Phosphodiesterase-4 Inhibition and Brain Tumor Growth

To the Editor: We read with great interest the December 1, 2008, article by Goldhoff et al. (1) on the role of cyclic AMP phosphodiesterase-4 (PDE4) in brain tumor growth. The authors found that PDE4 is expressed in human brain tumors of glial and neuronal lineage (glioblastoma, medulloblastoma, ependymoma, and meningioma). In addition, overexpression of PDE4A1, a brain-specific isoform of PDE4, in Daoy medulloblastoma and U87 glioblastoma cells was associated with increased tumor growth in intracranial xenografts. Conversely, the PDE4 inhibitor rolipram promoted tumor regression and enhanced survival in mice bearing U87 xenografts. Based on these findings, the authors conclude that PDE4 is a novel molecular target for brain tumor therapy and PDE4 inhibitors such as rolipram should be evaluated in clinical trials for malignant brain tumors. We would like to address two issues concerning the study by Goldhoff et al. (1).

First, we too have recently examined the effects of rolipram on the growth of brain tumor cells and have found results complementary to those of Goldhoff et al. (1). Although Goldhoff et al. (1) have shown that PDE4A1 overexpression in medulloblastoma cells stimulated tumor growth and rolipram suppressed the growth of glioblastoma xenografts, they did not address whether rolipram can also inhibit the growth of experimental medulloblastoma. We have recently observed that rolipram significantly inhibits proliferation of Daoy medulloblastoma cells in vitro. In our experiments, treatment with 10 μmol/L rolipram reduced cell viability measured by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay by 36.12% compared with controls at 48 hours after treatment (P < 0.001, n = 3 experiments in sextuples). This finding supports and extends those reported by Goldhoff et al. (1) and to our knowledge provides the first evidence that rolipram inhibits proliferation of medulloblastoma cells.

Second, although we agree that PDE4 is a promising target for the development of novel therapeutic strategies for glioblastoma and medulloblastoma, we would like to point out that rolipram might, under certain conditions, stimulate rather than inhibit brain tumor cell growth. We have recently reported (2) that rolipram as well as other agents that enhance cellular cyclic AMP levels induced a significant increase in proliferation of U138-MG human glioblastoma cells when the cells were stimulated by gastrin-releasing peptide, a neuropeptide that acts as a growth factor in several types of cancer. These findings suggest that additional studies are required to further characterize the effects of PDE4 inhibitors in preclinical models before rolipram is evaluated in clinical trials for malignant brain tumors.

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Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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References
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