Review

$\frac{1}{\text{Vol. 3, 85-98, January/February 1994}}$ Cancer Epidemiology, Biomarkers & Prevention 85
Chemopreventive Drug Development: Perspectives and Progress

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Abstract

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Abstract
Chemoprevention drug development has the goal of
identifying safe and effective chemopreventive agents for** ralo Allo, Calilorina _(C.C.S.)
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developing chemopreventive agents: (a) identif **Chemoprevention drug development has the goal of identifying safe and effective chemopreventive agents for clinical use. Several distinctive strategies are pursued in developing chemopreventive agents: (a) identifying and Chemoprevention arig development has the goal of**
identifying safe and effective chemopreventive agents for
clinical use. Several distinctive strategies are pursued in
developing chemopreventive agents: (a) identifying
an **the consideration consideration** developing chemopreventive agents: (a) identifying
and validating predysplastic and early dysplastic lesions
that can be used instead of cancers as endpoints for
measuring chemopreventive developing chemopreventive agents: (a) identitying
and validating predysplastic and early dysplastic lesions
that can be used instead of cancers as endpoints for
measuring chemopreventive activity; (b) identifying and
test and validating predysplastic and early dysplastic lesions
that can be used instead of cancers as endpoints for
measuring chemopreventive activity; (b) identifying and
testing candidate agents based on considerations of
mec mat can be used instead of cancers as endpoints for
measuring chemopreventive activity; (*b*) identifying and
testing candidate agents based on considerations of
mechanisms of action; (*c*) evaluating combinations of
agent measuring chemopreventive activity; (*b*) identifying and
testing candidate agents based on considerations of
mechanisms of action; (*c*) evaluating combinations of
agents with potential for maximizing efficacy and
minimiz **desung canologies agents based on considerations of**
mechanisms of action; (*c*) evaluating combinations of
agents with potential for maximizing efficacy and
minimizing toxicity; and (*d*) applying a systematic
methodolog mecnanisms or action; (*c*) evaluating combinations or
agents with potential for maximizing efficacy and
minimizing toxicity; and (*d*) applying a systematic
methodology for identifying and ranking candidate
agents at each minimizing toxicity; and (*a*) applying a systematic
methodology for identifying and ranking candidate
agents at each stage of development to ensure discovery
of the best agents and most effective use of available
resource methodology for identifying and ranking candidate
agents at each stage of development to ensure discovery
of the best agents and most effective use of available
resources.
This article discusses 22 drugs and three drug
com

agents at each stage of development to ensure discove
of the best agents and most effective use of available
resources.
This article discusses 22 drugs and three drug
combinations which have reached an advanced stage
devel or the best agents and most effective use or available
resources.
This article discusses 22 drugs and three drug
combinations which have reached an advanced stage of
development as chemopreventive agents. The first
generat resources.

This article discusses 22 drugs and three drug

combinations which have reached an advanced stage of

development as chemopreventive agents. The first

generation of drugs are the most advanced, now being

in P **interval combinations** which have reached an advanced stage of development as chemopreventive agents. The first generation of drugs are the most advanced, now being in Phase II and Phase III clinical trials. These drugs i **all-trans-N-(4-hydroxyphenyl)retinamidel, calcium,** development as chemopreventive agents. The first
generation of drugs are the most advanced, now being
in Phase II and Phase III clinical trials. These drugs
include several retinoids [vitamin A, 13-*cis*-retinoic acid,
al **generation of drugs are the most advanced, now being**

in Phase II and Phase III clinical trials. These drugs

include several retinoids [vitamin A, 13-cis-retinoic acid,

all-*trans-N*-(4-hydroxyphenyl)retinamide], calc In Phase II and Phase III Clinical trials. These di
include several retinoids [vitamin A, 13-*cis*-retital
all-*trans-N*-(4-hydroxyphenyl)retinamide], calcit
β-carotene, tamoxifen, and finasteride. The sec
generation drug Include several retinolds (vitamin A, 13-*cis*-retinoic acid,
all-*trans-N*-(4-hydroxyphenyl)retinamide], calcium,
β-carotene, tamoxifen, and finasteride. The second
generation drugs are those in Phase I clinical trials. all-*trans-N*-(4-nydroxypnenyiretinamide), calcium,
β-carotene, tamoxifen, and finasteride. The second
generation drugs are those in Phase I clinical trials. Fro
most to least advanced, these drugs are
2-difluoromethylorn β-carotene, tamoxiren, and tinasteriae. The second
generation drugs are those in Phase I clinical trials. I
most to least advanced, these drugs are
2-difluoromethylornithine, sulindac, piroxicam, oltip
N-acetyl-*I*-cystei most to least advanced, these drugs are

2-difluoromethylornithine, sulindac, piroxicam, oltipraz,
 N-acetyl-*I*-cysteine, aspirin, ibuprofen, carbenoxolone,

18*β*-glycyrrhetinic acid, and the combination of

2-difluoro most to least advanced, these drugs are
2-difluoromethylornithine, sulindac, piroxicam, oltipraz,
N-acetyl-*I*-cysteine, aspirin, ibuprofen, carbenoxolone,
18β-glycyrrhetinic acid, and the combination of
2-difluoromethy 2-amuoromethylornithine, sulindac, piroxicam, olupraz,
 N-acetyl-*I*-cysteine, aspirin, ibuprofen, carbenoxolone,

18β-glycyrrhetinic acid, and the combination of

2-difluoromethylornithine with piroxicam. The third

ge *N*-acetyl-*i*-cystelne, aspirin, ibuproten, carbehoxolone,
18β-glycyrrhetinic acid, and the combination of
2-difluoromethylornithine with piroxicam. The third
generation includes agents with significant evidence of
chemop **Top-gycyrmeunte actu, and the combination of**
2-difluoromethylornithine with piroxicam. The third
generation includes agents with significant evidence of
chemopreventive activity in animal models. These agent
are now in p 2-amuoromethylorminime with piroxicam. The third
generation includes agents with significant evidence of
chemopreventive activity in animal models. These age
are now in preclinical toxicity testing. They are
S-allyl-*I*-cy generation includes agents with significant evidence of
chemopreventive activity in animal models. These agen
are now in preclinical toxicity testing. They are
S-allyl-*I*-cysteine, phenhexyl isothiocyanate, curcumin,
ella chemopreventive activity in animal models. I
are now in preclinical toxicity testing. They a
S-allyl-*I*-cysteine, phenhexyl isothiocyanate, c
ellagic acid, fumaric acid, fluasterone, and th
combinations of all-*trans-N* are now in preclinical toxicit

S-allyl-*I*-cysteine, phenhexyl

ellagic acid, fumaric acid, flu

combinations of all-*trans-N*-

with oltipraz and all-*trans-N*-

retinamide with tamoxifen. with oltipraz and all-*trans-N*-(4-hydroxyphenyl)
retinamide with tamoxifen.
Introduction
As the understanding of the process of cancer increases, pre-
ventive intervention is becoming scientifically practical for

Introduction

Example 11 Set in the transmit ventile intervention
 Introduction

As the understanding of the process of cancer increases, preventive intervention is becoming scientifically practical for

measuring safe and effective chemopreventive agents for
 clinical use. Several distinctive strategies are pursued in
 developing chemopreventive agents:
 and validating predysplastic and early dysplastic lesions
 many cancers. While prevention of exposure and changes in
diet may someday alter incidence, chemical intervention many cancers. While prevention of exposure and changes in
diet may someday alter incidence, chemical intervention
offers an attractive approach with potential for more immemany cancers. While prevention of exposure and changes
diet may someday alter incidence, chemical intervential
offers an attractive approach with potential for more imme-
diate results. The NCI's² chemoprevention drug de many cancers. While prevention of exposure and change
diet may someday alter incidence, chemical intervent
offers an attractive approach with potential for more imr
diate results. The NCI's² chemoprevention drug develo
m many cancers. While prevention of exposure and changes in
diet may someday alter incidence, chemical intervention
offers an attractive approach with potential for more imme-
diate results. The NCI's² chemoprevention drug diet may someday alter incidence, chemical intervention
offers an attractive approach with potential for more imme-
diate results. The NCI's² chemoprevention drug develop-
ment program, which has been described previousl offers an attractive approach with potential for more imme-
diate results. The NCI's² chemoprevention drug develop-
ment program, which has been described previously (1–3),
has as a goal the identification of safe and ef diate results. The NCI's² chemoprevention drug development program, which has been described previously (1–3), has as a goal the identification of safe and effective chemical agents for the prevention of human cancers. T ment program, which has been described previously (1–3), has as a goal the identification of safe and effective chemical agents for the prevention of human cancers. This program is an applied drug development science effor has as a goal the identification of safe and effective chemical
agents for the prevention of human cancers. This program is
an applied drug development science effort with clinical
trials as the endpoint. It begins with th agents for the prevention of human cancers. This program is
an applied drug development science effort with clinical
trials as the endpoint. It begins with the identification of
candidate agents for development and the cha an applied drug development science effort with clinical trials as the endpoint. It begins with the identification of candidate agents for development and the characterization of these candidates for efficacy using *in vit* trials as the endpoint. It begins with the identification of candidate agents for development and the characterization of these candidates for efficacy using *in vitro* and animal screens. Promising agents are then further candidate agents for development and the characterization
of these candidates for efficacy using *in vitro* and anin
screens. Promising agents are then further tested in anin
models to evaluate the design of regimens for c of these candidates for efficacy using *in vitro* and animal screens. Promising agents are then further tested in animal models to evaluate the design of regimens for clinical testing and use. Agents judged to have potenti screens. Promising agents are then further tested in animal
models to evaluate the design of regimens for clinical testing
and use. Agents judged to have potential as human chemo-
preventives are subjected, as appropriate, models to evaluate the design of regimens for clinical testing
and use. Agents judged to have potential as human chemo-
preventives are subjected, as appropriate, to preclinical tox-
icity and pharmacokinetic studies. The and use. Agents judged to have potential as human chemo-
preventives are subjected, as appropriate, to preclinical tox-
icity and pharmacokinetic studies. The most successful
agents then progress to clinical trials. The pu preventives are subjected, as appropriate, to preclinical toxicity and pharmacokinetic studies. The most successful agents then progress to clinical trials. The purpose of this article is to discuss the strategies, perspec icity and pharmacokinetic studies. The most successful
agents then progress to clinical trials. The purpose of this
article is to discuss the strategies, perspectives, and progress
of chemoprevention drug development, ofte agents then progress to clinical trials. The purpose of this article is to discuss the strategies, perspectives, and progress of chemoprevention drug development, often using examples from the NCl program. As evidence of p article is to discuss the strategies, perspectives, and proof chemoprevention drug development, often using amples from the NCI program. As evidence of progres status and rationale for development of agents that currappear amples from the NCI program. As evidence of progress, the status and rationale for development of agents that currently appear to be most promising (Table 1) are reviewed.
Strategies for Chemopreventive Drug Development
 status and rationale for development of agents that currently
appear to be most promising (Table 1) are reviewed.
**Strategies for Chemopreventive Drug Development
Epithelial Lesions that Are Targets for Chemopreventive**

appear to be most promising (Table 1) are reviewed.
Strategies for Chemopreventive Drug Development
**Epithelial Lesions that Are Targets for Chemopreven
Agents.** The rational design and development of chemop
ventive agen **Strategies for Chemopreventive Drug Development**
Epithelial Lesions that Are Targets for Chemoprevential
Agents. The rational design and development of chemopreventive agents requires a clear understanding of the epit **Strategies for Chemopreventive Drug Development**
Epithelial Lesions that Are Targets for Chemopreventive
Agents. The rational design and development of chemopre-
ventive agents requires a clear understanding of the ep **Epithelial Lesions that Are Targets for Chemopreventive**
Agents. The rational design and development of chemopre-
ventive agents requires a clear understanding of the epithe-
lial lesions that are targets for the action **Agents.** The rational design and development of chemopre-
ventive agents requires a clear understanding of the epithe-
lial lesions that are targets for the action of these agents. Fig.
1 diagrams the early development of ventive agents requires a clear understanding of the epithe-
lial lesions that are targets for the action of these agents. Fig.
1 diagrams the early development of epithelial neoplasia. A
major target epithelial lesion is lial lesions that are targets for the action of these agents. Fig. 1 diagrams the early development of epithelial neoplasia. A major target epithelial lesion is that of histologically visible neoplasia very early in its de 1 diagrams the early development of epithelial neoplasia.

major target epithelial lesion is that of histologically visib

neoplasia very early in its development, long before it is

vades across the basement membrane. Thi major target epithelial lesion is that of histologically visible
neoplasia very early in its development, long before it in-
vades across the basement membrane. This "intraepithelial
neoplasia," as it is called at this sta neoplasia very early in its development, long before it in-
vades across the basement membrane. This "intraepithelial
neoplasia," as it is called at this stage, begins as a mono-
clonal focus near the basement membrane and vades across the basement membrane. This "intraepithelial neoplasia," as it is called at this stage, begins as a mono-
clonal focus near the basement membrane and expands up-
ward and laterally. When it finally becomes inv neoplasia," as it is called at this stage, begins as a morclonal focus near the basement membrane and expands u
ward and laterally. When it finally becomes invasive acre
the basement membrane, it is at this point termed "c clonal focus near the basement membrane and expands up-
ward and laterally. When it finally becomes invasive across
the basement membrane, it is at this point termed "cancer."
Prior to invasion, the morphological changes o ward and laterally. When it finally becomes invasive across
the basement membrane, it is at this point termed "cancer."
Prior to invasion, the morphological changes of intraepi-
the ial neoplasia are collectively termed "d the basement membrane, it is at this point termed "cancer."
Prior to invasion, the morphological changes of intraepi-
the ial neoplasia are collectively termed "dysplasia." It is the
consensus of pathologists that carcinom Prior to invasion, the morphological changes of intraepi-
the lial neoplasia are collectively termed "dysplasia." It is the
consensus of pathologists that carcinoma *in situ* and severe
dysplasia form an indistinguishable the lial neoplasia are collectively termed "dysplasia." It is the consensus of pathologists that carcinoma *in situ* and severe dysplasia form an indistinguishable continuum (4). The other major target lesion for chemoprev consensus of pathologists that carcinoma *in situ* and severe dysplasia form an indistinguishable continuum (4). The other major target lesion for chemopreventive agents may be termed "predysplasia," which is the stage of dysplasia form an indistinguishable continuum (4). The other major target lesion for chemopreventive agents may be termed "predysplasia," which is the stage of neoplastic development after initiating DNA mutational changes

Received 4/5/93; revised 7/6/93; accepted 7/i 6/93.

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² The abbreviations used are: NCI, National Cancer Institute; AFB₁, aflatoxin
² The abbreviations used are: NCI, National Cancer Institute; AFB₁, aflatoxin
B + B(a)P -borzo(a) pyrope: DEMO, 2.4ifluoromethylorgith ² The abbreviations used are: NCI, National Cancer Institute; AFB₁, aflatoxin
B₁; B(*a*)P, benzo(*a*)-pyrene; DFMO, 2-difluoromethylornithine; DHEA, de-
hydroepiandrosterone; DMBA, 7,12-dimethylbenz(*a*)anthracene; D ² The abbreviations used are: NCI, National Cancer Institute; AFB₁, aflatoxin B₁; B(a)P, benzo(a)-pyrene; DFMO, 2-difluoromethylornithine; DHEA, dehydroepiandrosterone; DMBA, 7,12-dimethylbenz(a)anthracene; DMH, 1,2-B₁; B(a)P, benzo(a)-pyrene; DFMO, 2-difluoromethylornithine; DHEA, de-
hydroepiandrosterone; DMBA, 7,12-dimethylbenz(a)anthracene; DMH,
1,2-dimethyl-hydrazine; G6PDH, glucose-6-phosphate dehydrogenase; CSH,
glutathione; glutathione; 4-HPR, all-trans-N-(4-hydroxyphenyl)retinamide; MNU,
N-methyl-N'-nitrosourea; MTD, maximum tolerated dose; NNK, 4-(methyl-
nitrosamino)-1-(3-pyridyl)-1-butanone; NOEL, no observed effect level;
NSAID, nonstero

Previous development by the pharmaceutical industry.

 $b +$, Testing is completed or in progress.

' For Phase II and III studies, numbers in parentheses, number of trials.

(I Second- and third-generation agents are listed in order from most to least

appear morphologically normal. The natural history of in-
traepithelial neoplasia in the major human epithelia, with appear morphologically normal. The natural history of in-
traepithelial neoplasia in the major human epithelia, with
implications for chemopreventive strategy, has been reappear morphologically normal. The natural history of intraepithelial neoplasia in the major human epithelia, with
implications for chemopreventive strategy, has been re-
cently reviewed (5). The field of chemoprevention r appear morphologically normal. The natural history of in-
traepithelial neoplasia in the major human epithelia, with
implications for chemopreventive strategy, has been re-
cently reviewed (5). The field of chemoprevention appear morphologically normal. The natural history of in-
traepithelial neoplasia in the major human epithelia, with
implications for chemopreventive strategy, has been re-
cently reviewed (5). The field of chemoprevention traepithelial neoplasia in the major human epithelia, vimplications for chemopreventive strategy, has been cently reviewed (5). The field of chemoprevention rests the fundamental concept that the progression of neopliquil implications for chemopreventive strategy, has been re-
cently reviewed (5). The field of chemoprevention rests on
the fundamental concept that the progression of neoplasia
will be much easier to slow or eliminate with che cently reviewed (5). The field of chemoprevention rests on the fundamental concept that the progression of neoplasia will be much easier to slow or eliminate with chemopreventive agents at the predysplastic and dysplastic the fundamental concept that the progression of neoplasis will be much easier to slow or eliminate with chemopre ventive agents at the predysplastic and dysplastic stages of neoplastic development than with chemotherapeuti will be much easier to slow or eliminate with chemopre-
ventive agents at the predysplastic and dysplastic stages of
neoplastic development than with chemotherapeutic agents
at the postinvasive, cancer stage of neoplastic ventive agents at the predysplastic and dysplastic stages of
neoplastic development than with chemotherapeutic agents
at the postinvasive, cancer stage of neoplastic development.
The scientific basis for this concept is th neoplastic development than with chemotherapeutic agents
at the postinvasive, cancer stage of neoplastic development.
The scientific basis for this concept is the progression of cells
from a normal homogeneous state to mor at the postinvasive, cancer stage of neoplastic development.
The scientific basis for this concept is the progression of cells
from a normal homogeneous state to more and more het-
erogeneity as carcinogenesis evolves. The The scientific basis for this concept is the progression of ce
from a normal homogeneous state to more and more herogeneity as carcinogenesis evolves. Therefore, more ce
can be affected by treatment in early stages of carc from a normal homogeneous state to more and more het-
erogeneity as carcinogenesis evolves. Therefore, more cells
can be affected by treatment in early stages of carcinogenesis
when they are more homogeneous than in later erogeneity as carcinogenesis evolves. Therefore, more cells
can be affected by treatment in early stages of carcinogenesis
when they are more homogeneous than in later heterog-
eneous stages. An important element of chemop can be affected by treatment in early stages of carcinogenesis
when they are more homogeneous than in later heterog-
eneous stages. An important element of chemopreventive
drug development is the identification and validat when they are more homogeneous the
eneous stages. An important element
drug development is the identification
markers for predysplasia and dysplasia
points for chemopreventive activity.
General Mechanisms of Chemopre Figure 1 and the Homogeneous than in take heleog-
eneous stages. An important element of chemopreventive
drug development is the identification and validation of
markers for predysplasia and dysplasia that can serve as end

drug development is the identification and validation
markers for predysplasia and dysplasia that can serve as e
points for chemopreventive activity.
General Mechanisms of Chemopreventive Activity.
other important aspect markers for predysplasia and dysplasia that can serve as end-
points for chemopreventive activity.
General Mechanisms of Chemopreventive Activity. An-
other important aspect in the development of chemopre-
ventive agents points for chemopreventive activity.
General Mechanisms of Chemopreventive Activity. An-
other important aspect in the development of chemopre-
ventive agents is the mechanism(s) by which they inhibit
cancers. As is evid **General Mechanisms of Chemopreventive Activity.**

other important aspect in the development of chemoventive agents is the mechanism(s) by which they in

cancers. As is evident in the discussions of individual an

below, t other important aspect in the development of chemopre-
ventive agents is the mechanism(s) by which they inhibit
cancers. As is evident in the discussions of individual agents
below, the knowledge of mechanisms of chemoprev ventive agents is the mechanism(s) by which they inhibit cancers. As is evident in the discussions of individual agents below, the knowledge of mechanisms of chemoprevention is far from complete, and the multiple possible

have (e.g., the retinoids) confounds the discovery of the most
important mechanisms. Nevertheless, the known pharmahave (e.g., the retinoids) confounds the discovery of the methods in mortant mechanisms. Nevertheless, the known pharm
cological properties of the agents being evaluated and t have (e.g., the retinoids) confounds the discovery of the most
important mechanisms. Nevertheless, the known pharma-
cological properties of the agents being evaluated and the
experimental testing data on various classes o have (e.g., the retinoids) confounds the discovery of the most
important mechanisms. Nevertheless, the known pharma-
cological properties of the agents being evaluated and the
experimental testing data on various classes o have (e.g., the retinoids) confounds the discovery of the most
important mechanisms. Nevertheless, the known pharma-
cological properties of the agents being evaluated and the
experimental testing data on various classes o important mechanisms. Nevertheless, the known pharma-
cological properties of the agents being evaluated and the
experimental testing data on various classes of agents pro-
vide very useful insights into mechanism that may cological properties of the agents being evaluated and the experimental testing data on various classes of agents pro-
vide very useful insights into mechanism that may lead to the
development of more effective chemopreven experimental testing data on various classes of agents provide very useful insights into mechanism that may lead to the development of more effective chemopreventive drugs. In some cases, the pharmacological activity of a vide very useful insights into mechanism that may lead to the development of more effective chemopreventive drugs. In some cases, the pharmacological activity of a compound suggests very specifically the target tissues and cancers against which a chemopreventive drug may be active. F some cases, the pharmacological activity of a compound
suggests very specifically the target tissues and cancers
against which a chemopreventive drug may be active. For
example, an antiestrogen-such as tamoxifen would be d suggests very specifically the target tissues and cancers against which a chemopreventive drug may be active. For example, an antiestrogen such as tamoxifen would be developed for use against estrogen-sensitive cancers suc against which a chemopreventive drug may be active. For example, an antiestrogen such as tamoxifen would be developed for use against estrogen-sensitive cancers such as those of the breast. In other cases, the testing of c example, an antiestrogen such as tamoxifen would be developed for use against estrogen-sensitive cancers such as those of the breast. In other cases, the testing of classes of compounds known to have a very general chemopr veloped for use against estrogen-sensitive cancers such as
those of the breast. In other cases, the testing of classes of
compounds known to have a very general chemopreventive
activity may lead to the discovery of tissue Exercise of the breast. In other cases, the testing of classes of pounds known to have a very general chemopreventive ity may lead to the discovery of tissue specificities, such ose of antiinflammatories in colon and bladd compounds known to have a very general chemopreventive
activity may lead to the discovery of tissue specificities, such
as those of antiinflammatories in colon and bladder.
Table 2 presents a working classification of the

activity may lead to the discovery of tissue specificities, such
as those of antiinflammatories in colon and bladder.
Table 2 presents a working classification of the che--
mopreventive agents listed in Table 1 arranged ac as those of antiinflammatories in colon and bladder.
Table 2 presents a working classification of the che-
mopreventive agents listed in Table 1 arranged according to
structure or pharmacological effects associated with ch Table 2 presents a working classification of the c
mopreventive agents listed in Table 1 arranged according
structure or pharmacological effects associated with c
mopreventive activity. Note that many of the agents fall i
 structure or pharmacological effects associated with che-
mopreventive activity. Note that many of the agents fall into
more than one class. Moreover, the list of classes is undoubt-
edly incomplete.

In Table 2, the specific chemopreventive activities and mopreventive activity. Note that many of the agents tall into
more than one class. Moreover, the list of classes is undoubt-
edly incomplete.
In Table 2, the specific chemopreventive activities and
structures are grouped i edly incomplete.

In Table 2, the specific chemopreventive activities and

structures are grouped into three general classes. The first is

inhibitors of cellular proliferation (antiproliferatives), mani-

fested in such s In Table 2, the specific chemopreventive activities and structures are grouped into three general classes. The first is inhibitors of cellular proliferation (antiproliferatives), manifested in such specific mechanisms as O structures are grouped into three general classes. The first is
inhibitors of cellular proliferation (antiproliferatives), mani-
fested in such specific mechanisms as ODC inhibition, pro-
tein kinase C inhibition, and anti inhibitors of cellular proliferation (antiproliferatives), mani-
fested in such specific mechanisms as ODC inhibition, pro-
tein kinase C inhibition, and antiestrogenic activity. Anti-
proliferatives include retinoids, pol fested in such specific mechanisms as ODC inhibition, pr
tein kinase C inhibition, and antiestrogenic activity. An
proliferatives include retinoids, polyphenols, antihormone
calcium, DFMO, and the DHEA analogue, fluasteron tein kinase C inhibition, and antiestrogenic activity. Aproliferatives include retinoids, polyphenols, antihormocalcium, DFMO, and the DHEA analogue, fluasteron
second general class is carcinogen blocking agents. Blung is proliferatives include retinoids, polyphenols, antihormones, calcium, DFMO, and the DHEA analogue, fluasterone. A second general class is carcinogen blocking agents. Blocking is often produced by enhancing the carcinogen-
 calcium, DFMO, and the DHEA analogue, fluasterone. A
second general class is carcinogen blocking agents. Block-
ing is often produced by enhancing the carcinogen-
detoxifying enzymes, especially the Phase II metabolic en-
 second general class is carcinogen blocking agents. Blocking is often produced by enhancing the carcinogen-
detoxifying enzymes, especially the Phase II metabolic en-
zymes, including GSH *S*-transferases, which perform
co ing is often produced by enhancing the carcinoge
detoxifying enzymes, especially the Phase II metabolic e
zymes, including GSH *S*-transferases, which perfo
conjugation and other reactions. Wattenberg and Talal
(6–8) have detoxifying enzymes, especially the Phase II metabolic en-
zymes, including GSH S-transferases, which perform
conjugation and other reactions. Wattenberg and Talalay
(6–8) have emphasized the desirability of selecting chem zymes, including GSH *S*-transferases, which perform
conjugation and other reactions. Wattenberg and Talalay
(6–8) have emphasized the desirability of selecting chemo-
preventive agents which induce mostly Phase II metabol conjugation and other reactions. Wattenberg and Talalay (6–8) have emphasized the desirability of selecting chemo-
preventive agents which induce mostly Phase II metabolic
enzymes as opposed to compounds which induce both
 $(6-8)$ have emphasized the desirability of selecting chemo-
preventive agents which induce mostly Phase II metabolic
enzymes as opposed to compounds which induce both
Phase I mixed function oxidases and Phase II enzymes. preventive agents which induce mostly Phase II metabolic
enzymes as opposed to compounds which induce both
Phase I mixed function oxidases and Phase II enzymes. In-
duction of mixed function oxidases carries the potential

duction of mixed function oxidases carries the potential of activating procarcinogens.
A third general class of inhibitors is antioxidants, such as S-allyl-*I*-cysteine, curcumin, *N*-acetyl-1-cysteine, NSAIDs, and polyphe activating procarcinogens.

A third general class of inhibitors is antioxidants,

such as S-allyl-l-cysteine, curcumin, N-acetyl-L-cysteine,

NSAIDs, and polyphenols. These agents trap electrophilic

sites on activated car A third general class of inhibitors is antioxidan
such as S-allyl-*I*-cysteine, curcumin, *N*-acetyl-i-cystein
NSAIDs, and polyphenols. These agents trap electrophil
sites on activated carcinogens, scavenge oxygen-free rac such as S-allyl-*I*-cysteine, curcumin, N-acetyl-1-cysteine, NSAIDs, and polyphenols. These agents trap electrophilic sites on activated carcinogens, scavenge oxygen-free radicals and organic free radicals, and terminate l NSAIDs, and polyphenols. These agents trap electrophilic sites on activated carcinogens, scavenge oxygen-free radicals and organic free radicals, and terminate lipid peroxidation. These activities may be either a direct or sites on activated carcinogens, scavenge oxygen-free radicals and organic free radicals, and terminate lipid peroxi-
dation. These activities may be either a direct or indirect
effect of the antioxidant agent. Examples of cals and organic free radicals, and terminate lipid peroxi-
dation. These activities may be either a direct or indirect
effect of the antioxidant agent. Examples of agents with in-
direct antioxidant effects are those that dation. These activities may be either a direct or indire
effect of the antioxidant agent. Examples of agents with i
direct antioxidant effects are those that enhance the Pha
II metabolizing enzymes, thereby elevating elec effect of the antioxidant agent. Examples of agents with idirect antioxidant effects are those that enhance the Pha-
II metabolizing enzymes, thereby elevating electroph
trapping potential via increased GSH production and direct antioxidant effects are those that enhance the Phall metabolizing enzymes, thereby elevating electroph
trapping potential via increased GSH production and indi
tion of the enzyme GSH peroxidase. The antioxidant mec
 II metabolizing enzymes, thereby elevating electrophile
trapping potential via increased GSH production and induc-
tion of the enzyme GSH peroxidase. The antioxidant mecha-
nism is reputed to be both antimutagenic (9) and tion of the enzyme GSH peroxidase. The antioxidant mechanism is reputed to be both antimutagenic (9) and antipro-
liferative (10).
Combinations of Agents. At least two factors limit the po-
tential usefulness of chemopr

nism is reputed to be both antimutagenic (9) and antipro-
liferative (10).
Combinations of Agents. At least two factors limit the po-
tential usefulness of chemopreventives in the clinic. One is
that cancers are not redu liferative (10).
Combinations of Agents. At least two factors limit the po-
tential usefulness of chemopreventives in the clinic. One is
that cancers are not reduced to zero by administration of
these agents. The second **Combinations of Agents.** At least two factors limit the potential usefulness of chemopreventives in the clinic. One is that cancers are not reduced to zero by administration of these agents. The second is toxicity. Severa tential usefulness of chemopreventives in the clinic. One is
that cancers are not reduced to zero by administration of
these agents. The second is toxicity. Several very promising
agents are toxic at efficacious doses. The that cancers are not reduced to zero by administration of these agents. The second is toxicity. Several very promising agents are toxic at efficacious doses. The simultaneous or sequential administration of multiple inhibi these agents. The second is toxicity. Several very promising
agents are toxic at efficacious doses. The simultaneous or
sequential administration of multiple inhibitors can increase
the efficacy of chemopreventive agents a agents are toxic at efficacious doses. The simultaneous or sequential administration of multiple inhibitors can increase the efficacy of chemopreventive agents and reduce toxicity. Such an approach uses differences in the sequential administration of multiple inhibitors can increase
the efficacy of chemopreventive agents and reduce toxicity.
Such an approach uses differences in the mechanisms of
cancer inhibition among the agents to increas the efficacy of chemopreventive agents and reduce toxicity.
Such an approach uses differences in the mechanisms of
cancer inhibition among the agents to increase the inhibitory
activity. Further, the increased efficacy ach Such an approach uses differen
cancer inhibition among the agen
activity. Further, the increased e
levels of cancer inhibition at lowe
doses of the individual agents.

Fig. 1. Development of Epithelial Neoplasia. In estimating the severity of intraepithelial neoplasia (dysplasia), the extent of the lesion as well as the deviation from normal cellular morphology is used. Adapted from Boone ef al. (5), with permission.

Positiveeffects have been demonstrated in animal mod-Positive effects have been demonstrated in animal models using combinations of two chemopreventive agents. Sev-
eral of the combinations have shown synergism; *i.e.*, the Positive effects have been demonstrated in animal mod-
els using combinations of two chemopreventive agents. Sev-
eral of the combinations have shown synergism; *i.e.*, the
inhibitory potency of the combinations of agents Positive effects have been demonstrated in animal models using combinations of two chemopreventive agents. Several of the combinations have shown synergism; *i.e.*, the inhibitory potency of the combinations of agents was Positive effects have been demonstrated in animal models using combinations of two chemopreventive agents. Several of the combinations have shown synergism; *i.e.*, the inhibitory potency of the combinations of agents was els using combinations of two chemopreventive agents. Several of the combinations have shown synergism; *i.e.*, the inhibitory potency of the combinations of agents was greater than the sum of the potencies of the single a eral of the combinations have shown synergism; *i.e.*, the inhibitory potency of the combinations of agents was greater than the sum of the potencies of the single agents. Synergistic chemopreventive activity has been repo inhibitory potency of the combinations of agents was greater
than the sum of the potencies of the single agents. Synergistic
chemopreventive activity has been reported for DFMO and
piroxicam in rat colon (11, 12) and for 4 than the sum of the potencies of the single agents. Synergistic chemopreventive activity has been reported for DFMO and piroxicam in rat colon $(11, 12)$ and for 4-HPR and tamoxifen in rat mammary $(13, 14)$. In other stu than the sum of the potencies of the single agents. Synergistic sible mechanisms of action.

chemopreventive activity has been reported for DFMO and

piroxicam in rat colon (11, 12) and for 4-HPR and tamoxifen

in rat mam piroxicam in rat colon (11, 12) and for 4-HPR and tamoxifen
in rat mammary (13, 14). In other studies (data not shown),
synergistic activity has been observed in hamster lung for
 β -carotene with 4-HPR and with vitamin in rat mammary (13, 14). In other studies (data not shown), synergistic activity has been observed in hamster lung for β -carotene with 4-HPR and with vitamin A and for 4-HPR with oltipraz. Likewise, combinations of DFMO synergistic activity has been observed in hamster lung for β -carotene with 4-HPR and with vitamin A and for 4-HPR with oltipraz. Likewise, combinations of DFMO with 4-HPR and with oltipraz and 4-HPR with oltipraz have s β -carotene with 4-HPR and with vitamin A and for 4-HPR with oltipraz, Likewise, combinations of DFMO with 4-HPR and with oltipraz and 4-HPR with oltipraz have synergistic activity in the bladder. Three of these combina with oltipraz. Likewise, combinations of DFMO with 4-HPR
and with oltipraz and 4-HPR with oltipraz have synergistic
activity in the bladder. Three of these combinations—DFMO
and piroxicam, 4-HPR and oltipraz, and 4-HPR and and with oltipraz and 4-HPR with oltipraz have synergistic activity in the bladder. Three of these combinations—DFMO and piroxicam, 4-HPR and oltipraz, and 4-HPR and tamoxifen—are currently undergoing toxicology testing in activity in the bladder. Three of these combinations—DFMO
and piroxicam, 4-HPR and oltipraz, and 4-HPR and 1
tamoxifen—are currently undergoing toxicology testing in
the NCI chemopreventive drug development program.
These and piroxicam, 4-HPR and oltipraz, and 4-HPR and tamoxifen—are currently undergoing toxicology testing in the NCI chemopreventive drug development program.
These three combinations are proceeding because of the promise the tamoxifen—are currently undergoing toxicology testing in
the NCI chemopreventive drug development program.
These three combinations are proceeding because of the
promise they and their single agent components have against
 the NCI chemopreventive drug development program.
These three combinations are proceeding because of the
promise they and their single agent components have against
cancers in colon and bladder, lung and bladder, and brea These three combinations are proceeding because of the promise they and their single agent components have against cancers in colon and bladder, lung and bladder, and breast, respectively. The other combinations, which in promise they and their single age cancers in colon and bladder, l
respectively. The other combin
β-carotene or vitamin A, are scl
the NCI in the coming year.
Prioritization of Newer Chemo cancers in colon and bladder, lung and bladder, and breast, respectively. The other combinations, which include either β -carotene or vitamin A, are scheduled for further testing by the NCI in the coming year.
Prioritiz

ment, a systematic methodology for identifying and ranking β-carotene or vitamin A, are scheduled for further testing by
the NCI in the coming year.
Prioritization of Newer Chemopreventive Agents. Because
of the many compounds under consideration for develop-
ment, a systematic the NCI in the coming year.
 Prioritization of Newer Chemopreventive Agents. Because

of the many compounds under consideration for develop-

ment, a systematic methodology for identifying and ranking

candidate chemopre **Prioritization of Newer Chemopreventive Agents.** Because of the many compounds under consideration for development, a systematic methodology for identifying and ranking candidate chemopreventive agents is essential to fin of the many compounds under consideration for develop-
ment, a systematic methodology for identifying and ranking
candidate chemopreventive agents is essential to find the
best agents and to make the best use of available ment, a systematic methodology for identifying and ranking
candidate chemopreventive agents is essential to find the
best agents and to make the best use of available resources.
In the NCI program, this activity ranges fro candidate chemopreventive agents is essential to find thest agents and to make the best use of available resource
In the NCI program, this activity ranges from selecting ca
didates for initial testing in efficacy screens,

nission.
fying those agents for preclinical toxicity and Phase I clinical
trials. At each stage, criteria are applied to set priorities for fying those agents for preclinical toxicity and Phase I clinical
trials. At each stage, criteria are applied to set priorities for
the agents. In most cases, these priorities are based on four fying those agents for preclinical toxicity and Phase I clinical
trials. At each stage, criteria are applied to set priorities for
the agents. In most cases, these priorities are based on four
factors: efficacy; toxicity; fying those agents for preclinical toxicity and Phase I clinical
trials. At each stage, criteria are applied to set priorities for
the agents. In most cases, these priorities are based on four
factors: efficacy; toxicity; fying those agents for preclinic
trials. At each stage, criteria a
the agents. In most cases, thes
factors: efficacy; toxicity; com
sible mechanisms of action.
Efficacy is judged by pre trials. At each stage, criteria are applied to set priorities for the agents. In most cases, these priorities are based on four factors: efficacy; toxicity; commercial availability; and possible mechanisms of action.
Effic the agents. In most cases, these priorities are based on four

factors: efficacy; toxicity; commercial availability; and possible mechanisms of action.
Efficacy is judged by previous animal studies, *in vitro* results (*e.g.*, inhibition of cell transformation and antimutagenesis), ep sible mechanisms of action.

Efficacy is judged by previous animal studies, *in vitro*

results (*e.g.,* inhibition of cell transformation and antimuta-

genesis), epidemiology studies, and anecdotal reports in hu-

mans. Efficacy is judged by previous animal studies, *in vitro* results $(e.g.,$ inhibition of cell transformation and antimuta-
genesis), epidemiology studies, and anecdotal reports in humans. Toxicity is determined by formal tox results (e.g., inhibition of cell transformation and antimuta-
genesis), epidemiology studies, and anecdotal reports in hu-
mans. Toxicity is determined by formal toxicology studies in
animals, case reports in humans, and, genesis), epidemiology studies, and anecdotal reports in humans. Toxicity is determined by formal toxicology studies in animals, case reports in humans, and, when available, previous clinical experience. The commercial ava mans. Toxicity is determined by formal toxicology studies in animals, case reports in humans, and, when available, previous clinical experience. The commercial availability of large amounts of agents at reasonable cost is factor. Cost is generally related to ease of synthesis or isolation, the amount of agent manufactured for other com-
mercial uses, and the interest of the manufacturer in provious clinical experience. The commercial availability of large amounts of agents at reasonable cost is an important factor. Cost is generally related to ease of synthesis or isolation, the amount of agent manufactured for large amounts of agents at reasonable cost is an important factor. Cost is generally related to ease of synthesis or isolation, the amount of agent manufactured for other commercial uses, and the interest of the manufactur factor. Cost is generally related to ease of synthesis or isolation, the amount of agent manufactured for other com-
mercial uses, and the interest of the manufacturer in pro-
moting the development of the agent as a cance lation, the amount of agent manufactured for other com-
mercial uses, and the interest of the manufacturer in pro-
moting the development of the agent as a cancer
chemopreventive. Possible mechanisms of action may be
used mercial uses, and the interest of the manufacturer in p
moting the development of the agent as a cano
chemopreventive. Possible mechanisms of action may
used to lower the ranking of a candidate when other age
with the same moting the development of the agent as a cancer
chemopreventive. Possible mechanisms of action may be
used to lower the ranking of a candidate when other agents
with the same mechanism of action and range of chemo-
prevent chemopreventive. Possible mechanisms of action may be used to lower the ranking of a candidate when other agents with the same mechanism of action and range of chemo-
preventive activity are already under development, or t used to lower the ranking of a candidate when other age
with the same mechanism of action and range of chem
preventive activity are already under development, or
promote a candidate agent that is desirable because it h
mul with the same mechanism
preventive activity are all
promote a candidate ager
multiple mechanisms by v
preventive effect.
Other factors that ma entive activity are already under development, or to note a candidate agent that is desirable because it has siple mechanisms by which it may produce its chemoentive effect.
Other factors that may be considered, particular promote a candidate agent that is desirable because it has
multiple mechanisms by which it may produce its chemo-
preventive effect.
Other factors that may be considered, particularly for
agents ready for toxicology and Ph

multiple mechanisms by which it may produce its chemo-
preventive effect.
Other factors that may be considered, particularly for
agents ready for toxicology and Phase I clinical trials, are
pharmacokinetics, the availabili preventive effect.

Other factors that may be considered, particularly for

agents ready for toxicology and Phase I clinical trials, are

pharmacokinetics, the availability of appropriate dosage for-

mulations, and regula agents ready for toxicology and Phase I clinical trials, are
pharmacokinetics, the availability of appropriate dosage for-
mulations, and regulatory status for clinical use (e.g., a can-
didate agent that already was appro pharmacokinetics, the availability of appropriate dosage for-
mulations, and regulatory status for clinical use (e.g., a can-
didate agent that already was approved by the U.S. Food and
Drug Administration for human use wo

Status of Chemopreventive Agents Currently Under Development

Status of Chemopreventive Agents Currently Under
Development
Table 1 presents the 22 drugs and three drug combinations
that currently have reached an advanced level of develop-**Status of Chemopreventive Agents Currently Under
Development**
Table 1 presents the 22 drugs and three drug combination
that currently have reached an advanced level of development as chemopreventives. Based on the status **Status of Chemopreventive Agents Currently Under**
Development
Table 1 presents the 22 drugs and three drug combinations
that currently have reached an advanced level of develop-
ment as chemopreventives. Based on the st **Development**
Table 1 presents the 22 drugs and three drug combinations
that currently have reached an advanced level of develop-
ment as chemopreventives. Based on the status of their de-
velopment, the chemopreventive dr Table 1 presents the 22 drugs and three drug combinations for that currently have reached an advanced level of development as chemopreventives. Based on the status of their development, the chemopreventive drugs in Table that currently have reached an advanced level of development as chemopreventives. Based on the status of their development, the chemopreventive drugs in Table 1 are grouped into three generations. Chemopreventive agents in ment as chemopreventives. Based on the status of their development, the chemopreventive drugs in Table 1 are grouped into three generations. Chemopreventive agents in the first generation are well documented clinically or velopment, the chemopreventive drugs in Table 1 and grouped into three generations. Chemopreventive agents in the first generation are well documented clinically or epidemiologically and are now in Phase II or Phase III cl grouped into three generations. Chemopreventive agents in
the first generation are well documented clinically or epi-
demiologically and are now in Phase II or Phase III clinical
trials. Second-generation drugs are those w the first generation are well documented clinically or epi-
demiologically and are now in Phase II or Phase III clinical
trials. Second-generation drugs are those which have dem-
onstrated chemopreventive efficacy in anima demiologically and are now in Phase II or Phase III clinical
trials. Second-generation drugs are those which have dem-
onstrated chemopreventive efficacy in animal studies, have
been through toxicological testing in rats a trials. Second-generation drugs are those which have demonstrated chemopreventive efficacy in animal studies, have been through toxicological testing in rats and dogs, and are now in Phase 1 clinical trials. Third-generati onstrated chemopreventive efficacy in animal studies, have
been through toxicological testing in rats and dogs, and are
now in Phase 1 clinical trials. Third-generation agents are
those which have demonstrated chemoprevent testing. **First-Generation Agents.** Several first and uses, and are now in Phase I clinical trials. Third-generation agents are those which have demonstrated chemopreventive efficacy in animal studies and are now undergoing toxicol those which have demonstrated chemopreventive efficacy
in animal studies and are now undergoing toxicology
testing.
First-Generation Agents. Several first-generation agents al-
ready have progressed significantly as che

in animal studies and are now undergoing toxicology
testing.
First-Generation Agents. Several first-generation agents al-
ready have progressed significantly as chemopreventive
agents; these are the retinoids, β -caro **First-Generation Agents.** Several first-generation agents already have progressed significantly as chemopreventive agents; these are the retinoids, β -carotene, and calcium. Many animal efficacy studies have been compl

noids, which demonstrate chemopreventive activity in noids, which demonstrate chemopreventive activity in
mammary glands, bladder, and skin (reviewed in Refs. 15
and 16). Several epidemiology studies have examined the noids, which demonstrate chemopreventive activity in
mammary glands, bladder, and skin (reviewed in Refs. 15
and 16). Several epidemiology studies have examined the
relationship between blood levels of vitamin A and cancer relationship between the mopreventive activity in
mammary glands, bladder, and skin (reviewed in Refs. 15
and 16). Several epidemiology studies have examined the
relationship between blood levels of vitamin A and cancer
ri moids, which demonstrate chemopreventive activity
mammary glands, bladder, and skin (reviewed in Refs.
and 16). Several epidemiology studies have examined relationship between blood levels of vitamin A and can-
risk (*e.g.* mammary glands, bladder, and skin (reviewed in Refs. 15 and 16). Several epidemiology studies have examined the relationship between blood levels of vitamin A and cancer risk (*e.g.*, Refs. 17–22). Retinoids are active in and 16). Several epidemiology studies have examined the relationship between blood levels of vitamin A and cancer risk (e.g., Refs. 17–22). Retinoids are active in the proliferation and progression stages of carcinogenesis relationship between blood levels of vitamin A and cancer risk (e.g., Refs. 17–22). Retinoids are active in the proliferation and progression stages of carcinogenesis (23). Retinoids inhibit several activities involved in risk (e.g., Refs. 17–22). Retinoids are active in the proliferation and progression stages of carcinogenesis (23). Retinoids inhibit several activities involved in tumor promotion, including induction of ODC; they probably tion and progression stages of carcinogenesis (23). Retinoids inhibit several activities involved in tumor promotion, including induction of ODC; they probably participate in signal transduction via cellular receptors. The inhibit several activities involved in tumor promotion, in-
cluding induction of ODC; they probably participate in sig-
nal transduction via cellular receptors. They induce terminal
differentiation in selected cells, and t nal transduction via cellular receptors. They induce terminal differentiation in selected cells, and this activity may be mediated by binding to receptors. They stimulate intercellular communication and are immunostimulant differentiation in selected cells, and this activity may be me-
diated by binding to receptors. They stimulate intercellular
communication and are immunostimulants. Unfortunately,
there is also significant potential toxici diated by binding to receptors. They stimulate intercellular
communication and are immunostimulants. Unfortunately,
there is also significant potential toxicity associated with reti-
noids. For example, vitamin A and many communication and are immunostimulants. Unfortunately,
there is also significant potential toxicity associated with reti-
noids. For example, vitamin A and many of its analogues
accumulate in liver and cause hepatic damage there is also significant potential toxicity associated with reti-
noids. For example, vitamin A and many of its analogues
accumulate in liver and cause hepatic damage; they also can
cause eye damage, and they are teratoge noids. For example, vitamin A and many of its analogues
accumulate in liver and cause hepatic damage; they also can
cause eye damage, and they are teratogens (24). Although
the toxicity of certain of the efficacious synthe accumulate in liver and cause hepatic damage; they also can
cause eye damage, and they are teratogens (24). Although
the toxicity of certain of the efficacious synthetic retinoids
such as 4-HPR appears to be less severe th cause eye damage, and they are teratogens (24). Although
the toxicity of certain of the efficacious synthetic retinoids
such as 4-HPR appears to be less severe than that of vitamin
A, there is still concern. Because of thi the toxicity of certain of the efficacious synthetic retinoids
such as 4-HPR appears to be less severe than that of vitamin
A, there is still concern. Because of this potential toxicity,
clinical trials of the synthetic r inical trials of the synthetic retinoids have been limited
patients with previous cancers and those at high risk for
nncer.
The rationale for the development of β -carotene as a
nemopreventive agent is based on case-con

to patients with previous cancers and those at high risk for
cancer.
The rationale for the development of β -carotene as a
chemopreventive agent is based on case-control epidemi-
ology data from lung cancer patients $(2$ cancer.
The rationale for the development of β -carotene as a chemopreventive agent is based on case-control epidemi-
ology data from lung cancer patients (21, 25–33), a chemical
structure indicating ability to scavenge The rationale for the development of β -carotene as a chemopreventive agent is based on case-control epidemi-
ology data from lung cancer patients $(21, 25-33)$, a chemical
structure indicating ability to scavenge free chemopreventive agent is based on case-control epidemi-
ology data from lung cancer patients $(21, 25-33)$, a chemical
structure indicating ability to scavenge free radicals, and bio-
conversion to vitamin A. Unlike the r ology data from lung cancer patients (21, 25–33), a chemical structure indicating ability to scavenge free radicals, and bioconversion to vitamin A. Unlike the retinoids, there is little concern about toxicity; however, t structure indicating ability to scavenge free radicals, and bio-
conversion to vitamin A. Unlike the retinoids, there is little
concern about toxicity; however, there are only scattered
animal efficacy results. Several cl concern about toxicity; however, there
animal efficacy results. Several clinical
are ongoing which include well subjects
cancer (e.g., chronic smokers) as well a
cancerous lesions (e.g., colon polyps).
These clinical trial al efficacy results. Several clinical trials of β -carotene mgoing which include well subjects at increased risk for er (*e.g.*, chronic smokers) as well as patients with pre-
erous lesions (*e.g.*, colon polyps).
These are ongoing which include well subjects at increased risk for cancer (e.g., chronic smokers) as well as patients with precancerous lesions (e.g., colon polyps).
These clinical trials are not yet completed, except that the

cancer (e.g., chronic smokers) as well as patients with pre-
cancerous lesions (e.g., colon polyps).
These clinical trials are not yet completed, except that
there has been one negative result from a randomized trial
of cancerous lesions (e.g., colon polyps).
These clinical trials are not yet completed, except that
there has been one negative result from a randomized trial
of β -carotene in skin cancer (34). Although this outcome
appea These clinical trials are not yet completed, except that
there has been one negative result from a randomized trial
of β -carotene in skin cancer (34). Although this outcome
appears to be conclusive, the dosage used may there has been one negative result from a randomized trial
of β -carotene in skin cancer (34). Although this outcome
appears to be conclusive, the dosage used may have been
too low to be effective in skin. Encouraging r appears to be conclusive, the dosage used may have been
too low to be effective in skin. Encouraging results have been
obtained from a preliminary trial of β -carotene in patients
with oral leukoplakia, which is associat too low to be effective in skin. Encouraging results have been
obtained from a preliminary trial of β -carotene in patients
with oral leukoplakia, which is associated with increased
risk of oral cancer and, particularly obtained from a preliminary trial of β -carotene in patients
with oral leukoplakia, which is associated with increased
risk of oral cancer and, particularly in the presence of dys-
plasia, is considered a premalignant l with oral leukoplakia, which is associated with increased
risk of oral cancer and, particularly in the presence of dys-
plasia, is considered a premalignant lesion (35, 36). Of 24
patients treated with 30 mg β -carotene risk of oral cancer and, particularly in the presence of dys-
plasia, is considered a premalignant lesion $(35, 36)$. Of 24
patients treated with $30 \text{ mg } \beta$ -carotene/day, 17 showed signs
of lesion regression within 3 mon plasia, is considered a premalignant lesion (35, 36). Of 24
patients treated with 30 mg β -carotene/day, 17 showed signs
of lesion regression within 3 months (35). Meanwhile, the
activity of β -carotene in animal effic patients treated with 30 mg β -carotene/day, 17 showed signs
of lesion regression within 3 months (35). Meanwhile, the
activity of β -carotene in animal efficacy experiments is pro-
viding insight for interpreting the of lesion regression within 3 months (35). Meanwhile, the activity of β -carotene in animal efficacy experiments is pro-
viding insight for interpreting the clinical data. One difficulty
with obtaining reliable results activity of β -carotene in animal efficacy experiments is pro-
viding insight for interpreting the clinical data. One difficulty
with obtaining reliable results in animal efficacy studies has
been poor absorption of die widing insight for interpreting the clinical data. One difficulty
with obtaining reliable results in animal efficacy studies has
been poor absorption of dietary β -carotene in rodents (see,
for example, Ref. 37). Recent with obtaining reliable results in animal efficacy studies has
been poor absorption of dietary β-carotene in rodents (see,
for example, Ref. 37). Recently, chemopreventive efficacy
has been observed in studies with inject been poor absorption of dietary β -carotene in rodents (see,
for example, Ref. 37). Recently, chemopreventive efficacy
has been observed in studies with injectable forms of
 β -carotene where adequate blood levels of t has been observed in studies with injectable forms of β -carotene where adequate blood levels of the agent have been obtained. For example, injectable β -carotene inhibited the induction of mammary carcinoma induced i β -carotene where adequate blood levels of the agent have
been obtained. For example, injectable β -carotene inhibited
the induction of mammary carcinoma induced in rats by
MNU (data not shown). Also, this form of the been obtained. For example, injectable β -carotene inhibited
the induction of mammary carcinoma induced in rats by
MNU (data not shown). Also, this form of the agent proved
to be efficacious against carcinogen-induced l the induction of mammary carcinoma induced in rats by
MNU (data not shown). Also, this form of the agent proved
to be efficacious against carcinogen-induced lung tumors
when administered in combination with vitamin A, olti MNU (data not shown). Also, this form of the agent proved
to be efficacious against carcinogen-induced lung tumors
when administered in combination with vitamin A, oltipraz,
or DFMO; under the conditions of these experimen Proficacious against carcinogen-induced lung tumors

In administered in combination with vitamin A, oltipraz,

FMO; under the conditions of these experiments, none

e agents was effective when administered alone (38).

Pro when administered in combination with vitamin A, oltipraz,
or DFMO; under the conditions of these experiments, none
of the agents was effective when administered alone (38).
Prominent among ongoing clinical trials of first

or DFMO; under the conditions of these experiments, none
of the agents was effective when administered alone (38).
Prominent among ongoing clinical trials of first gen-
eration drugs is the six-center CARET study, which i of the agents was effective when administered alone (38).

Prominent among ongoing clinical trials of first gen-

eration drugs is the six-center CARET study, which is testing

the chemopreventive effect of a combination Prominent among ongoing clinical trials of first generation drugs is the six-center CARET study, which is testing the chemopreventive effect of a combination of 25,000 international units vitamin A and 30 mg β -carotene eration drugs is the six-center CARET study, which is testing
the chemopreventive effect of a combination of 25,000 in-
ternational units vitamin A and 30 mg β -carotene/day in
preventing lung cancer in heavy smokers an the chemopreventive effect of a combination of 25,000 in-
ternational units vitamin A and 30 mg β -carotene/day in
preventing lung cancer in heavy smokers and workers ex-
posed to asbestos (39). Trials of 13-*cis*-retin ternational units vitamin A and 30 mg β -carotene/day in preventing lung cancer in heavy smokers and workers exposed to asbestos (39). Trials of 13-c*is*-retinoic acid in preventing oral leukoplakia (36, 40, 41), second

a Agents listed in order from most to least advanced in development.
b +, Chemopreventive activity observed; significant at *P* < 0.05; -, no significant chemopreventive activity observed.

 $b +$, Chemopreventive activity observed; significant at $P < 0.05$; -, no significant c
chronic smokers (43) are underway. Positive results have
been obtained in studies of oral leukoplakia (36, 40) and in chronic smokers (43) are underway. Positive results have
been obtained in studies of oral leukoplakia (36, 40) and in
prevention of second primary head and neck tumors (42).
4-HPR is now being tested for chemopreventive ef chronic smokers (43) are underway. Positive results habeen obtained in studies of oral leukoplakia (36, 40) and prevention of second primary head and neck tumors (4) 4-HPR is now being tested for chemopreventive effect can been obtained in studies of oral leukoplakia
prevention of second primary head and ne
4-HPR is now being tested for chemoprev-
cancer in the opposite breast of patients w
gone mastectomy for breast cancer (24).
Phase II cl ention of second primary head and neck tumors (4.
PR is now being tested for chemopreventive effect of
er in the opposite breast of patients who have undo
mastectomy for breast cancer (24).
Phase II clinical trials of calc 4-HPR is now being tested for chemopreventive effect
cancer in the opposite breast of patients who have une
gone mastectomy for breast cancer (24).
Phase II clinical trials of calcium in preventing ade
matous polyps of the

cancer in the opposite breast of patients who have under-
gone mastectomy for breast cancer (24).
Phase II clinical trials of calcium in preventing adeno-
matous polyps of the colon are in progress. The chemopre-
ventive p gone mastectomy for breast cancer (24). an

Phase II clinical trials of calcium in preventing adeno-

matous polyps of the colon are in progress. The chemopre-

ventive potential of calcium was first shown by its protectiv matous polyps of the colon are in progress. The chemopre-
ventive potential of calcium was first shown by its protective
effect against proliferation in the colon of patients at high risk
for cancer (44-46). Calcium has sh effect against proliferation in the colon of patients at high risk
for cancer (44–46). Calcium has shown chemopreventive
activity at the cellular level (44, 45, 47, 48), in animals (49–
51), and clinically (48). A total do activity at the cellular level (44, 45, 47, 48), in animals (49–

51), and clinically (48). A total dose of 2000 mg elemental

calcium/day has been proposed to be the likely efficacious

and highest nontoxic dose that can

calcium/day has been proposed to be the likely efficacious
and highest nontoxic dose that can be recommended cur-
rently (48).
Tamoxifen is a well known antiestrogen used in the
adjuvant therapy of breast cancer (52). This rently (48) .

Tamoxifen is a well known antiestrogen used in the

adjuvant therapy of breast cancer (52). This clinical use ini-

tially was based on its efficacy in causing the regression of

carcinogen-induced mammary Tamoxifen is a well known antiestrogen used in the adjuvant therapy of breast cancer (52). This clinical use initially was based on its efficacy in causing the regression of carcinogen-induced mammary tumors in rats, as we adjuvant therapy of breast cancer (52). This clinical use initially was based on its efficacy in causing the regression of carcinogen-induced mammary tumors in rats, as well as its ability to prevent new tumors in the same tially was based on its efficacy in causing the regression of carcinogen-induced mammary tumors in rats, as well as its ability to prevent new tumors in the same animals $(53, 54)$.
Recently a Phase III trial of tamoxifen carcinogen-induced mammary tumors in rats, as well as its ability to prevent new tumors in the same animals $(53, 54)$.
Recently a Phase III trial of tamoxifen for the prevention of breast cancer began (55) . Finasteride ability to prevent new tumors in the same animals (53, 54).
Recently a Phase III trial of tamoxifen for the prevention of
breast cancer began (55). Finasteride is an inhibitor of tes-
tosterone 5α -reductase. Interest i Recently a Phase III trial of tamoxifen for the prevention of
breast cancer began (55). Finasteride is an inhibitor of tes-
tosterone 5 α -reductase. Interest in it as a potential chemo-
preventive agent arose because of breast cancer began (55). Finasteride is an inhibitor of tes-
tosterone 5α -reductase. Interest in it as a potential chemo-
preventive agent arose because of its efficacy in treatment of
proliferative disease in prostat tosterone 5 α -reductase. Interest in it as a potential chemo-
preventive agent arose because of its efficacy in treatment of
proliferative disease in prostate, benign prostatic hyperplasia
(56). A Phase III trial of fina

proliferative disease in prostate, benign prostatic hyperplasia (56). A Phase III trial of finasteride for the prevention of prostate cancer has recently begun.
Second- and Third-Generation Agents. For second- and third-(56). A Phase III trial of finasteride for the prevention of pr
tate cancer has recently begun.
Second- and Third-Generation Agents. For second- a
third-generation agents, much evidence establishing the
fficacy as chemop tate cancer has recently begun.
Second- and Third-Generation Agents. For second- and
third-generation agents, much evidence establishing their
efficacy as chemopreventive agents has come from preclini-
cal efficacy studi **Second- and Third-Generation Agents.** For second- and third-generation agents, much evidence establishing their efficacy as chemopreventive agents has come from preclinical efficacy studies. Table 3 shows the efficacy of third-generation agents, much evidence establishing the
efficacy as chemopreventive agents has come from preclincal efficacy studies. Table 3 shows the efficacy of some
these agents in the animal models of carcinogenesis t efficacy as chemopreventive agents has come from preclini-
cal efficacy studies. Table 3 shows the efficacy of some of
these agents in the animal models of carcinogenesis that are
part of the NCI chemopreventive drug devel cal efficacy studies. Table 3 shows the efficacy of some of these agents in the animal models of carcinogenesis that are part of the NCI chemopreventive drug development screening process. The models have been described in these agents in the animal models of carcinogenesis that are
part of the NCI chemopreventive drug development screen-
ing process. The models have been described in detail pre-
viously (1, 3, 57). The chemopreventive activ ing process. The models have been described in detail previously (1, 3, 57). The chemopreventive activities and rationale for developing these agents is summarized below.

DFMO alkylates and irreversibly blocks ODC, preven

viously (1, 3, 57). The chemopreventive activities and rationale for developing these agents is summarized below.
DFMO alkylates and irreversibly blocks ODC, preventing conversion of ornithine to putrescine. This is the fi tionale for developing these agents is summarized below.

DFMO alkylates and irreversibly blocks ODC, prevent-

ing conversion of ornithine to putrescine. This is the first and

rate-limiting step in polyamine synthesis, DFMO alkylates and irreversibly blocks ODC, preventing conversion of ornithine to putrescine. This is the first and rate-limiting step in polyamine synthesis, which is closely linked to cell proliferation (58–60). ODC is b thus may be a mechanism for inhibiting step in polyamine synthesis, which is closely
linked to cell proliferation (58–60). ODC is believed to be
important in tumor promotion (61, 62), and its inhibition
thus may be a mecha

themopreventive activity observed.
mouse (68) urinary bladder, and rat mammary gland (68–
72). Previous clinical trials of DFMO involving cancer pamouse (68) urinary bladder, and rat mammary gland (68–
72). Previous clinical trials of DFMO involving cancer pa-
tients established a p.o. MTD for DFMO of 9–12 g/m²/day mouse (68) urinary bladder, and rat mammary gland (68–72). Previous clinical trials of DFMO involving cancer patents established a p.o. MTD for DFMO of 9–12 g/m²/day (approximately 230–300 mg/kg body weight/day) (73, 74) mouse (68) urinary bladder, and rat mammary gland (68–72). Previous clinical trials of DFMO involving cancer patients established a p.o. MTD for DFMO of 9–12 g/m²/day (approximately 230–300 mg/kg body weight/day) (73, 74 mouse (68) urinary bladder, and rat mammary gland (68–72). Previous clinical trials of DFMO involving cancer patients established a p.o. MTD for DFMO of 9–12 g/m²/day (approximately 230–300 mg/kg body weight/day) (73, 74 72). Previous clinical trials of DFMO involving cancer patients established a p.o. MTD for DFMO of 9–12 g/m^2 /day (approximately 230–300 mg/kg body weight/day) (73, 74). The dose-limiting side effects observed included d tients established a p.o. MTD for DFMO of 9–12 g/m²/day
(approximately 230–300 mg/kg body weight/day) (73, 74).
The dose-limiting side effects observed included diarrhea,
anemia, leukopenia, thrombocytopenia, and loss of (approximately 230–300 mg/kg body weight/day) (73, 74).
The dose-limiting side effects observed included diarrhea,
anemia, leukopenia, thrombocytopenia, and loss of hearing
acuity. Chronic (1-year) p.o. toxicity studies in The dose-limiting side effects observed included diarrhea,
anemia, leukopenia, thrombocytopenia, and loss of hearing
acuity. Chronic (1-year) p.o. toxicity studies in rats and dogs
found NOELs at 400 mg/kg body weight/day anemia, leukopenia, thrombocytopenia, and loss of hearing
acuity. Chronic (1-year) p.o. toxicity studies in rats and dogs
found NOELs at 400 mg/kg body weight/day and <50 mg/kg
bw/day (the lowest dosage tested), respective acuity. Chronic (1-year) p.o. toxicity studies in rats and dogs
found NOELs at 400 mg/kg body weight/day and <50 mg/kg
bw/day (the lowest dosage tested), respectively. A recently
completed Phase I cancer prevention clinica found NOELs at 400 mg/kg body weight/day and <50 mg/kg
bw/day (the lowest dosage tested), respectively. A recently
completed Phase I cancer prevention clinical trials showed
drug effect with no toxicity, particularly otoxi bw/day (the lowest dosage tested), respectively. A recently
completed Phase I cancer prevention clinical trials showed
drug effect with no toxicity, particularly otoxicity, in patients
treated with a low dose level of 500 completed Phase I cancer prevention clinical trials showed
drug effect with no toxicity, particularly otoxicity, in patients
treated with a low dose level of 500 mg/m²/day (13 mg/kg
body weight/day) for 10–12 months (75) drug effect with no toxicity, particularly otoxicity, in patients
treated with a low dose level of 500 mg/m²/day (13 mg/kg
body weight/day) for 10–12 months (75), suggesting that this
dose level is appropriate as a start otoxicity. Four of the same in the second the second second is appropriate as a starting point for further clinical
Four of the second animal studies are characterizing the
city.
Four of the second generation chemopreventive agents
S dose level is appropriate as a starting point for further clinical
studies. Additional animal studies are characterizing the
otoxicity.
Four of the second generation chemopreventive agents
are NSAIDs, sulindac, piroxicam,

studies. Additional animal studies are characterizing the otoxicity.
Four of the second generation chemopreventive agents
are NSAIDs, sulindac, piroxicam, aspirin, and ibuprofen. A
prominent biological activity of the NSAI otoxicity.

Four of the second generation chemopreventive agents

are NSAIDs, sulindac, piroxicam, aspirin, and ibuprofen. A

prominent biological activity of the NSAIDs is inhibition of

the synthesis of prostaglandins an Four of the second generation chemopreventive agents
are NSAIDs, sulindac, piroxicam, aspirin, and ibuprofen. A
prominent biological activity of the NSAIDs is inhibition of
the synthesis of prostaglandins and other eicosan prominent biological activity of the NSAIDs is inhibition of
the synthesis of prostaglandins and other eicosanoids, par-
ticularly inhibition of fatty acid cyclooxygenase (e.g., Refs. prominent biological activity of the NSAIDs is inhibition of
the synthesis of prostaglandins and other eicosanoids, par-
ticularly inhibition of fatty acid cyclooxygenase (e.g., Refs.
76–78). Epidemiological and experiment the synthesis of prostaglandins and other eicosanoids, par-
ticularly inhibition of fatty acid cyclooxygenase (e.g., Refs.
76–78). Epidemiological and experimental data strongly
suggest that carcinogenesis in epithelial ti ticularly inhibition of fatty acid cyclooxygenase (*e.g.*, Re
76–78). Epidemiological and experimental data strong
suggest that carcinogenesis in epithelial tissues may
modulated by inhibiting some aspects of the prostagla 76–78). Epidemiological and experimental data strong
suggest that carcinogenesis in epithelial tissues may
modulated by inhibiting some aspects of the prostagland
biosynthetic cascade (*e.g.*, Refs. 76, 77, 79, 80). The me suggest that carcinogenesis in epithelial tissues may be
modulated by inhibiting some aspects of the prostaglandin
biosynthetic cascade (*e.g.*, Refs. 76, 77, 79, 80). The mecha-
nism(s) may involve reductions not only in modulated by inhibiting some aspects of the prostaglandin
biosynthetic cascade (*e.g.*, Refs. 76, 77, 79, 80). The mecha-
nism(s) may involve reductions not only in growth-
promoting tissue prostaglandin levels but also in biosynthetic cascade (*e.g.*, Refs. 76, 77, 79, 80). The mechanism(s) may involve reductions not only in growth-
promoting tissue prostaglandin levels but also in suppressed
immune surveillance (81, 82) and in oxidation (promoting tissue prostaglandin levels but also in suppressed
immune surveillance (81, 82) and in oxidation (activation)
of proximate carcinogens (80, 83, 84).
In animal studies, NSAIDs have chemopreventive ac-
tivity in nu

In animal studies, NSAIDs have chernopreventive acimmune surveillance (81, 82) and in oxidation (activation)
of proximate carcinogens (80, 83, 84).
In animal studies, NSAIDs have chemopreventive ac-
tivity in numerous tissues. They reduce formation of both
colon polyps an of proximate carcinogens (80, 83, 84).
In animal studies, NSAIDs have chemopreventive ac-
tivity in numerous tissues. They reduce formation of both
colon polyps and carcinomas in laboratory animals given
carcinogens (11, 6 In animal studies, NSAIDs have chemopreventive activity in numerous tissues. They reduce formation of both colon polyps and carcinomas in laboratory animals given carcinogens (11, 66, 85–95). They also inhibit the inductio colon polyps and carcinomas in laboratory animals given carcinogens $(11, 66, 85-95)$. They also inhibit the induction of tumors in rat urinary bladder $(96, 97)$, hamster buccal colon polyps and carcinomas in laboratory animals given
carcinogens (11, 66, 85–95). They also inhibit the induction
of tumors in rat urinary bladder (96, 97), hamster buccal
pouch (98, 99), rat mammary gland (100–103), mo carcinogens (11, 66, 85–95). They also inhibit the in
of tumors in rat urinary bladder (96, 97), hamster
pouch (98, 99), rat mammary gland (100–103), mo
(104–108) and duodenum (88), and hamster es
(109), pancreas (110), an mors in rat urinary bladder (96, 97), hamster buccal

h (98, 99), rat mammary gland (100–103), mouse skin

-108) and duodenum (88), and hamster esophagus

), pancreas (110), and uterine cervix (111).

In animal efficacy sc pouch (98, 99), rat mammary gland (100–103), mouse skin
(104–108) and duodenum (88), and hamster esophagus
(109), pancreas (110), and uterine cervix (111).
In animal efficacy screens carried out under the NCI
chemopreventi

(104–108) and duodenum (88), and hamster esophagus (109), pancreas (110), and uterine cervix (111).
In animal efficacy screens carried out under the NCI
chemopreventive drug development program (Table 3), the
NSAIDs were (109), pancreas (110), and uterine cervix (111).

In animal efficacy screens carried out under the NCl

chemopreventive drug development program (Table 3), the

NSAIDs were active in the rat colon (aspirin, ibuprofen,

pir In animal efficacy screens carried out under the NCI
chemopreventive drug development program (Table 3), the
NSAIDs were active in the rat colon (aspirin, ibuprofen,
piroxicam), rat mammary (piroxicam), mouse bladder (ibuchemopreventive drug development program (Table 3), the NSAIDs were active in the rat colon (aspirin, ibuprofen, piroxicam), rat mammary (piroxicam), mouse bladder (ibu-
profen, piroxicam), and mouse skin (piroxicam). Suli NSAIDs were active in the rat colon (aspirin, ibuprofen, piroxicam), rat mammary (piroxicam), mouse bladder (ibu-
profen, piroxicam), and mouse skin (piroxicam). Sulindac
has not been tested in the NCI screens but has demo preliminary clinical studies, sulindac has also shown dra-
matic effects in causing the total or almost total regression preliminary clinical studies, sulindac has also shown dra-
matic effects in causing the total or almost total regression
of colorectal adenomatous polyps in patients with familial preliminary clinical studies, sulindac has also shown dra-
matic effects in causing the total or almost total regression
of colorectal adenomatous polyps in patients with familial
adenomatous polyposis and Gardner's syndro preliminary clinical studies, sulindac has also shown dra-
matic effects in causing the total or almost total regression
of colorectal adenomatous polyps in patients with familial
adenomatous polyposis and Gardner's syndro preliminary clinical studies, sulindac has also shown dra-
matic effects in causing the total or almost total regression
of colorectal adenomatous polyps in patients with familial
adenomatous polyposis and Gardner's syndro matic effects in causing the total or almost total regression
of colorectal adenomatous polyps in patients with familial p
adenomatous polyposis and Gardner's syndrome (112, w
113). In one of these studies, regression was of colorectal adenomatous polyps in patients with famil
adenomatous polyposis and Gardner's syndrome (11
113). In one of these studies, regression was seen in 9 p
tients with familial adenomatous polyposis in less than
mon adenomatous polyposis and Gardner's syndrome (112, 113). In one of these studies, regression was seen in 9 patients with familial adenomatous polyposis in less than 4 months of treatment (113). A recent major epidemiologic 113). In one of these studies, regression was seen in 9 patients with familial adenomatous polyposis in less than 4 months of treatment (113). A recent major epidemiological study also suggests that NSAIDs have promise in tients with familial adenomatous polyposis in less than 4 months of treatment (113). A recent major epidemiological study also suggests that NSAIDs have promise in the clinic as chemopreventives. Regular aspirin use (16 ti months of treatment (113). A recent major epidemiological
study also suggests that NSAIDs have promise in the clinic
as chemopreventives. Regular aspirin use (16 times/month
or more often) has been reported to reduce the r study also suggests that NSAIDs have promise in the clinic
as chemopreventives. Regular aspirin use (16 times/month
or more often) has been reported to reduce the relative risk
of death from colon cancer by 40% (79). For c as chemopreventives. Regular aspirin use (16 times/month or more often) has been reported to reduce the relative risk of death from colon cancer by 40% (79). For clinical use as chemopreventives, the goal is to identify do of death from colon cancer by 40% (79). For clinical use as significant toxicity in certain clinical settings. For example, chemopreventives, the goal is to identify dosages/regimens which are efficacious in cyclooxygenase of death from colon cancer by 40% (79). For clinical use as
chemopreventives, the goal is to identify dosages/regimens
which are efficacious in cyclooxygenase inhibition and non-
toxic with respect to the gastrointestinal chemopreventives, the goal is to identity dosages/regimens
which are efficacious in cyclooxygenase inhibition and non-
toxic with respect to the gastrointestinal upset, ulcers, and
eephropathy which limit NSAID usage in ot

toxic with respect to the gastrointestinal upset, ulcers, and
nephropathy which limit NSAID usage in other applications.
Oltipraz is a synthetic dithiolthione related to naturally
occurring 1,2-dithiolthiones found in cruc nephropathy which limit NSAID usage in other applications.

Oltipraz is a synthetic dithiolthione related to naturally

occurring 1,2-dithiolthiones found in cruciferous veg-

etables. It is a schistosomicidal drug that ha Oltipraz is a synthetic dithiolthione related to natura
occurring 1,2-dithiolthiones found in cruciferous ve
tables. It is a schistosomicidal drug that has demonstrat
chemopreventive efficacy in many animal model system
O occurring 1,2-dithiolthiones found in cruciferous veg-
etables. It is a schistosomicidal drug that has demonstrated
chemopreventive efficacy in many animal model systems.
Oltipraz inhibited the induction of forestomach an etables. It is a schistosomicidal drug that has demonstrated chemopreventive efficacy in many animal model systems.
Oltipraz inhibited the induction of forestomach and pulmo-
nary tumors in mice by $B(a)P$, N , N' -diethy chemopreventive efficacy in many animal model systems.
Oltipraz inhibited the induction of forestomach and pulmo-
nary tumors in mice by $B(a)P$, N , N' -diethylnitrosamine and
uracil mustard (114). It also protected aga Oltipraz inhibited the induction of forestomach and pulmo-
nary tumors in mice by $B(a)P$, N , N' -diethylnitrosamine and
uracil mustard (114). It also protected against AFB_1 -induced
liver cancer (115), azaserine-induc mary tumors in mice by $B(a)P$, N , N' -diethylnitrosamine and uracil mustard (114). It also protected against AFB_1 -induced liver cancer (115), azaserine-induced pancreatic cancer,³ and spontaneous hematopoietic tumor uracil mustard (114). It also protected against AFB₁-induced
liver cancer (115), azaserine-induced pancreatic cancer,³
and spontaneous hematopoietic tumors (113) in rats. As
shown in Table 3, oltipraz has been highly e liver cancer (115), azaserine-induced pancreatic cancer,³
and spontaneous hematopoietic tumors (113) in rats. As
shown in Table 3, oltipraz has been highly effective in ani-
mal screens carried out under the NCI chemopre and spontaneous hematopoietic tumors (113) in rats. A
shown in Table 3, oltipraz has been highly effective in an
mal screens carried out under the NCI chemopreventiv
drug development program; positive results have been see shown in Table 3, oltipraz has been highly effective in ani-
mal screens carried out under the NCI chemopreventive
drug development program; positive results have been seen
in hamster lung and trachea, mouse and rat colon, mal screens carried out under the NCI chemopreventive drug development program; positive results have been seen in hamster lung and trachea, mouse and rat colon, rat mam-
mary, mouse bladder, and mouse skin. The activity a drug development program; positive results have been seen
in hamster lung and trachea, mouse and rat colon, rat mam-
mary, mouse bladder, and mouse skin. The activity against
azoxymethane-induced colon cancer in rats has b mary, mouse bladder, and mouse skin. The activity against
azoxymethane-induced colon cancer in rats has been re-
ported in the literature (117).
Although the mechanism of this activity is not fully un-
derstood, the antica

azoxymethane-induced colon cancer in rats has been re-
ported in the literature (117).
Although the mechanism of this activity is not fully un-
derstood, the anticarcinogenic potential of oltipraz was first
suggested by it ported in the literature (117).
Although the mechanism of this activity is not fully un-
derstood, the anticarcinogenic potential of oltipraz was first
suggested by its chemoprotective, radioprotective, and an-
timutagenic Although the mechanism of this activity is not fully understood, the anticarcinogenic potential of oltipraz was first suggested by its chemoprotective, radioprotective, and antimutagenic properties. Ansher *et al.* (118) derstood, the anticarcinogenic potential of oltipraz was first
suggested by its chemoprotective, radioprotective, and an-
timutagenic properties. Ansher *et al.* (118) demonstrated that
oltipraz protected against hepatotox suggested by its chemoprotective, radioprotective, and antimutagenic properties. Ansher *et al.* (118) demonstrated that oltipraz protected against hepatotoxicity in mice induced by acetaminophen and carbon tetrachloride. timutagenic properties. Ansher *et al.* (118) demonstrated that oltipraz protected against hepatotoxicity in mice induced by acetaminophen and carbon tetrachloride. The agent also in-
hibited AFB₁-induced hepatotoxicity oltipraz protected against hepatotoxicity in mice induced by
acetaminophen and carbon tetrachloride. The agent also in-
hibited AFB₁-induced hepatotoxicity and DNA adduct for-
mation in rat liver (119). Oltipraz administ acetaminophen and carbon tetrachloride. The agent also in-
hibited AFB₁-induced hepatotoxicity and DNA adduct for-
mation in rat liver (119). Oltipraz administered p.o. in-
creases liver GSH levels and induces enzymes in hibited AFB₁-induced hepatotoxicity and DNA adduct for-
mation in rat liver (119). Oltipraz administered p.o. in-
creases liver GSH levels and induces enzymes involved in
electrophile detoxification, *i.e.*, GSH *S*-tran mation in rat liver (119). Oltipraz administered p.o. in-
creases liver GSH levels and induces enzymes involved in
electrophile detoxification, *i.e.*, GSH *S*-transferases, epoxide
hydrolase, and NAD(P)H:quinone oxidoredu creases liver GSH levels and induces enzymes involved in
electrophile detoxification, *i.e.*, GSH S-transferases, epoxide
hydrolase, and NAD(P)H:quinone oxidoreductase (118–
120). GSH is present in high concentrations in m electrophile detoxification, *i.e.*, GSH *S*-transferases, epoxide
hydrolase, and NAD(P)H:quinone oxidoreductase (118–
120). GSH is present in high concentrations in most cells,
where it functions to inactivate electrophil hydrolase, and NAD(P)H:quinone oxidoreductase (118–
120). GSH is present in high concentrations in most cells,
where it functions to inactivate electrophilic carcinogens
and scavenge oxygen-free radicals. It also reacts wi where it functions to inactivate electrophilic carcinogens
and scavenge oxygen-free radicals. It also reacts with hy-
drogen peroxide catalyzed by glutathione peroxidase and
prevents the formation of other more reactive ox and scavenge oxygen-free radicals. It also reacts with hy-
drogen peroxide catalyzed by glutathione peroxidase and
prevents the formation of other more reactive oxygen com-
pounds (121). The chemopreventive and chemoprotec drogen peroxide catalyzed by glutathione peroxidase and
prevents the formation of other more reactive oxygen com-
pounds (121). The chemopreventive and chemoprotective
efficacy of oltipraz in liver has been attributed to t prevents the formation of other more reactive oxygen com-
pounds (121). The chemopreventive and chemoprotective
efficacy of oltipraz in liver has been attributed to these ac-
tivities (115, 118, 122). There also is some ev pounds (121). The chemopreventive and chemoprotective efficacy of oltipraz in liver has been attributed to these activities (115, 118, 122). There also is some evidence that oltipraz may have antiproliferative effects that efficacy of oltipraz in liver has been attributed to these activities (115, 118, 122). There also is some evidence that oltipraz may have antiproliferative effects that may or may not be directly related to modulation of G tivities (115, 118, 122). There also is some evidence that
oltipraz may have antiproliferative effects that may or may
not be directly related to modulation of GSH and the Phase
II metabolic enzymes. For example, in effica oltipraz may have antiproliferative effects that may or may not be directly related to modulation of GSH and the Phase II metabolic enzymes. For example, in efficacy studies in rat colon (123) and mammary cited in Table 3, not be directly related to modulation of GS
II metabolic enzymes. For example, in effic
colon (123) and mammary cited in Table
effective even when it was administered on
with the carcinogen had been completed.
Besides the tabolic enzymes. For example, in efficacy studies in rat

in (123) and mammary cited in Table 3, the agent was

tive even when it was administered only after treatment

the carcinogen had been completed.

Besides the wide colon (123) and mammary cited in Table 3, the agent was
effective even when it was administered only after treatment
with the carcinogen had been completed.
Besides the wide spectrum of its efficacy, oltipraz is an
interes

effective even when it was administered only after treatment
with the carcinogen had been completed.
Besides the wide spectrum of its efficacy, oltipraz is an
interesting candidate for further development as a cancer
chemo with the carcinogen had been completed.

Besides the wide spectrum of its efficacy, oltipraz is an

interesting candidate for further development as a cancer

chemopreventive agent because of its apparent low toxicity.

Ea Besides the wide spectrum of its efficacy, oltipraz is an interesting candidate for further development as a cancer chemopreventive agent because of its apparent low toxicity.
Early studies of acute and subacute toxicity o

administration (124). In chronic (1-year) toxicity studies in

rats and dogs carried out under the NCI drug development administration (124). In chronic (1-year) toxicity studies in
rats and dogs carried out under the NCI drug developmen
program, NOELs were established at 10 and 15 mg/kg body administration (124). In chronic (1-year) toxicity studies in
rats and dogs carried out under the NCI drug development
program, NOELs were established at 10 and 15 mg/kg body
weight, respectively, with minimal toxic effect administration (124). In chronic (1-year) toxicity studies in
rats and dogs carried out under the NCI drug development
program, NOELs were established at 10 and 15 mg/kg body
weight, respectively, with minimal toxic effect administration (124). In chronic (1-year) toxicity studies in
rats and dogs carried out under the NCI drug development
program, NOELs were established at 10 and 15 mg/kg body
weight, respectively, with minimal toxic effect rats and dogs carried out under the NCI drug development
program, NOELs were established at 10 and 15 mg/kg body
weight, respectively, with minimal toxic effects present at 60
mg/kg body weight (the highest dosage tested). program, NOELs were established at 10 and 15 mg/kg body
weight, respectively, with minimal toxic effects present at 60
mg/kg body weight (the highest dosage tested). Observation
of schistosomiasis patients in clinical tria weight, respectively, with minimal toxic effects present at 60 mg/kg body weight (the highest dosage tested). Observation of schistosomiasis patients in clinical trials also indicated that oltipraz is tolerated on p.o. adm mg/kg body weight (the highest dosage tested). Observation
of schistosomiasis patients in clinical trials also indicated
that oltipraz is tolerated on p.o. administration (125, 126).
Despite these encouraging results, much of schistosomiasis patients in clinical trials also indicated
that oltipraz is tolerated on p.o. administration (125, 126).
Despite these encouraging results, much work remains to be
done to determine the appropriate chron that oltipraz is tolerated on p.o. administration (125, 126).
Despite these encouraging results, much work remains to be
done to determine the appropriate chronic clinical dosage
regimen for chemoprevention studies. The ag Despite these encouraging results, much work remains to be
done to determine the appropriate chronic clinical dosage
regimen for chemoprevention studies. The agent has shown
significant toxicity in certain clinical setting regimen for chemoprevention studies. The agent has shown
significant toxicity in certain clinical settings. For example,
acute administration at high doses (up to 2 g) in schistoso-
miasis therapy was discontinued due to d significant toxicity in certain clinical settings. For examplacute administration at high doses (up to 2 g) in schistos miasis therapy was discontinued due to delayed side effects especially phototoxicity (127). In a 6-mon acute administration at high doses (up to 2 g) in schistoso-
miasis therapy was discontinued due to delayed side effects,
especially phototoxicity (127). In a 6-month Phase I clinical
trial at 125 and 250 mg/day, side effe miasis therapy was discontinued due to delayed side effects,
especially phototoxicity (127). In a 6-month Phase I clinical
trial at 125 and 250 mg/day, side effects included photo-
sensitivity, heat intolerance, gastrointe trial at 125 and 250 mg/day, side effects included photo-
sensitivity, heat intolerance, gastrointestinal discomfort,
neurological abnormalities, and an altered taste; the lower
dose was considered to be in excess of the M trial at 125 and 250 mg/day, side effects included photo-
sensitivity, heat intolerance, gastrointestinal discomfort,
neurological abnormalities, and an altered taste; the lower
dose was considered to be in excess of the M

neurological abnormalities, and an altered taste; the lower
dose was considered to be in excess of the MTD (128).
In animal screens cited in Table 3, N-acetyl-*l*-cysteine
had chemopreventive activity in the hamster trache dose was considered to be in excess of the MTD (128).
In animal screens cited in Table 3, N-acetyl-*l*-cyste
had chemopreventive activity in the hamster trachea, rat
lon, rat mammary, and mouse bladder models. Publish
stud In animal screens cited in Table 3, N-acetyl-*l*-cysteine
had chemopreventive activity in the hamster trachea, rat co-
lon, rat mammary, and mouse bladder models. Published
studies indicate that N-acetyl-*l*-cysteine preve had chemopreventive activity in the hamster trachea, rat colon, rat mammary, and mouse bladder models. Publishe studies indicate that N-acetyl-*I*-cysteine prevented urethan induced lung tumors in mice (129) and DMH-induce lon, rat mammary, and mouse bladder models. Published
studies indicate that N-acetyl-*I*-cysteine prevented urethane-
induced lung tumors in mice (129) and DMH-induced colon
tumors in rats (130). Like oltipraz, N-acetyl-*I* studies indicate that N-acetyl-*I*-cysteine prevented urethane-
induced lung tumors in mice (129) and DMH-induced colon
tumors in rats (130). Like oltipraz, N-acetyl-*I*-cysteine stimu-
lates intracellular production of GS induced lung tumors in mice (129) and DMH-induced colon
tumors in rats (130). Like oltipraz, N-acetyl-*l*-cysteine stimu-
lates intracellular production of GSH and activity of GSH
S-transferases; it is readily deacetylated tumors in rats (130). Like oltipraz, N-acetyl-*l*-cysteine stimu-
lates intracellular production of GSH and activity of GSH
S-transferases; it is readily deacetylated to form cysteine in
the body, which enhances GSH synthe lates intracellular production of GSH and activity of GSH
S-transferases; it is readily deacetylated to form cysteine in
the body, which enhances GSH synthesis (131). These ac-
tivities may be the basis of its chemoprevent S-transferases; it is readily deacetylated to form cysteine in
the body, which enhances GSH synthesis (131). These ac-
tivities may be the basis of its chemopreventive potential.
Toxicity is considered low and the drug has the body, which enhances GSH synthesis (131). These activities may be the basis of its chemopreventive potential.
Toxicity is considered low and the drug has been marketed
for years as a mucolytic agent (Mucomyst) and for Toxicity is considered low and the drug has been marketed
for years as a mucolytic agent (Mucomyst) and for treatment
of acetaminophen poisoning. Chronic toxicity studies in rats
and dogs at dosages up to 1 g/kg body weigh for years as a mucolytic agent (Mucomyst) and for treatment
of acetaminophen poisoning. Chronic toxicity studies in rats
and dogs at dosages up to 1 g/kg body weight/day and 300
mg/kg body weight/day, respectively, did not of acetaminophen poisoning. Chronic toxicity studies in rats
and dogs at dosages up to 1 g/kg body weight/day and 300
mg/kg body weight/day, respectively, did not show any sig-
nificant toxicities (132). Phase I cancer pr and dogs at dosages up to 1 g/kg body weight/day ar
mg/kg body weight/day, respectively, did not show a
nificant toxicities (132). Phase I cancer prevention tri
currently planned for 1.6 g/m²/day, possibly escalat
6.4 g g body weight/day, respectively, did not show any sig-
ant toxicities (132). Phase I cancer prevention trials are
ently planned for 1.6 g/m²/day, possibly escalating to
 $\frac{1}{n^2}$ /day (or 42 to 169 mg/kg body weight/da mificant toxicities (132). Phase I cancer prevention trials are
currently planned for 1.6 g/m^2 /day, possibly escalating to
6.4 g/m^2 /day (or 42 to 169 mg/kg body weight/day).
18 β -Glycyrrhetinic acid is found in lico

currently planned for 1.6 g/m^2 /day, possibly escalating to 6.4 g/m^2 /day (or 42 to 169 mg/kg body weight/day).
18 β -Glycyrrhetinic acid is found in licorice root and has antiinflammatory effects by mechanisms that ap 6.4 g/m^2 /day (or 42 to 169 mg/kg body weight/day).
18 β -Glycyrrhetinic acid is found in licorice root and
has antiinflammatory effects by mechanisms that appear to
differ from the NSAIDs. It has been used at concentra 18 β -Glycyrrhetinic acid is found in licorice root and
has antiinflammatory effects by mechanisms that appear to
differ from the NSAIDs. It has been used at concentrations
up to 2% in ointments for the treatment of vari has antiinflammatory effects by mechanisms that appear to differ from the NSAIDs. It has been used at concentrations up to 2% in ointments for the treatment of various skin diseases (133). Carbenoxolone is the succinic aci differ from the NSAIDs. It has been used at concentrations
up to 2% in ointments for the treatment of various skin dis-
eases (133). Carbenoxolone is the succinic acid ester of 18 β -
glycyrrhetinic acid and is also a pot eases (133). Carbenoxolone is the succinic acid ester of 18 β -glycyrrhetinic acid and is also a potent antiinflammatory; it is used in the treatment of peptic ulcers. It appears to act locally on the stomach, possibly by tion of protective mucus (133). Five intertaince acid and is also a potent antiinflammatory; it
ed in the treatment of peptic ulcers. It appears to act
ly on the stomach, possibly by stimulating the produc-
of protective mucus (133).
Both 18β-glycyrrhet is used in the treatment of peptic ulcers. It appears to act locally on the stomach, possibly by stimulating the production of protective mucus (133).
Both 18 β -glycyrrhetinic acid and its saponin parent, glycyrrhizin, h

locally on the stomach, possibly by stimulating the production of protective mucus (133).
Both 18β-glycyrrhetinic acid and its saponin parent
glycyrrhizin, have shown chemopreventive activity in vari
ous animal models. Gly ion of protective mucus (133).

Both 18 β -glycyrrhetinic acid and its saponin parent,

glycyrrhizin, have shown chemopreventive activity in vari-

ous animal models. Glycyrrhizin inhibited the development

of liver tumo Both 18 β -glycyrrhetinic acid and its saponin parent, glycyrrhizin, have shown chemopreventive activity in various animal models. Glycyrrhizin inhibited the development of liver tumors in mice and rats (reviewed by Nish glycyrrhizin, have shown chemopreventive activity in vari-
ous animal models. Glycyrrhizin inhibited the development
of liver tumors in mice and rats (reviewed by Nishino in Ref.
134) and 18β-glycyrrhetinic acid inhibited ous animal models. Glycyrrhizin inhibited the development
of liver tumors in mice and rats (reviewed by Nishino in Ref.
134) and 18β-glycyrrhetinic acid inhibited tumor promotion
in mouse skin (134, 135). In studies cite of liver tumors in mice and rats (reviewed by Nishino in Ref. 134) and 18β -glycyrrhetinic acid inhibited tumor promotion in mouse skin (134, 135). In studies cited in Table 3, 18 β -glycyrrhetinic acid exhibited chemo 134) and 18 β -glycyrrhetinic acid inhibited tumor promotion
in mouse skin (134, 135). In studies cited in Table 3, 18 β -
glycyrrhetinic acid exhibited chemopreventive efficacy in
the mouse colon, mouse skin, and rat m in mouse skin (134, 135). In studies cited in Table 3, 18 β -glycyrrhetinic acid exhibited chemopreventive efficacy in the mouse colon, mouse skin, and rat mammary models. Carbenoxolone was efficacious in the rat mammary glycyrrhetinic acid exhibited chemopreventive efficacy in
the mouse colon, mouse skin, and rat mammary models.
Carbenoxolone was efficacious in the rat mammary model.
The mechanism of chemopreventive activity of these agen the mouse colon, mouse skin, and rat mammary models.
Carbenoxolone was efficacious in the rat mammary model.
The mechanism of chemopreventive activity of these agents
is not well understood, but is believed to be related t Carbenoxolone was efficacious in the rat mammary model.
The mechanism of chemopreventive activity of these agents
is not well understood, but is believed to be related to their
antiinflammatory potential, as evidenced by The mechanism of chemopreventive activity of these agents
is not well understood, but is believed to be related to their
antiinflammatory potential, as evidenced by the inhibition
by 18 β -glycyrrhetinic acid of the infla is not well understood, but is believed to be related to their
antiinflammatory potential, as evidenced by the inhibition
by 18β-glycyrrhetinic acid of the inflammation associated
with tumor promotion in mouse skin (134). by 18*β*-glycyrrhetinic acid of the inflammation associated with tumor promotion in mouse skin (134). 18*β*-Glycyrrhetinic acid also inhibits numerous other biological activities associated with tumor promotion, especially with tumor promotion in
Clycyrrhetinic acid also inhi
activities associated with tun
mediated by signal transdue
viewed by Nishino (134)].
Although Phase I clinica wrrhetinic acid also inhibits numerous other biological
ities associated with tumor promotion, especially those
iated by signal transduction via protein kinase C [re-
ed by Nishino (134)].
Although Phase I clinical trials activities associated with tumor promotion, especially those
mediated by signal transduction via protein kinase C [re-
viewed by Nishino (134)].
Although Phase I clinical trials with 18 β -glycyrrhetinic
acid are still un

ⁱ B. D. Roebuck, unpublished results (116).

in the planning stages, previous studies with carbenoxolone indicate that these two agents will be well tolerated in a in the planning stages, previous studies with carbenoxolone

indicate that these two agents will be well tolerated in a ph

chemoprevention dosage regimen. As an antiulcer and an-

inflammatory agent, carbenoxolone has und in the planning stages, previous studies with carbenoxolor indicate that these two agents will be well tolerated in chemoprevention dosage regimen. As an antiulcer and a tiinflammatory agent, carbenoxolone has undergone ex in the planning stages, previous studies with carbenoxolone indicate that these two agents will be well tolerated in a chemoprevention dosage regimen. As an antiulcer and antiinflammatory agent, carbenoxolone has undergone indicate that these two agents will be well tolerated in a chemoprevention dosage regimen. As an antiulcer and antiinflammatory agent, carbenoxolone has undergone extensive clinical testing at doses up to 300 mg/day (136). chemoprevention dosage regimen. As an antiulcer and antiinflammatory agent, carbenoxolone has undergone extensive clinical testing at doses up to 300 mg/day (136). At doses above 100 mg/day, severe side effects have been o tiinflammatory agent, carbenoxolone has undergone extensive clinical testing at doses up to 300 mg/day (136). At doses above 100 mg/day, severe side effects have been observed, consisting mainly of diastolic hypertension, sive clinical testing at doses up to 300 mg/day (136). At doses
above 100 mg/day, severe side effects have been observed,
consisting mainly of diastolic hypertension, edema, and hy-
pokalemia. Although these side effects w above 100 mg/day, severe side effects have been observed, consisting mainly of diastolic hypertension, edema, and hypokalemia. Although these side effects were still present at 100 mg/day, they were seen in only a few perc consisting mainly of diastolic hypertension, edema, and hypokalemia. Although these side effects were still present at 100 mg/day, they were seen in only a few percent of patients. Therefore, it appears that 100 mg/day wou pokalemia. Although these side effects were still present 100 mg/day, they were seen in only a few percent of patier
Therefore, it appears that 100 mg/day would be the MTD
carbenoxolone in the context of cancer chemopreven 100 mg/day, they were seen in only a few percent of patients.
Therefore, it appears that 100 mg/day would be the MTD for
carbenoxolone in the context of cancer chemoprevention.
This dosage is still much higher than the est Therefore, it appears that 100 mg/day would be the MTD for carbenoxolone in the context of cancer chemoprevention.
This dosage is still much higher than the estimated chemo-
preventive dose in humans. The dose for humans e carbenoxolone in the context of cancer chemoprevention.
This dosage is still much higher than the estimated chemo-
preventive dose in humans. The dose for humans equivalent
to the chemopreventive dose in the rat mammary mo preventive dose in humans. The dose for humans equivalent
to the chemopreventive dose in the rat mammary model,
calculated on the basis of relative surface area, is only 10
mg/day. For 18β-glycyrrhetinic acid, our chronic to the chemopreventive dose in the rat mammary model,
calculated on the basis of relative surface area, is only 10
mg/day. For 18β-glycyrrhetinic acid, our chronic toxicity (
studies in rats and dogs established NOELs in mg/day. For 18 β -glycyrrhetinic acid, our chronic toxicity
studies in rats and dogs established NOELs in the rat at 1000
mg/kg body weight/day and in the dog at 300 mg/kg body
weight/day. Phase I clinical trials are eva studies in rats and dogs established NOELs in the rat at 1000 mg/kg body weight/day and in the dog at 300 mg/kg body
weight/day. Phase I clinical trials are evaluating doses up to
500 mg/m²/day (approximately 13 mg/kg body weight/day).
S-Allyl-l-cysteine is a water soluble organos

weight/day. Phase I clinical trials are evaluating doses up to 500 mg/m²/day (approximately 13 mg/kg body weight/day).

S-Allyl-*I*-cysteine is a water soluble organosulfur com-

pound found in garlic. For many years, th 500 mg/m²/day (approximately 13 mg/kg body weight/day)
 S-Allyl-*l*-cysteine is a water soluble organosulfur com

pound found in garlic. For many years, there has been a hig

level of interest in the potential chemopr *S-Allyl-l-cysteine is a water soluble organosulfur conpound found in garlic. For many years, there has been a highevel of interest in the potential chemopreventive effects garlic, onion, and their components. Studies of t* pound found in garlic. For many years, there has been a high
level of interest in the potential chemopreventive effects of
garlic, onion, and their components. Studies of these com-
pounds have been reviewed recently (137) level of interest in the potential chemopreventive effects of garlic, onion, and their components. Studies of these compounds have been reviewed recently (137). Epidemiological studies have shown inverse correlations betwe garlic, onion, and their components. Studies of these epounds have been reviewed recently (137). Epidemiolo studies have shown inverse correlations between garancer incidence and consumption of vegetables in the *lium* gen pounds have been reviewed recently (137). Epidemiological studies have shown inverse correlations between gastric cancer incidence and consumption of vegetables in the *Allium* genus (138, 139). Garlic oil has shown chemop studies have shown inverse correlations between gastric cancer incidence and consumption of vegetables in the *Allium* genus (138, 139). Garlic oil has shown chemopreventive activity in mouse skin (140) and cervix (141), a cancer incidence and consumption of vegetables in the *Allium* genus (138, 139). Garlic oil has shown chemopreventive activity in mouse skin (140) and cervix (141), and several of its volatile, lipophilic components (parti *Iium* genus (138, 139). Garlic oil has shown chemopreventive activity in mouse skin (140) and cervix (141), and several of its volatile, lipophilic components (particularly, diallyl sulfide) have shown chemopreventive ac tive activity in mouse skin (140) and cervix (141), and several
of its volatile, lipophilic components (particularly, dially
sulfide) have shown chemopreventive activity in mouse co-
lon and stomach (142–144). Diallyl sulf of its volatile, lipophilic components (particularly, dial
sulfide) have shown chemopreventive activity in mouse c
lon and stomach (142–144). Diallyl sulfide also inhibit
skin cancer induced in mice by DMBA (145), esophage sulfide) have shown chemopreventive activity in mouse co-
lon and stomach (142–144). Diallyl sulfide also inhibited
skin cancer induced in mice by DMBA (145), esophageal
cancer induced in rats by N-nitrosobenzylmethylamine Ion and stomach (142–144). Diallyl sulfide also inhibited
skin cancer induced in mice by DMBA (145), esophageal
cancer induced in rats by N-nitrosobenzylmethylamine
(146), glandular stomach cancer induced in rats by
N-meth skin cancer induced in mice by DMBA (145), esophageal
cancer induced in rats by *N*-nitrosobenzylmethylamine
(146), glandular stomach cancer induced in rats by
N-methyl-*N'*-nitrosoguanidine (147). In an NCI-sponsored
st cancer induced in rats by *N*-nitrosobenzylmethylamine (146), glandular stomach cancer induced in rats by *N*-methyl-*N'*-nitrosoguanidine (147). In an NCI-sponsored study in hamsters, diallyl disulfide strongly inhibited shown). N -methyl- N' -nitrosoguanidine (147). In an NCI-sponsored study in hamsters, diallyl disulfide strongly inhibited the induction of tracheal tumors in hamsters by MNU (data not shown). The volatility and pungency of the

study in hamsters, diallyl disulfide strongly inhibited the in-
duction of tracheal tumors in hamsters by MNU (data not
shown).
The volatility and pungency of the lipophilic garlic
compounds make them difficult to test and duction of tracheal tumors in hamsters by MNU (data not shown).
The volatility and pungency of the lipophilic garlic
compounds make them difficult to test and unpalatable.
These disadvantages have led recently to interest shown).
The volatility and pungency of the lipophilic garlicompounds make them difficult to test and unpalatable
These disadvantages have led recently to interest in the wate
soluble, less aromatic components such as S-all The volatility and pungency of the lipophilic garl
compounds make them difficult to test and unpalatabl
These disadvantages have led recently to interest in the wat
soluble, less aromatic components such as S-allyl-*I*-cys compounds make them difficult to test and unpalat
These disadvantages have led recently to interest in the soluble, less aromatic components such as *S*-allyl-*I*-cyst
On p.o. administration the compound inhibited *C*
indu e disadvantages have led recently to interest in the wate
ble, less aromatic components such as S-allyl-*l*-cysteine
p.o. administration the compound inhibited DMH
ced colon tumors in female C57BL mice (148).
The mechanism soluble, less aromatic components such as S-allyl-*I*-cysteine.
On p.o. administration the compound inhibited DMH-
induced colon tumors in female C57BL mice (148).
The mechanism of action of the garlic sulfur com-
pounds i

On p.o. administration the compound inhibited DMH-
induced colon tumors in female C57BL mice (148).
The mechanism of action of the garlic sulfur com-
pounds is not well understood but appears to be related to
electrophile induced colon tumors in female C57BL mice (148).
The mechanism of action of the garlic sulfur com
pounds is not well understood but appears to be related to
electrophile detoxification. Like oltipraz and N-acetyl-l
cystein The mechanism of action of the garlic sulfur com-
pounds is not well understood but appears to be related to
electrophile detoxification. Like oltipraz and N-acetyl-*I-*
cysteine, S-allyl-*I*-cysteine (148) and other garli pounds is not well understood but appears to be related to
electrophile detoxification. Like oltipraz and N-acetyl-L-
cysteine, S-allyl-L-cysteine (148) and other garlic sulfur com-
pounds (143) enhance the activity of GSH electrophile detoxification. Like oltipraz and *N*-acetyl-*I*-cysteine, S-allyl-*I*-cysteine (148) and other garlic sulfur compounds (143) enhance the activity of GSH *S*-transferases.
Also, diallyl sulfide and, probably, cysteine, S-allyl-*I*-cysteine (148) and other garlic sulfur com-
pounds (143) enhance the activity of GSH S-transferases.
Also, diallyl sulfide and, probably, other garlic sulfides in-
hibit cytochrome P450IIE1 which is i pounds (143) enhance the activity of GSH *S*-transferases. h
Also, diallyl sulfide and, probably, other garlic sulfides in-
hibit cytochrome P450IIE1 which is involved in metabolic U
activation of carcinogens such as DMH a hibit cytochrome P45011E1 which is involved in metabolic
activation of carcinogens such as DMH and N-methyl-N'-
initrosoguanidine (137, 149). Preclinical acute and sub-
chronic (90-day) toxicity evaluations of S-allyl-*I*activation of carcinogens such as DMH and N-methyl-N'-
nitrosoguanidine (137, 149). Preclinical acute and sub-
chronic (90-day) toxicity evaluations of S-allyl-*l*-cysteine in
rats and dogs are currently underway. Human to low. chronic (90-day) toxicity evaluations of S-allyl-/-cysteine in reasonably could be administered p.o. An acute toxicity
rats and dogs are currently underway. Human toxicity of the agent has not been characterized but is ant rats and dogs are currently underway. Human toxicity of the

agent has not been characterized but is anticipated to be very
low.
Several arylalkyl isothiocyanates have been shown to
inhibit mammary, forestomach, and lung tumors induced by
PAHs and nitrosamines in rats and mice (150– low.
Several arylalkyl isothiocyanates have been shown to
inhibit mammary, forestomach, and lung tumors induced by
PAHs and nitrosamines in rats and mice (150–154). Tobacco
smoking is a significant risk for several major h Several arylalkyl isothiocyanates have been shown to
inhibit mammary, forestomach, and lung tumors induced by
PAHs and nitrosamines in rats and mice (150–154). Tobacco
smoking is a significant risk for several major human PAHs and nitrosamines in rats and mice (150–154). Tobacco smoking is a significant risk for several major human cancers including those in the lung, other sites in the upper aerodigestive tract, and bladder (*e.g.*, Ref.

are therefore of high interest. Arylalkyl isothiocyanates, and phenhexyl isothiocyanate in particular, may be such agents are therefore of high interest. Arylalkyl isothiocyanates, and
phenhexyl isothiocyanate in particular, may be such agents
in the lung. A series of arylalkyl isothiocyanates with alkyl are therefore of high interest. Arylalkyl isothiocyanates, and
phenhexyl isothiocyanate in particular, may be such agents
in the lung. A series of arylalkyl isothiocyanates with alkyl
chains ranging from two (phenethyl iso are therefore of high interest. Arylalkyl isothiocyanates, and
phenhexyl isothiocyanate in particular, may be such agents
in the lung. A series of arylalkyl isothiocyanates with alkyl
chains ranging from two (phenethyl iso are therefore of high interest. Arylalkyl isothiocyanates, and
phenhexyl isothiocyanate in particular, may be such agents
in the lung. A series of arylalkyl isothiocyanates with alkyl
chains ranging from two (phenethyl iso phenhexyl isothiocyanate in particular, may be such agents
in the lung. A series of arylalkyl isothiocyanates with alkyl
chains ranging from two (phenethyl isothiocyanate) to six
(phenhexyl isothiocyanate) carbons inhibite in the lung. A series of arylalkyl isothiocyanates with alkyl
chains ranging from two (phenethyl isothiocyanate) to six
(phenhexyl isothiocyanate) carbons inhibited lung tumors
induced in mice by the tobacco-specific carci chains ranging from two (phenethyl isothiocyanate) to six
(phenhexyl isothiocyanate) carbons inhibited lung tumors
induced in mice by the tobacco-specific carcinogen NNK
(152, 153). In these studies, the length of the alky (phenhexyl isothiocyanate) carbons inhibited lung tu induced in mice by the tobacco-specific carcinogen (152, 153). In these studies, the length of the alkyl chathe isothiocyanates proved to be an important determ of the p induced in mice by the tobacco-specific carcinogen NNK
(152, 153). In these studies, the length of the alkyl chain in
the isothiocyanates proved to be an important determinant
of the potency of chemopreventive activity. Ch (152, 153). In these studies, the length of the alkyl chain in
the isothiocyanates proved to be an important determinant
of the potency of chemopreventive activity. Chemopreven-
tive efficacy increased as the alkyl chain w the isothiocyanates proved to be an important determinant
of the potency of chemopreventive activity. Chemopreven-
tive efficacy increased as the alkyl chain was elongated.
Thus, phenhexyl isothiocyanate, the most potent o of the potency of chemopreventive activity. Chemopreventive efficacy increased as the alkyl chain was elongated.
Thus, phenhexyl isothiocyanate, the most potent of the agents tested, was 50–100 times more potent than phene tive efficacy increased as the alkyl chain was elongated.
Thus, phenhexyl isothiocyanate, the most potent of the
agents tested, was 50–100 times more potent than phenethyl
isothiocyanate (154, 156). Although the reasons fo Thus, phenhexyl isothiocyanate, the most potent of the agents tested, was 50–100 times more potent than phenethyl isothiocyanate (154, 156). Although the reasons for this structure-activity relationship have not been eluci (157) isothiocyanate (154, 156). Although the reasons for this structure-activity relationship have not been elucidated, increased lipophilicity and stability have been suggested (157).
The available evidence indicates that a pr structure-activity relationship have not been elucidated, in-
creased lipophilicity and stability have been suggested
(157).
The available evidence indicates that a primary mecha-
nism of the inhibition of NNK carcinogenes

creased lipophilicity and stability have been suggest
(157). The available evidence indicates that a primary mech
nism of the inhibition of NNK carcinogenesis by arylalk
isothiocyanates is prevention of NNK-DNA adduct form (157).
The available evidence indicates that a primary mecha-
nism of the inhibition of NNK carcinogenesis by arylalkyl
isothiocyanates is prevention of NNK-DNA adduct forma-
tion (157). Preliminary results of toxicology t The available evidence indicates that a primary mechanism of the inhibition of NNK carcinogenesis by arylalkyl isothiocyanates is prevention of NNK-DNA adduct formation (157). Preliminary results of toxicology testing in r isothiocyanates is prevention of NNK-DNA adduct formation (157). Preliminary results of toxicology testing in rats indicate low toxicity. Anticipated toxicities include minor weight loss and fatty changes in the liver, as tion (157). Preliminary results of toxicology testing in rats
indicate low toxicity. Anticipated toxicities include minor
weight loss and fatty changes in the liver, as seen in F344 rats
fed phenethyl isothiocyanate at dos rate low toxicity. Anticipated toxicities include minor
ht loss and fatty changes in the liver, as seen in F344 rats
henethyl isothiocyanate at doses of 3 or 6 μ mol/g (ap-
imately 490 or 980 mg/kg) diet for 13 weeks (15 weight loss and fatty changes in the liver, as seen in F344 rats
fed phenethyl isothiocyanate at doses of 3 or 6 µmol/g (ap-
proximately 490 or 980 mg/kg) diet for 13 weeks (153, 158).
Curcumin is the major yellow pigment

fed phenethyl isothiocyanate at doses of 3 or 6 µmol/g (approximately 490 or 980 mg/kg) diet for 13 weeks (153, 158).
Curcumin is the major yellow pigment in turmeric and
curry and is obtained from the rhizome of the plant proximately 490 or 980 mg/kg) diet for 13 weeks (153, 158).
Curcumin is the major yellow pigment in turmeric and
curry and is obtained from the rhizome of the plant *Curcuma*
longa. It is of high interest both because of Curcumin is the major yellow pigment in turmeric and
curry and is obtained from the rhizome of the plant *Curcuma*
longa. It is of high interest both because of its potential for
chemopreventive activity and its apparent curry and is obtained from the rhizome of the plant *Curcuma*
longa. It is of high interest both because of its potential for
chemopreventive activity and its apparent low toxicity; *i.e.*,
it is already a common dietary *longa*. It is of high interest both because of its potential for chemopreventive activity and its apparent low toxicity; *i.e.*, it is already a common dietary component. In animal cancer screens cited in Table 3, curcumi chemopreventive activity and its apparent low toxicity; *i.e.,* it is already a common dietary component. In animal cancer screens cited in Table 3, curcumin had chemopreventive activity in mouse colon and MNU rat mammary it is already a common dietary component. In animal cancer
screens cited in Table 3, curcumin had chemopreventive
activity in mouse colon and MNU rat mammary models. In
other studies, the agent had tumor inhibitory activit screens cited in Table 3, curcumin had chem
activity in mouse colon and MNU rat mammar
other studies, the agent had tumor inhibitory as
two-stage DMBA/TPA mouse skin model (159-
the induction of skin tumors by B(a)P (162). ity in mouse colon and MNU rat mammary models. In
r studies, the agent had tumor inhibitory activity in the
stage DMBA/TPA mouse skin model (159–161) and in
nduction of skin tumors by B(a)P (162).
Curcumin may have chemopr other studies, the agent had tumor inhibitory activity in the
two-stage DMBA/TPA mouse skin model (159–161) and in
the induction of skin tumors by B(a)P (162).
Curcumin may have chemopreventive activity via mul-
tiple mech

two-stage DMBA/TPA mouse skin model $(159-161)$ and in
the induction of skin tumors by $B(a)P(162)$.
Curcumin may have chemopreventive activity via mul-
tiple mechanisms. It is a potent antiinflammatory agent
 $(162-165)$. the induction of skin tumors by B(a)P (162).

Curcumin may have chemopreventive activity via mul-

tiple mechanisms. It is a potent antiinflammatory agent

(162–165). It inhibited arachidonic acid metabolism in

CD-1 mouse Curcumin may have chemopreventive activity via mul-
tiple mechanisms. It is a potent antiinflammatory agent
(162–165). It inhibited arachidonic acid metabolism in
CD-1 mouse skin by blocking both the lipoxygenase and
cycl tiple mechanisms. It is a potent antiinflammatory agent (162–165). It inhibited arachidonic acid metabolism in CD-1 mouse skin by blocking both the lipoxygenase and cyclooxygenase pathways (162, 166). There is also eviden (162–165). It inhibited arachidonic acid metabolism in CD-1 mouse skin by blocking both the lipoxygenase and cyclooxygenase pathways (162, 166). There is also evidence that it inhibits phospholipase A_2 (162). Curcumin CD-1 mouse skin by blocking both the lipoxygenase an cyclooxygenase pathways (162, 166). There is also evidence that it inhibits phospholipase A_2 (162). Curcumin exhibit strong antioxidant activity (167, 168), being an cyclooxygenase pathways (162, 166). There is also evidence
that it inhibits phospholipase A_2 (162). Curcumin exhibits
strong antioxidant activity (167, 168), being an effective
scavenger of superoxide radicals (169). O that it inhibits phospholipase A_2 (162). Curcumin exhibitions antioxidant activity (167, 168), being an effect scavenger of superoxide radicals (169). On topical applation, curcumin inhibited TPA-induced DNA synthesis strong antioxidant activity (167, 168), being an effective
scavenger of superoxide radicals (169). On topical appli-
cation, curcumin inhibited TPA-induced DNA synthesis in
mouse skin as measured by tritiated thymidine inc scavenger of superoxide radicals (169). On topical application, curcumin inhibited TPA-induced DNA synthesis in
mouse skin as measured by tritiated thymidine incorpora-
tion, demonstrating the inhibitory effect of curcumin cation, curcumin inhibited TPA-induced DNA synthesis in
mouse skin as measured by tritiated thymidine incorpora-
tion, demonstrating the inhibitory effect of curcumin on pro-
liferation (160). It also may inhibit the metab mouse skin as measured by tritiated thymidine incorporation, demonstrating the inhibitory effect of curcumin on pro-
liferation (160). It also may inhibit the metabolic activation
and DNA binding of PAH carcinogens (162, 1 tion, demonstrating the inhibitory effect of curcumin on pro-
liferation (160). It also may inhibit the metabolic activation
and DNA binding of PAH carcinogens (162, 170, 171). As
noted above, curcumin is not expected to e liferation (160). It also may inhibit the metabolic activation DNA binding of PAH carcinogens (162, 170, 171). *A* noted above, curcumin is not expected to exhibit much to icity in humans. Toxic effects of chronic exposure and DNA binding of PAH carcinogens (162, 170, 171). As
noted above, curcumin is not expected to exhibit much tox-
icity in humans. Toxic effects of chronic exposure in humans
have not been characterized apart from respirat noted above, curcumin is not expected to exhibit much toxicity in humans. Toxic effects of chronic exposure in humans
have not been characterized apart from respiratory symptoms and allergic dermatitis in spice factory wor icity in humans. Toxic effects of chronic exposure in humans
have not been characterized apart from respiratory symp-
toms and allergic dermatitis in spice factory workers (172).
Ulcerogenic effects have been reported in r toms and allergic dermatitis in spice factory workers (172).
Ulcerogenic effects have been reported in rats (173). In our
acute toxicity study in rats, curcumin was not toxic; *i.e.*, 50%
lethal dose >3.5 *g*/kg body weigh Ulcerogenic effects have been reported in rats (173). In our acute toxicity study in rats, curcumin was not toxic; *i.e.*, 50% lethal dose >3.5 *g/*kg body weight, the highest dose that reasonably could be administered p.o acute toxicity study in rats, curcumin was nethal dose >3.5 g/kg body weight, the reasonably could be administered p.o. by study in dogs and subchronic (90-day) to in rats and dogs are currently underway. Ellagic acid repr I dose >3.5 g/kg body weight, the highest dose tonably could be administered p.o. An acute toxic in dogs and subchronic (90-day) toxicity evaluation is and dogs are currently underway.
Ellagic acid represents the naturally reasonably could be administered p.o. An acute toxicity
study in dogs and subchronic (90-day) toxicity evaluations
in rats and dogs are currently underway.
Ellagic acid represents the naturally occurring polyphe-
nols whic

study in dogs and subchronic (90-day) toxicity evaluations
in rats and dogs are currently underway.
Ellagic acid represents the naturally occurring polyphe-
nols which have recently received much attention as po-
tential c in rats and dogs are currently underway.

Ellagic acid represents the naturally occurring polyphe-

nols which have recently received much attention as po-

tential chemopreventives (*e.g.*, Refs. 174–181). Besides el-

l nols which have recently received much attention as pential chemopreventives (*e.g.*, Refs. 174–181). Besides elagic acid, this class of agents includes the green tecatechins and various flavonoids. Ellagic acid itself is tential chemopreventives (e.g., Refs. 174–181). Besides el-
lagic acid, this class of agents includes the green tea
catechins and various flavonoids. Ellagic acid itself is found
in a number of fruits and vegetables, incl lagic acid, this class of agents includes the green tea catechins and various flavonoids. Ellagic acid itself is found in a number of fruits and vegetables, including grapes, strawberries, raspberries, and nuts (182) . C

NEVIEW. CREMOPLEVERING DTUG DEVEROPMENT
inhibition of the mutagenicity of PAHs. In animal studies it
has shown chemopreventive activity against tumors induced inhibition of the mutagenicity of PAHs. In animal studies it
has shown chemopreventive activity against tumors induced
by PAHs in mouse skin on topical administration (184–188) inhibition of the mutagenicity of PAHs. In animal studies it
has shown chemopreventive activity against tumors induced
by PAHs in mouse skin on topical administration (184–188)
and in mouse lung on i.p. administration (184 inhibition of the mutagenicity of PAHs. In animal studies it
has shown chemopreventive activity against tumors induced
by PAHs in mouse skin on topical administration (184–188)
and in mouse lung on i.p. administration (184 inhibition of the mutagenicity of PAHs. In animal studies it
has shown chemopreventive activity against tumors induced
by PAHs in mouse skin on topical administration (184–188)
and in mouse lung on i.p. administration (184 has shown chemopreventive activity against tumors induced
by PAHs in mouse skin on topical administration (184–188)
and in mouse lung on i.p. administration (184, 187, 188). It
also inhibited nitrosamine-induced esophageal and in mouse lung on i.p. administration (184, 187, 188). It also inhibited nitrosamine-induced esophageal papillomas on p.o. administration (189). In animal screens cited in Table 3, ellagic acid reduced tumor multiplicit inhibited nitrosamine-induced esophageal papillomas

.o. administration (189). In animal screens cited in Table

lagic acid reduced tumor multiplicity in rat colon and

inoma incidence in mouse bladder when fed in the diet on p.o. administration (189). In animal screens cited in Table 3, ellagic acid reduced tumor multiplicity in rat colon and carcinoma incidence in mouse bladder when fed in the diet.
The chemopreventive activity of ellagic

3, ellagic acid reduced tumor multiplicity in rat colon and carcinoma incidence in mouse bladder when fed in the diet.
The chemopreventive activity of ellagic acid may be related generally to its antioxidant potential, but carcinoma incidence in mouse bladder when fed in the diet.
The chemopreventive activity of ellagic acid may be
related generally to its antioxidant potential, but it also ap-
pears to be related specifically to its ability The chemopreventive activity of ellagic acid may be related generally to its antioxidant potential, but it also appears to be related specifically to its ability to prevent metabolic activation of carcinogens and binding o related generally to its antioxidant potential, but it also appears to be related specifically to its ability to prevent metabolic activation of carcinogens and binding of the activated carcinogens to DNA. For PAHs, its ch pears to be related specifically to its ability to prevent meta-
bolic activation of carcinogens and binding of the activated form carcinogens to DNA. For PAHs, its chemopreventive activity
has been attributed to inhibitio carcinogens to DNA. For PAHs, its chemopreventive activity
has been attributed to inhibition of mixed function oxidases
involved in activating the carcinogens and to binding to the
activated form of the carcinogens (190). has been attributed to inhibition of mixed function oxidases
involved in activating the carcinogens and to binding to the
activated form of the carcinogens (190). For nitrosamine car-
cinogens, its activity has been attrib involved in activating the carcinogens and to binding to the activated form of the carcinogens (190). For nitrosamine car cinogens, its activity has been attributed to site-specific bind ing to DNA, thereby preventing reac activated form of the carcinogens (190). For nitrosamine car-

cinogens, its activity has been attributed to site-specific bind-

ing to DNA, thereby preventing reaction of the carcinogens

with DNA (191). As is likely the colon may be limited by its poor absorption on p.o. admin-
istration (190, 192). Uses in cancer prevention might require ing to DNA, thereby preventing reaction of the carcinogens
with DNA (191). As is likely the case for all polyphenols,
chemopreventive activity of ellagic acid at sites other than
colon may be limited by its poor absorption with DNA (191). As is likely the case for all polyphenols
chemopreventive activity of ellagic acid at sites other thar
colon may be limited by its poor absorption on p.o. admin
istration (190, 192). Uses in cancer preventi chemopreventive activity of ellagic acid at sites other than
colon may be limited by its poor absorption on p.o. admin-
istration (190, 192). Uses in cancer prevention might require
formulations facilitating absorption (19 colon may be limited by its poor absorption on p.o. administration (190, 192). Uses in cancer prevention might require formulations facilitating absorption (193). Oral toxicity studies have not been completed; however, in istration (190, 192). Uses in cancer prevention might require
formulations facilitating absorption (193). Oral toxicity stud-
ies have not been completed; however, in chemoprevention
studies cited in Table 3, no significa formulations facilitating absorption (193). Oral toxicity studies have not been completed; however, in chemopreventio studies cited in Table 3, no significant toxicity was seen a dose levels up to 6 g/kg diet/day. Ellagic ies have not been completed; however, in chemoprevention
studies cited in Table 3, no significant toxicity was seen at
dose levels up to 6 g/kg diet/day. Ellagic acid is known to be
pharmacologically active by other routes studies cited in Table 3, no significant toxicity was seen at
dose levels up to 6 g/kg diet/day. Ellagic acid is known to be
pharmacologically active by other routes of administration.
For example, at low i.v. dosages (0.2 dose levels up to 6 g/kg diet/day. Elpharmacologically active by other
For example, at low i.v. dosages ((to human cancer patients, ellagic a
blood coagulation system (194).
Fumaric acid has good poter macologically active by other routes of administraties example, at low i.v. dosages (0.22 mg/kg body weight man cancer patients, ellagic acid activated the intrind coagulation system (194).
Fumaric acid has good potential For example, at low i.v. dosages (0.22 mg/kg body weight) to human cancer patients, ellagic acid activated the intrinsic blood coagulation system (194).
Fumaric acid has good potential for further development because of it

to human cancer patients, ellagic acid activated the intrinsi
blood coagulation system (194).
Fumaric acid has good potential for further develop
ment because of its lack of toxicity, as well as its cheme
preventive activi blood coagulation system (194).
Fumaric acid has good potential for further develop-
ment because of its lack of toxicity, as well as its chemo-
preventive activity. It is a metabolic intermediate in mam-
malian tissues (c Fumaric acid has good potential for further development because of its lack of toxicity, as well as its chemo-
preventive activity. It is a metabolic intermediate in mam-
malian tissues (citric acid and urea cycles) and is ment because of its lack of toxicity, as well as its chemo-
preventive activity. It is a metabolic intermediate in mam-
malian tissues (citric acid and urea cycles) and is a generally
recognized as safe substance used comm preventive activity. It is a metabolic intermediate in m
malian tissues (citric acid and urea cycles) and is a gener
recognized as safe substance used commercially in food
beverages as an antioxidant, acidulant, flavoring malian tissues (citric acid and urea cycles) and is a generally recognized as safe substance used commercially in food and beverages as an antioxidant, acidulant, flavoring agent, feed additive, and cure accelerator (195, recognized as safe substance used commercially in food and beverages as an antioxidant, acidulant, flavoring agent, feed additive, and cure accelerator (195, 196). The chemopreventive efficacy of fumaric acid was shown first by Kuroda and associates. They identified fumaric acid a additive, and cure accelerator (195, 196). The chemopre-
ventive efficacy of fumaric acid was shown first by Kuroda
and associates. They identified fumaric acid as the compo-
nent of the herb *Capsella bursa-pastoris* resp ventive efficacy of fumaric acid was shown first by Kuroda
and associates. They identified fumaric acid as the compo-
nent of the herb *Capsella bursa-pastoris* responsible for its
antiproliferative and antiinflammatory pr and associates. They identified fumaric acid as the component of the herb *Capsella bursa-pastoris* responsible for its antiproliferative and antiinflammatory properties by which the herb inhibited the growth of transplan nent of the herb *Capsella bursa-pastoris* responsible for its
antiproliferative and antiinflammatory properties by which
the herb inhibited the growth of transplanted tumors in mice
(197) and gastric ulcers in rats (198) antiproliferative and antiinflammatory properties by which
the herb inhibited the growth of transplanted tumors in mice
(197) and gastric ulcers in rats (198). It also reduced the liver
toxicity of the carcinogens mitomyc the herb inhibited the growth of transplanted tumors in mice
(197) and gastric ulcers in rats (198). It also reduced the liver
toxicity of the carcinogens mitomycin C and AFB₁ (199). In
a series of studies, they showed t (197) and gastric ulcers in rats (198). It also reduced the liver toxicity of the carcinogens mitomycin C and AFB₁ (199). In a series of studies, they showed that fumaric acid had chemopreventive activity in mouse forest toxicity of the carcinogens mitomycin C and AFB_1 (199). In
a series of studies, they showed that fumaric acid had che-
mopreventive activity in mouse forestomach (200), rat liver
(201, 202), and mouse lung (200). Subseq a series of studies, they showed that fumaric acid had che-
mopreventive activity in mouse forestomach (200), rat liver
(201, 202), and mouse lung (200). Subsequently, the agent
demonstrated chemopreventive effects in stud mopreventive activity in mouse forestomach (200), rat liver (201, 202), and mouse lung (200). Subsequently, the agent demonstrated chemopreventive effects in studies in MNU hamster trachea and MNU rat mammary models (see T demonstrated chemopreventive effects in studies in MNU
hamster trachea and MNU rat mammary models (see
Table 3).
The mechanism of the chemopreventive action of fu-
maric acid has not been elucidated, but may be related to

hamster trachea and MNU rat mammary models (see
Table 3).
The mechanism of the chemopreventive action of fu-
maric acid has not been elucidated, but may be related to
its antioxidative potential. On the basis of the studie Table 3). The mechanism of the chemopreventive action of fu-
maric acid has not been elucidated, but may be related to
its antioxidative potential. On the basis of the studies cited
above, fumaric acid appears to be active The mechanism of the chemopreventive action of fumaric acid has not been elucidated, but may be related to its antioxidative potential. On the basis of the studies cited above, fumaric acid appears to be active in later st maric acid has not been elucidated, but may be related to
its antioxidative potential. On the basis of the studies cited
above, fumaric acid appears to be active in later stages of
carcinogenesis. For example, in the studi its antioxidative potential. On the basis of the studies cited above, fumaric acid appears to be active in later stages carcinogenesis. For example, in the studies in mouse fore stomach, rat liver, and mouse lung cited abo above, fumaric acid appears to be active in later stages of
carcinogenesis. For example, in the studies in mouse fore-
stomach, rat liver, and mouse lung cited above, it was active
when given after treatment with the carci stomach, rat liver, and mouse lung cited above, it was active
when given after treatment with the carcinogen was com-
pleted. Also, in the rat mammary study cited in Table 3,
fumaric acid significantly increased tumor late pleted. Also, in the rat mammary study cited in Table 3,
fumaric acid significantly increased tumor latency but did
not decrease tumor incidence or multiplicity.
From studies reported in the literature, fumaric acid ap-
pe

From studies reported in the literature, fumanic acid apfumaric acid significantly increased tumor latency but did
not decrease tumor incidence or multiplicity.
From studies reported in the literature, fumaric acid ap-
pears to have little toxicity (196, 203–205). In 6-week dos not decrease tumor incidence or multiplicity.
From studies reported in the literature, fumaric acid appears to have little toxicity (196, 203–205). In 6-week dose tolerance studies preparatory to the chemoprevention scree From studies reported in the literature, fumaric acid appears to have little toxicity (196, 203–205). In 6-week dose tolerance studies preparatory to the chemoprevention screens cited in Table 3, no toxicity was observed

be noted that the high dose tolerance might be related to
poor absorption from the gastrointestinal tract (cited in Ref.
205). Additional preclinical acute and subchronic toxicity be noted that the high dose tolerance might be related to
poor absorption from the gastrointestinal tract (cited in Ref.
205). Additional preclinical acute and subchronic toxicity
evaluations are scheduled in rats and dogs poor absorption from the gastrointestinal tract (cited in Ref. 205). Additional preclinical acute and subchronic toxicity evaluations are scheduled in rats and dogs. oted that the high dose tolerance might be related to
absorption from the gastrointestinal tract (cited in Ref. Additional preclinical acute and subchronic toxicity
uations are scheduled in rats and dogs.
Schwartz *et al.* poor absorption from the gastrointestinal tract (cited in Ref. 205). Additional preclinical acute and subchronic toxicity evaluations are scheduled in rats and dogs. Schwartz *et al.* (206–216), as well as other investigat

205). Additional preclinical acute and subchronic toxicity evaluations are scheduled in rats and dogs.
Schwartz et al. (206–216), as well as other investigators, have demonstrated the chemopreventive activity of the andro evaluations are scheduled in rats and dogs.
Schwartz et al. (206–216), as well as other investigators,
have demonstrated the chemopreventive activity of the an-
drogen DHEA in numerous animal models. DHEA is a potent
inhib Schwartz *et al.* (206–216), as well as other investigators,
have demonstrated the chemopreventive activity of the an-
drogen DHEA in numerous animal models. DHEA is a potent
inhibitor of G6PDH. The primary function of thi have demonstrated the chemopreventive activity of the an-
drogen DHEA in numerous animal models. DHEA is a potent
inhibitor of G6PDH. The primary function of this enzyme is
catalysis of the formation of extramitochondrial drogen DHEA in numerous animal models. DHEA is a potent
inhibitor of G6PDH. The primary function of this enzyme is
catalysis of the formation of extramitochondrial NAD(P)H
and ribose 5-phosphate. Schwartz has hypothesized inhibitor of G6PDH. The primary function of this enzyme is
catalysis of the formation of extramitochondrial NAD(P)H
and ribose 5-phosphate. Schwartz has hypothesized two
ways in which inhibition of G6PDH may mediate the ch catalysis of the formation of extramitochondrial NAD(P)H
and ribose 5-phosphate. Schwartz has hypothesized two
ways in which inhibition of G6PDH may mediate the che-
mopreventive activity of DHEA (216). First, DHEA inhibit and ribose 5-phosphate. Schwartz has hypothesized two
ways in which inhibition of G6PDH may mediate the che-
mopreventive activity of DHEA (216). First, DHEA inhibits
the activity of carcinogens such as B(a)P, AFB₁, and mopreventive activity of DHEA (216). First, DHEA inhibits
the activity of carcinogens such as $B(a)P$, AFB_1 , and DMBA
which require metabolic activation via mixed function oxi-
dases (216–219). Mixed function oxidases req the activity of carcinogens such as $B(a)P$, AFB_1 , and DMBA which require metabolic activation via mixed function oxidases ($216-219$). Mixed function oxidases require NAD(P)H as a cofactor. Thus, since inhibition of G cinogens. Secondly, DHEA also inhibits tumor promotion dases (216–219). Mixed function oxidases require NAD(P)H
as a cofactor. Thus, since inhibition of G6PDH reduces the
formation of NAD(P)H, it consequently reduces the activity
of mixed function oxidases and the activation o as a cofactor. Thus, since inhibition of G6PDH reduces the formation of NAD(P)H, it consequently reduces the activity of mixed function oxidases and the activation of certain carcinogens. Secondly, DHEA also inhibits tumor formation of NAD(P)H, it consequently reduces the activity
of mixed function oxidases and the activation of certain car-
cinogens. Secondly, DHEA also inhibits tumor promotion
and proliferative activity induced by TPA (210 of mixed function oxidases and the activation of certain car-
cinogens. Secondly, DHEA also inhibits tumor promotion
and proliferative activity induced by TPA (210, 220). Cell
proliferation requires NAD(P)H-dependent DNA s cinogens. Secondly, DHEA also inhibits tumor promotion
and proliferative activity induced by TPA (210, 220). Cell
proliferation requires NAD(P)H-dependent DNA synthesis,
and DNA synthesis in mouse epidermis and mammary tis and proliferative activity induced by TPA (210, 220). Cell
proliferation requires NAD(P)H-dependent DNA synthesis,
and DNA synthesis in mouse epidermis and mammary tissue
also is inhibited by DHEA (221). Accordingly, reduc also is inhibited by DHEA (221). Accordingly, reduction of
the NAD(P)H pool by inhibition of G6PDH could inhibit
carcinogen-induced cell proliferation.
Unfortunately, the chemopreventive potential of DHEA DNA synthesis in mouse epidermis and mammary tissue
is inhibited by DHEA (221). Accordingly, reduction of
NAD(P)H pool by inhibition of G6PDH could inhibit
inogen-induced cell proliferation.
Unfortunately, the chemoprevent also is inhibited by DHEA (221). Accordingly, reduction of
the NAD(P)H pool by inhibition of G6PDH could inhibit
carcinogen-induced cell proliferation.
Unfortunately, the chemopreventive potential of DHEA
is compromised by

the NAD(P)H pool by inhibition of G6PDH could inhibit
carcinogen-induced cell proliferation.
Unfortunately, the chemopreventive potential of DHEA
is compromised by some undesirable pharmacological ef-
fects: potent hormona carcinogen-induced cell proliferation.

Unfortunately, the chemopreventive potential of DHEA

is compromised by some undesirable pharmacological ef-

fects: potent hormonal (222), liver-enlarging (223), and

peroxisome-pro Unfortunately, the chemopreventive potential of DHEA
is compromised by some undesirable pharmacological ef-
fects: potent hormonal (222), liver-enlarging (223), and
peroxisome-proliferating activities (223, 224). To elimin is compromised by some undesirable pharmacological effects: potent hormonal (222), liver-enlarging (223), and
peroxisome-proliferating activities (223, 224). To eliminate
these side effects while preserving chemopreventive fects: potent hormonal (222), liver-enlarging (223), and
peroxisome-proliferating activities (223, 224). To eliminate
these side effects while preserving chemopreventive activity,
Schwartz designed several analogues (216, peroxisome-proliferating activities (223, 224). To eliminate
these side effects while preserving chemopreventive activity,
Schwartz designed several analogues (216, 223, 225). One
of these analogues, fluasterone (16 α -f these side effects while preserving chemopreventive activity, Schwartz designed several analogues (216 , 223 , 225). One of these analogues, fluasterone (16α -fluoro-DHEA; DHEA analogue 8354) is particularly promisi Schwartz designed several analogues (216, 223, 225). One
of these analogues, fluasterone (16 α -fluoro-DHEA; DHEA
analogue 8354) is particularly promising and is being de-
veloped in the NCI chemopreventive drug program. of these analogues, fluasterone (16 α -fluoro-DHEA; DHE
analogue 8354) is particularly promising and is being d
veloped in the NCl chemopreventive drug program. Flu
asterone does not have the androgenic or liver toxicity
 analogue 8354) is particularly promising and is being developed in the NCI chemopreventive drug program. Flu-
asterone does not have the androgenic or liver toxicity of
DHEA (223). It was a more potent inhibitor of tumor i veloped in the NCI chemopreventive drug program. Flu-
asterone does not have the androgenic or liver toxicity of
DHEA (223). It was a more potent inhibitor of tumor initia-
tion and promotion in the DMBA/TPA mouse skin mod asterone does not have the androgenic or liver toxicity
DHEA (223). It was a more potent inhibitor of tumor initi
tion and promotion in the DMBA/TPA mouse skin moo
than DHEA (220), and, in animal studies cited in Table 3,
 DHEA (223). It was a more potent inhibitor of tumor init
tion and promotion in the DMBA/TPA mouse skin moo
than DHEA (220), and, in animal studies cited in Table 3
was effective in the rat mammary gland against MN
induced tion and promotion in the DMB_/
than DHEA (220), and, in animal
was effective in the rat mamm_i
induced cancers (226) and in in
methane-induced tumors (12).
Subchronic studies in rats (u than DHEA (220), and, in animal studies cited in Table 3, it
was effective in the rat mammary gland against MNU-
induced cancers (226) and in rat colon against azoxy-
methane-induced tumors (12).
Subchronic studies in rats

induced cancers (226) and in rat colon against azoxy-
methane-induced tumors (12).
Subchronic studies in rats (up to 1 g/kg body weight/
day) and dogs (up to 250 mg/kg body weight/day) have es-
tablished a NOEL of 250 mg/k methane-induced tumors (12).

Subchronic studies in rats (up to 1 g/kg body weight/

day) and dogs (up to 250 mg/kg body weight/day) have es-

tablished a NOEL of 250 mg/kg body weight for fluasterone

in both species; no Subchronic studies in rats (up to 1 g/kg body weight/
day) and dogs (up to 250 mg/kg body weight/day) have es-
tablished a NOEL of 250 mg/kg body weight for fluasterone
in both species; no target organs with histopathology day) and dogs (up to 250 mg/kg body weight/day) have es-
tablished a NOEL of 250 mg/kg body weight for fluasterone
in both species; no target organs with histopathology were
identified in either study. Effects seen at the tablished a NOEL of 250 mg/kg body weight for fluasterone
in both species; no target organs with histopathology were
identified in either study. Effects seen at the high doses tested
included dose-related weight loss (>10% in both species; no target organs with histopathology were
identified in either study. Effects seen at the high doses tested
included dose-related weight loss (>10% at 1 g/kg body
weight/day) and hypocholesterolemia (at 50 identified in either study. Effects seen at the high doses tested
included dose-related weight loss (>10% at 1 g/kg body
weight/day) and hypocholesterolemia (at 500 mg/kg body
weight/day and 1 g/kg body weight/day) in the included dose-related weight loss (>10% at 1 g/kg body
weight/day) and hypocholesterolemia (at 500 mg/kg body
weight/day and 1 g/kg body weight/day) in the male rats. The
relevance of these effects to the potential of flua weight/day and 1 g/kg body weight/day) in the male rats. T
relevance of these effects to the potential of fluasterone is
clinical use has not yet been evaluated. Particularly, t
minimal effective doses of fluasterone have relevance of these effects to the potential of fluasterone for clinical use has not yet been evaluated. Particularly, the minimal effective doses of fluasterone have not been determined. Pharmacokinetic evaluations are cur clinical use has not yet been evaluated. Particularly, the minimal effective doses of fluasterone have not been determined. Pharmacokinetic evaluations are currently underway and chronic toxicity studies are planned. Like mined. Pharmacokinetic evaluations are currently underway and chronic toxicity studies are planned. Like some of
the other compounds discussed, fluasterone may require for-
mulations designed to augment bioavailability.
Future Directions

The progress that has been made to date indicates that chemulations designed to augment bioavailability.
Future Directions
The progress that has been made to date indicates that che-
moprevention research will soon begin to yield practical
applications for the reduction of canc **Future Directions**
The progress that has been made to date indicates that ch
moprevention research will soon begin to yield practic
applications for the reduction of cancer incidence. Non
theless, the time and resources r **Future Directions**
The progress that has been made to date indicates that che-
moprevention research will soon begin to yield practical
applications for the reduction of cancer incidence. None-
theless, the time and resou The progress that has been made to date indicates that che-
moprevention research will soon begin to yield practical
applications for the reduction of cancer incidence. None-
theless, the time and resources required to car moprevention research will soon begin to yield practical applications for the reduction of cancer incidence. None-
theless, the time and resources required to carry out a full
clinical evaluation of a chemopreventive agent applications for the reduction of cancer incidence. None-
theless, the time and resources required to carry out a full
clinical evaluation of a chemopreventive agent in a cancer
incidence reduction study is of great concer

to limit the progression of neoplasms before they become
trank cancers. To address this goal, as well as the concern to limit the progression of neoplasms before they become
frank cancers. To address this goal, as well as the concern
for time and resources, the role of Phase II clinical studies has for limit the progression of neoplasms before they become
frank cancers. To address this goal, as well as the concern
for time and resources, the role of Phase II clinical studies has
been expanding to evaluate markers in to limit the progression of neoplasms before they become
frank cancers. To address this goal, as well as the concern
for time and resources, the role of Phase II clinical studies has
been expanding to evaluate markers in p to limit the progression of neoplasms before they becc
frank cancers. To address this goal, as well as the conc
for time and resources, the role of Phase II clinical studies
been expanding to evaluate markers in predysplas frank cancers. To address this goal, as well as the concern
for time and resources, the role of Phase II clinical studies has
been expanding to evaluate markers in predysplastic and
dysplastic tissue as endpoints for evalu for time and resources, the role of Phase II clinical studies has
been expanding to evaluate markers in predysplastic and
dysplastic tissue as endpoints for evaluation of chemopre-
ventive agents. Studies in patients with been expanding to evaluate markers in predysplastic and
dysplastic tissue as endpoints for evaluation of chemopre-
ventive agents. Studies in patients with dysplastic lesions—
cervical dysplasia, oral leukoplakia, superfic dysplastic tissue as endpoints for evaluation of chemopre-
ventive agents. Studies in patients with dysplastic lesions—
cervical dysplasia, oral leukoplakia, superficial bladder can-
cers, and actinic keratoses—have been i ventive agents. Studies in patients with dysplastic lesions cervical dysplasia, oral leukoplakia, superficial bladder carres, and actinic keratoses—have been initiated recent These and other Phase II studies will be used t cervical dysplasia, oral leukoplakia, superficial bladder cancers, and actinic keratoses—have been initiated recently.
These and other Phase II studies will be used to search for and validate earlier markers that are endpo cers, and actinic keratoses—have been initiated recently.
These and other Phase II studies will be used to search for
and validate earlier markers that are endpoints for chemo-
prevention. In these studies, various potenti These and other Phase II studies will be used to search for
and validate earlier markers that are endpoints for chemo-
prevention. In these studies, various potential markers of ab-
normal cellular proliferation and differ and validate earlier markers that are endpoints for chemo-
prevention. In these studies, various potential markers of ab-
normal cellular proliferation and differentiation and genetic
changes such as abnormal gene expressi prevention. In these studies, various potential markers of abnormal cellular proliferation and differentiation and genetic changes such as abnormal gene expression (including on-cogenes and tumor suppressors), altered DNA normal cellular proliferation and differentiation and genetic
changes such as abnormal gene expression (including on-
cogenes and tumor suppressors), altered DNA content, and
chromosome structural changes may be evaluated. changes such as abnormal gene expression (including
cogenes and tumor suppressors), altered DNA content,
chromosome structural changes may be evaluated. More
perimentation in animal models related to the validatio
markers cogenes and tumor suppressors), altered DNA content, and
chromosome structural changes may be evaluated. More ex-
perimentation in animal models related to the validation of
markers also has begun. Recently, in the NCI che chromosome structural changes may be evaluated. More ex-
perimentation in animal models related to the validation of
markers also has begun. Recently, in the NCl chemopre-
vention drug development program, studies of poten perimentation in animal models related to the validation of markers also has begun. Recently, in the NCI chemoprevention drug development program, studies of potential markers have been initiated in mouse and rat colon, ha markers also has
vention drug de
markers have bee
buccal pouch, ha
and rat bladder.
New techno vention drug development program, studies of potential markers have been initiated in mouse and rat colon, hamster buccal pouch, hamster pancreas, hamster and mouse lung, and rat bladder.
New technologies are also expected markers have been initiated in mouse and rat colon, hamster buccal pouch, hamster pancreas, hamster and mouse lung, and rat bladder.
New technologies are also expected to benefit chemo-
prevention research, especially dete

buccal pouch, hamster pancreas, hamster and mouse lung,
and rat bladder.
New technologies are also expected to benefit chemo-
prevention research, especially detection and validation of
early markers. Particularly interest and rat bladder.

New technologies are also expected to benefit chemo-

prevention research, especially detection and validation of

early markers. Particularly interesting are techniques, such

as fine needle aspiration a New technologies are also expected to benefit chemo-
prevention research, especially detection and validation of
early markers. Particularly interesting are techniques, such
as fine needle aspiration and the polymerase cha prevention research, especially detection and validation of
early markers. Particularly interesting are techniques, such
as fine needle aspiration and the polymerase chain reaction,
that will allow early and rare lesions t early markers. Particularly interesting are techniques, such
as fine needle aspiration and the polymerase chain reaction,
that will allow early and rare lesions to be detected relatively
noninvasively. Likewise, as knowled as fine needle aspiration and the polymerase chain reaction, that will allow early and rare lesions to be detected relatively noninvasively. Likewise, as knowledge in molecular biology and the basic cellular processes in c that will allow early and rare lesions to be detected relatively
noninvasively. Likewise, as knowledge in molecular biology
and the basic cellular processes in carcinogenesis increases,
chemopreventive agents that are dire noninvasively. Likewise, as knowledge in molecular biology
and the basic cellular processes in carcinogenesis increases,
chemopreventive agents that are directed to repair or sup-
press early genetic lesions and control ce and the basic cellu
chemopreventive
press early genet
mechanisms (e.g.,
may be possible.
To date, che mopreventive agents that are directed to repair or sup-
is early genetic lesions and control cellular growth
hanisms (e.g., programmed cell death, angiogenesis)
be possible.
To date, chemoprevention research efforts have f press early genetic lesions and control cellular growth
mechanisms (e.g., programmed cell death, angiogenesis)
may be possible.
To date, chemoprevention research efforts have fo-
cused primarily on cancers of the colon, lu

mechanisms (*e.g.,* programmed cell death, angiogenesis)
may be possible.
To date, chemoprevention research efforts have fo-
cused primarily on cancers of the colon, lung, breast, and
bladder. In the NCI drug development p may be possible.

To date, chemoprevention research efforts have fo-

cused primarily on cancers of the colon, lung, breast, and

bladder. In the NCI drug development program, models for

evaluating potential chemopreventi To date, chemoprevention research efforts have fo-
cused primarily on cancers of the colon, lung, breast, and
bladder. In the NCI drug development program, models for
evaluating potential chemopreventive agents in prostate cused primarily on cancers of the colon, lung, breast, and bladder. In the NCI drug development program, models for evaluating potential chemopreventive agents in prostate and pancreas are being investigated. Other cancers bladder. In the NCI drug development program, models for
evaluating potential chemopreventive agents in prostate and
pancreas are being investigated. Other cancers with high
incidence or mortality are expected to be addres evaluating potential chemopreventive agents in prostate and
pancreas are being investigated. Other cancers with high
incidence or mortality are expected to be addressed within
the next few years—particularly, brain cancers

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