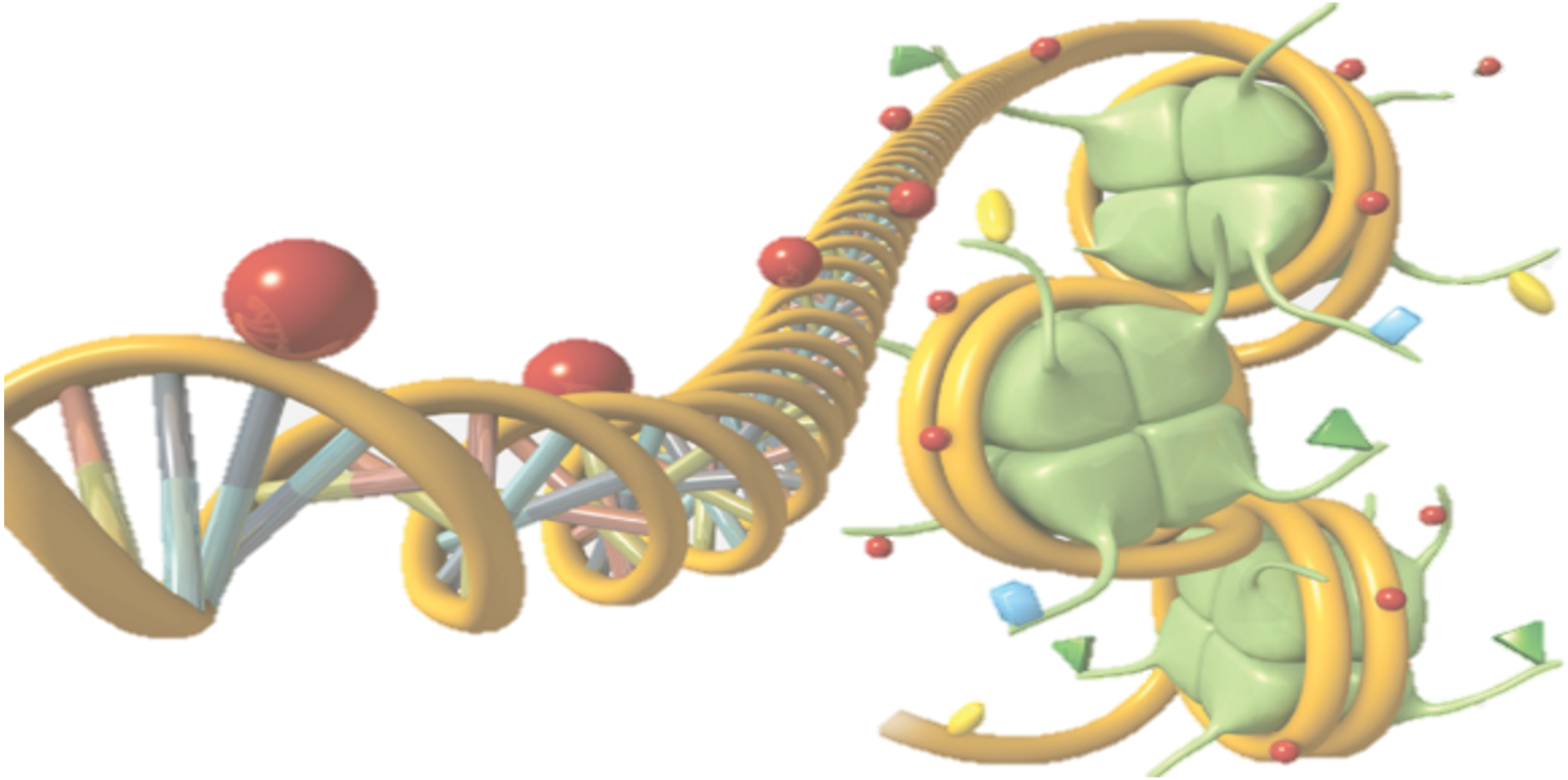


Epigenomics in Precision Medicine:

Illuminating Personalized Strategies Beyond Genomics

Gwen Lomberk, PhD
glomberk@mcw.edu
Medical College of Wisconsin
Precision Medicine Program
Institute for Health & Equity

Learning Objectives

- **Understand the basic principles of epigenomics and their role in precision medicine**
- **Identify potential clinical applications of epigenomics in precision medicine**
- **Create a framework for designing epigenomic studies in precision medicine**

Consider…

We have been explaining the cycle of life, health, disease, and inheritance, primarily, through the coding capacity of DNA

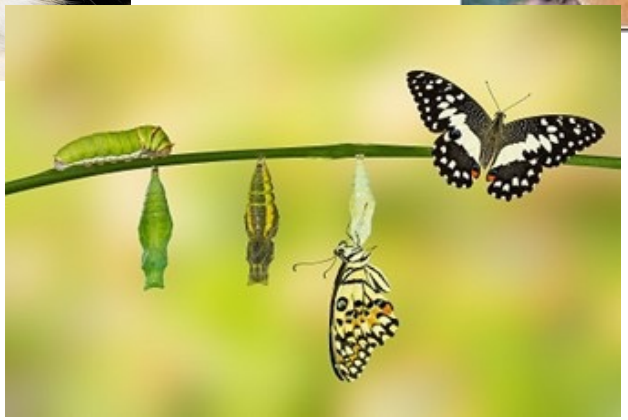
However,…

We must consider a knowledge gap:

Within and among organisms there are inherited variations which cannot be explained by the coding capacity of DNA…

Consider…

Remarkable Phenotypic Differences with the Same DNA



In other words, genomics cannot explain many mechanisms underlying the cycle of life and disease.

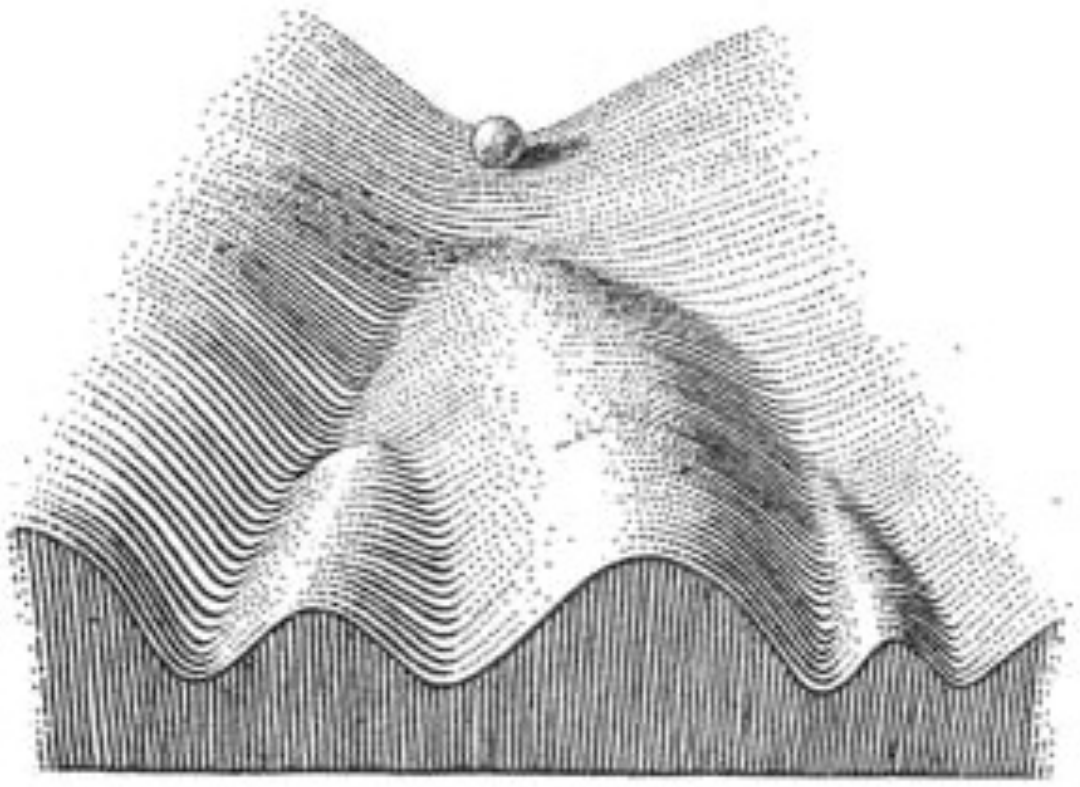
We need to consider the concepts and methodologies of Epigenetics & Epigenomics.

What is Epigenetics?!!?

Epigenetics: Definition and History

C.H. Waddington coined the term Epigenetics in 1942:

Above or in addition to genetics to explain differentiation



Epigenetics: Definition and History

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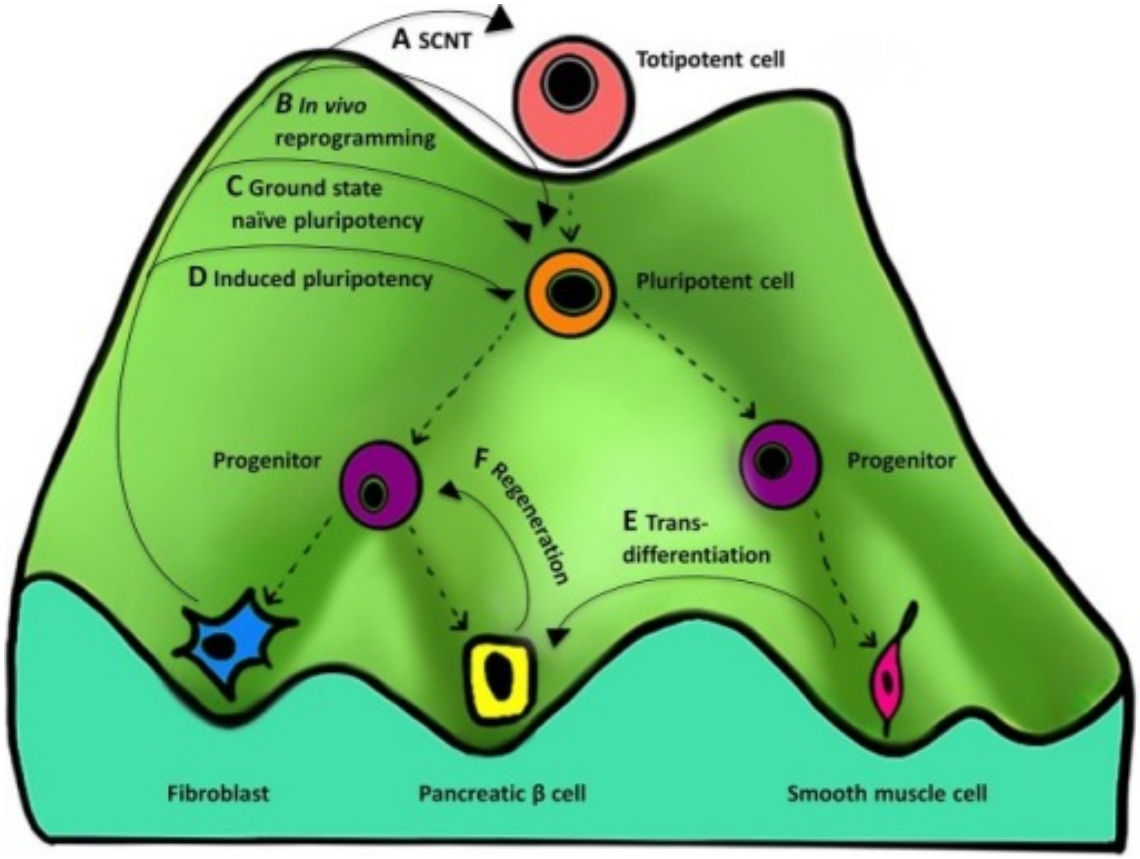
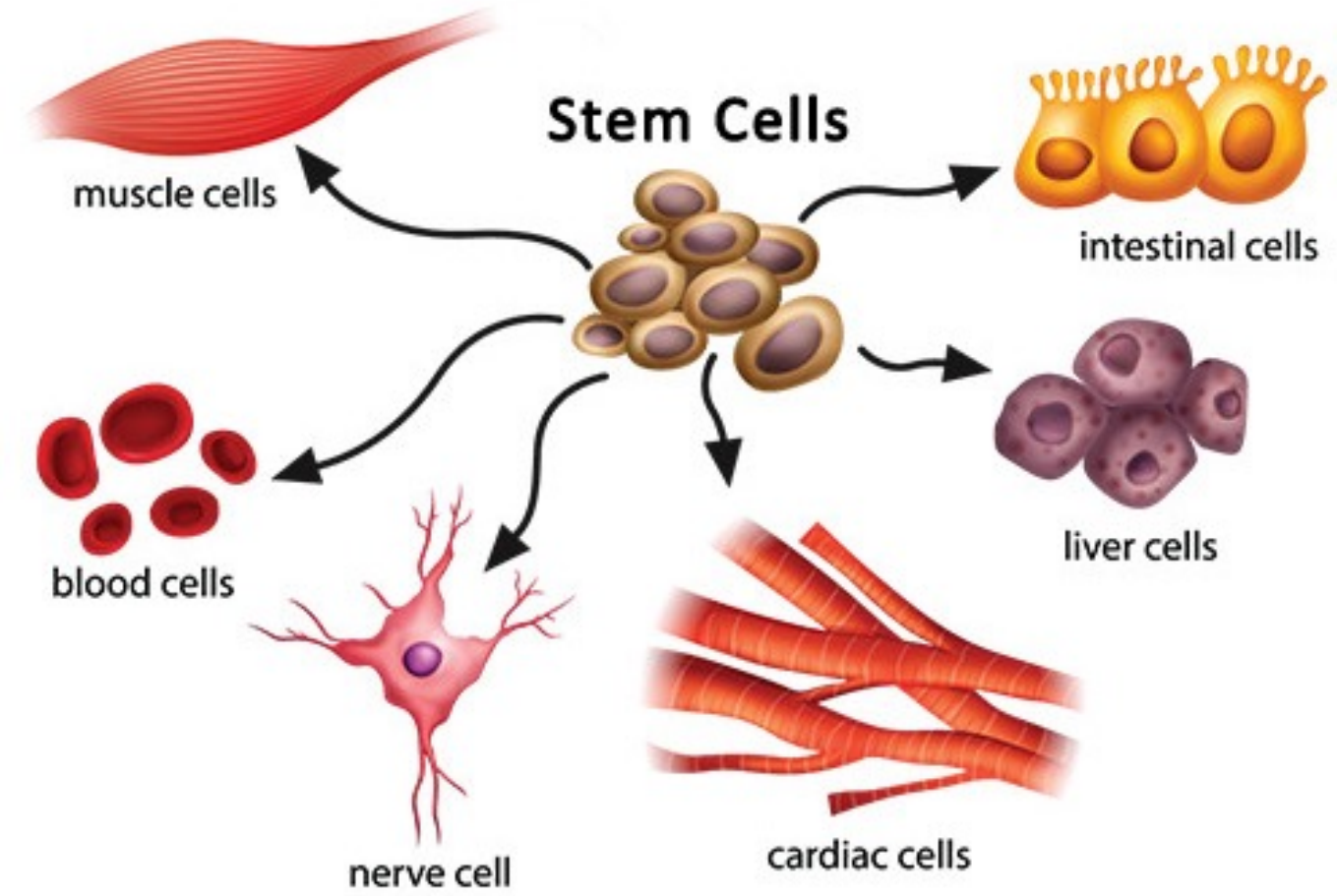


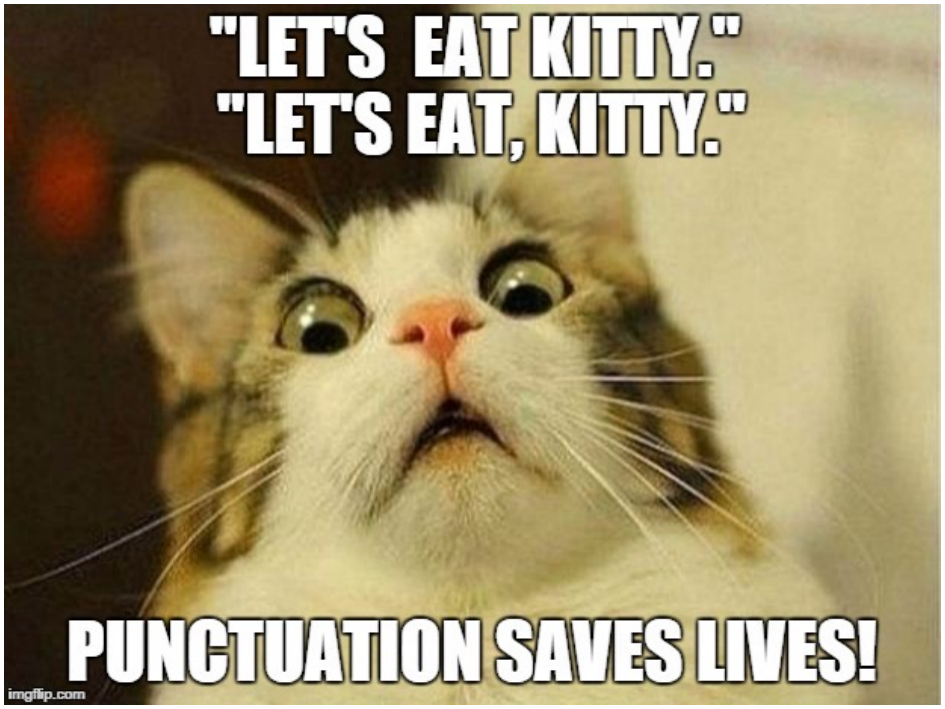
Strict Definition of Epigenetics

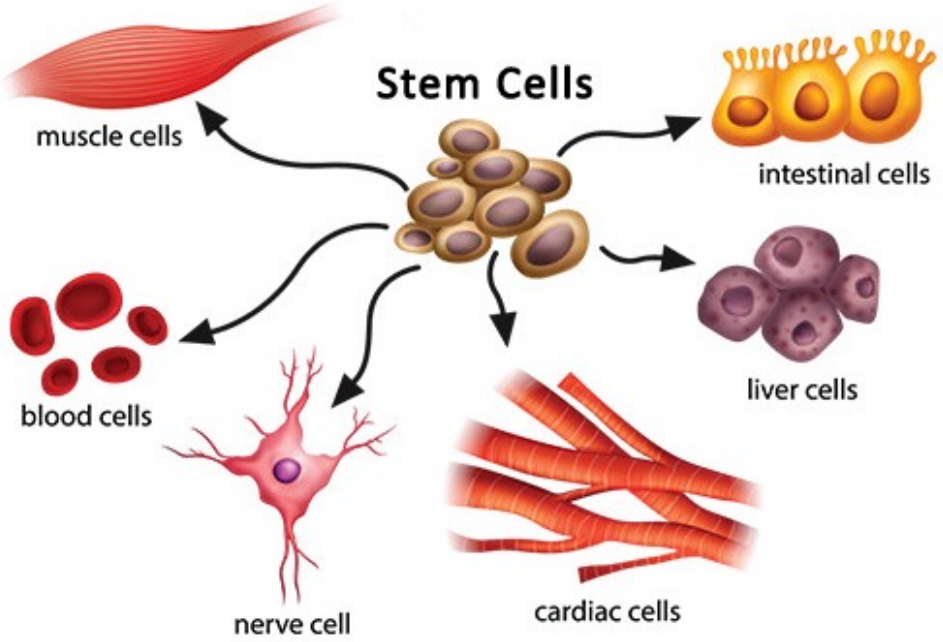
The study of heritable changes in genome function that occur *without alterations to the DNA sequence*

Particular states that define cell identity are attained by heritable instructions — the epigenetic marks that determine <u>whether</u>, <u>when</u> and <u>how</u> particular genetic information will be read



Each cell type has a different “punctuation”





Thus, the DNA gives us the potential to be who we are

but…

Epigenetics transforms this potential into the reality of who we are

Epigenetics *vs* Epigenomics

EPIGENOMICS is the study of the complete set of epigenetic modifications on the genetic material of a cell, known as the EPIGENOME.

Is there a code?

The Epigenomic Coding Capacity Relies on Writing, Reading and Erasing Chemical Marks on the DNA and Associated Proteins (Chromatin)

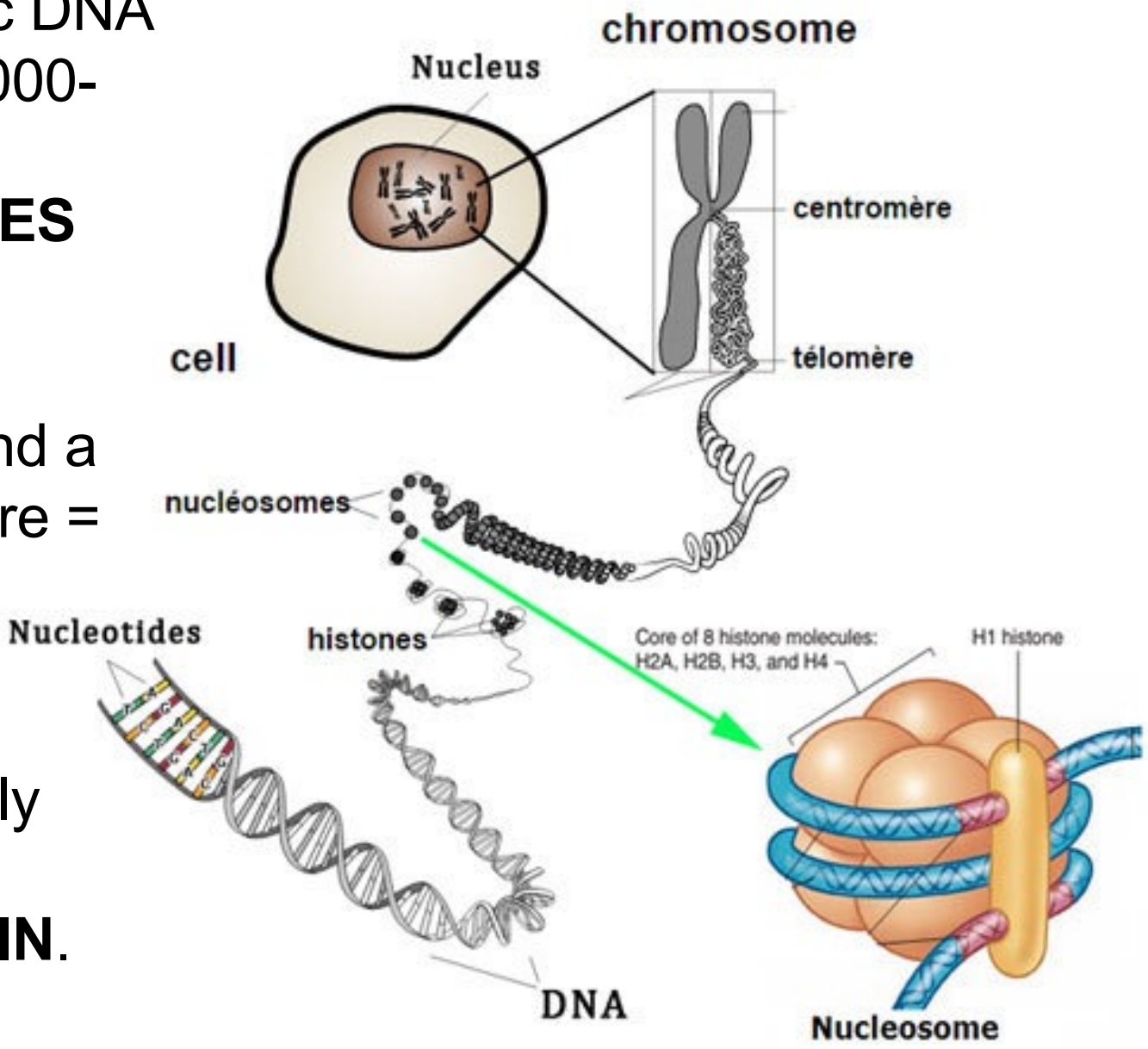
Marks on Chromatin are at the Mechanistic Core of Epigenetics

Basic unit of Chromatin = Nucleosome

Eukaryotic genomic DNA is compacted >10,000-fold by highly basic proteins = **HISTONES**

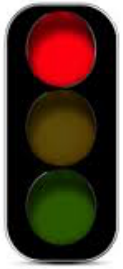
~150bp of DNA is wrapped ~2X around a histone octamer core = **NUCLEOSOME**

The result is a highly structured entity termed **CHROMATIN**.

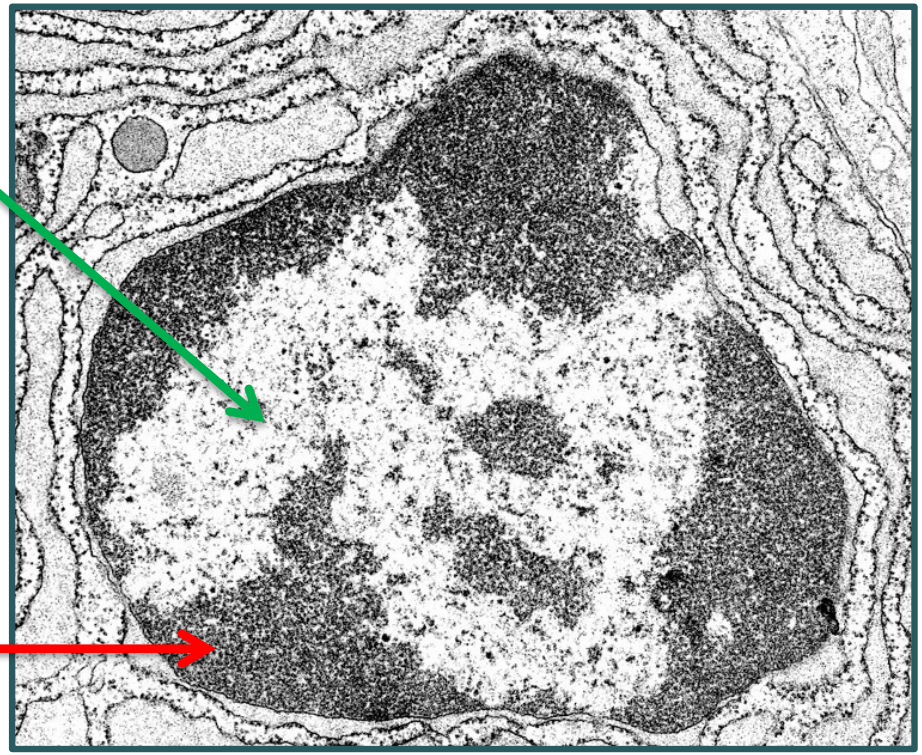


Chromatin compaction influences the transcriptional activity of DNA

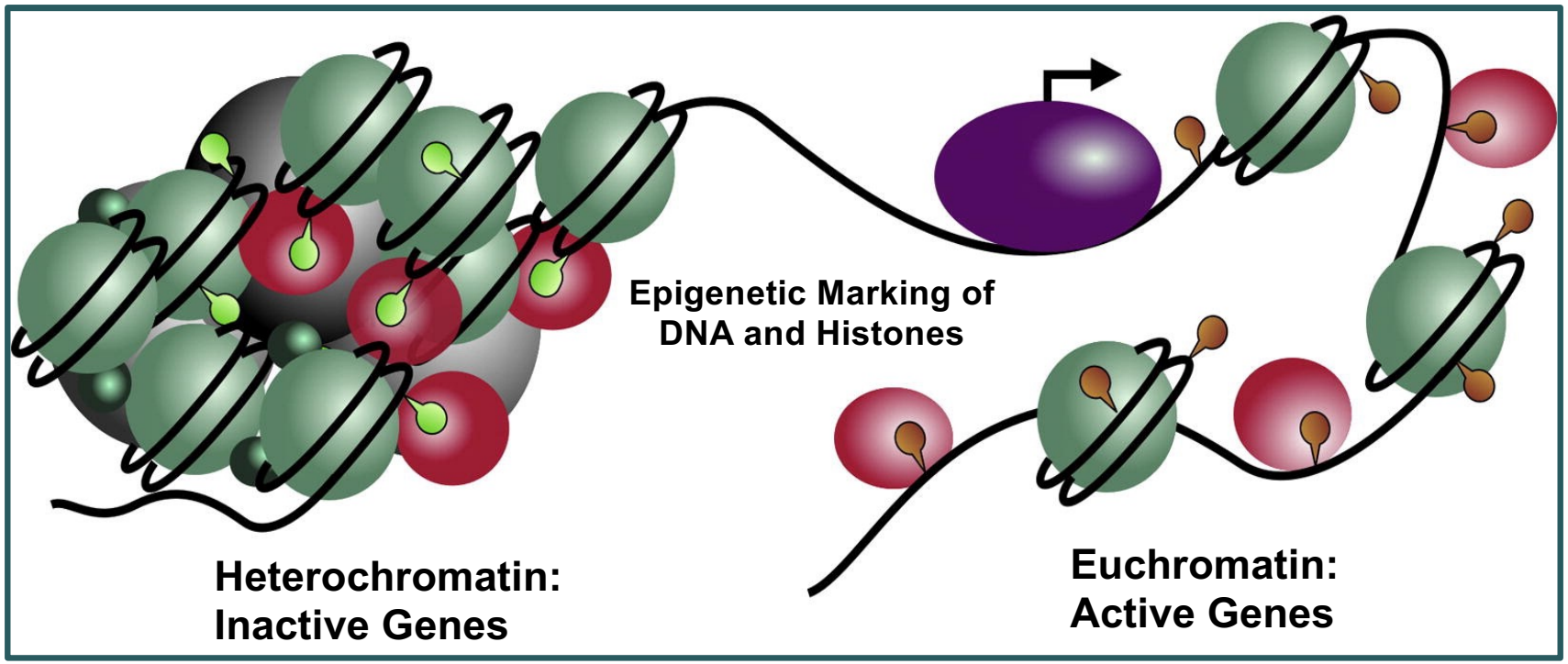
Euchromatin:
Less densely compact,
transcriptionally active
chromatin



Heterochromatin:
Highly compact,
transcriptionally silent
chromatin

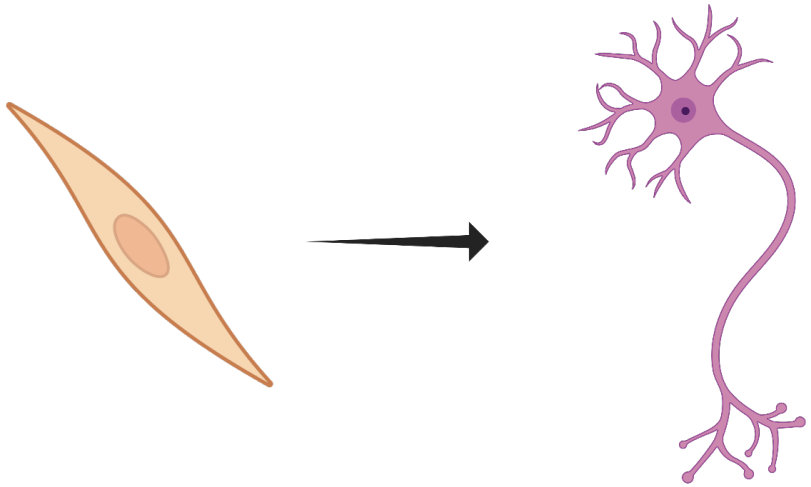


Chromatin Can Adopt Active and Repressive States



Physiological or Pathological Stimuli Chemically Modify (Mark) the Genome and the Epigenome. These Marks are Interpreted into Defined Patterns of Gene Expression that Give Rise to the Inheritable Phenotypes.

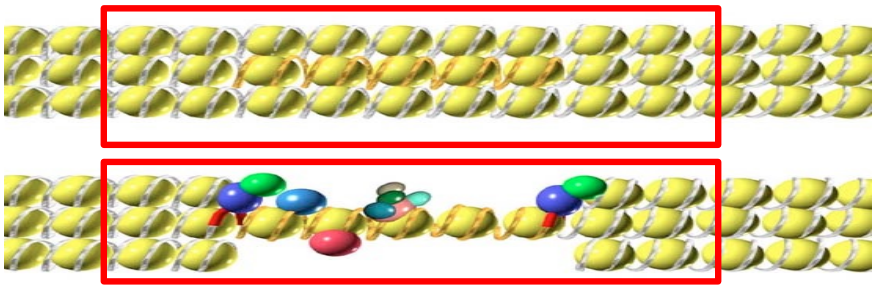
Consider Going from a Fibroblast to a Neuron



Neuronal genes sequestered and silenced by heterochromatin

Fibroblast

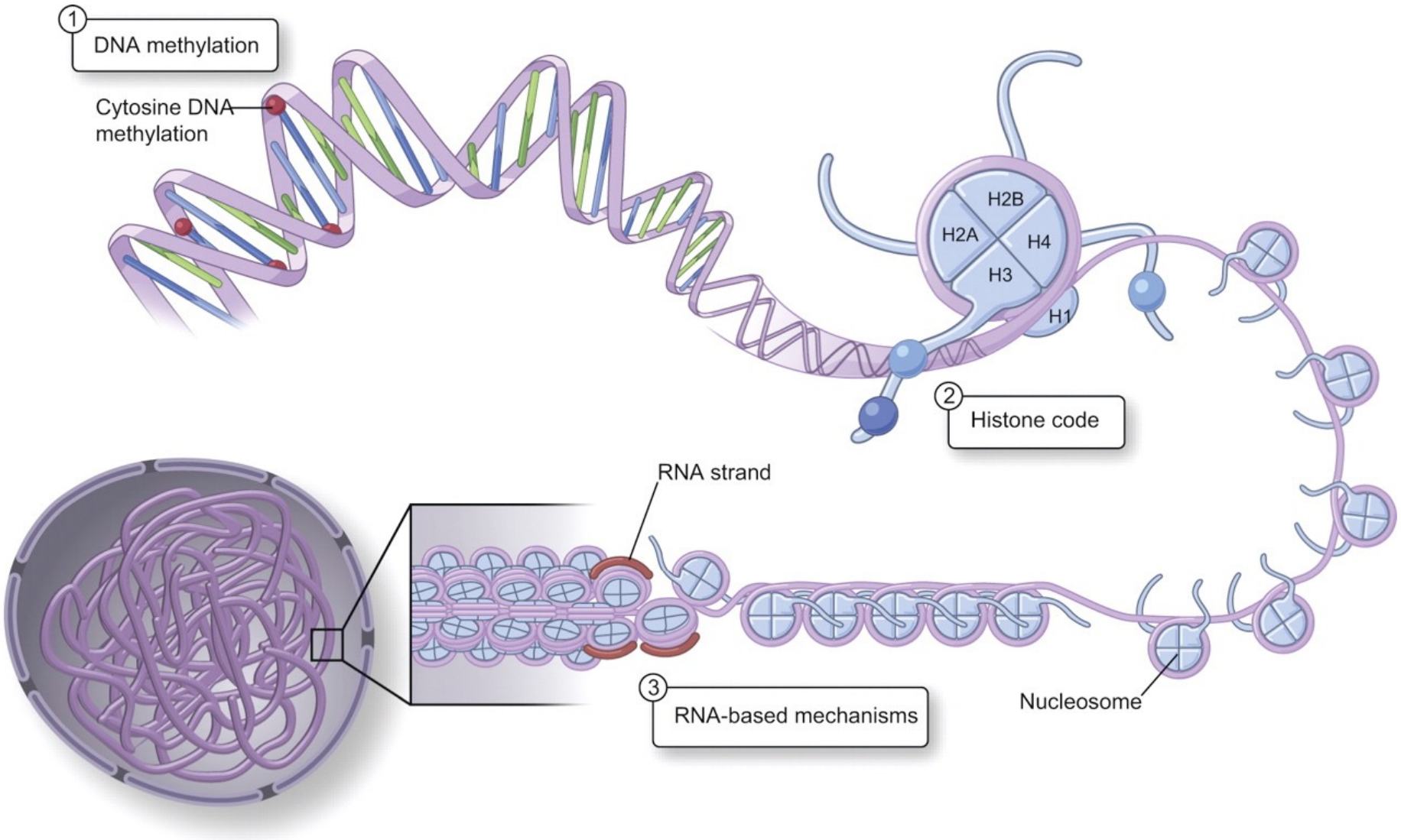
Neuron



Neuronal genes activated by forming euchromatin

Fibroblast genes are turned off by heterochromatin silencing marks while neuronal genes are turned on by euchromatin-forming marks

Epigenetic Mechanisms



https://doi.org/10.1152/japplphysiol.00131.2010

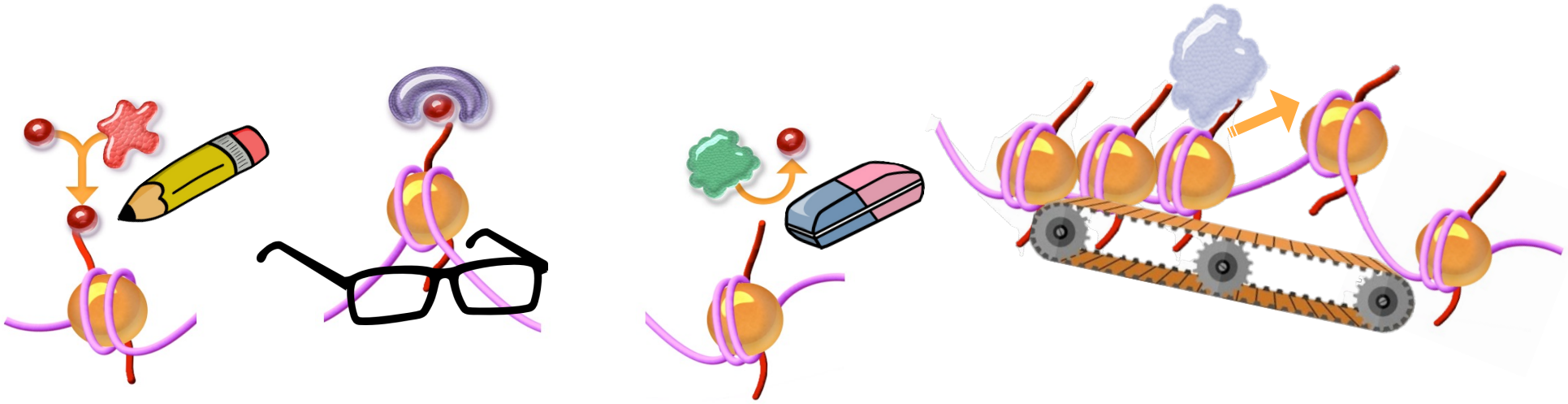
Regulators of the Epigenetic Code: Writers, Erasers, Readers, and Movers

Epigenetic Marks are deposited by **writer enzymes** to turn genes on/off

Epigenetic Marks are interpreted by **reader proteins** to turn genes on/off

Epigenetic Marks are removed by **eraser enzymes** to reverse previous codes

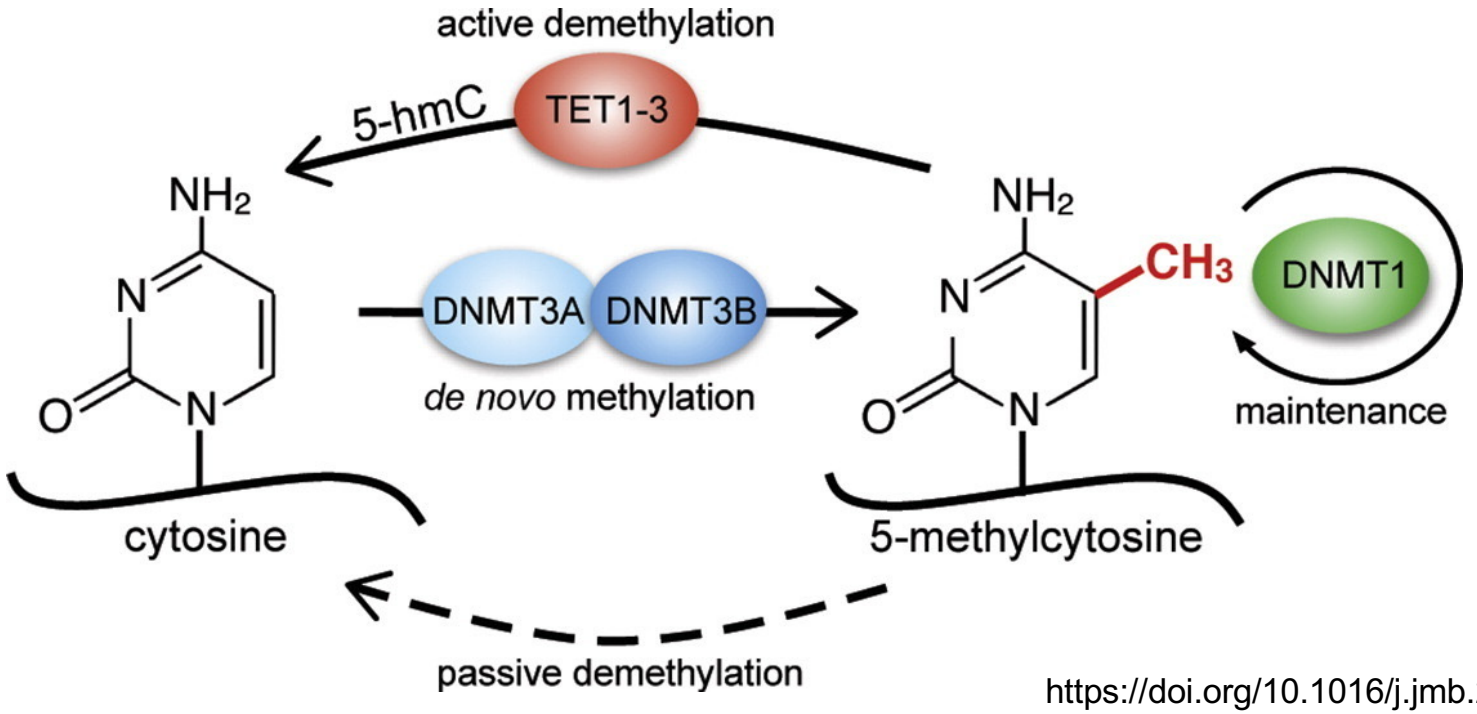
Nucleosomes are moved by **remodeler enzymes** to open and close chromatin



Modified histone residues serve as recognition marks that facilitate or prevent binding of proteins to TRANSLATE THE EPIGENETIC CODE

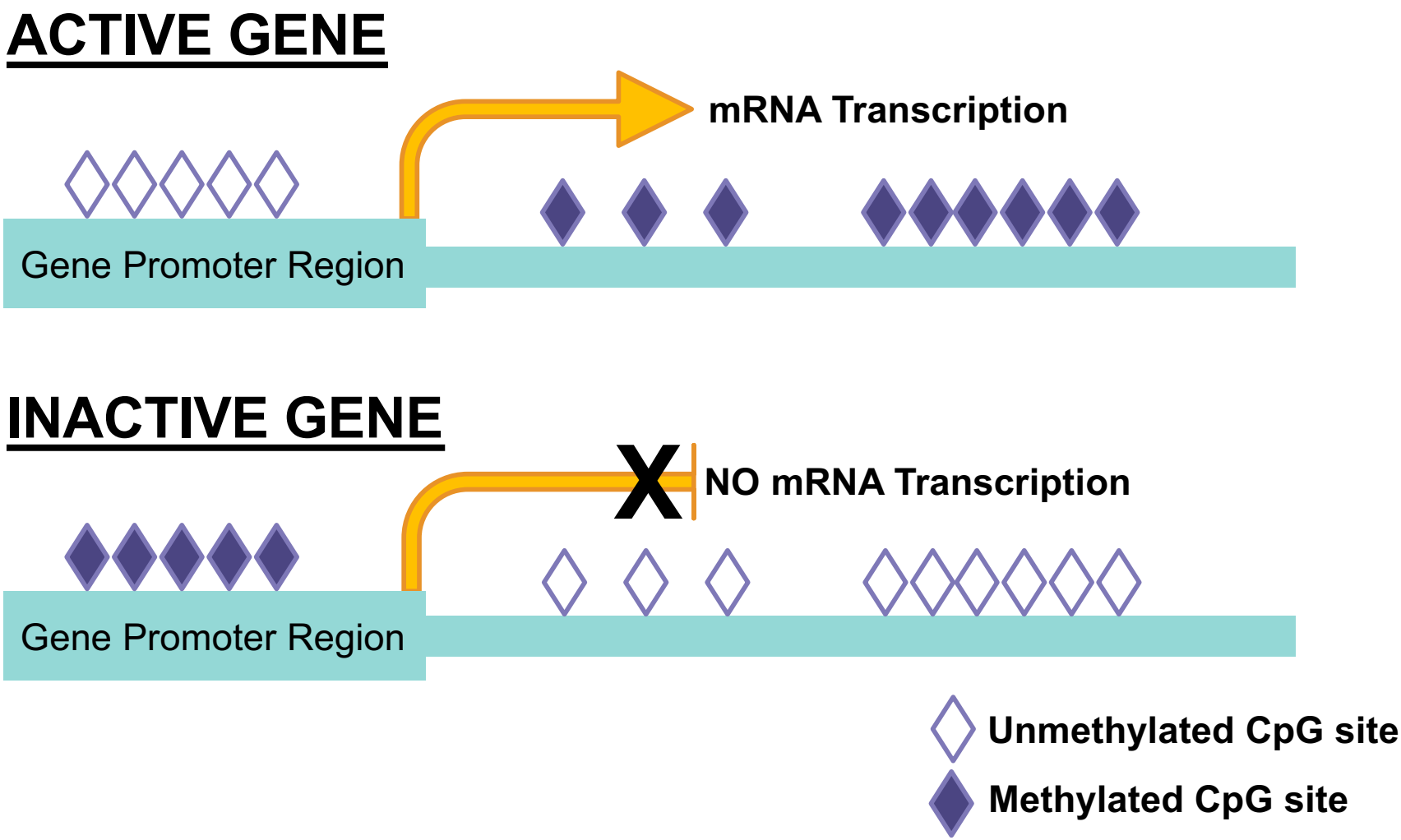
1. DNA methylation

- addition of a methyl group to a cytosine base
- associated with gene silencing in eukaryotes
- defects in mammals are embryonic lethal

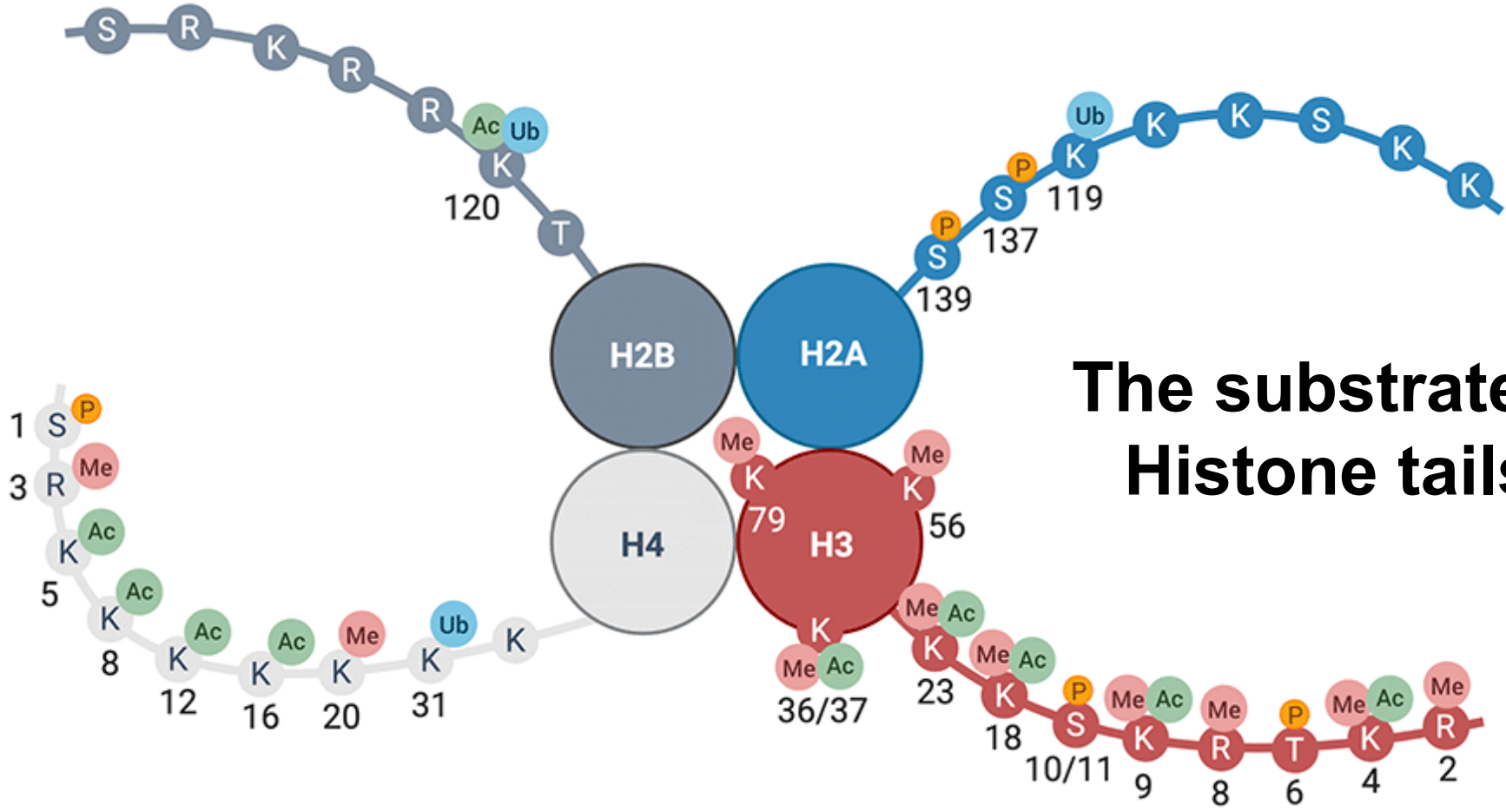


https://doi.org/10.1016/j.jmb.2017.02.008

Regulation of gene expression through DNA methylation



2. The Histone Code

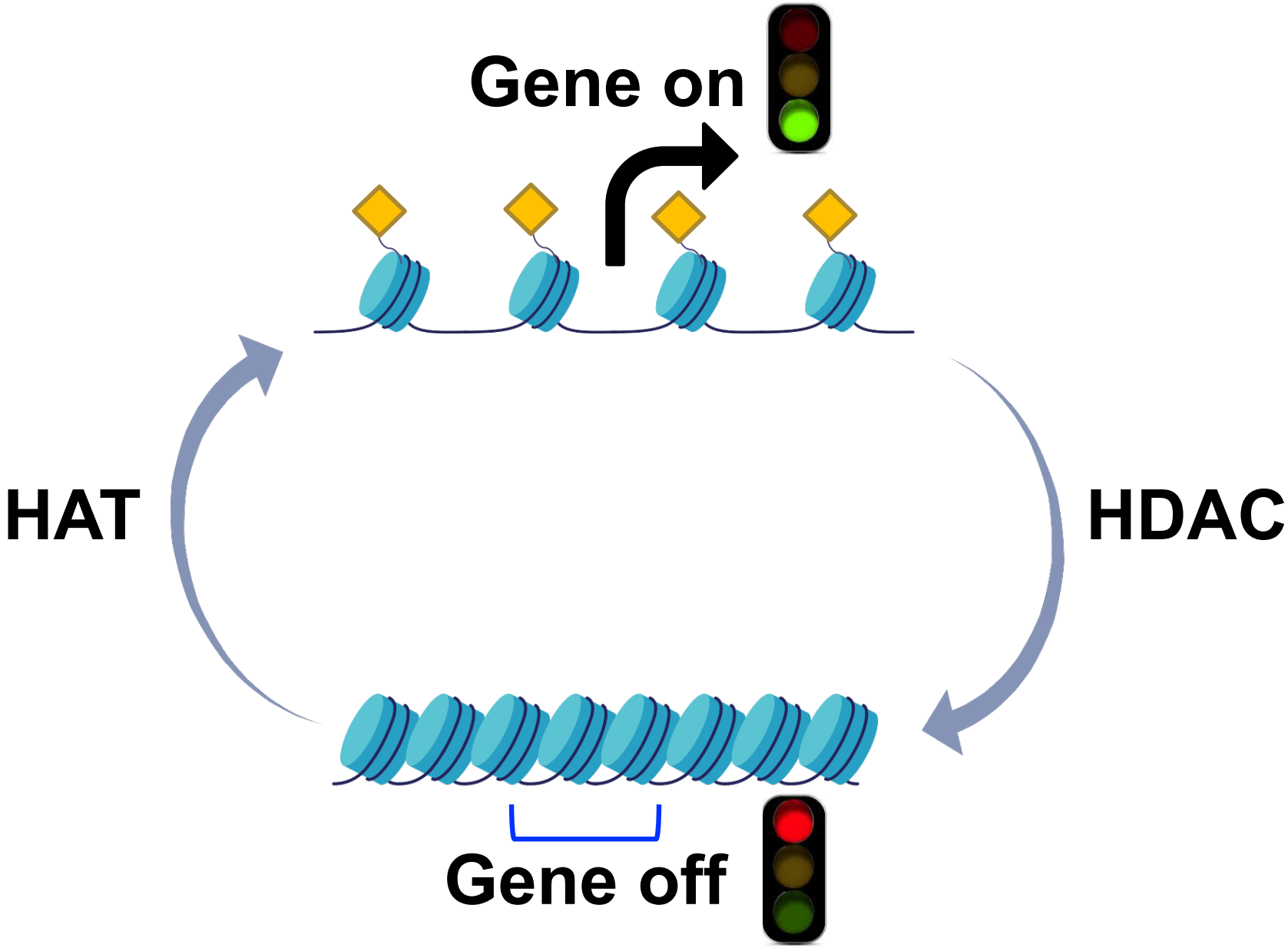


Most common modifications:

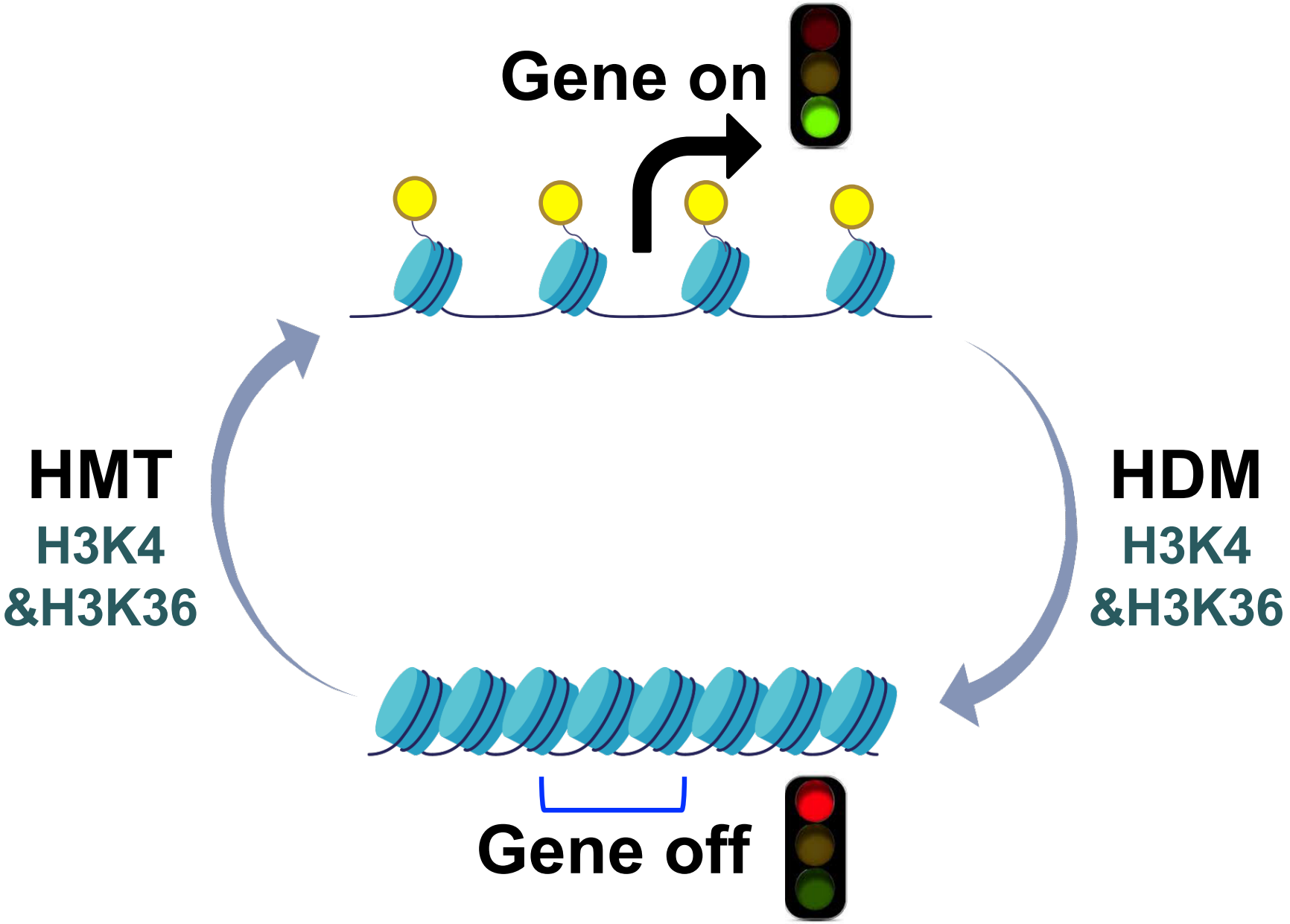
Me Methylation
Ac Acetylation
Ub Ubiquitination
P Phosphorylation

Patterns of these modifications form the "histone code"

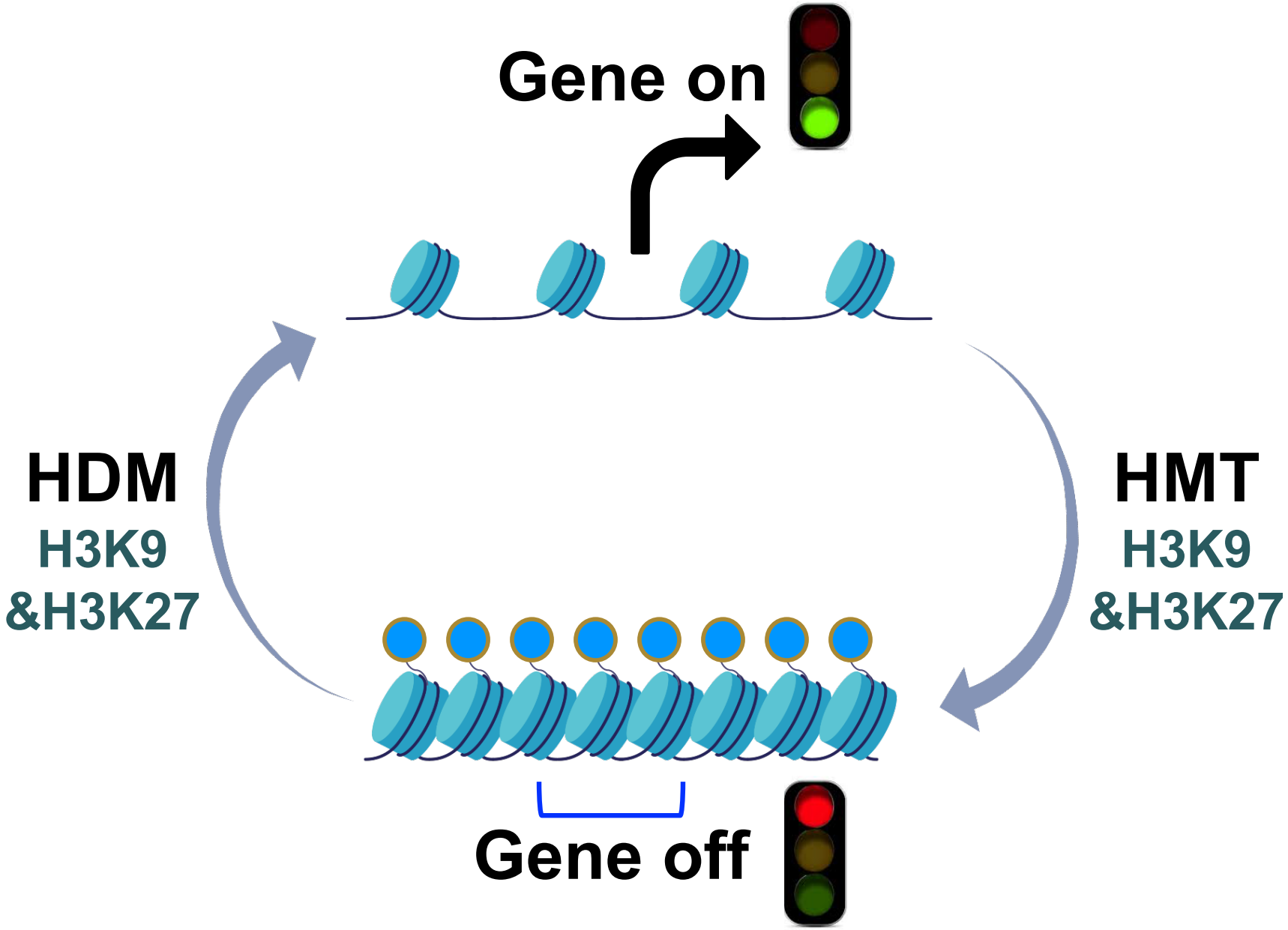
Histone Acetylation⇔ Deacetylation



H3K4 & H3K36
Methylation⇔ Demethylation



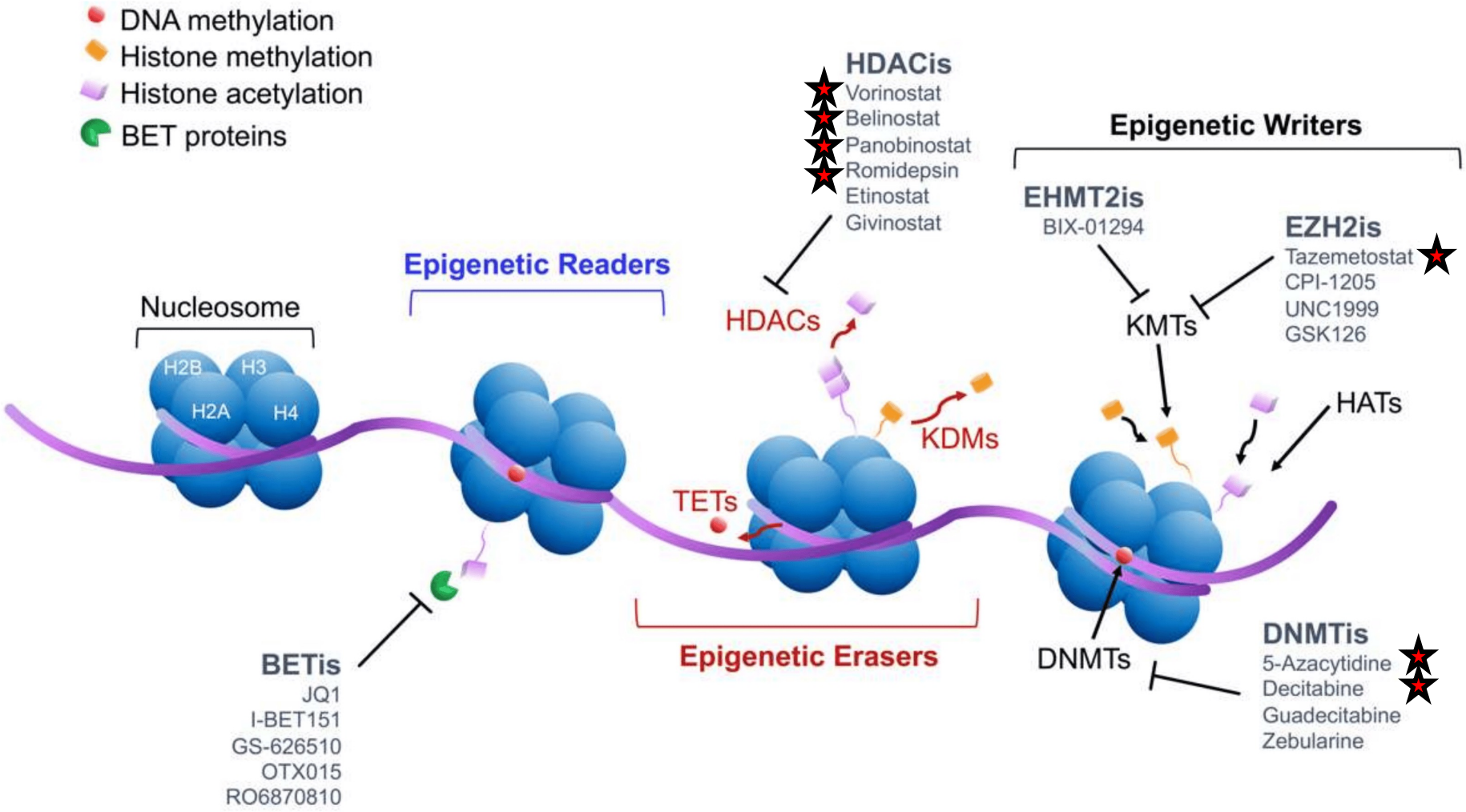
H3K9 & H3K27
Methylation⇔ Demethylation



EPIGENETIC MARK SUMMARY – GENERAL "RULES"

Epigenetic Mark	Location	General Effect
DNA methylation	Gene Promoter CpG island/TSS	Transcriptional Repression
DNA methylation	Gene Body	Transcriptional Activation
Histone acetylation	Gene Promoter CpG island/TSS	Transcriptional Activation
H3K4me3	Gene Promoter CpG island/TSS	Transcriptional Activation
H3K9me3	Gene promoter and body	Transcriptional Repression
H3K27me3	Gene promoter and body	Transcriptional Repression
H3K36me3	Gene body	Transcriptional Activation

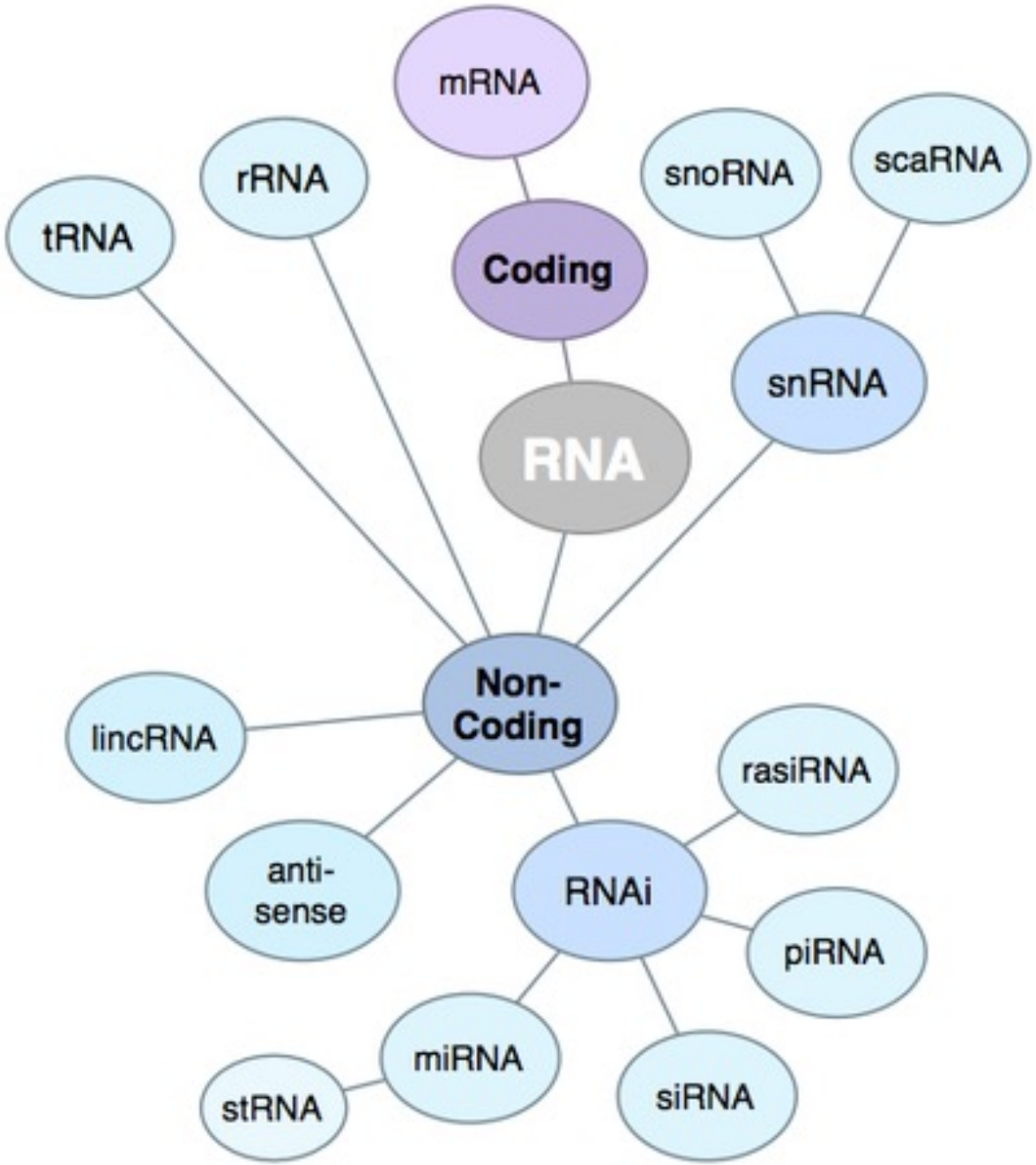
Targeting Epigenetic Modifications



FDA approved

https://www.mdpi.com/2072-6694/12/3/682

3. non-coding RNAs



As much as 98% of the transcriptional output from the human genome may be comprised of non-coding RNAs

Non-coding RNAs

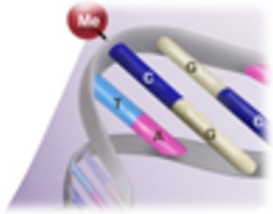
- **RNA function is highly complex.**
- **Some of the ncRNA from "junk" DNA have important roles in gene regulation during normal development and disease.**
- **ncRNAs function as accessory molecules to the writers, readers, and erasers involved in chromatin modification.**

How to Map Epigenomic Landscapes

Epigenetic Modifications

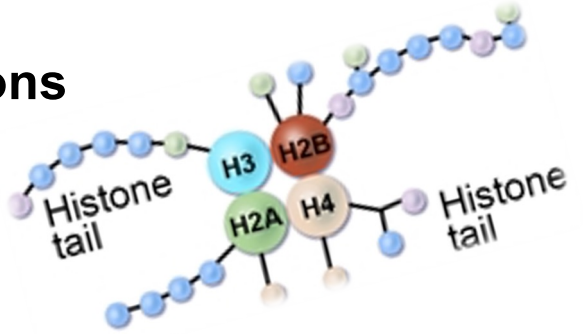
Commonly Used Method

DNA Methylation



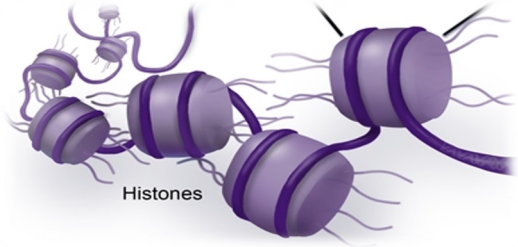
- **Methyl array (EPIC)**
- **Whole Genome Bisulfite sequencing (WGBS)**
- **Reduced Representation Bisulfite sequencing (RRBS)**

Histone Modifications



- **Chromatin Immunoprecipitation with sequencing (ChIP-seq)**

Chromatin Accessibility



- **Assay for Transposase-Accessible Chromatin with sequencing (ATAC-seq)**

Non-coding RNA

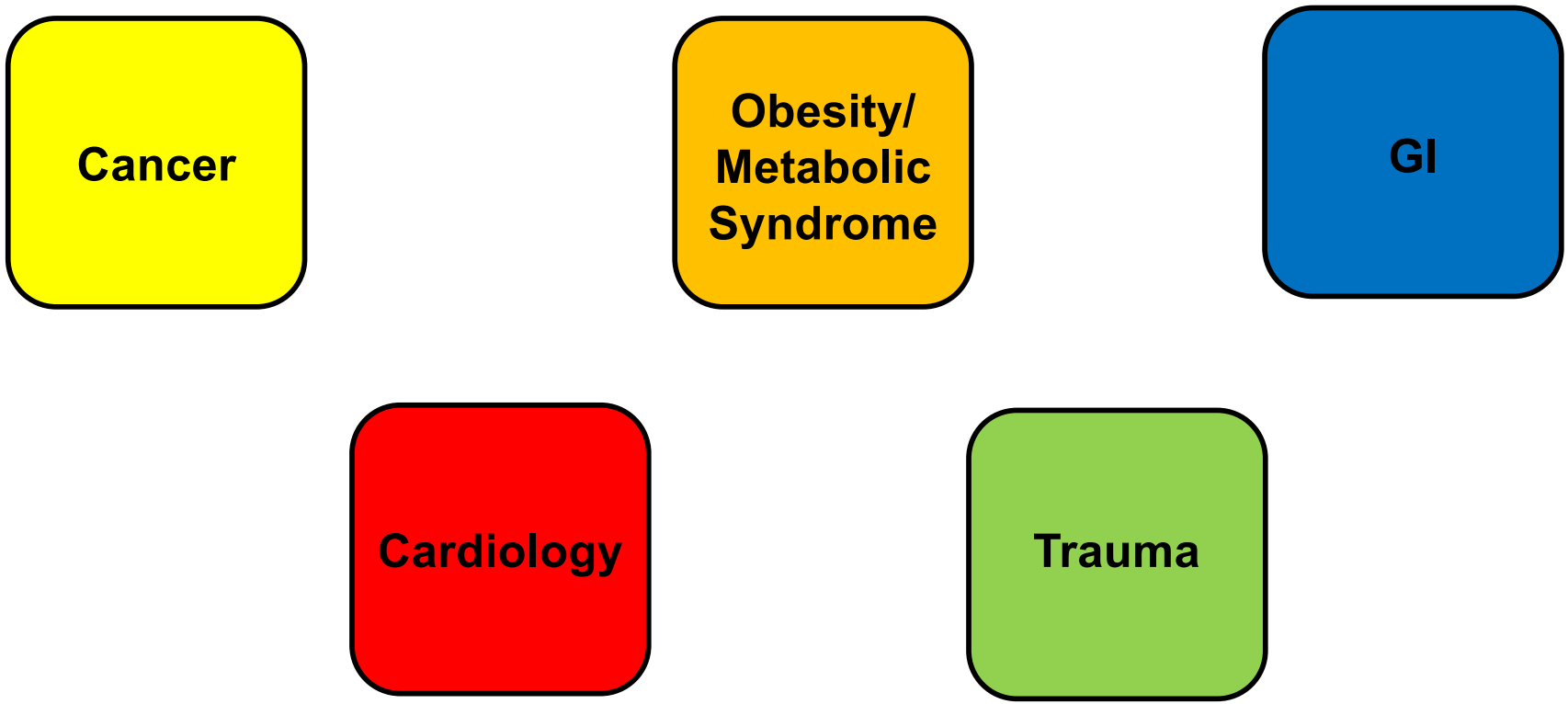
miRNA

- **smallRNA sequencing**
- **miRNA microarray**

lncRNA

- **RNA sequencing (RNA-seq)**

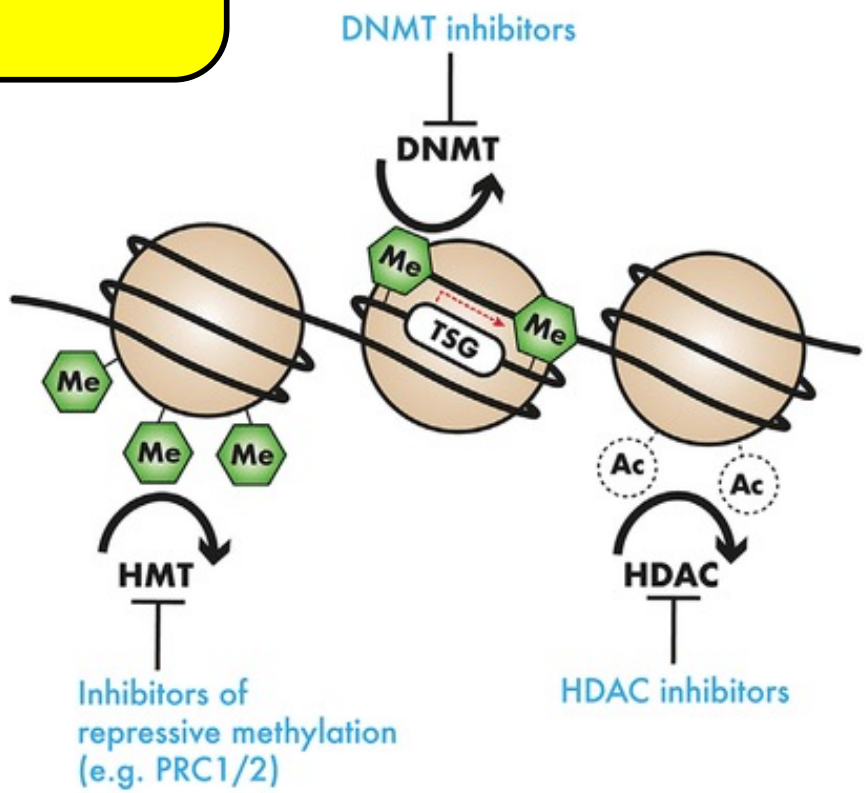
What about the role of Epigenomics in Disease?



Just like genetic alterations…epigenetic mechanisms can lead to the inherited *aberrant silencing or activation of genes, thereby, leading to diseases*

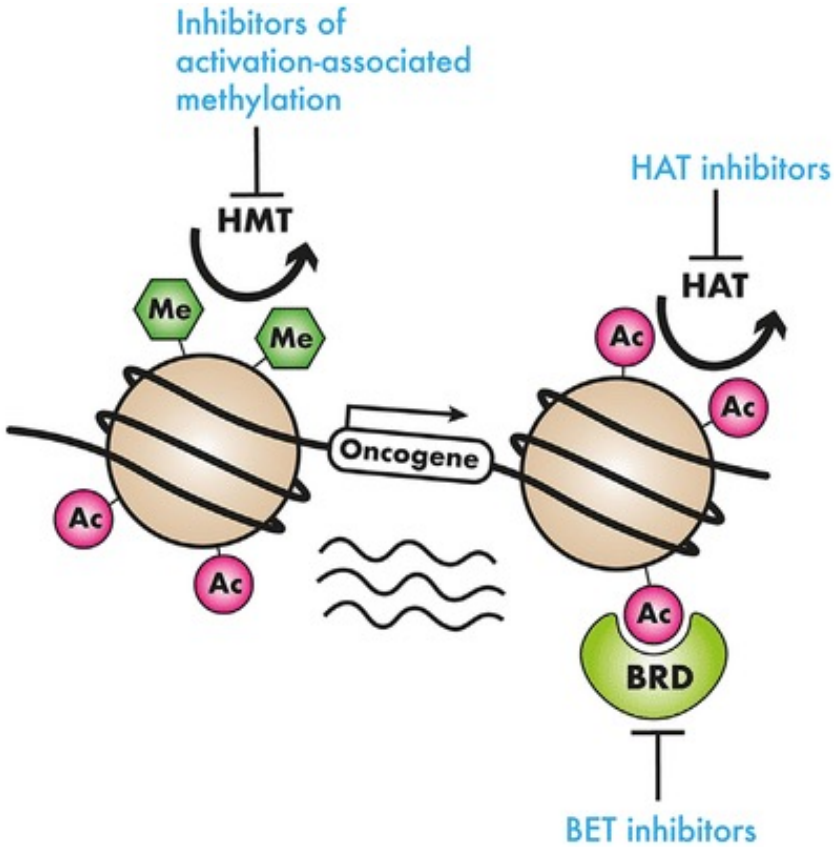
Cancer

Tumor Suppressor Genes



Repressed tumor suppressor gene expression (heterochromatin)

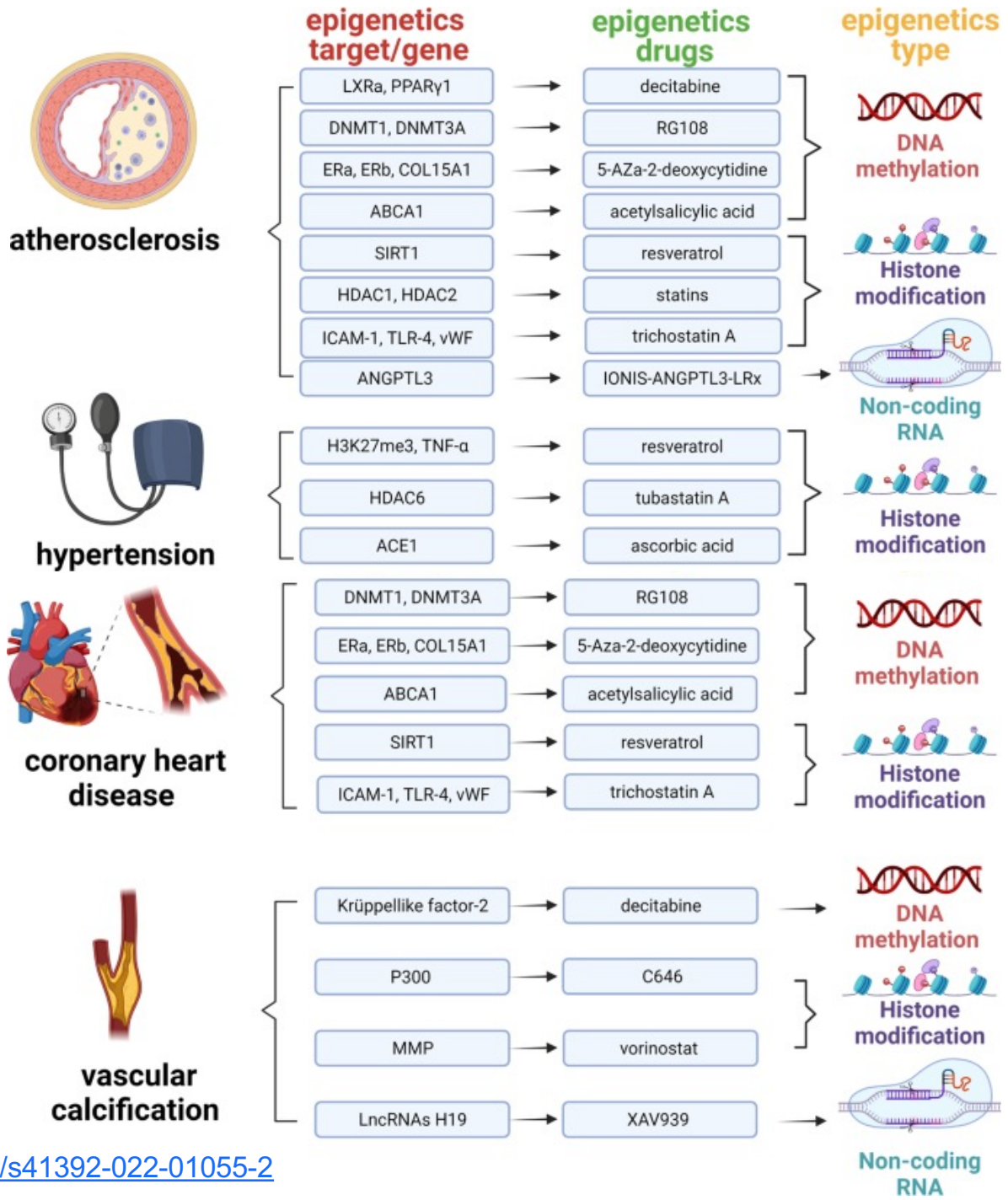
Oncogenes



Activated oncogene expression (euchromatin)

https://www.frontiersin.org/articles/10.3389/fonc.2018.00041/full
Front Oncol. 2018 Feb 23;8:41.

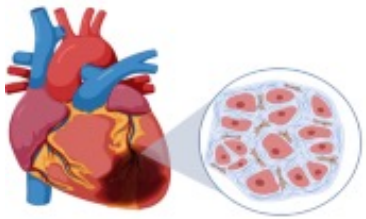
Cardio-vascular Disease



https://www.nature.com/articles/s41392-022-01055-2

Signal Transduct Target Ther. 2022 Jun 25;7(1):200. doi: 10.1038/s41392-022-01055-2; PMC9233709

Cardio-vascular Disease



myocardial infarction

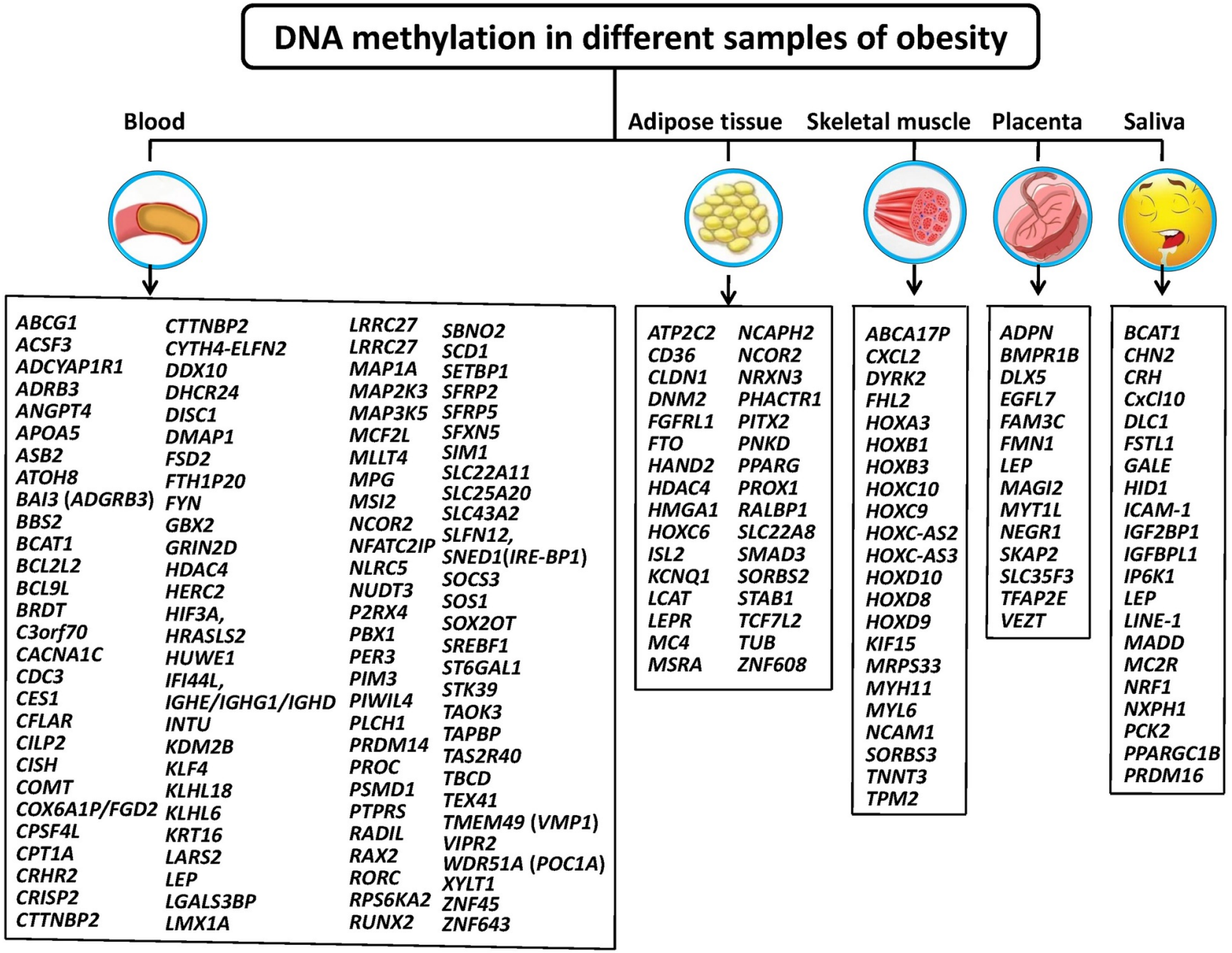
heart failure

epigenetics target/gene	epigenetics drugs	epigenetics type
FOXO3a	entinostat	Histone modification
AKT-1, TNFa	trichostatin A	
HDAC6	VPA	
NP	tributyl butyrate	
HSF1	SAHA	
SIRT1, COX-2	SRT1720	Non-coding RNA
PCSK9	alirocumab	
TUMOR necrosis factor-A	5-azacytidine	DNA methylation
mitochondria genes	chaetocin	Histone modification
SIRT1, IL-6	resveratrol	
GATA4, P300	curcumin	
VEGF, eNOS, ANG-1	trichostatin A	
ANP, BNP	emodin	
IL-6, STAT3	mocetinostat	
β-SMA	JQ1	
miRNA-92a	MRG-110	Non-coding RNA
miRNA-132	CDR132L	

https://www.nature.com/articles/s41392-022-01055-2

Signal Transduct Target Ther. 2022 Jun 25;7(1):200. doi: 10.1038/s41392-022-01055-2; PMC9233709

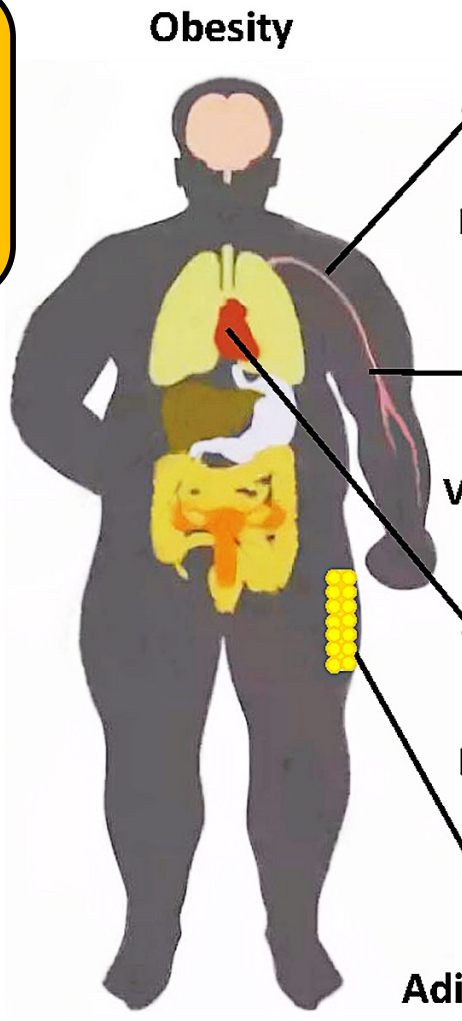
Obesity/ Metabolic Syndrome

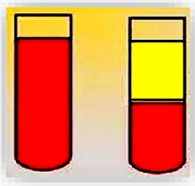


https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9670650/

Diabetol Metab Syndr. 2022 Nov 17;14(1):171. doi: 10.1186/s13098-022-00947-1.

Obesity/ Metabolic Syndrome





Blood sample

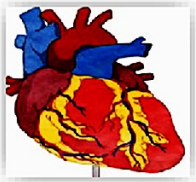
miR-122
miR-125b
miR-130b
miR-130b
miR-142

miR-142-3p
miR-15b
miR-221
miR222
miR-28-3p

MiR-31
miR-423-5p
miR-486-3p
miR-486-5p
miR-519d

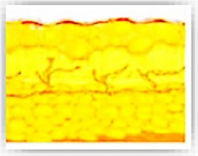
Vascular tissue

miRNA-103-3p
miRNA-124a
miRNA-126
miRNA-150
miRNA-16



Heart tissue

miRNA-130b
miRNA-208a
miRNA-29c
miRNA-410-5p
miRNA-451



Adipose tissue

miR-133
miR-155
miR-193b-365
miR-27b
miR-30b/c
miR-32
miR-328

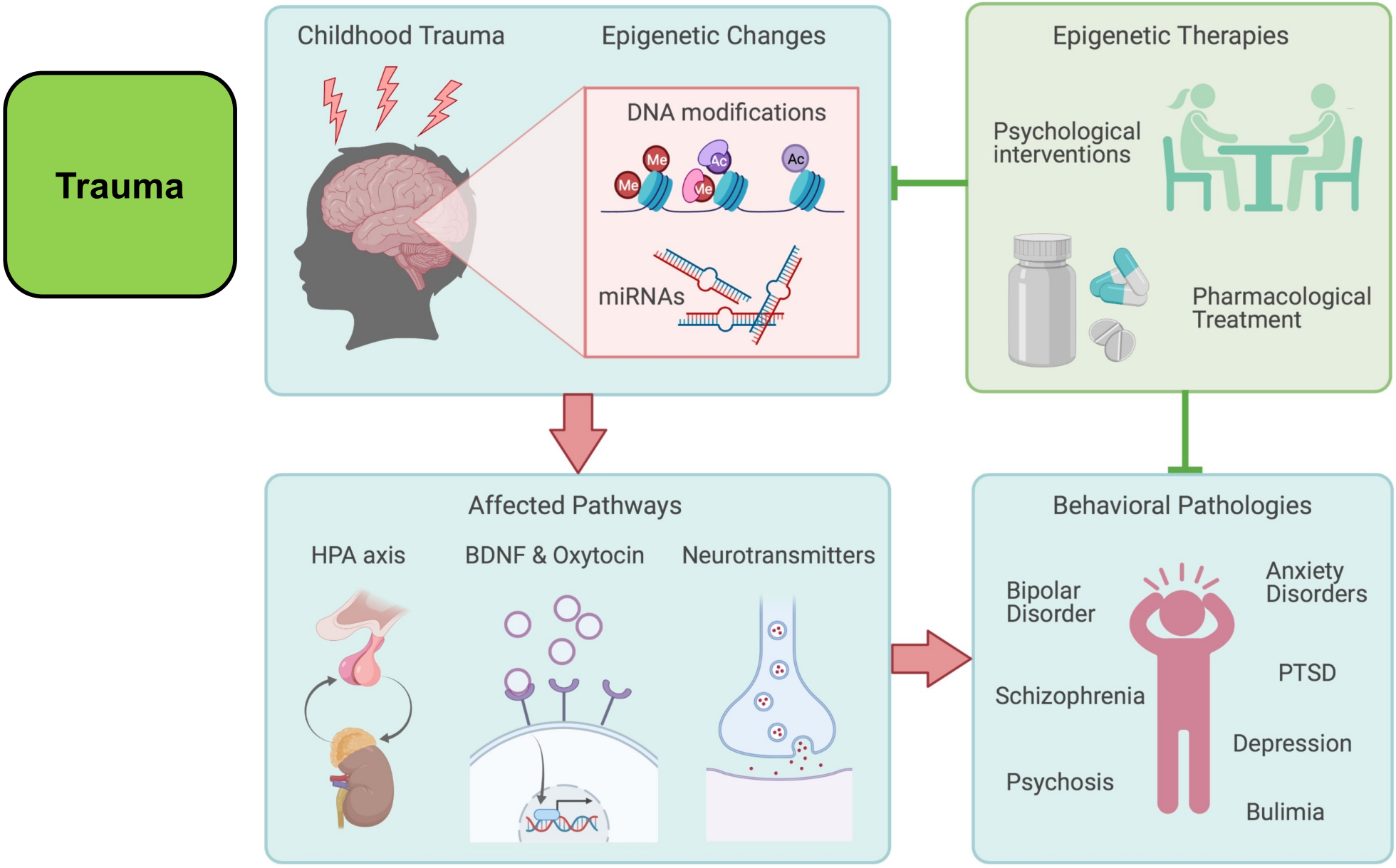
miR-34a
miR-378
miR-455
miRNA-103
miRNA-10a-5p
miRNA-1229
miRNA-125b

miRNA-130p
miRNA-139-5p
miRNA-143
miRNA-146b
miRNA-148
miRNA-181-5p
miRNA-185

miRNA-196a
miRNA-199-5p
miRNA-221
miRNA-23a-3p
miRNA-484
miRNA-519d
miRNA-99a

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9670650/

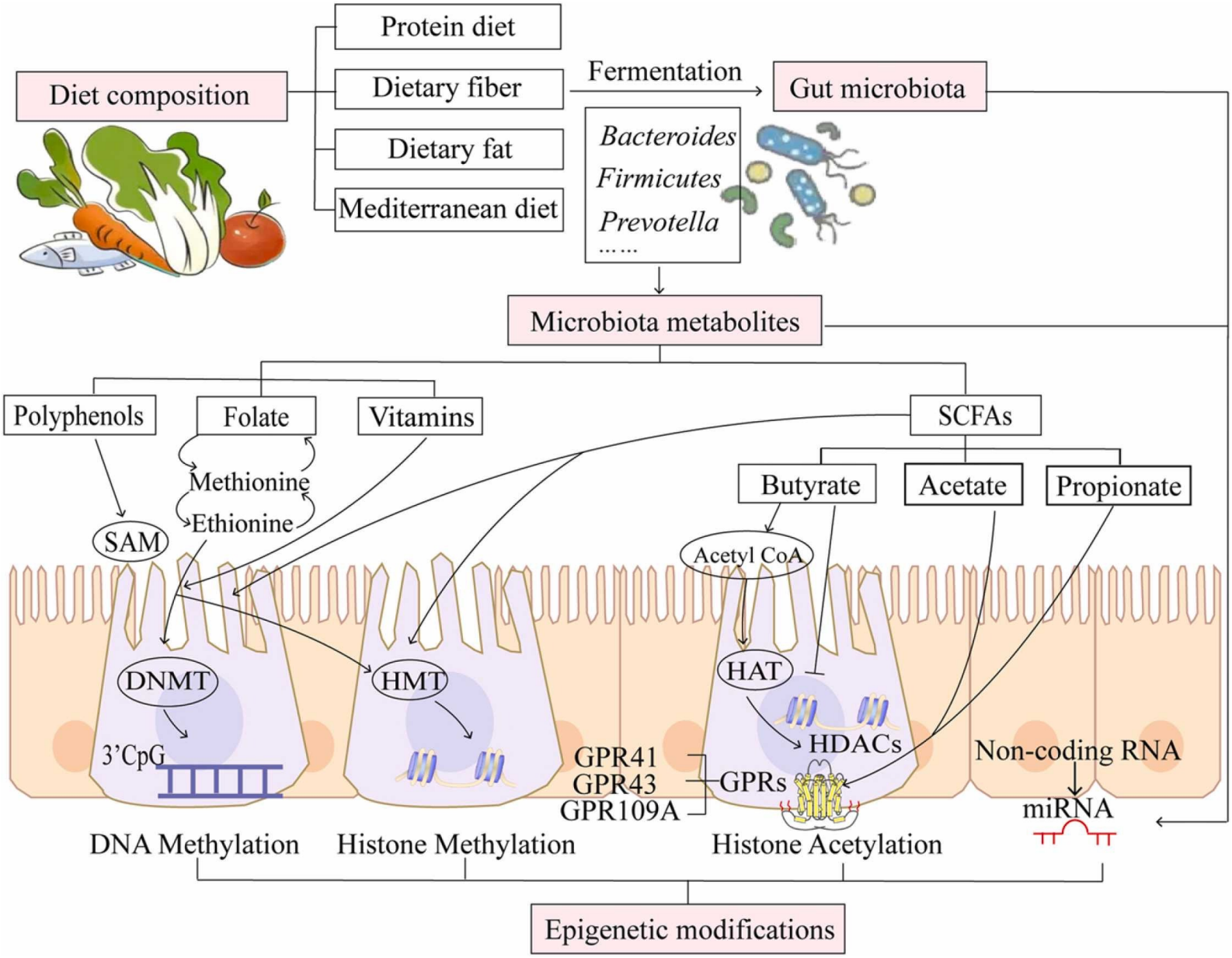
Diabetol Metab Syndr. 2022 Nov 17;14(1):171. doi: 10.1186/s13098-022-00947-1.



https://www.sciencedirect.com/science/article/pii/S014976342100484X?via%3Dihub

Neurosci Biobehav Rev. 2022 Jan;132:1049-1066.

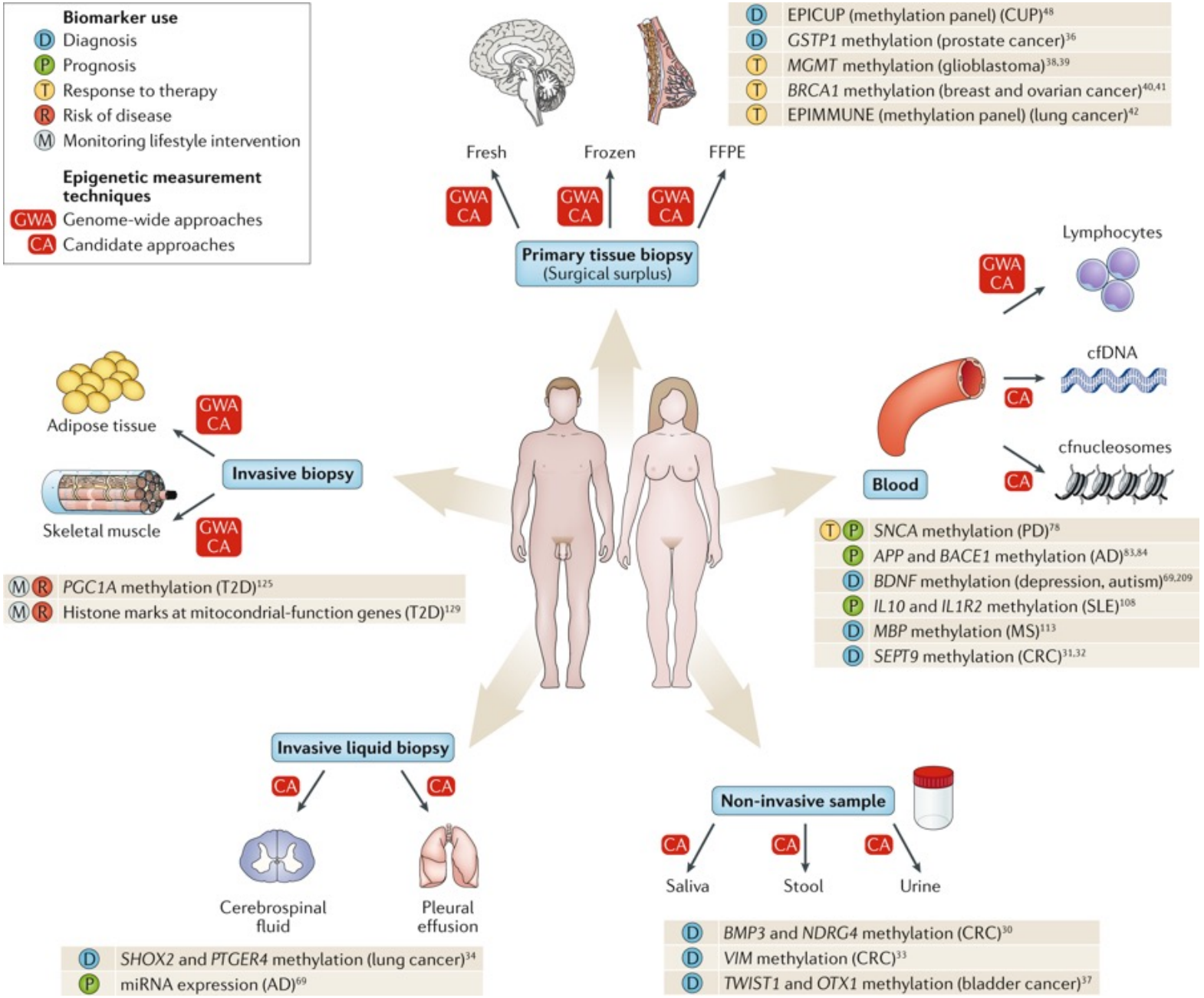
GI



https://www.sciencedirect.com/science/article/pii/S0753332222006795?via%3Dihub/

Biomed Pharmacother. 2022 Sep;153:113290. doi: 10.1016/j.biopha.2022.113290.

Clinical Epigenetics - Seizing Opportunities for Translation



Nat Rev Genet. 2019 Feb;20(2):109-127.

In Summary

- Epigenetic mechanisms include DNA methylation, histone modifications, and non-coding RNAs.
- Epigenetic modifications, which involve adding or removing chemical tags on DNA or histone proteins, impact gene expression in normal and disease states.
- Epigenetic writers, readers, and erasers are viable drug targets with some FDA-approved and others in clinical trials; thus, it is possible to reverse aberrant epigenetic changes.
- Epigenomics contributes to precision medicine by offering personalized treatment strategies based on individual epigenetic profiles and identifying epigenetic biomarkers associated with specific diseases or treatment responses.