Targeting the cancer epigenome for therapy

The Epigenome

- The epigenome consists of specific covalent modifications of chromatin components — which include DNA, RNA and proteins (such as histones) — that ensure the somatic inheritance of differentiated states.
  - The structure and function of the epigenome are controlled by these covalent marks, which are applied by enzymes (writers) to the 147 bp of DNA and the eight histone components of a nucleosome
  - These marks instruct the proteins that recognize them (readers) to identify and remodel particular genomic regions to modulate gene expression.
  - The plasticity of the epigenome owes much to the existence of erasers; that is, enzymes capable of removing active and repressive marks.

- Tumor cells not only are activated by genetic and epigenetic alterations, but also routinely use epigenetic processes to ensure their escape from chemotherapy and host immune surveillance.

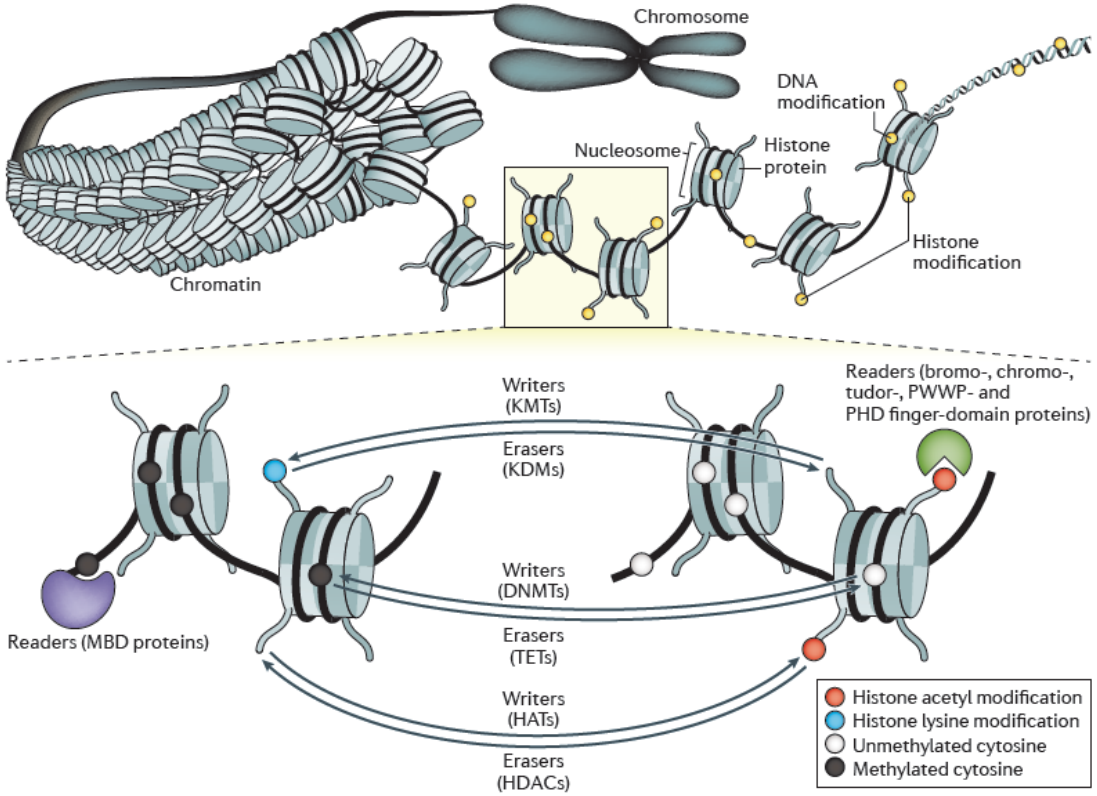

Figure 1 | **Modulation of covalent modifications on chromatin.** A 147 bp sequence of DNA is wrapped around a core of eight histone proteins to compact the genome into nucleosomes and then into chromatin and chromosomes. A subset of covalent modifications (yellow circles) on both the histone and DNA components, which control accessibility of DNA to transcription factors and other regulators, are shown. Covalent marks are established by 'writers', such as histone lysine methyltransferases (KMTs), histone acetyltransferases (HATs) and DNA methyltransferases (DNMTs). These modifications are interpreted by 'readers', including methyl-CpG binding domain (MBD) proteins on the DNA and multiple proteins for the histone marks as shown. Progress over the past decade has shown that almost all of the marks can be removed by 'erasers', such as histone demethylases (KDMs), histone deacetylases (HDACs) and by the ten-eleven translocation (TET) family of 5-methylcytosine oxidases. The interplay between these enzymes helps to establish and maintain cellular identity in addition to the central role of transcription factors by regulating access to the DNA sequence. PHD, plant homeodomain.

Drugs targeting the epigenome

- There has been a growing emphasis of recent drug discovery efforts on targeting the epigenome that includes:
  - DNA methylation
  - Histone modifications

- Several new drugs are being tested and some already approved by the US Food and Drug Administration (FDA)

- Neoplastic (e.g., lymphoma) and pre-neoplastic lesions have been observed in toxicology studies with rodents as short as 3 months in duration, which is highly unusual.

- Is it appropriate to use Healthy Subjects for these classes of drugs?