Featured Article

Celecoxib Modulates the Capacity for Prostaglandin E$_2$ and Interleukin-10 Production in Alveolar Macrophages from Active Smokers

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Abstract

Purpose: Preclinical data suggest that the cyclooxygenase (COX)-2-prostaglandin (PG) E$_2$ signaling pathway plays an essential role in conferring the malignant phenotype in non-small cell lung cancer. We hypothesized that treatment with oral celecoxib, a selective COX-2 inhibitor, would favorably alter biomarkers of lung cancer risk. This study evaluated the feasibility of COX-2 inhibition as a form of chemoprevention for lung cancer.

Experimental Design: Heavy active smokers were enrolled into a pilot study and treated with celecoxib. Bronchoscopy with bronchoalveolar lavage was performed both before and after 1 month of celecoxib treatment to recover alveolar macrophages (AMs) and lining fluid for study. After harvest, AMs were immediately stimulated in vitro with the calcium ionophore A23187. AMs obtained from smokers before treatment and from nonsmoking control subjects were also cultured overnight with SC58236, a selective COX-2 inhibitor, with or without lipopolysaccharide stimulation.

Results: Treatment with celecoxib significantly reduced calcium ionophore-stimulated PGE$_2$ production from AMs recovered from smokers. AMs recovered from smokers, but not nonsmokers, were primed to produce high levels of PGE$_2$ and interleukin (IL-10) when stimulated with lipopolysaccharide, and SC58236 significantly abrogated the production of these factors. Moreover, both plasma and bronchoalveolar lavage fluid obtained from treated subjects significantly reduced the production of PGE$_2$ that resulted when a lung cancer cell line, A549, was stimulated with IL-1$eta$ or A23187.

Conclusions: Our findings suggest that oral celecoxib is capable of inhibiting the overproduction of PGE$_2$, as well as modulating the production of IL-10 in the lung microenvironment in individuals at risk for lung cancer.

Introduction

Accumulating evidence suggests that NSAIDs that inhibit the synthesis of PGs can reduce the incidence of a variety of cancers. The evidence derives from rodent models of chemical-induced carcinogenesis (1), epidemiological studies, and clinical trials in patients with familial adenomatous polyposis (2). COXs (COX-1 and COX-2) are enzymes that catalyze the formation of PGs from arachidonic acid (3). Whereas COX-1 is involved in the homeostasis of various physiological functions, COX-2 is up-regulated in response to a variety of stimuli including growth factors, cytokines, and carcinogens and is responsible for many inflammatory processes. The simultaneous inhibition of COX-1 (constitutively expressed) and COX-2 (inducible isoform), however, interferes with the maintenance functions of COX-1 and thereby increases the risk of serious side effects, such as peptic ulcer disease. This problem may be avoided by selective inhibition of the COX-2 enzyme (4, 5).

Many effects of NSAIDs on cancer have been ascribed to the effects of these drugs on COX-2. COX-2 has been implicated in the development of colon cancer and may play a role in promoting invasion, metastasis, angiogenesis, and resistance to apoptosis, as well as suppression of antitumor immunity in several tumor types (6–11). Our laboratory first reported the presence of COX-2 protein in squamous cell carcinomas and adenocarcinomas of the lung (11). Others also reported similar findings (12–14). In addition, COX-2 protein is overexpressed in preneoplastic alveolar epithelium, suggesting its role in tumorigenesis (15).

Animal models and human trials for colon cancer suggest that systemic inhibition of COX-2 can act as an effective chemopreventive therapy. In a very similar manner, treatment with COX-2-specific inhibitors protects mice from lung tumorigenesis (16). The abbreviations used are: NSAID, nonsteroidal anti-inflammatory drug; PG, prostaglandin; COX, cyclooxygenase; NSCLC, non-small cell lung cancer; AM, alveolar macrophage; BAL, bronchoalveolar lavage; LPS, lipopolysaccharide; IL, interleukin; EIA, enzyme immunoassay.
esis caused by the tobacco-specific nitrosamine, 4-(methyl nitro-
saminomethyl)-1-(3-pyridyl)-1-butanone (1). In addition to this direct
relationship between the overexpression of COX-2 and lung
cancer, overexpression of COX-2 and/or PGE_2 is associated
with a variety of well-established lung cancer risk factors,
including antitumor immunity via an imbalance between the
production of IL-10 and IL-12 by both tumors and immune
regulatory cells, such as peripheral blood lymphocytes, macro-
phages, and dendritic cells (11, 16–19). Overproduction of
PGE_2 in the lung microenvironment also produces immunosup-
pressive effects on T cells, natural killer cells, and antigen-
presenting cells, resulting in enhanced tumor growth (20, 21).

As part of a pilot study to evaluate the feasibility of
celecoxib as a chemopreventive agent for lung cancer, 20 heavy
current smokers were recruited and treated with a 6-month
course of oral celecoxib. To determine the effects of celecoxib
on altering surrogate end point biomarkers of carcinogenesis in
the lung, serial bronchoscopies with BAL were performed.
Treatment with oral celecoxib inhibited the production of PGE_2
when AMs were stimulated ex vivo with A23187. In addition,
AMs from pretreatment samples were cultured overnight with
SC58236, a COX-2-selective inhibitor, with or without LPS
stimulation. SC58236 significantly abrogated the LPS-induced
overproduction of PGE_2. Stimulation of AMs with LPS also
significantly induced IL-10 production, and SC58236 decreased
this effect. Moreover, plasma and BAL fluid obtained from
treated subjects abrogated the capacity for IL-1β and A23187 to
stimulate PGE_2 production by human NSCLC cells in vitro,
respectively. These results support the hypothesis that oral ad-
ministration of celecoxib is capable of modulating the intrapul-
monary production of PGE_2 and IL-10 and may favorably
impact on these procarcinogenic forces within the lung micro-
environment.

Materials and Methods

Celecoxib Clinical Study Design. Active heavy smokers
45 years of age or older, with a smoking history of at least 20
pack-years, were recruited and treated with oral celecoxib (Cele-
brex; Pfizer, New York, NY) at a dose of 400 mg twice daily
for 6 months. Written informed consent was obtained in accord-
ance with the UCLA Institutional Review Board. Patients were
screened with chest X-ray and fluorescence (LIFE) bronchos-
copy (Xillix, Vancouver, Canada) to rule out the presence of
lung cancer. Only subjects without evidence of lung cancer at
baseline who met all entry criteria (Table 1) were enrolled. All
patients underwent repeat white light bronchoscopy with BAL
at 4 weeks after starting treatment and are scheduled to undergo
repeat LIFE bronchoscopy at 6 months. Serial bronchial muco-
sal biopsies, BAL fluid, and blood specimens are being col-
lected for biomarker analyses to determine treatment responses.
Bronchoscopy with BAL was also performed in a group of
healthy nonsmokers to provide control AMs for comparison
studies.

Blood Samples. Plasma samples collected in vacutainer
tubes containing EDTA were obtained from subjects at baseline,
1 month, and 6 months of treatment. Samples were stored at
−80°C until analysis.

| Table 1  Study enrollment criteria |
|------------------|------------------|
| **Inclusion**    | Age ≥ 45 (yrs)  |
|                  | Smoking history ≥ 20 pack-years |
| **Exclusion**    | Concurrent use of NSAIDs |
|                  | Hypersensitivity to celecoxib or NSAIDS |
|                  | Documented allergic-type reaction to sulfonamides |
|                  | Liver dysfunction |
|                  | Hypertension or cardiac conditions aggravated by fluid retention and edema |
|                  | Previous history of gastrointestinal ulceration, bleeding, or perforation |
|                  | Renal dysfunction |
|                  | End stage respiratory disease (e.g., FEV1 < 0.8 liters, resting or exertional hypoxemia) |
|                  | Unstable angina |
|                  | Other malignancy |
|                  | Pregnancy |
|                  | Concurrent use of medication known to alter or be affected by alteration of the hepatic p450 2C9 and 2D6 enzymes |

Patients with concurrent medical conditions that may interfere with completion of tests, therapy, or the follow-up schedule

BAL and in Vitro Stimulation of AMs. Subjects were
prepped with a combination of topical anesthesia (20% benzo-
caine spray to pharynx plus 2% topical lidocaine as needed) and
conscious sedation using midazolam and meperidine according
to institutional guidelines. A fiberoptic bronchoscope (Olympus
BF20D, Olympus America Inc., Melville, NY) was advanced
into the airway and wedged into a subsegment of the right
middle lobe. Four 60-ml aliquots of room temperature saline
were serially lavaged and recovered by manual syringe suction.
Recovered fluid was passed through a 100-μm sterile nylon
filter (Becton Dickinson, San Jose, CA) to remove mucus and
particulates, pooled, and centrifuged at 300 × g for 8 min at
4°C. The BAL fluid was then harvested, aliquoted, and stored at
−80°C until analysis.

PGE_2 production was stimulated by two methods. For
calcium ionophore stimulation, BAL cell pellets were first
washed in HBSS (Sigma-Aldrich, St. Louis, MO) and then
resuspended in X-Vivo 15 serum-free medium (Biowhittaker,
Walkersville, MD) to a concentration of 5 × 10⁶ cells/ml. Cells
were incubated with 2 μM A23187 (Calbiochem, San Diego,
CA) for 30 min, and the culture supernatants were harvested and
stored at −80°C until analysis. BAL cells were also washed
once in PBS (Irvine Scientific, Santa Ana, CA) and resuspended in
X-Vivo 15 serum-free medium (Biowhittaker) to a concen-
tration of 0.5 × 10⁶ cells/ml. Control cells and cells stimulated
with 5 μg/ml LPS (Escherichia coli 026:B6; Sigma-Aldrich)
were cultured with or without SC58236, a selective COX-2
inhibitor belonging to the same 1,5-diarylpyrazole class of
COX-2 inhibitors as celecoxib (800 ng/ml; Pfizer; Ref. 22) at
37°C. After 24 h of incubation, the conditioned supernatants
were harvested and stored at −80°C until analysis. Stock solu-
tions of SC58236 were prepared at a concentration of 1 mg/ml
in DMSO and stored at −80°C.

Effects of Subjects’ Plasma and BAL Fluid on Produc-
tion of PGE_2 by a NSCLC Cell Line. Most human NSCLC
cells produce PGE_2 when stimulated (11). As a model for the
impact of celecoxib on overproduction of PGE₂, the human lung adenocarcinoma cell line A549 was obtained from American Type Culture Collection (Manassas, VA) and studied in vitro. Cells were maintained as monolayers in an atmosphere of 5% CO₂ in air at 37°C in 25-cm² tissue culture flasks containing 5.0 ml of RPMI 1640 supplemented with 10% fetal bovine serum, 100 units/ml penicillin, 0.1 mg/ml streptomycin, and 2 mM glutamine (JRH Biosciences, Lenexa, KS). For coculture with BAL fluid, 8 × 10⁵ A549 cells were plated in wells from a 12-well plate in 700 µl of RPMI 1640 and incubated at 37°C for 2 h. Matched BAL fluids (300 µl) obtained from subjects before and after 1 month of treatment or RPMI 1640 were then added (final concentration, 30%), and cells were incubated at 37°C for an additional hour, followed by stimulation with A23187 (2 µM) for 30 min. For cocultures with plasma, 3 × 10⁵ cells were plated in 800 µl of RPMI 1640 in a 12-well plate and incubated at 37°C for 2 h. Two hundred µl of plasma obtained before treatment and after 1 month of treatment were added (final concentration, 20%), and cells were incubated at 37°C for an additional hour. Cells were then stimulated with IL-1β (200 units/ml) for 24 h. All culture supernatants were harvested and stored at −80°C until analysis.

Measurement of PGE₂. PGE₂ concentrations in BAL, conditioned AMs, and tumor cell culture supernatant were measured by ELISA using a PGE₂ EIA kit (Cayman Chemical, Ann Arbor, MI). Absorbance was determined at 405 nm by Molecular Devices Microplate Reader (Sunnyvale, CA).

Measurement of IL-10 and IL-12 Production in AMs. IL-10 and IL-12 levels were measured by ELISA. Rat antihuman IL-10 capture antibody and rat biotinylated antihuman IL-10 monoclonal antibody pairs were obtained from PharMingen (San Diego, CA). ELISA was performed as described previously (11). The human IL-12 ELISA kit was obtained from R&D System (Minneapolis, MN), and the assay was performed according to the manufacturer’s instructions.

Statistical Analysis. The effects of celecoxib on intrapulmonary PGE₂ production were determined by comparing BAL levels with those obtained at 1 month after treatment using paired t tests. Similarly, the effects of celecoxib on the production of PGE₂ by cultured AMs and A549 cells were determined by paired t tests. Batch analyses were performed for each subject/comparison group to eliminate interassay variability.

Results

Subject Characteristics. The patient cohort consisted of 9 males and 11 females with a mean age of 54 years and a mean smoking history of 42 pack-years (Table 2). Ten subjects had evidence of airflow obstruction defined as a forced expiratory volume in one second < 80% predicted (mean of 66%). Five subjects had at least one family member with a history of lung cancer. The celecoxib dose of 400 mg twice daily was well tolerated with no serious adverse events reported to date. All 20 subjects have completed the 1 month follow-up bronchoscopy, but longer term follow-up is still ongoing. Four healthy nonsmokers without respiratory symptoms or airflow obstruction also underwent bronchoscopy (mean age, 30 years of age).

Orally Administered Celecoxib Modulates the Capacity for AMs to Produce PGE₂ in Active Smokers. BAL fluids obtained from active smokers before and after 1 month of treatment with celecoxib were first analyzed for relative changes in the concentrations of PGE₂ as a measure of its effect on COX-2 activity within the lung microenvironment. However, PGE₂ levels in BAL fluid were generally below the level of detection for EIA (data not shown). We therefore evaluated the effect of celecoxib therapy on the calcium ionophore-stimulated production of PGE₂ by BAL cells. As reported previously, BAL cells collected from active smokers consisted of >90% AMs (23). Freshly isolated AMs collected from six subjects before and after celecoxib treatment were stimulated with A23187 for 30 min. On the average, A23187 caused more than a 3-fold increase in PGE₂ production by cells obtained at baseline, before celecoxib treatment. In contrast, AMs recovered from subjects after treatment with oral celecoxib were refractory to A23187 stimulation with the production of PGE₂ inhibited by 69%, as compared with the baseline response (Fig. 1; mean ± SE; P < 0.01; n = 6).

Plasma and BAL Fluid Obtained from Treated Subjects Abrogated PGE₂ Production by Stimulated NSCLC Cells in Vitro. COX-2 expression is up-regulated when NSCLC cells are stimulated with inflammatory cytokines such as IL-1β. The resultant overproduction of PGE₂ by tumor cells has been implicated as a driving force for carcinogenesis (11, 16). We evaluated plasma and BAL fluid to determine whether oral celecoxib produced an environment capable of reducing PGE₂ production in tumor cells. To induce production of PGE₂, A549 cells were either stimulated

| Table 2 Baseline subject characteristics |
| Parameter | Mean | Range |
| Age (yrs) | 54 | 47–78 |
| Gender (M/F) | 9/11 | |
| Smoking history (pack-ys) | 42 | 20–159 |
| Ethnicity, A/B/C/H* | 1/2/15/2 | |
| COPD* (n) | 10 | |
| Family history of lung cancer (n) | 5 | |

* A/B/C/H, Asian/Black/Caucasian/Hispanic.

* COPD, chronic obstructive pulmonary disease.
for 24 h with IL-1β or stimulated for 30 min with A23187. Stimulation of A549 cells with IL-1β in control media increased PGE₂ production on average by 5-fold. Addition of baseline plasma augmented this to a 10-fold increase. However, the addition of plasma from patients receiving celecoxib almost completely abrogated this induction. Similarly, post-treatment BAL fluid also abrogated the capacity for A23187 to increase PGE₂ production in A549 cells by 85% (Fig. 2, A and B; mean ± SE; P < 0.01; n = 3).

In Vitro Treatment with SC58236 Blocks LPS-Induced Production of PGE₂ by AMs Recovered from Smokers. Oral administration of celecoxib blocked the capacity for stimulated AMs to produce PGE₂. To model this effect in vitro, BAL cells recovered from smokers before treatment were cultured for 24 h in media containing the COX-2 inhibitor SC58236 (800 ng/ml). Concentrations of PGE₂ in the culture supernatant were reduced by an average of 82% compared with untreated cells. Stimulation with LPS significantly increased the PGE₂ production by an average of 17.5-fold, and coculture with SC58236 abrogated the LPS-induced PGE₂ production by an average of 75% (P < 0.05). Interestingly, AMs from nonsmokers were less responsive to LPS and produced lower levels of PGE₂ when stimulated. However, addition of SC58236 still blocked the response to LPS in nonsmoker AMs. These data suggest that AMs from active smokers are primed to produce higher levels of PGE₂ when exposed to inflammatory stimuli (Fig. 3).

Inhibition of COX-2 Blocks the Release of IL-10 by LPS-Stimulated AMs from Smokers, but not from Nonsmokers. Changes in IL-10 production were also analyzed in the same sets of conditioned AM cell culture supernatants as described above. LPS significantly induced the production of IL-10 by an average of 12.8-fold, and treatment with SC58236 significantly reduced LPS-induced IL-10 production by an average of 24% (n = 10).

Discussion

This pilot study focused on the feasibility of using an oral COX-2 inhibitor, celecoxib, as a chemopreventive agent to
In the lung microenvironment, we first evaluated the modulation of PGE\(_2\) levels for the effect of oral celecoxib on PGE\(_2\) production in the lung microenvironmental relevant parameters such as the production of PGE\(_2\) and whether systemic administration of celecoxib would significantly impact the pulmonary environment and inhibit important cellular sources of PGE\(_2\) overproduction.

To determine the effect of oral celecoxib on PGE\(_2\) production in the lung microenvironment, we first evaluated the modulation of PGE\(_2\) levels in BAL fluid after celecoxib treatment. However, the levels of PGE\(_2\) in BAL fluid were either below or at the detection limits of EIA. This is primarily due to an intrinsic limitation of the sampling technique, which invariably dilutes the specimens below the sensitivity of EIA. Because AMs are the predominant effector cells in the lung microenvironment and are a major source of PGE\(_2\) production, we studied the effect of celecoxib on the production of PGE\(_2\) in AMs obtained from active smokers before and after treatment. We demonstrated that oral administration of celecoxib significantly abrogated the capacity for calcium ionophore to stimulate PGE\(_2\) synthesis in AMs freshly collected from active smokers. This finding provides the first evidence that oral celecoxib, at a dose of 400 mg twice daily, is capable of inhibiting PGE\(_2\) synthesis within the lung microenvironment of active smokers.

To further understand the potential significance of celecoxib treatment on lung carcinogenesis, we evaluated the functional effects of bronchoalveolar lining fluid and plasma obtained from treated subjects on the synthesis of PGE\(_2\) by the human NSCLC cell line AS49. Plasma obtained from baseline significantly increased the stimulatory effect of IL-1\(\beta\) on PGE\(_2\) production, and plasma from treated subjects completely abrogated the IL-1\(\beta\)-induced up-regulation of PGE\(_2\) by AS49 cells.

Presumably, tobacco smoke may have generated proinflammatory mediators in the plasma that synergistically augmented the effects of IL-1\(\beta\) in the culture medium. For example, Ryder et al. (24) reported that peripheral blood mononuclear cells from tobacco smokers produced more IL-1\(\beta\) and transforming growth factor \(\beta\) than those of nonsmokers. Alternatively, certain plasma factors may be required for IL-1\(\beta\) to exert its maximal stimulatory effect on COX-2 induction. Similarly, posttreatment BAL fluid also abrogated the capacity for A23187 to induce PGE\(_2\) synthesis. These findings, although indirect, further support the notion that oral celecoxib either reached a high enough concentration in the lung microenvironment to directly impair PGE\(_2\) production by tumor cells or altered other host-derived endogenous proteins or cytokines capable of indirectly inhibiting PGE\(_2\) production. Our findings also corroborate with the recent report by Altorki et al. (25) that coadministration of oral celecoxib (400 mg, twice daily) was sufficient to normalize the marked increase in intratumoral PGE\(_2\) levels found in NSCLC patients after treatment with paclitaxel and carboplatin.

PGE\(_2\) is an important COX-2 dependent regulator of cell-mediated immunity and a potent inducer of Th2 immune responses (16). It up-regulates the synthesis of IL-10 in a variety of immune-regulatory cells and suppresses Th1 responses (26–31). One of the mechanisms by which PGE\(_2\) may facilitate tumorigenesis is via the suppression of antitumor immunity. Tumor-derived PGE\(_2\) has been shown to inhibit host antitumor immunity by creating an imbalance between the production of IL-10 and IL-12 in lymphocytes and macrophages. Both IL-10 and IL-12 are critical regulatory elements of cell-mediated antitumor immunity. Whereas IL-12 induces type 1 cytokine production and effective antitumor cell-mediated responses (18, 26), IL-10 overproduction at the tumor site has been implicated in tumor-mediated immune suppression. IL-10 has the capacity to inhibit antitumor responses through several pathways such as limiting type 1 cytokine production (28–30), antigen presentation (32, 33), and antigen-specific T-cell proliferation (34). In a murine Lewis lung carcinoma model, COX-2 inhibition decreased IL-10 and restored IL-12 production by antigen-presenting cells. Restoration of the balance between IL-10 and IL-12 in vivo promoted antitumor immunity, resulting in concomitant reduction of tumorogenesis (26).

AMs play a key role in modulating local immune functions (35). They are the first major cell type to encounter inhaled toxins and are responsible for the clearance of these particles. As part of the natural defense against unwanted alveolar inflammation and airway reactivity, human AMs can secrete high levels of PGE\(_2\) that can prevent the cytokine-induced activation of T cells and natural killer cells (20, 21). In this study, we found that 800 ng/ml SC58236 significantly reduced both constitutive and LPS-induced PGE\(_2\) production by AMs from active smokers. In addition, SC58236 significantly reduced both constitutive and LPS-induced IL-10 production by AMs from active smokers, without altering the production of IL-12. To our knowledge, this is the first report demonstrating that COX-2 inhibition downregulates IL-10 production by LPS-stimulated human AMs from smokers. It is conceivable that cigarette smoking may have created an immunosuppressive environment in the respiratory tract of active smokers, in part, by altering this cytokine network through the COX-2/PGE\(_2\) signaling pathway. It is notable that
Celecoxib Inhibits PGE$_2$ Production in Lungs of Smokers

This down-regulation of IL-10 occurred in 8 of the 10 subjects, suggesting that this response may be heterogeneous. The precise mechanisms that may account for this heterogeneity are unclear.

It is also of interest that the response to celecoxib in BAL cells recovered from active smokers differed from that observed with cells obtained from healthy nonsmokers. Unstimulated AMs from smokers produced significantly more PGE$_2$ than those from nonsmokers, suggesting that tobacco smoking up-regulates the expression of COX-2. This is further supported by the fact that treatment with SC58236 reduced AM PGE$_2$ production to a similar level in both smokers and nonsmokers. These findings are consistent with previous studies suggesting that benzo(a)pyrene, a polycyclic aromatic hydrocarbon in tobacco smoke, has the capacity to induce COX-2 gene transcription (36, 37). Thus, tobacco-derived products may act directly to up-regulate COX-2. Alternatively, tobacco products may induce cytokine and inflammatory cascades leading to the induction of AM COX-2 expression. In addition, tobacco smoking appears to have “primed” the AMs to the stimulatory effect of LPS because both the stimulatory effect of LPS and the inhibitory effects of SC58236 on AM PGE$_2$ production from nonsmokers are much less dramatic than those in smokers. Furthermore, AMs from smokers produced less IL-10 in response to LPS than those from smokers, and SC58236 had no effect on LPS-stimulated IL-10 production in nonsmokers.

The fact that SC58236 does not completely block the LPS-induced IL-10 production in AMs of smokers suggests that other COX-2-independent mechanisms are involved in the up-regulation of IL-10 in response to LPS stimulation. LPS is known to produce immunomodulatory effects in AMs via a variety of mechanisms, including activation of second messenger pathways (38). Our data suggest that the differences in responsiveness to LPS between smokers and nonsmokers may be due to up-regulation of COX-2 enzymes in AMs by tobacco smoke. Celecoxib may therefore be more effective at protecting the tobacco-specific nitrosamine, augmented LPS-induced IL-10 production from nonsmokers. This response may be heterogeneous. The precise mechanisms that may account for this heterogeneity are unclear.

In summary, results from interim analysis of this pilot study suggest that oral celecoxib is capable of impacting the lung microenvironment by blocking the overproduction of PGE$_2$ in active smokers. In addition, celecoxib may be able to reverse the immunosuppressive effect from tobacco smoking by reversing the imbalance between IL-10 and IL-12 production in AMs, which may in turn restore antitumor immunity in the lungs of smokers. These findings support the potential and continued investigation of celecoxib as a chemopreventive agent for lung cancer.

Acknowledgments

We thank Jessica Baillow, Brad Adams, Angela Tsu, Thy Dana, Grace Ibrahim, and John Dermand for excellent technical assistance and Jaime Masferrer (Pfizer) for helpful discussion and for generously supplying SC58236.

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