WHITE PAPER

Epigenetic modifications and how they relate to cancer development and therapy

Epigenetics in short

The concept of epigenetics was proposed by Conrad Waddington in the 1940s as a process where the phenotype of organisms could be modified by changes in gene expression rather than changes in the genetic code directly.

As a working concept, it grew into a new branch of genetics that explores how environmental factors such as lifestyle, toxins, stress, and others can cause epigenetic modifications that drastically alter the expression and silencing of genes throughout the life of an organism. These contributions are critical to understanding how organisms exhibit drastic adaptability during their lifetime and not simply at the scale of species and populations (which typically become fitter over generations).

The field of epigenetics has introduced revolutionary notions to the understanding of heredity. Where it was previously thought that heredity was a function of DNA sequence alterations (or mutations) carried over to the next generation, it is now understood that epigenetic modifications can create new phenotypes that are inherited by later generations, without modifying the inherited DNA sequence itself.

Due to its vast implication in our understanding of gene regulation, epigenetics has ramifications in most fields of biology, from academic fields like evolutionary biology to incredibly applicable studies in agronomy and medicine.

The three types of epigenetic modifications

DNA methylation

DNA methylation is a process by which a methyl group (CH3) is added to the C5 position of cytosines in CpG sites (DNA regions where a cytosine is followed by a guanine) in a DNA sequence (Figure 1). It is the main type of epigenetic modification that regulates gene expression and maintains the stability of the genome.

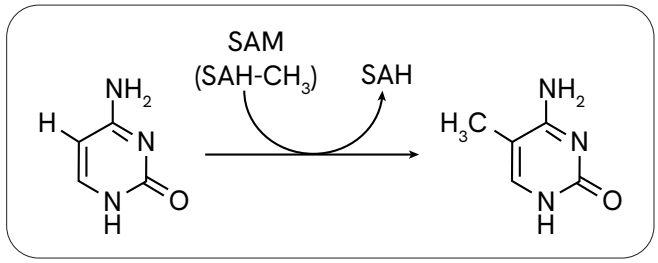

Figure 1: Addition of methyl group on C5 position of cytosine

The effects of DNA methylation at CpG sites are not entirely described, but the process often promotes local repression of genes and/or gene silencing. This is due to the added methyl groups acting as inhibitors of transcription factors and other DNA-interacting proteins. In practice, DNA methylation promotes local DNA compacting, making it less accessible and readable for transcription and replication purposes, which prevents transcription or replication of the DNA in the region where methylation occurs (Figure 2).

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DNA methylation patterns vary depending on the cell type and tissues where they occur. This allows for the specialization of cells in different directions using the same genetic information. Beyond cell types and tissues, DNA methylation is also heavily affected by environmental factors, such as lifestyle, diet, stress, exposure to stress or toxins, and UV lights. Changes in DNA methylation have also been linked to biological processes such as embryonic development, aging, and certain diseases. For this reason, it can be a marker of the progression of cell senescence and various cancers. As it is an epigenetic modification, DNA methylation has the potential to transmit from one generation to another. The differential expression of alleles from the mother or father can even be decided via genomic imprinting. This is where methylated alleles are repressed and genes are expressed differently depending on which parent they are inherited from.

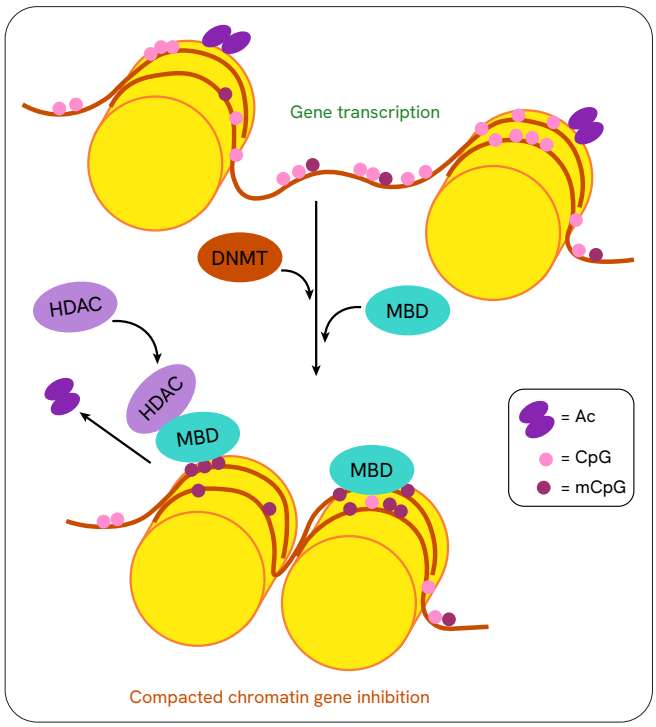

Figure 2: The addition of methyl groups to DNA by DNA methyltransferases promotes methyl-CpG-binding domains recruitment, which in turn recruits histone deacetylases (HDACs). The combined DNA-methylation and histone deacetylation results in an increased compact chromatin state of DNA.

The process of DNA methylation is carried out by a dedicated family of enzymes called DNA methyltransferases (DNMTs). These exist as different types carrying specialized roles with tightly regulated activity and control from internal factors such as the local availability of methylation reaction co-factor S-adenosylmethionine (SAM).

- DNMT1 acts as the main maintenance methyltransferase and carries existing DNA methylation patterns over to newly formed DNA during replication.
- DNMT3A and DNMT3B are de novo methyltransferases that create new DNA methylation patterns, either during early development or in response to external signals. They are key DNA methylation effectors and bring variability to this type of epigenetic modification.
- DNMT3L acts as a regulatory actor to DNMT3A and DNMT3B. It helps to target specific DNA regions while also enhancing their activity.

It is worth noting that other proteins are capable of DNA methylation, albeit in a less significant capacity, such as the MBD family (methyl-CpG-binding domain). In addition to their lower DNA methylation abilities, this family plays a role in DNA compaction by recruiting histone deacetylases, which further increase DNA compaction around histones. [1,2]

Histone modification

Histones are a family of proteins with a key role in the organization and regulation of DNA. They exist in five types (H1, H2A, H2B, H3, and H4) and act as spools that DNA can wrap around in a condensed chromatin state. Individually, histones are rather small (>20 kDa except for H1 which is 31-33 kDa), but they assemble in larger octameric nucleosome particles made of two copies of all histone types except H1. Each nucleosome carries an average of two turns of condensed DNA which sticks to the structure due to the overall positive charges carried by the histones because of their positively-charged amino acids. Histones can be subject to modifications such as methylation, acetylation, phosphorylation, and ubiquitination which all affect their ability to assemble, disassemble, and stick to DNA. All of these properties regulate the physical access of proteins to the genome. Because of the way histones condense and wrap DNA around themselves, they oversee which portions of it are accessible to transcription enzymes and other partners that modify or replicate it. By sliding along the DNA sequence, histones cover and uncover different sections prompting the expression of new sequences and the repression of others. For these reasons, histone modifications are critical to gene silencing and expression (Figure 3).

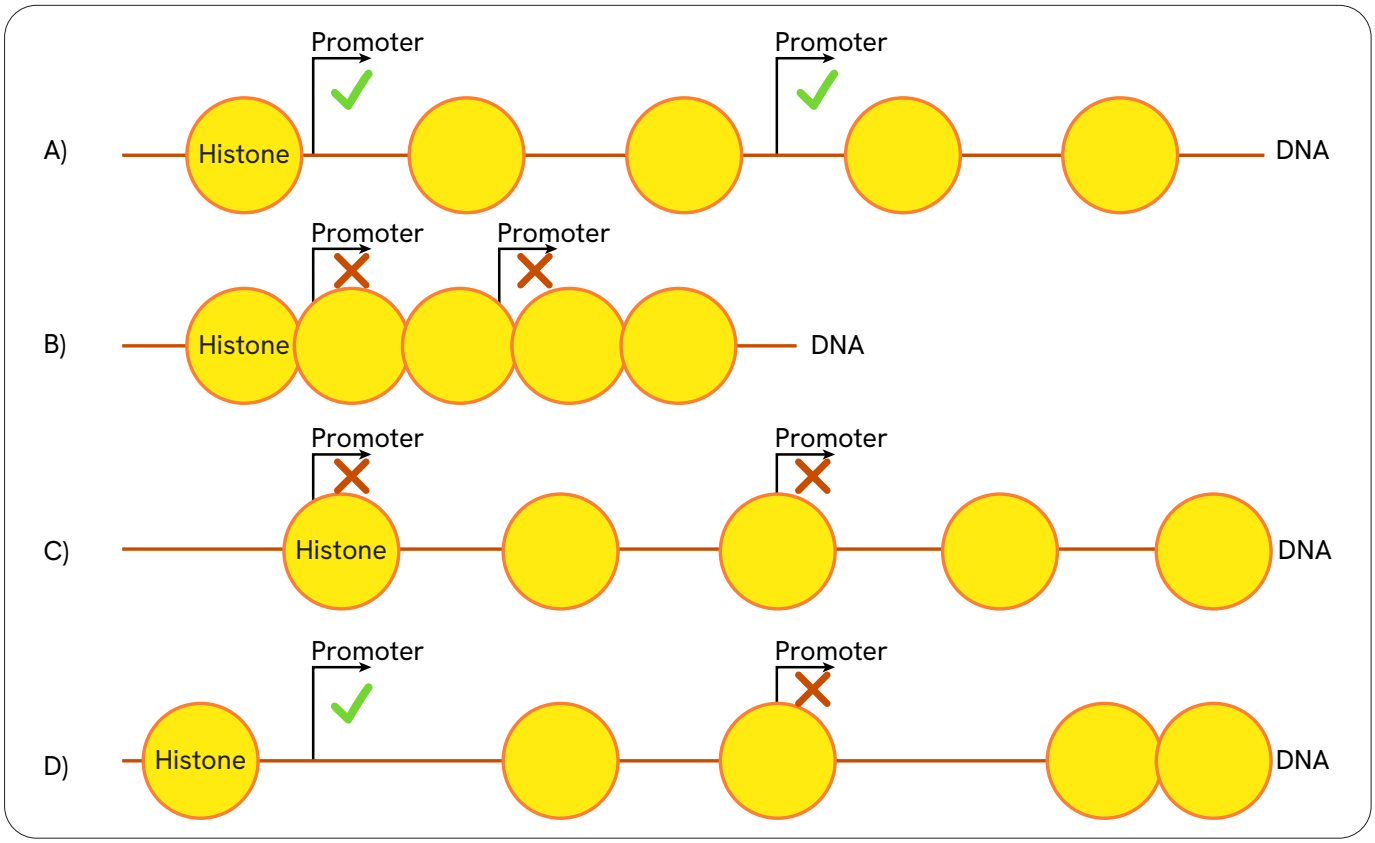

Figure 3: The acetylation/methylation state of histone nucleosomes is key to regulating DNA accessibility as it determines the position of histones and DNA compaction. A) Regular state of compaction, histones are spaced, and gene promoters are accessible. B) Compacted chromatin state, histones are tightly grouped, and promoters are inaccessible. C) and D) different histone sliding scenarios are possible. All histones of a region can slide together (C) or only some of them may do so (D). Promoter accessibility varies according to the histone positions.

This role of histones in DNA regulation is postulated under the "Histone code" hypothesis and is increasingly studied in the context of diseases like cancer, where gene mutation and/or silencing is key. H3 and H4 acetylations are the most investigated histone modifications and are found to promote the transcription of genes consistently. Histone methylation on lysine residues is the second most commonly studied histone modification, especially on H3, and is a promoter of DNA condensation that limits DNA access and represses gene expression. The complexities of histone methylation leave many unknowns about its exact effects. For acetylation and methylation, there are opposite processes of de-acetylation and de-methylation performed by histone deacetylases and demethylases, respectively, which open potential avenues for future therapeutic regulation. [3,4]

Non-coding RNA

Non-coding RNAs (ncRNAs) are RNA strands that do not code for protein sequences and are not translated into proteins, even though they are transcribed from DNA like all other RNA. Rather, they fulfill an array of functions related to the regulation of cellular processes. With epigenetic mechanisms, ncRNAs are understood to contribute to the regulation of chromatin structure and therefore gene expression via DNA accessibility and readability. They fulfill these roles via direct interaction with other nucleic acids (DNA, RNA) and proteins. There are different types of ncRNAs, characterized by their size and properties:

- Long non-coding RNAs (lncRNAs) are strands that are longer than 200 nucleotides and interact with various complexes that modify chromatin. They notably carry negative charges that can neutralize the positive charges

of histone nucleosomes and promote chromatin decompaction. Another way lncRNA affects DNA is through direct interaction, where it forms a hybrid structure with DNA, such as a triple helix or R-loop, that modifies the stability and readability of the DNA. Finally, they can act as scaffolds or guides to other DNA-regulatory proteins, and promote the recruitment of these actors to specific DNA regions. [5]

- MicroRNAs (miRNAs) are shorter RNA strands of about 22 nucleotides. They play a significant role by binding to specific target messenger RNAs (mRNAs) and downregulating their stability and/or translation rate. In some cases, they can promote the degradation of their target mRNA directly. Overall, they are responsible for an important part of DNA/RNA regulation which has ramifications for epigenetics as they can target genes involved in DNA methylation or histone modification, which determine the epigenetics landscape. [6,7]
- Small interfering RNAs (siRNAs) are similar in size to miRNAs and share similar functions in the context of epigenetics as they promote gene silencing by targeting specific mRNA for degradation or translational repression.

The precise mechanisms by which ncRNAs regulate epigenetic processes remain in parts undescribed. With cell-type and tissue-dependent functions, they are reliant on environmental factors and developmental stages. Two main axes seem to be involved in the recruitment and modeling of regulatory complexes by lncRNAs, and the promotion/inhibition of histone modification and DNA methylation by miRNAs and siRNAs. Emerging evidence highlights the significant role of ncRNAs as a regulator of the regulation of other types of epigenetic modifications. This adds a layer of complexity to our understanding of gene expression and cellular function. [6–8]

Relevance to oncology and targets related to cancer

Epigenetics is highly relevant to the study of cancer as it can lead to the activation or silencing of genes involved in disease development, with significant consequences on tumor growth and progression. All three types of epigenetic modifications play diverse roles in tumorigenesis and cancer progression (DNA methylation, histone modification, and the regulation of ncRNAs). The identification of epigenetic changes in cancer cells has led to the development of new diagnostics and treatments and has provided a better understanding of the underlying mechanisms of the disease, but much remains to be studied.

Epigenetic changes have also been identified in the cells of healthy individuals, suggesting that these changes may be involved in the early stages of cancer development. For example, studies have shown that certain genetic mutations are more likely to occur in individuals with a history of epigenetic modifications. Epigenetic changes can also be inherited from one generation to the next and may contribute to the increased risk of cancer in some families.

DNA methylation in cancer

DNA methylation is one of the most investigated epigenetic mechanisms, and its role in cancer has been extensively studied. Specifically, certain genes can be silenced due to hypermethylation of their promoter regions, which renders them inaccessible to transcription enzymes and leads to the loss of the corresponding gene and its tumor suppressor functions. This is often the case with tumor suppressor p53 in many cancers, but also BRCA1 and RB1 (breast cancer, osteoblastoma, glioblastoma, lung cancers, etc.). Hypomethylation of oncogenic genes like MYC and ERBB2 can have similar pro-cancer effects, as these promote cancer when mutated or expressed in unusually large levels. Other genes with roles in cell life can also be affected, with deleterious consequences in cell-cycle regulation, apoptosis, immunity, cell adhesion, and DNA repair.

The epigenome of cancer cells is deeply modified compared to healthy cells and frequently features genome-wide hypomethylation that promotes oncogenic genes while also exhibiting region-specific CpG hypermethylation of tumor suppressor gene promoters, silencing said genes. The mechanisms that drive these patterns of hypo- and hypermethylation are still unclear, but it has been observed that the former tends to occur in repetitive portions of the DNA, gene deserts, intron sequences, and promoters with a lack of CpG sites. On the other hand, hypermethylation is understood to be favored by clonal selection of the

cells that exhibit it, since tumor suppressor gene silencing can move the cells toward unchecked growth and provide them with a population advantage. There might be multiple mechanisms at play in this selection (regulation of transcription factors, non-coding DNA influence, acetylation/methylation state of histones), but the exact contribution of each remains to be described. This makes clear that therapeutic potential lies in the grey area of DNA hypermethylation processes. [2,9]

Histone modifications in cancer

Modern high-throughput sequencing techniques have made genome-wide mapping of DNA changes during tumorigenesis possible, bringing new insight into the exact events happening at the molecular level. Two types of histone modifications stand out: acetylation and methylation.

On the acetylation side is a family of proteins thoroughly studied: histone deacetylases (HDACs). This family of at least 18 members is assumed to directly regulate the expression of about 10% of all genes, as shown by global expression profiling experiments. As suggested by their name, HDACs remove acetyl groups from lysine residues of histones, not only changing said histones but also stirring them toward or away from particular post-translational modifications that could also affect lysine residues, like methylation or ubiquitination. HDACs mediate DNA regulation via their effects on histones, and as such they are subject to tight regulation themselves either through protein-protein interaction or careful post-translational modifications. HDACs are typically found to be overexpressed in multiple cancers, which begs the question of their role in oncogenic epigenetic processes and labels them as potential therapeutic targets. Generally speaking, deacetylation of histone promotes more condensed chromatin states, which decreases the accessibility and readability of DNA and results in lower expression or even silencing of tumor suppressor genes. The BRCA1 gene is an example of such a silenced gene in breast cancer.

On the methylation side, two types of enzymes play opposing roles: the histone methyltransferases (HMTs) and the lysine-specific demethylases (LSDs). The former is responsible for the addition of methyl groups. The alteration of specific methylation patterns like H3K9 and H3K27 has been associated with oncogenic gene silencing in many cancers (Table 1).

Table 1: Examples of histone methylation associated with cancer types [9]

Type of histone methyltransferase aberration	Type of methylation	Type of cancer-associated
Overexpression of EZH2	Trimethylation of H3 k27	Breast and prostate cancer
Overexpression of G9a	Methylation of H3 K9	Liver cancer
Chromosomal translocation of MLL	Methylation of H3 K4	Leukemic progression

The LSDs have the opposite effect and remove methyl groups from histones. Usually, they work in tandem with HMTs to maintain methylation patterns over time, but they have also been linked to cancer progression in some cases. For instance, the first LSD to be identified, LSD1, is upregulated in prostate cancer. LSD1-inhibition experiments on in vitro neuroblastoma models resulted in decreased proliferation, which hints at potential future therapeutic targets. [10]

Non-coding RNA in cancer

Among all non-coding RNAs (ncRNAs) involved in epigenetic regulations, microRNAs (miRNAs) have the most impact on cancer development. As small ncRNAs that regulate gene expression via inhibition/sequestration/degradation of coding mRNA transcripts, they stand in the way of multiple genes' translation into proteins and have been found to play protective or deleterious roles in many cancer types. As epigenetic factors, it is understood that their expression is a function of external parameters, including environmental (toxins, pollutants, radiation, and UV light), lifestyle (nutrition, stress levels, sleep pattern, smoking habits, and physical exercise), or infection/inflammation-related factors.
Our current understanding of miRNAs suggests they are responsible for the regulation of multiple tumorigenesis-related processes such as cell mobility, cell proliferation, invasion, epithelial-mesenchymal transition, apoptosis/survival, and regulation of tumor-suppressor genes. [9]

There is accumulating evidence of aberrant miRNA patterns being associated with many cancer types, either acting as tumor suppressors or oncogenes depending on the genes they interact with (Table 2).

Table 2: Examples of miRNA associated with cancer types [11]

miRNA	Tumor type	Target genes
let-7	NSCLC	RAS
miR-21	colorectal cancer, cancer of the stomach, lung cancer	MYCN, ATM, FXR, EGR2, MXD1, PIAS3, SOCS6, HIF-1a
miR-17-92	breast cancer	AIB1 (miR-17-5p), E2F1 (miR-17-5p, miR-20a), TGFBR2 (miR-20a), Tsp1 and CTGF
miR-106a	colorectal cancer, pancreatic cancer, prostate cancer	Rb1
miR-221, miR-222, miR-146b	thyroid, papillary cancer	KIT
miR-182	lung cancer	Rsu1, Mtss1, Pai1, Timp1
miR-155	colorectal cancer, lung cancer, pancreatic cancer	RAD51, VHL, SOCS1
miR-372, miR-373	testis, germ cell tumors	LATS2
miR-221/222	stomach cancer, prostate cancer	p27, PTEN

The future of epigenetics in cancer

Epigenetic defects have been identified in almost every type of cancer, which highlights the key role epigenetics plays in tumorigenesis and underscores the potential for future successful therapeutic avenues in this field. Abnormal patterns of DNA methylation and modifications to histones have already been recognized as important targets for therapeutic endeavors that aim to reverse the aberrant state of cancer cells. To that end, demethylating or hypomethylating agents are being investigated for their ability to inhibit DNA methyltransferases, preventing further methylation and gene silencing, with the hope of increasing the expression of silenced tumor suppressor genes.

So far, these agents lack the specificity that acceptable and safe therapeutic drugs need to operate so close to patients' genetic information. In their current state, many of these agents present risks of genome-wide hypomethylation, potentially activating genes that are meant to remain silent and promoting genomic instability. To address these challenges, researchers are developing drugs that target specific genomic regions for more precise and tailored treatments.

Histone deacetylase (HDAC) inhibitors have already shown promise and successful applications in patients, and many synthesized hybrid molecules with enhanced inhibitory effects have already hit the stage of clinical trials and approved therapies. Ongoing efforts are being made to develop compounds that selectively target individual members of all HDAC classes, providing more specific and effective therapeutic options.

Certain epigenetic tests have already become standard-of-care in specific scenarios, such as the detection of MLH1 and MSH2 methylation in colorectal cancer genetic screening, BMP3 and NDRG4 methylation in Cologuard fecal DNA colon cancer screening, and MGMT promoter methylation in glioblastoma treatment selection. These tests have demonstrated their clinical utility and importance. Beyond testing, as of 2021, it was reported that seven epigenetic agents had received FDA approval for application in various cancers. These seven were split into three families of molecules: DNMT inhibitors, HDAC inhibitors, and EZH2 inhibitors (Table 3). Many more are being investigated or going through trials as of 2023, with the NIH reporting just over 150 active clinical trials investigating epigenetic agents in the context of cancer.

Epigenetic-based therapies show promising results overall, but their integration into clinical practice comes with significant challenges due to their close and critical relationship with patients' genetic information. Additional research is necessary to gain a deeper understanding of these mechanisms. Over time, it is hoped that epigenetic therapies will fulfill their ambitious promises, serving as early predictive biomarkers and enabling personalized approaches to cancer treatment tailored to each patient's specific needs. [10,12]

Table 3: FDA-approved epigenetic agents for cancer treatment (Apr 2021)[12]

FDA-approved epigenetic agent	Mechanism of action	Type of cancer
5-azacytidine	DNMT1 inhibitor acts as a hypomethylation agent	Acute myeloid leukemia
5-aza-2'-deoxycytidine		
FK-228	HDAC inhibitor of HDAC1, HDAC2, HDAC4, HDAC6	Cutaneous T-cell lymphoma
SAHA	HDAC inhibitor	Cutaneous T-cell lymphoma
PDX-101	HDAC inhibitor	Refractory cutaneous T-cell lymphoma
LBH-589	HDAC inhibitor	Multiple myeloma
Tazmetostat	EZH2 methyltransferase inhibitor	Epithelioid sarcoma
Chidamide	HDAC inhibitor of HDAC1, HDAC2, HDAC3, HDAC10	Peripheral T-cell lymphoma

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DETECTION KITS	HTRF	AlphaLISA	LANCE
Binding Domain A - 500 points	62BDAPEG		
Binding Domain B - 500 points	62BDBPEG		
Binding Domain C - 500 points	62BDCPEG		
Binding Domain Discovery - 500 points	62BDDPEG		
Histone H3 2-methyl K4 - 500 points	62KA2PAE		
Histone H3 3-methyl K27 - 500 points	62KC3PAE		
Histone H3 2-methyl K36 - 500 points	62KD2PAE		
Histone H3 total - 500 points	62NH3PAE		
Methyltransferase assay - 1000 points	62SAHPEB		
SIRT1 - 1000 points	64SI1PEB		
Histone H3 acetyl K9 - 500 points		AL714C	
Histone H3 2-methyl K4 - 500 points		AL716C	
Histone H3 2-methyl K9 - 500 points		AL717C	
Histone H3 K4 - 500 points		AL719C	

DETECTION KITS	HTRF	AlphaLISA	LANCE
Histone H3 acetyl K27 - 500 points		AL720C	
Histone H3 2-1-methyl K27 - 500 points		AL721C	
Histone H3 3-methyl K27 - 500 points		AL722C	
Histone H3 2-methyl K27 - 500 points		AL723C	
H2A total - 500 points		AL725C	
Histone H4 total - 500 points		AL729C	
Histone H3 2-methyl K79 - 500 points		AL748C	
BRD4BD1/H4K5,8,12,16 - 500 points			TRF1609C

TOOLBOX	HTRF	AlphaLISA	AlphaPlex	LANCE
Histone H3 0-methyl K4 Eu-labeled Ab - 500 points	61KA0KAE			
Histone H3 1-methyl K4 Eu-labeled Ab - 500 points	61KA1KAE			
Histone H3 2-methyl K4 Eu-labeled Ab - 500 points	61KA2KAE			
Histone H3 3-methyl K4 Eu-labeled Ab - 500 points	61KA3KAE			
Histone H3 0-methyl K9 Eu-labeled Ab - 500 points	61KB0KAE			
Histone H3 1-methyl K9 Eu-labeled Ab - 500 points	61KB1KAE			
Histone H3 2-methyl K9 Eu-labeled Ab - 500 points	61KB2KAE			
Histone H3 1-methyl K27 Eu-labeled Ab - 500 points	61KC1KAE			
Histone H3 2-methyl K27 Eu-labeled Ab - 500 points	61KC2KAE			
Histone H3 3-methyl K27 Eu-labeled Ab - 500 points	61KC3KAE			
Histone H3 1-methyl K36 Eu-labeled Ab - 500 points	61KD1KAE			
Histone H3 2-methyl K36 Eu-labeled Ab - 500 points	61KD2KAE			
Histone H3 phospho S10 Eu-labeled Ab - 500 points	61P07KAE			
Histone H3 acetyl K9 beads - 250 µg		AL114C		
Histone H3 1-2-methyl K4 beads - 250 µg		AL116C		
Histone H3 2-methyl K9 beads - 250 µg		AL117C		
Histone H3 Ab - 2 µg		AL118C		
Histone H3 K4 beads - 250 µg		AL119C		
Histone H3 acetyl K27 beads - 250 µg		AL120C		
Histone H3 2-1-methyl K27 beads - 250 µg		AL121C		
Histone H3 3-methyl K27 beads - 250 µg		AL122C		
Histone H3 2-methyl K36 beads - 250 µg		AL123C		
p53 acetyl K382 beads - 250 µg		AL124C		
Histone H3 K9/K27 beads - 250 µg		AL138C		
Histone H3 methyl R2 beads - 250 µg		AL139C		
Lysine acetyl beads - 250 µg		AL143C		
O-GlcNAc beads - 250 µg		AL144C		
Histone H4 beads - 250 µg		AL145C		

TOOLBOX	HTRF	AlphaLISA	AlphaPlex	LANCE
Histone H4 Ab - 2 µg		AL146C		
Histone H3 C-ter beads - 250 µg		AL147C		
Histone H3 2-methyl K79 Ab - 2 µg		AL148C		
Histone H4 methyl R3 beads - 250 µg		AL150C		
methyl-Arg beads - 250 µg		AL151C		
Histone H3 2-methyl K36 beads - 250 µg		AL152C		
Histone H3 K4 beads - 250 µg			AP119TB-C	
Histone H3 Eu-labeled Ab - 250 µg				TRF0125-D
Histone H3 phospho S10 Eu-labeled Ab - 10 µg				TRF0210-D
Histone H3 phospho T3 Eu-labeled Ab - 10 µg				TRF0211-D
Histone H3 acetyl K9 Eu-labeled Ab - 10 µg				TRF0400-D
Histone H3 1-2-methyl K4 Eu-labeled Ab - 10 µg				TRF0402-D
Histone H3 2-methyl K9 Eu-labeled Ab - 10 µg				TRF0403-D
Histone H3 K4 Eu-labeled Ab - 10 µg				TRF0404-D
Histone H3 acetyl K27 Eu-labeled Ab - 10 µg				TRF0405-D
Histone H3 2-methyl K27 Eu-labeled Ab - 10 µg				TRF0406-D
Histone H3 3-methyl K27 Eu-labeled Ab - 10 µg				TRF0407-D
Histone H3 2-methyl K36 Eu-labeled Ab - 10 µg				TRF0408-D
p53 acetyl K382 Eu-labeled Ab - 10 µg				TRF0409-D
Histone H3 K9/K27 Eu-labeled Ab - 10 µg				TRF0411-D
Lysine acetyl Eu-labeled Ab - 10 µg				TRF0412-D
O-GlcNAc Eu-labeled Ab - 10 µg				TRF0413-D
Histone H4 methyl R3 Eu-labeled Ab - 10 µg				TRF0414-D
methyl-Arg Eu-labeled Ab - 10 µg				TRF0415-D

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