The Convergent Development of Molecular-Targeted Drugs for Cancer Treatment and Prevention
Scott M. Lippman1 and John V. Heymach1,2

Abstract
Advances in our understanding of multistep and field carcinogenesis are erasing the clear demarcation of intraepithelial neoplasia from invasive neoplasia. The growing ability to define very high risk of cancer is forging important commonalities between prevention and therapy, such as in potential prognostic/predictive markers, agents, and side effects that patients would be willing to tolerate, and the logistics of definitive trials. The emergence of promising new molecular-targeted agents and new technologies for screening and early detection provides new opportunities for applying clinical trial designs that integrate therapy and prevention end points. Such trials may be used to facilitate targeted drug development and help identify strategies for both cancer prevention and advanced cancer therapy. These several advances are creating a convergence of cancer therapy with cancer prevention that promises to streamline the development of targeted drugs and improve the control of major cancers.

Advances in the molecular biology of carcinogenesis are gradually erasing any clear demarcation between preinvasive and invasive neoplasia and are bringing about a convergence between cancer therapy and prevention research. Several models of multistep field carcinogenesis reflect the convergence of precancer and cancer biology. The growing ability to define very high risk of cancer is further bridging the gap between therapy and prevention. The final piece of the convergence puzzle is molecular-targeted drug development, which is already providing settings for the convergent development of targeted therapy and prevention drugs (1, 2).

The Biology of Convergence

Precancer and cancer. The convergences of intraepithelial neoplasia (IEN) with cancer and of prevention with therapy are well illustrated by lung carcinogenesis (Fig. 1). Lung lesions with abnormal molecular or other changes progress from a few hundred thousand cells in relatively small, histologically normal clonal patches (3) to 107 cells in the first clinically detectable cancer to 1012 cells in very large, advanced tumors at the end stage of disease. The size and number of subclones in a clonal patch contribute to its risk of developing into cancer (4–6), and patches at a high cancer risk can be defined as IEN. Since the coining of the term IEN, its definition has been linked to cancer risk; the common definition of IEN heretofore has included the presence of the risk factor dysplasia (7). As defined in this review, however, IEN need not include dysplasia because molecular factors of high risk can be present in nondysplastic lesions. There is a substantial overlap between the molecular characteristics of IEN and invasive cancer, although cancer typically has a larger number of alterations that increases as the cancer advances toward metastatic end-stage disease. This accumulation of alterations in tumors leads to a high degree of molecular heterogeneity and explains in large part the enormous difficulty, including drug resistance, of treating more advanced stages of cancer.

IEN and invasive cancer cells also undergo similar cellular changes, including increased proliferation and loss of apoptosis. The angiogenic switch, or the initial acquisition of a vascular supply, may also be turned on in association with subclinical invasion and is an obligate step for a lesion to grow beyond 1 to 2 mm3 and eventually metastasize (8). Given these overlapping characteristics of IEN and invasive cells, molecular-targeted drugs currently in development (largely in therapy settings) have the potential to be used in both cancer chemoprevention, such as high-risk IEN settings, and in cancer therapy, such as in adjuvant treatment of patients with resected early-stage tumors. Advances in screening and early detection are partly driving this molecular-targeted drug convergence. Spiral computed tomography (CT) screening in the lung allows detection of IEN and very early cancers (9, 10), identifying patients who may need chemoprevention or chemotherapy. Molecular early detection strategies under development (e.g., proteomics and imaging) promise to further bridge the “no man’s land” (Fig. 1) between classic and separate prevention and therapy. Although the convergent

**Authors’ Affiliations:** Departments of 1Thoracic/Head and Neck Medical Oncology and 2Cancer Biology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas

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**Requests for reprints:** Scott M. Lippman, Department of Thoracic/Head and Neck Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Unit 432, 1515 Holcombe Boulevard, Houston, TX 77030-4009. Phone: 713-745-5439; Fax: 713-745-2012; E-mail: slippman@mdanderson.org.

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issues described here derive largely from lung carcinogenesis, the same principles apply to carcinogenesis of other sites, differing somewhat in details but not in substance. Indeed, convergent prevention and therapy already seems to have taken place in the Breast Cancer Prevention Trial of the selective estrogen receptor modulator tamoxifen in women at an increased risk of breast cancer (11). Breast cancer incidence began decreasing in the tamoxifen arm versus in the placebo arm quite early in the trial. This early separation between the arms was likely due to treating microscopic, subclinical, and undetected breast cancer in the otherwise healthy higher-risk women; preventing completely new cancer probably was not a major factor at this point in the trial because such cancer likely would require more time to develop, become detectable, and influence incidence comparisons (12). The difference in breast cancer rates widened over time, however, suggesting an increased preventive effect of tamoxifen later in the trial. A similar treatment-preventive effect likely occurs in the adjuvant breast cancer treatment setting (13). Whether in the breast, lung, head and neck, or other sites, molecular-targeted agents that delay or quell transformation of preinvasive cells and lesions, suppress the angiogenic switch, or eradicate subclinical invasive cells and tumors would provide the important benefit of delaying or preventing the occurrence and burden of clinically evident cancer (14, 15). Just as it is virtually impossible to define the precise beginning of cancer versus the ending of IEN, it is virtually impossible to clearly discriminate between cancer prevention and cancer therapy when treating, for example, a lesion of between 10,000 cells and $10^7$ cells (the size at which spiral CT can detect early lung cancer). Therefore, this middle ground, formerly a “no man’s land”, represents an opportunity for convergent expertise that is not overly concerned with the labels “prevention” and “therapy.”

**Elucidation of the clonal patch.** Although clonal patches are well mapped in the lung (3, 16), clonal patch biology is better elucidated in the head and neck, where neoplastic and normal-appearing tissues are easily seen and sampled. An oral IEN patch (defined as having the risk of developing into invasive cancer) can extend invisibly for several centimeters within visible clinically/histologically normal oral tissue. Genetic changes in one part of this submucosal IEN patch may cause a visible oral IEN. Changes in another part may result in microscopic oral cancer. Changes in yet another part may cause clinically detectable oral cancer. The stage of any one of these various manifestations reflects in large part its number of accumulated subclones. Many patterns of visible oral neoplasia, from a single oral IEN or cancer to several multifocal, geographically distinct IENs and cancers that occur at various time points, are possible within a single extensive submucosal patch of oral IEN. The visible lesion, invasive or not, is the tip of an iceberg of submucosal IEN, or "microneoplasia," that spreads laterally in the epithelial field and from which genetically linked IENs or primary tumors can develop at any location or time. Therefore, genetically linked second local cancers in curatively treated oral cancer patients may very well be second primary tumors (SPT) rather than recurrences. This conclusion strongly supports prevention or convergent approaches designed to reduce the clinical occurrence and burden of new cancers in this setting.

Several molecular, primarily microsatellite, studies support the submucosal, lateral spread of oral IEN underlying clinical oral neoplasia. Persisting genetic changes have been detected at the site of visible oral IENs that have been completely removed.
or have responded completely (clinically and histologically) to systemic therapy (17, 18). Geographically distinct oral IENs and cancers have been shown to be genetically related (19). A prospective study of second cancers in 55 curatively treated early-stage head and neck cancer patients found that 61% of the second cancers that met rigorous clinical criteria for an SPT were clonally related to the original tumor (20, 21). Several studies using microsatellite markers alone or after fluorescence, which illumined the surrounding tissue, found evidence of a clonal patch surrounding the oral IEN or tumor in a substantial percentage of cases (22–26). Parallel findings in the lung indicate that epidermal growth factor receptor (EGFR) mutations can mark an IEN patch of histologically normal tissue surrounding a lung adenocarcinoma (16). Two studies examined clonality in first and second oral cancers and in the margins, or intervening mucosa (25, 26). One study was premised on examining SPTs, the other on examining local recurrences. The SPT analysis involved 10 patients with a second tumor >3 cm (but <6 cm) from the original tumor and that may or may not have been synchronous. In 6 of the 10 cases (60%), microsatellite studies showed that the first and second cancers and the intervening mucosa were clonally related, suggesting a single IEN patch (25). The local recurrence analysis involved 13 patients with a second cancer that was <2 cm from, and within 3 years of, the first cancer. Five cases (38%) seemed to be SPTs [based on a mix of shared (early) and different (later) clonal alterations within the initial and second cancers and intervening mucosa; ref. 26]; three cases were molecularly ambiguous; and five cases seemed to be local recurrences (no evidence of molecular alterations in the intervening mucosa and virtually genetically identical first and second cancers).

**Risk Modeling for Cohort Identification**

The development of reliable models and markers of cancer risk is a key factor in identifying cohorts for convergent drug development. Encouraging recent work in the lung with the potential to produce relatively simple, feasible risk models includes classic epidemiology-based and molecular-based models. A large case-control epidemiologic study involving smoking status, family history, age, prior respiratory disease, asbestos exposure, and other epidemiologic factors has developed a risk model that can identify relatively high-risk individuals (27). Studies of molecular risk factors in smokers and chronic obstructive pulmonary disease patients have shown that hypermethylation in multiple genes (assessed in sputum samples) predict lung cancer development (28) or that abnormalities in any two of the DNA sequences from centromere 6, 5p15, 7p12 (EGFR), and 8q24 (cMYC), which were assessed by fluorescence in situ hybridization, gave a lung cancer odds ratio of 17.5 (29). The fluorescence in situ hybridization abnormalities were more predictive than were the hypermethylated genes, and the highest sensitivity was associated with abnormalities involving EGFR.

Risk modeling, however, has not progressed as far in the lung as it has in the head and neck, mainly for practical reasons such as ease in sampling lesions or tumors and adjacent tissue (30–32). A relatively simple and practical model of head and neck cancer risk involves microsatellite markers of allelic imbalance, primarily in the form of loss of heterozygosity (LOH), in patients with oral IEN alone (i.e., no oral cancer history). In a study using two microsatellite markers, LOH at 3p and/or 9p was associated with a 25% 3-year oral cancer risk (33). In a study using 18 microsatellite markers to assess eight chromosomal arms including 3p and 9p, LOH at two or more chromosomal sites was associated with a 40% 3-year cancer risk (34). The largest study was conducted in 116 patients and used 19 microsatellite markers to assess seven chromosomal arms in oral IEN ranging from hyperplasia to moderate dysplasia. LOH at 3p and/or 9p was associated with a 25% 3-year cancer risk (and occurred in 97% of the IEN lesions that progressed to cancer; ref. 35). Further data from this large study indicated a 35% 3-year oral cancer risk associated with oral IEN having LOH at 3p and/or 9p plus allelic imbalance at one or more of the sites 4q, 8p, 11q, 13q, or 17p (20); this high risk was not significantly reduced by complete removal of the clinical lesion (18).

Practical risk models based on microsatellite analyses of allelic imbalance/LOH and/or microsatellite instability also have been evaluated in patients with curatively treated cancer of the oral cavity or other head and neck sites. Three studies in this setting, which are related through the concept of submucosal, lateral oral IEN described previously, have consistently identified 3-year oral cancer risks of ~70% (36–38). The risk in each study involved molecular assessments of nontumor tissue in areas adjacent or near to the treated tumor. In most patients, the tissue was clinically or histologically normal or hyperplastic to moderately dysplastic (including leukoplakia). The largest study (68 patients) found that a high risk was associated with LOH at 3p and/or 9p in visible IEN developing after and near the original tumor (37). One study examined five microsatellite markers in 26 patients, finding that microsatellite instability in the margins of the original tumor was associated with a high risk of a second cancer (38). The third study examined 10 microsatellite markers of microsatellite instability or LOH in 25 informative cases, finding that similar clonality in the original tumor and its margins was associated with a high second-cancer risk (36).

LOH criteria are being used to select high-risk patients with oral IEN-alone or curatively-treated oral cancer for the ongoing phase III (cancer end point) Erlotinib Prevention of Oral Cancer (EPOC) trial, which targets EGFR for oral cancer prevention. EGFR is the only validated clinical target in head and neck cancer, and an EGFR inhibitor is a Food and Drug Administration–approved therapy for this disease. EGFR expression is increased in head and neck IEN; and suppression of cyclin D1 (downstream of EGFR) in head and neck IEN reduces cancer risk (39, 40). EPOC is the first prevention trial to use a molecular risk marker as an eligibility criterion and thus addresses the need to use high-risk premalignant conditions for molecular-targeted chemoprevention to maximize a drug’s benefit-to-risk ratio. This approach is personalized preventive medicine that limits potential adverse agent effects to individuals in greatest need. To further personalize EGFR inhibitor prevention in the future, correlative studies will examine the association of EGFR amplification with outcomes in EPOC. These studies are based on very recent data showing that EGFR amplification is associated with a poor prognosis in head and neck cancer patients and sensitivity to EGFR tyrosine-kinase inhibitors (TKI) in head and neck cancer cell lines and is detected in oral IEN (41, 42). These findings parallel more
mature findings in the lung, where EGFR amplification is associated with a poor prognosis and correlates with the clinical efficacy of EGFR TKIs in non–small cell lung carcinoma, and correlates with increased cancer risk in lung IEN (29, 43, 44). EPOC also reflects characteristics of the convergence of cancer prevention with cancer therapy, which are similarities in the molecular features of precancer and cancer and of SPTs and recurrence, similarities in the prognostic/predictive markers of very high risk individuals without cancer and of curatively treated cancer patients, and use of the same molecular-targeted agents for therapy or prevention. That EGFR inhibitors are Food and Drug Administration approved in advanced cancers of the head and neck (cetuximab) and lung (erlotinib) further highlights the convergence. Prevention trials in high-risk IEN can have a size and duration, costs, and ethical considerations (e.g., high cancer risk justifies potential serious adverse effects) resembling those of therapy trials (32). Other relatively simple cancer risk models incorporate a limited number of molecular markers with or without clinical and histologic factors that predict the cancer risk of IEN (30, 45). Although advanced head and neck and lung cancer patients who respond to standard EGFR inhibitors do not typically survive long enough to allow longer-term assessments of the broader preventive and therapeutic implications, such opportunities should arise as the EGFR inhibitors become used in better-prognosis (e.g., adjuvant) settings.

There is also substantial ongoing work in developing more complex risk models. Models incorporating genomic and proteomic risk profiles are in development for predicting recurrence in resected early-stage lung cancer patients (46). The same type of modeling is being developed for cancer risk in IEN patients. Comprehensive pharmaco-ecogenetic (genetic, metabolic, and environmental) models of prostate cancer risk are in development and incorporate risk factors involved with androgen metabolism, diet, insulin resistance and the insulin-like growth factor axis, inflammation, and oxidative stress and DNA repair as assessed in IEN and tumor tissue, plasma, blood, and epidemiologic and clinical data from men who participated in the Prostate Cancer Prevention Trial (32, 47). As illustrated by this work based on the Prostate Cancer Prevention Trial, model building can be very complicated depending on the number of variables (which can be in the thousands) and size of the cohort in which the model is being developed. The larger, more comprehensive models are harder to develop, interpret, and apply in the clinic.

### Molecular-Targeted Drug Development

Molecular-targeted drug development is likely to further blur the distinction between cancer therapy and prevention. A new generation of targeted drugs with acceptable therapeutic indices for both prevention and therapy is emerging from the molecular study of neoplasia (IEN and cancer), drug effects on relevant pathways, and cancer risk/prognosis. A very promising signaling pathway for targeted potentially convergent agents in the lung is the phosphatidylinositol 3-kinase/Akt signaling pathway (48). Tobacco carcinogens induce Akt activation and lung carcinogenesis. The Akt pathway is activated in bronchial premalignancy (both proximal airway and alveolar, or peripheral, epithelium) in smokers and patients with lung IEN or cancer. Preclinical in vivo studies show that deguelin and myo-inositol have preventive activity in lung adenocarcinoma tumorigenesis, in part via suppressing the phosphatidylinositol 3-kinase/Akt pathway (48). The kinase mammalian target of rapamycin (mTOR), which is downstream of Akt, is activated in lung premalignancy and is required for malignant progression in the lung. The mTOR inhibitor CCI-779 (at a higher but not lower dose) blocked malignant progression of atypical adenomatous hyperplasia lesions with activated mTOR expression in the alveoli of mice that develop lung cancer because of activated K-ras (49). mTOR drives tumorigenesis in part through macrophages, a prominent component of the tumor microenvironment, and the antitumor effect of mTOR inhibition required the presence of the tumor microenvironment. mTOR inhibitors also have been tested extensively in early clinical development in the setting of advanced lung cancer and so are promising agents for convergent drug development.

### Table 1. Three early-phase designs for convergent prevention and therapy trials

<table>
<thead>
<tr>
<th>Name</th>
<th>Cohort</th>
<th>End point(s)</th>
<th>Agents</th>
<th>Duration</th>
<th>N</th>
<th>Correlative opportunities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose-finding</td>
<td>Cancer (one type)</td>
<td>Toxicity</td>
<td>Oral molecular-targeted agents</td>
<td>Highly variable</td>
<td>Highly variable</td>
<td>Preliminary biomarker responses</td>
</tr>
<tr>
<td>Therapy with imbedded</td>
<td>Advanced cancer (one type)</td>
<td>Tumor response; imbedded IEN</td>
<td>Oral molecular-targeted agents</td>
<td>Highly variable</td>
<td>Highly variable</td>
<td>Target modulation and drug effects</td>
</tr>
<tr>
<td>pre-therapy evaluation</td>
<td></td>
<td>response</td>
<td></td>
<td></td>
<td></td>
<td>(dosing, mechanism); predictive markers of response, resistance</td>
</tr>
<tr>
<td>Preresection, window of</td>
<td>IEN and early-stage cancer</td>
<td>Tumor and IEN response</td>
<td>Oral molecular-targeted agents</td>
<td>3-6 weeks</td>
<td>20-30 patients per arm</td>
<td>Target modulation and drug effects (dosing, mechanism); predictive markers of response, resistance</td>
</tr>
<tr>
<td>opportunity (stratified)</td>
<td>(stratified)</td>
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*Reflecting the variability seen in optimal biological dose-finding phase I therapy trials.
†Ranging from the durations and sample sizes of phase II therapy trials to durations and sizes of phase III adjuvant trials.
‡The number of patients can vary widely and beyond the variables noted in the column, depending on target response rates and other factors of the design.
As discussed in detail elsewhere (1, 2, 32), molecular-targeted research is vital for identifying candidate agents, selecting and prioritizing these agents for clinical development, and assessing end points of clinical trials.

Convergent Trial Designs Based on Identified Cohorts, Agents, and End Points

Precancer and cancer are part of a continuum and therefore have certain molecular, cellular, or microenvironmental events in common, including events shown to be associated with the ability of cancer cells to metastasize (8, 50). Therefore, the molecular targets relevant to advanced cancer likely also are relevant to precancer, supporting the argument that early assessments of novel drugs in the setting of phase I trials in advanced cancer are relevant to prevention as well as therapy. This dual relevance has important implications for convergent trial designs because many of the most promising targeted drugs in preclinical development are first tested clinically in phase I therapy trials, the results of which can help justify candidate drugs for convergent testing such as that proposed here.

Early-phase testing would be the most practical venue for conducting convergent trials. After the potential for therapy and/or prevention is shown in early-phase trials, then definitive trials to establish efficacy would be essentially therapy or prevention, not both. Three convergent early-phase trial designs involving molecular-targeted agents are (a) dose-finding trials to determine the tolerable, active dose of an agent for subsequent phase II testing in either prevention or therapy. The convergent trial designs proposed here are illustrated in Fig. 2.

Fig. 2. Convergent design for evaluating drugs and their molecular targets for potential chemoprevention and/or treatment (A). This design features the lung peripheral premalignant lesions atypical adenomatous hyperplasia (AAH) and bronchioloalveolar carcinoma (BAC) or cancer but could apply as well to other sites of cancer and related premalignant lesions. Potential follow-up studies suggested by results of the convergent trial are shown in (B). FNA, fine needle aspiration.
therapy; (b) a therapy design (in cancer patients) with imbedded prevention end points (e.g., IEN) for agents with preventive potential based on mechanistic and safety characteristics; and (c) trials before resection in a mixed population of IEN and cancer patients and based on the molecular and clinical relevance of the IEN and cancer. The outlines of these three designs are presented in Table 1. The dose-finding design would include assessments of pharmacodynamic effects on tumor and surrounding or surrogate tissue in addition to assessments of safety and biomarker modulation levels. This design is convergent because the same trial may suggest doses of the same drug that would differ for prevention (a dose with lower biological activity, higher safety) or therapy (higher activity, lower safety). The imbedding design can include a full phase II or III trial in cancer settings with a prevalent IEN. Rectal aberrant crypt foci in colon cancer trials are an example of an imbedded design. Aberrant crypt foci can be identified by magnifying endoscopy, are thought to be precursors of adenomas, and seem to respond to nonsteroidal anti-inflammatory drugs and EGFR TKIs. Another imbedded convergence approach is to assess at-risk tissue in adjuvant trials, for example, via bronchoscopy in adjuvant lung cancer trials. A recent study detected EGFR tyrosine kinase domain mutations that predict sensitivity to EGFR inhibitors in histologically normal lung tissue surrounding a primary lung adenocarcinoma with EGFR mutations (16). This field effect may signal a higher risk of an SPT, which could be prevented, and is associated with sensitivity to EGFR TKIs, which could help select patients most likely to benefit from adjuvant therapy with an EGFR TKI.

Figure 2 depicts the design for a trial in a mixed patient population with peripheral lung IEN (group 1) or cancer (group 2), which is often beyond the reach of bronchoscopic detection. Identified by CT and a subsequent fine needle aspiration, group 1 patients would have atypical alveolar or bronchioloalveolar proliferation likely denoting adenomatous hyperplasia or bronchioloalveolar carcinoma (although microinvasion cannot be ruled out) and group 2 patients would have early-stage cancer (some with adenomatous hyperplasia or bronchioloalveolar carcinoma in proximate tissue). The finding of similar molecular profiles in CT screening–identified early tumors and clinically detected tumors supports the relevance of CT screening–detected cancer to drug development (51, 52). Patients would be randomized to one or more doses of a molecular-targeted agent or placebo. Pretherapy tumor or IEN tissue would be analyzed for biomarkers of potential activity and of response and resistance to the trial agent. After 3 to 6 weeks, the patients would have another CT to measure lesion size, and the cancers and most of the IENs (previously suspected of cancer) would be resected, as clinically indicated. Biomarker assessments of resected tumor and IEN tissues would give insights into the effects of a drug on its known target(s). Results of this study would be highly relevant to future prevention or therapy trials in the lung. The IENs are preselected for potential aggressiveness (e.g., for a short doubling time between consecutive CT scans just before study enrollment) and the cancers are preselected for early stage. The study could identify promising targeted agents and molecular targets, for example, K-ras mutations (found progressively in adenomatous hyperplasia, bronchioloalveolar carcinoma, and adenocarcinoma), for future late-phase chemoprevention trials. Providing insights into targeted drug mechanisms, optimal dose, and predictive markers of sensitivity or resistance, novel convergent trials also could be very helpful in choosing drugs for a future trial in advanced lung cancer. This potential function was shown by recent data indicating that ras mutations marked potential resistance and EGFR mutations and/or amplification marked potential sensitivity of clinically detected early-stage lung cancer to EGFR TKIs (53). Although set in part in the same disease timing covered by a neoadjuvant trial, this trial is not neoadjuvant in the classic sense: It includes IEN and earliest-stage cancer patients, and the clinical objectives are not designed to enhance definitive local therapy, which generally will have been scheduled before entry into the convergent trial design proposed here. With regard to the cancer patients, this trial is really a preresection, window-of-opportunity trial for assessing potential drug effects in future chemoprevention and chemotheraphy trials of more standard design.

Conclusions

Advances in molecular-targeted drug development are highlighting the convergence of cancer prevention and therapy. The ability of cancer researchers to develop drugs in a convergent manner will be critical for coping 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. Although classic therapy and prevention drug testing no doubt will continue, convergent drug development potentially will unite therapists and chemopreventionists within the previous “man’s land” of neoplasia (Fig. 1), in which invasion and preinvasion are not clearly defined and much of the work to control major cancers is needed.

References


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