proliferation rate, nuclear morphometry, and nucleolar morphometry. University of Illinois, Chicago, Contract no. NO1-CN-25492-05. Final Report.

Moon RC. 1997a. Chemoprevention of carcinogen-induced lung tumors by carotenoids, DHEA, and sulindac in strain a mice. University of Illinois, Chicago, Contract no. NO1-CN-55164. Final Report.

Moon RC. 1997b. Chemopreventive studies employing a transgenic mouse yields prostate/breast tumors in male/female mice. University of Illinois, Chicago, Contract no. NO1-CN-55152. Final Report.

Moon RC, Detrisac CJ, Thomas CF, Kelloff GJ. 1992a. Chemoprevention of experimental bladder cancer. J Cell Biochem Suppl 16I:134–138.

Moon RC, Kelloff GJ, Detrisac CJ, Steele VE, Thomas CF, Sigman CC. 1992b. Chemoprevention of MNU-induced mammary tumors in the mature rat by 4-HPR and tamoxifen. Anticancer Res 12:1147–1154.

Moon RC, Rao KVN, Detrisac CJ, Kelloff GJ. 1992c. Hamster lung cancer model of carcinogenesis and chemoprevention. Adv Exp Med Biol 320:55–61.

Moon RC, Rao KVN, Detrisac CJ, Kelloff GJ. 1992d. Animal models for chemoprevention of respiratory cancer. Monogr Natl Cancer Inst 13:45–49.

Moon RC, Kelloff GJ, Detrisac CJ, Steele VE, Thomas CF, Sigman CC. 1993. Chemoprevention of OH-BBN-induced bladder cancer in mice by piroxicam. Carcinogenesis 14:1487–1489.

Moon RC, Kelloff GJ, Detrisac CJ, Steele VE, Thomas CF, Sigman CC. 1994a. Chemoprevention of OH-BBN-induced bladder cancer in mice by oltipraz, alone and in combination with 4-HPR and DFMO. Anticancer Res 14:5–11.

Moon RC, Rao KVN, Detrisac CJ, Kelloff GJ, Steele VE, Doody LA. 1994b. Chemoprevention of respiratory tract neoplasia in the hamster by oltipraz, alone and in combination. Intl J Oncol 4:661–667.

Morse MA, Kresty LA, Steele VE, Kelloff GJ, Boone CW, Balentine DA, Harbowy ME, Stoner GD. 1997. Effects of theaflavins on *N*-nitrosomethylbenzylamine-induced esophageal tumorigenesis. Nutr Cancer 29:7–12.

Mukherjee B, Basu M, Chatterjee M. 2001. Effect of selenomethionine on *N*-methylnitronitrosoguanidine-induced colonic aberrant crypt foci in rats. Eur J Cancer Prev 10:347–355.

Mundi JR, Young CW, Warrell RP, Jr. 1994. Clinical pharmacology of all-*trans*-retinoic acid. Leukemia 8:s16–s21.

Nagano T, Takeyama M. 2001. Enhancement of salivary secretion and neuropeptide (substance P, α-calcitonin gene-related peptide) levels in saliva by chronic anethole trithione treatment. J Pharmacy Pharmacol 53:1697–1702.

Narisawa T, Fukaura Y, Terada K, Sekiguchi H. 1999. Inhibitory effects of ursodeoxycholic acid on *N*-methylnitrosourea-induced colon carcinogenesis and colonic mucosal telomerase activity in F344 rats. J Exp Clin Cancer Res 18:259–266.

Nobilis M, Pour M, Kunes J, Kopecky J, Kventina J, Svoboda Z, Sladkova K, Vortel J. 2001. High-performance liquid chromatographic determination of ursodeoxycholic acid after solid phase extraction of blood serum and detection-oriented derivatization. J Pharm Biomed Anal 24:937–946.

O'Dwyer PJ, Szarka C, Brennan JM, Laub PB, Gallo JM. 2000. Pharmacokinetics of the chemopreventive agent oltipraz and of its metabolite M3 in human subjects after a single oral dose. Clin Cancer Res 6:4692–4696.

Okamura H, Matsumto K, Hashimoto K, Yoshikawa K. 1991. A new method for quantifying keratinocyte differentiation using immunofluorescent staining of involucrin and cytofluorography. Exp Cell Res 192:647–650.

Pendyala L, Creaven PJ. 1995. Pharmacokinetic and pharmacodynamic studies of *N*-acetylcysteine: A potential chemopreventive agent during a phase I trial. Cancer Epidemiol Biomarkers Prev 4:245–251.

Pereira MA. 1993. Chemoprevention of AOM-induced foci of aberrant crypts in colons of rats treated with chemopreventive agents. Environmental Health Research and Testing, Inc., Contract no. NO1-CN-85096-01. Final Report.

Pereira MA. 1994. Chemoprevention of azoxymethane (AOM)-induced colon cancer in rats with selected polyamine synthesis inhibitors and substituted isothiocyanate. Environmental Health Research and Testing, Inc., Contract no. NO1-CN-25457-01. Final Report.

Pereira MA. 1995a. Intermediate biomarker modulation during AOM-induced colon cancer in rats treated with selected nonsteroidal anti-inflammatory drugs. Environ-

mental Health Research and Testing, Inc., Contract no. NO1-CN-25495-01. Final Report.
Pereira MA. 1995b. Use of mutation frequency modification as an intermediate biomarker in determining chemopreventive efficacy in the carcinogenesis process of mammary, lung, and colon epithelia, B:MNU-induced mammary tumor models in the rat. Environmental Health Research and Testing, Inc., Contract no. NO1-CN-25495-02B. Final Report.
Pereira MA. 1997a. Chemoprevention of AOM-induced foci of aberrant crypts in colons of rats treated with chemopreventive agents. Ohio State University, Medical College of Ohio, Contract no. NO1-CN-55175. Final Report.
Pereira MA. 1997b. Effects of aspirin and chemopreventive agent combinations on AOM-induced colon cancer in Fischer rats. Ohio State University, Medical College of Ohio, Contract no. NO1-CN-55174. Final Report.
Pereira MA. 1999. Effects of potential chemopreventive agents alone or in combination on azoxymethane (AOM)-induced colon cancer in fisher rats. Ohio State University, Medical College of Ohio, Contract no. NO1-CN-75102. Final Report.
Pereira MA, Barnes LH, Steele VE, Kelloff GJ, Lubet RA. 1996a. Piroxicam-induced regression of azoxymethane-induced aberrant crypt foci and prevention of colon cancer in rats. Carcinogenesis 17:373–376.
Pereira MA, Grubbs CJ, Barnes LH, Li H, Olson GR, Eto I, Juliana M, Whitaker LM, Kelloff GJ, Steele VE, Lubet RA. 1996b. Effects of the phytochemicals, curcumin, and quercetin, upon azoxymethane-induced colon cancer and 7,12-dimethylbenz[a]anthracene-induced mammary cancer in rats. Carcinogenesis 17:1305–1311.
Pereira MA, Li Y, Gunning WT, Kramer PM, Al-Yaqoub F, Lubet RA, Steele VE, Szabo E, Tao L. 2002. Prevention of mouse lung tumors by budesonide and its modulation of biomarkers. Carcinogenesis 23:1185–1192.
Pereira MA, Barnes LH, Rassman VL, Kelloff GV Steele VE. 1994. Use of azoxymethane-induced foci of aberrant crypts in rat colon to identify potential cancer chemopreventive agents. Carcinogenesis 15:1049–1054.
Prokopczyk B, Amin S, Desai DH, Kurtzke C, Upadhyaya P, El-Bayoumy K. 1997. Effects of 1,4-phenylenebis-(methylene)selenocyanate and selenomethionine on 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced tumorigenesis in A/J mouse lung. Carcinogenesis 18: 1855–1857.
Rao CV. 1999. Chemoprevention of azoxymethane (AOM)-induced foci of aberrant crypts in colons of rats treated with chemopreventive agents. American Health Foundation, Inc., Contract no. NO1-CN-65108. Final Report.
Rao CV, Tokumo K, Rigotty J, Zang E, Kelloff G, Reddy BS. 1991. Chemoprevention of colon carcinogenesis by dietary administration of piroxicam, α-difluoromethylornithine, 16a-fluoro-5-androsten-17-one, and ellagic acid individually and in combination. Cancer Res 51:4528–4534.
Rao CV, Rivenson A, Kelloff GJ, Reddy BS. 1995. Chemoprevention of azoxymethane-induced colon cancer by ascorbylpalmitate, carbenoxolone, dimethylfumarate, and *p*-methoxyphenol in male F344 rats. Anticancer Res 15:1199–1204.
Rao CV, Rivenson A, Zang E, Steele V, Kelloff G, Reddy BS. 1996. Inhibition of 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine-induced lymphoma formation by oltipraz. Cancer Res 56:3395–3398.
Rao CV, Wang C-X, Simi B, Lubet R, Kelloff G, Steele V, Reddy BS. 1997a. Enhancement of experimental colon cancer by genistein. Cancer Res 57:3717–3722.
Rao K, Bosland M, Lubet R, Steele V, Kelloff G, McCormick D. 1997b. Inhibition of rat prostate carcinogenesis by delayed administration of dehydroepiandrosterone. Proc Am Assoc Cancer Res 38:580, abstract no. 3893.
Rao KVN, Johnson WD, Bosland MC, Lubet RA, Steele VE, Kelloff GJ, McCormick DL. 1999. Chemoprevention of rat prostate carcinogenesis by early and delayed administration of dehydroepiandrosterone. Cancer Res 59:3084–3089.
Rao CV, Cooma I, Rodriguez JGR, Simi B, El-Bayoumy K, Reddy BS. 2000a. Chemoprevention of familial adenomatous polyposis development in the APC (min) mouse model 1,4-phenylene bis(methylene)selenocyanate. Carcinogenesis 21:617–621.
Rao CV, Kawamori T, Cooma I, Kelloff GJ, Steele VE, Reddy BS. 2000b. Prevention of familial adenomatous polyp development in APC(MIN) mice and azoxymethane (AOM)-induced colon carcinogenesis in F344 rats by perilla oil rich in w-3 fatty acids. Proc Am Assoc Cancer Res 41: abstract no. 530.
Ratko TA, Detrisac CJ, Rao KVN, Thomas CF, Kelloff GJ, Moon RC. 1990. Interspecies analysis of the chemopreventive efficacy of dietary α-difluoromethylornithine. Anticancer Res 10:67–72.
Ratko TA, Detrisac CJ, Mehta RG, Kelloff GJ, Moon RC. 1991. Inhibition of rat mammary gland chemical carcinogenesis by dietary dehydroepiandrosterone or a fluorinated analogue of dehydroepiandrosterone. Cancer Res 51:481–486.
Reddy BS. 1990. Chemoprevention of azoxymethane (AOM)-induced colon cancer in rats with selected prostaglandin synthesis inhibitors. American Health Foundation, Inc., Contract no. NO1-CN-85095-02. Final Report.
Reddy BS. 1992. Chemoprevention of azoxymethane (AOM) induced colon cancer in rats with selected chemopreventive agents. American Health Foundation, Inc., Contract no. NO1-CN-95153-01. Final Report.
Reddy BS. 1994. Chemoprevention of AOM-induced colon cancer in rats with selected polyamine synthesis inhibitors and isothiocyanate. American Health Foundation, Inc., Contract no. NO1-CN-85095-05. Final Report.
Reddy BS. 1995. Effects of potential chemopreventive agents on AOM-induced colon cancer in Fisher rats. American Health Foundation, Inc., Contract no. NO1-CN-25450-01. Final Report.
Reddy BS. 1997. Effects of potential chemopreventive agents on AOM-induced colon cancer in Fisher rats. American Health Foundation, Inc., Contract no. NO1-CN-55150. Final Report.
Reddy BS. 1998. Impact of dietary intervention in the modulation of early surrogate biomarkers of colonic neoplasia in animals at increased genetic risk. American Health Foundation, Inc., Contract no. NO1-CN-65031. Final Report.
Reddy BS. 1999. Effect of potential chemopreventive agents on azoxymethane (AOM)-induced colon cancer in Fisher rats. American Health Foundation, Inc., Contract no. NO1-CN-65119. Final Report.

Reddy BS, Rao CV, Rivenson A, Kelloff G. 1993a. Chemoprevention of colon carcinogenesis by organosulfur compounds. Cancer Res 53:3493–3498.

Reddy BS, Rao CV, Rivenson A, Kelloff G. 1993b. Inhibitory effect of aspirin on azoxymethane-induced colon carcinogenesis in F344 rats. Carcinogenesis 14:1493–1497.

Reddy BS, Wang C-X, Aliaga C, Rao CV, Lubet RA, Steele VE, Kelloff GJ. 1996. Potential chemopreventive activity of perillyl alcohol and enhancement of experimental colon carcinogenesis by folic acid and genistein. Proc Am Assoc Cancer Res 37:271, abstract no. 1849.

Reddy BS, Wang C-X, Samaha H, Lubet R, Steele VE, Kelloff GJ, Rao CV. 1997. Chemoprevention of colon carcinogenesis by dietary perillyl alcohol. Cancer Res 57: 420–425.

Reddy BS, Kawamori T, Lubet R, Steele V, Kelloff G, Rao CV. 1999b. Chemopreventive effects of *S*-methylmethane thiosulfonate and sulindac administered together during the promotion/progression stages of colon carcinogenesis. Carcinogenesis 20:1645–1648.

Reddy BS, Kawamori T, Lubet RA, Steele VE, Kelloff GJ, Rao CV. 1999b. Chemopreventive efficacy of sulindac sulfone against colon cancer depends on time of administration during carcinogenic process. Cancer Res 59:3387–3391.

Reddy BS, Hirose Y, Lubet RA, Steele VE, Kelloff GJ, Rao CV. 2000. Lack of chemopreventive efficacy of DL-selenomethionine in colon carcinogenesis. Int J Mol Med 5: 327–330.

Redpath JL, Elmore E. 2002. In vitro screening of chemopreventive agent using primary human epidermal cells. University of California, Irvine, Contract no. N01-CN-05104.

Regazzi BM, Rondanelli R, Ciaroelli L, Bartoli AL, Rampini A. 1986. Evaluation of the absorption from three ibuprofen formulations. Intl J Clin Pharmacol Res 6: 469–473.

Ripple GH, Gould MN, Stewart JA, Tutsch KD, Arzoomanian RZ, Alberti D, Feierabend C, Pomplun M, Wilding G, Bailey HH. 1998. Phase I clinical trial of perillyl alcohol administered daily. Clin Cancer Res 4:1159–1164.

Ripple GH, Gould MN, Arzoomanian RZ, Alberti D, Feierabend C, Simon K, Binger K, Tutsch KD, Pomplun M, Wahamaki A, Marnocha R, Wilding G, Bailey HH. 2000. Phase I clinical and pharmacokinetic study of perillyl alcohol administered four times a day. Clin Cancer Res 6:390–396.

Rodriguez-Burford C, Lubet RA, Eto I, Juliana MM, Kelloff GJ, Grubbs CJ, Steele VE. 1999. Effect of reduced body weight gain on the evaluation of chemopreventive agents in the methylnitrosourea-induced mammary cancer model. Carcinogenesis 20:71–76.

Ruffin MT, IV, Krishnan K, Rock CL, Normolle D, Vaerten MA, Peters-Golden M, Crowell J, Kelloff G, Boland CR, Brenner DE. 1997. Suppression of human colorectal mucosal prostaglandins: Determining the lowest effective aspirin dose. J Natl Cancer Inst 89:1152–1160.

Russell WC, Newman C, Williamson DH. 1975. A simple cytochemical technique for demonstration of DNA in cells infected with mycoplasmas and viruses. Nature 253: 461–462.

Samaha HS, Kelloff GJ, Steele V, Rao CV, Reddy BS. 1997. Modulation of apoptosis by sulindac, curcumin, phenylethyl-3-methylcaffeate, and 6-phenylhexyl isothiocyanate: Apoptotic index as a biomarker in colon cancer chemoprevention and promotion. Cancer Res 57:1301–1305.

Sharma S. 1994. Evaluation of dysplasia as an intermediate endpoint marker for carcinogen-induced urinary bladder carcinogenesis in female rats. ManTech Environmental Technology, Inc., Contract no. NO1-CN-25499-01. Final Report.

Sharma S. 1997. Efficacy studies of chemopreventive agents delivered by aerosol on pulmonary tumors formation in A/J mice. ManTech Environmental Technology, Inc., Contract no. NO1-CN-55176. Final Report.

Shilkaitis A, Graves J, Mehta RR, Hu L, You M, Lubet R, Steele V, Kelloff G, Christov K. 2000a. Bcl-2 and Bax are differentially expressed in hyperplastic, premalignant, and malignant lesions of mammary carcinogenesis. Cell Growth Differ 11:437–445.

Shilkaitis A, Green A, Steele V, Lubet R, Kelloff G, Christov K. 2000b. Neoplastic transformation of mammary epithelial cells in rats is associated with decreased apoptotic cell death. Carcinogenesis 21:227–233.

Shukla Y, Taneja P. 2002. Anticarcinogenic effect of black tea on pulmonary tumors in Swiss albino mice. Cancer Lett 176:137–141.

Spencer CM, McTavish D. 1995. Budesonide: A review of its pharmacological properties and therapeutic efficacy in inflammatory bowel disease. Drugs 50:854–872.

Steele VE, editor. 1997. In vitro assays for identifying potential chemopreventive agents. Special Issue. Meth Cell Sci 19:1–70.

Steele VE, Sharma S, Mehta R, Elmore E, Redpath JL, Rudd C, Bagheri D, Sigmon CC, Kelloff GJ. 1996. Use of in vitro assays to predict the efficacy of chemopreventive agents in whole animals. J Cell Biochem 26S:29–53.

Steele VE, Wyatt GP, Kelloff GJ, Elmore E. 1998. Differential growth response to exogenous calcium in normal and carcinogen-exposed primary human keratinocyte cell cultures. Anticancer Res 18:4067–4070.

Steele VE, Bagheri D, Balentine DA, Boone CW, Mehta R, Morse MA, Sharma S, Sigman CC, Stoner GD, Wargovich MJ, Weisburger JH, Zhu S, Kelloff GJ. 1999. Preclinical efficacy studies of green and black tea extracts (44367). Proc Soc Exp Biol Med 220:210–212.

Steele VE, Kelloff GJ, Balentine D, Boone CW, Mehta R, Bagheri D, Sigman CC, Zhu S, Sharma S. 2000. Comparative chemopreventive mechanisms of green tea, black tea and selected polyphenol extracts measured by in vitro bioassays. Carcinogenesis 21:63–67.

Stoner GD. 1997. Inhibition of nitrosomethlybenzylamine (NMBA)-induced carcinogenesis of rat esophagus monitored by computer-assisted image analysis (CIA): Screening and ranking of chemopreventive agents. Ohio State University, Division of Environmental Health, Contract no. NO1-CN-75105. Final Report.

Sutherland RM. 1990. Chemoprevention of DMBA-Induced Epidermal Tumorigenesis. SRI International, Contract no. NO1-CN-55455-02. Final Report.

Tanaka T, Makita H, Kawabata K, Mori H, El-Bayoumy K. 1997. 1,4-Phenylenebis(methylene)selenocyanate exerts exceptional chemopreventive activity in rat tongue carcinogenesis. Cancer Res 57:3644–3648.

Teichert J, Hermann R, Ruus P, Preiss R. 2003. Plasma kinetics, metabolism, and urinary excretion of alpha-

lipoic acid following oral administration in healthy volunteers. J Clin Pharmacol 43:1257–1267.
Tempero MA. 1990. Chemoprevention of MAM acetate-induced colon cancer. Eppley Institute, Contract no. NO1-CN-55451-07. Final Report.
Tempero MA. 1991. Chemoprevention of AOM-induced colon cancer in rats with selected chemopreventive agents. Eppley Institute, Contract no. NO1-CN-95150-01. Final Report, 9/91.
Traber MG, Winklhofer-Roob BM, Roob JM, Gholamali Khoschsorur G, Aigner R, Cross C, Rajasekhar Ramakrishnan R, Brigelius-Flohé R. 2001. Vitamin E kinetics in smokers and nonsmokers. Free Radic Biol Med 31:1368–1374.
van Stolk R, Stoner G, Hayton WL, Chan K, DeYoung B, Kresty L, Kemmenoe BH, Elson P, Rybicki L, Church J, Provencher K, McLain D, Hawk E, Fryer B, Kelloff G, Ganapathi R, Budd GT. 2000. Phase I trial of exisulind (sulindac sulfone, FGN-1) as a chemopreventive agent in patients with familial adenomatous polyposis. Clin Cancer Res 6:78–89.
Wargovich MJ. 1992. Chemoprevention of AOM-induced foci of aberrant crypts in colons of rats treated with chemopreventive agents. M.D. Anderson Cancer Center, Contract no. NO1-CN-85101-01. Final Report.
Wargovich MJ. 1994. Chemoprevention of azoxymethane-induced foci of aberrant crypts in colons of rats treated with chemopreventive agents. M.D. Anderson Cancer Center, Contract no. NO1-CN-85151-03. Final Report.
Wargovich MJ. 1996. Chemoprevention efficacy of various agents against AOM-induced foci of aberrant crypts in rats. M.D. Anderson Cancer Center, Contract no. NO1-CN-35570-01. Final Report.
Wargovich MJ. 1997. Chemoprevention of AOM-induced foci of aberrant crypts in colons of rats treated with chemopreventive agents. M.D. Anderson Cancer Center, Contract no. NO1-CN-55173. Final Report.
Wargovich MJ, Harris C, Chen C-D, Palmer C, Steele VE, Kelloff GJ. 1992. Growth kinetics and chemoprevention of aberrant crypts in the rat colon. J Cell Biochem Suppl 16:51–54.
Wargovich MJ, Chen CD, Harris C, Yang E, Velasco M. 1995. Inhibition of aberrant crypt growth by non-steroidal anti-inflammatory agents and differentiation agents in the rat colon. Intl J Cancer 60:515–519.
Wargovich MJ, Chen C-D, Jimenez A, Steele VE, Velasco M, Stephens LC, Price R, Gray K, Kelloff GJ. 1996. Aberrant crypts as a biomarker for colon cancer: Evaluation of potential chemopreventive agents in the rat. Cancer Epidemiol Biomarkers Prev 5:355–360.
Wargovich MJ, McKee K, De la Cerda J, Woods J, Steele VE. 1997. Inhibition of the promotion and progression of aberrant crypt foci in the rat colon by chemopreventive agents. Proc Am Assoc Cancer Res 38:210, abstract no. 1412.
Wargovich MJ, Jimenez A, McKee K, Steele VE, Velasco M, Woods J, Price R, Gray K, Kelloff GJ. 2000. Efficacy of potential chemopreventive agents on rat colon aberrant crypt formation and progression. Carcinogenesis 21: 1149–1155.
Wattenberg L. 2000. Efficacy studies of chemopreventive agents in animal models: Efficacy studies of chemopreventive agents delivered by aerosol on pulmonary tumorigenesis in hamsters. University of Minnesota, Contract no. NO1-CN-65109. Final Report.
Wattenberg LW, Wiedmann TS, Estensen RD, Zimmerman CL, Steele VE, Kelloff GJ. 1997. Chemoprevention of pulmonary carcinogenesis by aerosolized budesonide in female A/J mice. Cancer Res 57:5489–5492.
Wattenberg LW, Wiedmann TS, Estensen RD, Zimmerman CL, Galbraith AR, Steele VE, Kelloff GJ. 2000. Chemoprevention of pulmonary carcinogenesis by brief exposures to aerosolized budesonide or beclomethasone dipropionate and by the combination of aerosolized budesonide and dietary myo-inositol. Carcinogenesis 21:179–182.
Weber C, Dumont E. 1997. Pharmacokinetics and pharmacodynamics of 9-*cis*-retinoic acid in healthy men. J Clin Pharmacol 37:566–574.
Weisburger JH. 1996. Effects of EGCG and other tea extracts on colon and bladder cancer in rodents. American Health Foundation, Inc., Contract no. NO1-CN-35569-01. Final Report.
Weisburger JH, Rivenson A, Aliaga C, Reinhardt J, Kelloff GJ, Boone CW, Steele VE, Balentine DA, Pittman B, Zang E. 1998. Effect of tea extracts, polyphenols, and epigallocatechin gallate on azoxymethane-induced colon cancer. Proc Soc Exp Biol Med 217:104–108.
Weiss HL, Rodriguez-Burford C, Grubbs CJ, Grizzle WE. 2000. Longitudinal analysis of mammary cancer multiplicity in chemoprevention studies. Anticancer Res 20:2281–2288.
Wilke MS, Hsu BM, Wille JJ, Jr., Pittelkow MR, Scott RE. 1998. Biological mechanisms for the regulation of normal human keratinocyte proliferation and differentiation. Am J Pathol 131:171–181.
Wong SL, Awni WM, Cavanaugh JH, El-Shourbagy T, Locke CS, Dube LM. 1995. The pharmacokinetics of single oral doses of zileuton 200 to 800 mg, its enantiomers, and its metabolites, in normal healthy volunteers. Clin Pharmacokinet 29:9–21.
You M. 1998. Development and use of mouse models which contain mutations in p53 in chemoprevention assays. Ohio State University, Medical College of Ohio, Contract no. NO1-CN-65111. Final Report.
You M, Bergman G. 1998. Preclinical and clinical models of lung cancer chemoprevention. Hematol Oncol Clin North Am 12:1037–1053.
Young C, Osborne M. 1995. Phase I and pharmacokinetic studies of calcium glucarate. Sloan-Kettering Institute for Cancer Research, Contract no. N01-CN-15337-01. Final Report.
Zheng Y, Kramer PM, Olson G, Lubet RA, Steele VE, Kelloff GJ, Pereira MA. 1997. Prevention by retinoids of azoxymethane-induced tumors and aberrant crypt foci and their modulation of cell proliferation in the colon of rats. Carcinogenesis 18:2119–2125.
Zheng Y, Kramer PM, Lubet RA, Steele VE, Kelloff GJ, Pereira MA. 1999. Effect of retinoids on AOM-induced colon cancer in rats: Modulation of cell proliferation, apoptosis and aberrant crypt foci. Carcinogenesis 20:255–260.