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Strategy and Planning for Chemopreventive Drug Development: Clinical Development Plans II

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Abstract This is the second publication of Clinical Development Plans from the National Cancer Institute, Division of Cancer Prevention and Control, Chemoprevention Branch and Agent Development Committee. The Clinical Development Plans summarize the status of promising chemopreventive agents regarding evidence for safety and chemopreventive efficacy in preclinical and clinical studies. They also contain the strategy for further development of these drugs, addressing pharmacodynamics, drug effect measurements, intermediate biomarkers for monitoring efficacy, toxicity, supply and formulation, regulatory approval, and proposed clinical trials. Sixteen new Clinical Development Plans are presented here: curcumin, dehydroepiandrosterone, folic acid, genistein, indole-3-carbinol, perillyl alcohol, phenethyl isothiocyanate, 9-*cis*-retinoic acid, 13-*cis*-retinoic acid, *l*-selenomethionine and 1,4-phenylenebis(methylene)selenocyanate, sulindac sulfone, tea, ursodiol, vitamin A, and (+)-vorozole. The objective of publishing these plans is to stimulate interest and thinking among the scientific community on the prospects for developing these and future generations of chemopreventive drugs. © 1997 Wiley-Liss, Inc.

The first volume of 16 Clinical Development Plans from the NCI, DCPC Chemoprevention Branch and Agent Development Committee was published in 1994 [1]. As described in the introduction to that volume, the strategy and planning for NCI, DCPC clinical chemoprevention studies is carried out through the Prevention Trials Decision Network. The Decision Network has three operating committees—Endpoints and Biomarkers Committee, Large Trials Committee, and Agent Development Committee. The Chemoprevention Branch, working with and through the Agent Development Committee, provides scientific and administrative oversight for chemopreventive drug development, ranging from drug discovery and preclinical evaluation through conduct of clinical trials [2–5].

The Clinical Development Plans, prepared by the Chemoprevention Branch and the Agent Develop-

ment Committee, summarize the status of promising chemopreventive agents regarding evidence for safety and chemopreventive efficacy in preclinical, epidemiological and clinical studies. They also contain strategies for further development of the drugs, addressing pharmacodynamics, drug effect measurements, intermediate biomarkers for monitoring efficacy, toxicity, supply and formulation, regulatory approval, and proposed clinical trials. A significant aspect of the evaluation is complying with FDA guidelines for drugs to progress to clinical trials and for marketing approval. Although no formal FDA regulations exist specifically for cancer chemopreventive drugs, the Chemoprevention Branch and FDA have worked together to draft consensus guidance [5].

Sixteen new Clinical Development Plans are presented in this second volume:

- Curcumin
- Dehydroepiandrosterone (DHEA)
- Folic acid
- Genistein
- Indole-3-carbinol
- Perillyl alcohol
- Phenethyl isothiocyanate (PEITC)
- 9-*cis*-Retinoic acid
- 13-*cis*-Retinoic acid
- *l*-Selenomethionine
- 1,4-Phenylenebis(methylene)selenocyanate (*p*-XSC)
- Sulindac sulfone
- Tea
- Ursodiol
- Vitamin A
- (+)-Vorozole

These agents showed significant promise in preclinical efficacy (*e.g.*, curcumin, PEITC, 9-*cis*-retinoic acid, *p*-XSC) or epidemiological studies (*e.g.*, vitamin A, DHEA, folic acid, genistein, *l*-selenomethionine, tea). However, with the exceptions of 13-*cis*-retinoic acid and vitamin A, which have been studied extensively in clinical chemoprevention trials (see the Clinical Development Plans), and folic acid, which has been evaluated clinically for its protective effects against heart disease [6] and birth defects [7], as well as in some limited studies as an inhibitor of cervical cancer [8–11], the agents described are still in the very early stages of drug development. Among the remaining agents, sulindac sulfone may be the most advanced in terms of clinical development specifically as a chemopreventive drug. It has been evaluated in several Phase I studies in healthy volunteers, and is just completing a Phase I/IIa study in patients with familial adenomatous polyposis (FAP). One objective of this study is a preliminary and limited efficacy evaluation of the agent's effect on colon adenoma regression and prevention. Should the results be promising, the agent will move on to Phase II/III efficacy trials in FAP patients. Ursodiol is already marketed for dissolution of gall bladder stones and has been used to treat other diseases associated with high levels of bile acid production [12,13]. It is currently being evaluated in a Phase I study in patients at high risk for colorectal cancer, as part of a project to determine its efficacy in preventing cancer in this population.

The next furthest along may be 9-*cis*-retinoic acid and DHEA, which have sufficient previous clinical safety information to enter Phase II chemoprevention trials. Perillyl alcohol has some Phase I testing in breast cancer patients and will be evaluated in a Phase I study in high-risk, but asymptomatic patients. (+)-Vorozole has been tested in several Phase I/II studies in postmenopausal women to determine its chemotherapeutic activity in advanced breast cancer [14–17]. Also, selenized yeast, in which the selenium form is primarily *l*-selenomethionine, has been evaluated in large cancer prevention trials [18, 19], and so *l*-selenomethionine may also enter Phase II trials. The remaining agents are either just entering Phase I clinical studies (curcumin, genistein, indole-3-carbinol, PEITC) or still need chronic preclinical toxicity data before Phase I studies may start (*p*-XSC, tea).

The 16 agents in this group present several challenges for drug development. One is the role of deficiencies in determining potency and in selecting doses and populations for clinical studies. For example, results on folic acid in preventing cervical cancer have been inconsistent [8–11], at least partially because factors such as smoking and oral contraceptive use which deplete folic acid were not fully considered. Studies with selenium compounds, such as *l*-selenomethionine, appear to be most successful in populations with probable selenium deficiency [18, 19]. Also, the determination of selenium status is particularly important because of the narrow therapeutic index observed for many selenium compounds [18,19]. DHEA has both androgenic and estrogenic potential. While its potential chemopreventive activity may be related to restoring tissue and serum levels

that are depleted during aging, a key factor in evaluating DHEA's promise is ensuring that the exogenous drug does not exacerbate hormone-dependent cell growth and proliferation in precancers or early invasive disease.

Several of the agents are derived from dietary products—curcumin, genistein, and tea extracts. The preparation and characterization of optimal standardized mixtures, and purification of the active substance are challenges for the development of these substances. For example, the preclinical efficacy of curcumin summarized in the Clinical Development Plan has been determined primarily with food-grade agent, which is a mixture of curcuminoids ranging from 40–85% curcumin [20]. The Chemoprevention Branch is now investigating a purified curcumin, micronized for increased bioavailability. It is possible that this preparation will enhance both efficacy and toxicity. Two soy isoflavone mixtures containing genistein, other isoflavones (primarily daidzein), fat and carbohydrate are being developed in collaboration with Protein Technologies (St. Louis, MO). One is nearly "pure", containing 90% genistein; the second more closely resembles a natural soy product, containing 43% genistein. Similarly, T.J. Lipton (New Jersey) is supplying well-characterized tea polyphenol extracts for evaluation in preclinical studies.

In the preface to the first volume of Clinical Development Plans, it was noted that many of the agents considered were vanguard drugs, and it was likely that they would be replaced by more efficacious, less toxic agents with similar or related mechanisms of action. Nonsteroidal antiiflammatory drugs (NSAIDs), which have potent chemopreventive activity in colon and bladder, were discussed in this regard [1]. The toxicity of NSAIDs is apparently associated with inhibition of cyclooxygenase. One of the agents discussed here, sulindac sulfone, represents a second generation of NSAID-derived drugs. It is one of two major metabolites of the chemopreventive NSAID sulindac, appears to retain some of the chemopreventive efficacy of its parent, but it is not a potent inhibitor of cyclooxygenase. Tamoxifen was the lead antiestrogen described in the first volume [21]. Several other antiestrogenic compounds with the potential for higher efficacy and less toxicity are described in this second set of Clinical Development Plans. (+)-Vorozole is antiestrogenic by virtue of inhibiting steroid aromatase. One effect of indole-3-carbinol is altering the metabolism of estrogens toward more easily conjugated and less potent forms [22,23]. Genistein has weak estrogenic activity, and by binding to the estrogen receptor may interfere with the activity of more potent estrogens [24–27].

The Chemoprevention Branch and Agent Development Committee is continually preparing plans on new agents and updating the existing plans as new efficacy and toxicity data are available. Table I summarizes the current status of chemopreventive drug development for the 32 agents discussed in the first two volumes of Clinical Development Plans.

EXPLANATION OF DATA COVERED IN CLINICAL DEVELOPMENT PLANS

The Clinical Development Plans in this volume represent the work of the Chemoprevention Branch and Agent Development Committee from September 1994 through August 1996. The elements comprising the plans are described below.

DRUG IDENTIFICATION

The chemopreventive agent is usually identified by the USAN name for the drug substance or the registered name of the drug product being developed. Other identifiers are the Chemical Abstracts Service (CAS) Registry Number and the CAS 9th Collective Index Name. Also listed are any synonyms, such as common names, registered drug names in which the agent is an active ingredient, and alternate chemical names. Other salt forms and closely related derivatives are cited. The chemical structure of the agent is also included.

EXECUTIVE SUMMARY

The first part of this section is a brief statement of the regulatory status and indications of the agent, if applicable. If the agent is an approved drug or in clinical trials, the human therapeutic dose range is included. The reasons for developing the drug as a chemopreventive agent are then summarized. These may include relevant mechanism(s) of action, the tissues in which it modulates carcinogenesis (including intermediate biomarkers), and pharmacokinetic, pharmacodynamic and safety considerations. Comparisons with other drugs under development also may be made.

The progress to date in the agent's development as a chemopreventive drug is reviewed. The models in which preclinical efficacy was demonstrated are

summarized. A conclusion regarding the adequacy of these studies in supporting FDA requirements and the Chemoprevention Branch/FDA consensus guidance for clinical trials is then reached. Both NCI-sponsored and published studies are included in this evaluation. Any assays showing modulation of intermediate biomarkers of carcinogenesis by the agent are noted, since this is an important aspect for the future development of chemopreventive drugs.

Preclinical toxicity data from the Chemoprevention Branch testing program, the manufacturer's *Investigator's Brochure*, other IND or NDA filing information, and the literature are summarized. The relevant results are stated, plus an evaluation of their adequacy in fulfilling FDA requirements for approval to start clinical trials and complete development of the drug.

Next, any completed, existing, or planned NCI-sponsored clinical trials are summarized. Any relevant published epidemiological or clinical trial data may also be included.

Finally, information on the drug supply and formulation is provided. This may include the status of the drug supply, patent status, the means of acquiring the drug, the source, the formulation type, and the availability of a suitable placebo.

PRECLINICAL EFFICACY STUDIES

This section evaluates the extent to which chemopreventive efficacy has been demonstrated in preclinical models/assays. A conclusion regarding the adequacy of these studies in supporting further development is reached. The most compelling evidence for efficacy is from *in vivo* tumor modulation studies. Relevant *in vitro* assay results may be included to strengthen the evidence. In keeping with the design of IND and NDA submissions, NCI-sponsored results are discussed separately from published data.

Chemopreventive efficacy may also be demonstrated by at least one *in vivo* study which shows statistically significant modulation of an intermediate biomarker of carcinogenesis. The biomarker should reasonably predict modulation of tumor incidence/multiplicity or latency. A dose-related effect should also be demonstrated. Information on modulation of intermediate biomarkers is an important component of this section. A significant effort in the Chemoprevention Branch program is to identify and validate intermediate biomarkers of carcinogenesis and the potential for chemopreventive agents to modulate these markers. Such studies may also identify biomarkers for future evaluation as surrogate endpoints in clinical trials. The identity of the intermediate biomarkers and the tissues in which they were measured should be included from both NCI-sponsored studies and published studies from other sources.

The effective plasma concentration is included, if available, for each assay type so that the Phase I dosing strategy can be pharmacologically guided. If this concentration is not available, the efficacious dose is stated in the appropriate units.

PRECLINICAL SAFETY STUDIES

Safety: In this section, the animal toxicity studies sponsored by the NCI are critically evaluated for compliance with FDA requirements. Preclinical toxicity studies required by the FDA for initiation of Phase I and II clinical trials include investigations of acute (single dose) and subchronic (30-day, 90-day dosing) toxicity (incorporating pharmacokinetics), reproductive performance and genotoxicity. The toxicity studies should be conducted in two species, rodent and non-rodent, and should be of equal or greater duration than the proposed clinical trials. The route of administration should be equivalent to that for the clinical trial, unless a rationale can be provided for another route. When possible, the drug substance should be administered in the same form as the clinical trial formulation. As is usual in FDA-required toxicology studies, clinical signs, clinical chemistry, hematology, urinalysis and pathology should be assessed. Segment I (rat) and II (rat, rabbit) reproductive studies should be performed before clinical trials of long duration. In addition, deficiencies in the results or performance of the studies are noted.

Relevant information from published subchronic or chronic toxicity studies can be included to give an indication of the agent's relative toxicity. If available, toxicity data from the manufacturer's previous IND or NDA filing are summarized. In some cases, however, this information may not be readily accessible. A manufacturer's IND or NDA can be cross-referenced if the toxicology studies are adequate and the manufacturer agrees. For a long-used, approved drug, it may not be necessary to formally make reference to previous regulatory filings. Instead, the Summary Basis of Approval for such drugs is obtained and reviewed for this information. The MTD and the NOEL from the toxicity studies are listed if available.

This information may be useful in determining the human dose range.

ADME: This section summarizes the pharmacokinetics of the agent. ADME represents what the body does to the drug. Estimates of plasma $t_{1/2}$, AUC, C_{max}, C_{min}, C_{ss}, V_d, Cl_r, Cl_p and t_{max} are included, if available. These parameters provide a dose-concentration profile of the drug for guiding clinical dosing regimens. Species similarities and differences in the ADME of the agent are evaluated. The pharmacokinetics in certain species may also be relevant to the applicability of their toxicity or efficacy results to humans.

CLINICAL SAFETY: PHASE I STUDIES

All NCI-sponsored Phase I studies which have been completed, are in progress, or planned are described in this section. Relevant information from Phase IIa studies also is included. This is a narrative summary of the information contained in the data table (usually Table I) accompanying each Clinical Development Plan. Information from manufacturer-sponsored or published studies may be included as necessary, but is clearly designated as such.

Drug Effect Measurement: Drug effect measurements are tissue, plasma and urine indicators of the pharmacological activity of the drug. A biochemical change related to the drug should be correlated to an effective tissue, plasma or urine concentration of the active drug form. This also serves to estimate compliance. It should be noted that this measurement may be unrelated to tissue effects producing efficacy (*i.e.*, intermediate biomarkers) or toxicity. In this section, the identity and applicability of the drug effect measurement are assessed. Some of the criteria include correlation of the measurement level to dose, stability of the measurement with chronic drug intake, ease of obtaining a tissue/fluid sample, and accuracy and precision of the assay method for the drug effect measurement.

Safety: Single and multidose Phase I clinical trials are designed to investigate the dose-related pharmacokinetics and safety of the chemopreventive drug in a single-arm trial. The major endpoints are identification and incidence of the spectrum of adverse effects, including determination of a dose-response relationship. Ideally, dose-escalation should continue until minor side effects are seen in the majority of subjects at the highest dose [28]. In this section, the results of any Phase I trials are presented and evaluated based on the above functions.

Phase IIa trials may also produce safety data, although the primary endpoint is to identify the minimum dose at which a measurable biological effect occurs (*i.e.*, using a drug effect measurement or intermediate biomarker).

ADME: As for preclinical safety studies, values for pharmacokinetic parameters are identified. Distribution to the target tissue, drug metabolism, and the best dosing interval are addressed as appropriate. The pharmacokinetic profiles after acute and chronic dosing are compared for impact on the dosing schedule in future trials. Finally, validation of assays for the drug and its metabolites in body fluids/tissues are assessed.

CLINICAL EFFICACY: PHASE II/III STUDIES

As mentioned above, the minimum safe dose at which measurable biological effects can be observed has usually been determined in non-randomized, shorter Phase Ib/IIa trials. Phase IIb trials are randomized, placebo-controlled trials with intermediate endpoints and drug effect measurements as end points. A significant aspect of these trials is to identify intermediate biomarkers with the potential to serve as surrogate trial endpoints, to establish a dose-biomarker response relationship, and to select a safe dose for a Phase III trial. Also, potential side effects with chronic treatment may be more closely evaluated with standardized criteria for degree and frequency.

In this section, completed and ongoing Phase II trials are reviewed and evaluated for the characteristics and results described above. For Phase II trials in progress, the cohort, endpoints, and rationale are summarized. Epidemiological evidence of chemopreventive efficacy can be sufficient to support Phase II development of a drug. Examples are DHEA, folic acid, genistein, *l*-selenomethionine, and vitamin A. Some published clinical evidence may be available, such as the prevention of second primary head and neck cancers in patients treated with 13-*cis*-retinoic acid [29]. Proposed Phase II trials are also reviewed, with a discussion of the rationale.

PHARMACODYNAMICS

The pharmacodynamics of the chemopreventive agent are described. Influences of the interaction of the drug with a receptor (used in its widest definition) to produce a biological effect (toxicity or efficacy)

are evaluated. Considerations include the concentration of the drug required to produce an effect in a target tissue, or the length of time the receptor-drug interaction lasts.

An important aspect of this section is a comparison between the effective doses in animals and humans. When blood levels are available from preclinical assays, they are also compared with human data. Critical evaluation of these data can allow pharmacodynamically guided prediction of the effective human dose. AUC is considered the most appropriate predictor of biological effects across species [30]. When blood levels are not available, the magnitude and range between the toxic and effective doses are compared between animals and humans.

PROPOSED STRATEGY FOR CLINICAL DEVELOPMENT

This section recommends strategies for continued development of the drug, as well as approaches to solving identified problems or insufficiencies.

Drug Effect Measurement Issues

The applicability and reliability of drug effect measurements identified in animal and human studies are issues addressed here. Consideration is given to the sensitivity, reproducibility, and standardization of the analytical method for an acceptable drug effect measurement. Other issues discussed include tissue sampling and handling. A plan for addressing any inadequacies is included, if necessary.

Safety Issues

Strategies for overcoming any obstacles to clinical development of a drug with regard to toxicity are addressed in this section. This may involve special studies in preclinical models to characterize the adverse effect and its relationship to the administered dose.

Pharmacodynamics Issues

Any issues related to the drug-receptor interaction and the resulting biological effects are discussed in this section. Special consideration is given to the adequacy of the estimated therapeutic ratio.

Regulatory Issues

The fulfillment of FDA requirements for clinical testing is assessed in this section. Any additional toxicology studies needed are noted; the timing of these studies relative to the proposed clinical trials is also discussed.

Intermediate Biomarker Issues

Intermediate biomarkers are biological alterations in tissue occurring in carcinogenesis before malignant invasion. They include histological changes, and differentiation, proliferation, and genetic biomarkers. Preclinical studies identify potential biomarkers, standardize/validate assays for biomarkers (*e.g.*, sampling procedures, analytical techniques, parameters measured, data collection and data interpretation), demonstrate modulation by a chemopreventive agent, and evaluate intra/intersubject variability. The next step is to demonstrate that intermediate biomarker modulation correlates with decreased cancer incidence/multiplicity or increased latency. For epithelial cancers, the closest causal association exists between intraepithelial neoplasia (*i.e.*, histological/premalignant lesions) and in creased cancer risk. After the intermediate biomarker has been established, chemopreventive efficacy can be measured as modulation of this endpoint. Phase II clinical trials then explore similar aspects in human populations. Demonstrating the correlation between intermediate biomarker modulation and decreased cancer risk in longer Phase II chemoprevention trials will begin to validate the biomarker as a surrogate endpoint for future trials; final validation will be part of Phase III trials. All the aspects mentioned above which are related to identification, modulation, and validation of intermediate biomarkers are issues evaluated in this section.

Supply and Formulation Issues

The availability of bulk, finished dosage form, and placebo drug supply is reviewed in this section. Finished dosage forms can be procured by several methods, such as direct purchase, or free from the manufacturer in an acceptable formulation. Potential problems which affect supply of the drug for existing and planned preclinical and clinical studies include cessation of manufacture by the drug company, expiration or instability of present drug supply, and necessity to change formulations. When formulations are prepared from bulk drug, the process can take up to 12–14 months. All these issues affect the timing of proposed clinical trials.

Other formulation issues include palatability, odor, and bioavailability. In cases where the formu-

lation changes, it is necessary to incorporate a time period for preparation and testing the dosage forms in the Clinical Development Plan.

Clinical Studies Issues

This section includes the strategy for the clinical phase of development. The acceptability of the completed and existing clinical trials is assessed from a regulatory viewpoint. Additional proposed and planned Phase II trials are evaluated critically for relevance, priority, and need. The final goal of the development plan is to place chemopreventive drugs in Phase III trials to validate intermediate biomarkers as surrogate endpoints and to demonstrate cancer incidence reduction or extend the period until cancer onset or recurrence. These planned Phase III studies are reviewed in this section.

REFERENCES

Full bibliographic references to information contained in the plan are cited.

DATA TABLE (TABLE I)

This table shows completed, existing, proposed, and planned NCI-sponsored/funded Phase I, II, and III clinical trials. The first column includes the study contract or grant number, the title of the study, the Principal Investigator, the period of performance, and the IND number and sponsor. The second column lists the target organ (which is not generally applicable to Phase I trials). The third column includes a description of the cohort and its size. Next, the doses of the agent are listed with the duration of the study, including follow-up. The fifth column contains a description of all the study endpoints, including drug effect measurements, intermediate biomarkers, efficacy, and toxicity. If any of the endpoints have not fulfilled the criteria described above, this is noted. In the final column, the status (*i.e.*, complete, in progress, *etc.*) and adequacy of the study are indicated. If completed, the findings are listed, including pharmacokinetics parameters, efficacy measurements, and adverse effects. References to publications arising from the study are also listed.

DEVELOPMENT SCHEDULE CHART

This Gantt chart represents the development plan for the drug. The duration and timing of all preclinical efficacy, toxicology, and clinical trials are displayed graphically as bars stretched over a time period.

REFERENCES

1. Kelloff, G.J., Crowell, J.A., Boone, C.W., Steele, V.E., Lubet, R.A., Greenwald, P., Alberts, D.S., Covey, J.M., Doody, L.A., Knapp, G.G., Nayfield, S., Parkinson, D.R., Prasad, V.K., Prorok, P.C., Sausville, E.A. and Sigman, C.C. Strategy and planning for chemopreventive drug development: Clinical Development Plans. *J. Cell. Biochem.* 20: 55–299, 1994.
2. Kelloff, G.J., Boone, C.W., Malone, W.F. and Steele, V. Recent results in preclinical and clinical drug development of chemopreventive agents at the National Cancer Institute. In: Wattenberg, L., Lipkin, M., Boone, C.W. and Kelloff, G.J. (eds.) *Cancer Chemoprevention.* Boca Raton: CRC Press, 1992, pp. 41–56.
3. Kelloff, G.J., Boone, C.W., Crowell, J.A., Steele, V.E., Lubet, R. and Sigman, C.C. Chemopreventive drug development: Perspectives and progress. *Cancer Epidemiol. Biomarkers Prev.* 3: 85–98, 1994.
4. Kelloff, G.J., Boone, C.W., Steele, V.E., Crowell, J.A., Lubet, R. and Sigman, C.C. Progress in cancer chemoprevention: Perspectives on agent selection and short-term clinical intervention trials. *Cancer Res.* 54: 2015S–1024S, 1994.
5. Kelloff, G.J., Johnson, J.R., Crowell, J.A., Boone, C.W., DeGeorge, J.J., Steele, V.E., Mehta, M.U., Temeck, J.W., Schmidt, W.J., Burke, G., Greenwald, P. and Temple, R.J. Approaches to the development and marketing approval of drugs that prevent cancer. *Cancer Epidemiol. Biomarkers Prev.* 4: 1–10, 1995.
6. Boushey, C.J., Beresford, S.A.A., Omenn, G.S. and Motulsky, A.G. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease. *JAMA* 274: 1049–1057, 1995.
7. Chanarin, I. Adverse effects of increased dietary folate. Relation to measures to reduce the incidence of neural tube defects. *Clin. Invest. Med.* 17: 244–252, 1994.
8. Childers, J.M., Chu, J., Voigt, L.F., Feigl, P., Tamimi, H.K., Franklin, E.W., Alberts, D.S. and Meyskens, F.L., Jr. Chemoprevention of cervical cancer with folic acid: A Phase III Southwest Oncology Group Intergroup Study. *Cancer Epidemiol. Biomarkers Prev.* 4: 155–159, 1995.
9. Whitehead, N., Reyner, F. and Lindenbaum, J. Megaloblastic changes in the cervical epithelium. Association with oral contraceptive therapy and reversal with folic acid. *J. Am. Med. Assoc.* 226: 1421–1424, 1973.
10. Butterworth, C.E., Jr., Hatch, K.D., Gore, H., Mueller, H. and Krumdieck, C.L. Improvement in cervical dysplasia associated with folic acid therapy in users of oral contraceptives. *Am. J. Clin. Nutr.* 35: 73–82, 1982.
11. Butterworth, C.E., Jr., Hatch, K.D., Soong, S.J., Cole, P., Tamura, T., Sauberlich, H.E., Borst, M., Macaluso, M. and Baker, V. Oral folic acid supplementation for cervical dysplasia: A clinical intervention trial. *Am. J. Obstet. Gynecol.* 166: 803–809, 1992.
12. Attili, A.F., Rusticali, A., Varriale, M., Carli, L., Repice, A.M. and Callea, F. The effect of ursodeoxycholic acid on serum enzymes and liver histology in patients with chronic active hepatitis. A 12-month double-blind, placebo-controlled trial. *J. Hepatol.* 20: 315–320, 1994.
13. Lim, A.G. and Northfield, T.C. Ursodeoxycholic acid and primary biliary cirrhosis. *Br. Med. J.* 309: 491– 492, 1994.
14. Johnston, S.R.D., Smith, I.E., Doody, D., Jacobs, S.,

Robertshaw, H. and Dowsett, M. Clinical and endocrine effects of the oral aromatase inhibitor vorozole in postmenopausal patients with advanced breast cancer. *Cancer Res.* 54: 5875–5881, 1994.

15. Goss, P.E., Clark, R.M., Ambus, U., Weizel, H.A.E., Wadden, N.A., Crump, M., Walde, D., Tye, L.M., De Coster, R. and Bruynseels, J. Phase II study of vorozole (R83842), a new aromatase inhibitor, in postmenopausal women with advanced breast cancer in progression on tamoxifen. *Clin. Cancer Res.* 1: 287– 294, 1995.
16. Paridaens, R., Piccart, M., Nooy, M., Klijn, J.G.M., Rubens, R.D., Beex, L., Tomiak, E., van Vreckem, J. and Vinholes, J. Phase II study of the EORTC breast group with vorozole (R 83842), a new non-steroidal aromatase inhibitor in metastatic breast cancer (MBC)—Preliminary results. *Eur. J. Cancer* 29A: S86, abstract no. 455, 1993.
17. Borms, M., Vandebroek, J., Rutten, J., Tytgat, J., De Coster, R., Langenaeken, C. and Bruynseels, J. Vorozole-racemate (R 76713): A specific non-steroidal aromatase inhibitor pilot study in advanced postmenopausal breast cancer. *Eur. J. Cancer* 29A: S84, abstract no. 442, 1993.
18. Taylor, P.R., Li, B., Dawsey, S.M., Li, J.-Y., Yang, C.S., Guo, W. and Blot, W.J. Prevention of esophageal cancer: The nutrition intervention trials in Linxian, China. *Cancer Res.* 54: 2029S–1031S, 1994.
19. Blot, W.J., Li, J.-Y., Taylor, P.R., Guo, W., Dawsey, S., Wang, G.-Q., Yang, C.S., Zheng, S.-F., Gail, M., Li, G.-Y., Yu, Y., Liu, B., Tangrea, J., Sun, Y., Liu, F., Fraumeni, J.F., Jr., Zhang, Y.-H. and Li, B. Nutrition intervention trials in Linxian, China: Supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. *J. Natl. Cancer Inst.* 85: 1483–1492, 1993.
20. National Toxicology Program (NTP). Toxicology and carcinogenesis studies of turmeric oleoresin (CAS No. 8024-37-1) (major component 79%–85% curcumin, CAS No. 458-37-7) in F344/N rats and B6C3F$_1$ mice (feed studies). *NTP Technical Report Series*, No. 427, 1993.
21. Kelloff, G.J., Crowell, J.A., Boone, C.W., Steele, V.E., Lubet, R.A., Greenwald, P., Alberts, D.S., Covey, J.M., Doody, L.A., Knapp, G.G., Nayfield, S., Parkinson, D.R., Prasad, V.K., Prorok, P.C., Sausville, E.A. and Sigman, C.C. Clinical Development Plan: Tamoxifen. *J. Cell. Biochem.* 20: 252–267, 1994.
22. Bradlow, H.L., Michnovicz, J.J., Telang, N.T. and Osborne, M.P. Effects of dietary indole-3-carbinol on estradiol metabolism and spontaneous mammary tumors in mice. *Carcinogenesis* 12: 1571–1574, 1991.
23. Kojima, T., Tanaka, T. and Mori, H. Chemoprevention of spontaneous endometrial cancer in female Donryu rats by dietary indole-3-carbinol. *Cancer Res.* 54: 1446–1449, 1994.
24. Murrill, W.B., Brown, N.M., Zhang, J.-X., Manzolillo, P.A., Barnes, S. and Lamartiniere, C.A. Prepubertal genistein exposure suppresses mammary cancer and enhances gland differentiation in rats. *Carcinogenesis* 17: 1451–1457, 1996.
25. Brown, N.M. and Lamartiniere, C.A. Xenoestrogens alter mammary gland differentiation and cell proliferation in the rat. *Environ. Health Perspect.* 103: 708–713, 1995.
26. Shutt, D.A. and Cox, R.I. Steroid and phyto-oestrogen binding to sheep uterine receptors *in vitro*. *J. Endocrinol.* 52: 299–310, 1972.
27. Verdeal, K., Brown, R.R., Richardson, T. and Ryan, D.S. Affinity of phytoestrogens for estradiol-binding proteins and effect of coumestrol on growth of 7,12-dimethylbenz[*a*]anthracene-induced rat mammary tumors. *J. Natl. Cancer Inst.* 64: 285–290, 1980.
28. Goodman, G.E. The clinical evaluation of cancer chemoprevention agents: Defining and contrasting phase I, II, and III objectives. *Cancer Res.* 52: 2752S–2757S, 1992.
29. Hong, W.K., Lippman, S.M., Itri, L.M., Karp, D.D., Lee, J.S., Byers, R.M., Schantz, S.P., Kramer, A.M., Lotan, R., Peters, L.J., Dimery, I.W., Brown, B.W. and Goepfert, H. Prevention of second primary tumors with isotretinoin in squamous-cell carcinoma of the head and neck. *N. Engl. J. Med.* 323: 795–801, 1990.
30. Collins, J.M., Grieshaber, C.K. and Chabner, B.A. Pharmacologically guided phase I clinical trials based upon preclinical drug development. *J. Natl. Cancer Inst.* 82: 1321–1326, 1990.

Table I. Summary of Development Status on Agents in NCI, DCPC Chemopreventive Drug Development Program

Agent	Preclinical Efficacy[a]	Epidemiology[a]	Preclinical Safety & Pharmacology	Phase I Clinical Safety & Pharmacology			Phase II Clinical Efficacy		Pivotal Targets[f]
				Completed/ On Test	Drug Effect Measurement	Phase II Dose	Completed/ On Test	Planned	
N-Acetyl-*l*-cysteine (NAC)	✔ lung, mammary, colon, bladder	---	✔ FDA approved drug	✔ FDA approved drug OT multidose with oltipraz	✔ GSSG reductase in peripheral lymphocytes	✔ 600 mg qd	---	lung	lung** (w/ vitamin A)
Aspirin	✔[b] bladder, colon, liver, buccal pouch	✔ colon	✔ OTC[c,d]	✔ OTC	✔ tissue PGE_2	✔ 80, 325 mg/ day	OT colon (w/Ca^{++})	---	colon* (+)
Calcium	✔ colon	✔ colon	✔ dietary component	✔ dietary component	✔ serum Ca^{++}	✔ 1,500 mg/ day as Ca^{++}	OT colon (w/wo aspirin), colon (w/wo vitamin D_3)	---	colon*(+), colon **

Table I. Summary of Development Status on Agents in NCI, DCPC Chemopreventive Drug Development Program (*continued*)

Agent	Preclinical Efficacy[a]	Epidemiology[a]	Preclinical Safety & Pharmacology	Phase I Clinical Safety & Pharmacology			Phase II Clinical Efficacy		Pivotal Targets[f]
				Completed/ On Test	Drug Effect Measurement	Phase II Dose	Completed/ On Test	Planned	
β-Carotene	✔ colon, mammary, liver, skin	✔ lung, colon, esophagus, upper respiratory tract, oral cavity, cervix, ovary	✔ GRAS	✔ GRAS	✔ serum drug, LDL oxidation, DNA damage	✔ 30–50 mg qd issue[e]: dose-limiting skin yellowing	✔ oral cavity (+) OT cervix, colon	---	lung (w/wo vitamin E)* (NE), lung (w/vitamin A)* (NE), colon* (NE), multiple sites* (NE), multiple sites (w/Se + vitamin E)* (+) issue: pro-oxidant activity
Curcumin (Food Grade and Purified)	✔ colon, mammary, skin, duodenum, forestomach, tongue	---	✔ food grade: 90-day, carcinogenicity, reproductive effects OT purified: 90-day	OT single- and multidose	OT COX-1,2, PGE_2, lipoxygenase, 5(S)-HETE	---	---	colon, breast, oral cavity	colon, oral cavity, skin

Table I. Summary of Development Status on Agents in NCI, DCPC Chemopreventive Drug Development Program (*continued*)

Agent	Preclinical Efficacy[a]	Epidemiology[a]	Preclinical Safety & Pharmacology	Phase I Clinical Safety & Pharmacology			Phase II Clinical Efficacy		Pivotal Targets[f]
				Completed/ On Test	Drug Effect Measurement	Phase II Dose	Completed/ On Test	Planned	
Dehydroepiandrosterone (DHEA)	✔ mammary, colon, prostate, skin, liver, lung, cervix, lymphoma	✔ breast, stomach, ovary, bladder	✔ 6-month	✔ several multidose in males and females	✔ serum DHEA, DHEA-S, IGF-I OT G6PDH (lymphocytes)	✔ 200–300 mg/day	OT breast, prostate, multiple myeloma	---	breast, prostate
DHEA Analog 8354 (Fluasterone)	✔ colon, mammary, skin	✔ see DHEA	✔ 90-day, hormone effects	---	--- see DHEA	---	---	breast, prostate	breast, prostate
2-Difluoromethylornithine (DFMO)	✔ bladder, colon, mammary, liver, stomach, skin	---	✔ 1 year, ototoxicity, genotoxicity OT carcinogenicity, reproductive effects	✔ single- and multidose OT single- and multidose with piroxicam issues: ototoxicity, reproductive effects	✔ tissue polyamines	✔ 0.5 g/m^2/day (also, 0.25 g/m^2/day)	OT bladder, breast, cervix, oral cavity, esophagus	colon, prostate	colon, bladder, breast
Finasteride (Proscar®)	✔ prostate (BPH)	---	✔ FDA approved drug	✔ FDA approved drug	✔ serum DHT, PSA (shallow dose-response)	---	---	prostate	prostate**

Table I. Summary of Development Status on Agents in NCI, DCPC Chemopreventive Drug Development Program (*continued*)

Agent	Preclinical Efficacy[a]	Epidemiology[a]	Preclinical Safety & Pharmacology	Phase I Clinical Safety & Pharmacology			Phase II Clinical Efficacy		Pivotal Targets[f]
				Completed/ On Test	Drug Effect Measurement	Phase II Dose	Completed/ On Test	Planned	
Folic Acid	✔ colon, lung	✔ colon, cervix	✔ vitamin	✔ vitamin	✔ RBC folate, SAM/SAH, serum homocysteine, DNA methylation	✔ 5, 10 mg qd	✔ cervix (+, NE) OT colon	colon, lung	colon**, cervix* (NE), lung
Genistein (90% and 43% in Isoflavone Mixture)	✔ colon, mammary, skin	✔ breast	OT 90-day	OT single- and multidose	---	---	---	breast, prostate	breast, prostate
Glycyrrhetinic Acid/ Carbenoxolone	✔ mammary, colon, skin, liver	---	✔ 1-year	--- issue: hyperkalemia, hypertension	---	---	---	---	breast, colon
all-*trans*-*N*-(4-Hydroxyphenyl)retinamide (4-HPR)	✔ mammary, bladder, lung, prostate, liver, skin	---	✔ 1-year, reproductive effects, carcinogenicity issues: hemangiosarcomas in mice, teratogenicity	✔ single- and multidose issue: night blindness	✔ plasma retinol, IGF-1, TGFβ	✔ 200 mg qd, regular drug holidays (*e.g.*, 3 days/ month)	OT breast (w/ wo tamoxifen), bladder, lung, cervix, prostate, oral cavity, skin	---	breast**, cervix, skin, bladder**, lung, prostate
Ibuprofen	✔ colon, bladder, mammary, lung, buccal pouch	---	✔ OTC	✔ OTC	✔ tissue PGE_2	✔ 1,200 mg/ day	---	colon, bladder	colon, bladder

Table I. Summary of Development Status on Agents in NCI, DCPC Chemopreventive Drug Development Program *(continued)*

Agent	Preclinical Efficacy[a]	Epidemiology[a]	Preclinical Safety & Pharmacology	Phase I Clinical Safety & Pharmacology			Phase II Clinical Efficacy		Pivotal Targets[f]
				Completed/ On Test	Drug Effect Measurement	Phase II Dose	Completed/ On Test	Planned	
Indole-3-carbinol	✔ mammary, endometrium, colon, liver, lung, tongue, forestomach	---	✔ 90-day	OT single- and multidose	OT urinary 2-hydroxy estradiol	---	---	breast	breast
Oltipraz	✔ lung, colon, mammary, bladder, skin, lymphatic, forestomach	---	✔ 1-year, reproductive effects (teratology)	✔ single- and multidose OT single- and multidose w/NAC	OT GST/GSH and related enzymes	✔ 125 mg qd	OT lung, liver	breast, bladder, prostate	lung
Perillyl alcohol	✔ colon, breast, pancreas, liver	---	✔ 90-day	OT single- and multidose	OT IGF-I, TGFβ	---	---	breast, prostate	breast
Piroxicam	✔ bladder, colon, lung, tongue	---	✔ 90-day	✔ FDA approved drug OT single- and multidose with DFMO	OT PGE_2	✔ 10 mg qd	OT colon	colon, bladder (both w/wo NSAID)	colon, bladder (both w/ wo NSAID)

Table I. Summary of Development Status on Agents in NCI, DCPC Chemopreventive Drug Development Program (*continued*)

Agent	Preclinical Efficacy[a]	Epidemiology[a]	Preclinical Safety & Pharmacology	Phase I Clinical Safety & Pharmacology			Phase II Clinical Efficacy		Pivotal Targets[f]
				Completed/ On Test	Drug Effect Measurement	Phase II Dose	Completed/ On Test	Planned	
9-*cis*-Retinoic acid	✔ breast, skin, colon	---	✔ 90–135 day, reproductive effects (teratogenicity) issues: teratogenicity, retinol depletion	✔ single- and multidose issues: headache, lipid elevation, skin effects (cheilitis, dry skin)	OT RAR, RXR, IGF-I	---	---	breast, prostate (both w/wo antiestrogen)	breast, prostate (both w/wo antiestrogen), lung**
13-*cis*-Retinoic acid	✔ bladder, skin, lung, oral cavity, colon, mammary, pancreas	---	✔ FDA approved drug issues: teratogenicity, liver, lipids, skin (erythema, alopecia)	✔ FDA approved drug issues: teratogenicity, cheilitis, elevated lipids	OT RARβ, 4-oxo-13-*cis*-retinoic acid	OT low dose to limit toxicity: <1 mg/kg-bw/day	OT oral cavity	---	lung*, head and neck (+)
Selenium compounds: *l*-Selenomethionine	✔ mammary, colon, skin, lung, trachea, liver, stomach, pancreas	✔ bladder, breast, colon, esophagus, lung, prostate (often, higher cancer incidences associated with Se deficiency)	✔ 90-day issues: liver, blood toxicity	✔ long-term exposure to 200 and 400 μg/day as selenized yeast	OT plasma Se, toenail Se, GSH-Px	✔ 200, 400 μg Se/day	---	breast, prostate (both w/wo vitamin E)	breast, prostate (both w/wo vitamin E)

Table I. Summary of Development Status on Agents in NCI, DCPC Chemopreventive Drug Development Program (*continued*)

Agent	Preclinical Efficacy[a]	Epidemiology[a]	Preclinical Safety & Pharmacology	Phase I Clinical Safety & Pharmacology			Phase II Clinical Efficacy		Pivotal Targets[f]
				Completed/ On Test	Drug Effect Measurement	Phase II Dose	Completed/ On Test	Planned	
Selenium compounds: 1,4-Phenylenebis-(methylene)selenocyanate	✔ mammary, colon, lung (see also *l*-selenomethionine)	✔ (see *l*-selenomethionine)	OT 90-day	---	--- (see also *l*-selenomethionine)	---	---	breast, colon, lung	breast, colon
Sulindac	✔ colon, bladder, lung, forestomach	---	✔ FDA approved drug	✔ FDA approved drug	✔ tissue PGE_2	✔ 150, 200 mg bid	✔ colon (+, polyp regression, proliferation) OT colon	---	colon
Sulindac sulfone	✔ colon, breast	---	✔ 6-month, reproductive effects (Segment I, teratology) issue: liver enzyme elevation	✔ single- and multidose OT Phase I/IIa in FAP patients at 200, 300, 400 mg bid	OT apoptosis	OT 200, 300 mg bid	OT colon (Phase I/IIa in FAP patients)	colon, breast, cervix	colon
Tamoxifen	✔ mammary	---	✔ FDA approved drug	✔ FDA approved drug	OT TGFβ, SHBG	✔ 20 mg qd	OT breast (w/ wo 4-HPR)	---	breast**

Table I. Summary of Development Status on Agents in NCI, DCPC Chemopreventive Drug Development Program (*continued*)

Agent	Preclinical Efficacy[a]	Epidemiology[a]	Preclinical Safety & Pharmacology	Phase I Clinical Safety & Pharmacology			Phase II Clinical Efficacy		Pivotal Targets[f]
				Completed/ On Test	Drug Effect Measurement	Phase II Dose	Completed/ On Test	Planned	
Tea (including Tea Polyphenols)	✔ colon, duodenum, esophagus, forestomach, liver, lung, mammary, skin	✔ colon, breast, gall bladder, liver, lung, nasopharynx, stomach, pancreas, uterus	OT 90-day	---	--- plasma and urinary catechins, ODC, GSH/GST, PGE_2	---	---	colon, esophagus, lung, skin	colon, esophagus, lung
Ursodiol	✔ colon	---	✔ FDA approved drug	✔ FDA approved drug OT Phase I/IIa in subjects at high risk for colon cancer	✔ blood and fecal bile acids	---	---	colon	colon

Table I. Summary of Development Status on Agents in NCI, DCPC Chemopreventive Drug Development Program (*continued*)

Agent	Preclinical Efficacy[a]	Epidemiology[a]	Preclinical Safety & Pharmacology	Phase I Clinical Safety & Pharmacology			Phase II Clinical Efficacy		Pivotal Targets[f]
				Completed/ On Test	Drug Effect Measurement	Phase II Dose	Completed/ On Test	Planned	
Vitamin A	✔ skin, respiratory tract, breast, bladder, oral cavity, forestomach, colon, liver, pancreas	✔ lung, cervix, ovary, esophagus, larynx, oral cavity, nasopharynx. Also, breast, colon, prostate, lung associated with vitamin A deficiency	✔ vitamin issues: teratogenicity, liver, lipid, and skin effects (erythema, alopecia, thickening), bone loss	✔ vitamin issues: liver toxicity	**OT** RAR, ODC	--- 10,000–40,000 IU/ day possible	✔ cervix (+), skin, colon (+) **OT** lung	---	oral cavity* (+), oral cavity**, lung (w/β-carotene)* (NE), lung**, skin* (+), melanoma* (+), colon* (NE), cervix. Also, gastric* (NE) and esophagus* (NE) w/other vitamins and minerals **OT** cervix, lung, oral cavity
Vitamin D_3 and Analogs	✔ colon (w/wo Ca^{++}), mammary, skin	✔ colon, breast, prostate	✔ vitamin (vitamin D_3 and active metabolite) --- analogs issue: hypercalcemia	✔ vitamin (vitamin D_3 and active metabolite) --- analogs issues: hypercalcemia, hypercalciurea	**OT** TGFβ, plasma alkaline phosphatase, serum creatinine phosphokinase	✔ 400 IU vitamin D_3 --- analogs	**OT** colon (vitamin D_3 w/ wo Ca^{++})	colon, breast	colon, breast

Table I. Summary of Development Status on Agents in NCI, DCPC Chemopreventive Drug Development Program (*continued*)

Agent	Preclinical Efficacy[a]	Epidemiology[a]	Preclinical Safety & Pharmacology	Phase I Clinical Safety & Pharmacology			Phase II Clinical Efficacy		Pivotal Targets[f]
				Completed/ On Test	Drug Effect Measurement	Phase II Dose	Completed/ On Test	Planned	
Vitamin E	✔ skin, buccal pouch, tongue, skin, liver, pancreas, esophagus, small intestine	✔ pancreas, stomach, bladder, lung (often, higher cancer incidences in populations with low serum levels, w/wo Se deficiency)	✔ vitamin, GRAS	✔ vitamin, GRAS	✔ plasma α-tocopherol/lipid	✔ 400 IU/day	---	prostate, breast (both w/wo *l*-selenomethionine)	esophagus (w/Se)* (+), prostate* (+), breast**, multiple sites**. Also, breast, prostate (both w/Se)
(+)-Vorozole	✔ mammary	---	✔ issue: potential androgenicity (increased muscularity, ovarian weight, and body weight)	✔	OT plasma estradiol	--- 1–5 mg/day depresses estradiol significantly	---	breast, prostate	breast

[a]Target organs in which chemopreventive activity has been found in either Chemoprevention Branch-sponsored or published studies. [b]✔=Adequate testing/evidence for further development, **OT**=currently on test, --- = to be determined. [c]For ✔=description of testing/evidence on which further development is based, for **OT**=description of current testing. [d]Abbreviations are listed in Appendix A to this volume. [e]Issues are factors to be considered in further development efforts. [f]Cancer targets for Phase III chemopreventive efficacy studies: *=study completed, results follow in (), **=study in progress. Study results: +=positive, NE=no effect.