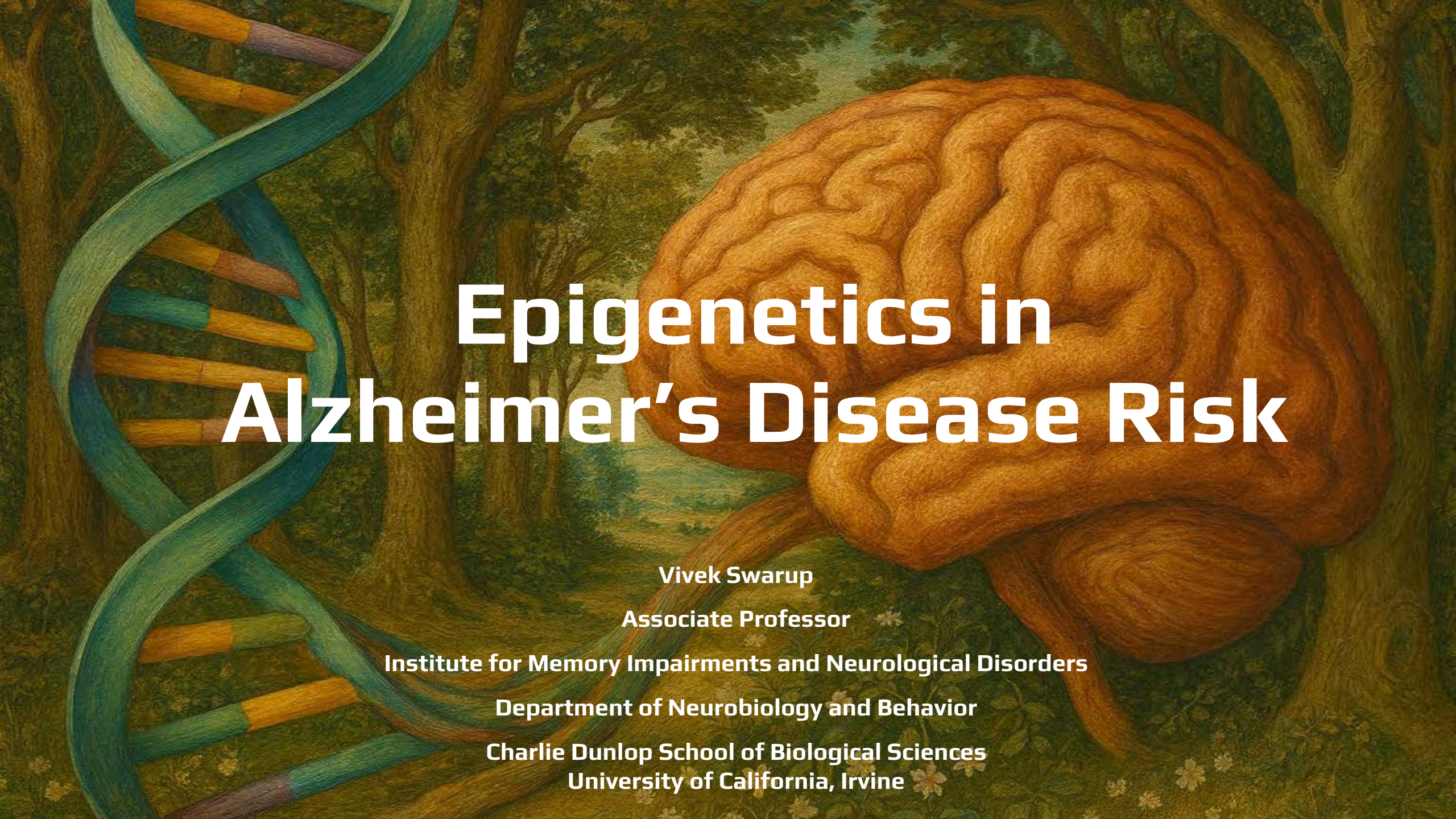


Epigenetics in Alzheimer's Disease Risk

Vivek Swarup

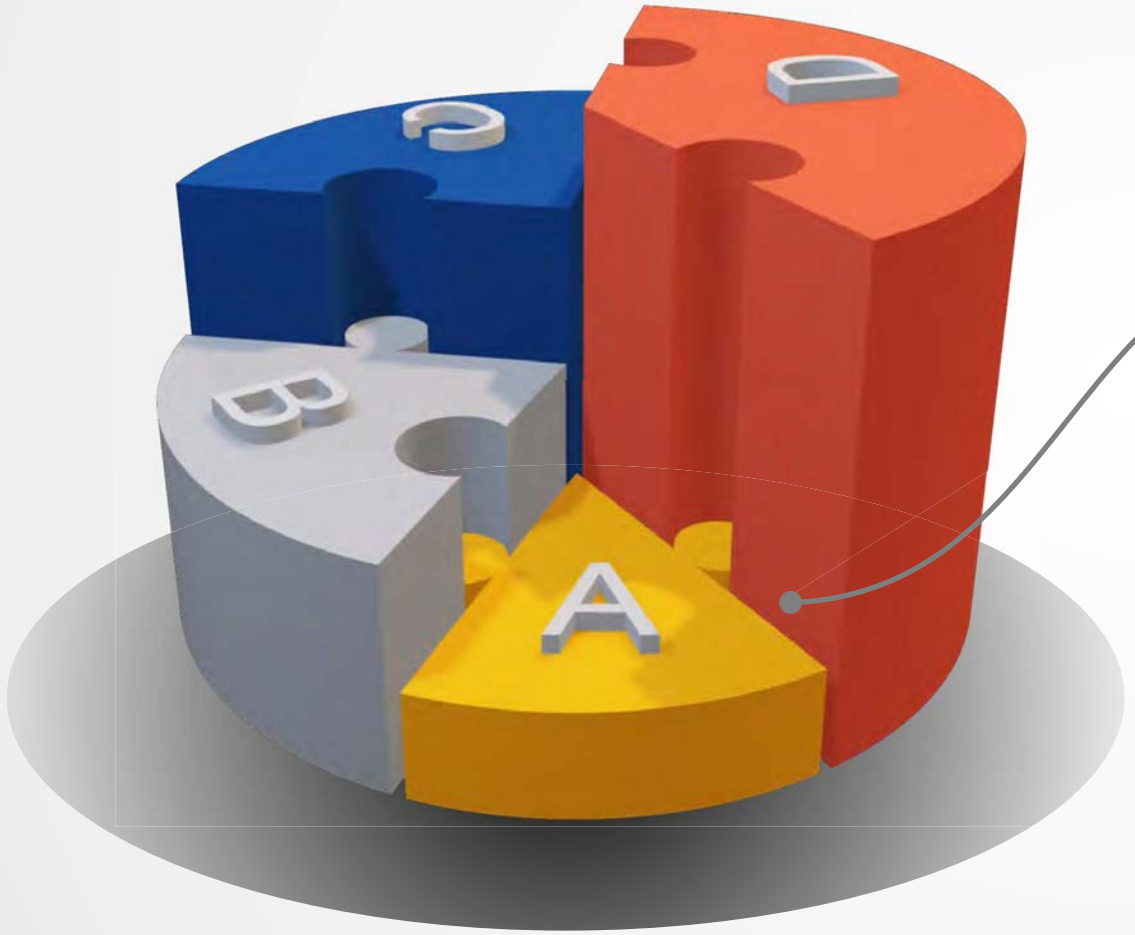
Associate Professor

Institute for Memory Impairments and Neurological Disorders

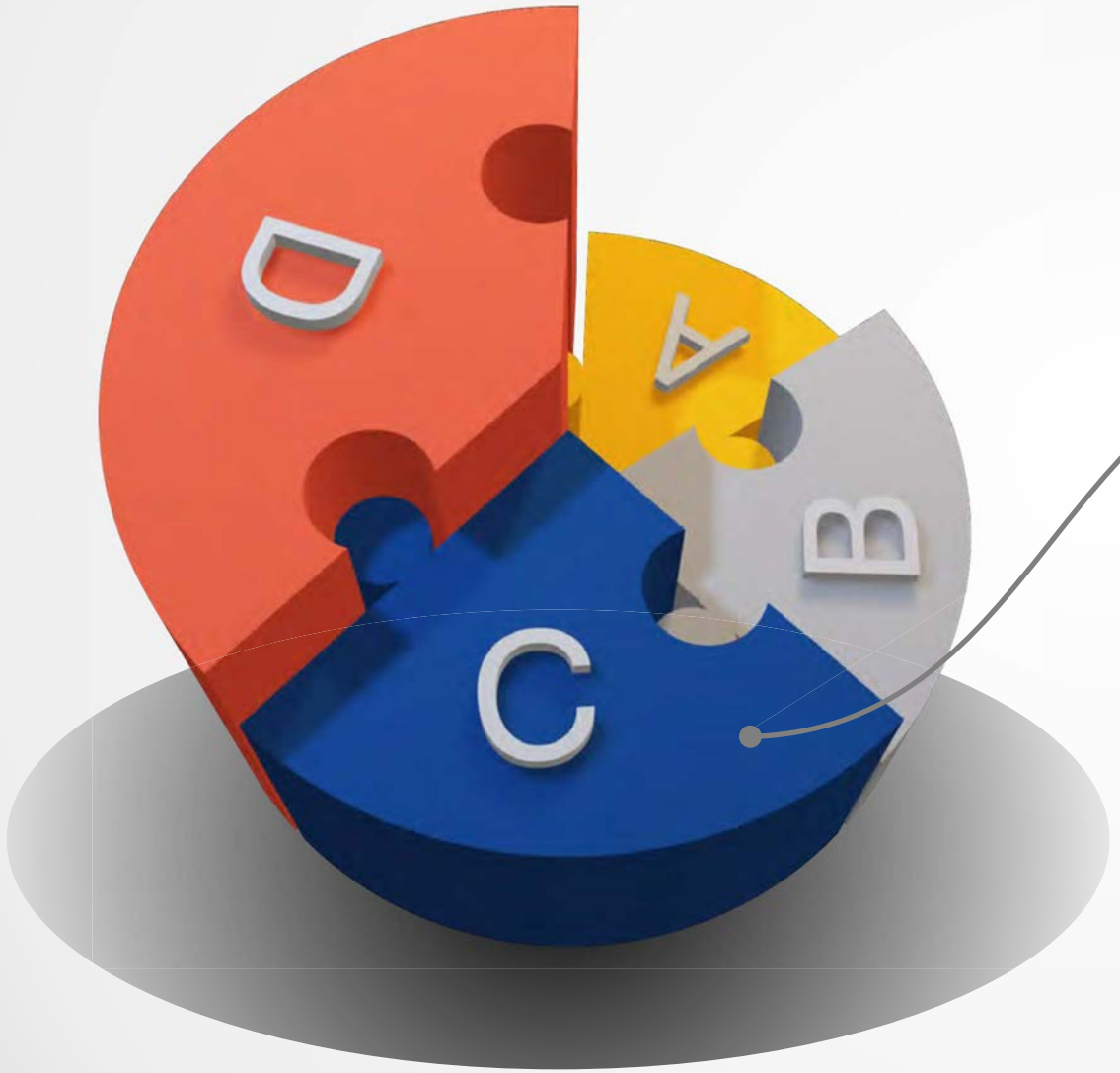
Department of Neurobiology and Behavior

Charlie Dunlop School of Biological Sciences
University of California, Irvine

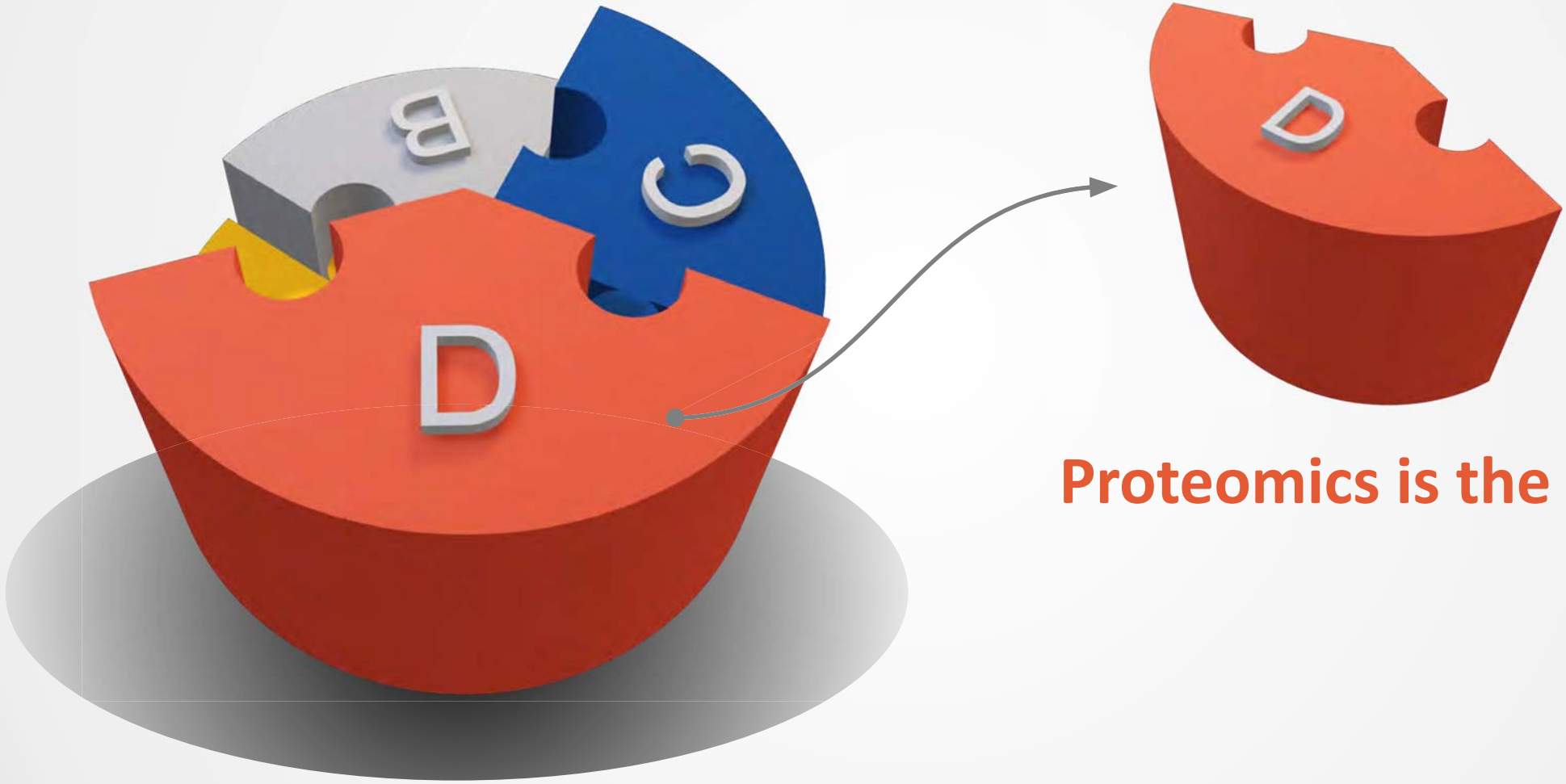
The plan, the promise and the truth …



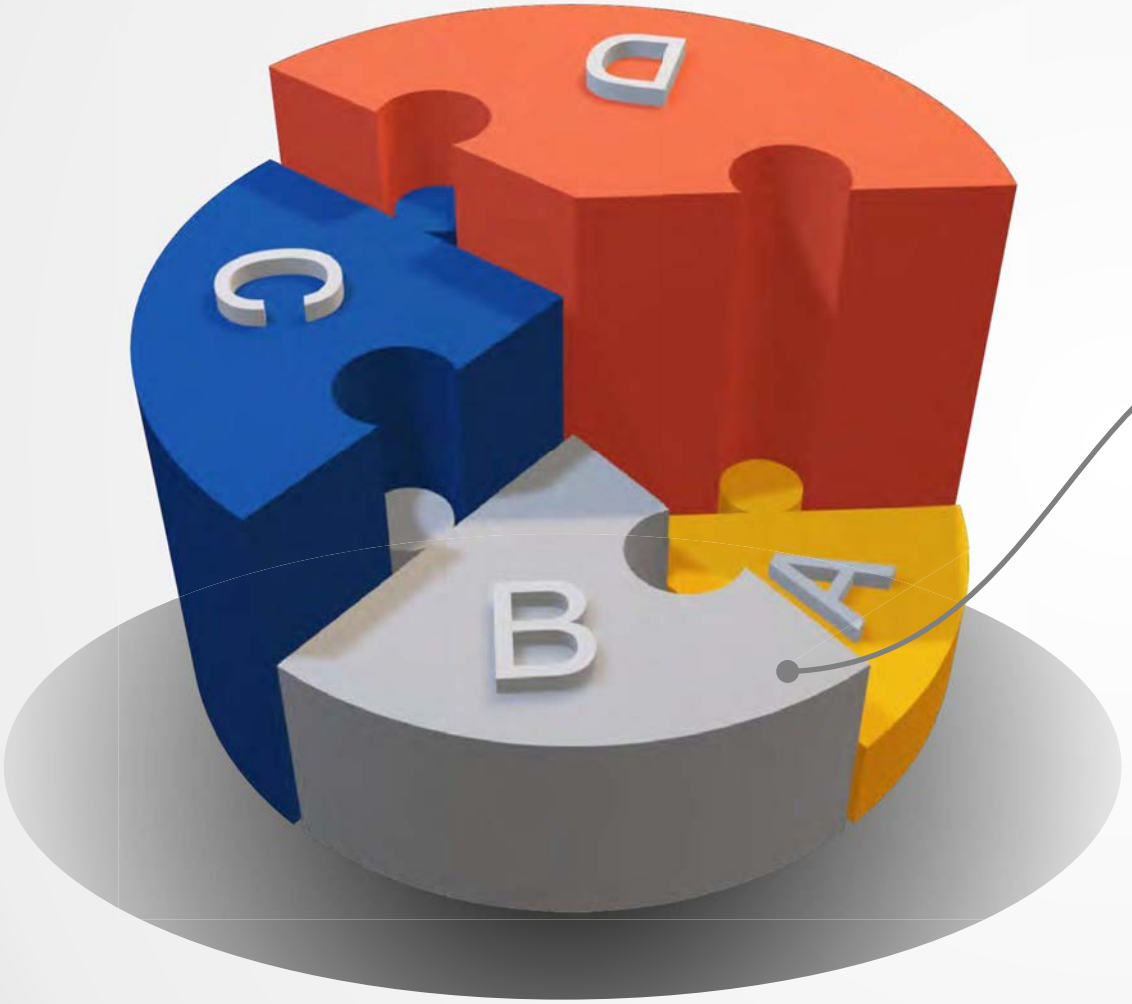
Genetics is the Plan



Transcriptomics is the promise



Proteomics is the truth



Epigenomics is the script

C

The Promise

Transcriptomics

B

The script

Epigenetics

D

The Truth

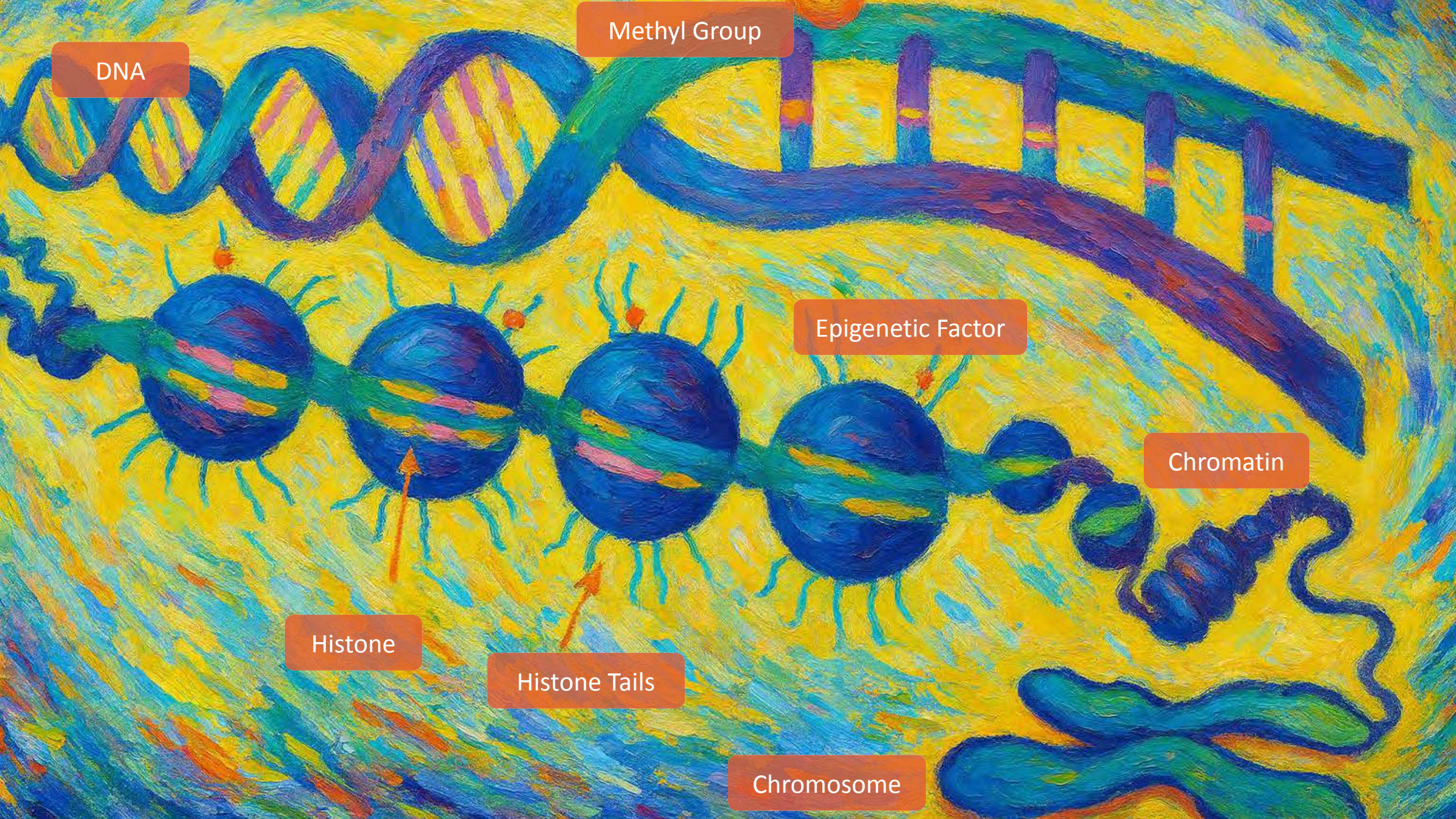
Proteomics

A

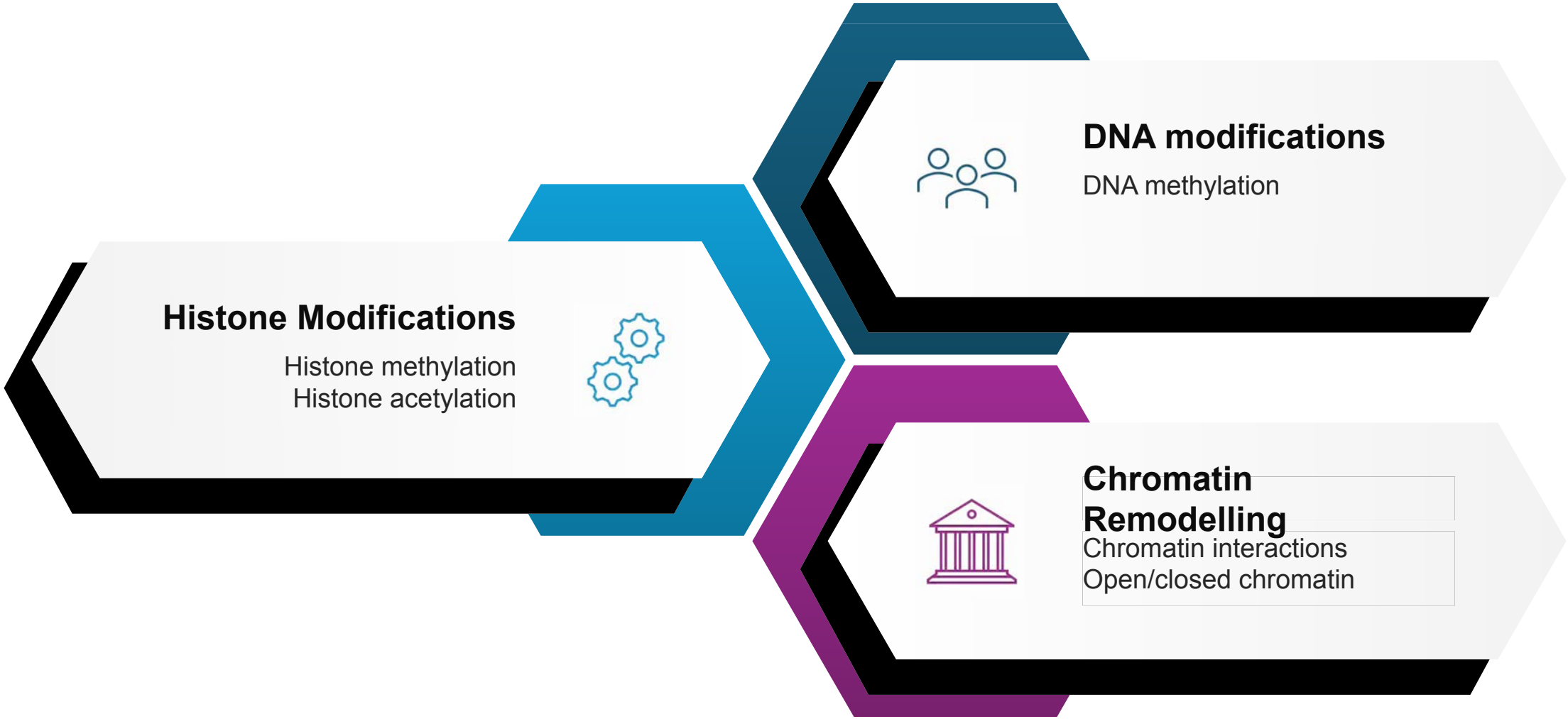
The plan

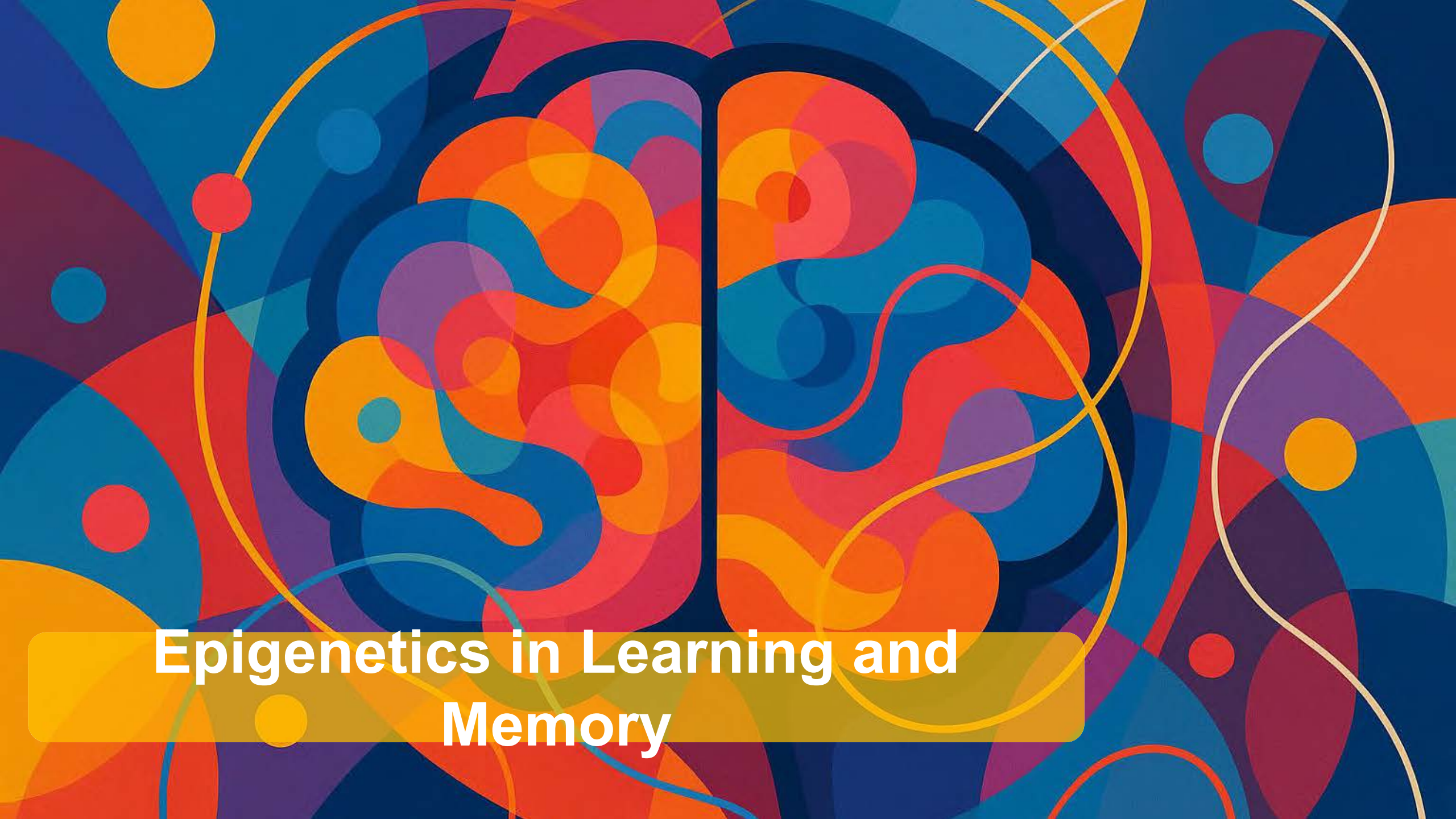
Genetics


Epigenetics is the bookmark and highlights
Epigenetics

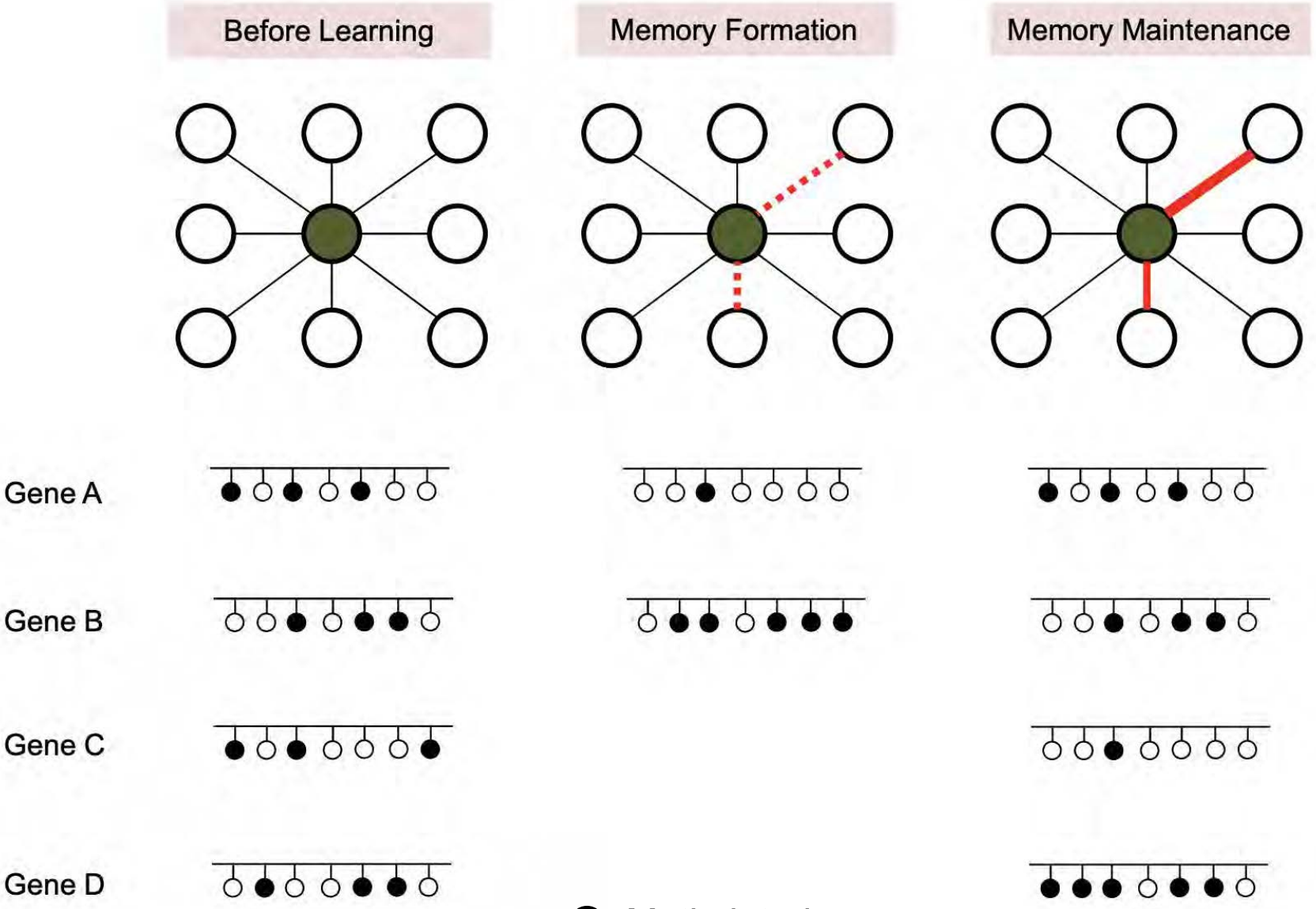

Methyl Group
DNA
Epigenetic Factor
Chromatin
Histone
Histone Tails
Chromosome

Well known DNA epigenetic mechanisms

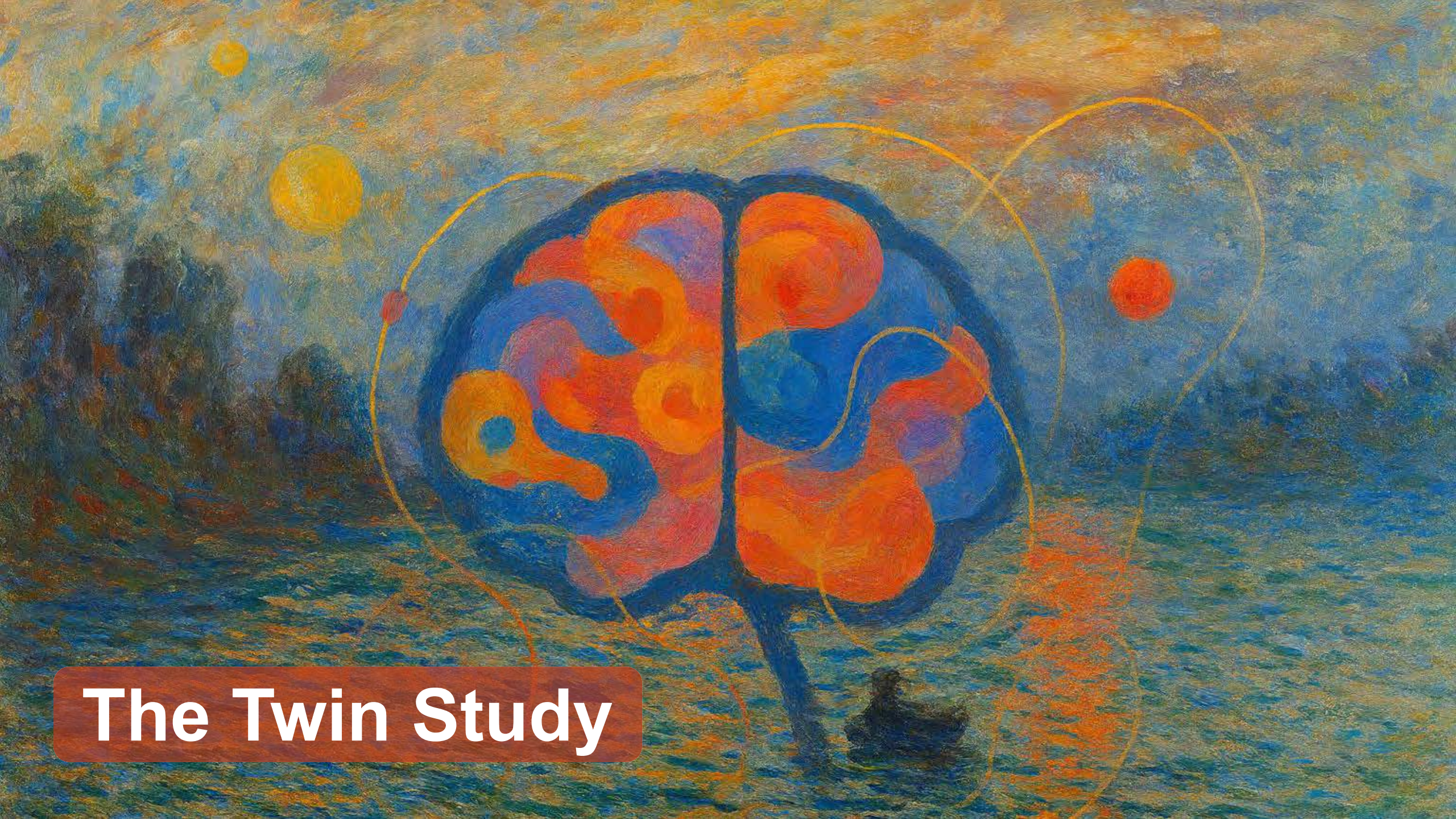




Epigenetics in Learning and Memory

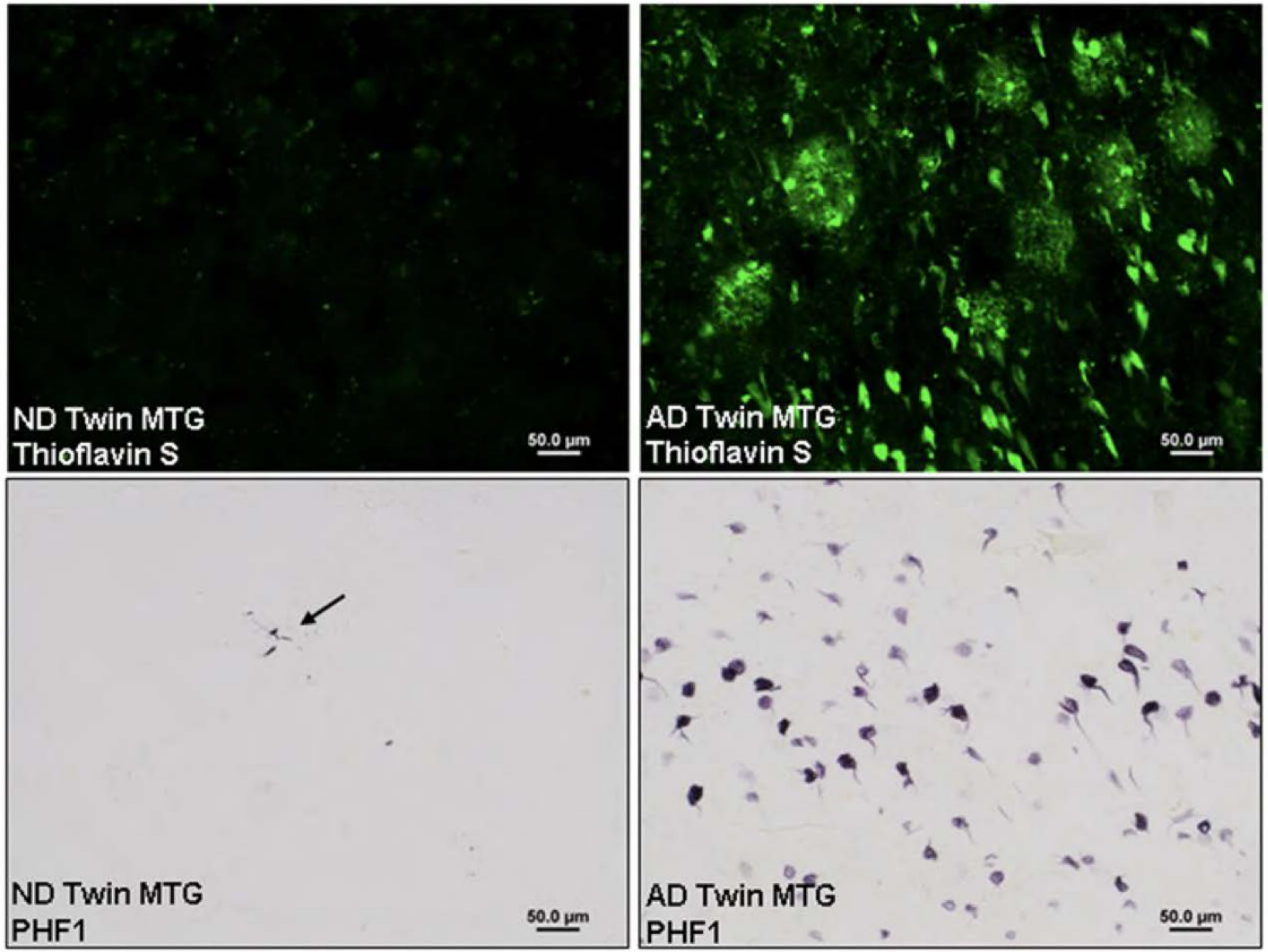


Yu et al. Molecular Brain 2011


The Twin Study

Divergence in Genetically Identical Twins

- **Genetically identical twins with divergent outcomes:** One twin - developed severe, late-onset Alzheimer's disease (Braak VI), while his cognitively intact twin (Braak II) remained disease-free until death, despite identical genetics and similar education/lifestyle.
- **Matched postmortem brain analysis:** Found profound epigenetic differences,



Non-demented Twin

Demented Twin

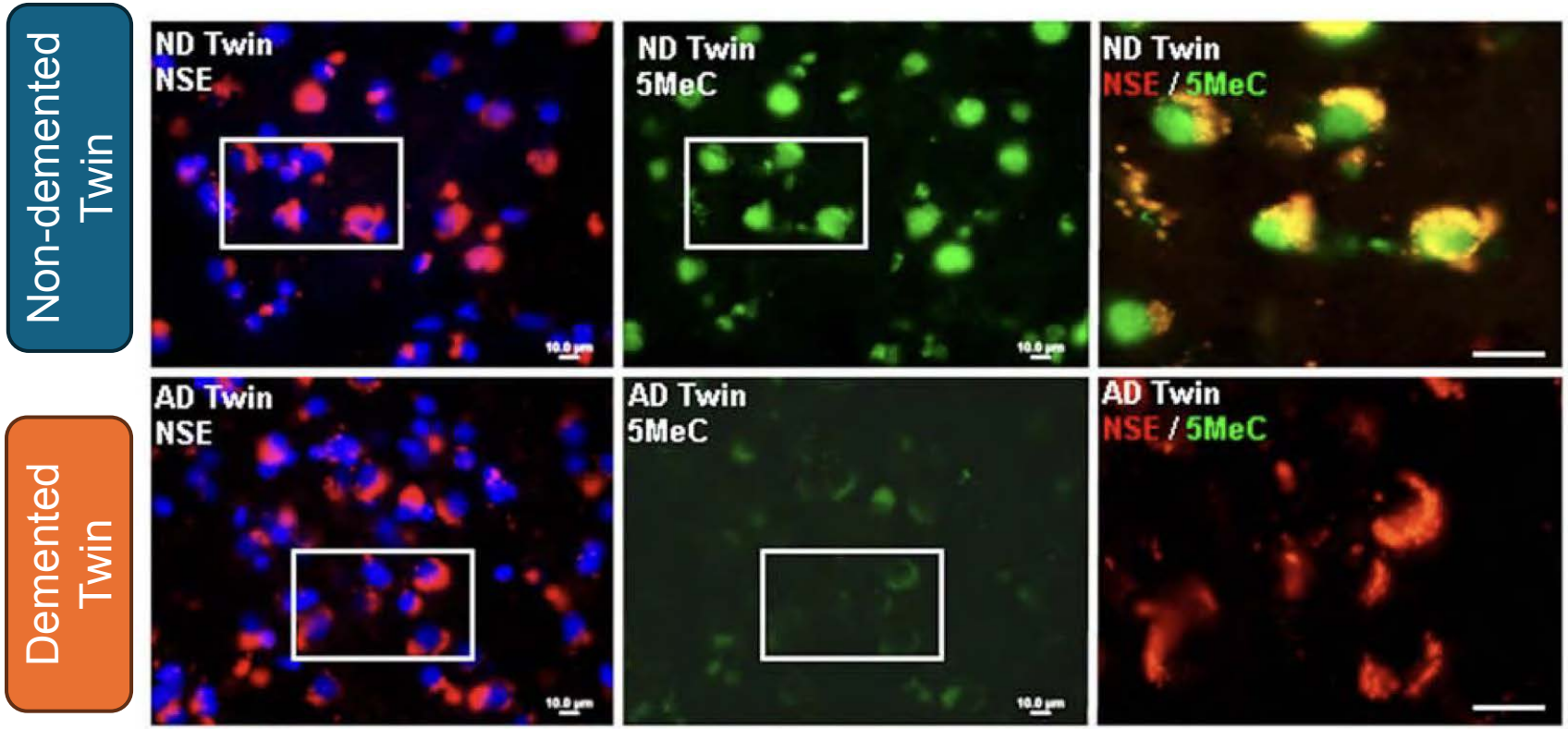
Mastroeni et al., 2009, Plos One

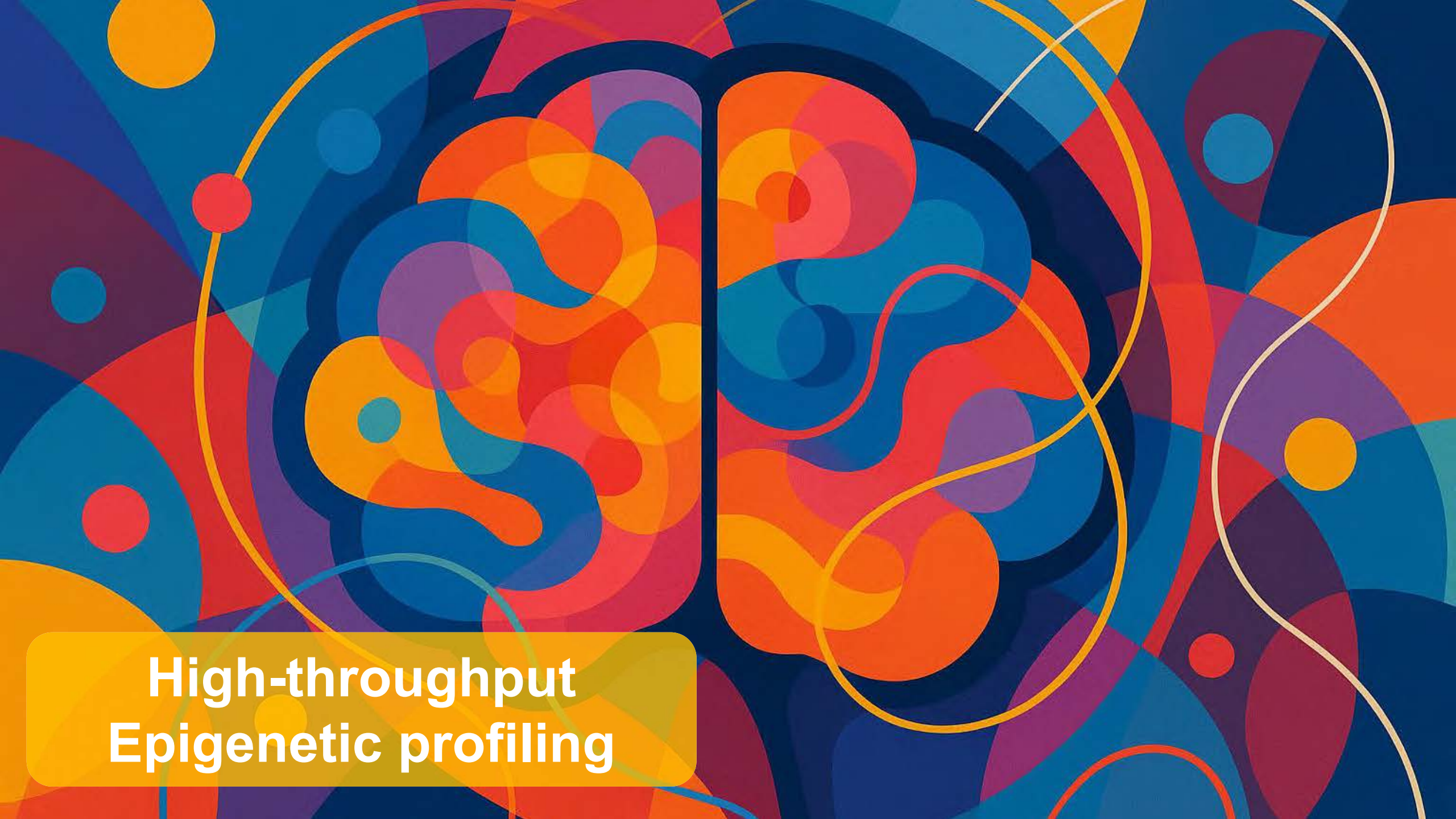
If genes don’t change …

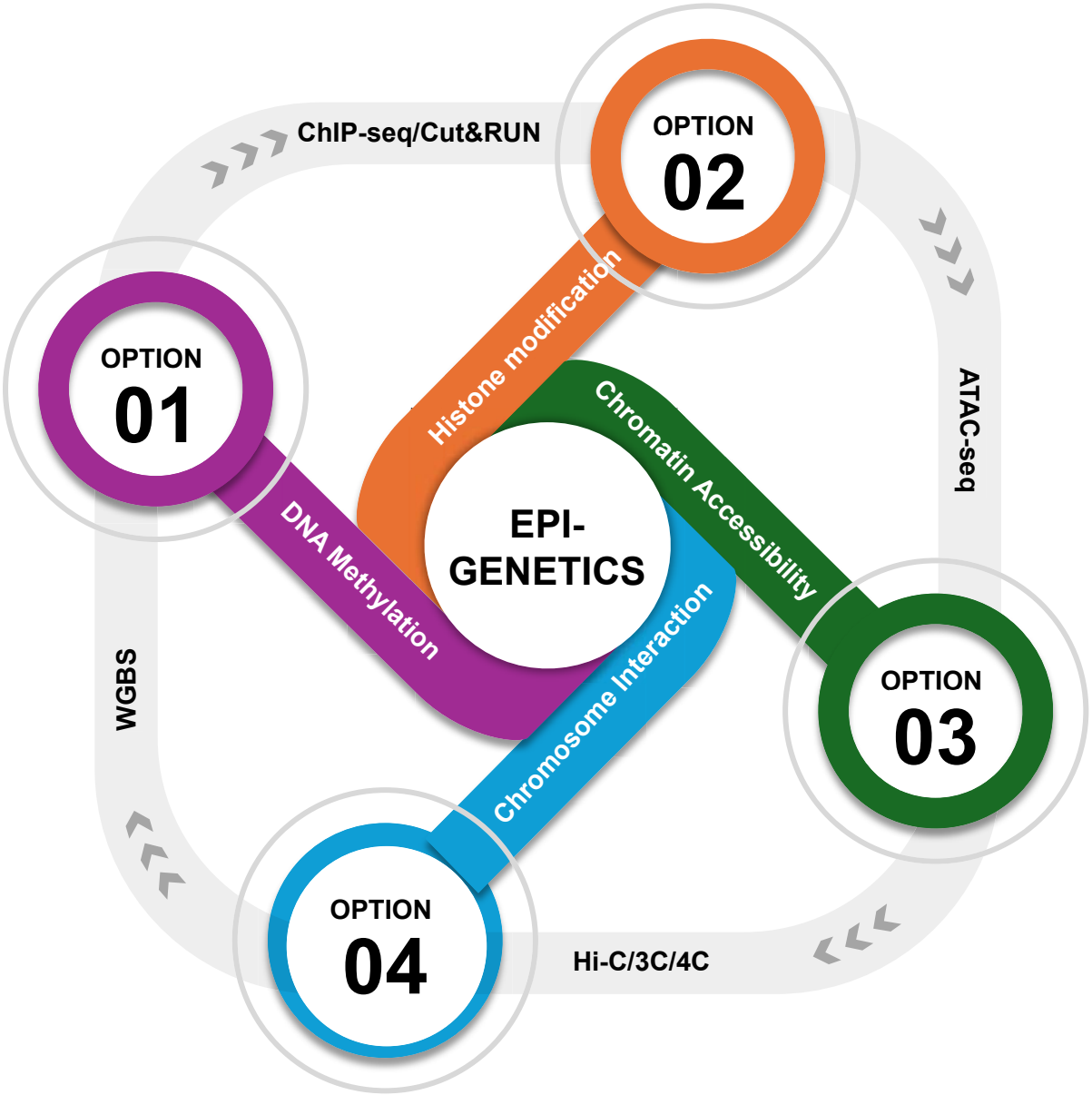
why do identical twins age differently or develop different diseases?

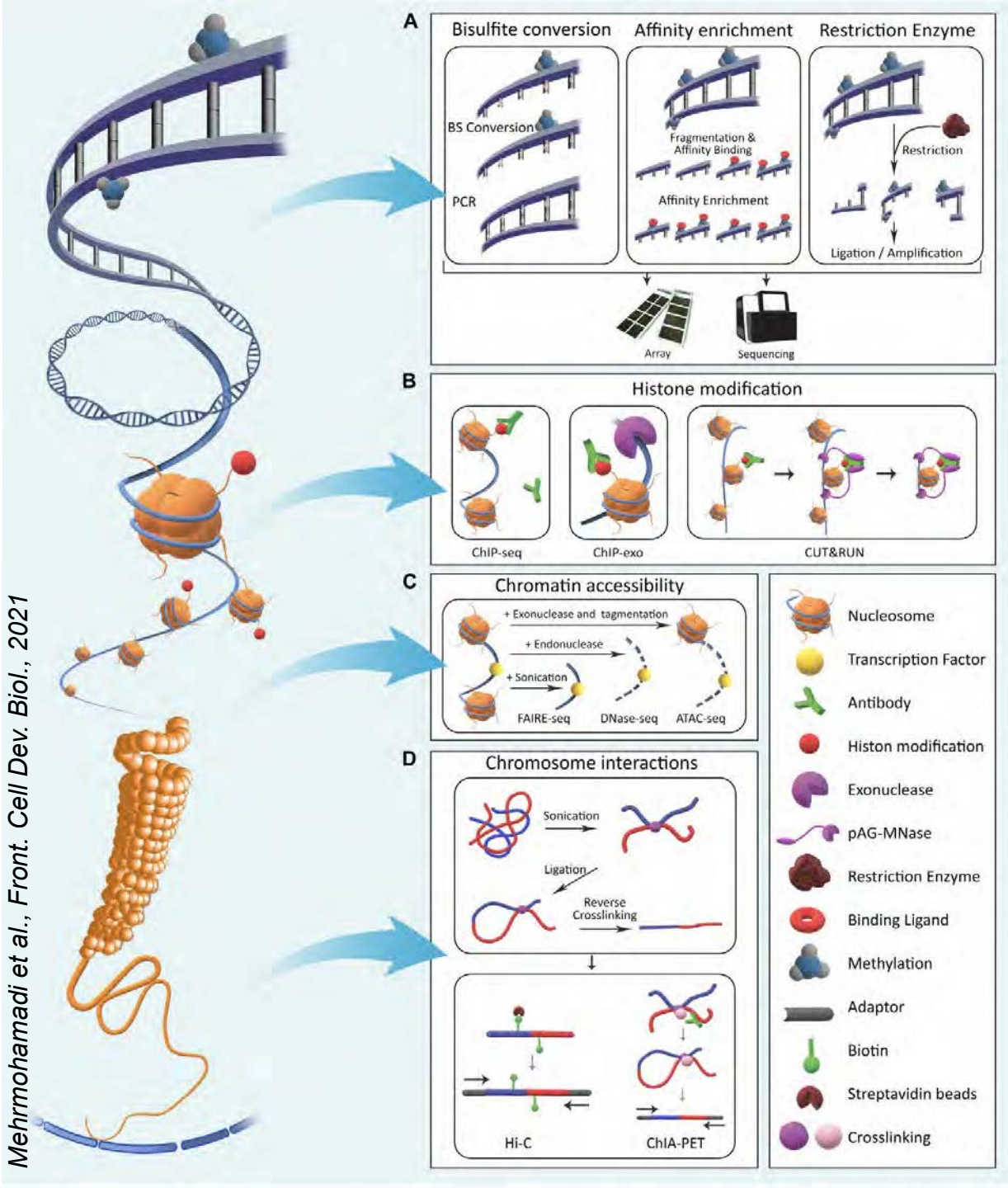
Epigenetic Divergence in Genetically Identical Twins

- **Marked global DNA hypomethylation** in cortical neurons, astrocytes, and microglia of the AD twin compared to the non-demented twin, especially in temporal neocortex .
- **Region- and cell-type specificity:** methylation unchanged in cerebellum but markedly reduced in AD-affected cortical layers II–III, implicating epigenetic dysregulation—not genetics—as a driver of Alzheimer's pathology




High-throughput
Epigenetic profiling

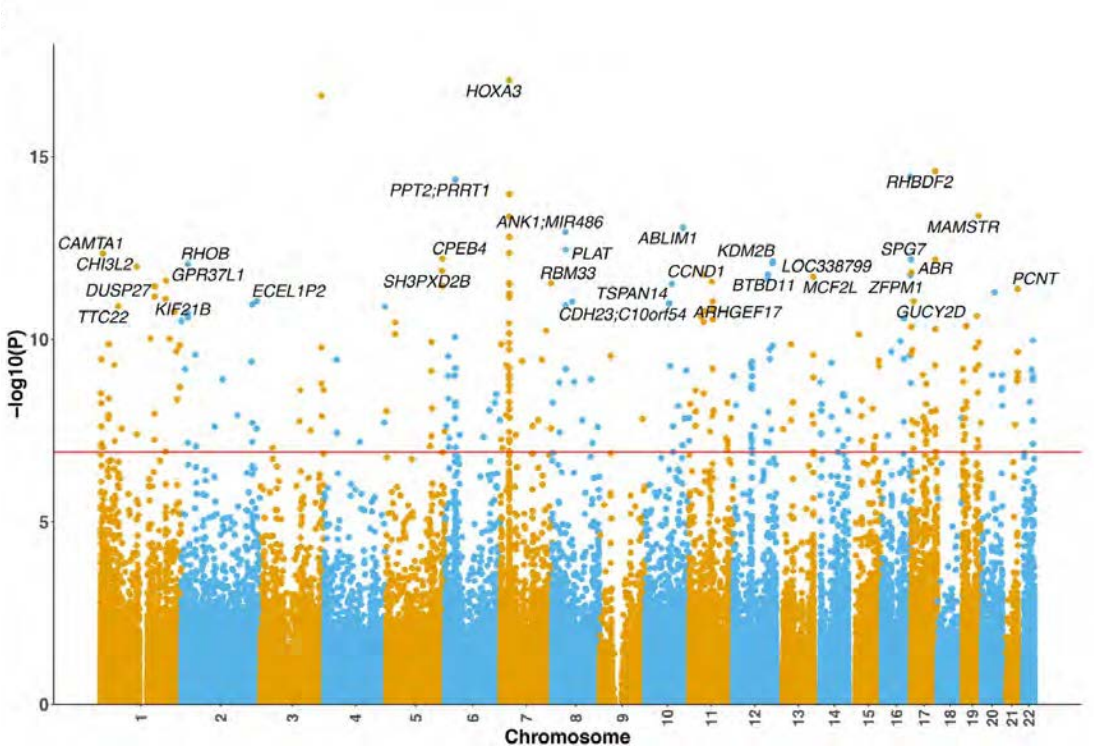

ChIP-seq/Cut&RUN
OPTION 02
OPTION 01
Histone modification
Chromatin Accessibility
DNA Methylation
EPI-GENETICS
ATAC-seq
WGBS
Chromosome Interaction
OPTION 03
OPTION 04
Hi-C/3C/4C


A
Bisulfite conversion
Affinity enrichment
Restriction Enzyme
BS Conversion
PCR
Fragmentation & Affinity Binding
Affinity Enrichment
Restriction
Ligation / Amplification
Array
Sequencing
B
Histone modification
ChIP-seq
ChIP-exo
CUT&RUN
C
Chromatin accessibility
+ Exonuclease and tagmentation
+ Endonuclease
+ Sonication
FAIRE-seq
DNase-seq
ATAC-seq
D
Chromosome interactions
Sonication
Ligation
Reverse Crosslinking
Hi-C
ChIA-PET
Nucleosome
Transcription Factor
Antibody
Histon modification
Exonuclease
pAG-MNase
Restriction Enzyme
Binding Ligand
Methylation
Adaptor
Biotin
Streptavidin beads
Crosslinking
Mehrmohamadi et al., Front. Cell Dev. Biol., 2021


Epigenetics in AD

DNA methylation signatures in AD

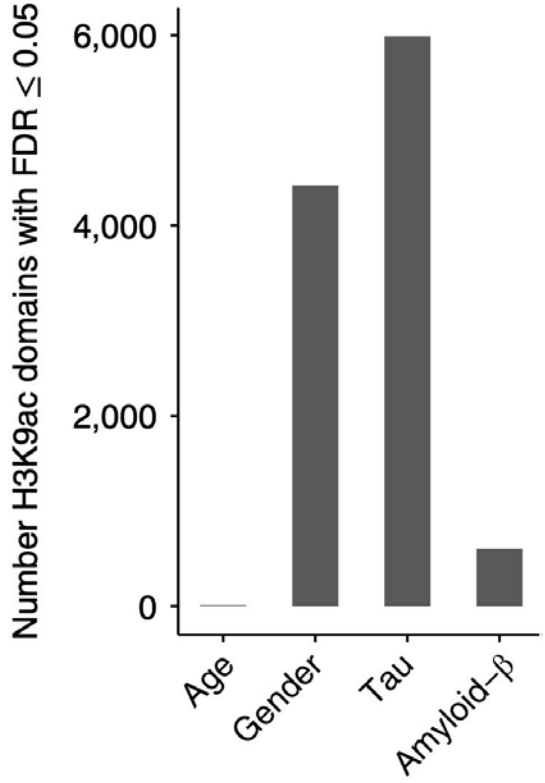
- **Widespread cortical DNA methylation changes** in AD, predominantly **hypermethylation** across 300+ loci, strongest in **non-neuronal (microglial, astrocytic)** populations.
- **Key genes affected:** *ANK1*, *SPI1 (PU.1)*, *HOXA3*, *TNFRSF1A*—linking **immune activation**, **developmental**, and **metabolic** pathways.
- **GO enrichment:** immune regulation, mitochondrial stress, and extracellular matrix remodeling—core **pathogenic axes** of AD.
- **Conclusion:** AD methylomic shifts are **cell-type-specific**, reflecting **glial epigenetic reprogramming** rather than neuronal loss.



Shireby et al., Nat. Comm., 2022
DNA methylation array > 300 samples

Histone modification signatures in A

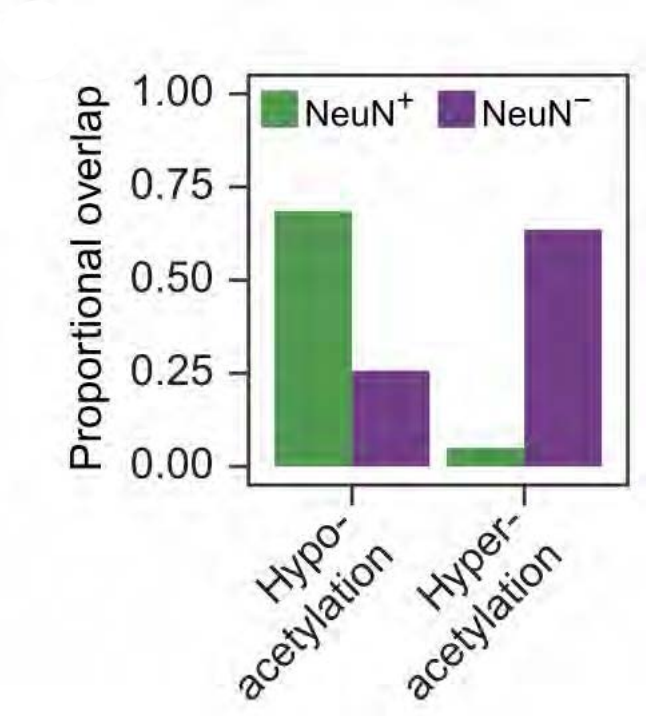
- >600 aged human **dorsolateral prefrontal cortex (DLPFC)** samples from the **Religious Orders Study and Rush Memory and Aging Project (ROS/MAP)**; profiled **H3K9ac** using **ChIP-seq**.
- **Tau drives widespread chromatin remodeling: 23%** H3K9ac domains (***mostly promoters***) associated with **tau burden**, but only 2% with amyloid-β; tau effects extended across multi-megabase genomic segments reflecting higher-order chromatin architecture .
- Corresponding **RNA-seq (n = 500)** from the same brains showed coordinated transcriptional shifts within these segments (ρ = 0.83 with H3K9ac), linking **tau pathology to altered transcription through chromatin restructuring** .



Klein et al., Nat. Neuro., 2019

3D chromatin dysregulation in AD

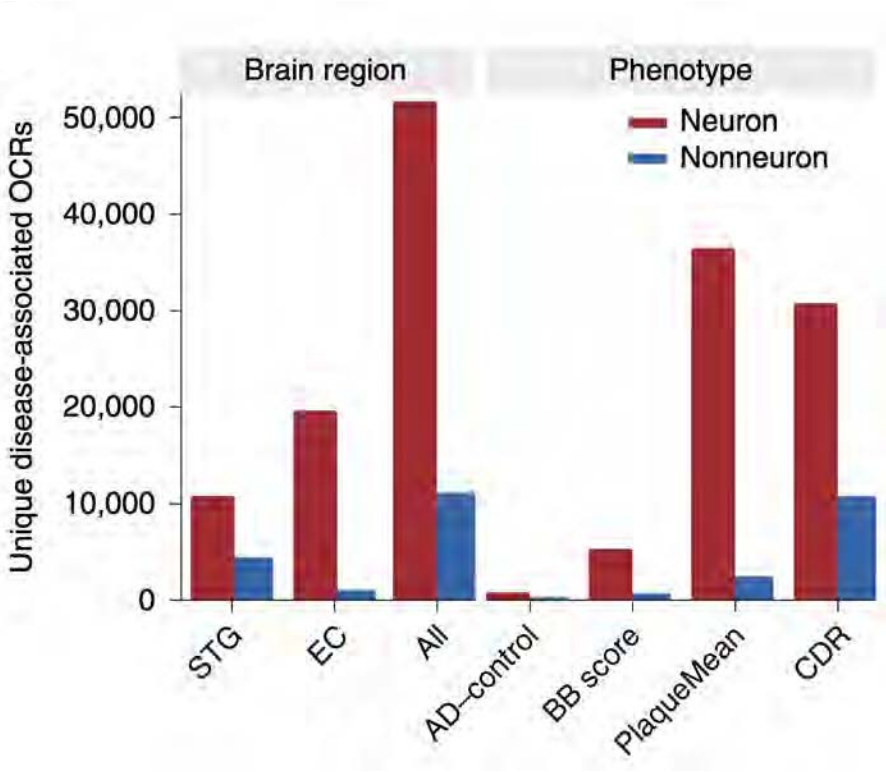
- Generated **Hi-C maps from sorted NeuN⁺ (neuronal) and NeuN⁻ (glial) nuclei** isolated from **four human dorsolateral prefrontal cortex (DLPFC)** samples; integrated with **H3K27ac ChIP-seq and RNA-seq** to construct **cell-type-specific 3D chromatin interaction maps** .
- AD-associated **hypoacetylation** localized to **neuronal enhancers (NeuN⁺)** → downregulation of synaptic genes; **hyperacetylation** confined to **glial enhancers (NeuN⁻)** → upregulation of astrocytic and oligodendrocytic genes .
- **AD GWAS heritability** enriched in **NeuN⁻ (glial) enhancers**, and **Hi-C–based H-MAGMA** identified **181 AD risk genes**, including *BIN1*, whose promoter interacts with AD risk loci specifically in glia .
- Together, findings reveal **cell-type-specific regulatory mechanisms in AD—genetic risk converges on microglia**, while **epigenetic remodeling involves astrocyte/oligodendrocyte activation** and **neuronal repression** .



Hu et al., Nat. Comm., 2021

Open-chromatin alterations in AD

- **ATAC-seq on NeuN⁺ (neuronal) and NeuN⁻ (non-neuronal) nuclei** from **entorhinal cortex (EC) and superior temporal gyrus (STG)** in the **MSBB-AD** cohort (**209 individuals; 636 libraries**), integrated with bulk RNA-seq and whole-genome data.
- Robust **disease-linked differences in open chromatin regions (OCRs)**, especially in **EC neurons**, highlighting **regional and cell-type specificity**.
- OCRs linked to target genes, explaining variance in expression and revealing **cell-specific enhancer–gene relationships** relevant to AD pathways.
- Definition of **cis-regulatory domains (CRDs)** and their **AD-related perturbations**, suggesting **higher-order regulatory reorganization** beyond single enhancers.



Bendl et al., Nat. Neuro., 2022

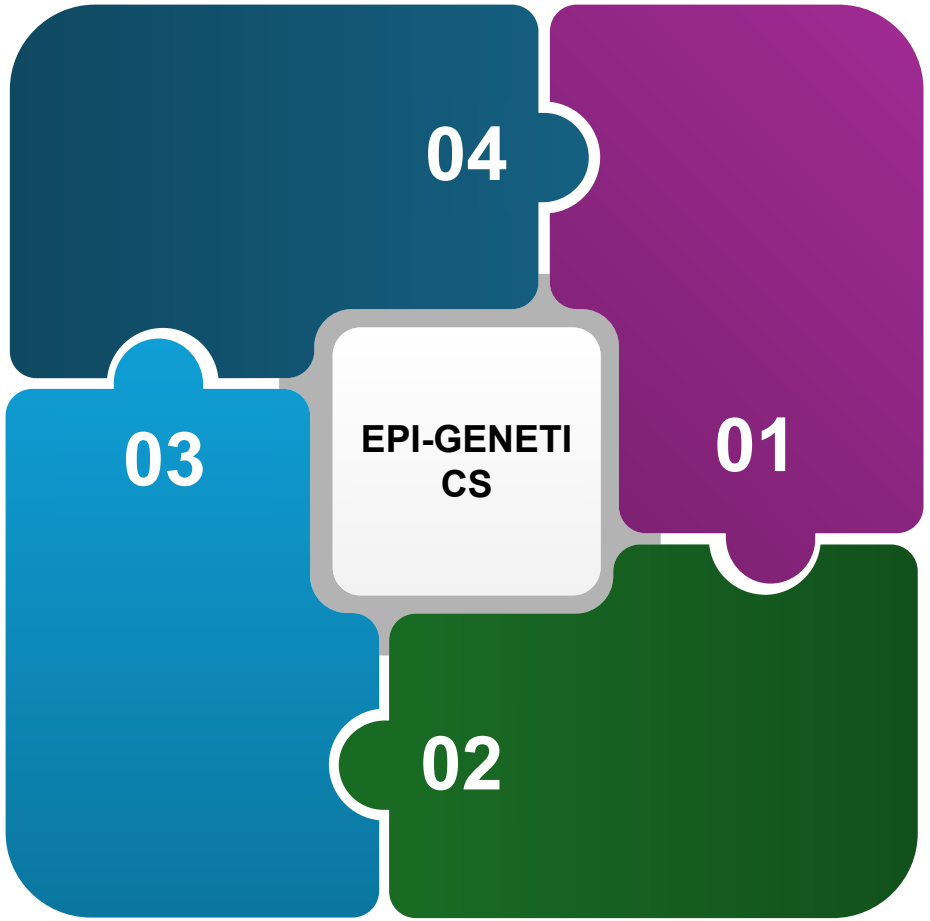
Summary

3D genome

Glial enhancer reorganization

Chromatin accessibility

Region-specific enhancer shifts



Histone acetylation

Tau-driven chromatin remodeling

DNA methylation

Glial hypermethylation signatures

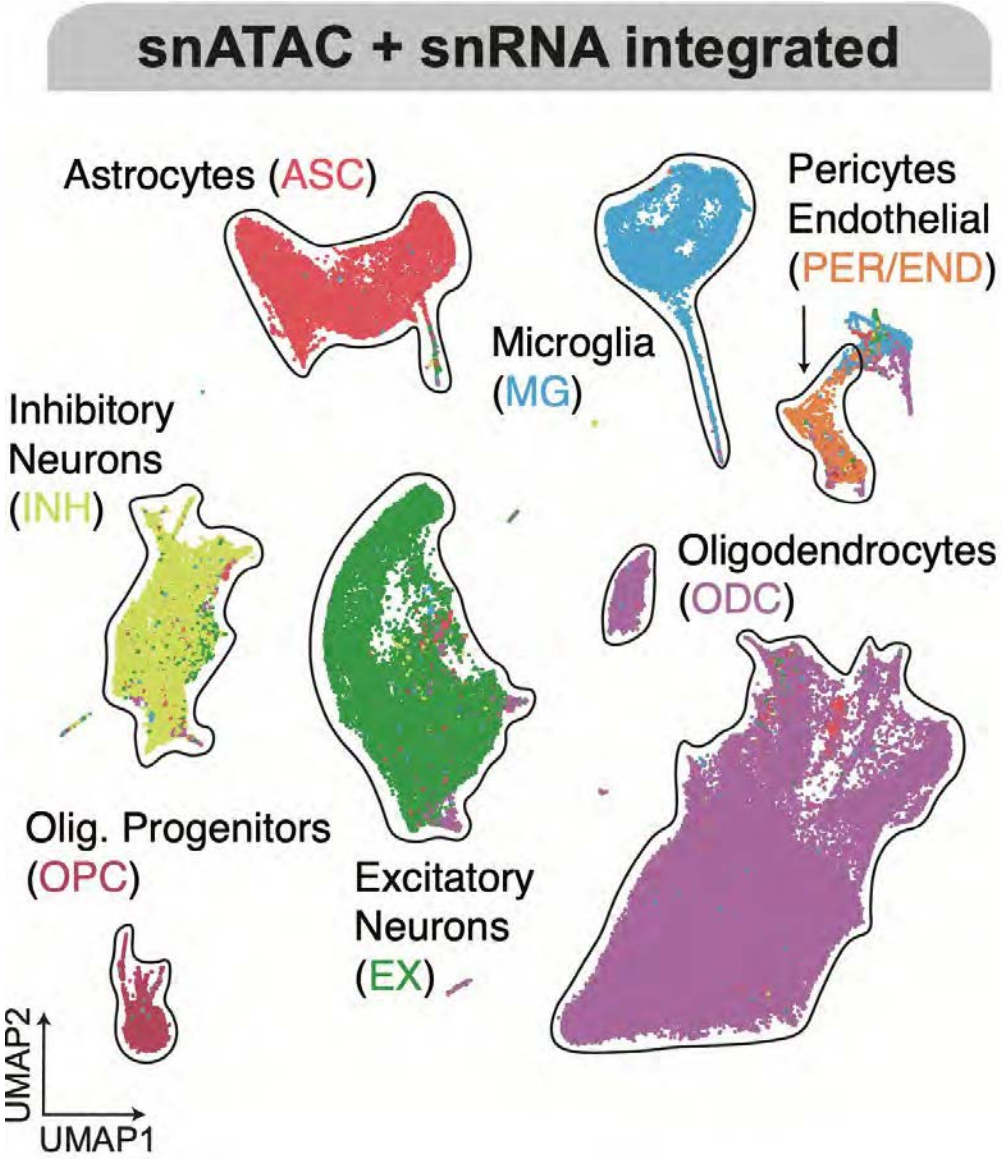
Bulk

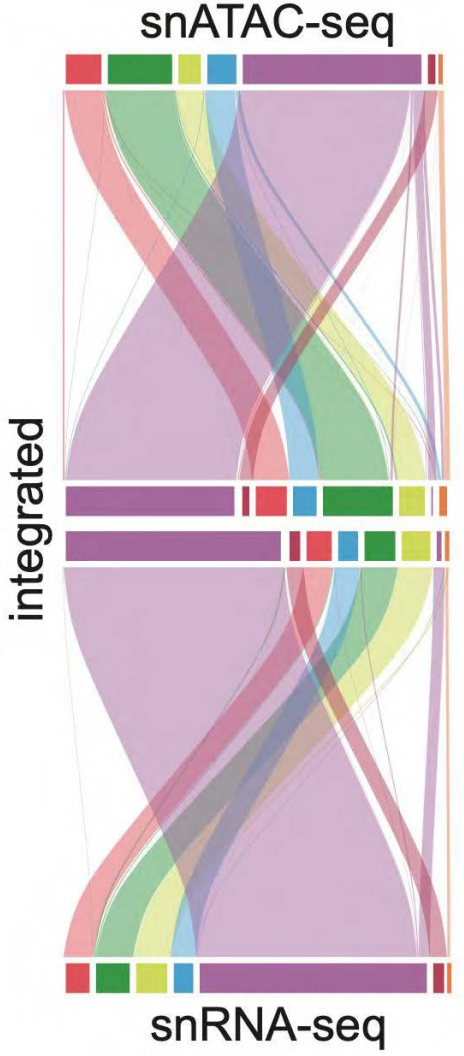
Single Cell

Spatial

The next evolution in epigenetics

Single-cell multi-omics in AD

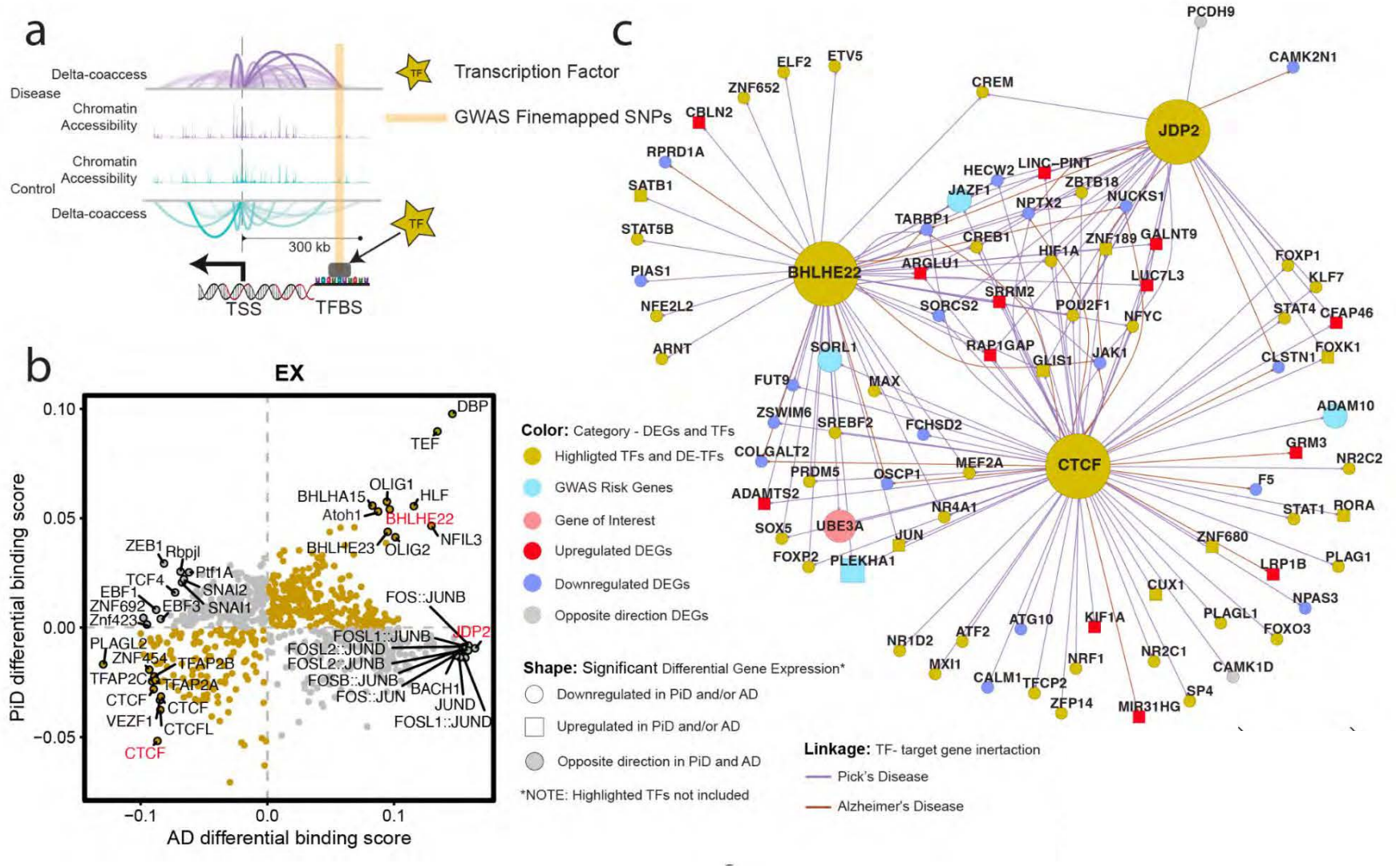




>192,000 nuclei

Morabito et al., Nature Genetics, 2021

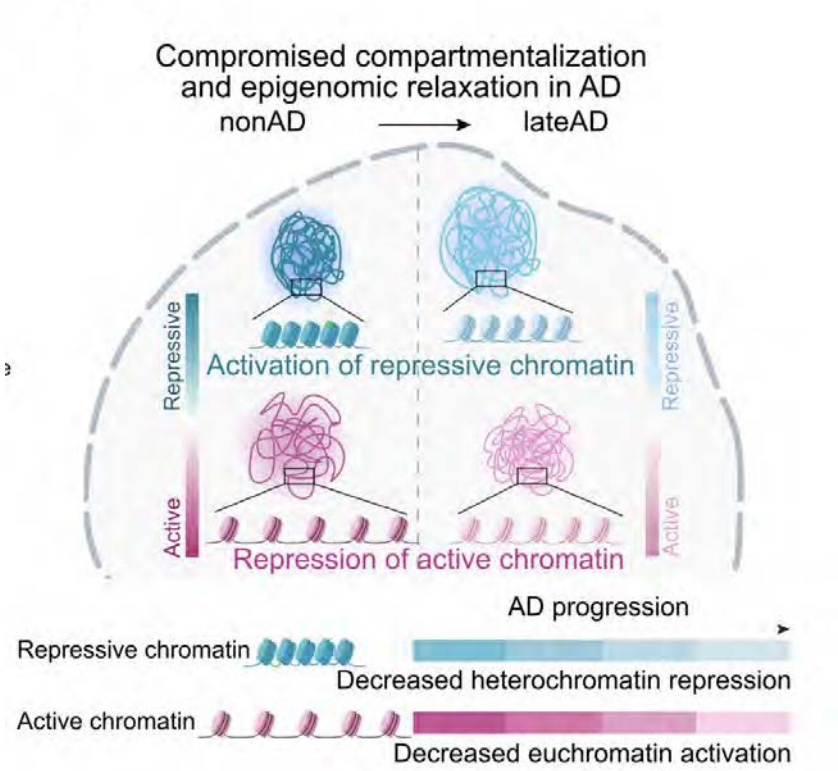
TF regulation in AD



Shi, Das … Swarup, et al., Science Advance, In Press

Epigenomic rewiring in AD

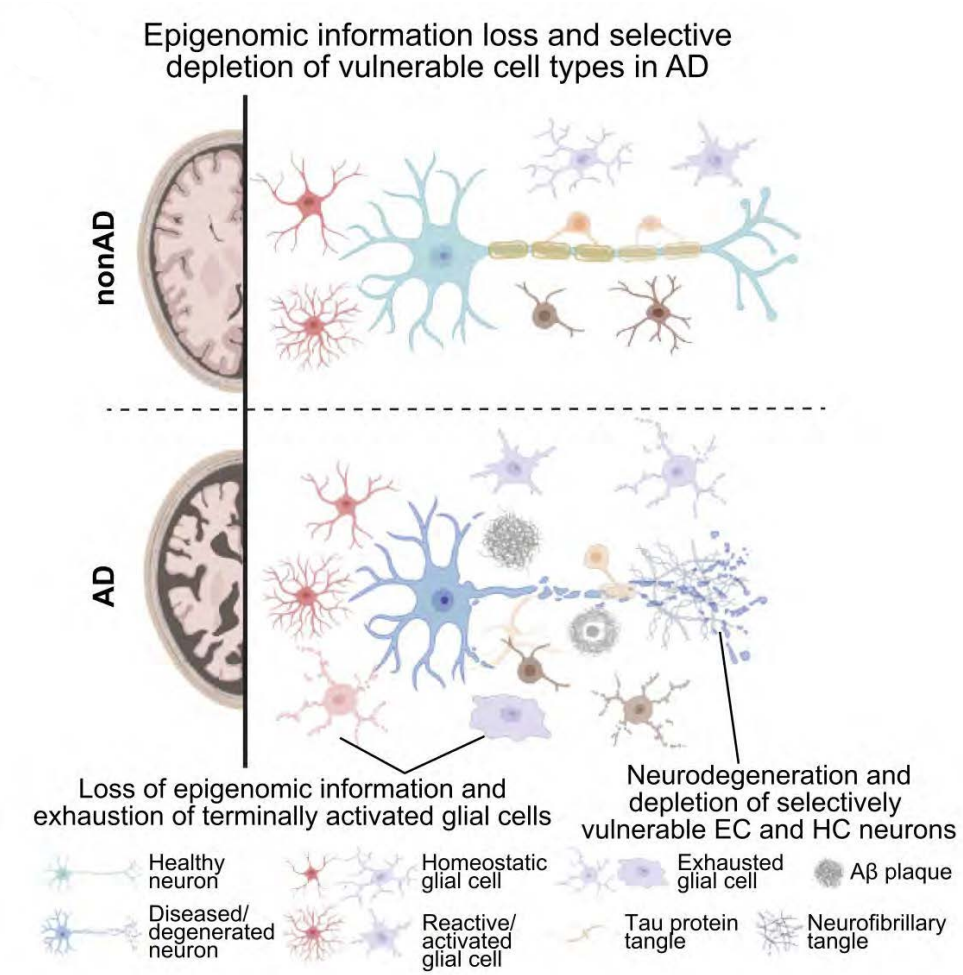
- Generated a single-cell multiomic atlas of **3.5 million nuclei** from **six brain regions** across **111 individuals** using **snATAC-seq, snRNA-seq, and multiome** profiling.
- During Alzheimer's progression, **repressive chromatin becomes activated** while **active chromatin becomes silenced**, reflecting large-scale epigenomic dysregulation.
- **Loss of chromatin compartmentalization** leads to **epigenomic relaxation** and **transcriptional instability**, driving neuronal vulnerability and cognitive decline.



Liu et al., Cell., 2025

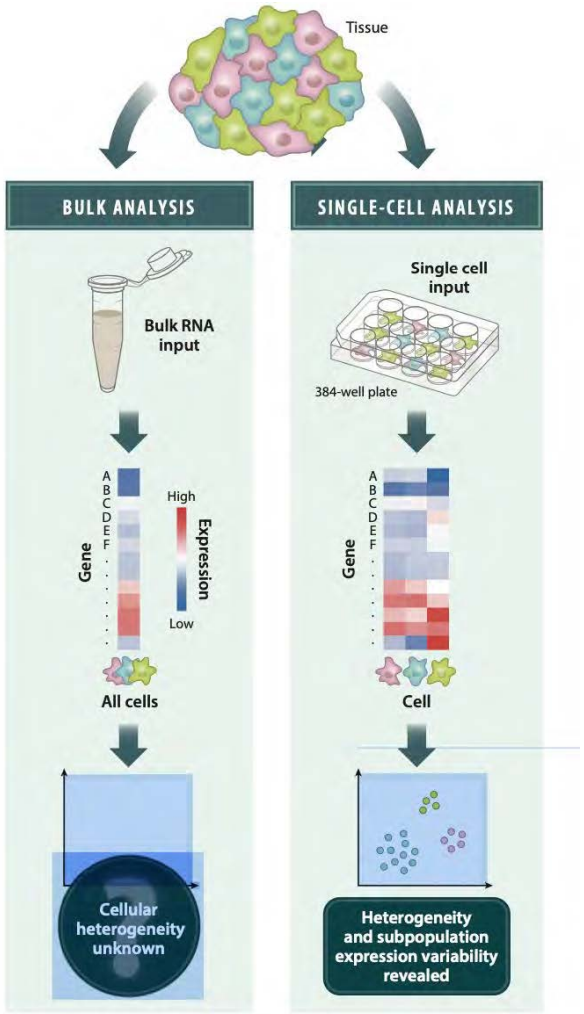
Epigenomic rewiring in AD

- AD progression leads to **loss of epigenomic information** and **exhaustion of activated glial cells**.
- **Reactive glia fail to maintain homeostasis**, contributing to tissue inflammation and degeneration.
- **Selective neuronal loss** occurs in **entorhinal and hippocampal regions**, driving **neurodegeneration and cognitive decline**.

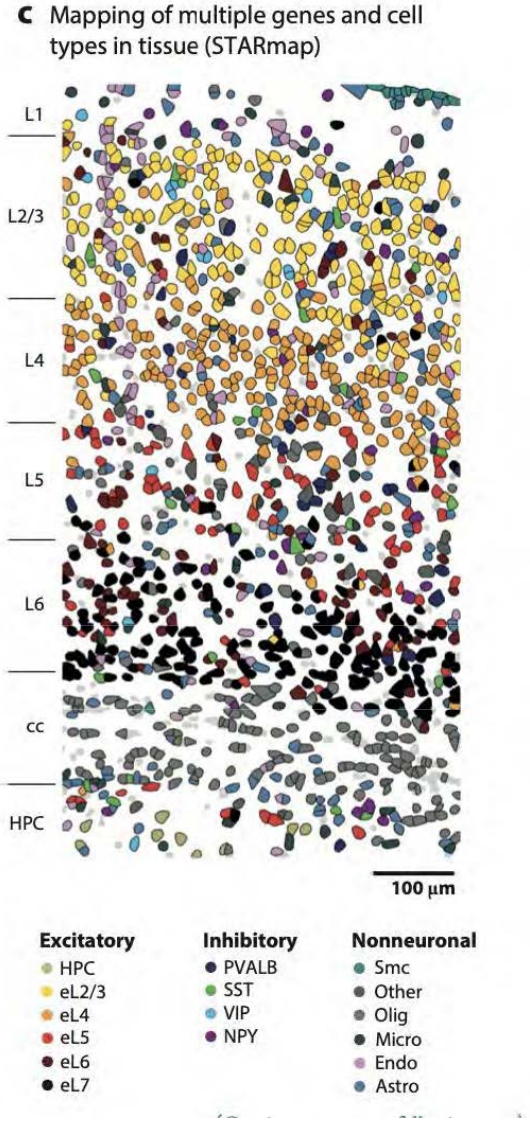


Liu et al., Cell., 2025

imitations of single-cell approaches

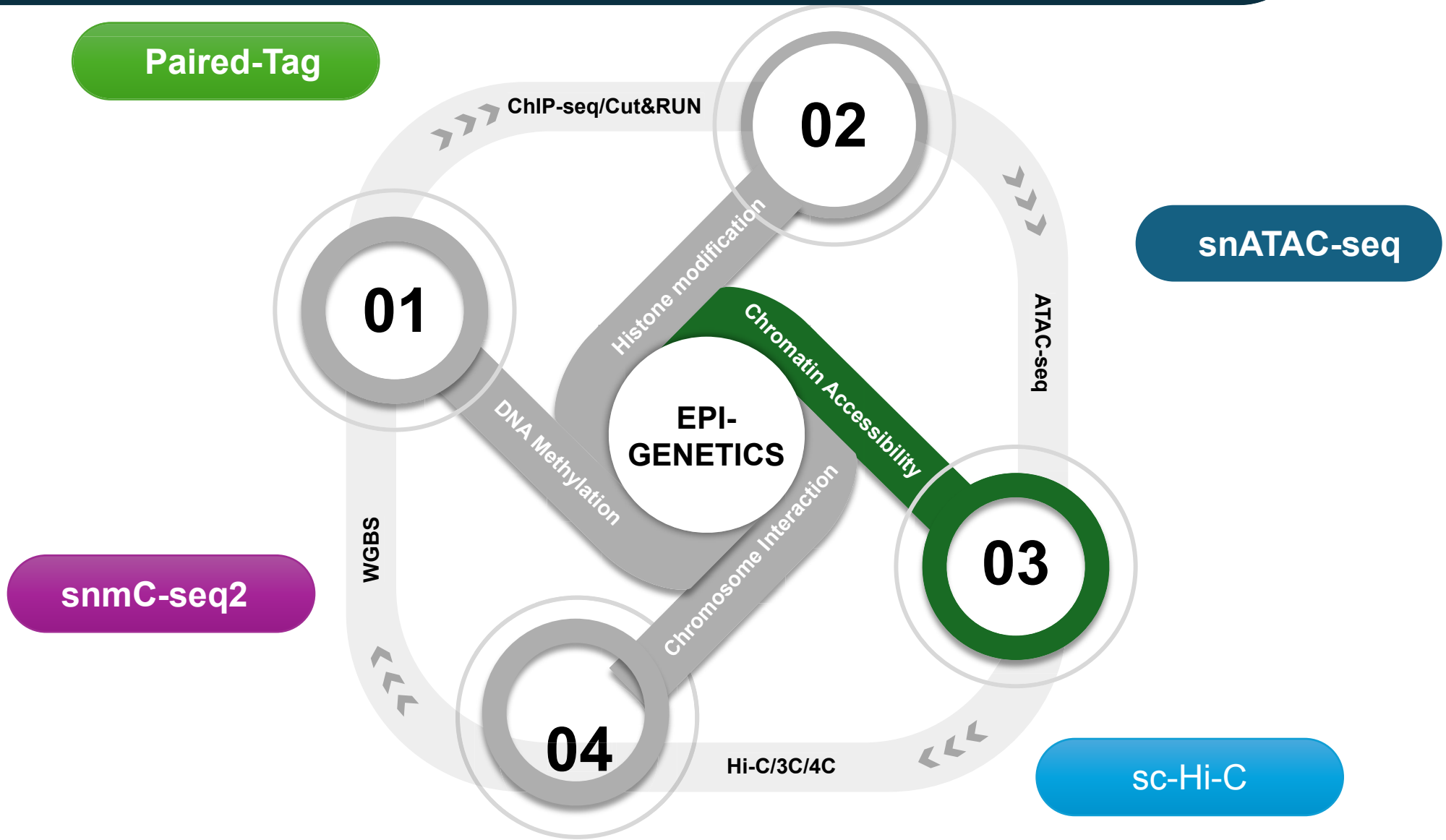


Spatial Epigenomics



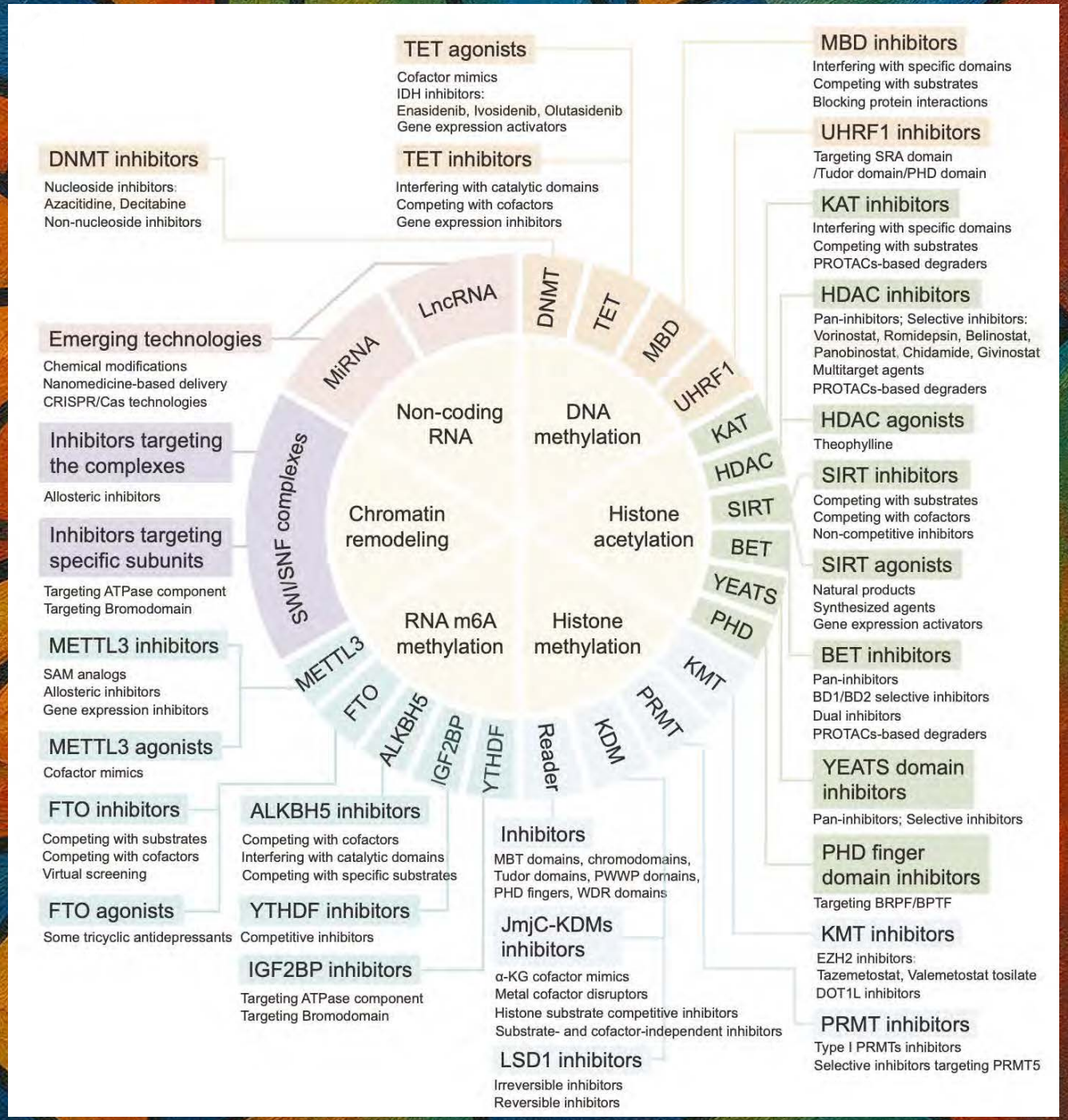
Ortiz et al., Ann. Rev. Neuroscience, 2021

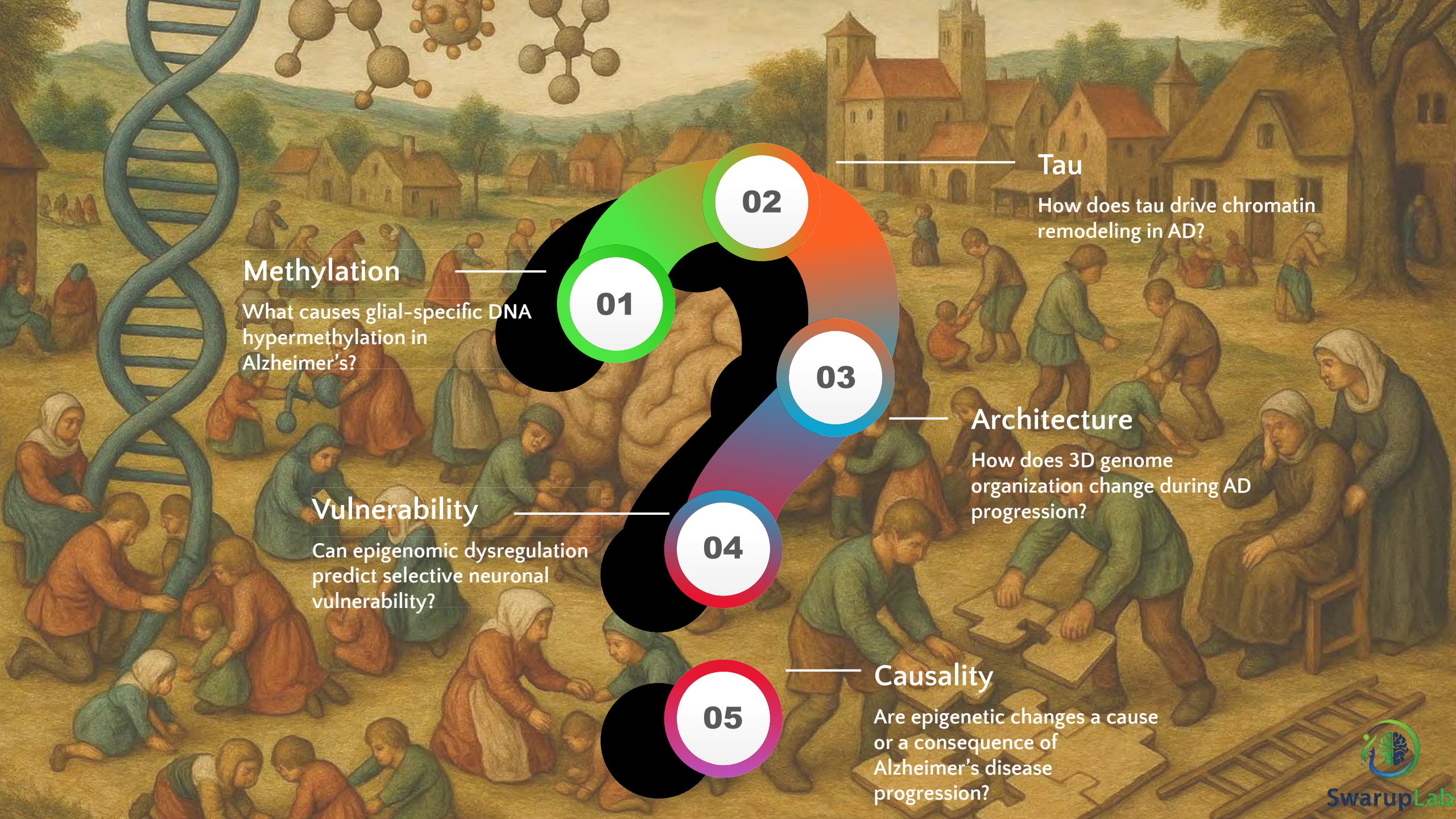
Limitations of single-cell approaches




THERAPEUTICS

Epigenetics in Therapeutics




01
Methylation
What causes glial-specific DNA hypermethylation in Alzheimer's?
02
Tau
How does tau drive chromatin remodeling in AD?
03
Architecture
How does 3D genome organization change during AD progression?
04
Vulnerability
Can epigenomic dysregulation predict selective neuronal vulnerability?
05
Causality
Are epigenetic changes a cause or a consequence of Alzheimer's disease progression?
SwarupLab