Thymine DNA Glycosylase (TDG) as a Novel Target for the Treatment of Melanoma and Other Cancers (Ref. No. 520-AB)

Background

Two known epigenetic alterations in cancer are CpG island methylation (CIMP) and genome-wide hypomethylation. In particular, about 20-40% of melanomas, triple-negative breast cancers, serious ovarian and serious endometrial cancers are characterized by a pervasive genome-wide hypomethylation that can be documented by mining the TCGA methylation data. Demethylating agents (e.g., decitabine and azacytidine) are an effective epigenetic therapy of cancer that target the CIMP phenotype with the intention of reactivating the expression of genes silenced by hypermethylation. However, there has been no effort to specifically target the genome-wide hypomethylation in cancer. It has been established that cancers with prominent genome-wide hypomethylation exhibit elevated expression of DNA demethylases working in pathways of active DNA demethylation. Accordingly, inhibition of these demethylases is expected to antagonize, correct and reprogram the genome-wide hypomethylation, thus suppressing oncogenic pathways and achieving a therapeutic benefit.

Summary of the Invention

Thymine DNA Glycosylase (TDG) is a well-known DNA repair enzyme. Researchers at Fox Chase Cancer Center have discovered that it is also an important epigenetic factor through its DNA demethylase activity, operating downstream of dioxygenases of the Ten-Eleven Translocation (TET) family. The TET-TDG pathway acts in dynamic and opposing balance with DNA methyltransferases to demethylate methyl CpG sites and thus activate gene expression. They also established TDG as a bona fide melanoma target: elevated TDG levels predict poor prognosis; knockdown of TDG in melanoma cell lines led to cell cycle arrest, senescence, loss of viability and clonogenic survival, and reduced tumor formation in xenograft assay. Importantly, inactivation of TDG in adult mice is well tolerated, which suggests a wide therapeutic window between normal and cancer cells.

New studies and computational method was applied to identify potential TDG-inhibitors, starting from TDG crystal structures. These studies led to discovery of first ever drug-like compound that inhibits TDG. The activity of identified compound was confirmed in biochemical assays using purified TDG, before advancing it to cellular studies. In melanoma cells it induces senescence/differentiation and increases levels of TDG substrate, 5-carboxylcytosine; the latter confirms on-target activity as a TDG inhibitor. Identified TDG inhibitor sensitizes cancer cells to killing by NK cells. Moreover, this is a completely new type of epigenetic therapy with the potential of combination with immune checkpoint blockade. The chemical structure of identified compound makes it highly amenable to producing of analogs, and derivatives.

Patent Status: A patent application has been filed.

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