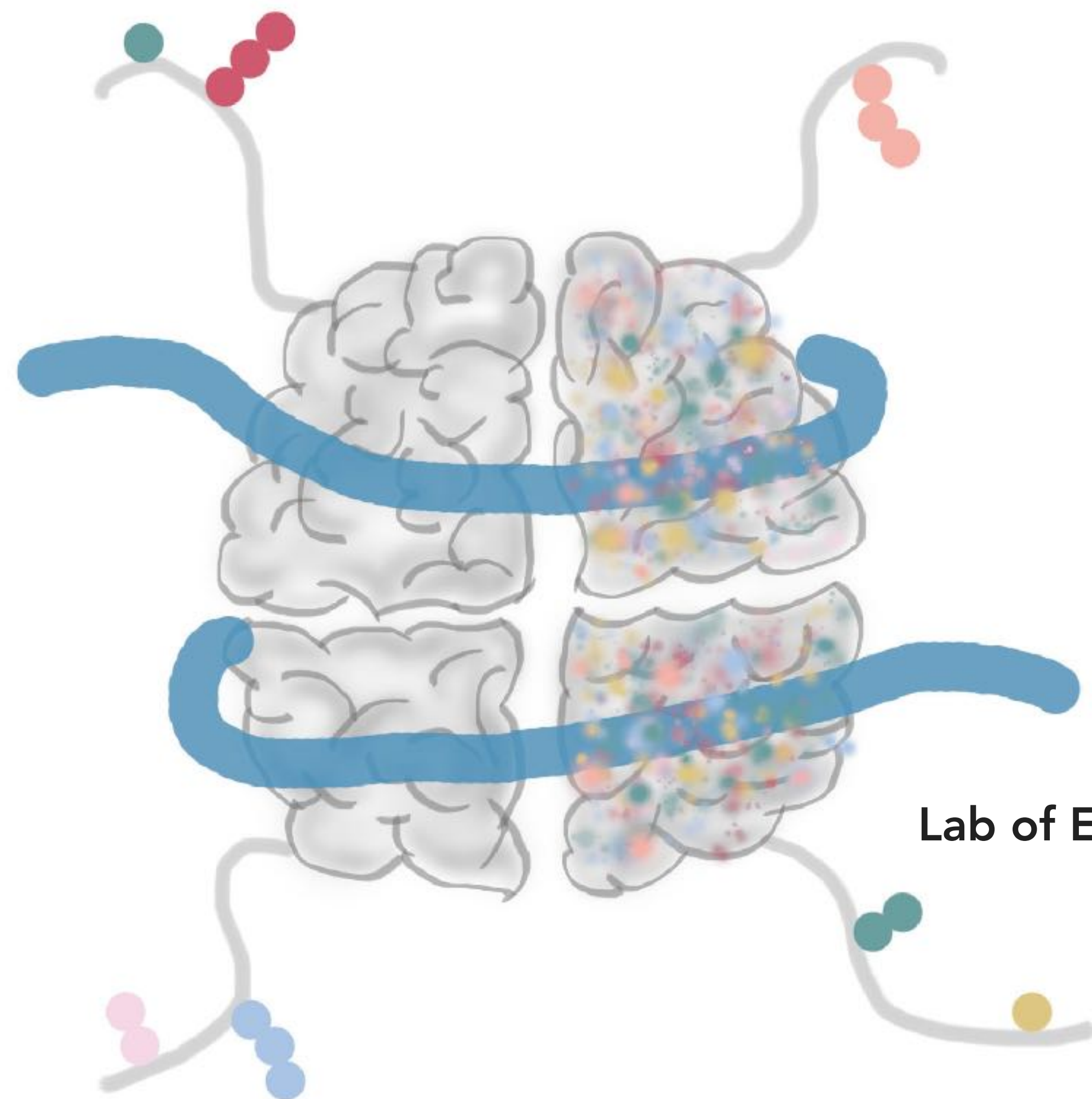


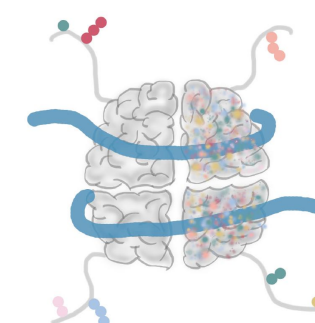


Epigenetic regulation of early human brain development

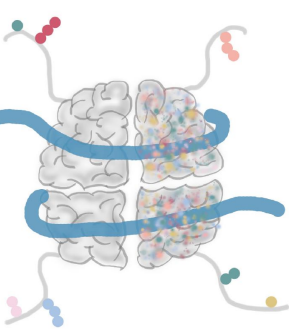
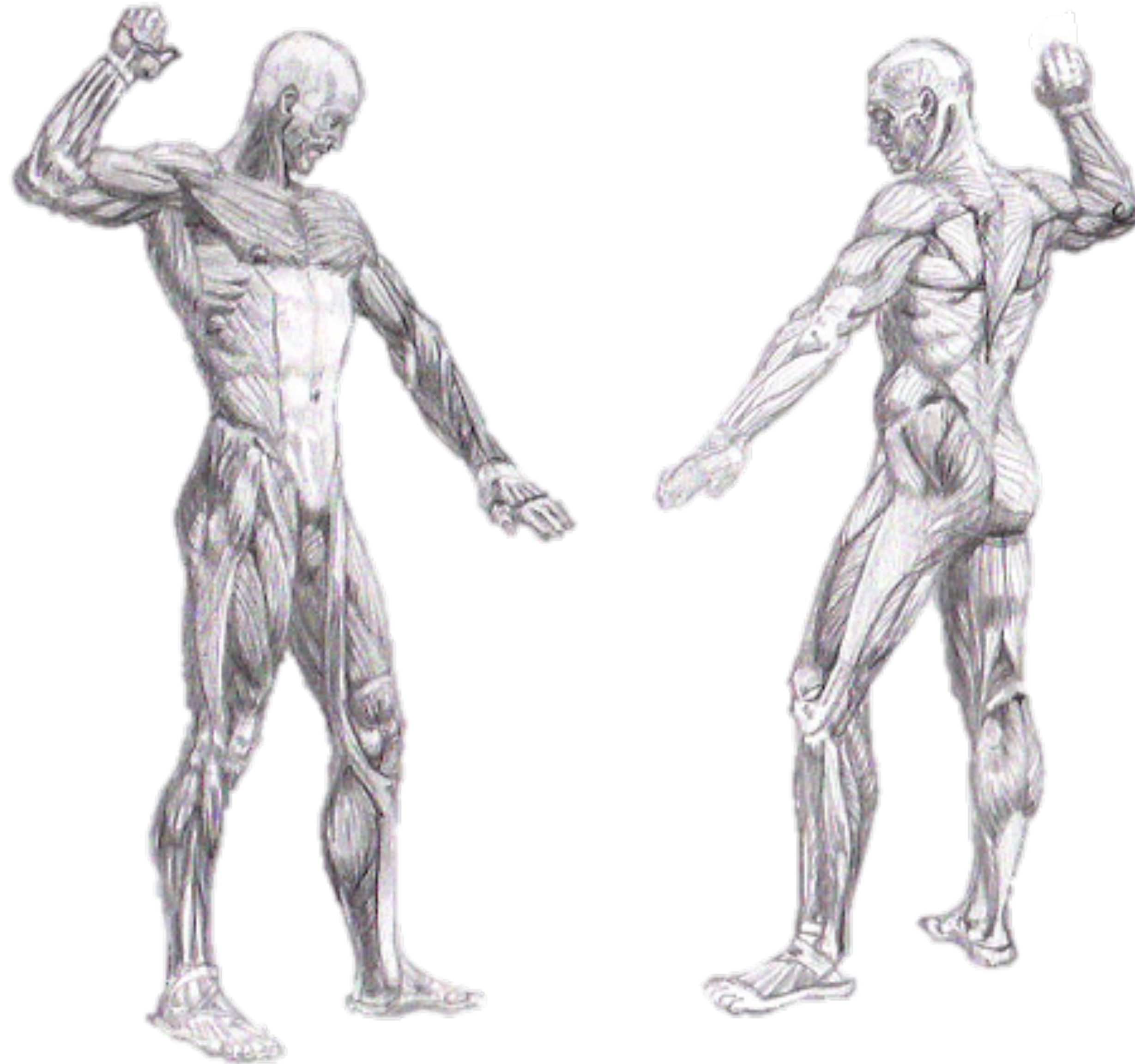
Fides Zenk

Ecole Polytechnique Federale Lausanne (EPFL)

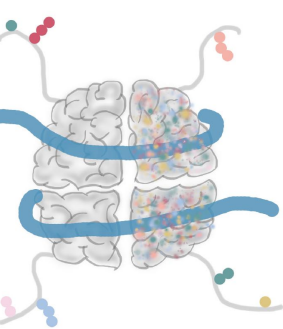
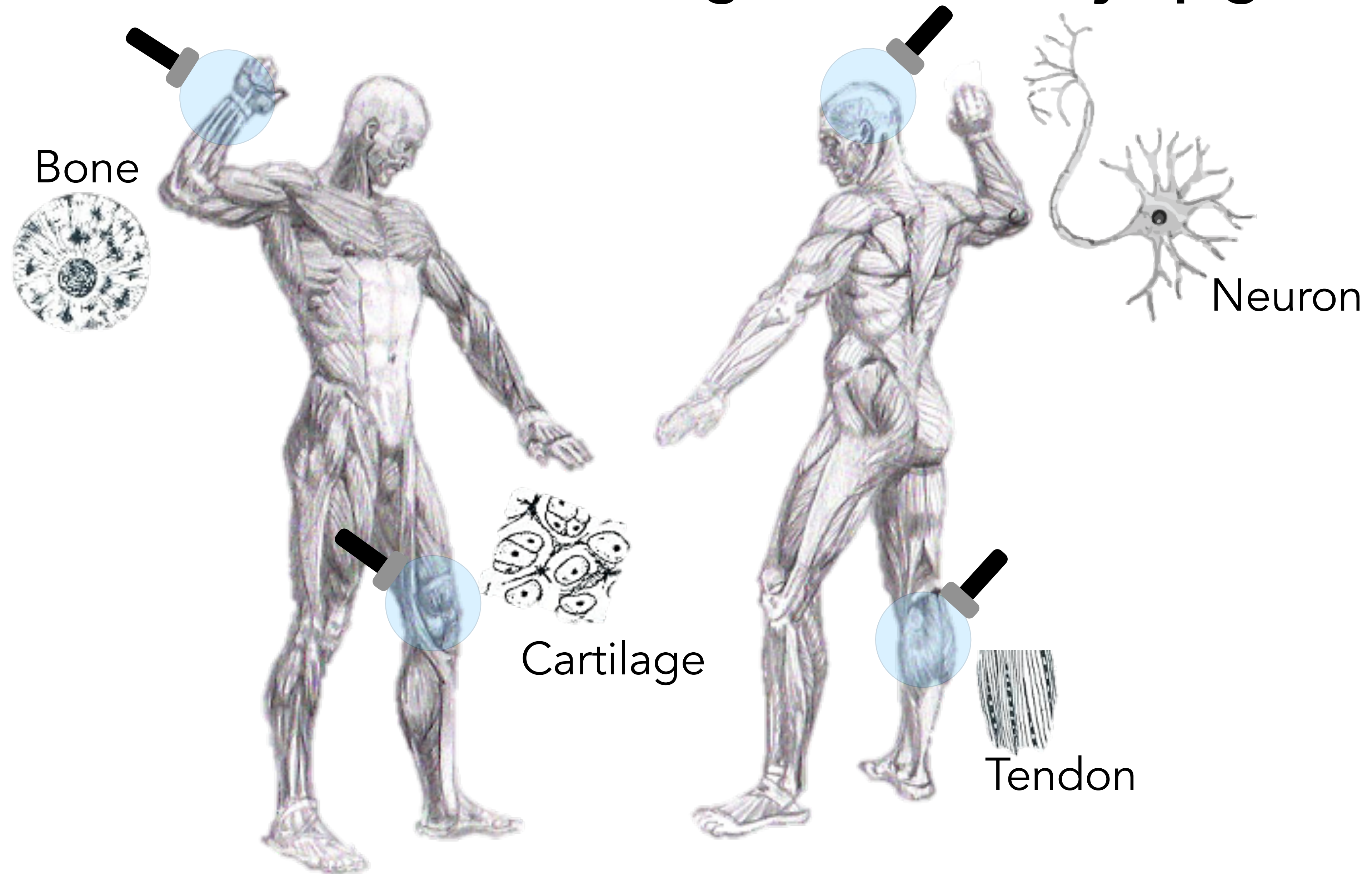
Lab of Epigenomics of Neurodevelopmental Disorders at Brain Mind Institute



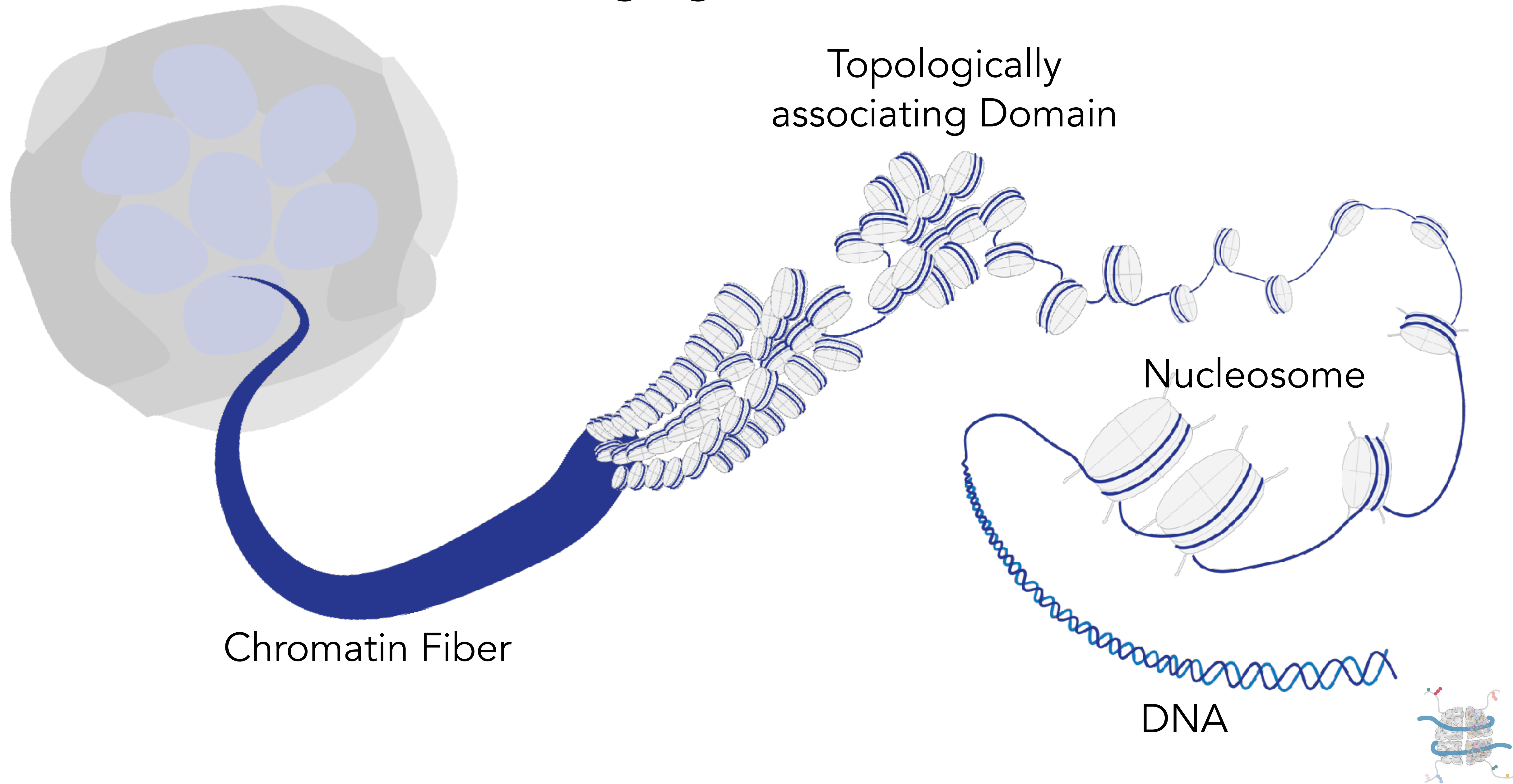
One genome - many epigenomes



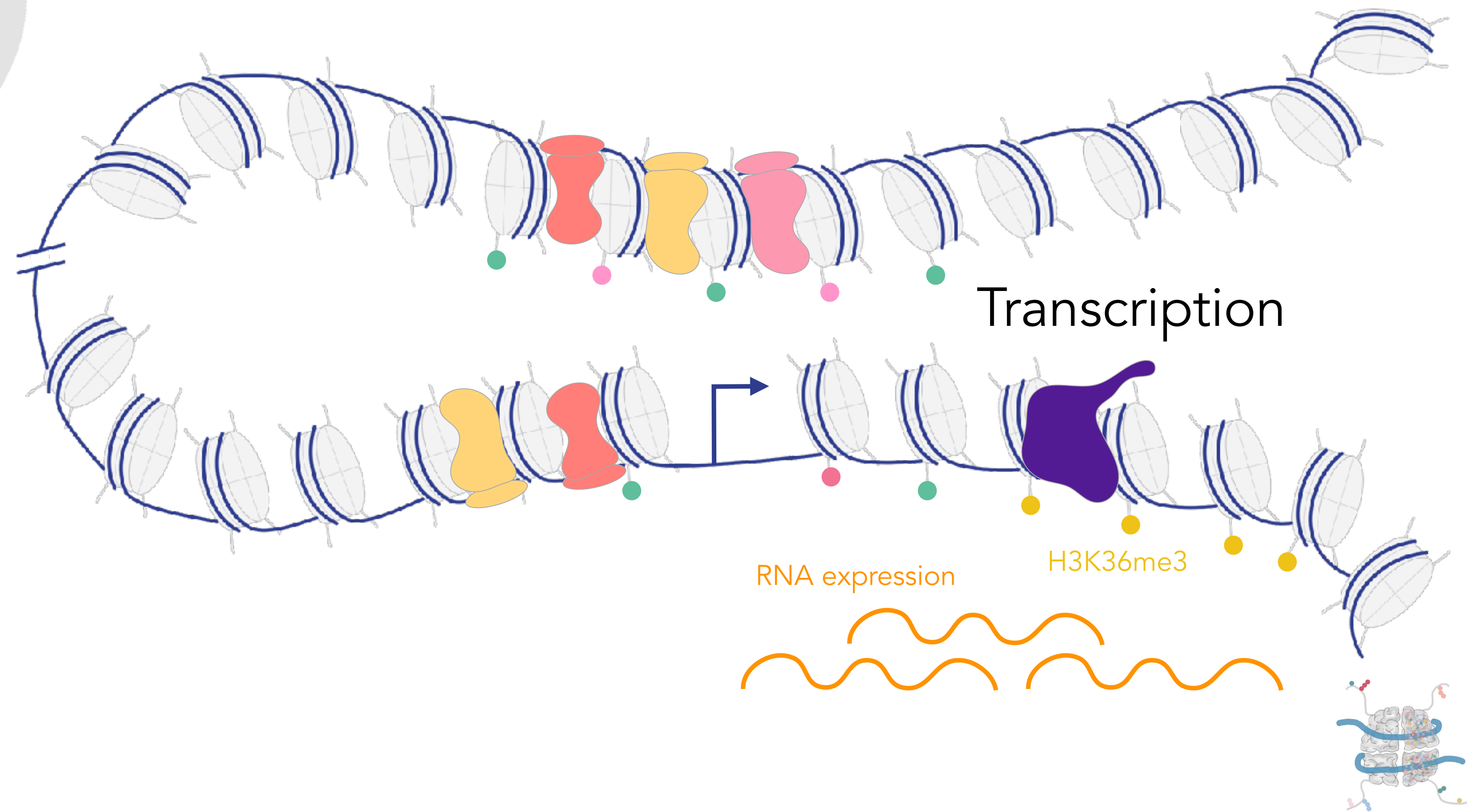
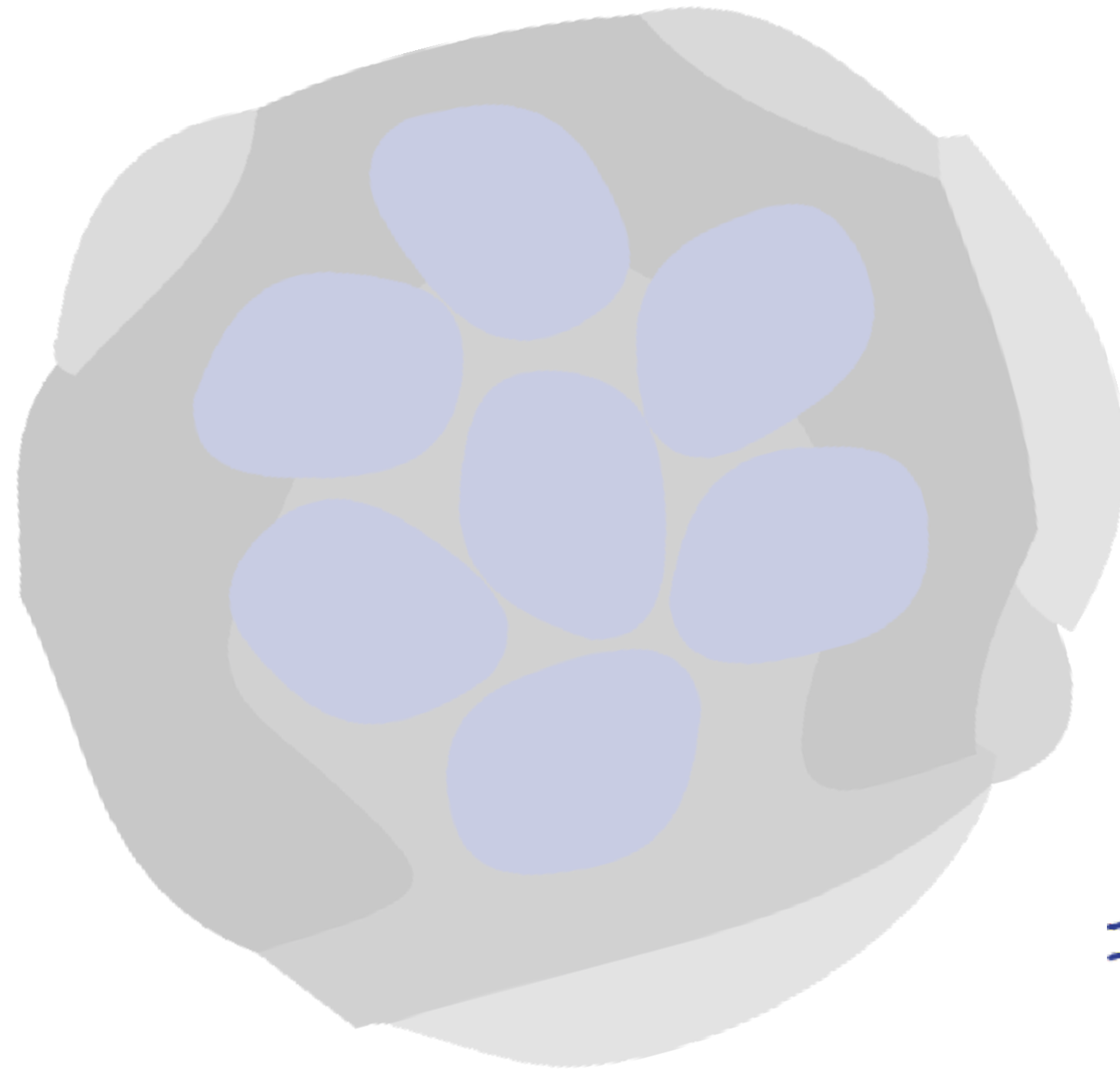
One genome - many epigenomes



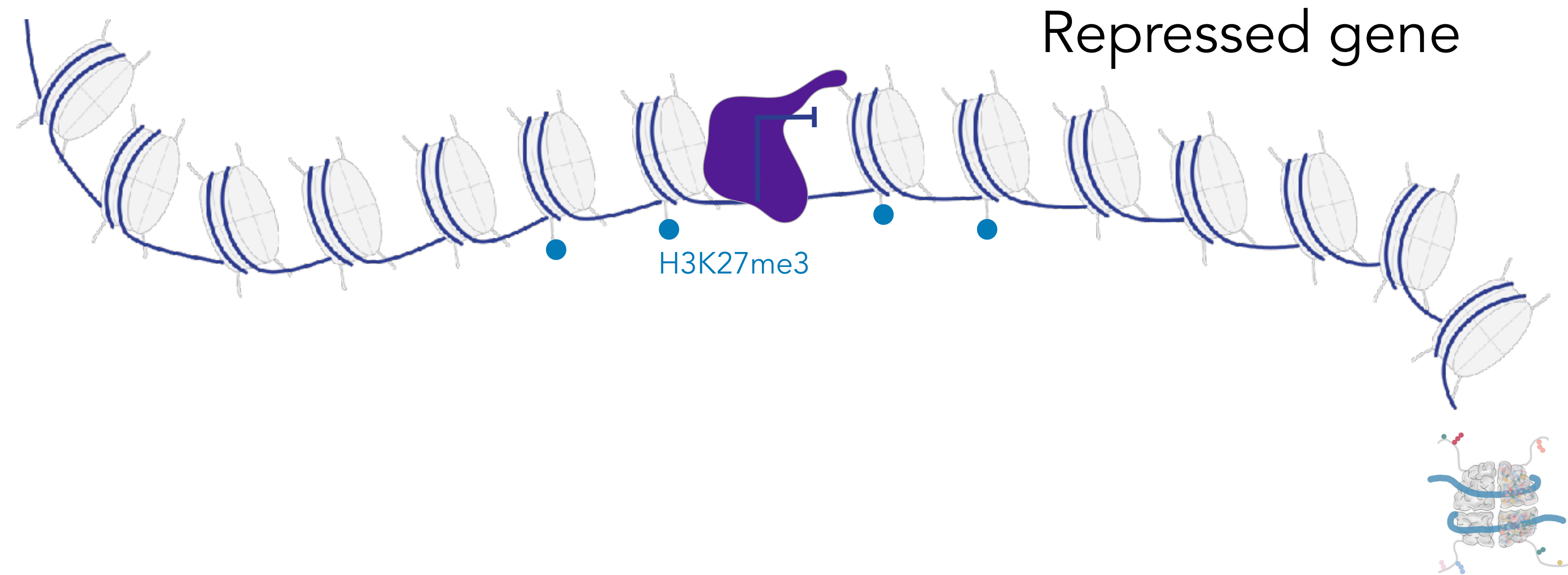
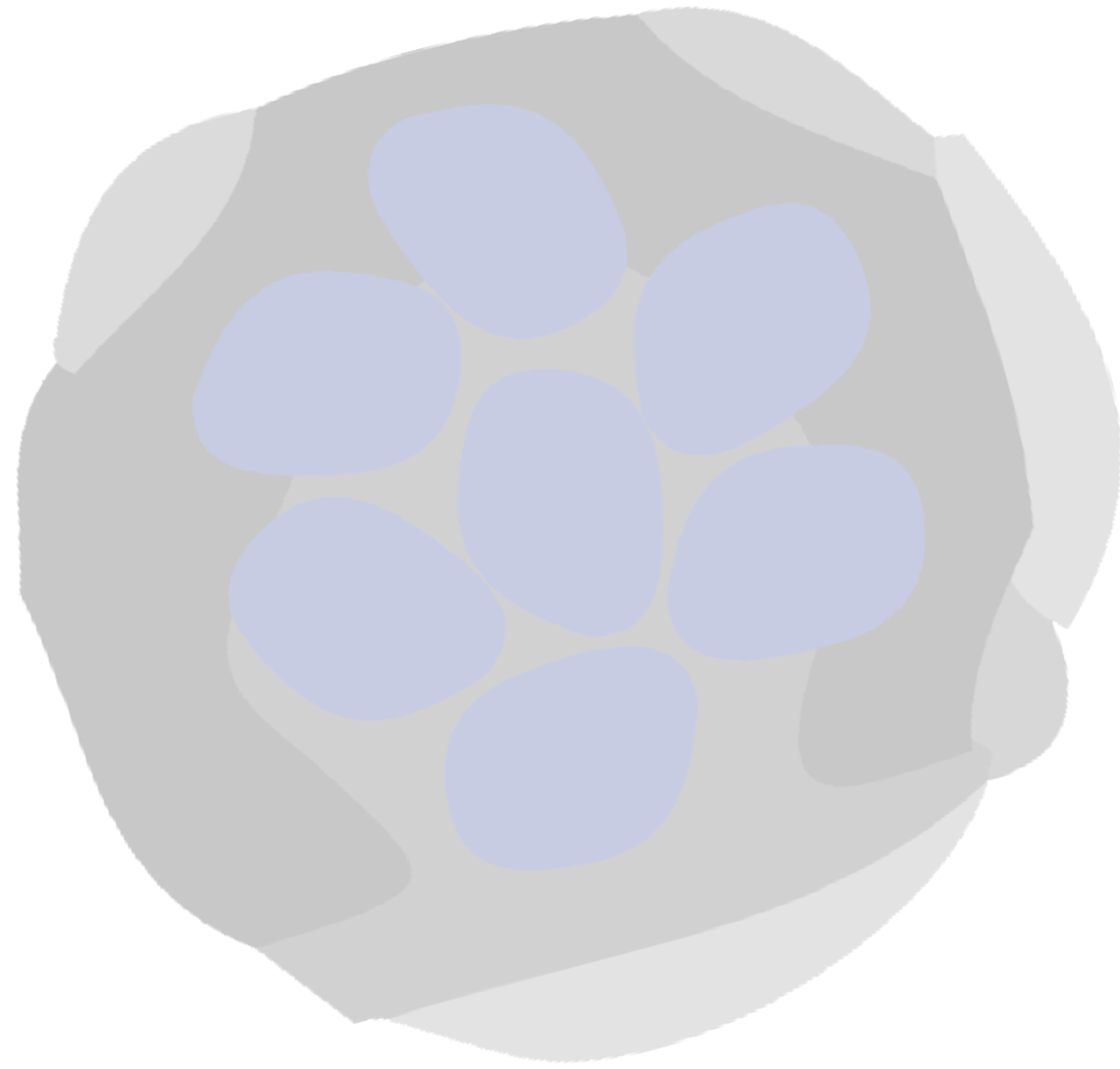
Packaging of Chromatin inside the Nucleus



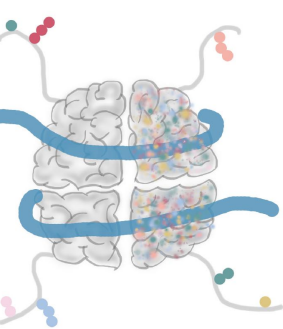
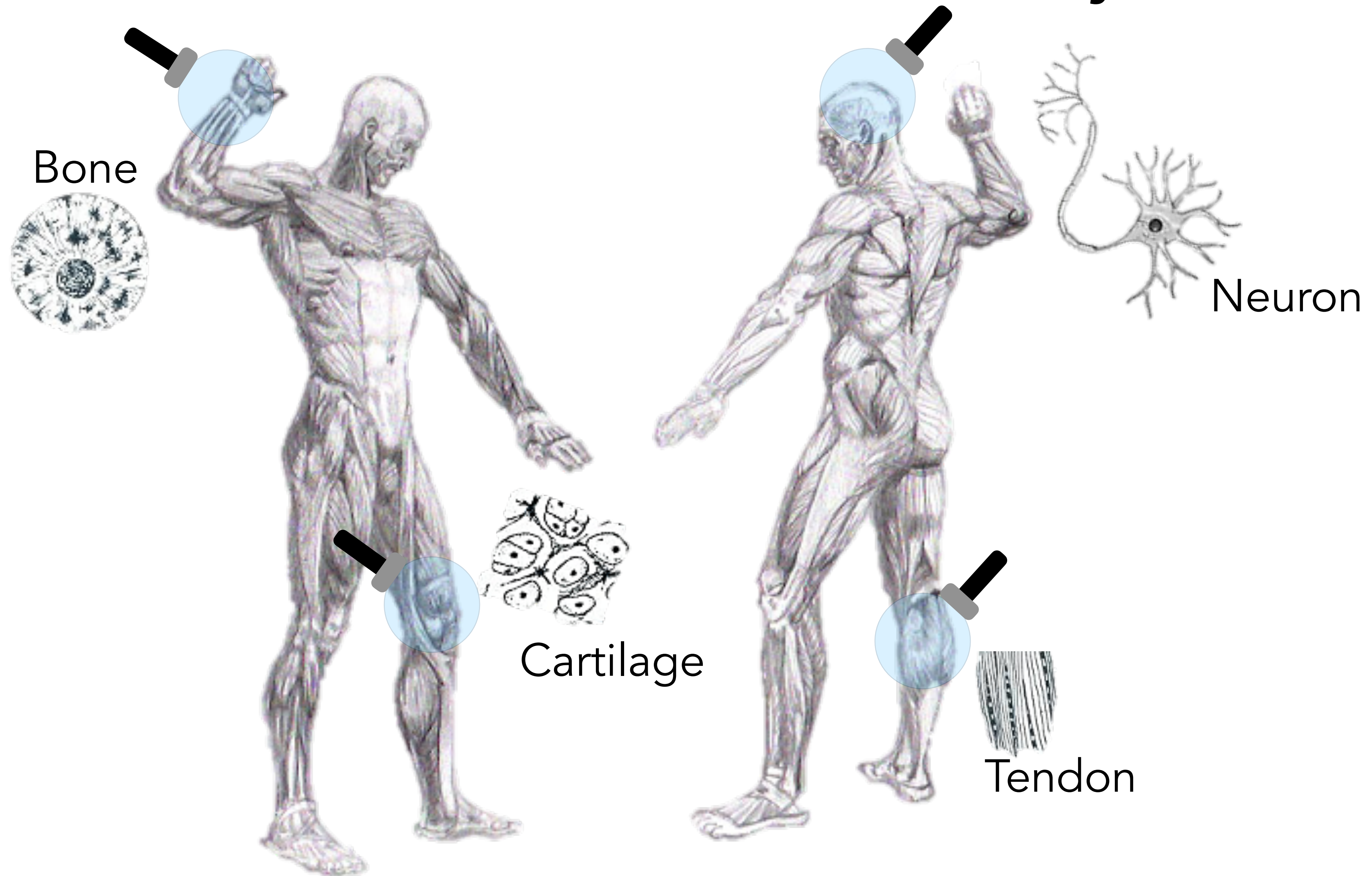
Epigenetic Mechanisms control Gene Activity



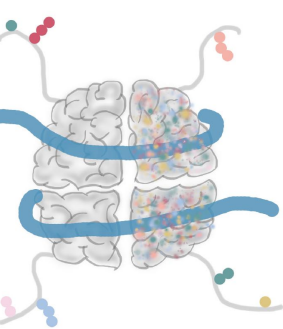
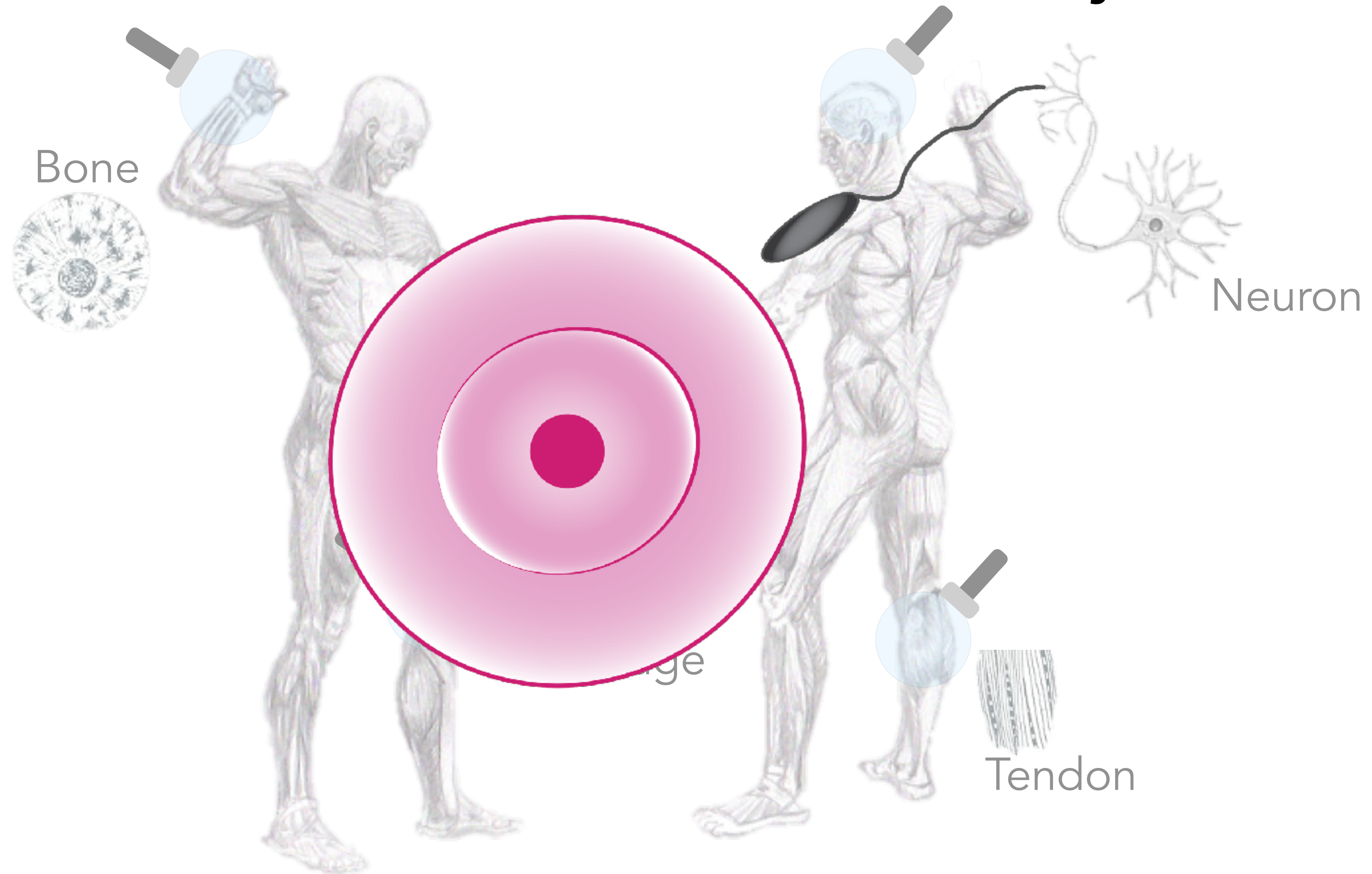
Epigenetic Mechanisms control Gene Activity



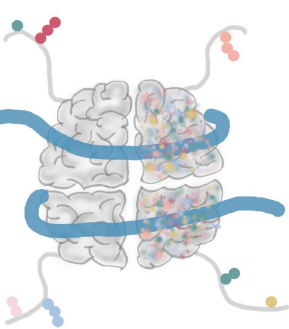
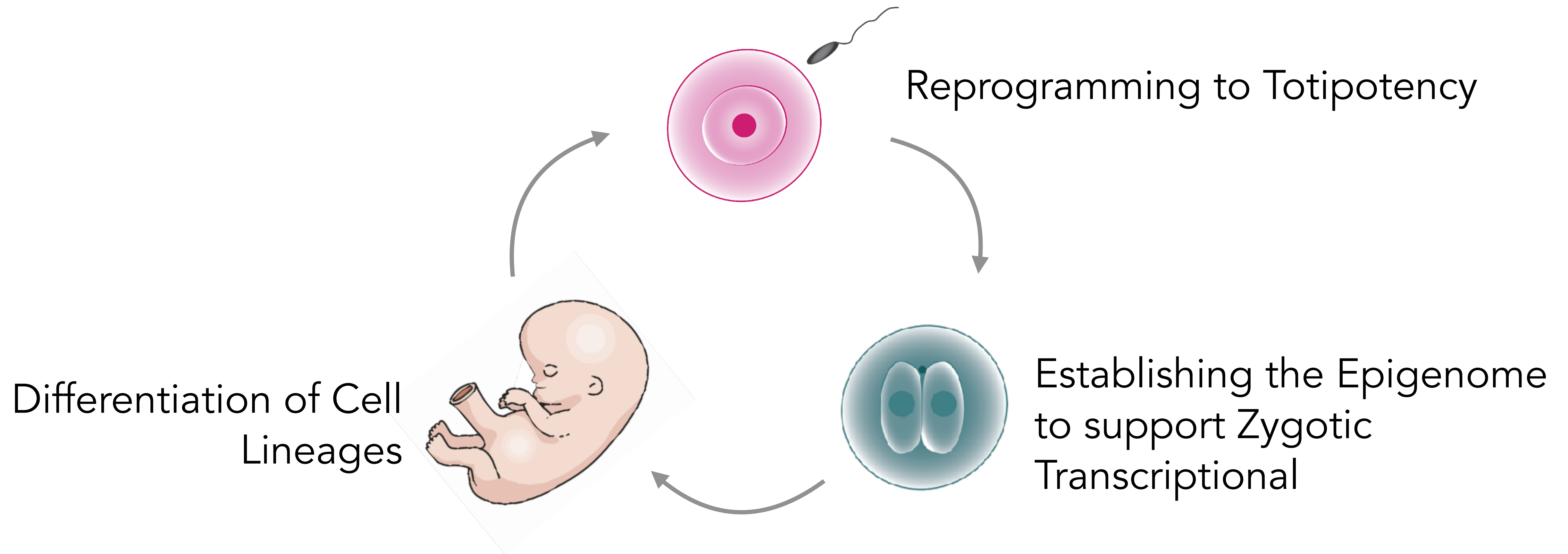
How is cellular identity established?



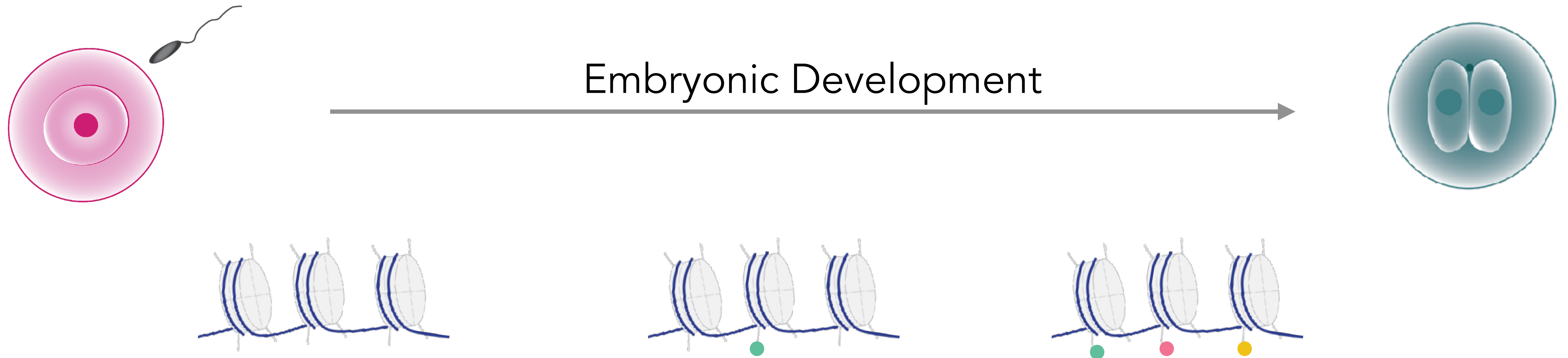
How is cellular identity established?



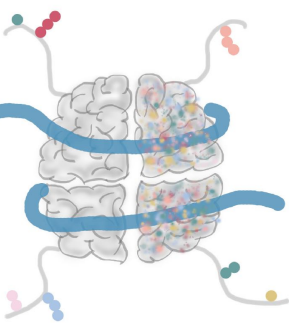
Gene regulatory patterns are established during early development



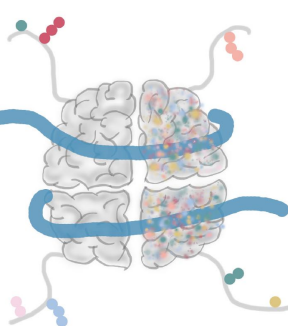
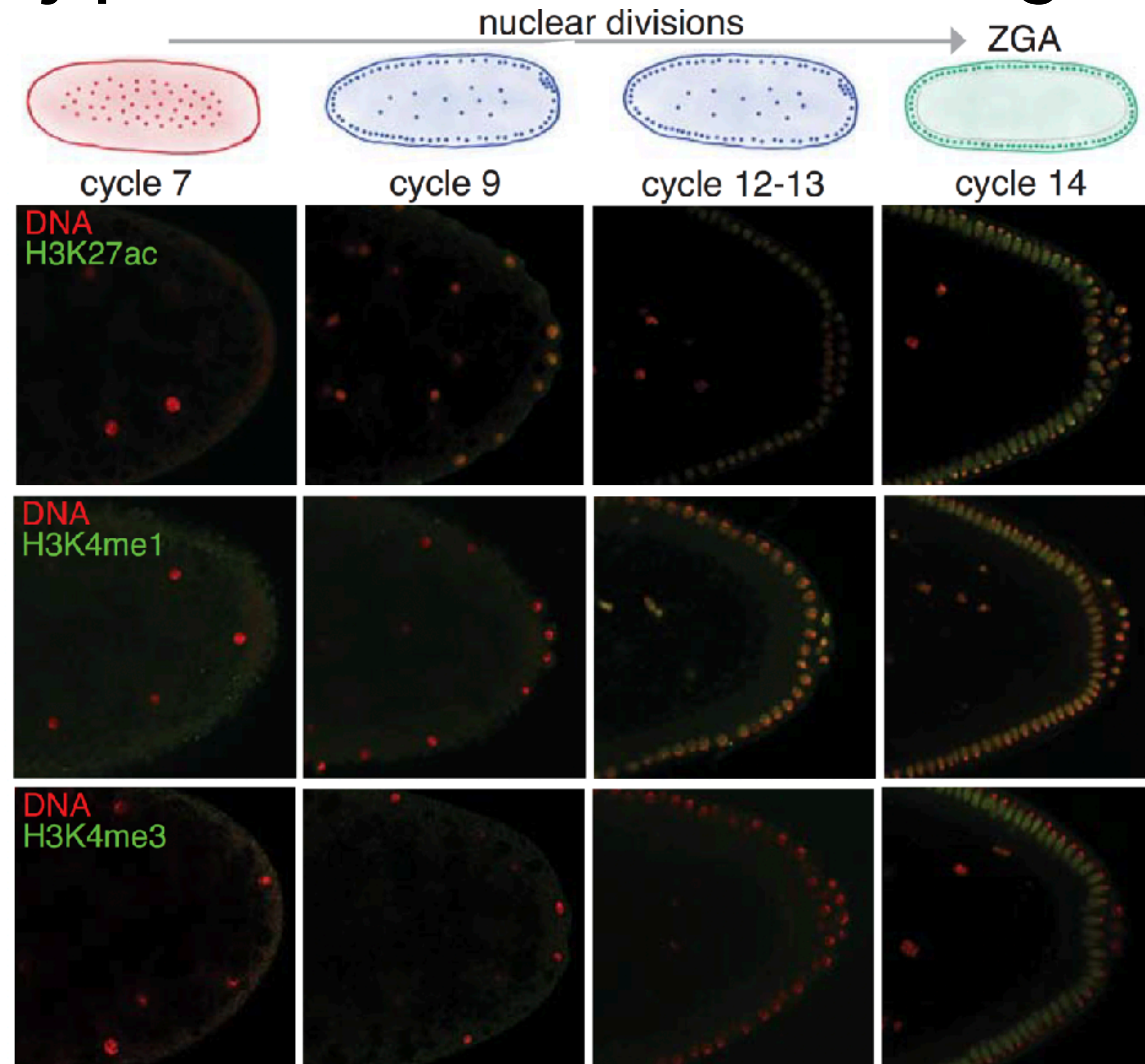
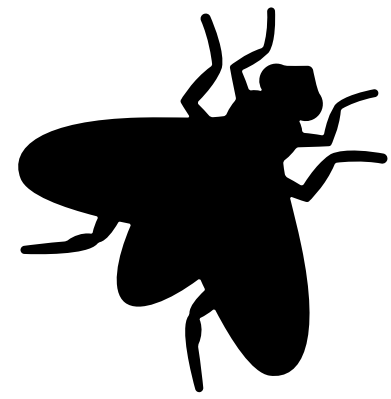
Gene regulatory patterns are established during early development



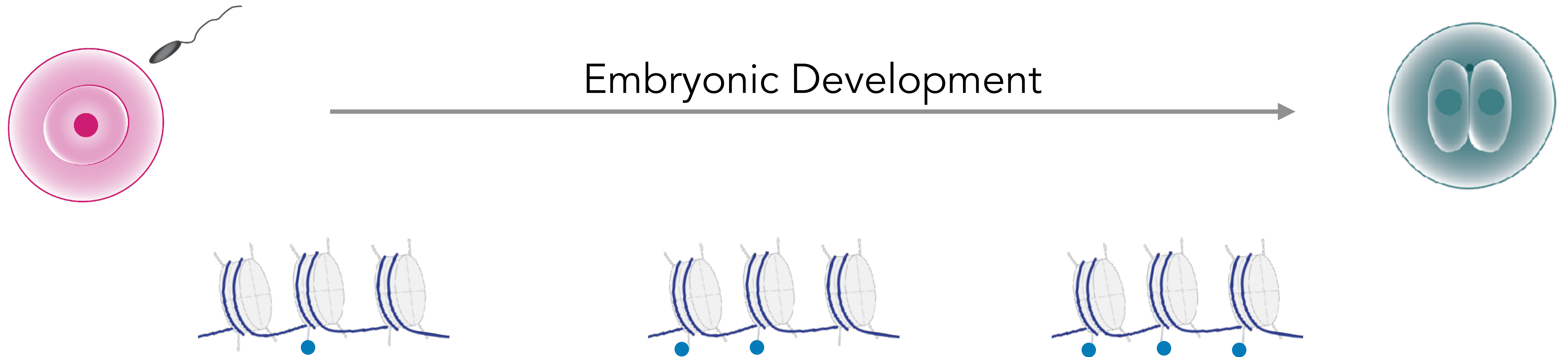
Histone modifications are gradually installed
before zygotic genome activation



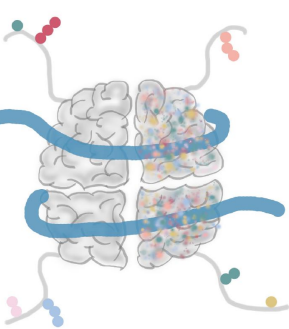
Gene regulatory patterns are established during early development



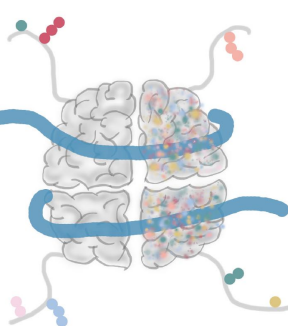
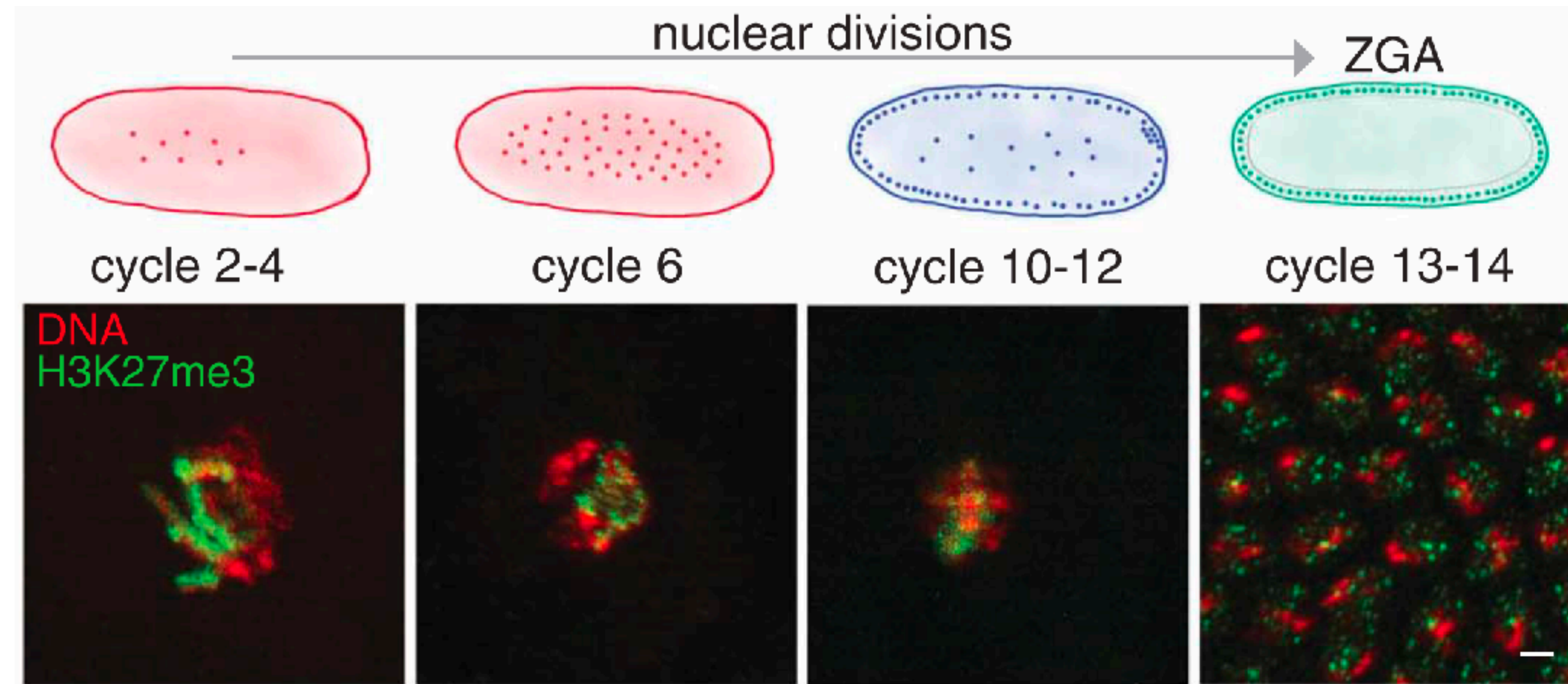
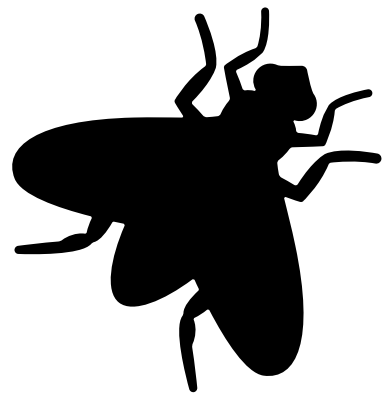
Gene regulatory patterns are established during early development



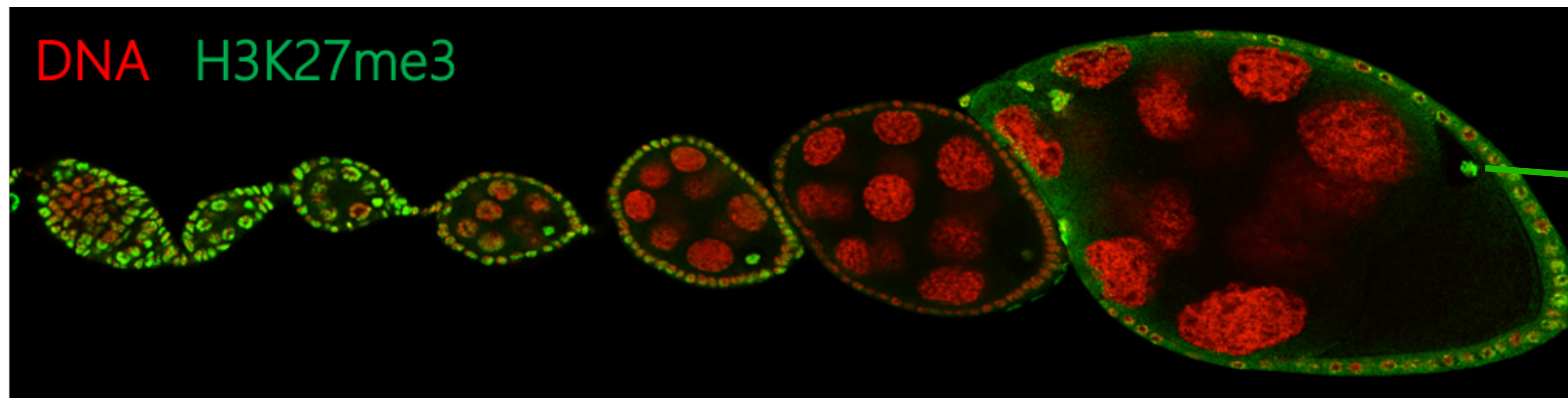
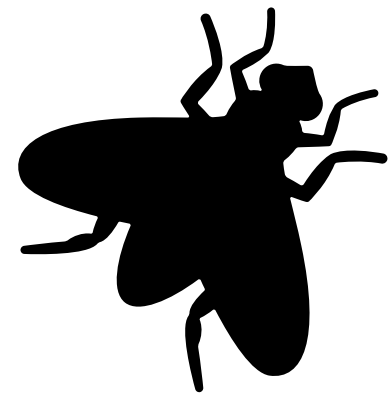
The repressive histone modification H3K27me3
is not remodelled in the early embryo



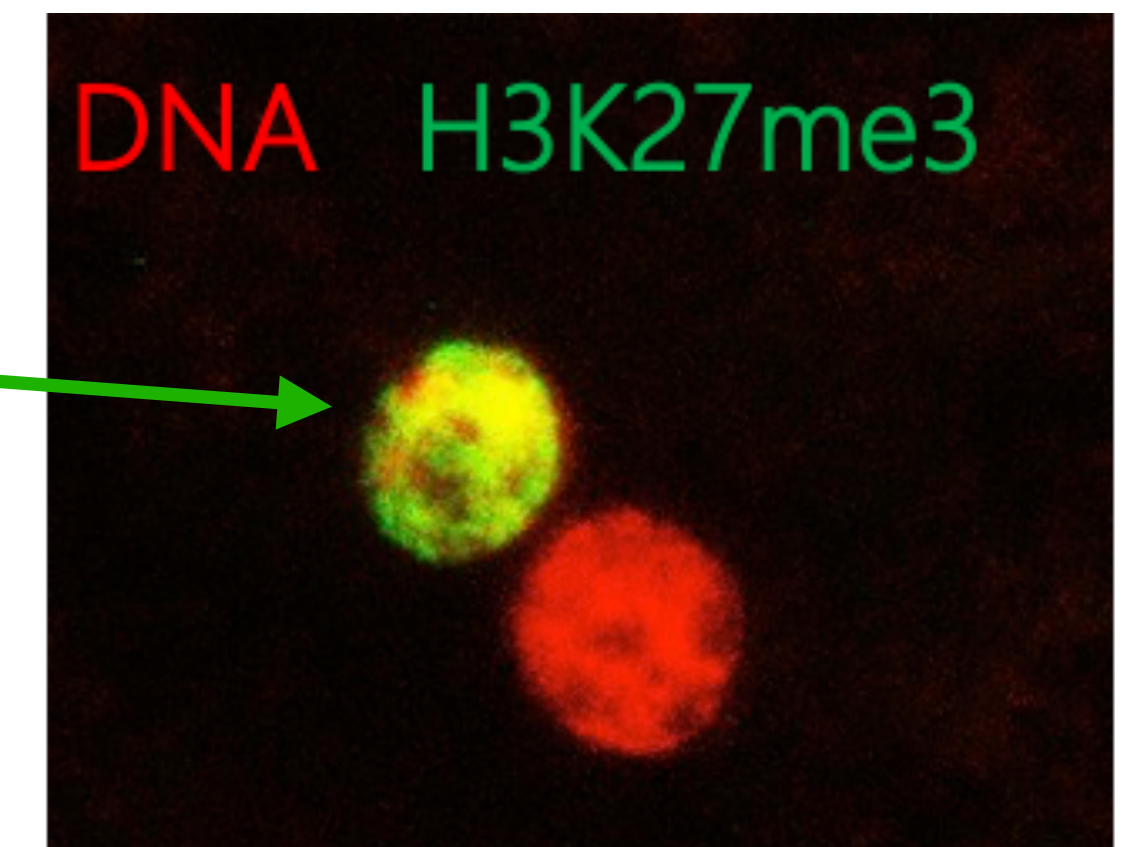
Gene regulatory patterns are established during early development



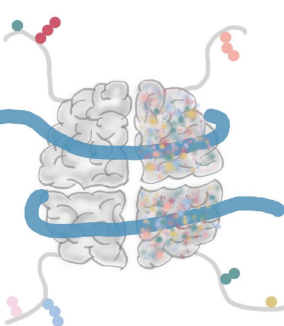
The repressive Histone Modification H3K27me3 is inherited



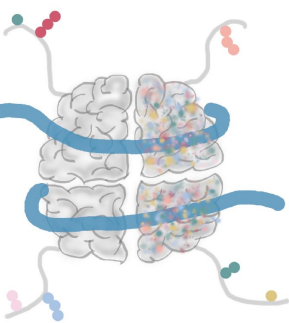
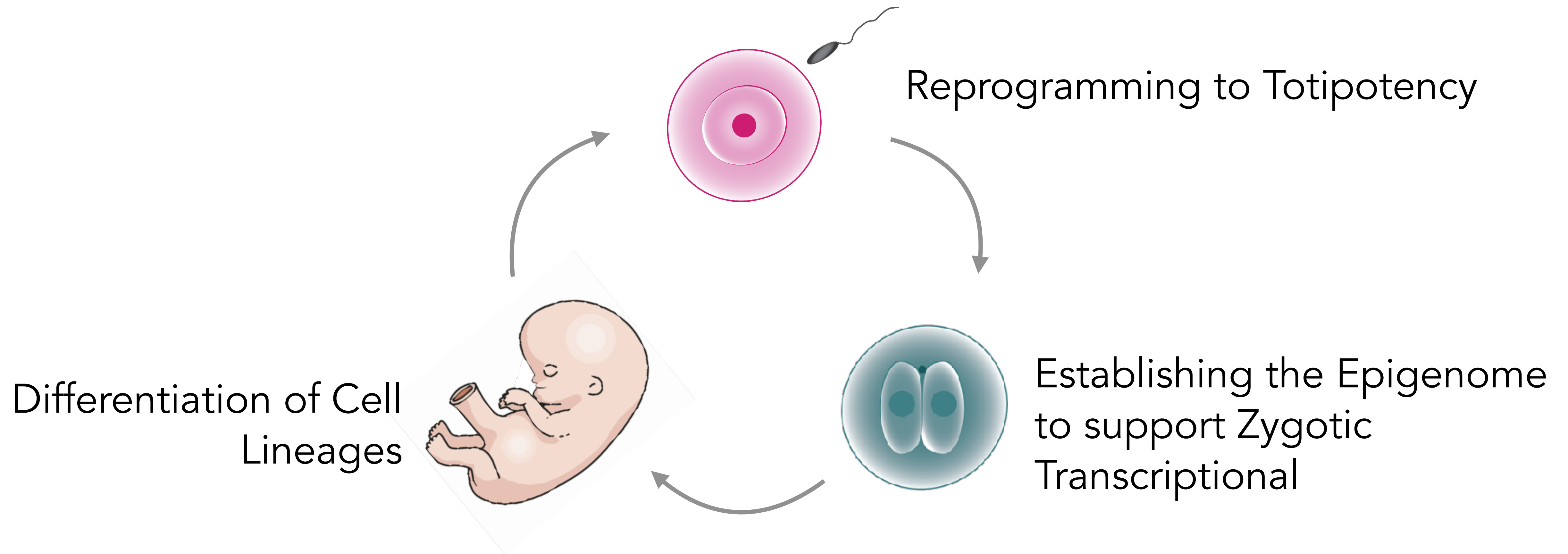
Maternal Germline



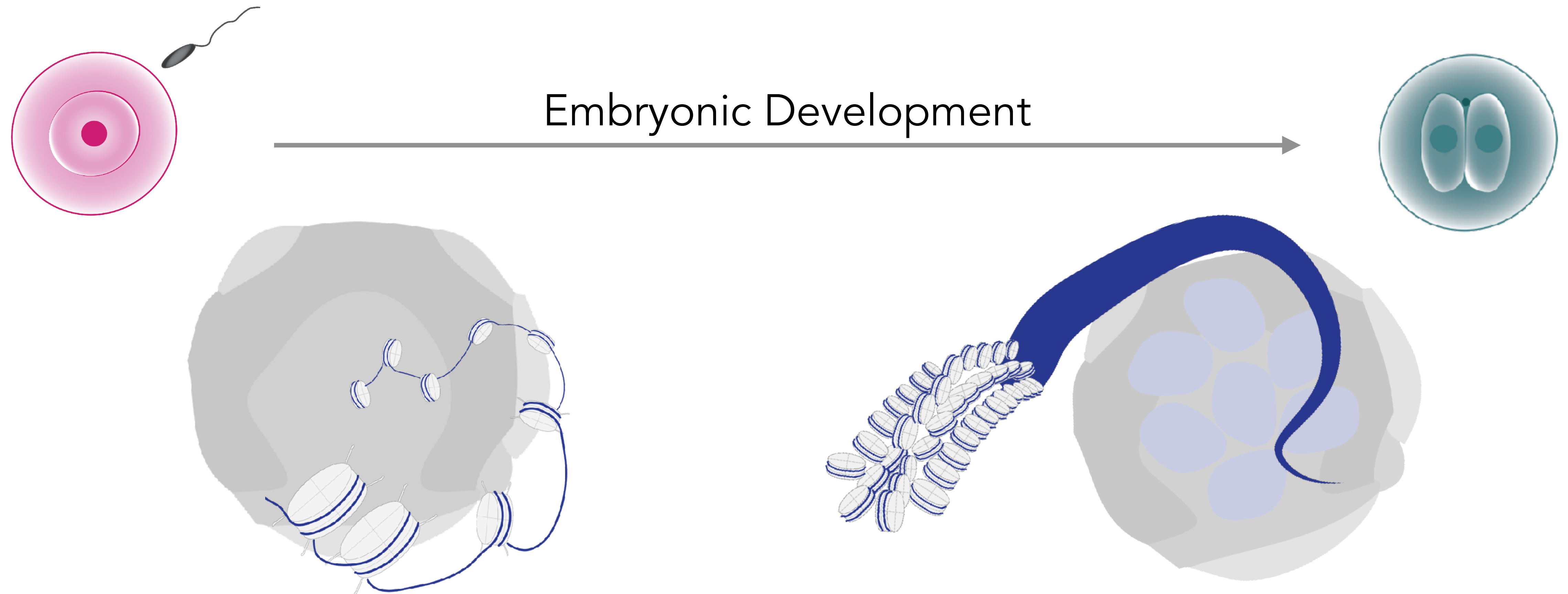
Early Embryo



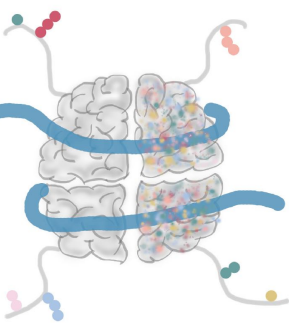
Gene regulatory patterns are established during early development



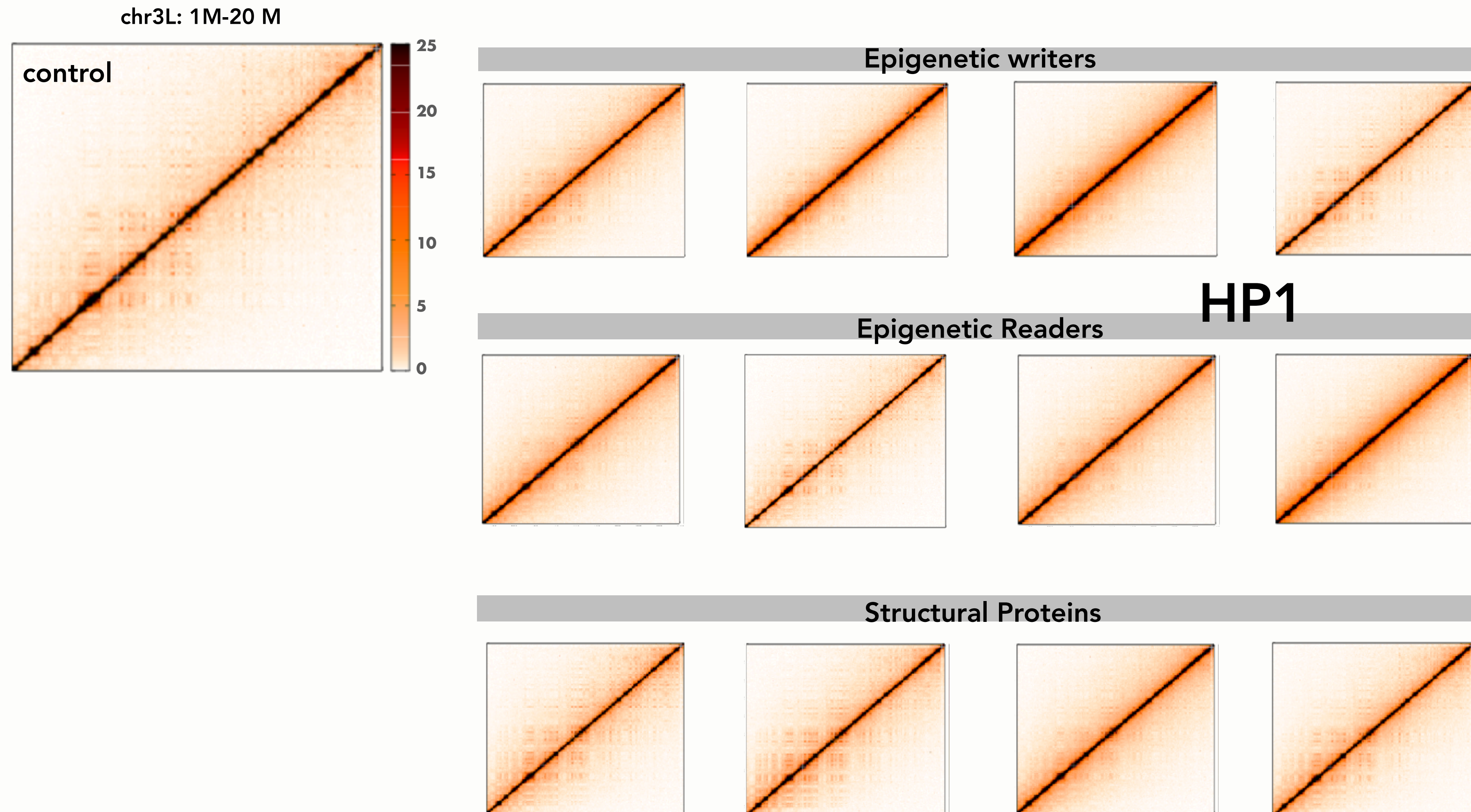
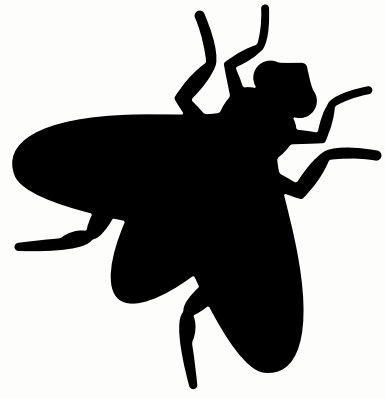
Gene regulatory patterns are established during early development



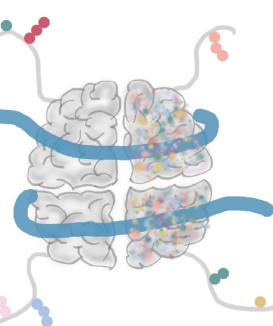
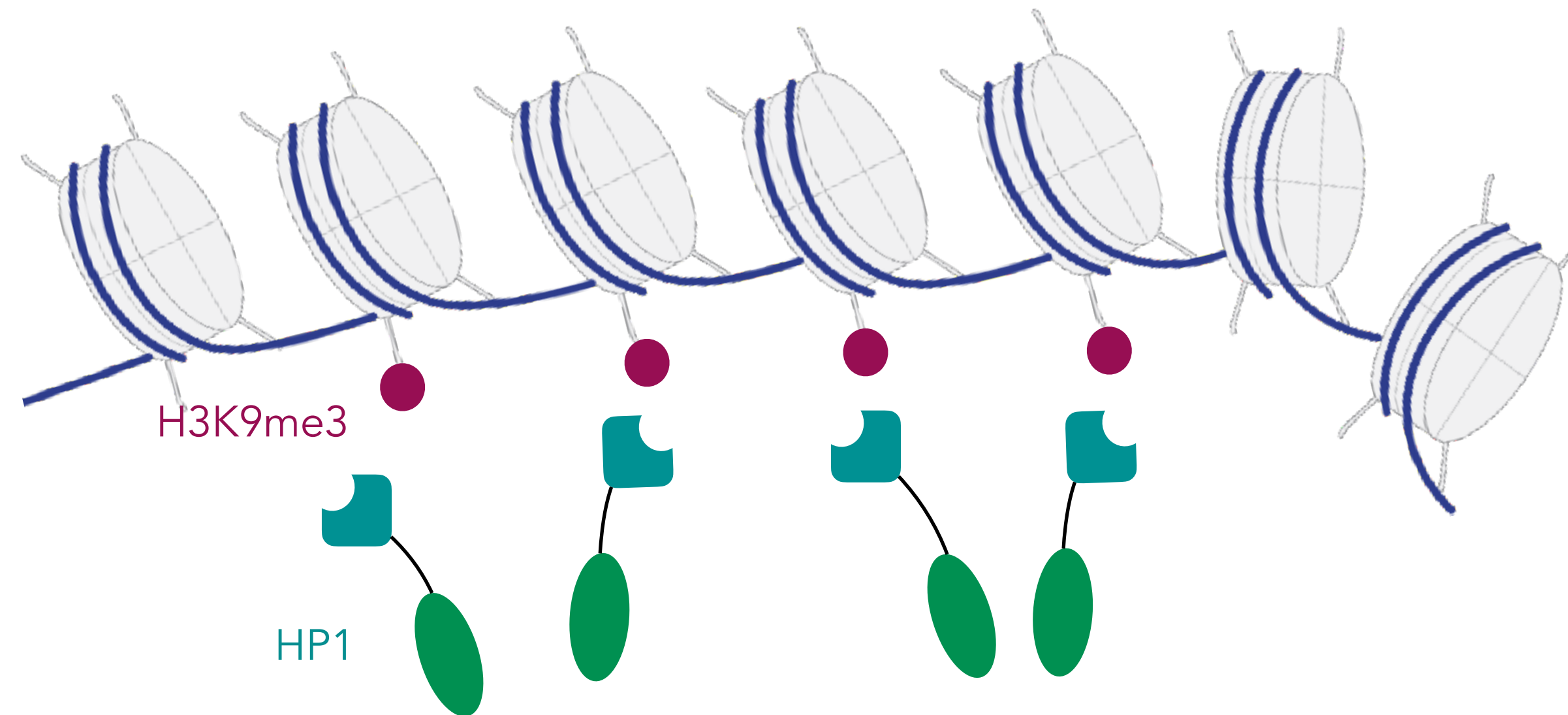
Higher Order Chromatin Structure is organized before ZGA



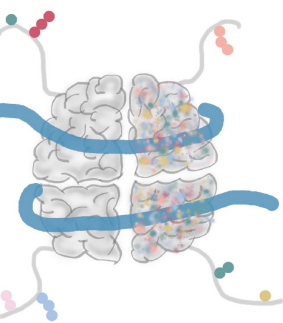
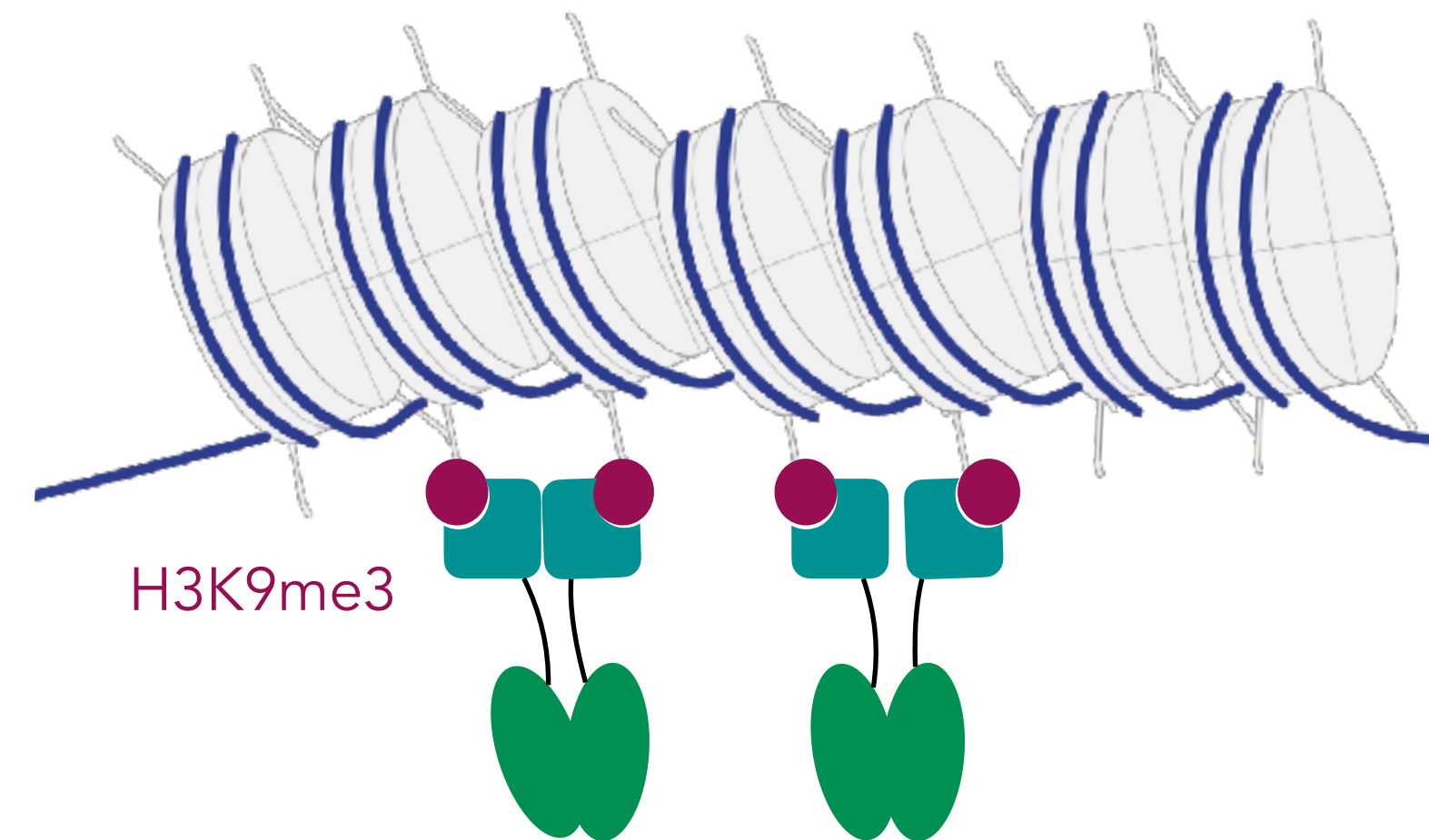
RNAi screen for chromatin factors involved establishing 3D genome organisation



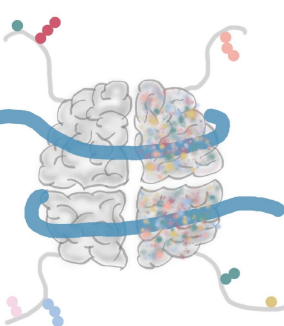
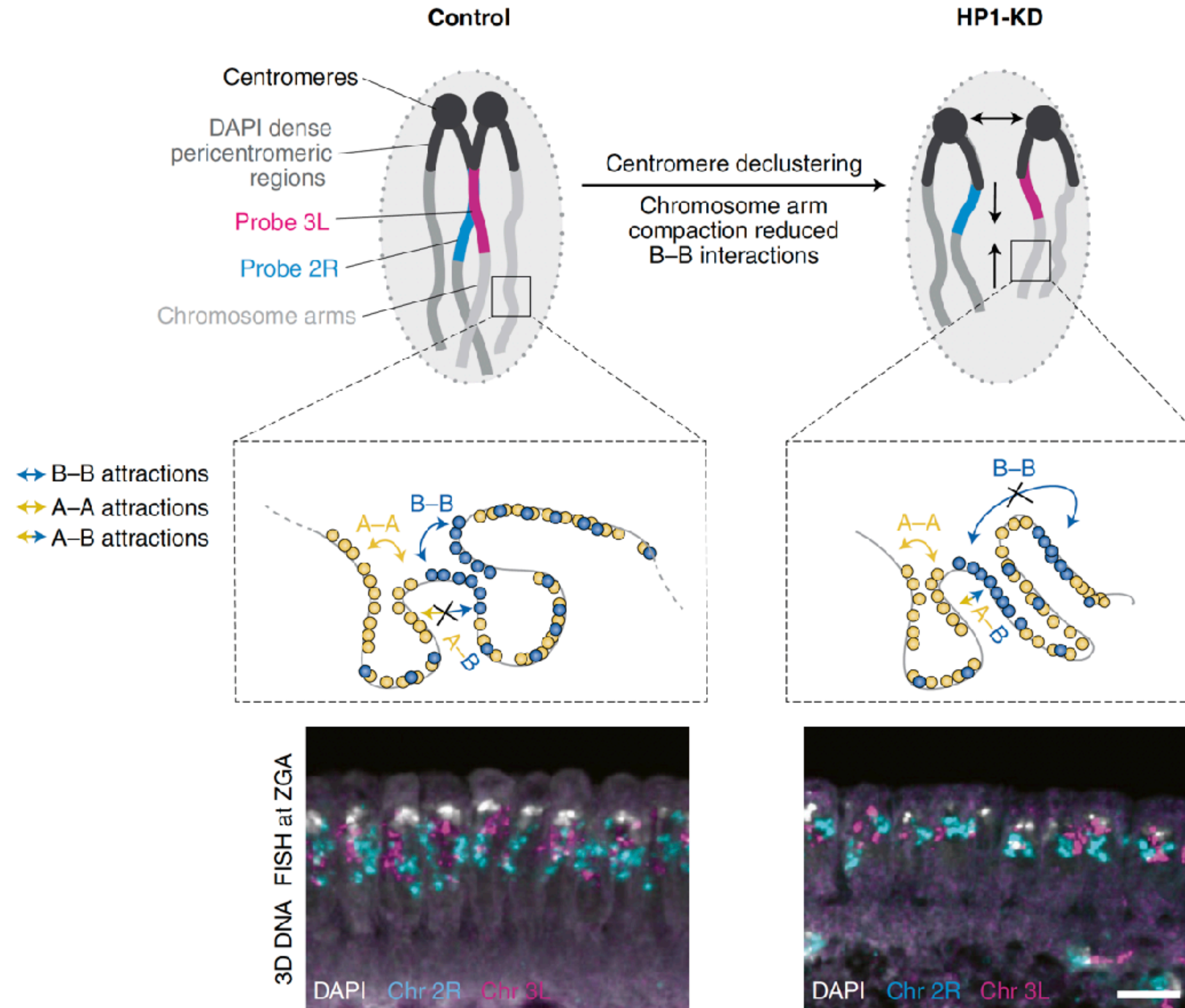
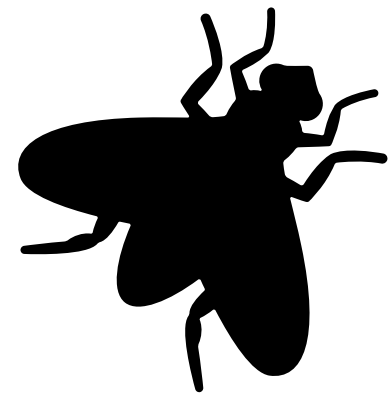
HP1 binds H3K9me3 and compacts Heterochromatin



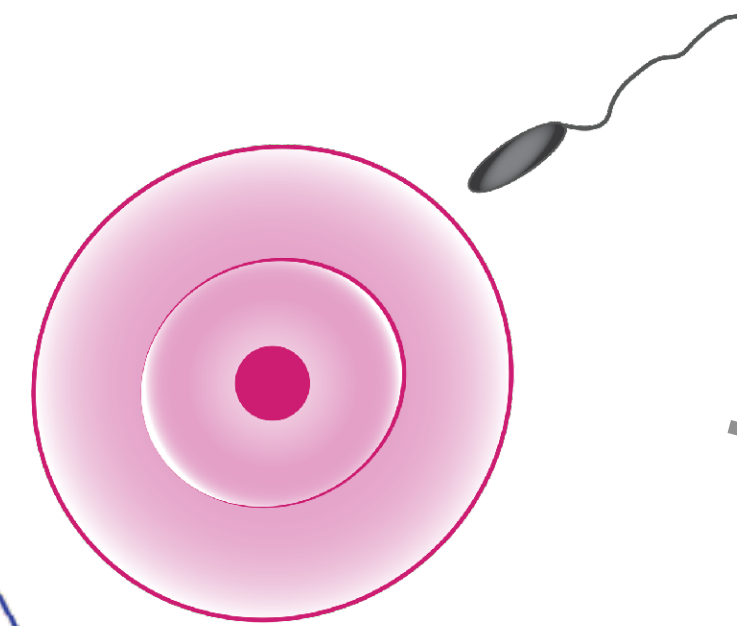
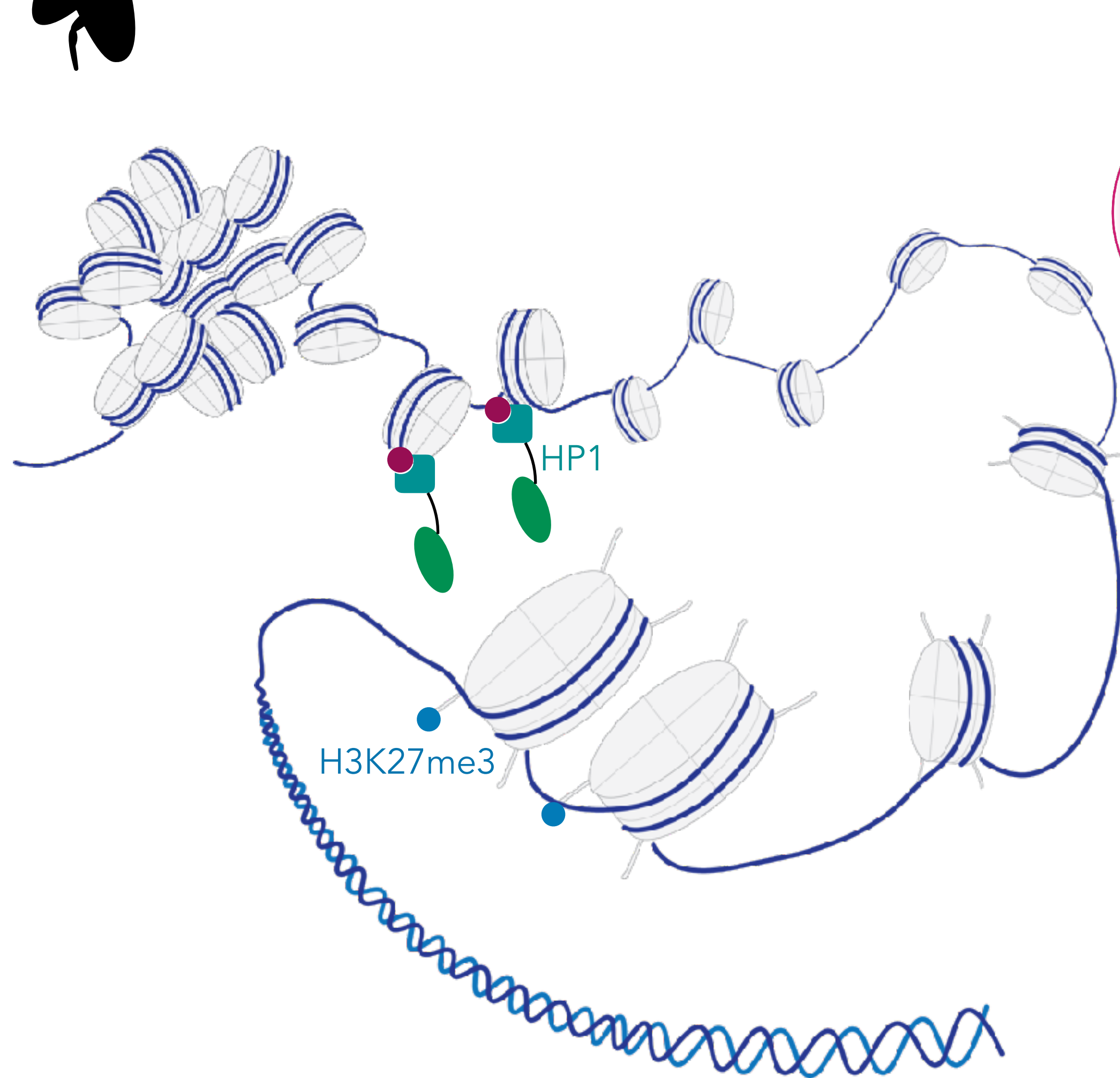
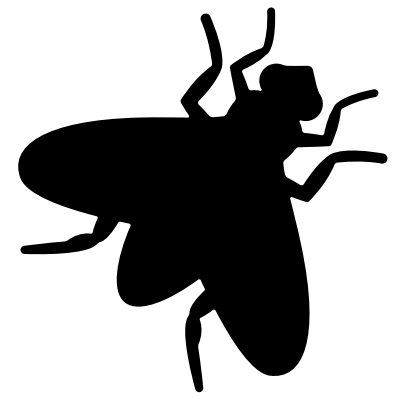
HP1 binds H3K9me3 and compacts Heterochromatin



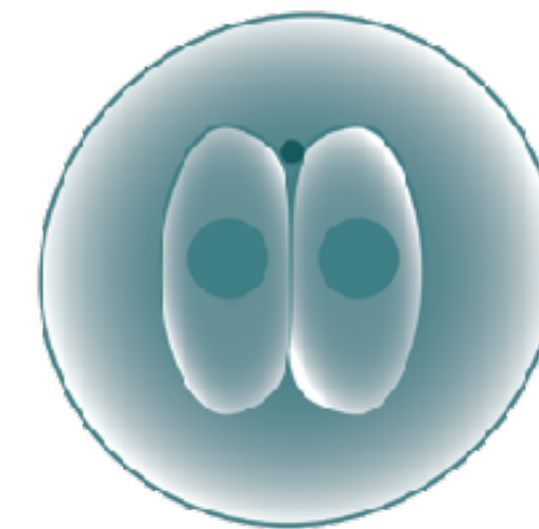
HP1 recruitment triggers Establishment of Chromatin 3D Organization



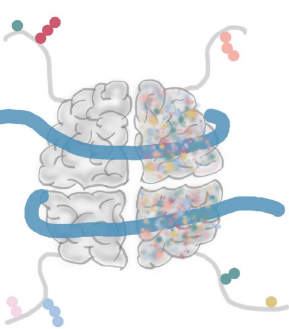
Gene regulatory patterns are established during early development



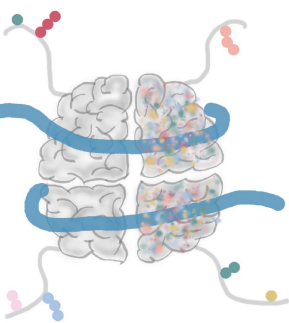
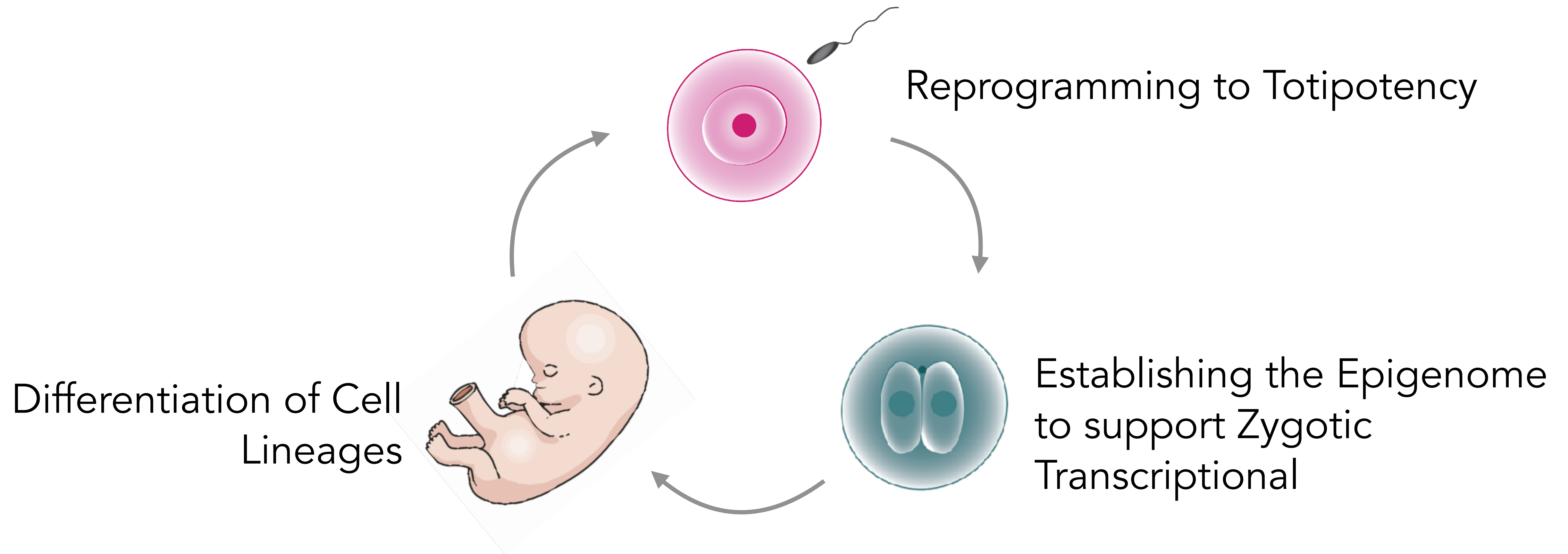
Reprogramming to Totipotency



Establishing the Epigenome
to support Zygotic
Transcriptional



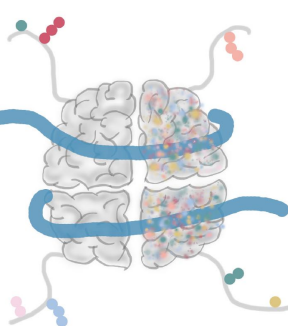
Gene regulatory patterns are established during early development



Understanding Human Brain Development

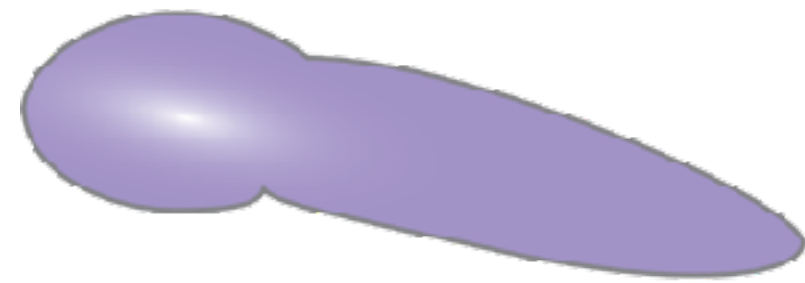


How does cellular diversity arise in the brain?

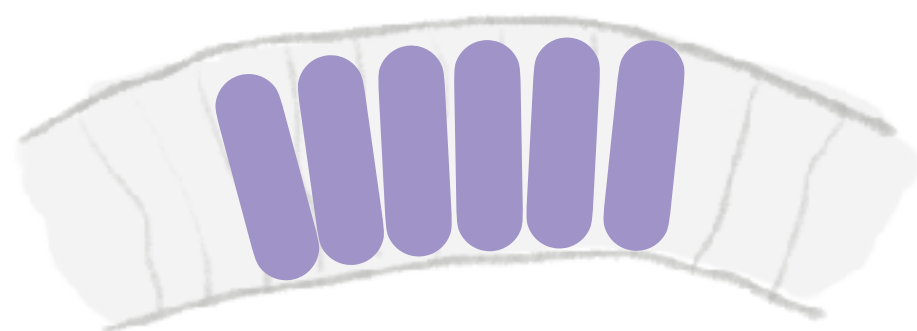


Understanding Human Brain Development

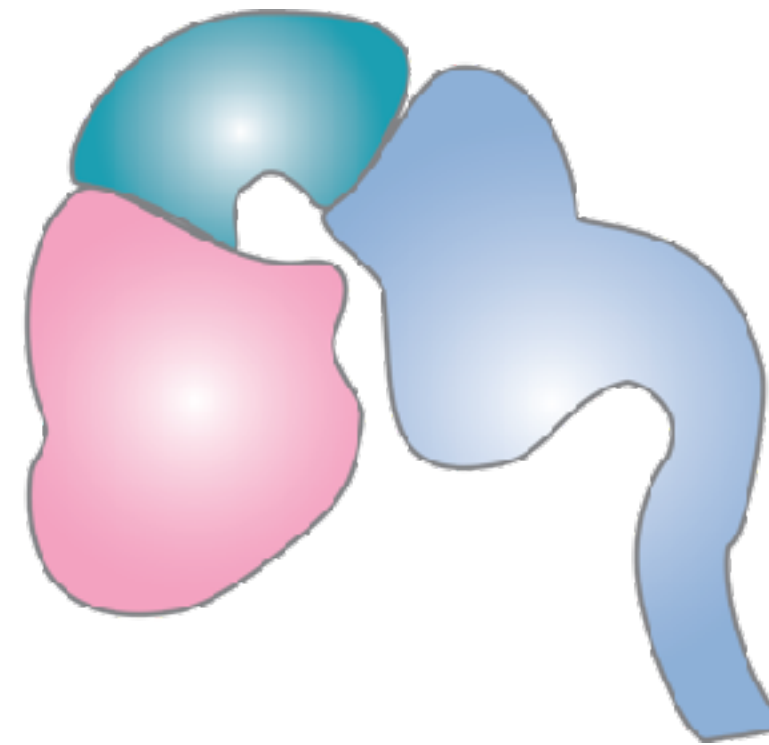
21 Days



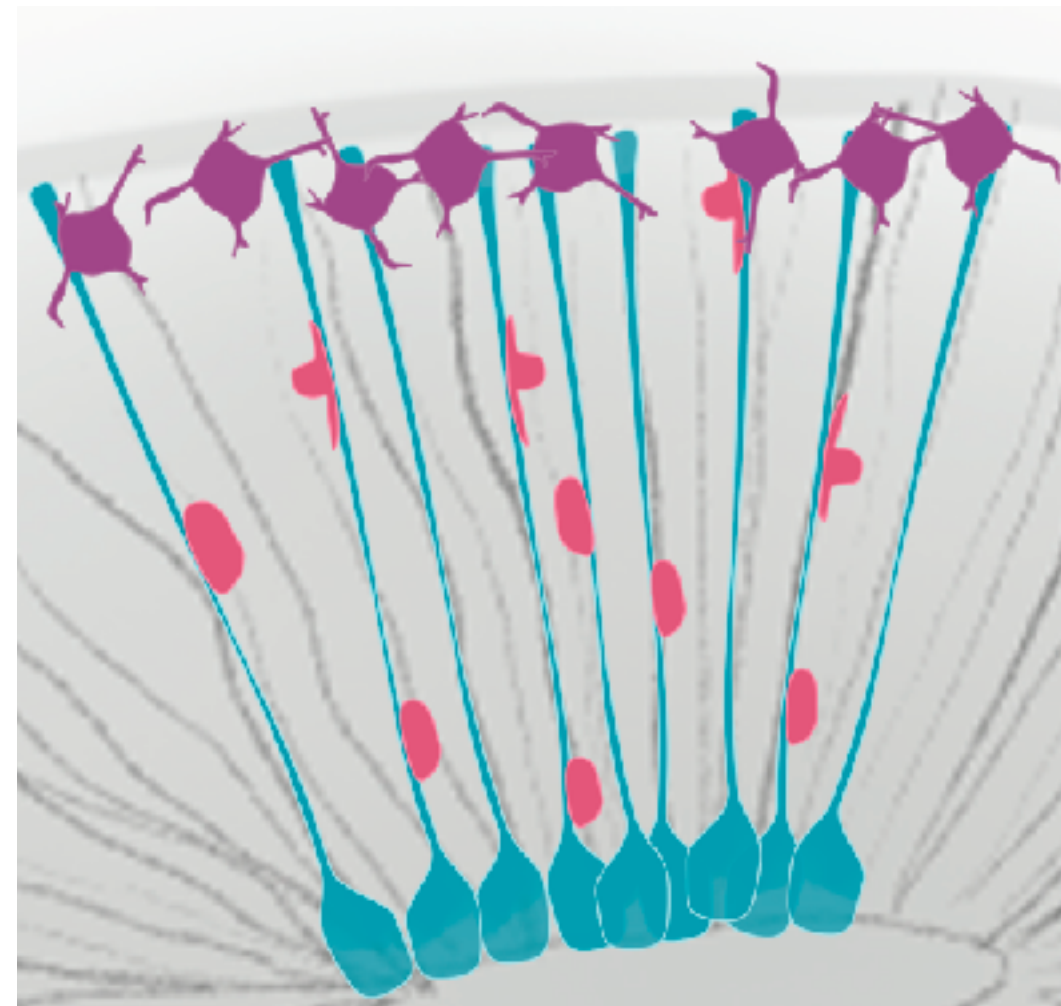
Formation of Neural Tube



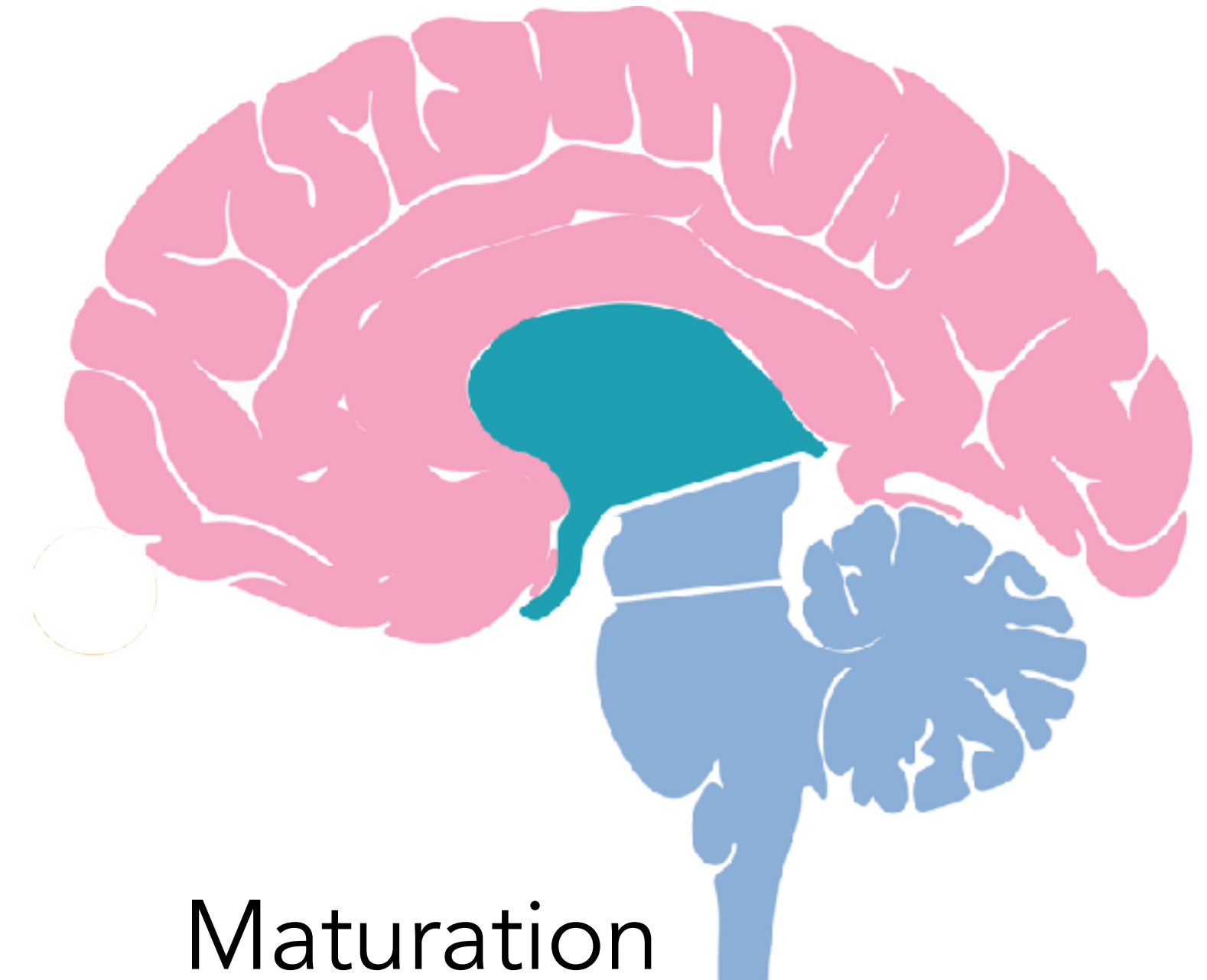
35-40 Days



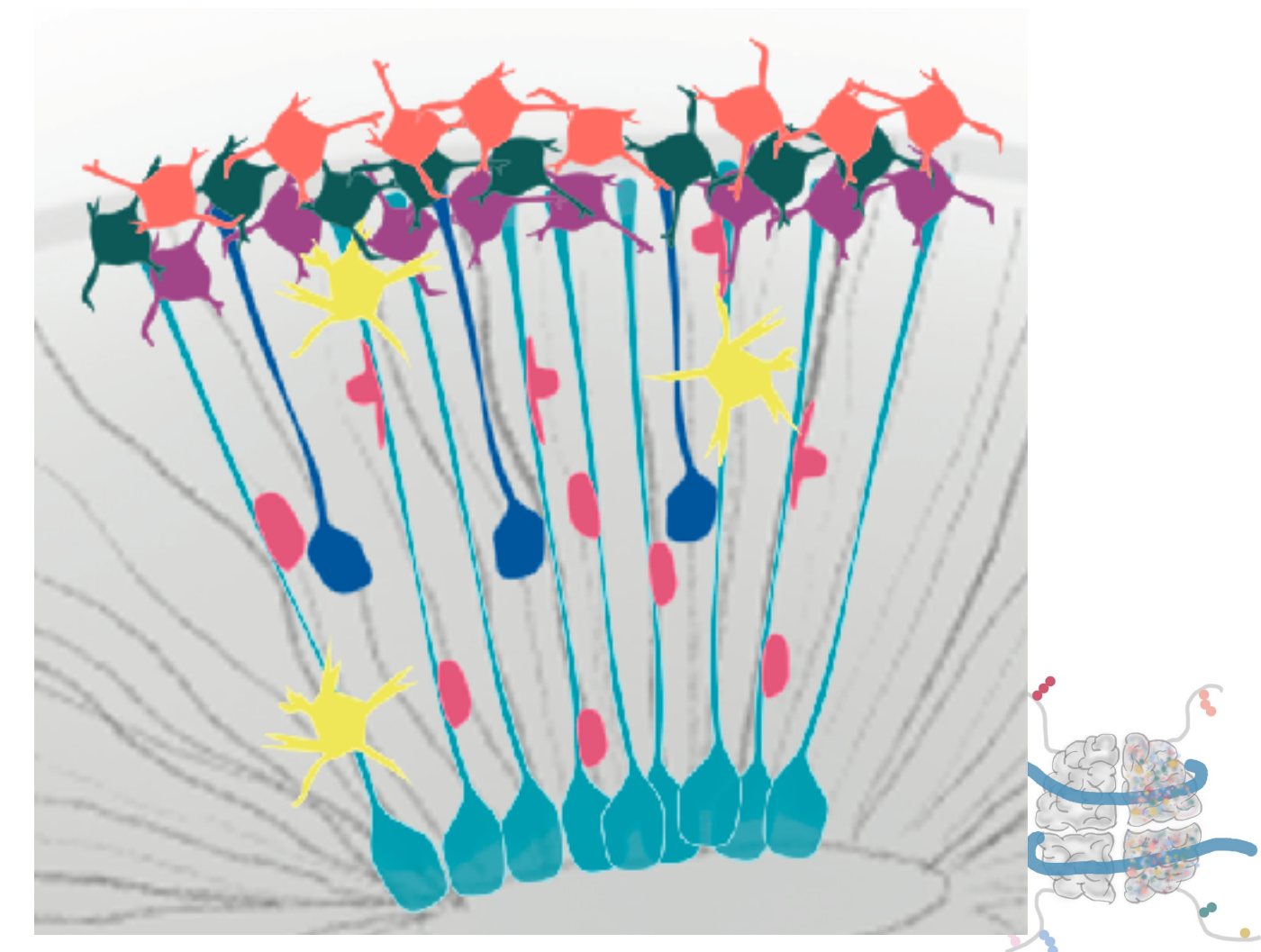
Regionalization



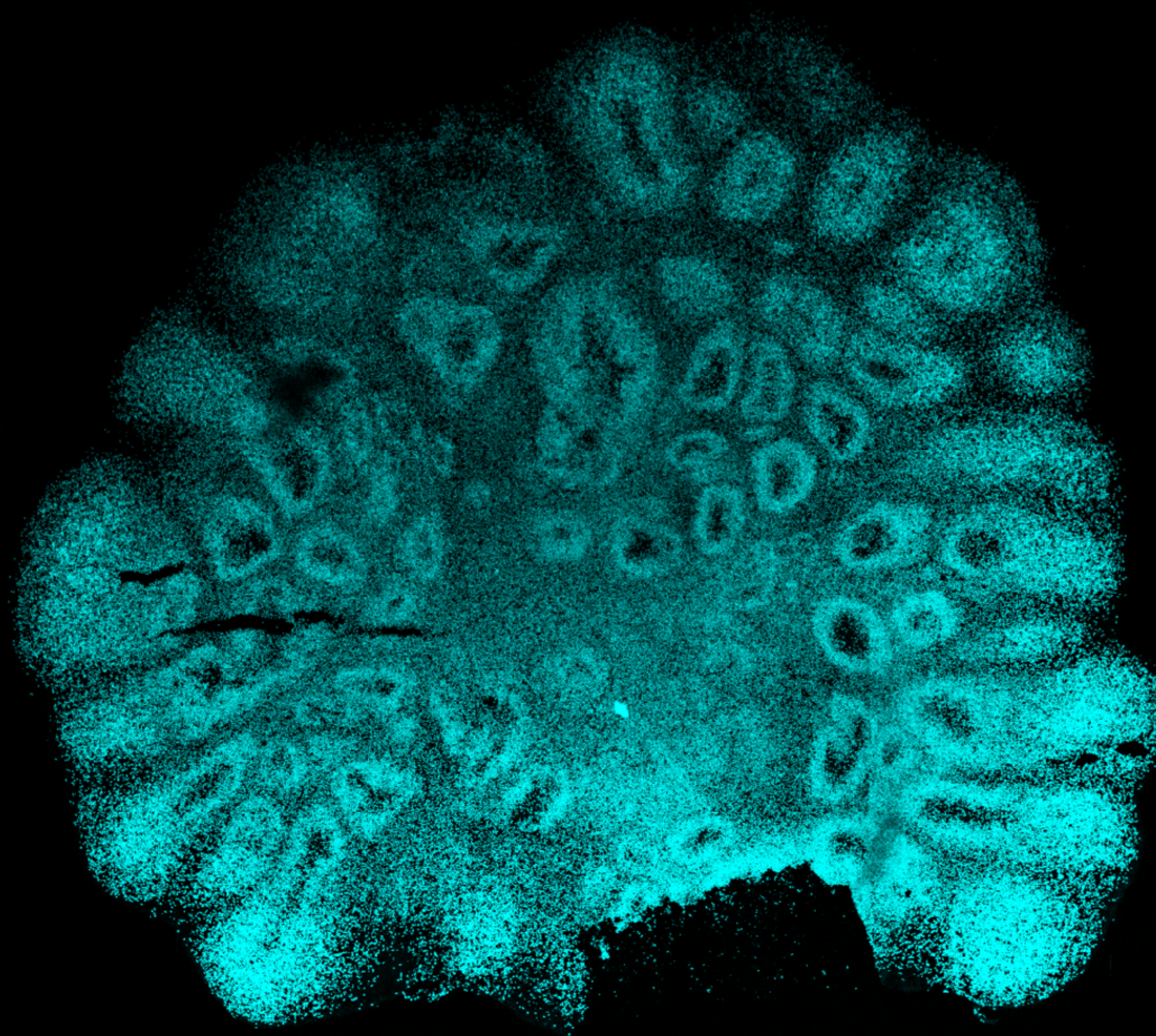
9 Months



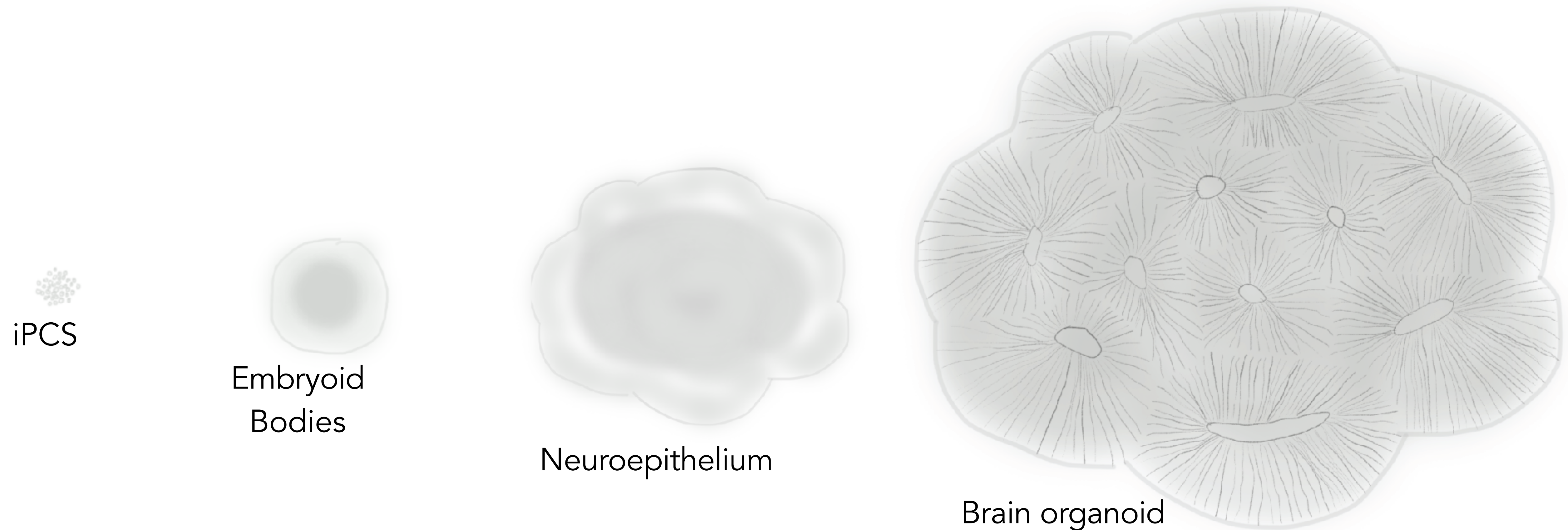
Maturation



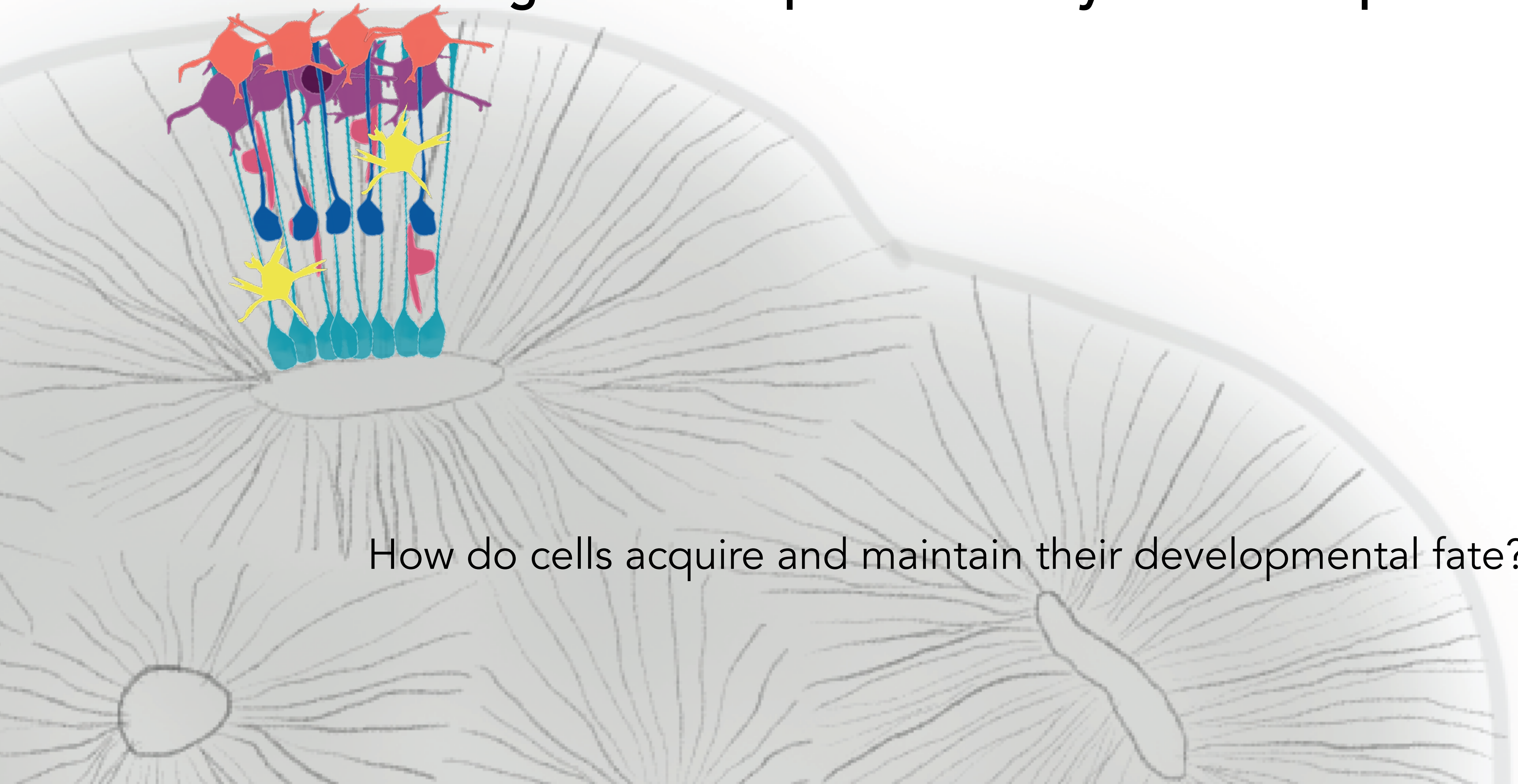
Understanding Human Brain Development using Neural Organoids



Human Neural Organoids recapitulate embryonic Development

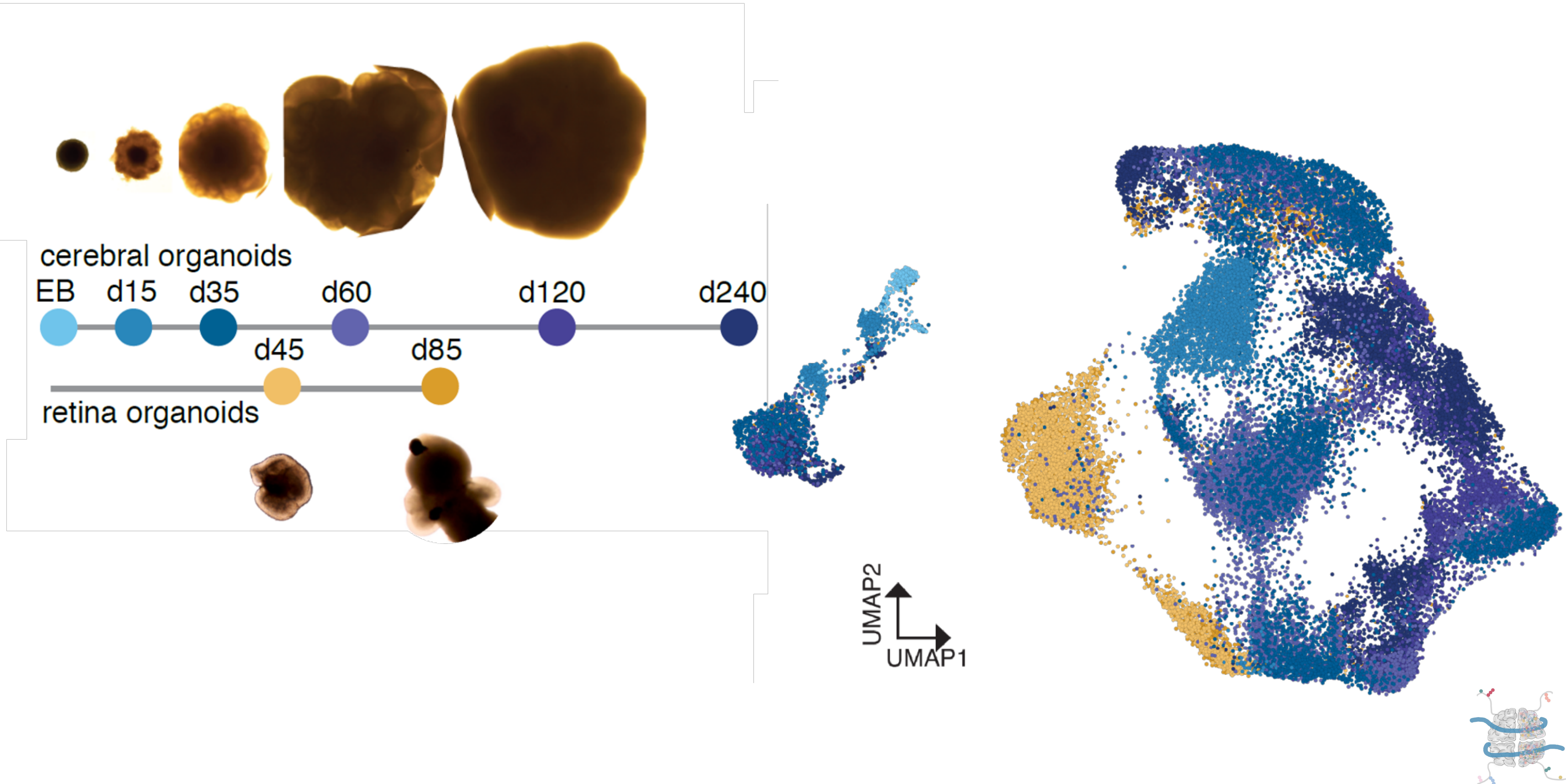


Human Neural Organoids recapitulate embryonic Development



How do cells acquire and maintain their developmental fate?

Reconstructing developmental transitions in human brain organoids



Organoids form different brain regions

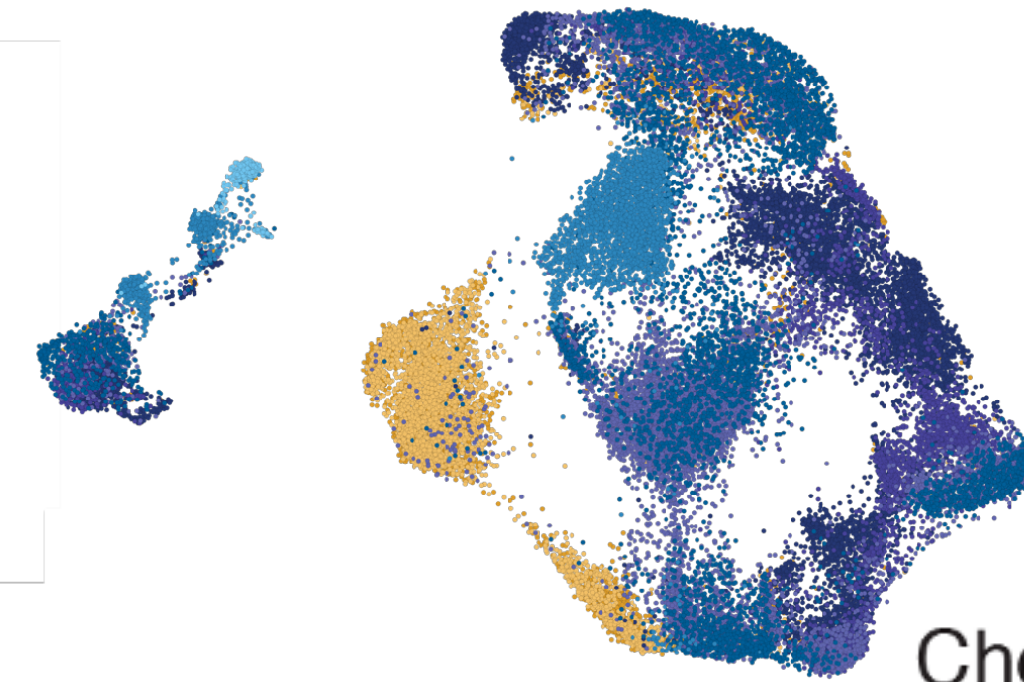
cerebral organoids

EB d15 d35 d60 d120 d240

d45

d85

retina organoids



38,149 cells

Choroid plexus

Diencephalon progenitors

Astrocytes

PSC

Non-neural ectoderm

Neuro-ectoderm

Mesen-/Rhombencephalon progenitors

Mesenchyme

Retinal progenitors (RPs)

Retinal ganglion cells (RGCs)

OPCs

Tel. prog.

IPs

Neurons

UMAP2
UMAP1

SIX6 (Retina)

POU5F1 (PSC)

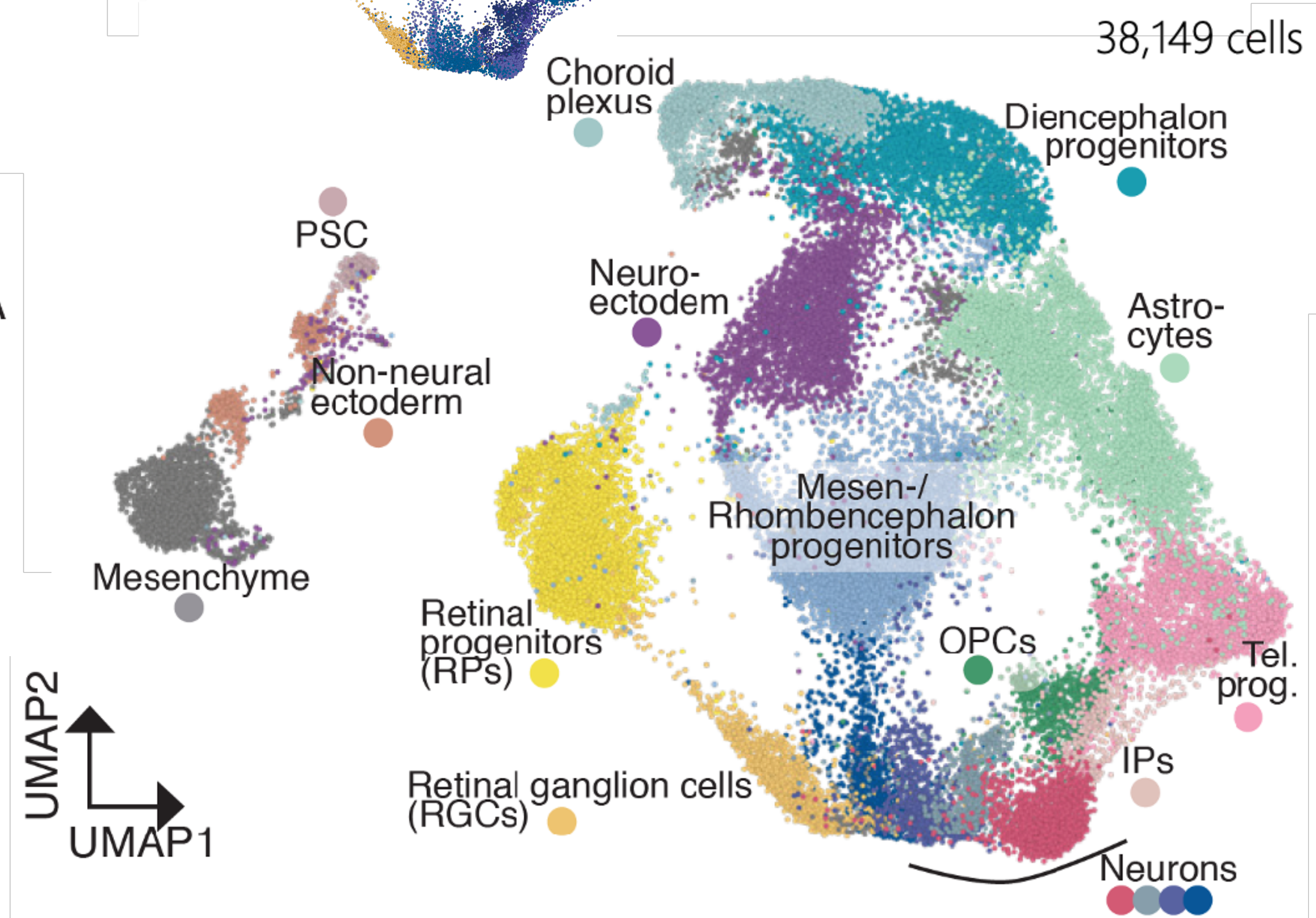
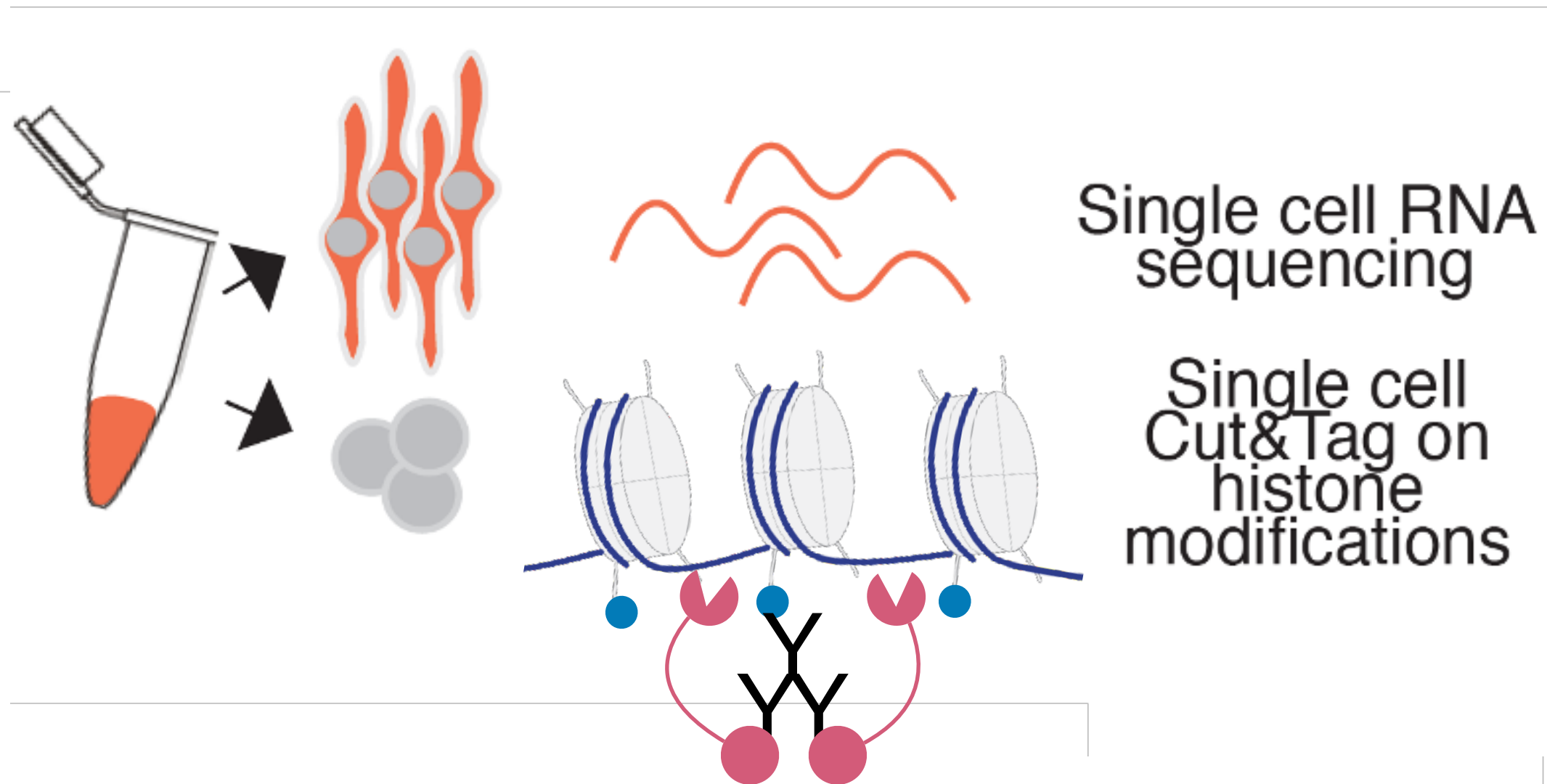
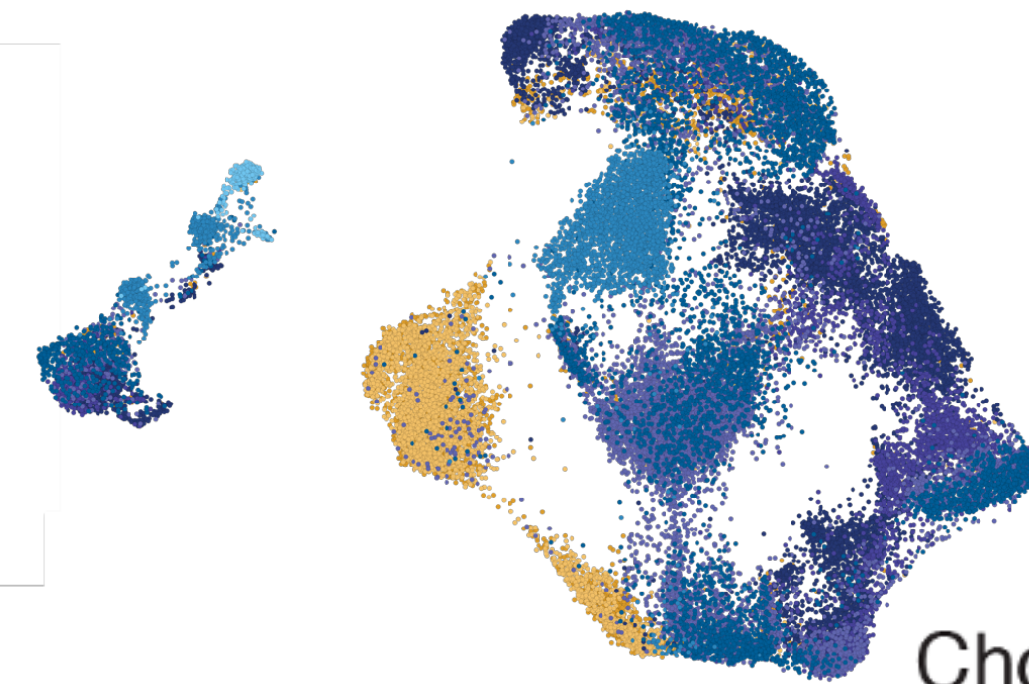
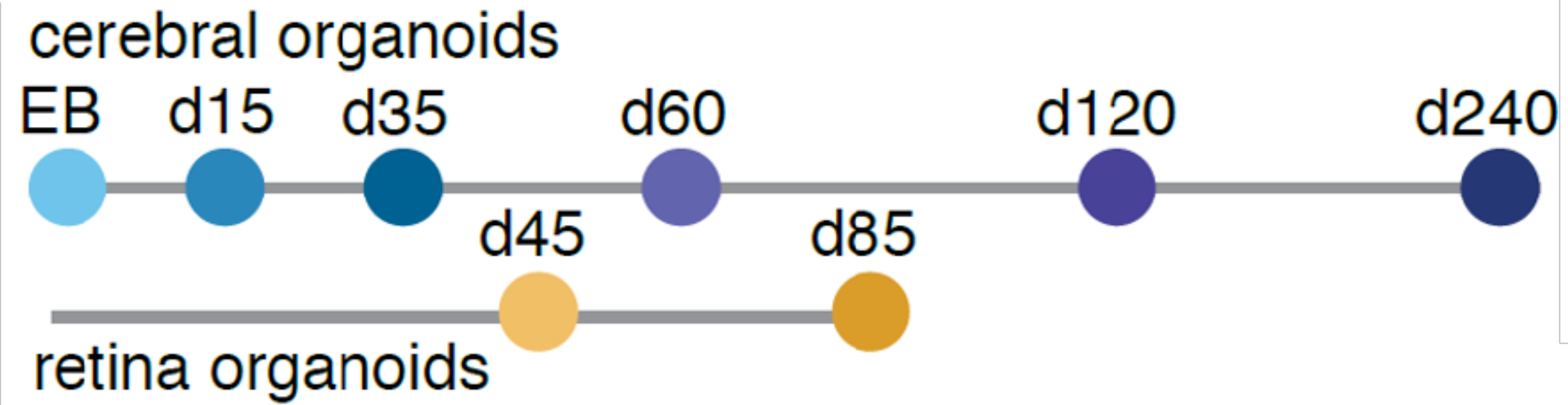
FOXP1 (Forebrain)

LHX5 (Neural progenitors & Non-tel. neurons)

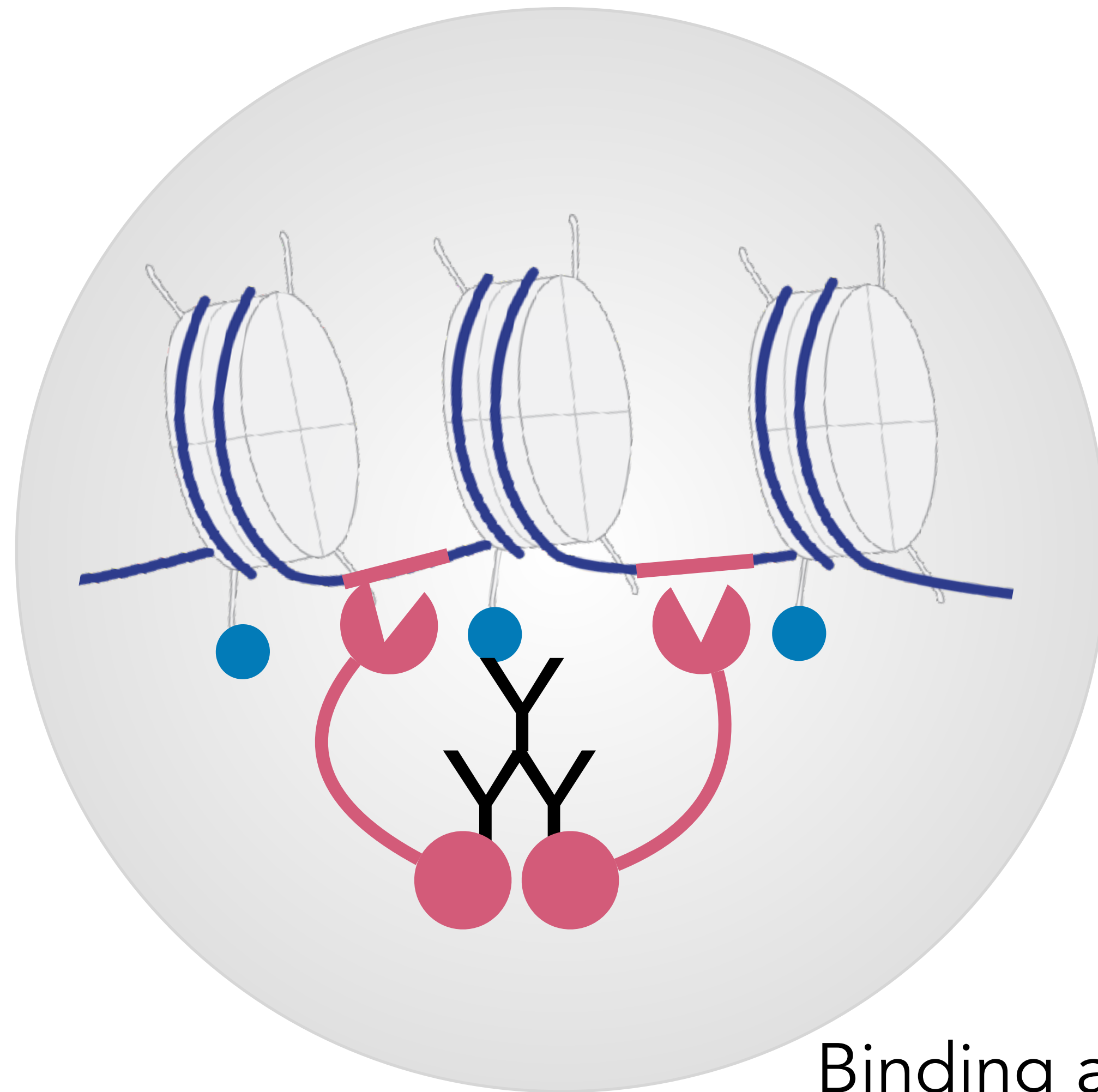
NEUROD2 (Cortical neurons)

HOXB2 (Rhomb. prog. & neurons)

Organoids form different brain regions

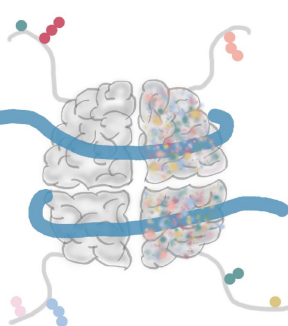
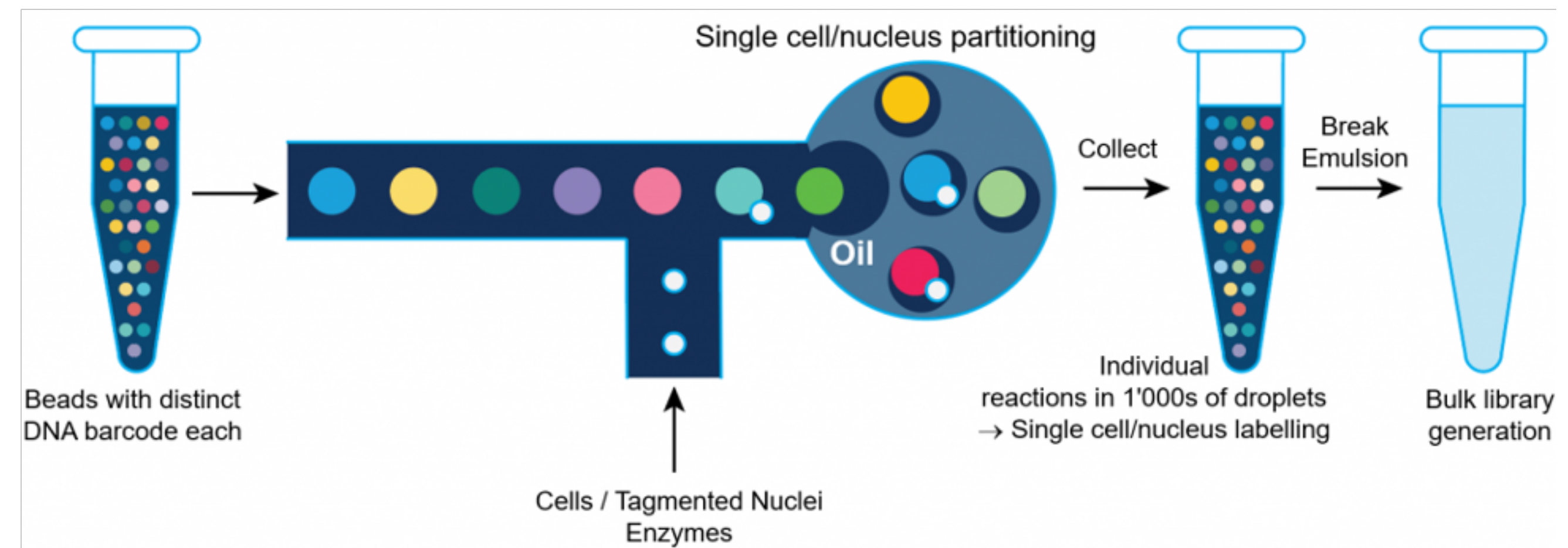


Mapping histone modifications in single cells with CUT&Tag



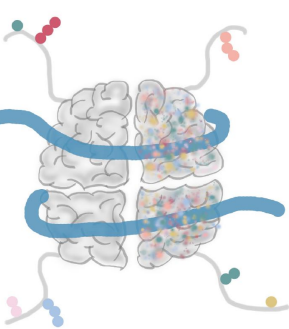
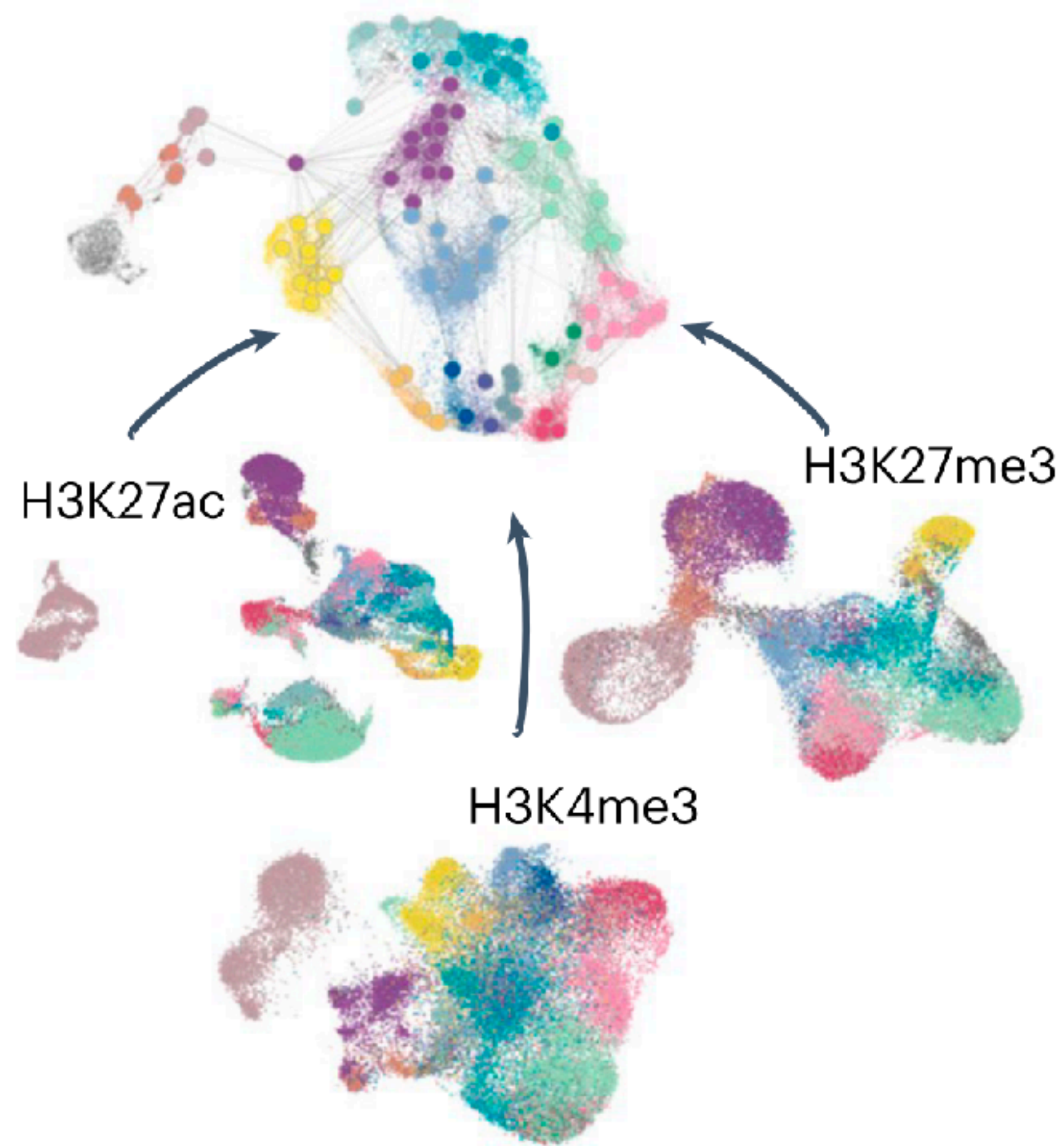
Binding and Tagmentation *in situ* inside the nucleus

Prepare single cell Cut&Tag libraries using 10x Genomics



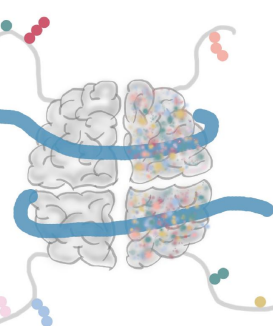
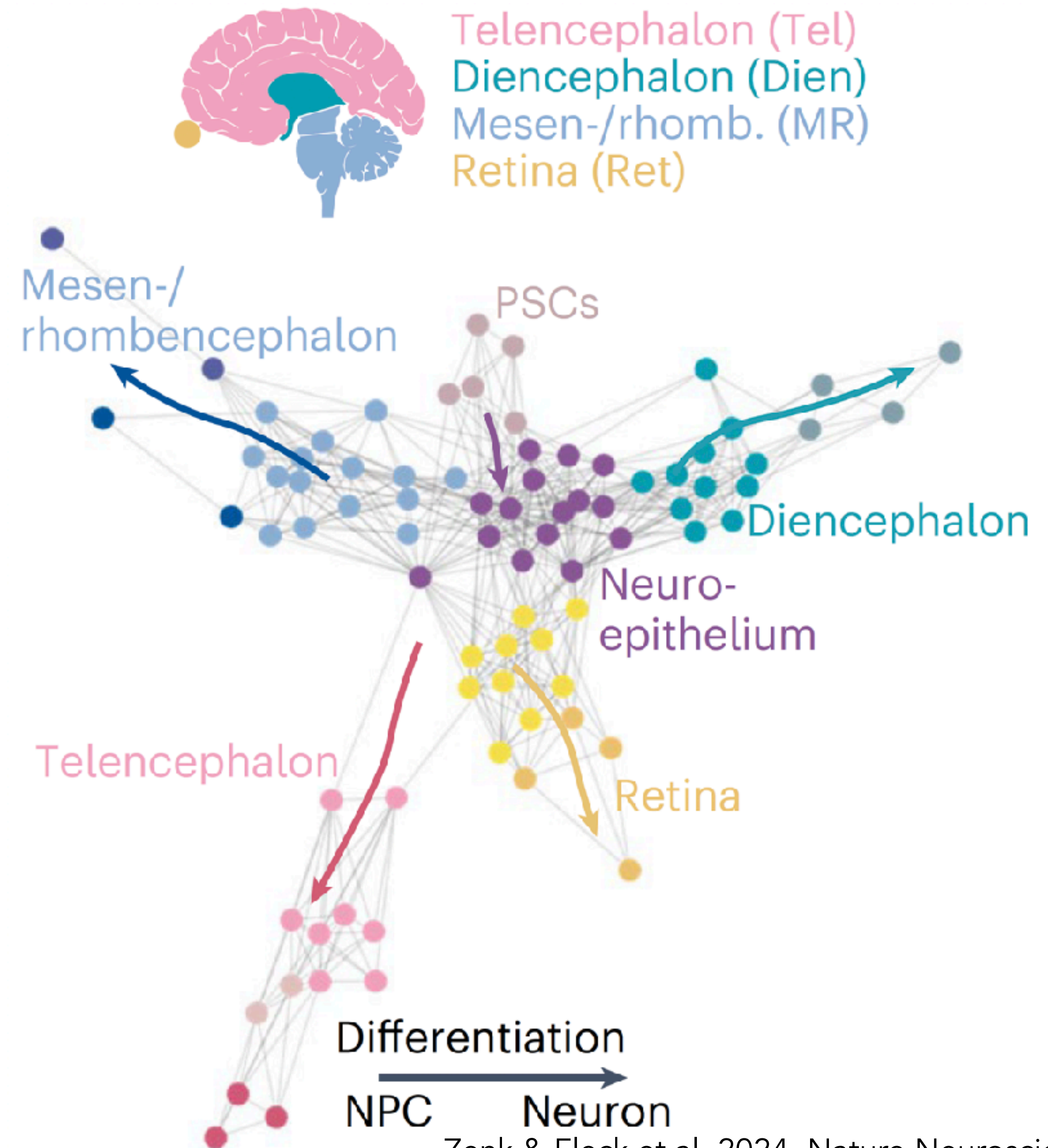
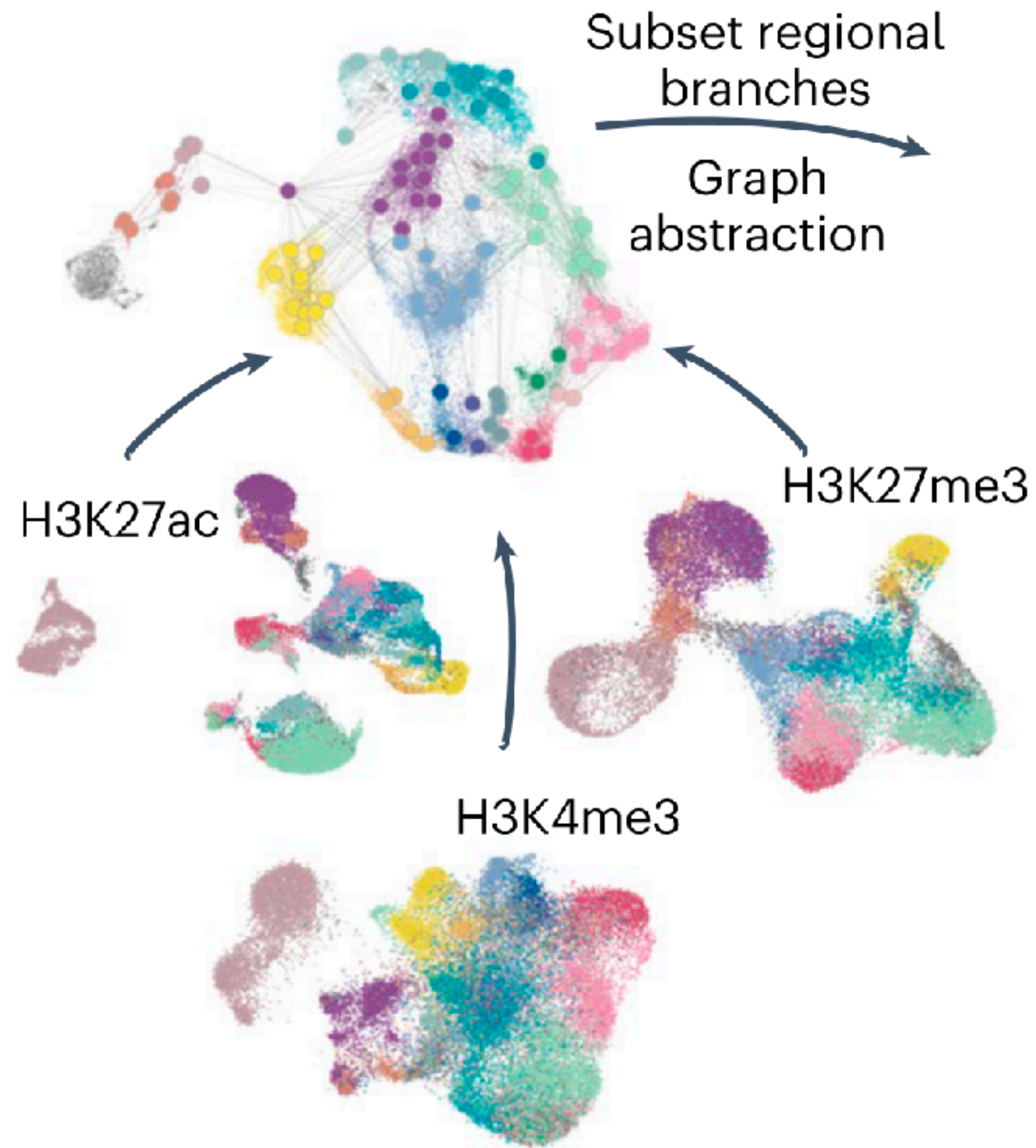
Integrating RNA expression and histone modifications

Multimodal integration of scRNA
and scCUT&Tag data in
high-resolution clusters

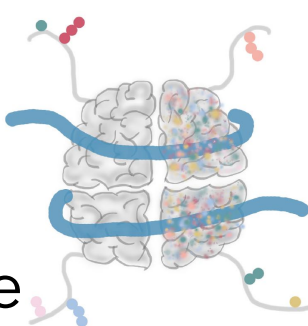
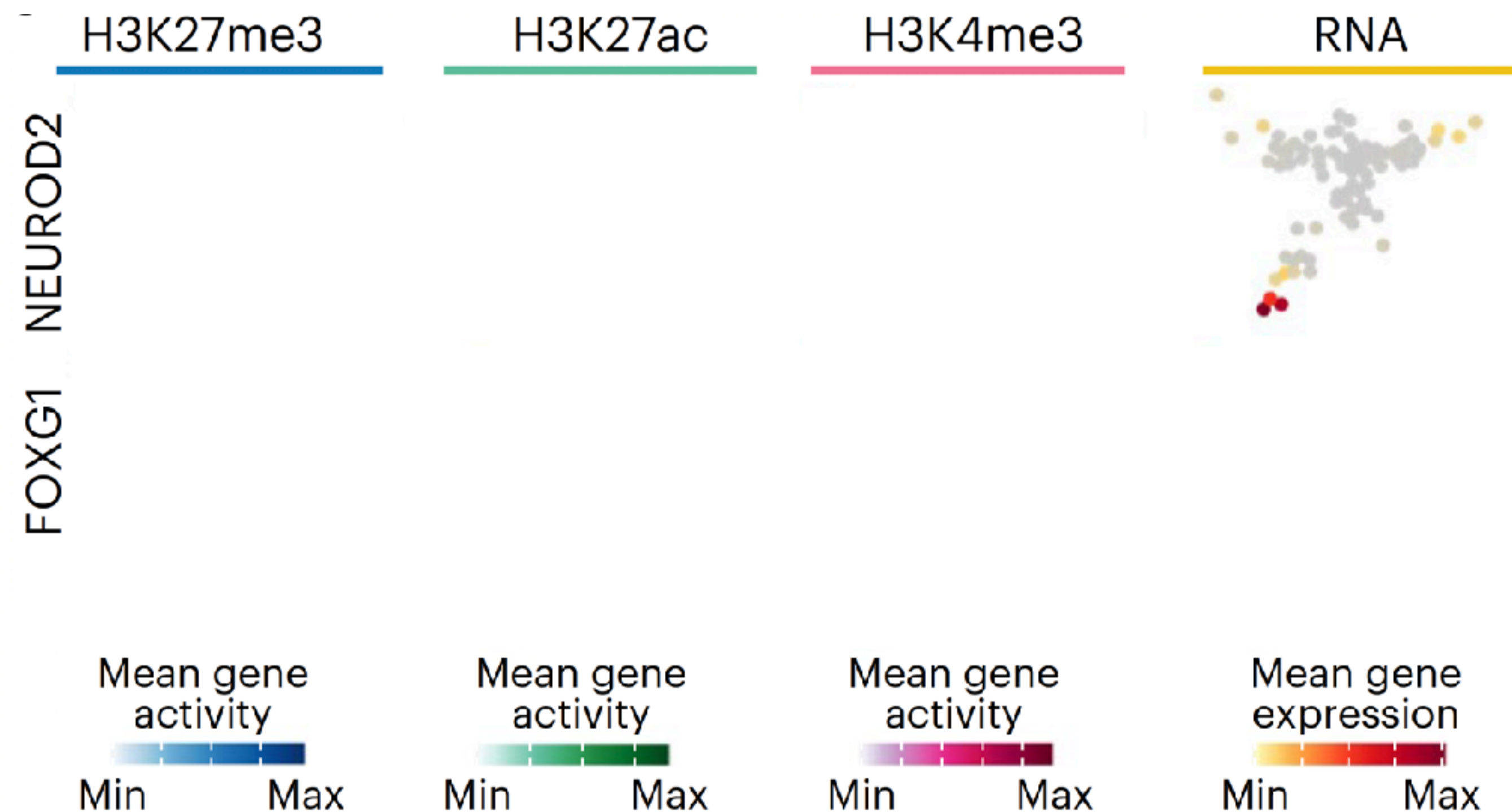
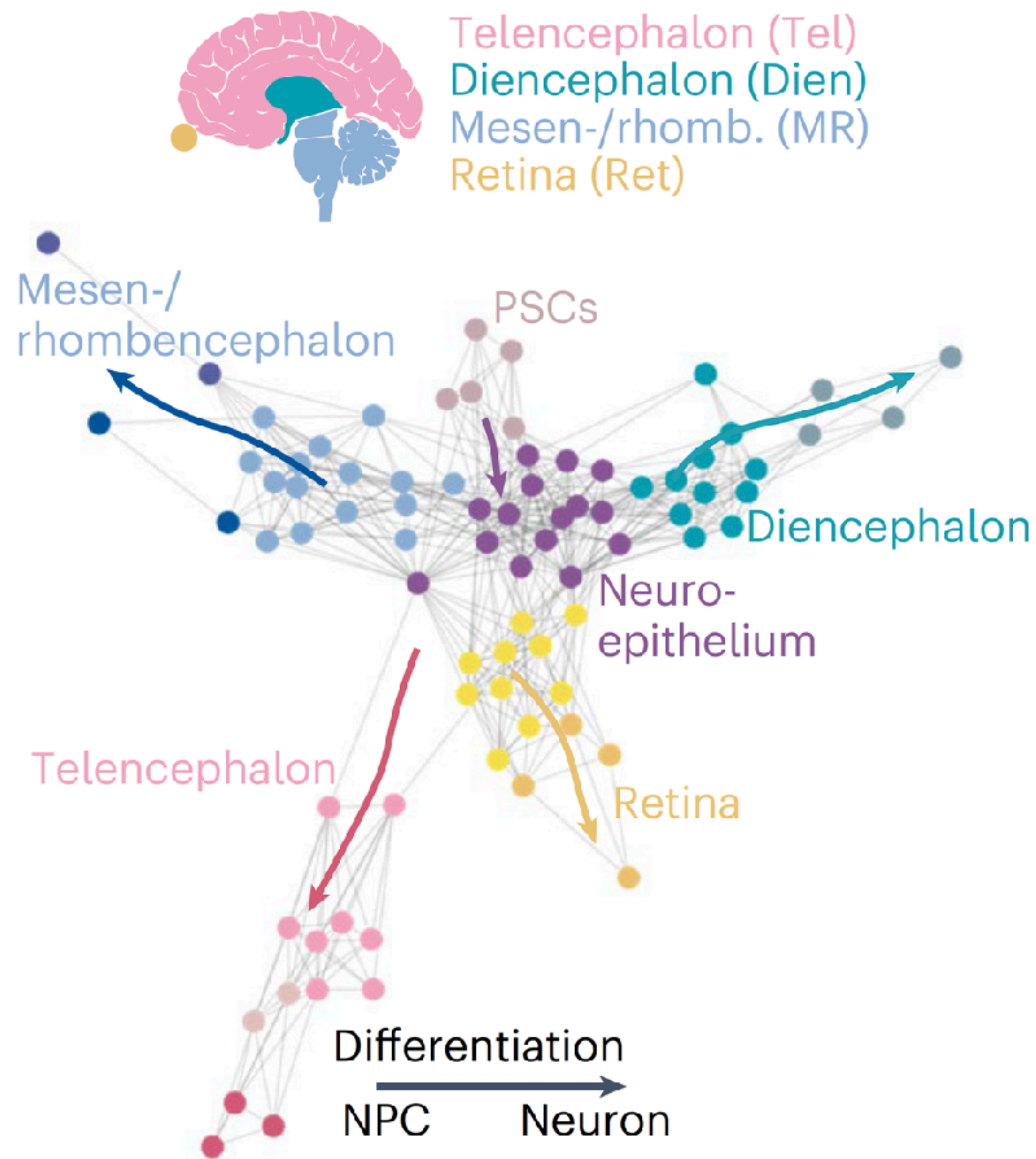


Integrating RNA expression and histone modifications

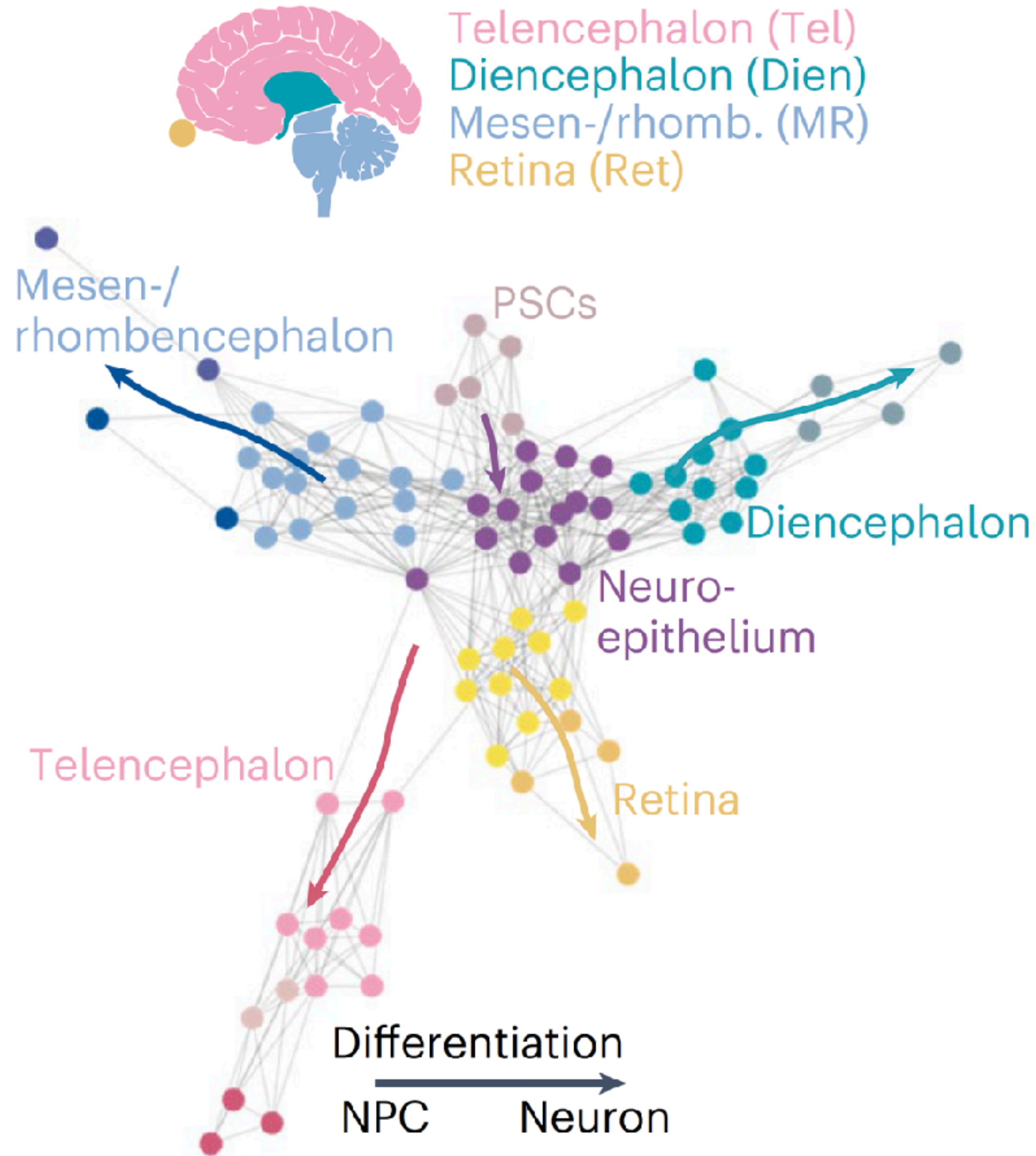
Multimodal integration of scRNA
and scCUT&Tag data in
high-resolution clusters



Building a model of gene regulation during brain development



Building a model of gene regulation during brain development

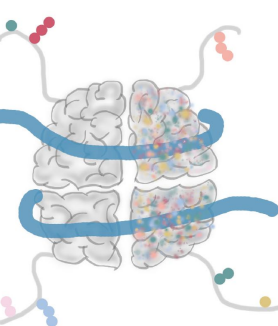


Check the regulatory pattern of any gene during early brain development!

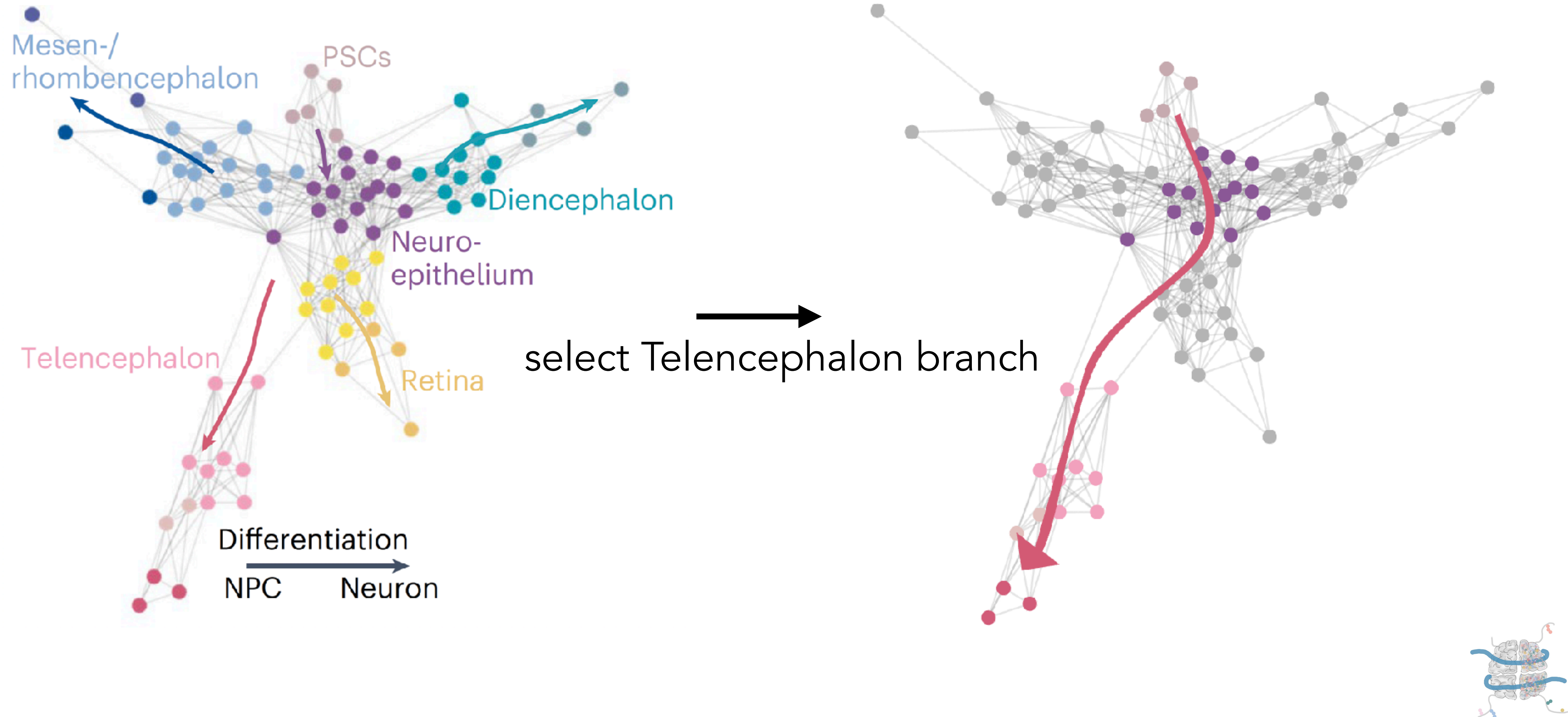
EpiScape



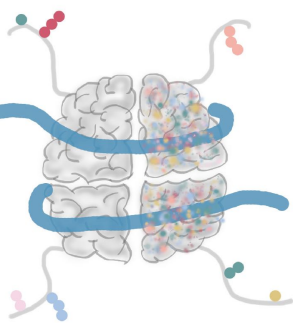
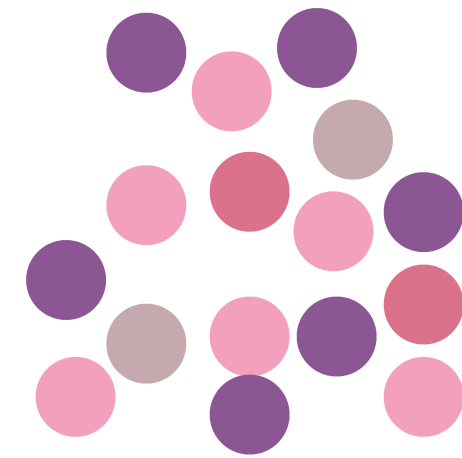
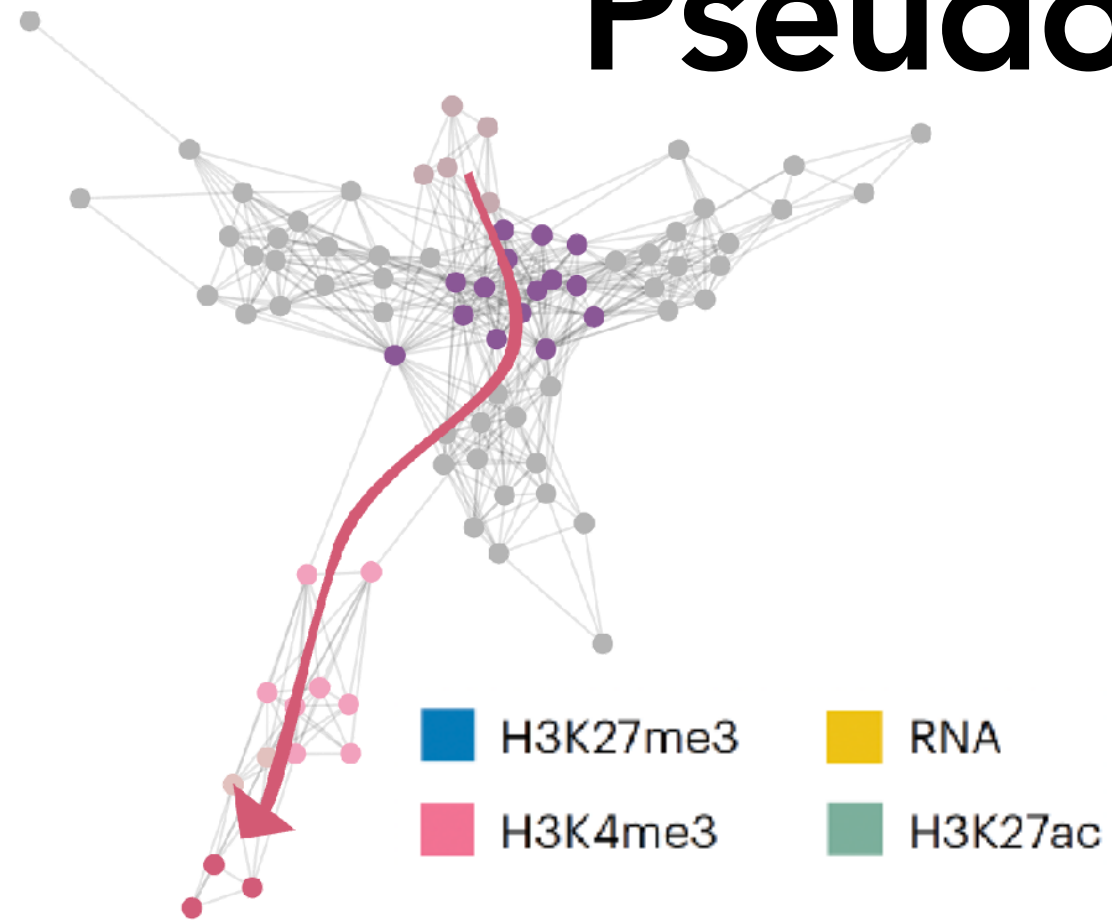
Zenk & Fleck et al. 2024, Nature Neuroscience



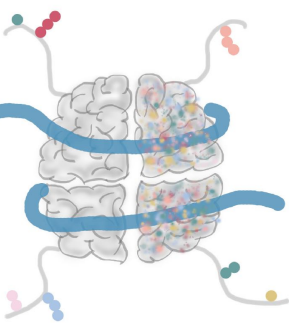
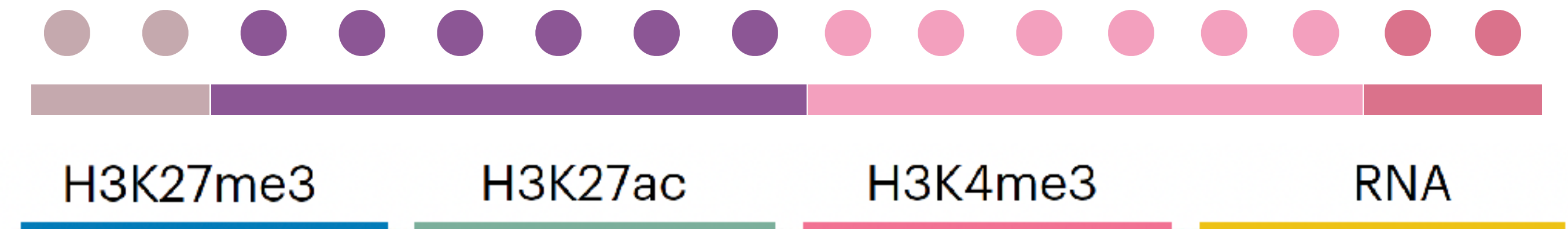
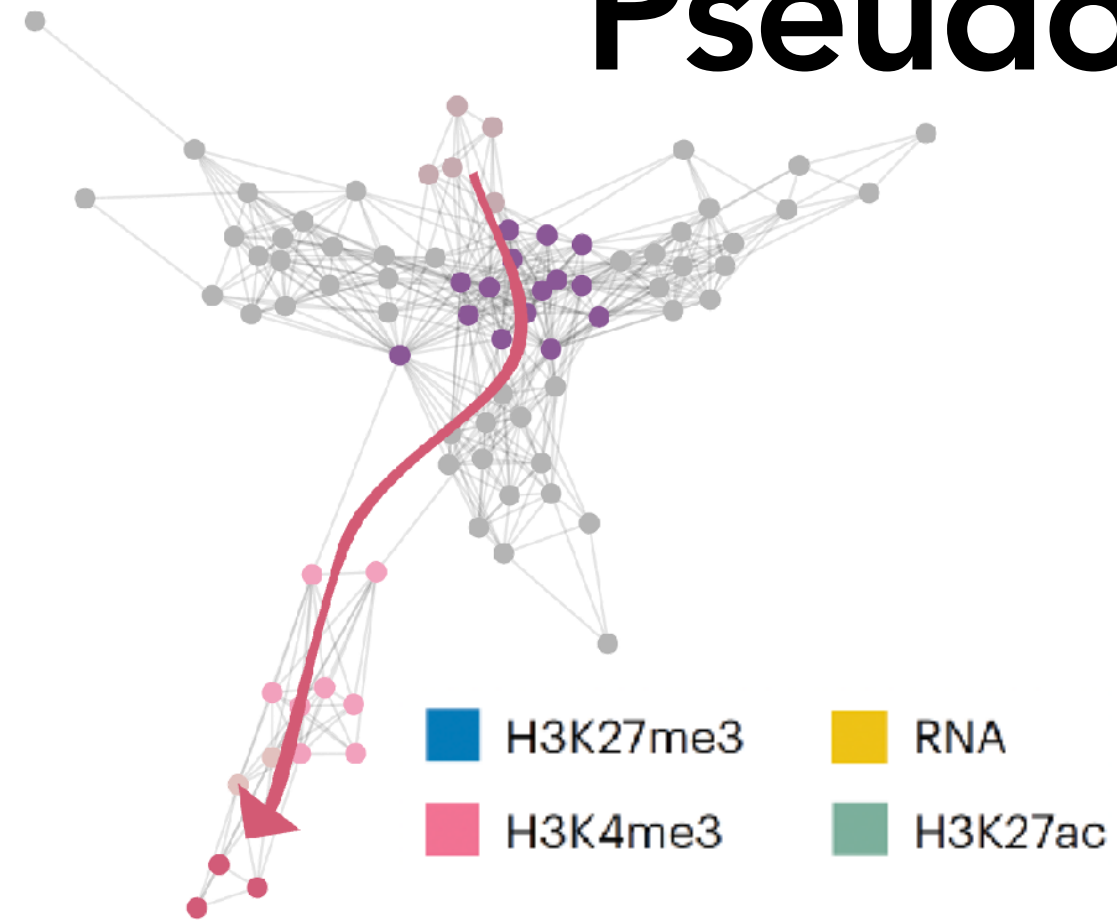
Investigating Chromatin Regulation during Differentiation



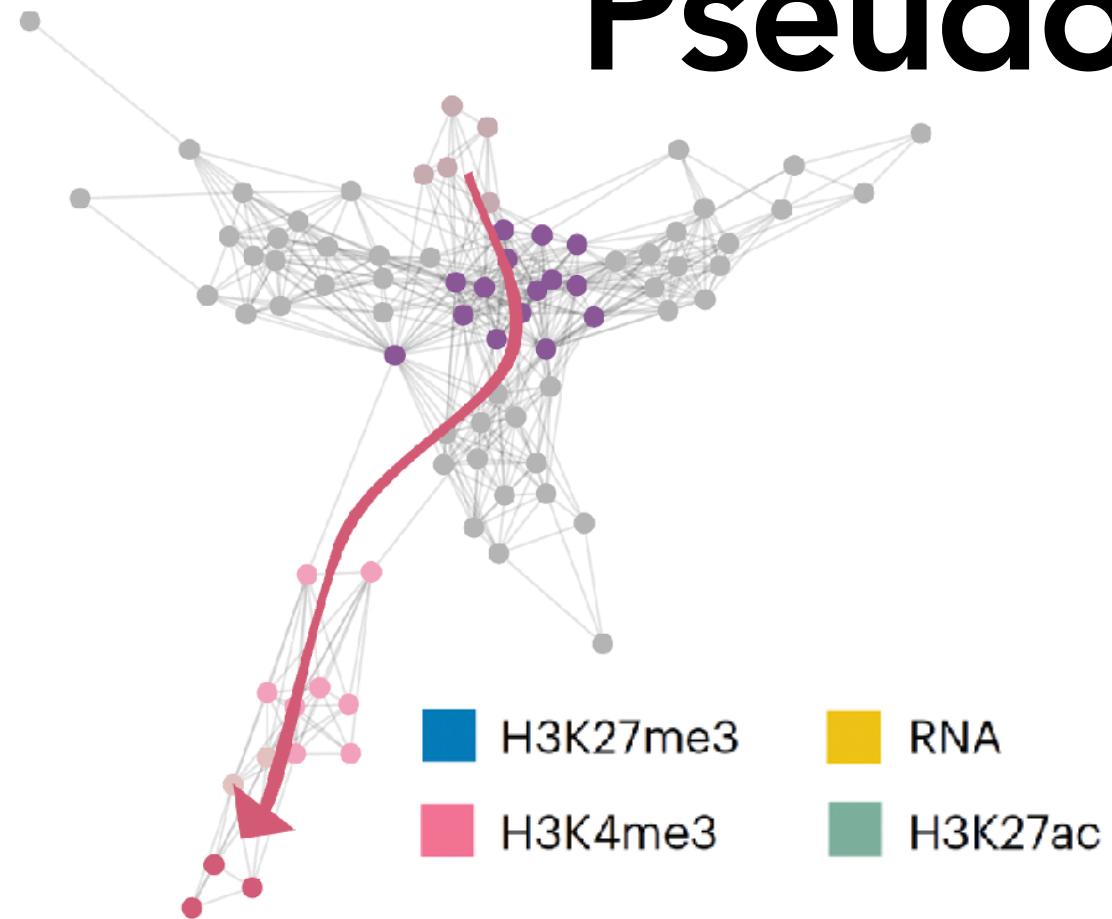
Pseudotime alignment of RNA and histone modifications



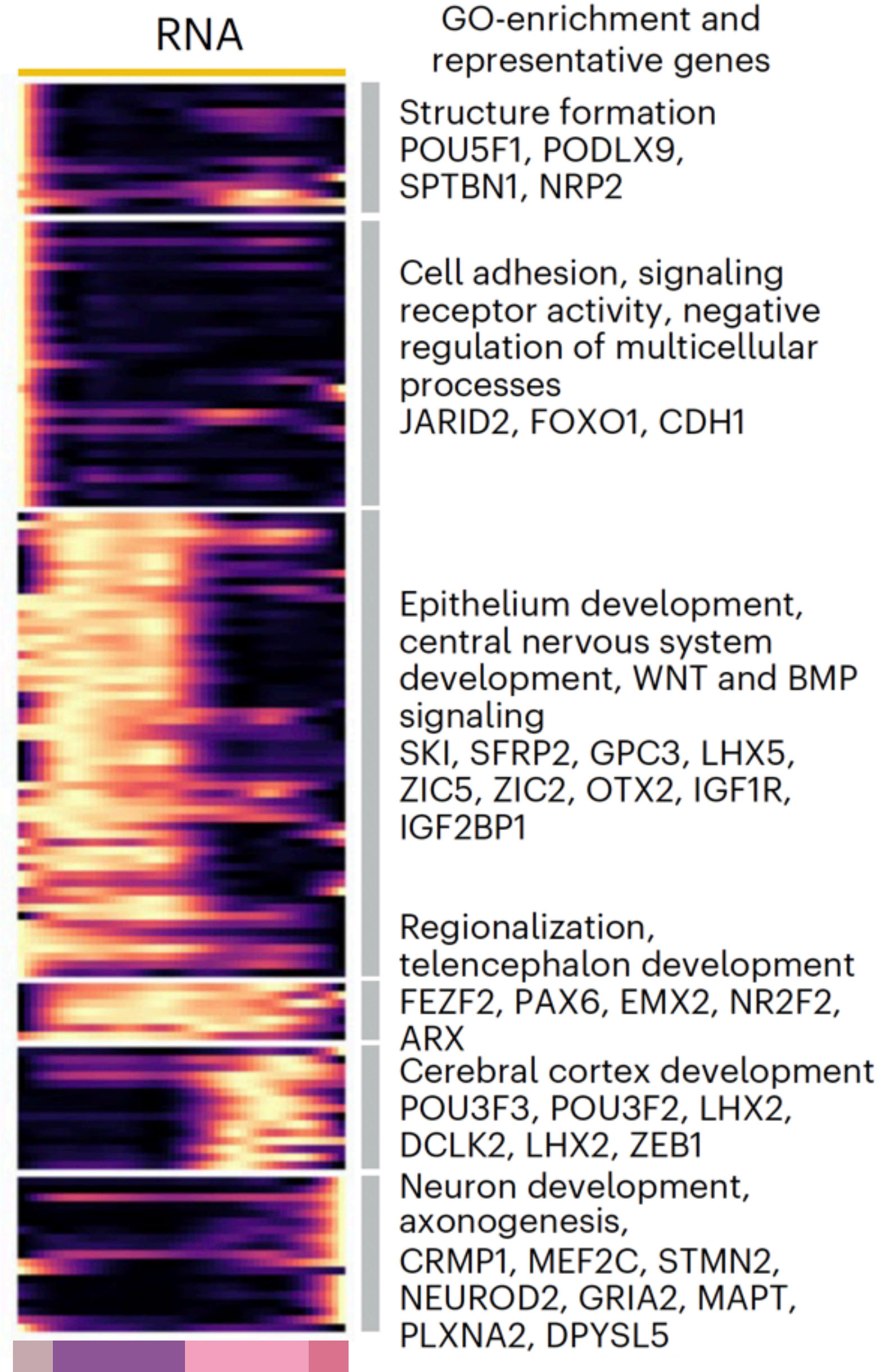
Pseudotime alignment of RNA and histone modifications



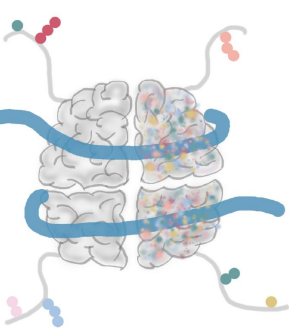
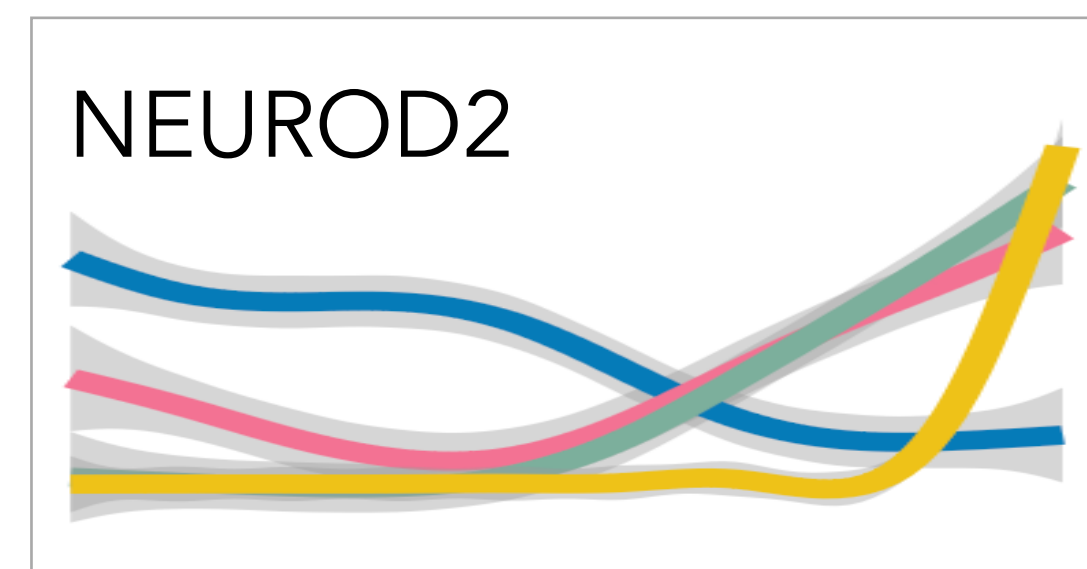
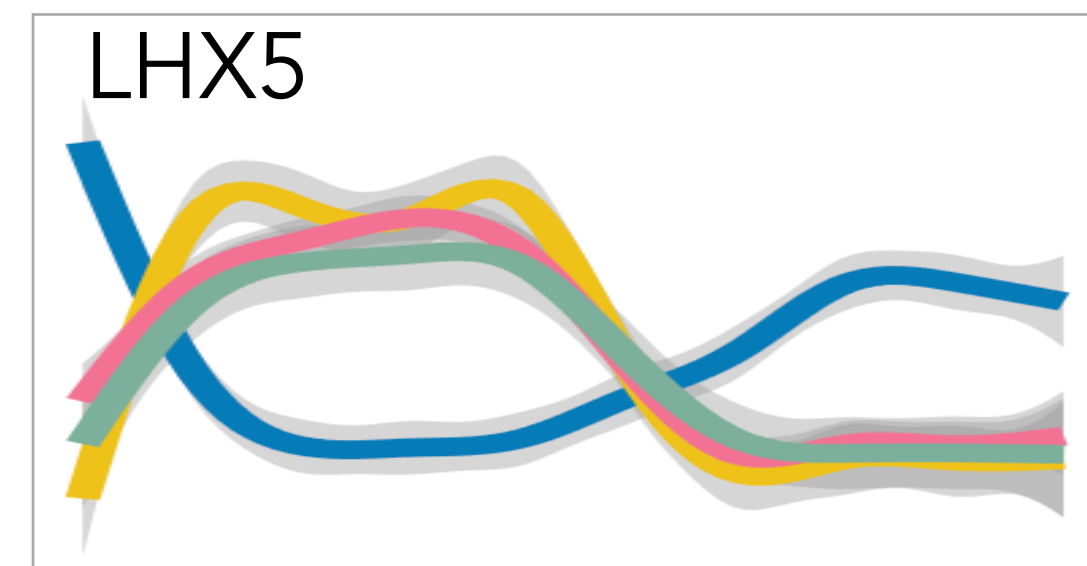
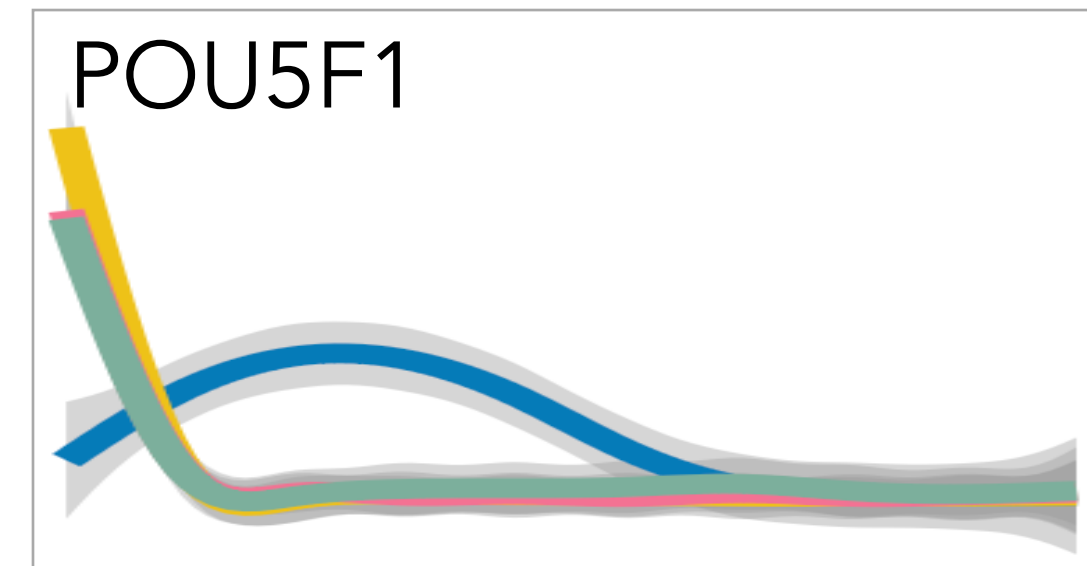
Pseudotime alignment of RNA and histone modifications



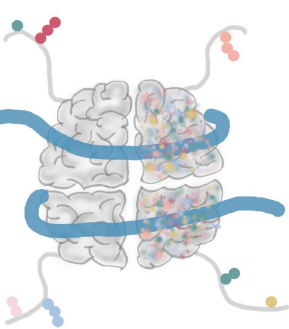
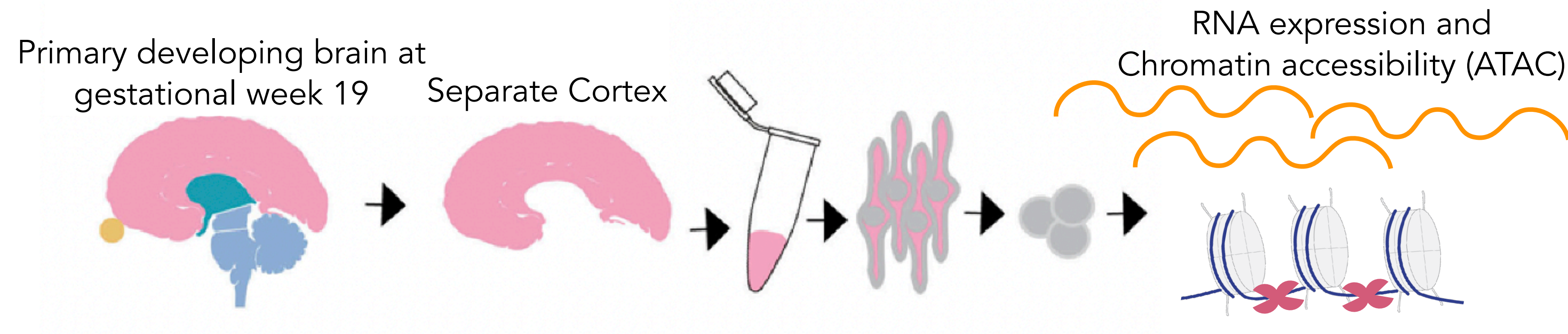
Min-max scaled gene expression/activity 0 1



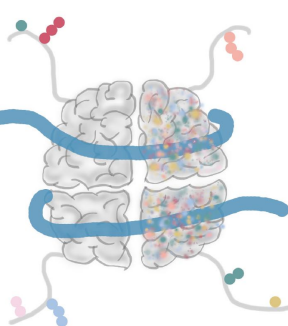
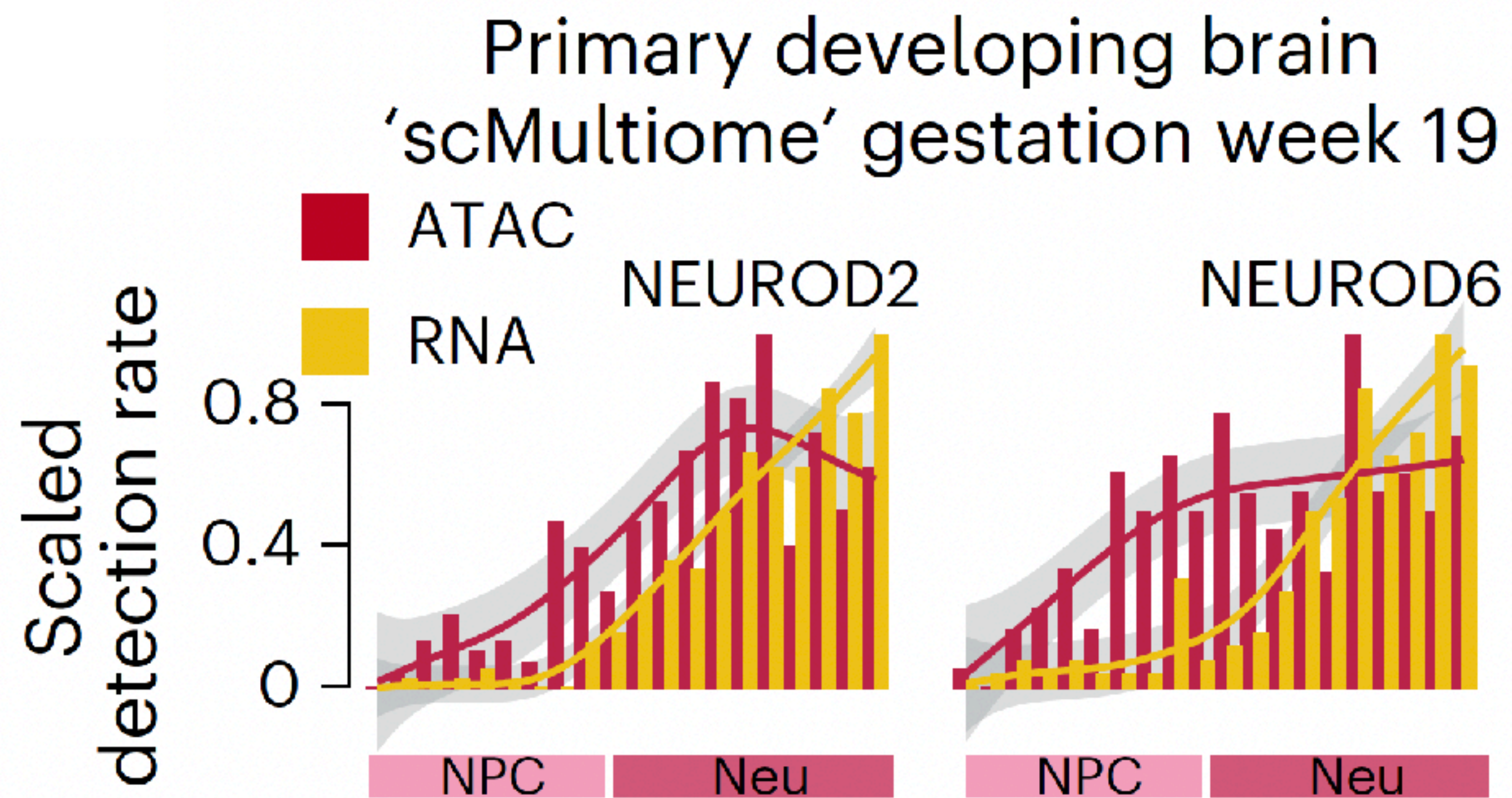
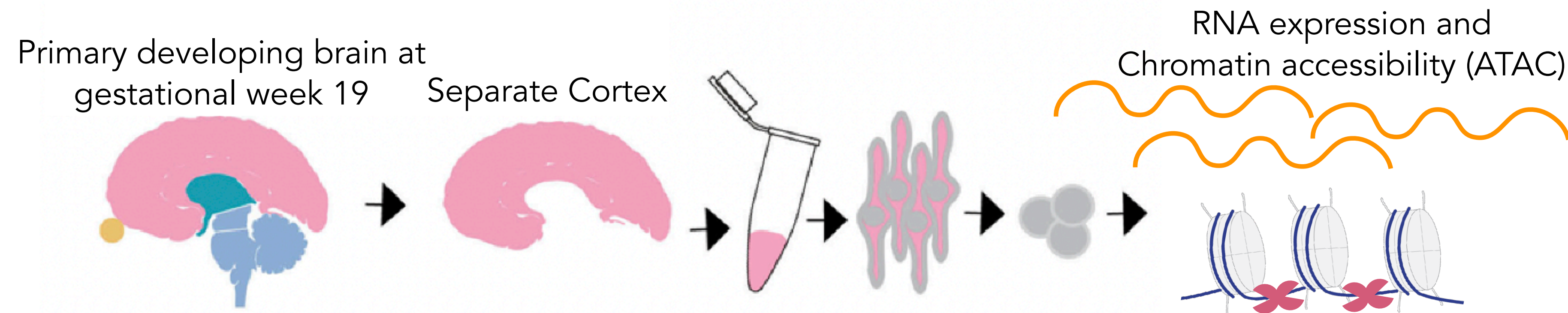
■ H3K27me3 ■ RNA
■ H3K4me3 ■ H3K27ac



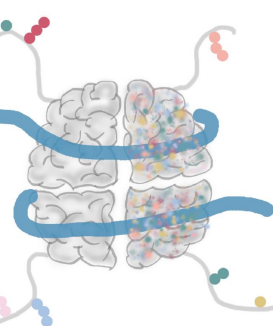
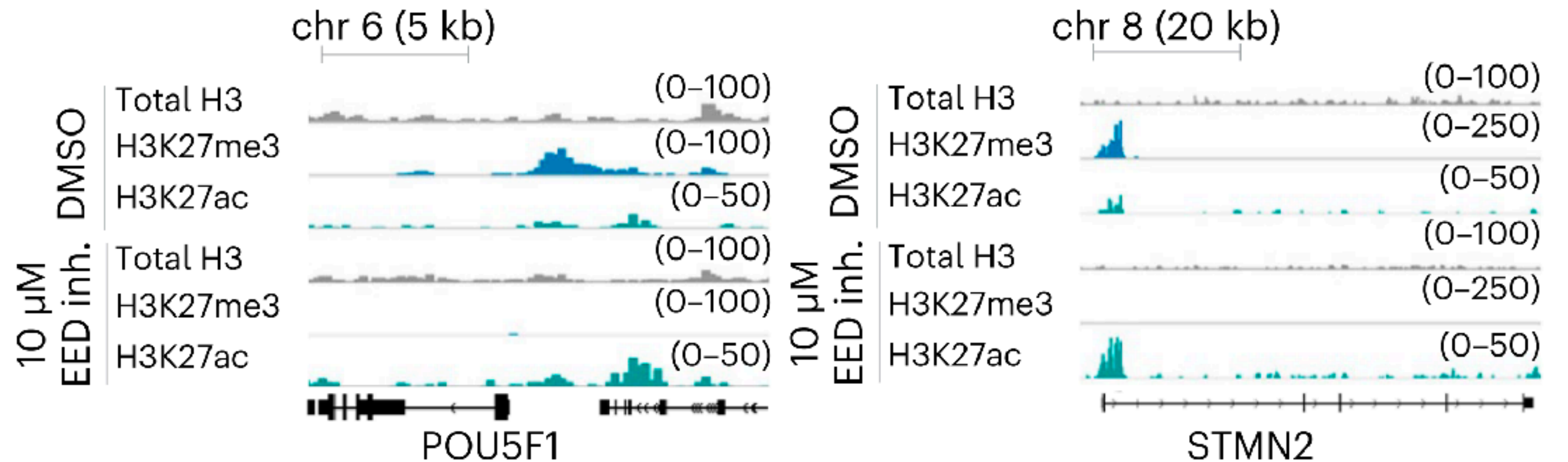
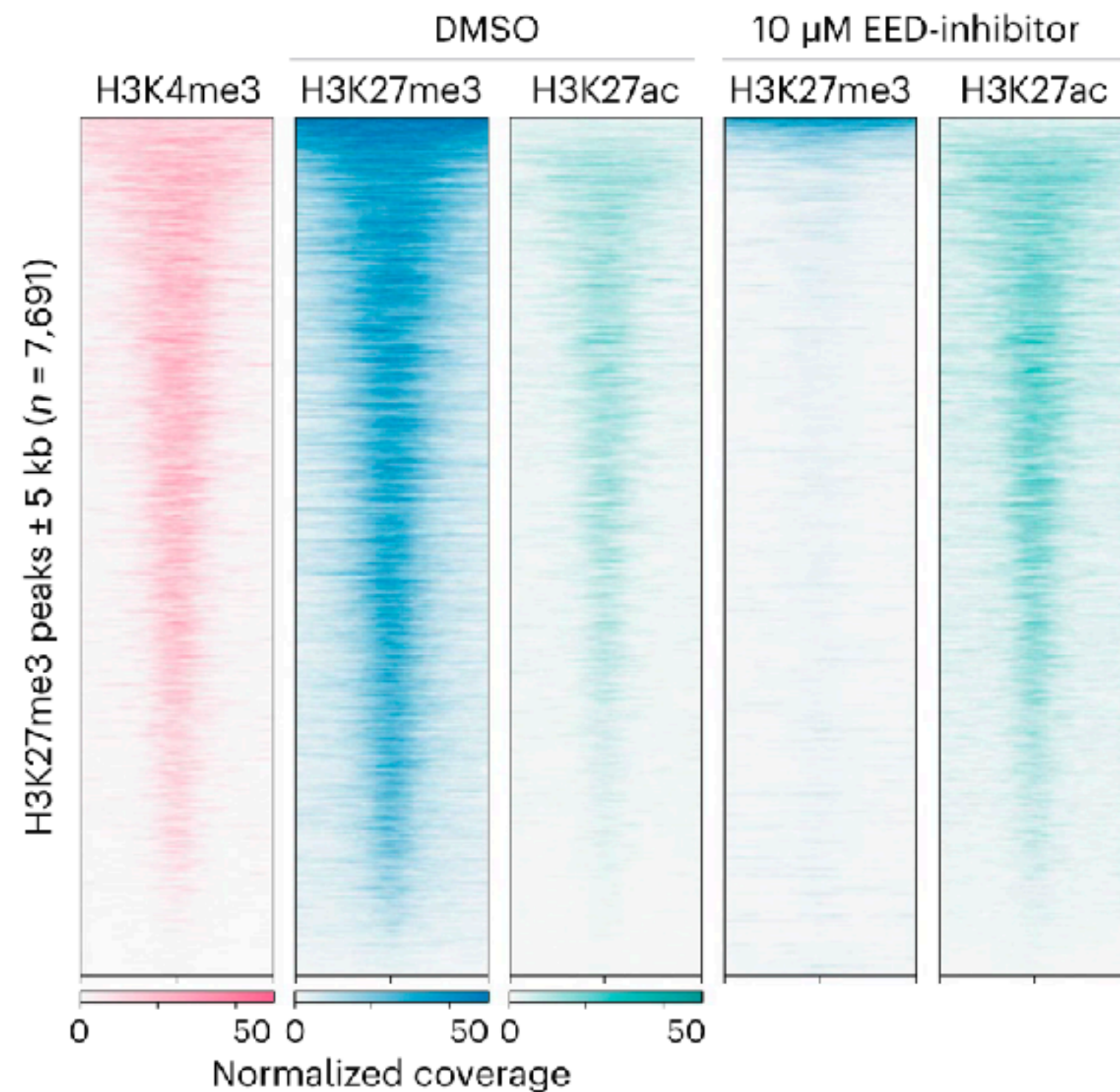
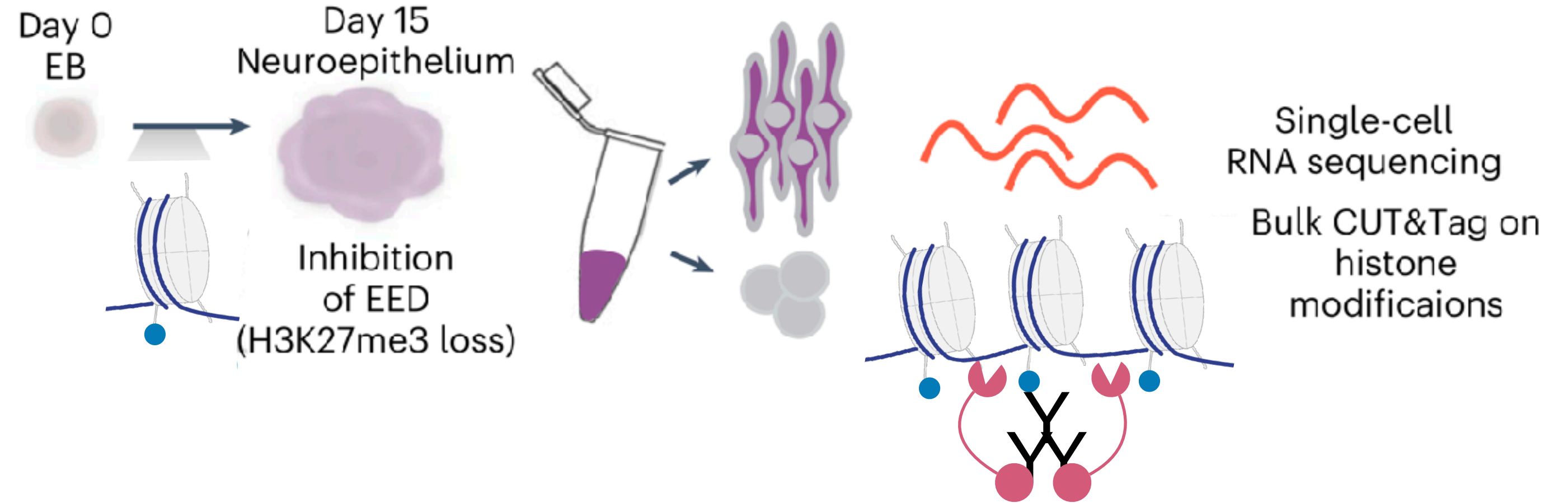
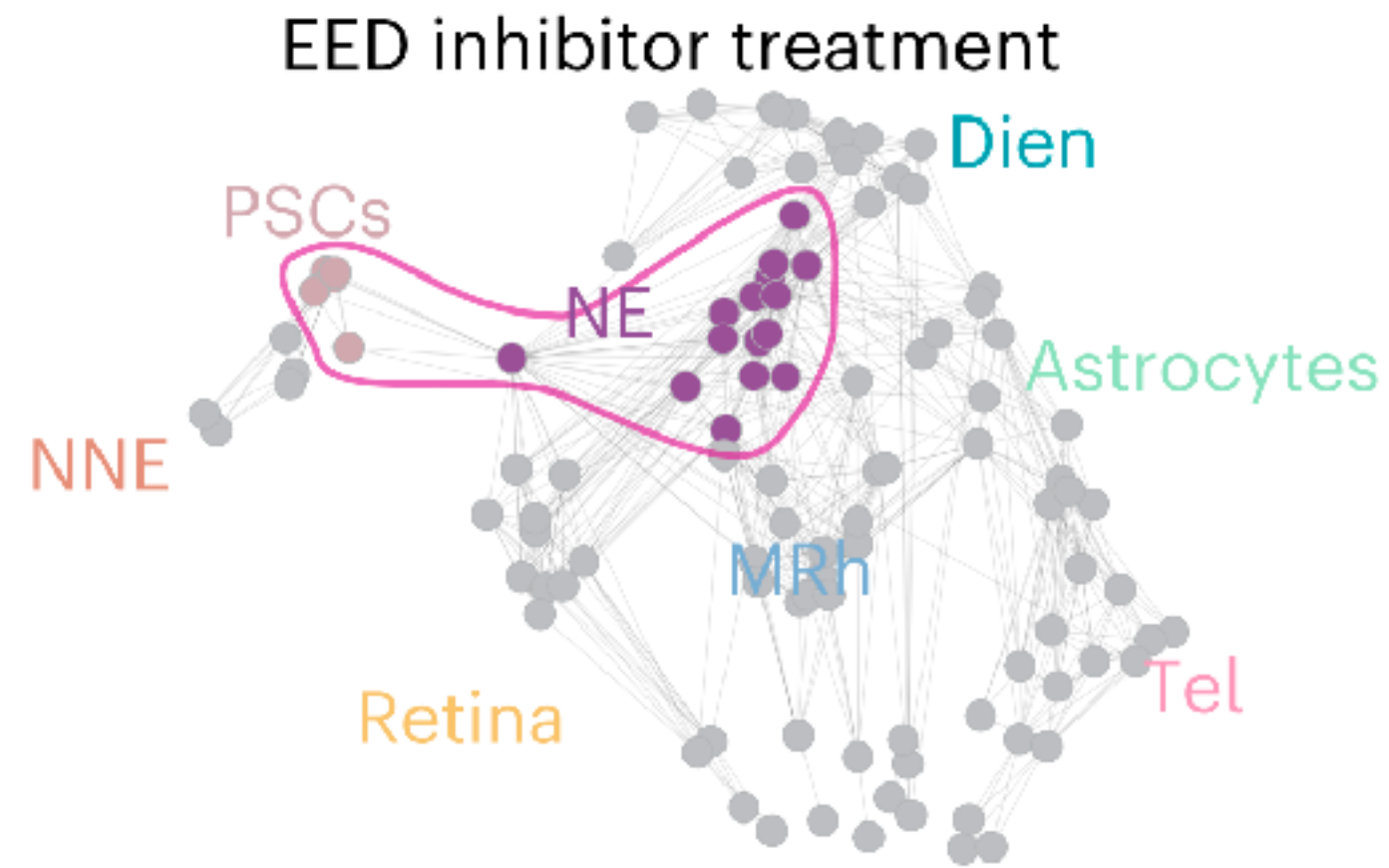
Chromatin accessibility precedes transcription at neuronal genes



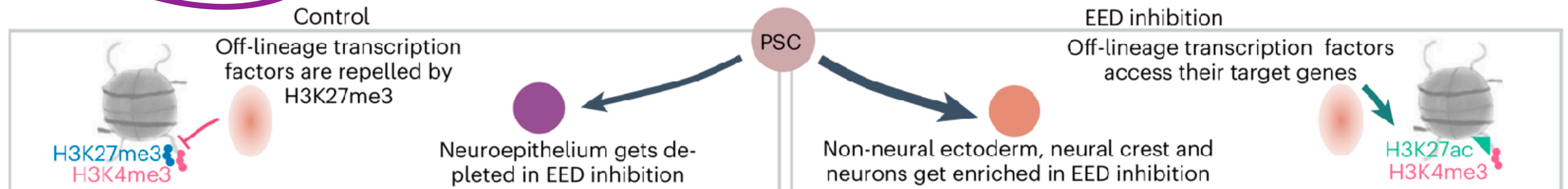
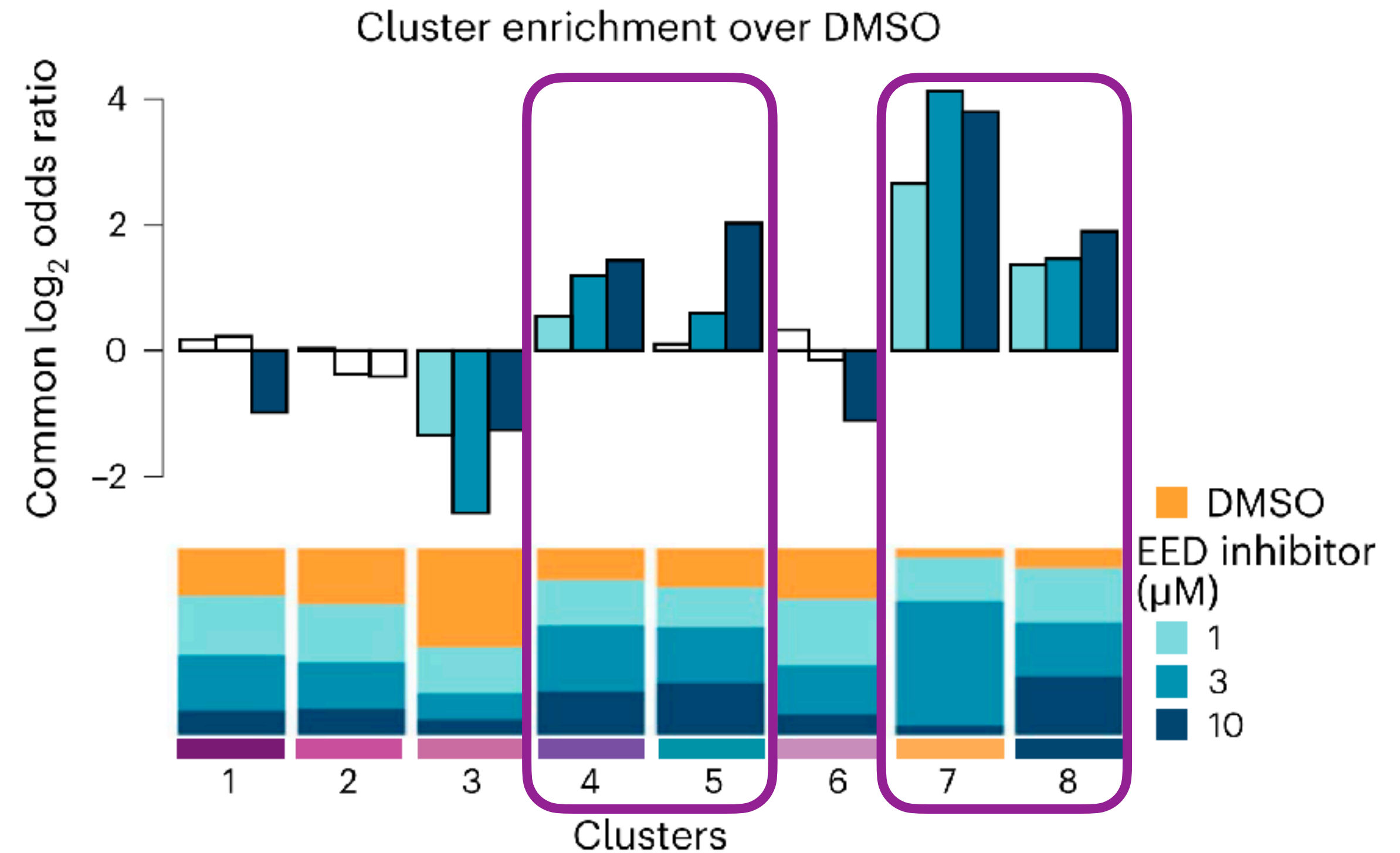
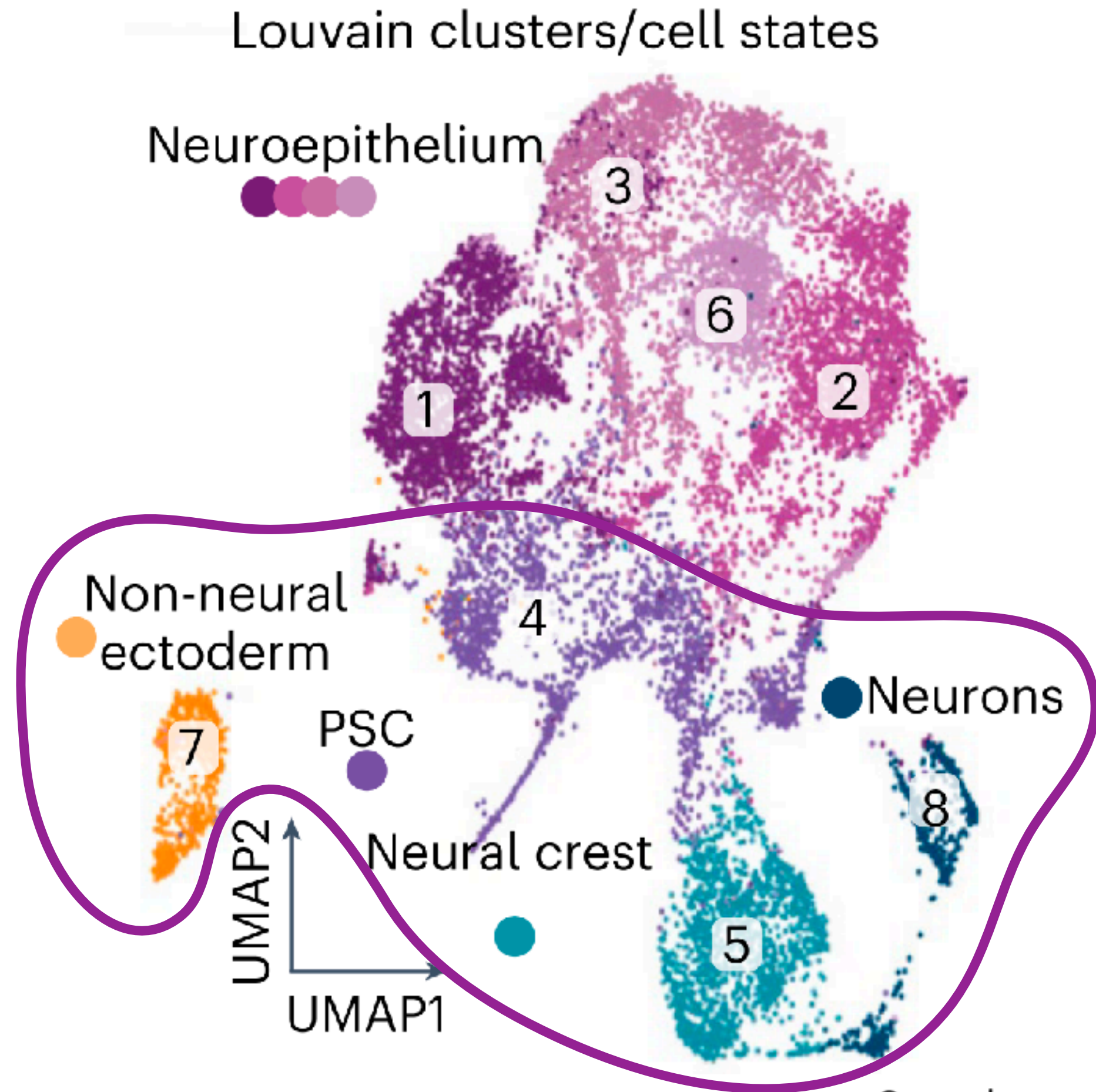
Chromatin accessibility precedes transcription at neuronal genes



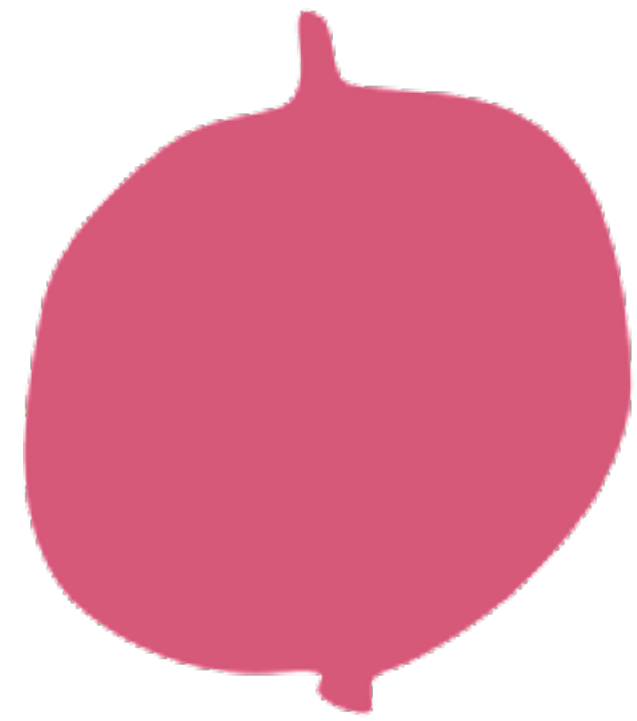
Functional role of Epigenetic Modifications in Organoid Development



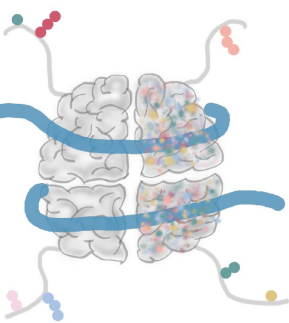
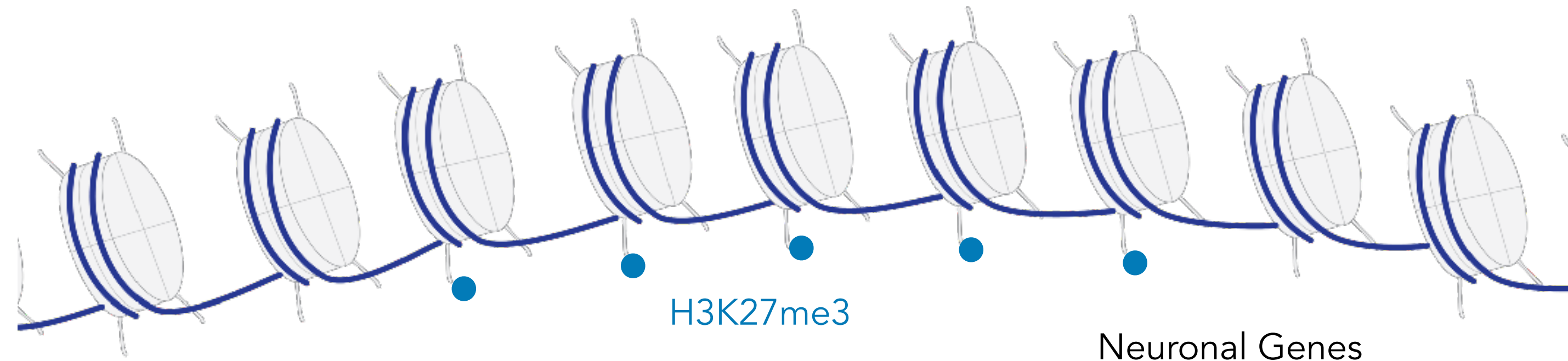
Functional role of Epigenetic Modifications in Organoid Development



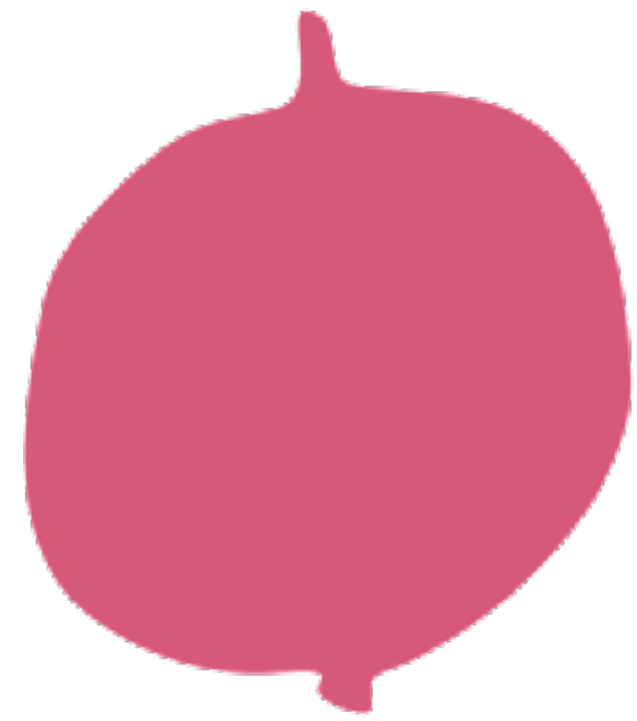
Mapping Dynamic Changes of the Epigenetic Landscape



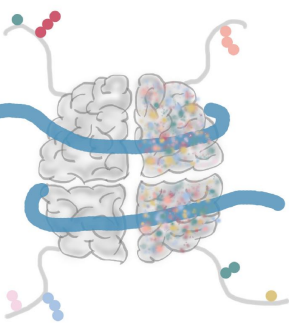
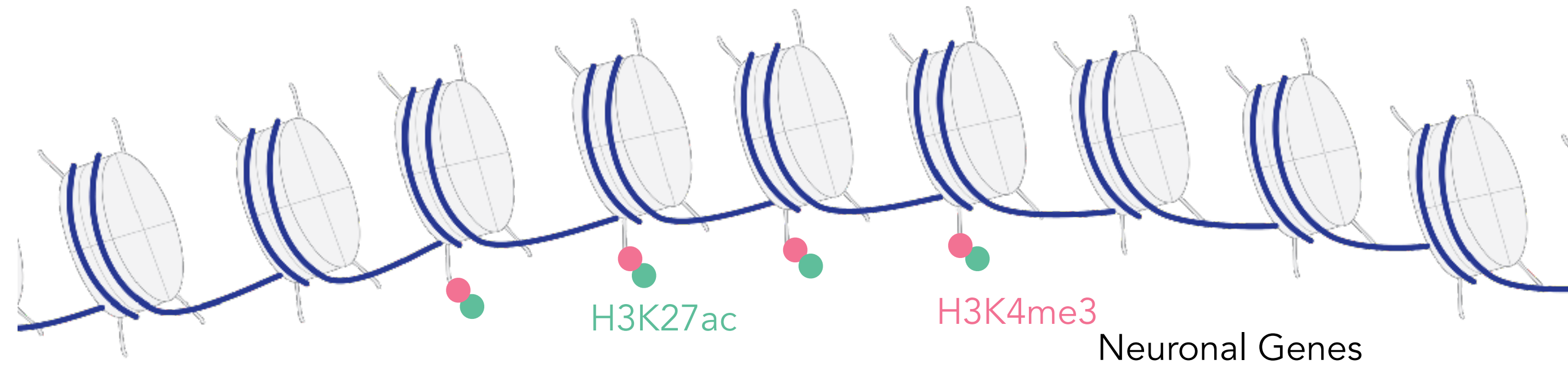
Progenitor



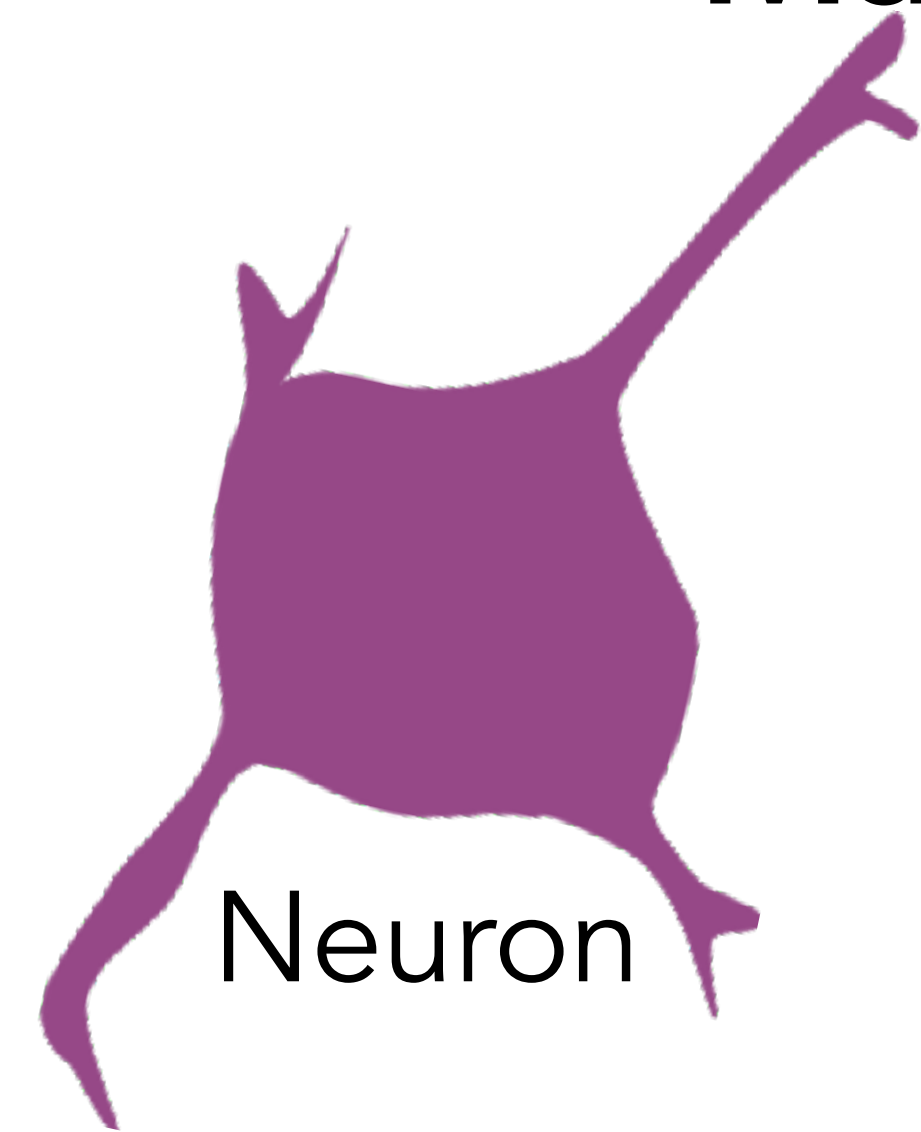
Mapping Dynamic Changes of the Epigenetic Landscape



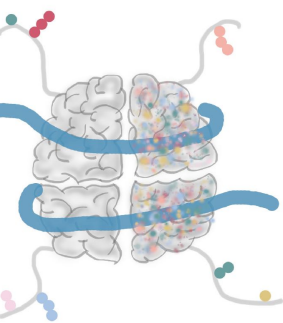
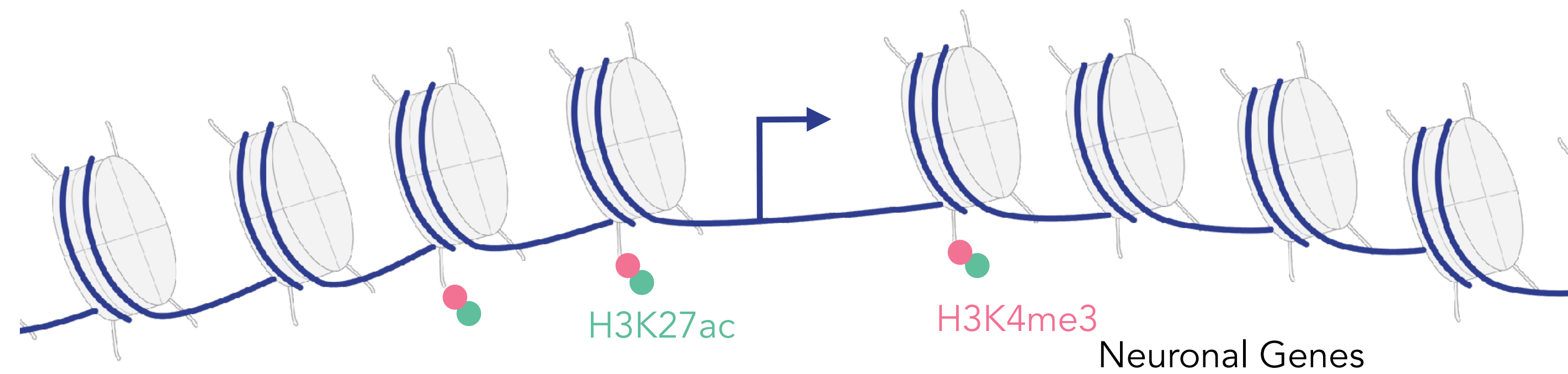
Progenitor



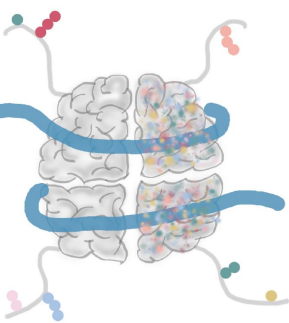
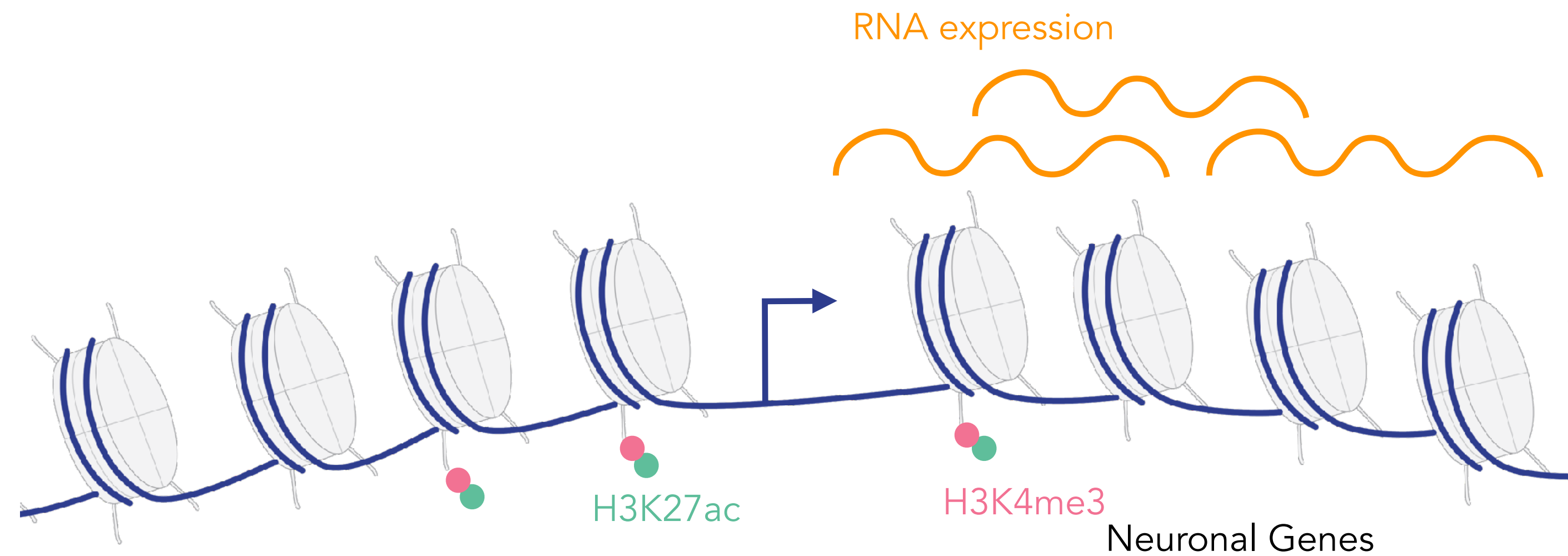
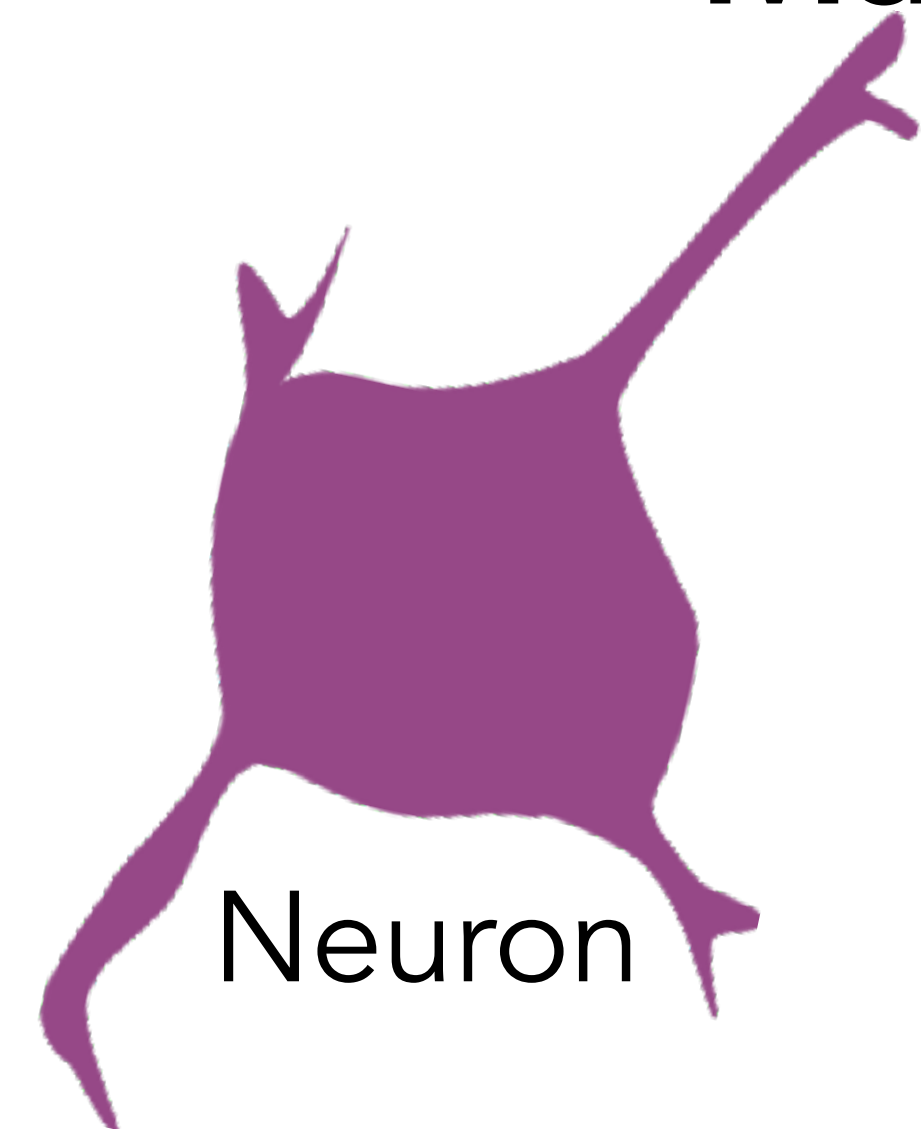
Mapping Dynamic Changes of the Epigenetic Landscape



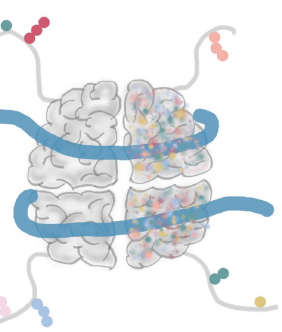
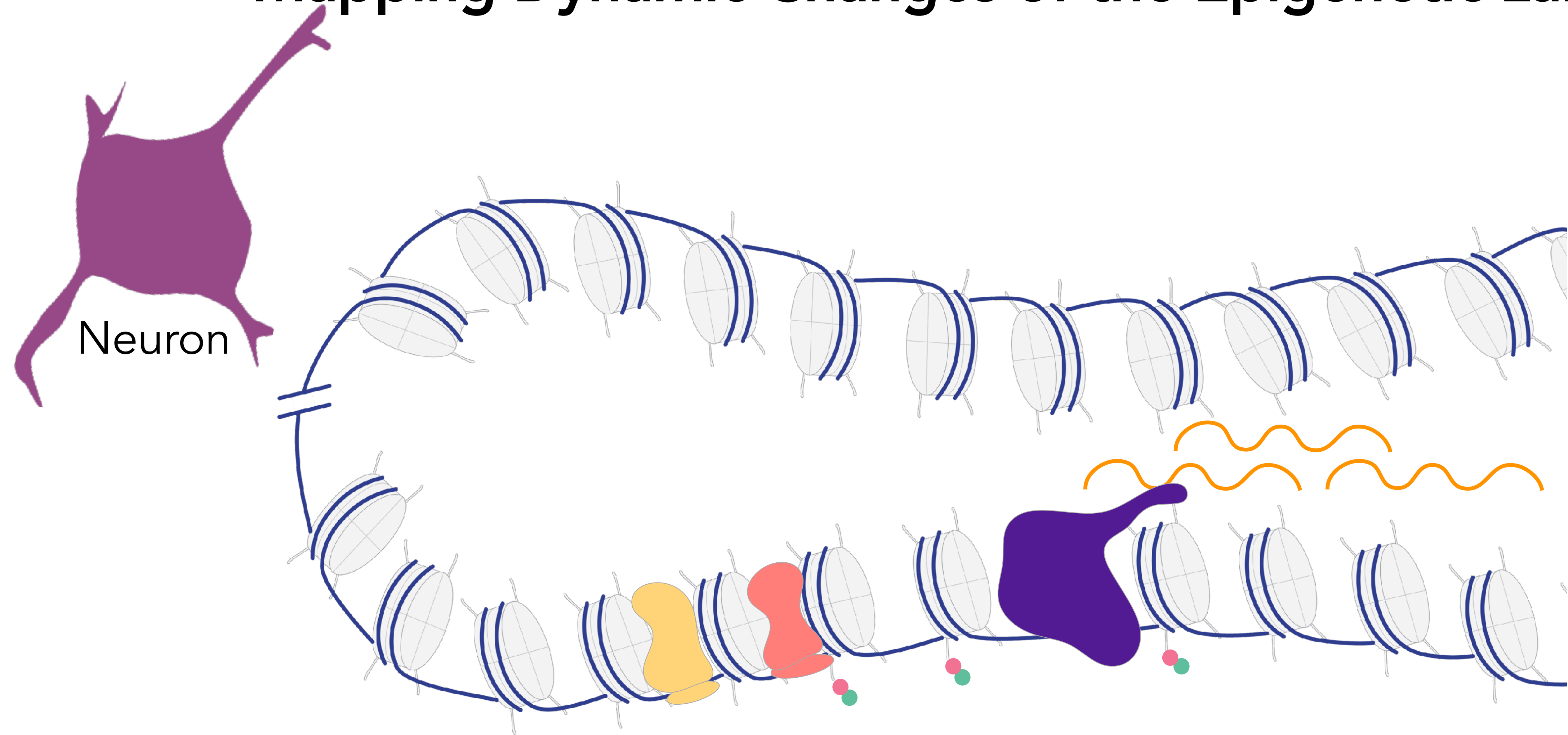
Neuron

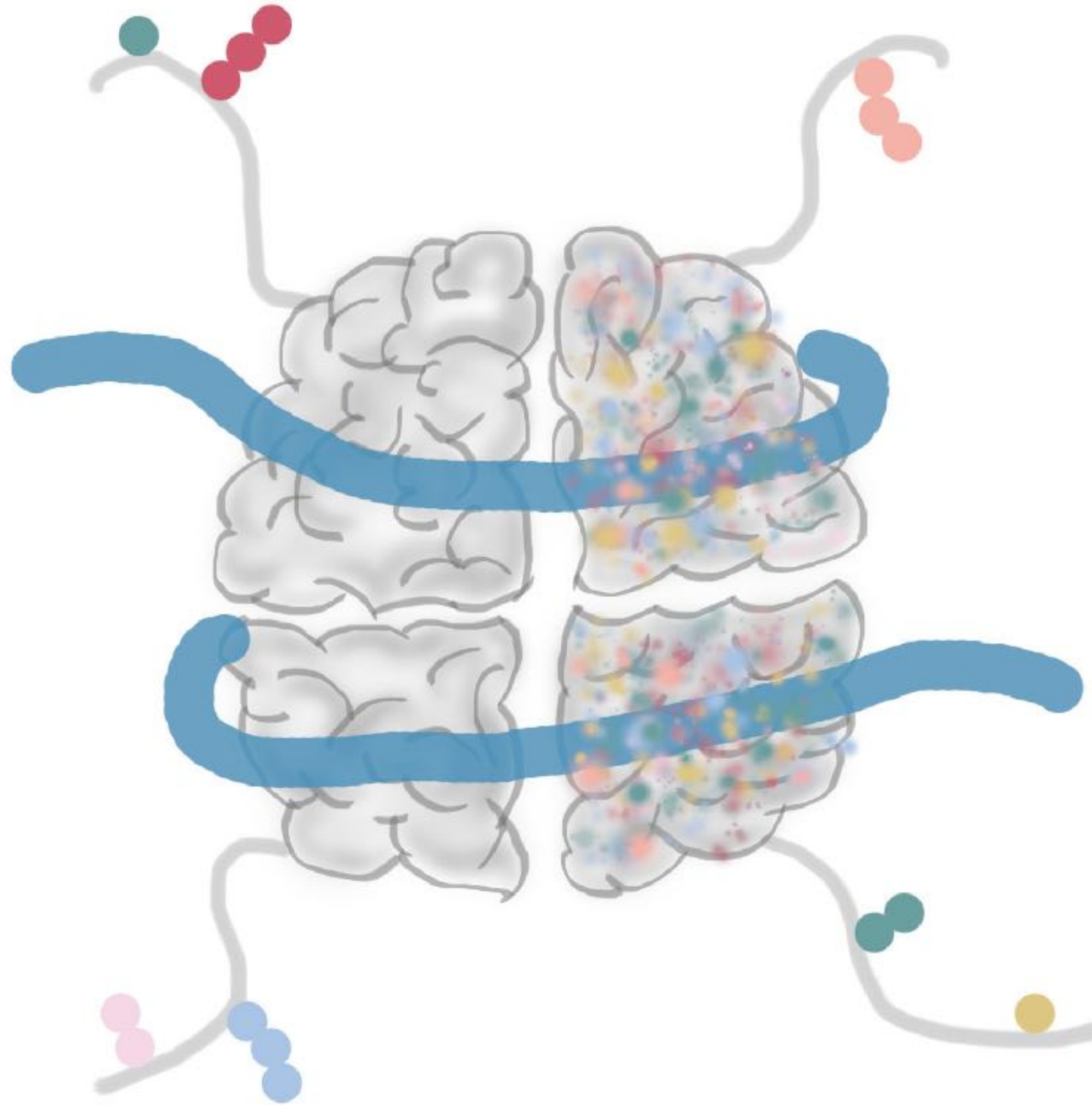


Mapping Dynamic Changes of the Epigenetic Landscape



Mapping Dynamic Changes of the Epigenetic Landscape





We use human neural organoid systems to study...

1. Brain development and cell differentiation
2. Molecular mechanisms of neurodevelopmental disorders
3. Maintenance of chromatin structure in postmitotic nuclei

