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EDITORIAL

# Did Targeted Therapy Fail Cyclooxygenase Too?

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There are considerable preclinical and clinical data showing that cyclooxygenase-2 (COX-2) plays an important role in the pathogenesis of non–small-cell lung cancers (NSCLC).[1,2] COX-2 is one of two isoforms of COX that catalyzes the conversion of arachidonic acid to prostaglandin (PG) $G_2$, which is then reduced to an unstable endoperoxide intermediate, $PGH_2$.[3] Specific PG synthases in turn metabolize $PGH_2$ to at least five structurally related bioactive lipid molecules, including $PGE_2$, $PGD_2$, $PGF_{2\alpha}$, $PGI_2$, and thromboxane $A_2$ ($TxA_2$).[3] COX-2 derived $PGE_2$ promotes angiogenesis, effects changes in cellular migration and invasive potential, alters cell cycle progression, reduces apoptosis, and inhibits immune surveillance; each of these factors contributes to the malignant phenotype.[3] In addition, selective COX-2 inhibitors have been shown to inhibit the growth of lung cancer cell lines and, in xenograft models, to enhance the effectiveness of selected chemotherapy agents against NSCLC cell lines.[4] Collectively, these findings provide a strong scientific rationale for combining an inhibitor of COX-2 with chemotherapy in the treatment of NSCLC. Such a trial is reported in this issue of the *Journal of Clinical Oncology* by Lilenbaum et al,[5] who combined celecoxib, a selective COX-2 inhibitor, with two different chemotherapy regimens (irinotecan plus docetaxel or irinotecan plus gemcitabine) in patients with recurrent NSCLC. However, the outcome of the trial is disappointing. In fact, when celecoxib was combined with irinotecan and docetaxel, the results were worse compared with irinotecan and docetaxel alone and toxicities were increased.

Celecoxib has many potential molecular targets, including some that are COX-2-independent.[6] However, the intended target in the Lilenbaum et al trial clearly was COX-2. Thus, at a minimum, it is critical to know two things: was COX-2 overexpressed in the treated tumors and did celecoxib inhibit intratumoral COX-2 activity? No such data are provided and, therefore, no definitive conclusion can be made regarding the efficacy of celecoxib in NSCLC based on the results of this trial. In fairness, it is extremely difficult to obtain adequate tumor samples to assess intratumoral COX-2 levels in recurrent NSCLC, and employing tissue from an earlier biopsy is hardly ideal as expression may change over time. However, this is not a trivial issue. Edelman and colleagues[7] recently reported that celecoxib combined with chemotherapy appeared to improve survival in selected NSCLC patients in whom high expression of intratumoral COX-2 was identified (as assessed by immunohistochemical staining) compared with patients with high COX-2 expression who were given chemotherapy alone. These data are consistent with an earlier study that found celecoxib combined with preoperative chemotherapy appeared to improve response rates in NSCLC relative to chemotherapy alone.[8] Accordingly, knowledge of the intratumoral COX-2 status might have provided considerable insight vis-à-vis the negative outcome of this trial.

Of course, to favorably modulate a molecular target like COX-2, the drug must be delivered to the intended target. If we assume that the tumors of the patients enrolled in this trial overall had high COX-2 activity, it is quite possible that the negative findings are simply the result of inadequate celecoxib dosing. Indeed, recent work carried out by Reckamp et al[9] indicate that maximum suppression of COX-2 activity, as assessed by changes in the level of the major urinary metabolite of $PGE_2$ (PGE-M),[10] requires a minimum daily celecoxib dose of at least 1,200 mg. This is a full one third higher than the dose used in the Lilenbaum et al study. Smoking status, also not commented on in this report, is an important determinant of COX-2 activity and endogenous $PGE_2$ levels, as well. Active smokers typically have higher COX-2 activity than former smokers, who in turn have higher COX-2 activity than never smokers.[11,12] In previous reports, a fixed dose of celecoxib inhibited $PGE_2$ production to a greater degree in never and former smokers compared with current smokers.[11,12] Not knowing the smoking status of the participants in the Lilenbaum trial makes interpretation of their data even more difficult. Notably, the choice of chemotherapy agents also may confound interpretation of this study, as taxanes have been shown to induce COX-2 in lung cancer cell lines by stimulating both transcription and mRNA stability leading to increase $PGE_2$ production.[13,14] The increase in $PGE_2$ that in part may account for the myalgias observed in some patients after paclitaxel therapy might also reduce the potential beneficial effects of celecoxib—particularly if the dose of the selective COX-2 inhibitor is fixed, as was the case in the Lilenbaum et al trial.

Is it possible that celecoxib contributed to a worse outcome, as suggested in one arm of this trial? Although COX-2 selective inhibitors suppress $PGE_2$ production, the potential inhibition of endothelial cell derived COX-2 activity and subsequent $PGI_2$ production may promote platelet aggregation and lead to an increased risk of coronary thrombosis and stroke.[15] However, there is no indication that patients in this study fared less well because of cardiac toxicity. However, $PGI_2$ also has been shown to suppress inflammation, prevent metastases, and inhibit the growth of micrometastases.[16,17] Thus, a decrease in $PGI_2$ levels could have an adverse effect on tumor growth particularly if $PGE_2$ levels remained elevated or increased relative to $PGI_2$ levels.[16] How might this occur in the presence of selective COX-2 inhibition? The microsomal form of PGE synthase (mPGES), the tissue-specific enzyme that preferentially converts $PGH_2$ to $PGE_2$, is often upregulated in NSCLC.[18] By contrast, 15-PG dehydrogenase (15-PGDH), the major enzyme responsible for $PGE_2$ metabolism and elimination, is



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frequently downregulated in NSCLC.[19,20] Thus, after selective COX-2 inhibition, $PGE_2$ levels may remain elevated in NSCLC due to upregulation of mPGES or downregulation of 15-PGDH (or some combination of these events) while at the same time $PGI_2$ levels decrease. This shift in the $PGE_2$:$PGI_2$ ratio may actually promote tumor growth rather than effect the desired growth inhibition (Fig 1).[16]

What do these data tell us regarding the role of COX-2 inhibition in the management of recurrent NSCLC? The data are simply insufficient to allow us to definitively answer this question. Unfortunately, this trial joins a long list of missed opportunities to better characterize and understand the biology underlying our therapeutic failures as well as our therapeutic successes. Ideally, future studies employing COX-2 inhibitors will attempt to select patients with tumors more amenable to the potentially beneficial effects of a drug like celecoxib. At a minimum, this might include an assessment of COX-2 expression by immunohistochemistry as suggested by the work of Edelman et al.[7] In addition, we and others have found that changes in urinary PGE-M levels also might be useful in this regard.[9-12] A marked reduction in urinary PGE-M levels after a brief course of celecoxib seemingly predicts for a better outcome with continued COX-2 inhibition compared with those patients with little or no change in PGE-M levels.[11] The immunohistochemistry and PGE-M data require confirmation, of course, but if validated the results suggest some lung cancers may be uniquely COX dependent and therefore more appropriate for inclusion in future studies employing COX inhibiting drugs. In addition, correlative studies are needed to assess the effectiveness of target acquisition and inhibition, such as measurement of the urinary metabolites of $PGE_2$. It also may be possible to better characterize lung tumors at the molecular level and to use the data to direct the choice of COX inhibitor therapy. For example, if a particular tumor demonstrates overexpression of COX-2 and downregulation of 15-PGDH, indomethacin might be a good agent to consider as it blocks COX activity at a clinically tolerable dose and upregulates 15-PGDH expression through its PPARγ (peroxisome proliferator-activated receptors–gamma) agonistic property.[20] Finally, because the activities of $PGE_2$ are mediated by a family of G protein, coupled receptors linked to diverse intracellular signaling pathways,[21] drugs that specifically target the receptors, rather than the upstream modulators, may circumvent some of the potential problems in assessing the role of COX inhibition we have explored. This approach has proved promising in preclinical studies.[22,23] We believe continued efforts to modulate the arachidonic acid pathway are appropriate—the results of this trial notwithstanding.

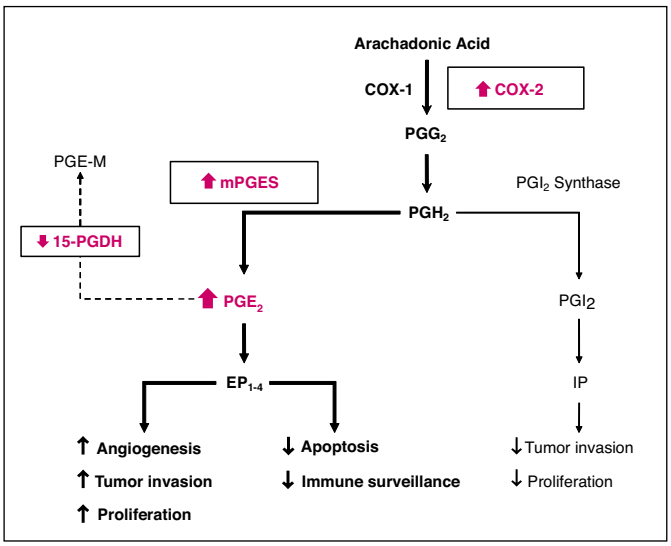


**Fig 1.** Cyclooxygenase-2 (COX-2) and microsomal form of PGE synthase (mPGES) are frequently upregulated in non–small-cell lung cancer and 15-PG dehydrogenase (15-PGDH) is frequently downregulated. This constellation of events contributes to increased $PGE_2$ levels that in turn promote angiogenesis, effect changes in cellular migration and invasive potential, alter cell cycle progression, reduce apoptosis and inhibit immune surveillance, each of which contributes to the malignant phenotype. By contrast PGI2 suppresses inflammation, prevent metastases, and inhibits the growth of micrometastases. EP1-4, $PGE_2$ receptors; IP, $PGI_2$ receptor.



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