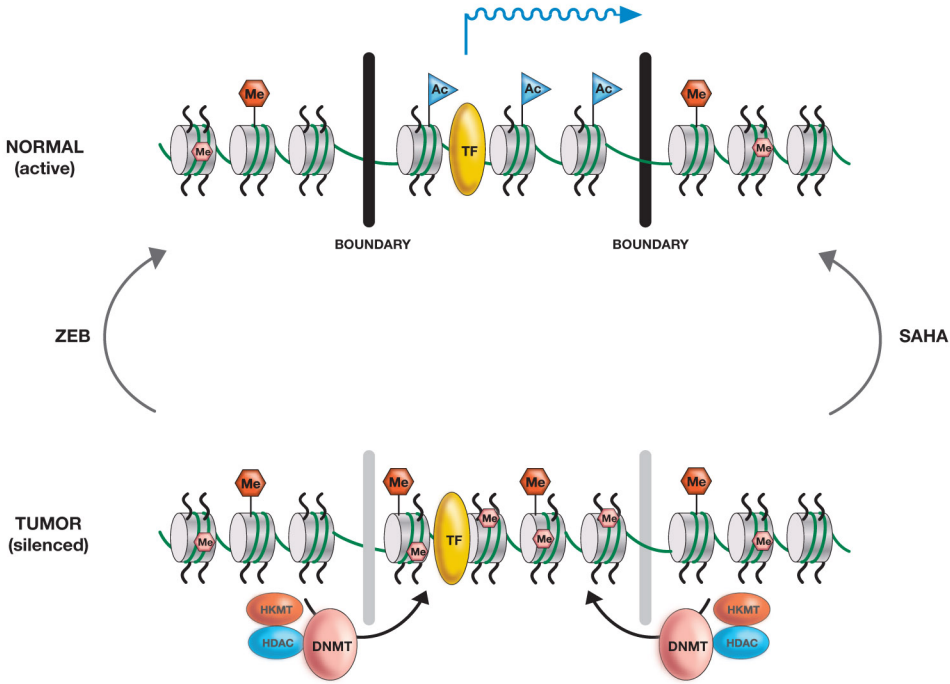

Figure 6. Model of the Relationships between DNA Methylation and Histone Modifications in the Promoter CpG Island Region of a Gene in Normal and Tumor Cells

In the expressed gene (*top*), a boundary is shown, the molecular nature of which is not yet characterized, which protects the CpG island surrounding the transcription start site (*green arrow*) from DNA methylation. CpG sites in CpG regions flanking this protective zone are, in contrast, DNA methylated (*pink hexagon marked M*) and associated with key silencing marks such as methylation of H3K9 (*red hexagon marked Me*). Key histone tail amino acids in the protected zone, such as H3K9, are in the acetylated state (*blue flags marked Ac*), and transcription factors (*yellow oval marked TF*) have access to the transcription start-site region. When the same gene is aberrantly silenced in a cancer cell (*bottom*), the CpG island is DNA-hypermethylated as the protective boundaries are now breached and not present. This methylation is maintained by DNA methyltransferase complexes (*pink ovals marked DNMT*), and methylcytosine-binding protein complexes that contain histone deactylases (*blue ovals marked HDAC*), and histone methyltransferases (*red ovals marked HKMT*) that catalyze key silencing methylation marks on histone amino acid tails such as H3K9. TF complexes are no longer active (*lack of green* arrow). The major approaches currently underpinning ongoing cancer epigenetic clinical trials are depicted and consist of either DNA methyltransferase inhibitors to block DNA hypermethylation or HDAC inhibitors to restore the acetylation status of key histone amino acid residues. As discussed in the text, some of the most promising anticancer therapies include combinatorial use of DNMT1 and HDAC inhibitors.