The convergence of cancer prevention and therapy in early-phase clinical drug development

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After decades of separate but not equal drug development, prevention and therapy are beginning to converge at the level of early-phase clinical testing. This highly beneficial convergence is due to spectacular molecular advances in our understanding of neoplasia (both cancer and precancer), cancer risk and prognosis, and the mechanisms by which novel drugs with less toxicity and more cytostatic activity profiles target specific molecular events to suppress malignant and premalignant cells. The future full convergence of prevention-therapy drug development (aided by technological advances, such as in molecular imaging) promises to hasten the progress of oncology in reducing the public health impact of the major cancers.

Cancer therapy and prevention drugs traditionally have developed along very separate tracks and with very different approaches, largely because of methods established prior to certain advances in molecular biology, such as those allowing analyses of specific growth factor signaling pathways. Early-phase clinical trials of novel therapy drugs generally establish the maximum tolerated dose (MTD) in advanced cancer patients with no options for further standard treatment (Eisenhauer et al., 2000). This approach emerged as an appropriate strategy for the development of cytotoxic agents with a narrow window between their toxic and effective doses, or a narrow therapeutic index. With toxic effective doses and usually intravenous administration, these agents were usually inappropriate for prevention. Early-phase preventive drug development typically has proceeded along far less structured lines that seemed appropriate for testing relatively nontoxic, frequently widely available agents, which often were suggested for a role in cancer prevention by observational and limited preclinical data.

Explosive advances in the molecular understanding of malignant and premalignant carcinogenesis, cancer risk and prognosis, and drug effects on relevant molecular targets and pathways have produced a new generation of molecular-targeted drugs with acceptable therapeutic indexes for both prevention and therapy. Early-phase drug development approaches for prevention and therapy no longer need to be mutually exclusive and indeed already have begun to converge. This article will focus on the molecular considerations and underpinnings, clinical settings, and rapid implementation of a practical program of convergent development of cancer prevention and therapy agents.

Molecular considerations of the prevention-therapy convergence

Many factors facilitate the prevention-therapy convergence, including a molecular rationale based on our rapidly advancing understanding of multistep neoplasia, growing recognition of intraepithelial neoplasia (IEN) and overlapping molecular alterations in IEN and cancer, advancing identification of molecular high risk associated with IEN, increasing emphasis on oral, bioavailable small molecules with a wide therapeutic index and targeting the abnormal molecular biology of neoplasia, and practical considerations of drug development timelines and the challenges inherent in identifying qualified novel agents for clinical trials.

Molecular rationale

Two important concepts support merging the early clinical development of cancer therapy and prevention agents: (1) "neoplasia" includes states of both "precancer" and "cancer," as elucidated by the multistep molecular signature of human carcinogenesis (Bishop and Weinberg, 1996); and (2) the molecular hallmarks of cancer development—evading apoptosis, self-sufficiency in growth signals, insensitivity to antigrowth signals, strong replicative potential, and sustained angiogenesis—are frequently present in both cancer and precancer (Hanahan and Weinberg, 2000). Recent studies suggest that many of the molecular and biochemical events leading to the increased proliferation and reduced apoptosis found in precancer and early invasive cancer are the same events that give cancer cells the ability to invade and metastasize (Bernards and Weinberg, 2002; Hynes, 2003). Therefore, the molecular targets relevant to advanced cancer likely also are relevant to precancer, supporting the argument that early assessments of novel drugs can be relevant to both prevention and therapy.

IEN

Illustrated by exquisite models of multistep oral and colorectal carcinogenesis (Califano et al., 1996; Vogelstein et al., 1988), IEN is a noninvasive lesion representing an often pathologically discernable intermediate state between normal epithelium and invasive cancer. Clinically relevant IEN has genetic abnormalities, loss of cellular control, phenotypic characteristics overlapping those of invasive cancer, and a substantial risk of cancer or biologically aggressive, potentially lethal cancer. The cancer risk of an IEN is a key issue in its selection as a relevant prevention endpoint for convergent drug development; molecular risk models, including those with somatic and constitutional genetic alterations (Spitz et al., 2004), will play an important role in assessing this risk (as well as cancer prognosis). Highest-risk IEN, e.g., in the colorectal region and oral cavity, will be especially useful for convergent drug development, as detailed later. The colorectal IEN familial adenomatous polyposis (FAP) is associated with a virtually 100% risk of colorectal cancer (Steinbach et al., 2000). High-risk oral IEN includes that with aneuploidy, which is associated with over a 50% risk of biologi-

cally aggressive oral cancer (Sudbo et al., 2004), or that with allelic imbalance (Lippman and Hong, 2001). IENs have varying degrees of cancer risk (depending on the organ site and specific lesion) (O'Shaughnessy et al., 2002), and some IENs are potentially less informative (e.g., because of a low transformation rate) than others as endpoints for drug development.

The diagnosis of IEN is increasing, probably largely because of the general aging of the population and because of technological advances, such as improvements in noninvasive imaging, endoscopic techniques, and molecular diagnostics. Even in the pancreas and other sites of aggressive malignancies with poor accessibility and incompletely characterized early-stage neoplasia, IENs and other early neoplastic lesions are beginning to be identified, have many genetic and molecular alterations also found in advanced cancer, and so are potential targets for prevention and therapy (Corless et al., 2002; Hruban et al., 2000; Li et al., 2004).

Molecular-targeted study in therapy and prevention

The primarily cytotoxic therapy agents developed in the past often affected fairly nonspecific targets such as DNA or tubulin. The dose, toxicity, and therapeutic effect of these agents generally are directly related, i.e., toxicity correlates with and so serves as a surrogate for activity. The phase II dose expected to provide a reasonable therapeutic index in cancer (and frequently too toxic for prevention) was derived from the phase I-defined MTD and pharmacokinetics. The MTD remains the primary outcome of many phase I trials, although new drugs increasingly modulate specific molecular targets (e.g., specific enzymes) involved in cell signaling, angiogenesis, or metastasis (Parulekar and Eisenhauer, 2004). The MTD likely continues to be used in phase I therapy trials because of the complexity and logistics of using molecular/cellular endpoints, unclear mechanisms of many drugs, and the argument that the MTD may have the greatest potential efficacy in cancer patients (Korn, 2004).

The MTD, however, may not be the optimal outcome of phase I testing of agents with more cytostatic activity profiles, or with a dose, toxicity, and response that frequently are not directly related. These agents may substantially modulate a molecular target, possibly even reaching a plateau in this activity, at doses well below that of dose-limiting toxicity, reducing the utility of toxicity as an activity surrogate. Therefore, it is extremely important for phase I dose escalation trials of molecular-targeted agents to attempt to define a range of doses that affect the agent's molecular target. These agents may also demonstrate dose responsiveness ranging well into the toxic end of the spectrum. An active dose well below dose-limiting toxicity or the MTD is important for the chronic dosing typical of prevention, and higher, more toxic doses may be suitable for cancer therapy.

Emerging data on cyclooxygenase-2 (COX-2) and its inhibitors in the colon provide a clear example of overlapping molecular targets for prevention and therapy. Early work showing that COX-2 was not expressed in normal colon cells and was expressed progressively in colon polyps (adenomas) and cancer led to testing nonsteroidal antiinflammatory drugs (NSAIDs) that specifically target (and inhibit) COX-2 (and thus downstream prostaglandin E_2 [PGE_2]) for colorectal cancer prevention. (These NSAIDs were developed initially for arthritis.) COX-2 also appears to be a key mediator of numerous cancer-related processes, including angiogenesis and mechanisms leading to invasion and metastasis (Dannenberg and Subbaramaiah, 2003; Thun et al., 2002). The selective COX-2-inhibitor celecoxib significantly reduced polyp burden and led to the U.S. Food and Drug Administration (FDA) approval of celecoxib as an adjunct to surgery in FAP patients (Steinbach et al., 2000). The active dose of this agent (400 mg/bid) has been shown to inhibit its target in pharmacodynamic studies within both cancer (Altorki et al., 2003) and IEN (L.J. Wirth et al., 2003, Proc. Frontiers in Cancer Prev. Res., abstract), and celecoxib induced apoptosis and inhibited proliferation in the adenomas of responsive FAP patients (Sinicrope et al., 2004). The NSAID sulindac also significantly reduced the polyp burden of FAP patients (Giardiello et al., 1993) and did so in correlation with the inhibition of protaglandins (PGE_2 and F_2) (Nugent et al., 1996) and proliferation (Nugent et al., 1993). Recent research has identified other pathways related to COX-2—e.g., pathways involving 15-lipoxygenase-1 (Hsi et al., 2004; Shureiqi et al., 2002), β-catenin (Boon et al., 2004), peroxisome proliferator-activated receptor (PPAR)-delta (He et al., 1999; Shureiqi et al., 2003), and transactivation of epidermal growth factor receptor (EGFR) signaling (Dannenberg et al., 2004; Pai et al., 2002)—that will improve our understanding of and provide new preventive and therapeutic targets for treating colorectal neoplasia.

The oral cavity and breast also have overlapping molecular targets suitable for prevention and therapy. Aneuploid oral IEN shares several molecular targets, including EGFR and COX-2, with oral cancer. The coexistence of these targets and interactions of their signaling pathways (Torrance et al., 2000) support combinatorial approaches in aneuploid oral IEN. Phase I therapy testing of EGFR inhibitors has produced candidate agents for oral cancer therapy (Cohen et al., 2003) and for prevention in aneuploid IEN patients. Similarly, the inactivation/mutation of p53 is an important event in advanced oral IEN and cancer, and targeting p53 has produced promising results in oral cancer prevention (Rudin et al., 2003) and therapy (Clayman et al., 1998; Khuri et al., 2000). Regarding the breast, HER2 is associated with high-grade ductal carcinoma in situ (Hoque et al., 2002) and a poor prognosis in breast cancer patients (Slamon et al., 1987), supporting the development of new oral HER2-targeted drugs (Rusnak et al., 2001) for breast cancer prevention and therapy. With highly specific rather than pleiotropic molecular effects, targeted agents may be more effective in earlier neoplasia (with fewer genetic alterations) than in advanced cancer (with more genetic alterations and tumor heterogeneity).

Molecular-targeted drug development issues

Practical drug development issues also support a convergent drug development approach. Laboratory research is producing an avalanche of molecular targeted agents with improving therapeutic indexes that emphasize the importance of streamlining the drug development process. Traditional drug development requires extremely long timelines for drug discovery, target validation, clinical development, and regulatory approval. Therefore, it is imperative that we develop innovative strategies that integrate early-phase prevention and therapy studies. A convergent approach will accelerate the drug development process, from introducing a novel molecular-targeted agent to producing the final results of a measurable clinical benefit for FDA review.

A practical model for the prevention-therapy convergence

This section outlines a practical program for implementing the convergence of cancer therapy and prevention drug development. Overlapping prevention-therapy targets and endpoints would be identified from molecular models of the cancer risk associated with IEN and of the development and progression of

cancer and IEN. This new approach integrates prevention endpoints into early-phase dose-escalation trials, which could be conducted in a mixed cancer population (traditional) or advanced specific-cancer population (when an agent shows compelling preclinical activity in a specific cancer). Whenever feasible, an imbedded prevention endpoint that examines the impact of the agent on a specific IEN should be integrated within phase I trials in specific cancer patients. Pharmacodynamic molecular effects involving targets and signaling pathways in broad phase I trials enrolling all cancer types would be assessed in an easily accessed surrogate tissue, such as the skin or peripheral blood mononuclear cells. For example, early clinical testing of EGFR inhibitors assessed phosho-EGFR in the normal skin of advanced cancer patients (Albanell et al., 2002), and early clinical testing of mammalian target of rapamycin (mTOR) inhibitors assessed inactivation of ribosome protein S6 kinase in peripheral blood mononuclear cells (Boulay et al., 2004). Molecular endpoints in a phase I trial conducted in specific-cancer patients would be measured in tumor tissue or the relevant IEN to get a clear picture of target-tissue effects. Clinical effects on the IEN and cellular effects (proliferation, apoptosis, angiogenesis) also would be monitored and evaluated for associations or correlations with the agent's molecular effects in deciding whether a particular agent should proceed in development for cancer prevention. Phase I pharmacokinetic assessments of the drug levels can determine the phase II dose, as occurred with HER2-targeting trastuzumab (Leyland-Jones et al., 2003). The overall potential of phase I testing is to determine a range of biologically active doses (potentially including the MTD) for further therapy and prevention testing.

Convergent phase II trials are more conducive (than are phase I trials) to imbedding IEN endpoints within trials conducted in advanced specific-cancer populations. The clinical effect of an agent on an imbedded IEN would be an important independent factor in deciding on future development for prevention. Convergent phase II trials also could be conducted (in the same time frame) in advanced cancer patients without an imbedded IEN and in IEN populations (most likely high-risk) without cancer. High-risk IEN would be preferable to all- or low-risk IEN, as it would provide better evidence of a potential preventive benefit and allow a better risk-benefit relationship for testing an investigational new agent. Molecular, cellular, and clinical evidence from the cancer-only setting could be compelling for prevention, just as such evidence from studies of IEN-only patients could be compelling for therapy. These complementary benefits are illustrated by celecoxib (400 mg/bid), which was suggested by prevention-related results in the high-risk IEN FAP for testing in colorectal cancer therapy (Koehne and Dubois, 2004).

Another important phase II model is short-term multiple-dose trials in preresection, earlier-stage cancer patients, whose resection tissue specimens lend themselves to assessments of target-site pharmacokinetics and pharmacodynamics in (and which may differ by) cancer, IEN, and normal-appearing tissue. For example, phase II preresection testing of a farnesyl transferase inhibitor in head and neck cancer patients (M.S. Kies et al., 2001, Proc. Amer. Assoc. Cancer Res., abstract) has produced promising results applicable to both prevention and therapy. This model can assess the effects of a range of doses (e.g., doses selected specifically for their potential benefit in IEN or early or advanced cancer patients). Preresection patients typically have untreated cancers that are less drug-resistant and so are more amenable to activity assessments than are advanced, heavily pretreated cancers. This model also can help select or exclude potential patients for longer-term phase II testing, as demonstrated by the ability of presurgical testing to identify tamoxifen's clear selectivity for estrogen-receptor (ER)-positive (versus ER-negative) breast tumors (Assersohn et al., 2003). Limited inherently by a short duration and the requirement to not compromise subsequent standard surgery and care, the preresection model may be too short-term to detect drug activity or unexpected toxicity. Therefore, preresection models should be used only as adjuncts to other, longer-term phase II trials.

Phase III trials of agents with promise (acceptable toxicity, target/pathway modulation, cellular and clinical effects on IEN and/or cancer) demonstrated in early-phase trials would be conducted separately for therapy and prevention. Whenever feasible, phase III prevention trials should assess whether cancer development correlates with the relevant IEN outcome, thereby helping to inform future early-phase testing and addressing the IEN's validity as a surrogate phase III endpoint. Phase III, as well as phase II, trials also should assess the molecular profiles of neoplasia to determine which IENs or cancers most likely will respond to a targeted agent (Spitz et al., 2004). For example, cyclin-D1 polymorphisms can mark the sensitivity of patients with advanced head and neck IEN to isotretinoin (likely related to effects on ubiquitin-dependent proteolysis) (Izzo et al., 2003), somatic activating EGFR mutations can predict response to gefitinib in non-small-cell lung cancer patients (Lynch et al., 2004; Paez et al., 2004), and mutations in KIT or platelet-derived growth factor receptor α predict response to imatinib in patients with gastrointestinal stromal tumors (Heinrich et al., 2003a, 2003b). Proteomic and genomic profiles may also indicate sensitivity to targeted agents, e.g., the sensitivity of patients with the advanced colorectal IEN FAP to celecoxib (proteomic) (Xiao et al., 2004) and of patients with ER-positive breast cancer to tamoxifen (genomic) (S. Paik et al., 2003, Breast Cancer Res., abstract).

Colorectal neoplasia is an excellent setting for imbedding an IEN endpoint in a phase I or II clinical trial conducted in an advanced cancer population. The impact of novel agents on the early clonal precursor of colorectal cancer, dysplastic aberrant crypt foci (ACF), could be examined in a phase I or II trial in advanced colorectal cancer patients, who typically have a high rate of ACF. Dysplastic ACF share many of the molecular alterations associated with adenomas and invasive colon cancer (Cheng and Lai, 2003). ACF in rectal mucosa can be accurately quantified and are responsive to clinically active interventions such as sulindac (Giardiello et al., 1993; Takayama et al., 1998) and aspirin (Baron et al., 2003; Shpitz et al., 2003). Therefore, advanced colon cancer patients on early clinical trials of novel agents with potential for colon cancer prevention could be serially examined using flexible sigmoidoscopy for the impact of the novel agent on rectal ACF. Effects on rectal dysplastic ACF (molecular, cellular, and clinical) could provide important insights into an agent's dose and toxicity, setting the stage for more definitive testing in patients with more advanced states of colorectal IEN, such as large and/or villous colorectal adenomas. Early-phase cancer trials with imbedded IENs would greatly accelerate prevention-therapy drug development. This approach will become increasingly feasible as new molecular and functional imaging techniques come on line for monitoring serial target-tissue changes (Morgan et al., 2003; Rao et al., 2003).

Oral neoplasia is another excellent setting for phase II study

in high-risk IEN patients without cancer. As outlined above, it is possible to identify oral IEN patients (primarily those with DNA aneuploidy) at a high risk for progression to invasive cancer and death, and this IEN has molecular targets, e.g., COX-2 overexpression and EGFR activation, that overlap with targets in oral cancer patients (Dannenberg et al., 2004). With no standard effective preventive treatment (Sudbo et al., 2004), aneuploid oral IEN patients are an appropriate population for the phase II study of novel drugs.

The practical implementation of convergent drug development also faces important hurdles and challenges. It has been difficult to identify IEN patients at the greatest risk of invasive cancer for phase II trials. Clinical trials of molecular-targeted agents are complex (e.g., because of issues involving serial biopsies and target and assay validations) (Korn, 2004; Parulekar and Eisenhauer, 2004; Tubbs et al., 2001). It can be difficult to define the range of biologically active doses of targeted agents. There are also national regulatory obstacles to convergent development. For example, calling the clinical setting "prevention" or "therapy" can lead regulatory agencies to make different decisions on the same agent in similar patient populations. Recognizing the potential for this problem, the FDA has created the new Office of Oncology Drug Products to eliminate cross-FDA Division inconsistencies in evaluating cancer prevention and therapy drugs.

Conclusions

Cancer prevention and therapy are converging and will continue to converge at the level of novel drug development. With the explosion of promising new molecular targeted drugs, the mounting costs of drug development, and the continuing high incidences and mortality rates of major cancers, it is urgent that prevention and therapy researchers collaborate to efficiently credential new drugs capable of treating the full range of neoplasia, from IEN to metastatic disease. An efficient and convergent drug development program could relatively quickly sort out the most from the least promising candidates among the many new molecular-targeted agents, accelerate promising new agent development for use in cancer prevention, and put unpromising agents on hold at a relatively early stage in the drug development process.

Although none have been developed convergently, molecular targeted drugs are already in late-stage clinical study or are FDA approved for both prevention and therapy. The selective estrogen-receptor modulator (SERM) tamoxifen moved from full clinical development and FDA approval for breast cancer therapy into clinical development and FDA approval for several breast cancer prevention settings (Lippman and Brown, 1999). The COX-2 inhibitor celecoxib has moved from FDA approval in a cancer prevention setting into cancer therapy trials (e.g., combined with other agents) (Dannenberg and Subbaramaiah, 2003; Koehne and Dubois, 2004), whereas aromatase inhibitors have moved from FDA-approved cancer therapy into cancer prevention trials (Dunn et al., 2004). It is not always even clear whether targeted drugs are preventing or treating subclinical cancer, as has been argued with respect to tamoxifen in the Breast Cancer Prevention Trial (Lippman and Brown, 1999) and finasteride in the Prostate Cancer Prevention Trial (Thompson et al., 2003), or whether the clinical setting represents precancer (prevention) or subclinical cancer (therapy) (Lippman and Hong, 2002), as illustrated by the conjoined prevention (of second primary tumors) and adjuvant therapy/recurrence settings involving curatively resected cancer patients (Leong et al., 1998; Swain et al., 2004).

The current inefficient system of serially developing drugs for therapy then prevention and vice versa creates unnecessary expense and delay in improving the public health via the full range of benefits offered by molecular-targeted drugs such as SERMs. Innovative convergent drug development may eventually redefine cancer, emphasizing molecular over physical/invasion characteristics. In a future of fully converged drug development, an invasive lesion with a low molecular risk of recurrence or mortality may be managed less aggressively than would be a preinvasive lesion with a very high molecular risk of advanced cancer and mortality. Intervening effectively in the full range of neoplasia promises to accelerate the progress of oncology toward achieving its major goal of eliminating the dire consequences of the major cancers.

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References

Albanell, J., Rojo, F., Averbuch, S., Feyereislova, A., Mascaro, J.M., Herbst, R., LoRusso, P., Rischin, D., Sauleda, S., Gee, J., et al. (2002). Pharmacodynamic studies of the epidermal growth factor receptor inhibitor ZD1839 in skin from cancer patients: Histopathologic and molecular consequences of receptor inhibition. J. Clin. Oncol. *20*, 110–124.

Altorki, N.K., Keresztes, R.S., Port, J.L., Libby, D.M., Korst, R.J., Flieder, D.B., Ferrara, C.A., Yankelevitz, D.F., Subbaramaiah, K., Pasmantier, M.W., et al. (2003). Celecoxib, a selective cyclo-oxygenase-2 inhibitor, enhances the response to preoperative paclitaxel and carboplatin in early-stage non-small-cell lung cancer. J. Clin. Oncol. *21*, 2645–2650.

Assersohn, L., Salter, J., Powles, T.J., A'hern, R., Makris, A., Gregory, R.K., Chang, J., and Dowsett, M. (2003). Studies of the potential utility of Ki67 as a predictive molecular marker of clinical response in primary breast cancer. Breast Cancer Res. Treat. *82*, 113–123.

Baron, J.A., Cole, B.F., Sandler, R.S., Haile, R.W., Ahnen, D., Bresalier, R., McKeown-Eyssen, G., Summers, R.W., Rothstein, R., Burke, C.A., et al. (2003). A randomized trial of aspirin to prevent colorectal adenomas. N. Engl. J. Med. *348*, 891–899.

Bernards, R., and Weinberg, R.A. (2002). A progression puzzle. Nature *418*, 823.

Bishop, J.M., and Weinberg, R.A., eds. (1996). Molecular Oncology. (New York: Scientific American, Inc.).

Boon, E.M., Keller, J.J., Wormhoudt, T.A., Giardiello, F.M., Offerhaus, G.J., van der Neut, R., and Pals, S.T. (2004). Sulindac targets nuclear beta-catenin accumulation and Wnt signalling in adenomas of patients with familial adenomatous polyposis and in human colorectal cancer cell lines. Br. J. Cancer *90*, 224–229.

Boulay, A., Zumstein-Mecker, S., Stephan, C., Beuvink, I., Zilbermann, F., Haller, R., Tobler, S., Heusser, C., O'Reilly, T., Stolz, B., et al. (2004). Antitumor efficacy of intermittent treatment schedules with the rapamycin derivative RAD001 correlates with prolonged inactivation of ribosomal protein S6 kinase 1 in peripheral blood mononuclear cells. Cancer Res. *64*, 252–261.

Califano, J., van der Riet, P., Westra, W., Nawroz, H., Clayman, G., Piantadosi, S., Corio, R., Lee, D., Greenberg, B., Koch, W., et al. (1996). Genetic progression model for head and neck cancer: Implications for field cancerization. Cancer Res. *56*, 2488–2492.

Cheng, L., and Lai, M.D. (2003). Aberrant crypt foci as microscopic precursors of colorectal cancer. World J. Gastroenterol. *9*, 2642–2649.

Clayman, G.L., el-Naggar, A.K., Lippman, S.M., Henderson, Y.C., Frederick, M., Merritt, J.A., Zumstein, L.A., Timmons, T.M., Liu, T.J., Ginsberg, L., et al. (1998). Adenovirus-mediated p53 gene transfer in patients with advanced recurrent head and neck squamous cell carcinoma. J. Clin. Oncol. *16*, 2221–2232.

Cohen, E.E., Rosen, F., Stadler, W.M., Recant, W., Stenson, K., Huo, D., and Vokes, E.E. (2003). Phase II trial of ZD1839 in recurrent or metastatic squamous cell carcinoma of the head and neck. J. Clin. Oncol. *21*, 1980–1987.

Corless, C.L., McGreevey, L., Haley, A., Town, A., and Heinrich, M.C. (2002). KIT mutations are common in incidental gastrointestinal stromal tumors one centimeter or less in size. Am. J. Pathol. *160*, 1567–1572.

Dannenberg, A.J., and Subbaramaiah, K. (2003). Targeting cyclooxygenase-2 in human neoplasia: Rationale and promise. Cancer Cell *4*, 431–436.

Dannenberg, A.J., Lippman, S.M., Mann, J.R., Subbaramaiah, K., and DuBois, R.N. (2004). COX-2 and EGFR: Pharmacological targets for chemoprevention. J. Clin. Oncol., in press.

Dunn, B.K., Wickerham, D.L., and Ford, L.G. Prevention of hormone-related cancers: Breast cancer. J. Clin. Oncol., in press.

Eisenhauer, E.A., O'Dwyer, P.J., Christian, M., and Humphrey, J.S. (2000). Phase I clinical trial design in cancer drug development. J. Clin. Oncol. *18*, 684–692.

Giardiello, F.M., Hamilton, S.R., Krush, A.J., Piantadosi, S., Hylind, L.M., Celano, P., Booker, S.V., Robinson, C.R., and Offerhaus, G.J. (1993). Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. N. Engl. J. Med. *328*, 1313–1316.

Hanahan, D., and Weinberg, R.A. (2000). The hallmarks of cancer. Cell *100*, 57–70.

He, T.C., Chan, T.A., Vogelstein, B., and Kinzler, K.W. (1999). PPARdelta is an APC-regulated target of nonsteroidal anti-inflammatory drugs. Cell *99*, 335–345.

Heinrich, M.C., Corless, C.L., Demetri, G.D., Blanke, C.D., von Mehren, M., Joensuu, H., McGreevey, L.S., Chen, C.J., Van den Abbeele, A.D., Druker, B.J., et al. (2003a). Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J. Clin. Oncol. *21*, 4342–4349.

Heinrich, M.C., Corless, C.L., Duensing, A., McGreevey, L., Chen, C.J., Joseph, N., Singer, S., Griffith, D.J., Haley, A., Town, A., et al. (2003b). PDGFRA activating mutations in gastrointestinal stromal tumors. Science *299*, 708–710.

Hoque, A., Sneige, N., Sahin, A.A., Menter, D.G., Bacus, J.W., Hortobagyi, G.N., and Lippman, S.M. (2002). Her-2/neu gene amplification in ductal carcinoma in situ of the breast. Cancer Epi. Biomarkers Prev. *11*, 587–590.

Hruban, R.H., Goggins, M., Parsons, J., and Kern, S.E. (2000). Progression model for pancreatic cancer. Clin. Cancer Res. *6*, 2969–2972.

Hsi, L.C., Xi, X., Lotan, R., Shureiqi, I., and Lippman, S.M. (2004). The histone deacetylase inhibitor suberoylanilide hydroxamic acid (SAHA) induces apoptosis via induction of 15-lipoxygenase-1 in colorectal cancer cells. Cancer Res., in press.

Hynes, R.O. (2003). Metastatic potential: Generic predisposition of the primary tumor or rare, metastatic variants—or both? Cell *113*, 821–823.

Izzo, J.G., Papadimitrakopoulou, V.A., Liu, D.D., den Hollander, P.L., Babenko, I.M., Keck, J., el-Naggar, A.K., Shin, D.M., Lee, J.J., Hong, W.K., and Hittelman, W.N. (2003). Cyclin D1 genotype, response to biochemoprevention, and progression rate to upper aerodigestive tract cancer. J. Natl. Cancer Inst. *95*, 198–205.

Khuri, F.R., Nemunaitis, J., Ganly, I., Arseneau, J., Tannock, I.F., Romel, L., Gore, M., Ironside, J., MacDougall, R.H., Heise, C., et al. (2000). A controlled trial of intratumoral ONYX-015, a selectively-replicating adenovirus, in combination with cisplatin and 5-fluorouracil in patients with recurrent head and neck cancer. Nat. Med. *6*, 879–885.

Koehne, C.H., and Dubois, R.N. (2004). COX-2 inhibition and colorectal cancer. Semin. Oncol. *31*, 12–21.

Korn, E.L. (2004). Nontoxicity endpoints in phase I trial designs for targeted, non-cytotoxic agents. J. Natl. Cancer Inst. *96*, 977–978.

Leong, P.P., Rezai, B., Koch, W.M., Reed, A., Eisele, D., Lee, D.J., Sidransky, D., Jen, J., and Westra, W.H. (1998). Distinguishing second primary tumors from lung metastases in patients with head and neck squamous cell carcinoma. J. Natl. Cancer Inst. *90*, 972–977.

Leyland-Jones, B., Gelmon, K., Ayoub, J.P., Arnold, A., Verma, S., Dias, R., and Ghahramani, P. (2003). Pharmacokinetics, safety, and efficacy of trastuzumab administered every three weeks in combination with paclitaxel. J. Clin. Oncol. *21*, 3965–3971.

Li, D., Xie, K., Wolff, R., and Abbruzzese, J.L. (2004). Pancreatic cancer. Lancet *363*, 1049–1057.

Lippman, S.M., and Brown, P.H. (1999). Tamoxifen prevention of breast cancer: An instance of the fingerpost. J. Natl. Cancer Inst. *91*, 1809–1819.

Lippman, S.M., and Hong, W.K. (2001). Molecular markers of the risk of oral cancer. N. Engl. J. Med. *344*, 1323–1326.

Lippman, S.M., and Hong, W.K. (2002). Cancer prevention science and practice. Cancer Res. *62*, 5119–5125.

Lynch, T.J., Bell, D.W., Sordella, R., Gurubhagavatula, S., Okimoto, R.A., Brannigan, B.W., Harris, P.L., Haserlat, S.M., Supko, J.G., Haluska, F.G., et al. (2004). Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N. Engl. J. Med. *350*, 2129–2139.

Morgan, B., Thomas, A.L., Drevs, J., Hennig, J., Buchert, M., Jivan, A., Horsfield, M.A., Mross, K., Ball, H.A., Lee, L., et al. (2003). Dynamic contrast-enhanced magnetic resonance imaging as a biomarker for the pharmacological response of PTK787/ZK 222584, an inhibitor of the vascular endothelial growth factor receptor tyrosine kinases, in patients with advanced colorectal cancer and liver metastases: Results from two phase I studies. J. Clin. Oncol. *21*, 3955–3964.

Nugent, K.P., Farmer, K.C., Spigelman, A.D., Williams, C.B., and Phillips, R.K. (1993). Randomized controlled trial of the effect of sulindac on duodenal and rectal polyposis and cell proliferation in patients with familial adenomatous polyposis. Br. J. Surg. *80*, 1618–1619.

Nugent, K.P., Spigelman, A.D., and Phillips, R.K. (1996). Tissue prostaglandin levels in familial adenomatous polyposis patients treated with sulindac. Dis. Colon Rectum *39*, 659–662.

O'Shaughnessy, J.A., Kelloff, G.J., Gordon, G.B., Dannenberg, A.J., Hong, W.K., Fabian, C.J., Sigman, C.C., Bertagnolli, M.M., Stratton, S.P., Lam, S., et al. (2002). Treatment and prevention of intraepithelial neoplasia: An important target for accelerated new agent development. Clin. Cancer Res. *8*, 314–346.

Paez, J.G., Janne, P.A., Lee, J.C., Tracy, S., Greulich, H., Gabriel, S., Herman, P., Kaye, F.J., Lindeman, N., Boggon, T.J., et al. (2004). EGFR mutations in lung cancer: Correlation with clinical response to gefitinib therapy. Science *304*, 1497–1500.

Pai, R., Soreghan, B., Szabo, I.L., Pavelka, M., Baatar, D., and Tarnawski, A.S. (2002). Prostaglandin E2 transactivates EGF receptor: A novel mechanism for promoting colon cancer growth and gastrointestinal hypertrophy. Nat. Med. *8*, 289–293.

Parulekar, W.R., and Eisenhauer, E.A. (2004). Phase I trial design for solid tumor studies of targeted, non-cytotoxic agents: Theory and practice. J. Natl. Cancer Inst. *96*, 990–997.

Rao, P.S., Tian, X., Qin, W., Aruva, M.R., Sauter, E.R., Thakur, M.L., and Wickstrom, E. (2003). 99mTc-peptide-peptide nucleic acid probes for imaging oncogene mRNAs in tumours. Nucleic Med. Commun. *24*, 857–863.

Rudin, C.M., Cohen, E.E., Papadimitrakopoulou, V.A., Silverman, S., Jr., Recant, W., el-Naggar, A.K., Stenson, K., Lippman, S.M., Hong, W.K., and Vokes, E.E. (2003). An attenuated adenovirus, ONYX-015, as mouthwash therapy for premalignant oral dysplasia. J. Clin. Oncol. *21*, 4546–4552.

Rusnak, D.W., Lackey, K., Affleck, K., Wood, E.R., Alligood, K.J., Rhodes, N., Keith, B.R., Murray, D.M., Knight, W.B., Mullin, R.J., et al. (2001). The effects of the novel, reversible epidermal growth factor receptor/ErbB-2 tyrosine kinase inhibitor, GW2016, on the growth of human normal and tumor-derived cell lines in vitro and in vivo. Mol. Cancer Ther. *1*, 85–94.

Shpitz, B., Klein, E., Buklan, G., Neufeld, D., Nissan, A., Freund, H.R., Grankin, M., and Bernheim, J. (2003). Suppressive effect of aspirin on aberrant crypt foci in patients with colorectal cancer. Gut *52*, 1598–1601.

Shureiqi, I., Jiang, W., Fischer, S.M., Xu, X., Chen, D., Lee, J.J., Lotan, R., and Lippman, S.M. (2002). GATA-6 transcriptional regulation of 15-lipoxygenase-1 during NSAID-induced apoptosis in colorectal cancer cells. Cancer Res. *62*, 1178–1183.

Shureiqi, I., Jiang, W., Zuo, X., Wu, Y., Stimmel, J.B., Leesnitzer, L.M., Morris, J.S., Fan, H.Z., Fischer, S.M., and Lippman, S.M. (2003). The 15-lipoxygenase-1 product 13-S-hydroxyoctadecadienoic acid down-regulates PPAR-delta to induce apoptosis in colorectal cancer cells. Proc. Natl. Acad. Sci. USA *100*, 9968–9973.

Sinicrope, F.A., Half, E., Morris, J.S., Lynch, P.M., Morrow, J.D., Levin, B., Hawk, E.T., Cohen, D.S., Ayers, G.D., Stephens, L.C., and Familial Adenomatous Polyposis Study Group. (2004). Cell proliferation and apoptotic indices predict adenoma regression in a placebo-controlled trial of celecoxib in familial adenomatous polyposis patients. Cancer Epidemiol. Biomarkers Prev. *13*, 920–927.

Slamon, D.J., Clark, G.M., Wong, S.G., Levin, W.J., Ullrich, A., and McGuire, W.L. (1987). Human breast cancer: Correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science *235*, 177–182.

Spitz, M.R., Wu, X., and Mills, G. Integrative epidemiology: From risk assessment to outcome prediction. J. Clin. Oncol., in press.

Steinbach, G., Lynch, P.M., Phillips, R.K., Wallace, M.H., Hawk, E., Gordon, G.B., Wakabayashi, N., Saunders, B., Shen, Y., Fujimura, T., et al. (2000). The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. N. Engl. J. Med. *342*, 1946–1952.

Sudbo, J., Lippman, S.M., Lee, J.J., Mao, L., Kildal, W., Sudbo, A., Sagen, S., Bryne, M., el-Naggar, A., Risberg, B., et al. (2004). The influence of resection and aneuploidy on mortality in oral leukoplakia. N. Engl. J. Med. *350*, 1405–1413.

Swain, S.M., Wilson, J.W., Mamounas, E.P., Bryant, J., Wickerham, D.L., Fisher, B., Paik, S., and Wolmark, N. (2004). Estrogen receptor status of primary breast cancer is predictive of estrogen receptor status of contralateral breast cancer. J. Natl. Cancer Inst. *96*, 516–523.

Takayama, T., Katsuki, S., Takahashi, Y., Ohi, M., Nojiri, S., Sakamaki, S., Kato, J., Kogawa, K., Miyake, H., and Niitsu, Y. (1998). Aberrant crypt foci of the colon as precursors of adenoma and cancer. N. Engl. J. Med. *339*, 1277–1284.

Thompson, I.M., Goodman, P.J., Tangen, C.M., Lucia, M.S., Miller, G.J., Ford, L.G., Lieber, M.M., Cespedes, R.D., Atkins, J.N., Lippman, S.M., et al. (2003). The influence of finasteride on the development of prostate cancer. N. Engl. J. Med. *349*, 215–224.

Thun, M.J., Henley, S.J., and Patrono, C. (2002). Nonsteroidal anti-inflammatory drugs as anticancer agents: Mechanistic, pharmacologic, and clinical issues. J. Natl. Cancer Inst. *94*, 252–266.

Torrance, C.J., Jackson, P.E., Montgomery, E., Kinzler, K.W., Vogelstein, B., Wissner, A., Nunes, M., Frost, P., and Discafani, C.M. (2000). Combinatorial chemoprevention of intestinal neoplasia. Nat. Med. *6*, 1024–1028.

Tubbs, R.R., Pettay, J.D., Roche, P.C., Stoler, M.H., Jenkins, R.B., and Grogan, T.M. (2001). Discrepancies in clinical laboratory testing of eligibility for trastuzumab therapy: Apparent immunohistochemical false-positives do not get the message. J. Clin. Oncol. *19*, 2714–2721.

Vogelstein, B., Fearon, E.R., Hamilton, S.R., Kern, S.E., Preisinger, A.C., Leppert, M., Nakamura, Y., White, R., Smits, A.M., and Bos, J.L. (1988). Genetic alterations during colorectal-tumor development. N. Engl. J. Med. *319*, 525–532.

Xiao, Z., Luke, B.T., Izmirlian, G., Umar, A., Lynch, P.M., Phillips, R.K., Patterson, S., Conrads, T.P., Veenstra, T.D., Greenwald, P., et al. (2004). Serum proteomic profiles suggest celecoxib-modulated targets and response predictors. Cancer Res. *64*, 2904–2909.