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Personalizing Lung Cancer Prevention Through a Reverse Migration Strategy

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Abstract

Lung cancer is the deadliest cancer in the United States and worldwide. Tobacco use is the one of the primary causes of lung cancer and smoking cessation is an important step towards prevention, but patients who have quit smoking remain at risk for lung cancer. Finding pharmacologic agents to prevent lung cancer could potentially save many lives. Unfortunately, despite extensive research, there are no known effective chemoprevention agents for lung cancer. Clinical trials in the past, using agents without a clear target in an unselected population, have shown pharmacologic interventions to be ineffective or even harmful. We propose a new approach to drug development in the chemoprevention setting: reverse migration, that is, drawing on our experience in the treatment of advanced cancer to bring agents, biomarkers, and study designs into the prevention setting. By identifying molecular drivers of lung neoplasia and using matched targeted agents, we hope to personalize therapy to each individual to develop more effective, tolerable chemo-prevention. Also, advances in risk modeling, using not only clinical characteristics but also biomarkers, may help us to select patients better for chemoprevention efforts, thus sparing patients at low risk for cancer the potential toxicities of treatment. Our institution has experience with biomarker-driven clinical trials, as in the recently reported *Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination* (BATTLE) trial, and we now propose to bring this trial design into the prevention setting.

Keywords

Chemoprevention; Lung cancer; Targeted therapies

1 Introduction

Lung cancer is the most common cause of cancer death, both in the United States and worldwide [1]. Once lung cancer is diagnosed, outcomes are poor, with only 15.6% of patients surviving 5 years after diagnosis (<http://seer.cancer.gov/statfacts/html/lungb.html>). Lung cancer prevention is an attractive goal. Smoking cessation is an important step towards this goal, but the risk of lung cancer remains elevated even after a patient has quit smoking. About half of all lung cancers are diagnosed in patients who have already quit smoking; therefore, tobacco cessation alone is not sufficient. Lung cancer chemoprevention is a promising field, though one that has met with only limited success.

Chemoprevention refers to the use of any agent, either synthetic, biologic, or natural, to suppress, reverse, or prevent carcinogenesis [2, 3]. Unfortunately, clinical trials of chemopreventive agents for lung cancer have been largely negative or even harmful [4–8]. To improve outcomes, we must change our approach to drug development. Historically, there have been two main approaches to development of therapeutics for chemoprevention. First is the development of agents, usually natural agents, that were identified in epidemiologic studies as potentially important in the development of cancer. Examples include beta-carotene [4, 5] and selenium [9]. The second approach has been to study agents developed for different indications in the setting of chemoprevention. Examples of this approach include the cyclo-oxygenase-2 (COX-2) inhibitors, initially developed for arthritis and later studied for the prevention of colon cancer [10–12]. We propose a new approach: reverse migration, that is, importing ideas and therapies developed in advanced cancer into the setting of chemoprevention [13].

2 Basics of Chemoprevention

Several concepts that are important in chemoprevention are the ideas of field cancerization and multistep carcinogenesis. “Field cancerization” was first described in 1953 with the study of histologically abnormal tissue surrounding oral cancer [14]. Slaughter et al. hypothesized that an injury from a toxin occurs at multiple locations within a field such as the aerodigestive tract, and carcinogenesis may occur at multiple sites. This field effect is responsible for the high rates of recurrence of squamous cell carcinoma of the oral cavity following local treatment. Though the initial observations of field cancerization focused on histologic changes, we now know that molecular changes can be found in histologically normal epithelium adjacent to tumors [15–17]. Thus, a premalignant lesion in one area of the lung implies increased risk of cancer throughout the lungs.

Multistep carcinogenesis was first described in 1938 [18]. Serial changes in the lungs of smokers were described on a histologic level by Auerbach et al., with a progression from hyperplasia to metaplasia to dysplasia to carcinoma in situ to invasive cancer [19, 20]. The earliest events in carcinogenesis are at the genomic level – additional events are necessary to induce phenotypical changes in the tissue.

Since carcinogenesis occurs in multiple steps and in multiple locations, we have opportunities to “detour carcinogenesis,” that is, to take steps to prevent the progression to invasive cancer in patients at risk for malignancy [21]. By understanding the molecular progression leading to cancer, we hope to identify mutations that drive cancer. Data suggests that in a single patient, primary and metastatic tumors are very similar genetically [22, 23]; it

is not unreasonable to think that premalignancy will also share characteristics with more advanced tumors. Agents that are effective against these drivers in the metastatic setting may also be useful in prevention, as part of a reverse migration approach.

Prevention efforts can target different groups of patients. With primary prevention, the focus is on healthy individuals who are at high risk; for example, current and former smokers. The goal of secondary prevention is to prevent progression to cancer in patients with premalignant lesions, such as intraepithelial neoplasia. Tertiary prevention aims to prevent the development of recurrent or second primary tumors in patients who have a history of cancer.

There have been notable successes in chemoprevention, as described in Table 1 [3, 10, 24–33]. Successful trials often involve known molecular targets that can be effectively inhibited by drugs; for example, hormone receptors in breast and prostate cancer [25, 27], and inflammation in colon cancer [30]. Alternatively, other successful trials have used vaccines to target viruses known to be involved in carcinogenesis, such as the human papilloma virus in cervical cancer [28] and hepatitis B in hepatocellular carcinoma [29]. Many negative trials have used agents identified from epidemiologic studies, without clear targets, such as beta-carotene [4, 5] or selenium [9].

2.1 History of Lung Cancer Chemoprevention

There have been extensive efforts in chemoprevention of nonsmall cell lung cancer (NSCLC), with many clinical trials using agents selected based on epidemiologic data. An influential 1981 review discussed data correlating intake of beta-carotene, which is partially converted to vitamin A in the body, with lower risk of cancer [34]. Based on this data, a number of trials tested vitamin supplementation as a cancer prevention strategy.

The alpha-tocopherol and beta-carotene (ATBC) trial randomized male smokers from Finland to either vitamin E, beta-carotene, a combination of both, or placebo [4]. Unexpectedly, beta-carotene supplementation was associated with an 18% increase in the risk of lung cancer, as well as a significant increase in overall mortality. Vitamin E had no significant effect on incidence of cancer or mortality. Patients in the study who consumed higher dietary amounts of beta-carotene and vitamin E, however, had lower risks of cancer, suggesting the supplementation may have different effects than dietary intake. Another large trial, the beta-carotene and retinol efficacy trial (CARET), was stopped after an interim analysis following the publication of the ATBC trial. This trial randomized patients to receive a combination of retinol and beta-carotene vs placebo. The patients in the active treatment group had a higher risk of lung cancer and all-cause mortality [5]. Interestingly, the increase in lung cancer incidence was seen in current smokers; in former smokers, a trend towards decreased lung cancer incidence with supplementation was noted.

Patients with surgically treated lung cancer are at a high risk for second primary tumors, with rates reported as high as 3% per year [35, 36]. This group has been extensively studied to determine if any chemopreventive agent can reduce risk. For example, in the Intergroup Lung Trial, patients with resected early stage NSCLC were randomized to receive either isotretinoin, a synthetic vitamin A derivative, or placebo [7]. There were no significant differences between the arms with respect to second primary tumors, recurrence, or survival, though subgroup analysis revealed increased mortality in the treatment arm for active smokers, and a trend towards benefit in never smokers. Other studies in this setting, using selenium [6] or a combination of retinol and *N*-acetylcysteine [8], have also been negative.

Currently, there are no proven chemoprevention agents for lung cancer (Table 2). To improve our chances of developing effective chemoprevention, we need a better understanding of the biology of lung cancer.

3 Molecular Biology of Lung Cancer

There are many different types of lung cancer, and different molecular pathways leading to each type. About 20% of lung cancer is small cell lung cancer, and the rest is NSCLC. In the United States, the most common subtype of NSCLC is adenocarcinoma, and squamous cell carcinoma is the second most common histology [37].

Adenocarcinomas classically originate in the peripheral airways. Though most patients diagnosed with adenocarcinoma have a history of cigarette smoking, this is the most common type of lung cancer in nonsmokers. The proportion of adenocarcinomas has been increasing over the past few decades – the reasons for this increase are unknown, but might include changing smoking habits or the increased use of filtered cigarettes. Atypical adenomatous hyperplasia is a precursor lesion for a subset of adenocarcinomas [38]; however, the precursor lesions of adenocarcinoma have been less extensively studied than those of squamous cell carcinoma.

Squamous cell carcinomas usually arise in the proximal airways. There is a strong association between squamous cell carcinoma and smoking. The precursor lesions of squamous cell carcinoma have been well described, and include squamous metaplasia and dysplasia [20, 39].

We now understand the mutations that drive certain subsets of these tumors.

3.1 KRAS

KRAS is a GTPase which is an early component of multiple cell signaling pathways. Mutations in *KRAS* are found in 20–30% of adenocarcinomas, and are very rarely found in squamous cell carcinoma [40, 41]. Mutations are often seen in atypical adenomatous hyperplasia, a precursor to adenocarcinoma [38, 41]. These mutations are more common in current and former smokers than nonsmokers [42] and they are associated with resistance to epidermal growth factor receptor (EGFR) inhibition [43]. There are no effective targeted therapies currently in clinical use for these patients. However, in a mouse model, combination therapy with a PI3K inhibitor and a MEK inhibitor is active against *KRAS*-mutant tumors [40], and agents in these families are in the early stages of clinical testing.

3.2 EGFR

EGFR is frequently involved in carcinogenesis and is an important regulator of growth in human cells. Activating mutations of *EGFR* have been described in patients with adenocarcinoma, and are present in 10% of adenocarcinomas in the U.S. and in higher numbers of Asian patients [44]. These mutations, specifically those in exons 19 and 21 activating the kinase domain of the enzyme, are associated with responsiveness to EGFR inhibition [44, 45]. These activating mutations are very rare in squamous cell carcinoma, but EGFR amplification is commonly seen [41]. About 5% of squamous cell carcinomas have mutations in the extracellular domain of EGFR, also known as the variant III *EGFR* mutation; these mutations do not confer sensitivity to EGFR inhibition and may confer resistance [46].

3.3 EML4-ALK

The *EML4-ALK* translocation was the first chromosomal translocation described in lung cancer. A rearrangement on chromosome 2 creates a constitutively activated anaplastic lymphoma kinase (ALK) that drives growth [47]. This translocation is found in about 3–7% of adenocarcinomas and does not occur in patients with either *KRAS* or *EGFR* mutations [47–49]. These patients are sensitive to treatment with crizotinib, an ALK/c-Met inhibitor [50]. This drug was recently FDA approved, along with a companion diagnostic test.

3.4 Other Molecular Changes

KRAS and *EGFR* mutations and *ALK* rearrangements are the most clinically important genetic abnormalities seen in NSCLC, but other changes are also seen. *BRAF* mutations are found in a small percentage of lung adenocarcinomas, 2% in one study [51]. *BRAF* inhibitors have been successful in the treatment of metastatic melanoma [52]; drugs in this class are also being investigated for NSCLC. The phosphatidylinositol 3'-kinase (PI3K) pathway includes Akt and mTOR, and tumor cells have increased activation of this pathway relative to normal cells [53]. The gene *PIK3CA*, which encodes the catalytic unit of PI3K, is mutated in approximately 5% of NSCLC [54]. There are a number of inhibitors of this pathway in clinical development, including mTOR inhibitors, Akt inhibitors, and PI3K inhibitors.

Mutations in *DDR2* have been identified as driver mutations in about 4% of squamous cell carcinomas [55]. This gene encodes for a kinase with roles in cell adhesion and proliferation [56]. Patients with this mutation may be more sensitive to treatment with dasatinib [55]. Also, amplifications of *FGFR1*, encoding for a fibroblast growth factor receptor, have been described in over 20% of squamous cell carcinomas [57].

Aberrant angiogenesis is one of the hallmarks of cancer [58], and vascular endothelial growth factor (VEGF) is a regulator of angiogenesis in both normal tissue and in malignancy [59]. VEGF and VEGF receptor are aberrantly expressed in lung cancer, and this expression may be associated with poor prognosis [60, 61]. VEGF-A is expressed more commonly in adenocarcinoma than squamous cell carcinoma [62]. Bevacizumab, a monoclonal antibody against VEGF receptor, has been shown to be effective in the first-line treatment of adenocarcinoma in combination with chemotherapy [59]. It is not used in squamous carcinomas due to an increased risk of serious bleeding [63].

Most lung cancers have alterations in pathways responsible for DNA repair. p53, a critical regulator of the cell cycle, apoptosis, and DNA repair, is an important tumor suppressor, and it is thought that more than half of all human cancers have mutations in *TP53* [64, 65]. *TP53* is mutated in the majority of NSCLCs, both adenocarcinoma and squamous cell carcinoma, and mutations are more common in smokers [41]. Though multiple attempts have been made to target p53 pharmacologically, there are no proven therapies targeting this important protein.

Our understanding of the molecular biology of lung cancer continues to evolve. The Tumour Sequencing Project examined 623 genes for mutations in 188 adenocarcinomas and identified a number of mutated genes not previously known to be associated with lung cancer [66]. Tumors with higher grade had more mutations than lower grade tumors, and smokers had more mutations than nonsmokers. Another study determined copy number alterations in lung adenocarcinoma. Many of the sites identified as consistently gained or lost in lung cancer have not been linked to a specific gene, suggesting that we have yet to discover many of the genes involved in lung carcinogenesis [67].

4 Personalizing Treatment of Lung Cancer

The standard treatment for advanced lung cancer is platinum-based combination therapy, but response rates are low and long term survival is rare [68, 69]. It seems unlikely that we will be able to improve outcomes substantially with a one-size-fits-all approach; we must learn to personalize therapy.

For patients with *EGFR* mutations and *ALK* rearrangements, targeted therapies are the standard front-line treatment [45, 50]. These treatment regimens are well tolerated and are associated with high response rates and extended time to progression, though they are not curative. Unfortunately, less than 15% of patients with adenocarcinoma have one of these genetic alterations; for the remainder of our patients, we do not yet have personalized therapy. A number of recent studies have used our improving understanding of the molecular biology of lung cancer to try to personalize therapy.

At M.D. Anderson we are working towards personalized lung cancer therapy with our biomarker-integrated approaches of targeted therapy for lung cancer elimination (BATTLE) program. In our first BATTLE trial [70], patients with advanced lung cancer had a CT-guided core biopsy, and this tissue was analyzed to create a biomarker profile. This profile helped to determine which of four targeted therapies a patient would receive. The hypothesis is that individual tumors are driven by a dominant signaling pathway, and by identification and targeting of that pathway we may be able to improve outcomes. Bayesian adaptive randomization was used, increasing the chances that an individual patient would receive a therapy from which he is predicted to derive benefit.

This trial demonstrated the feasibility of a biopsy-mandated approach in advanced lung cancer. Preliminary findings, such as a relatively high disease control rate with sorafenib in patients with *KRAS* mutations, have provided hypotheses for further studies.

The BATTLE program is expanding, and accrual is ongoing for two more studies. Both follow similar designs, with biopsies mandated on enrollment. The BATTLE-2 study enrolls patients with previously treated lung cancer to receive one of four targeted therapies or combinations; the BATTLE-Front Line trial enrolls patients with previously untreated lung cancer to receive combinations of chemotherapy and biologic therapy.

5 Personalizing Prevention of Lung Cancer

In treating lung cancer, it is not likely that any single agent will be effective in every patient. The same is true in lung cancer prevention. We propose reverse migration as a method to personalize chemoprevention. Reverse migration is the application to the prevention setting of concepts and ideas that have been developed in advanced cancer. Concepts like risk assessment, biomarker analyses, targeted therapeutics, surrogate endpoints, and predictive markers have been more thoroughly explored in the treatment of cancer, but all are potentially important for cancer prevention as well.

An example of reverse migration is the development of tamoxifen, as described in Table 3. Breast cancer has long been known to be hormonally driven in some patients. Tamoxifen is a selective estrogen receptor modulator, and has been used in the treatment of metastatic breast cancer for over 30 years [71]. It has also been shown to be effective in reducing the risk of recurrent cancer following surgical resection of a breast tumor [72], that is, in the tertiary prevention setting. As secondary prevention, tamoxifen decreases the risk of invasive breast cancer in patients with ductal carcinoma in situ, a premalignant lesion [73]. Tamoxifen is also effective as primary prevention, decreasing the risk of breast cancer in healthy postmenopausal women [25].

Though tamoxifen is the most thoroughly studied example of reverse migration, other examples of this strategy are emerging. In multiple myeloma, lenalidomide, an immunomodulating agent, is an effective treatment [74] and is also being studied for use in smoldering myeloma, the precursor stage to this malignancy. For patients with metastatic basal cell carcinoma, a hedgehog inhibitor, GDC-0449, can result in impressive responses [75]; for patients with Gorlin's syndrome, who are genetically predisposed to basal cell carcinoma, this same hedgehog inhibitor can suppress development of cancer [76]. As in breast cancer, antihormonal agents are effective for prostate cancer in the settings of advanced malignancy [77], localized disease [78], and chemoprevention [27]. In breast cancer, PARP inhibitors, which interfere with DNA repair and induce synthetic lethality, are associated with tumor response in patients with metastatic breast cancer patients and germline BRCA mutations [79]. Women with BRCA1 or BRCA2 mutations are at very high lifetime risk of breast cancer, up to 85% depending on the population studied, and PARP inhibitors may be useful in the chemoprevention setting for these women.

It is now time to begin using a reverse migration approach for the prevention of lung cancer. We are learning more about the biology of lung cancer every day, and genetic analysis of individual tumors is becoming less expensive, more accurate, and quicker [80]. Our targeted treatments for metastatic cancer are more tolerable than traditional cytotoxic chemotherapy; patients can be treated with targeted therapeutics like erlotinib for extended periods of time. Also, we now have experience with the type of biopsy-mandated, biomarker-driven clinical trials that will be necessary to make personalized chemoprevention a reality.

5.1 Personalizing Tertiary Chemoprevention

Tertiary chemoprevention is an obvious setting to develop chemopreventive agents using a reverse migration strategy. Patients with resected early stage lung cancer are at a high risk of recurrence and second primary tumors [35, 36]. In this group, an important concept is the identification of molecular targets, not only in the tumor but also in the surrounding tissue.

At MD Anderson we have an extensive program to identify risk factors for tumor recurrence following resection of early stage lung cancers, with a long term goal of developing new therapeutic approaches to adjuvant treatment and prevention. In one arm of these project, 49 patients with resected early stage NSCLC were enrolled to a prospective clinical trial in which they underwent serial bronchoscopies with biopsies yearly for 3 years [81]. Primary endpoints were recurrence and second primary tumors. Analysis is ongoing to determine which markers in the bronchial epithelium correlate with recurrence, but preliminary results show that activation of the PI3 kinase pathway puts patients at a higher risk of recurrence. This pathway may be a therapeutic target, and inhibitors of this pathway are currently in clinical development.

Another part of this project is a retrospective analysis of 370 resected early stage lung tumors. The expression of 23 prespecified biomarkers, selected from preclinical work as being important in carcinogenesis, were measured and correlated with outcomes, including recurrence free survival and overall survival [82]. Using these markers, a risk model was created, where patients could be classified as low, intermediate, or high risk based on expression of these markers.

We propose an idea for a BATTLE-type study in the adjuvant/tertiary prevention setting [13]; see Fig. 1 for a schema. In this study, patients undergoing surgical resection for early stage lung cancer would have biomarker analyses performed on both the tumors and the adjacent epithelium. Based on the molecular abnormalities found, patients would be assigned to a targeted treatment. For example, in patients with resected tumors bearing EGFR mutations, adjacent, histologically normal bronchial epithelium frequently harbors

mutations as well [83, 84]. Therefore, these patients would receive EGFR inhibitors, which are effective in the setting of advanced disease [45]. The current data for EGFR inhibitors in the adjuvant setting is mixed [85, 86]; a phase III trial (RADIANT) is ongoing which should address this issue. Patients with *ALK* rearrangements would receive crizotinib. Patients with overexpression of cyclin D1 could receive a combination of erlotinib and bexarotene; overexpression predicts response to this combination in the metastatic setting [87]. Patients with high levels of inflammatory markers, such as COX-2, could receive anti-inflammatory medications, and patients with alterations of the PI3K pathway could receive PI3K/Akt inhibitors. Primary endpoints would be recurrences and second primary tumors. Secondary endpoints would be tolerability, biomarker modulation, and correlation of biomarker modulation with outcome.

5.2 Personalizing Primary and Secondary Chemoprevention

To personalize chemoprevention successfully for patients with no history of cancer, we must be able to identify those at highest risk, perform screening studies appropriately, and treat those at high risk for cancer with targeted chemoprevention agents.

Risk assessment models have long incorporated demographic data, such as age, smoking history, and family history of cancer. Now, we are learning to incorporate biomarkers into these models. Biomarker assessment can be noninvasive, such as blood draws or buccal swabs, or invasive, like bronchoscopic biopsies. Recent epidemiologic studies have identified single nucleotide polymorphisms (SNPs) that can be used to create a risk prediction model that is more accurate than one incorporating only clinical characteristics [88]. Other studies have incorporated bronchoscopic biopsies into risk assessment models. A study by Gustafson et al. found that activation of the PI3 kinase pathway correlated with dysplasia [89]. Treating with an inhibitor of PI3 kinase, *myo*-inositol, effectively down-regulates this pathway and reverses dysplasia in some patients. This pathway, as discussed earlier, was also identified in an MD Anderson study as predicting increased risk of tumor recurrence following resection [81].

Screening for lung cancer is another opportunity to reduce mortality in patients at risk for lung cancer. Until recently there were no proven screening tests for lung cancer. Recently published results from the National Lung Screening Trial, however, show that yearly low-dose CT scans can decrease lung cancer mortality and all-cause mortality in a group of patients at high risk for lung cancer [90]. Enrolled participants were between 55 and 74 years of age and had at least a 30 pack-year history of cigarette smoking. Lung cancer mortality was decreased by 20% with CT scans compared to chest X-rays. Though these results are impressive, CT screening for lung cancer has not yet been universally accepted, possibly due to concerns regarding costs. Improved risk assessment could improve the cost-benefit ratio by avoiding scans in patients at lower risk for cancer.

Recent chemoprevention studies have used targeted agents and incorporated biomarker based endpoints. In two recently reported studies, patients were treated with celecoxib, a COX-2 inhibitor [91, 92]. COX-2 is a modulator of inflammation, and its overexpression is seen in premalignant lung lesions [93] and predicts a worse outcome in surgically resected early stage NSCLC [94, 95]. Both studies revealed a decrease in Ki-67, a marker of proliferation, in bronchial epithelium with celecoxib treatment [91, 92]. In addition, one study identified a biomarker predicting benefit from celecoxib [92]. A study reported by Keith et al. found that oral iloprost, a prostacyclin analog, reduced bronchial dysplasia in former smokers, though current smokers did not benefit [96]. A recent meta-analysis of randomized trials studying aspirin for cardiovascular disease prevention provided further evidence of the benefit of anti-inflammatory treatment – aspirin treatment was associated with a decrease in mortality from a number of cancers, including lung adenocarcinoma [97].

These studies are notably different from some of the older studies in lung cancer prevention. Studies like CARET and ATBC [4, 5] took agents without clear targets identified in epidemiologic studies directly into large clinical trials, enrolling thousands of patients, with endpoints related to cancer incidence. These studies were expensive and unsuccessful. Studies like those described above have utilized targeted agents and have incorporated correlative analyses. The number of patients enrolled is relatively small, and surrogate endpoints are used. With clinical trials like these, we can learn more about how these drugs work, and for whom they work, before bringing them to large, definitive trials.

In addition to any pharmacologic prevention treatments, smoking cessation remains critically important. Several clinical trials have shown that if patients continue smoking, chemoprevention can be ineffective and even harmful. In the CARET study, current smokers were harmed by treatment with beta-carotene and retinol, while former smokers had a trend towards lower lung cancer incidence with treatment [5]. In the Intergroup Lung Trial, current smokers had an increased risk of death with isotretinoin treatment, while former and never smokers had a trend towards benefit [7]. More recently, Keith et al. noted an improvement in endobronchial dysplasia in former smokers treated with iloprost, while current smokers had no histologic improvement [96]. The reasons for the lack of efficacy of chemoprevention in patients who continue tobacco use is likely due to interactions between tobacco carcinogens and chemopreventive agents. Beta-carotene may lead to induction of certain cytochrome P450 enzymes, causing increased bioactivation of tobacco-associated procarcinogens [98]; retinoids might have similar effects. Increased oxidative stress from supplementation is another hypothesized mechanism [99]. Future chemoprevention studies should focus on those patients who have already quit smoking – current smokers should be referred to intensive tobacco cessation programs.

6 Conclusions

There are significant barriers to the reverse migration approach, but also rewards for overcoming them. Though we frequently describe signaling pathways as simple, step-wise progressions, in cells they are often complex and there is crosstalk between pathways. Therefore, inhibiting a particular pathway may require multiple pharmacologic agents and may have unintended consequences. In addition, it has frequently been difficult to match biomarkers and targeted agents – we often cannot predict which patients will respond to therapy. Risk prediction is still difficult; models incorporating SNPs are only marginally more accurate than those incorporating clinical risk factors alone [88].

There are also practical barriers. Clinical trials are expensive, and the costs of clinical trials incorporating biopsies and biomarkers are even higher. There are regulatory issues involved when using biomarkers in clinical trials. Also, there is the issue of infrastructure. These types of trials require cooperation between many groups, including pathologists, statisticians, radiologists, pulmonologists, and oncologists, among others. There are issues regarding patient enrollment. Many healthy patients are not willing to enroll on clinical trials requiring biopsies, though we have been able to complete enrollment successfully on these types of trials in the past.

If we are able to overcome these challenges, there are significant rewards. Effective chemoprevention of lung cancer could potentially save many lives, and reverse migration may represent a more efficient and effective pathway to that goal. Our goal is to bring personalized therapy to every patient, from those at risk for cancer to those with metastatic disease (Fig. 2). For patients at lower risk for cancer, counseling on lifestyle changes could be offered; for those at higher risk, screening programs and chemoprevention studies should be considered.

Lung cancer is a molecularly heterogeneous disease, and should no longer be treated with a “one-size-fits-all” approach. In our BATTLE program for cancer treatment, we attempt to identify the molecular drivers of a patient's tumor so that we can hijack these drivers with molecularly matched agents. This approach is applicable not only to the treatment of advanced malignancy, but also to the prevention of cancer in patients at risk. Using what we have learned regarding the biology and treatment of lung cancer, we are now ready to take the BATTLE to the chemoprevention setting.

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Fig. 1. Schema for a personalized trial of tertiary chemoprevention/adjuvant treatment. The tumor and adjacent field will undergo biomarker analysis, and patients will be grouped based on marker status. Treatment will be assigned based on biomarkers [13]

Fig. 2.

Schema for a comprehensive BATTLE strategy against all stages of carcinogenesis, from pre-malignancy to advanced cancer. BATTLE (*upper left*) represents our trial program in advanced, previously treated lung cancer. BATTLE-frontline (BATTLE-FL, *upper right*) is our currently accruing trial in previously untreated advanced stage NSCLC. BATTLE-prevention (BATTLE-P, *bottom*) is our developing program in adjuvant treatment and prevention [13]

Table 1

Successes in chemoprevention

Intervention	Population	Target	Endpoint	Outcome
BCPT [25]	Tamoxifen Women >60	Estrogen receptor	Invasive breast cancer	49% decrease in invasive breast cancer
PCPT [27]	Finasteride Men 55	Testosterone production	Prostate cancer	25% reduction in prostate cancer
FUTURE II [28]	Vaccine Women >15,<26	HPV	Prenalignant cervical lesions	98% decrease in HPV 16/18 associated lesions
Baron et al. [32]	Aspirin Patients with adenomas	Inflammation	Adenomas	19% decrease in adenomas

BCPT Breast cancer prevention trial, *HPV* Human papilloma virus, *PCPT* Prostate cancer prevention trial

Table 2

Major phase III studies in lung cancer chemoprevention

	Intervention	Population	N	Endpoint	Outcome
ATBC [4]	β -Carotene, α -tocopherol	Male smokers	29,133	Lung cancer	Harmful
CARET [5]	β -Carotene, retinol	Current and former smokers	18,314	Lung cancer	Harmful
Lung Intergroup Trial [7]	Isotretinoin	Resected NSCLC	1,166	Second primary tumor (SPT)	Negative ^a
EUROSCAN [8]	Retinol, NAC	Resected NSCLC or HNSCC	2,592	SPT	Negative
Intergroup Selenium Study [6]	Selenium	Resected NSCLC	1,772	SPT	Negative

ATBC Alpha-tocopherol, beta-carotene cancer prevention study, CARET Carotene and retinol efficacy trial, NAC N-acetylcysteine, NSCLC non-small cell lung cancer, HNSCC head and neck squamous cell carcinoma

^aHarm in current smokers

Table 3
The reverse migration of tamoxifen [13]

	Treatment setting	Results
Tamoxifen vs DES, 1981 [71]	Metastatic disease ^a	Response rate 33% with tamoxifen
EBCTCG meta-analysis, 1998 [72]	Adjuvant treatment/tertiary prevention	47% decrease in breast cancer recurrence
B-24, 1999 [73]	DCIS/secondary prevention	43% decrease in invasive breast cancer
BCPT, 1998 [25]	Healthy women/primary prevention	49% decrease in invasive breast cancer

BCPT Breast cancer prevention trial, *DES* diethylstilbestrol, *DCIS* ductal carcinoma in situ, *EBCTCG* Early Breast Cancer Trialists' Collaborative Group

^a Hormone receptor status was not measured prior to enrollment on trial