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## BIOLOGY OF NEOPLASIA

# Correlation of O<sup>6</sup>-Methylguanine Methyltransferase (MGMT) Promoter Methylation With Clinical Outcomes in Glioblastoma and Clinical Strategies to Modulate MGMT Activity

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Resistance to alkylating agents via direct DNA repair by O<sup>6</sup>-methylguanine methyltransferase (MGMT) remains a significant barrier to the successful treatment of patients with malignant glioma. The relative expression of MGMT in the tumor may determine response to alkylating agents, and epigenetic silencing of the *MGMT* gene by promoter methylation plays an important role in regulating MGMT expression in gliomas. *MGMT* promoter methylation is correlated with improved progression-free and overall survival in patients treated with alkylating agents. Strategies to overcome MGMT-mediated chemoresistance are being actively investigated. These include treatment with nontoxic pseudosubstrate inhibitors of MGMT, such as O<sup>6</sup>-benzylguanine, or RNA interference-mediated gene silencing of *MGMT*. However, systemic application of MGMT inhibitors is limited by an increase in hematologic toxicity. Another strategy is to deplete MGMT activity in tumor tissue using a dose-dense temozolomide schedule. These alternative schedules are well tolerated; however, it remains unclear whether they are more effective than the standard dosing regimen or whether they effectively deplete MGMT activity in tumor tissue. Of note, not all patients with glioblastoma having *MGMT* promoter methylation respond to alkylating agents, and even those who respond will inevitably experience relapse. Herein we review the data supporting MGMT as a major mechanism of chemotherapy resistance in malignant gliomas and describe ongoing studies that are testing resistance-modulating strategies.

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