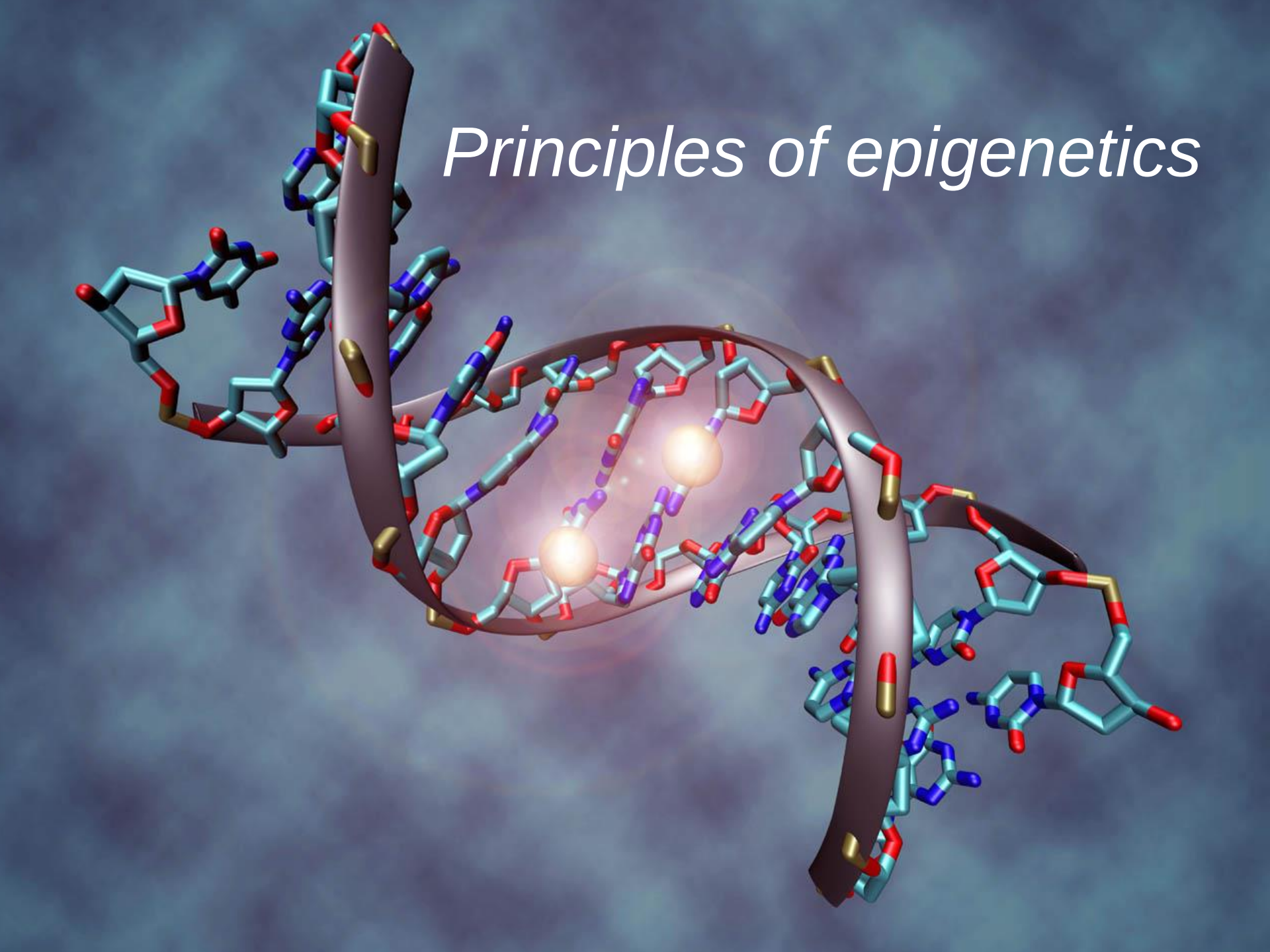

Principles of epigenetics

Epigenetics

Operational definition:

Study of heritable molecular and phenotypic changes resulting in altered gene expression that are not caused by DNA-mutations

Epigenetics

Epigenetics links to two origins:

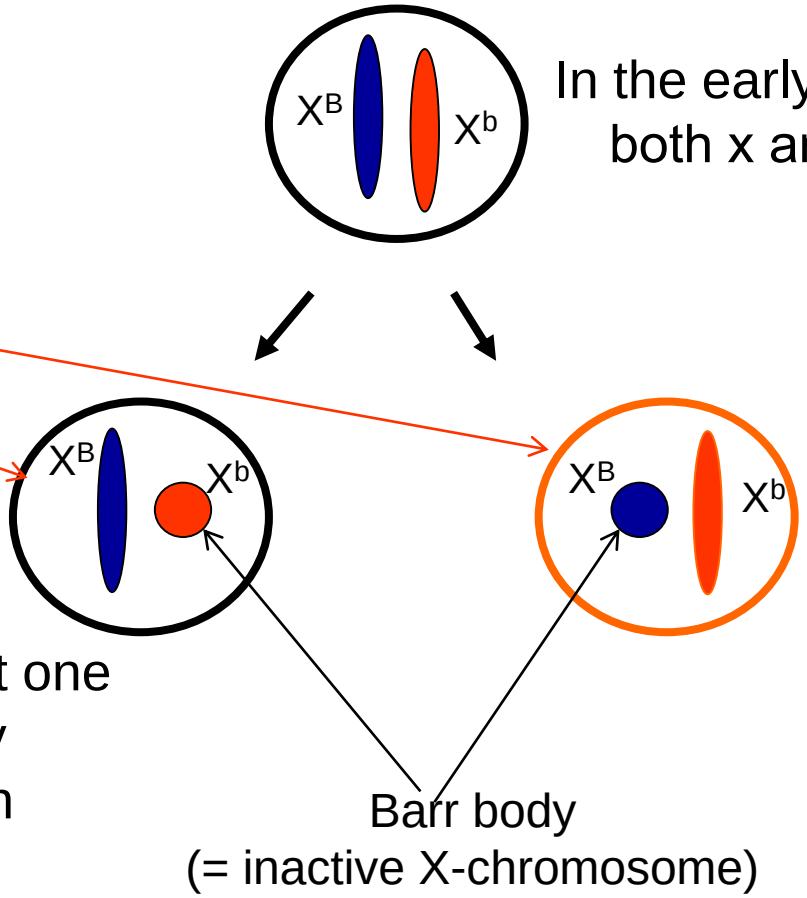
Epi Genetic and Epi Genesis

“inheritance” and “development”

Epigenetic control of coat colour genes on the X-chromosome of female cats

Three coloured „calico“ cats – are always females!
Their fur is patchy – resulting from a patchy clonal expansion of a coat colour gene expression.
How can we explain this phenomenon molecularly?

Epigenetic control of coat colour genes on the X-chromosome of female cats



Epigenetic control of coat colour genes on the X-chromosome of female cats

Some of the genes for the coat colour are located on the X-Chromosome.

Two different alleles of an X-linked copy are known: one causing yellow colour X^b, the other variant of the same gene black colour X^B.

Female cats have two copies of the X chromosome - they are XX and thus can carry the combination X^b_{yellow} / X^B_{black}.

In all mammlian females the genes of one of the chromosomes are epigentically silent.

Each cell of females therefore expresses only one of the two X linked copies of a gene either X^b = yellow or X^B = black

Calico cats have two different alleles of coat colour genes on the X – one for orange and one for black colour.

Epigenetics and Development

Non-reciprocal dominance of genes

donkey (female) X horse (male)

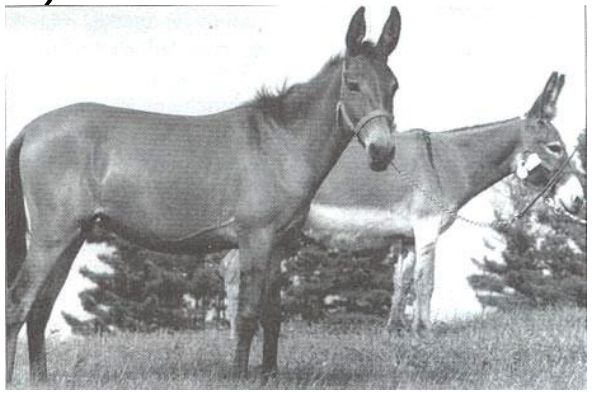
↓

Hinny (Maultier)

donkey (male) X horse (female)

↓

Mule (Maulesel)

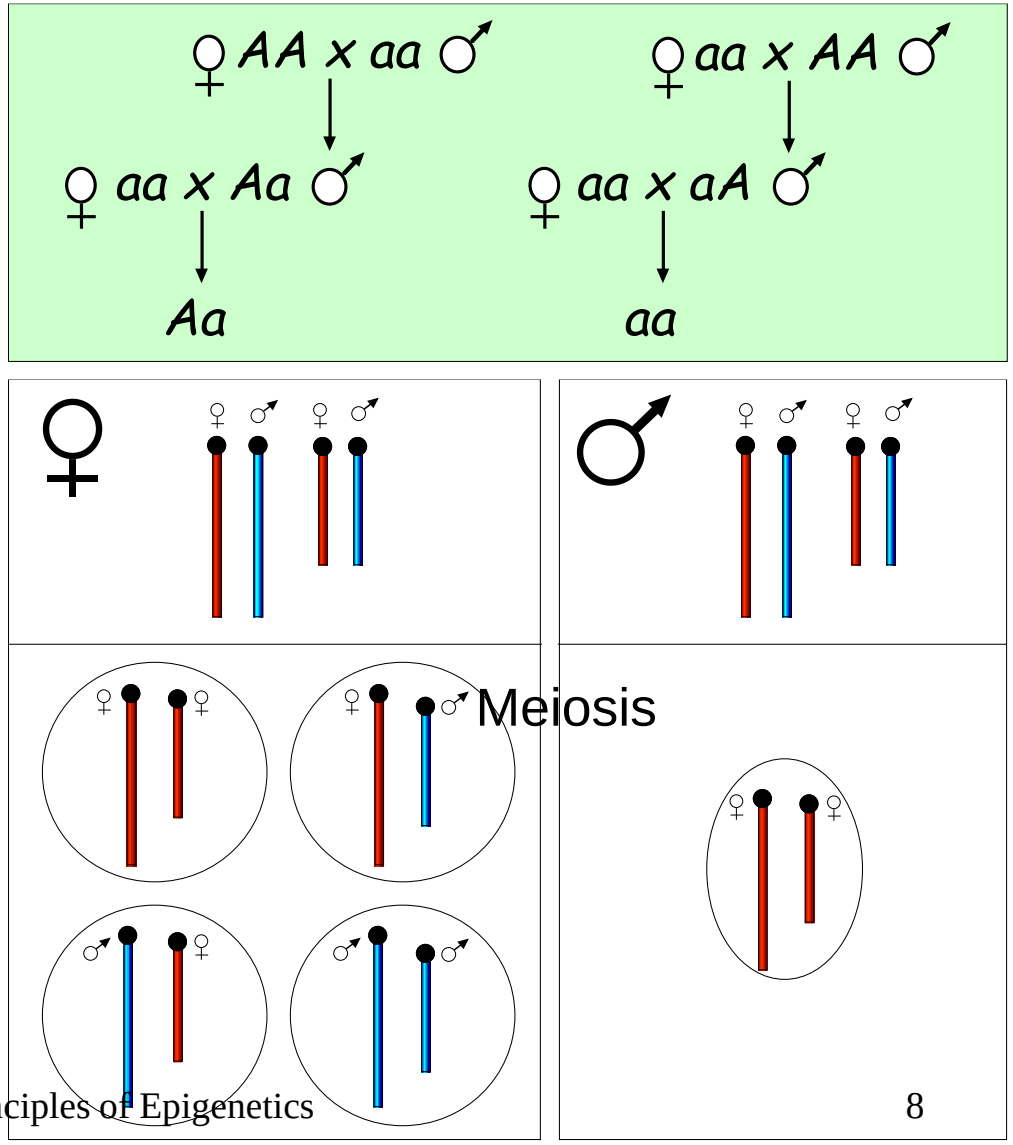


Finding: Maternal dominance on nuclear genes.

Explanation: Combination of mitochondrial inheritance of the oocyte influencing the genetic program probably by epigenetic changes

Epigenetics and Inheritance

Example:The selective elimination of chromosomes which leads to non-mendelian inheritance



In 1960 Helen Crouse shows that in *Sciara* only the maternal chromosomes are transmitted through the male germline

Epigenetics and Inheritance

Stable epigenetic traits (phenotype)

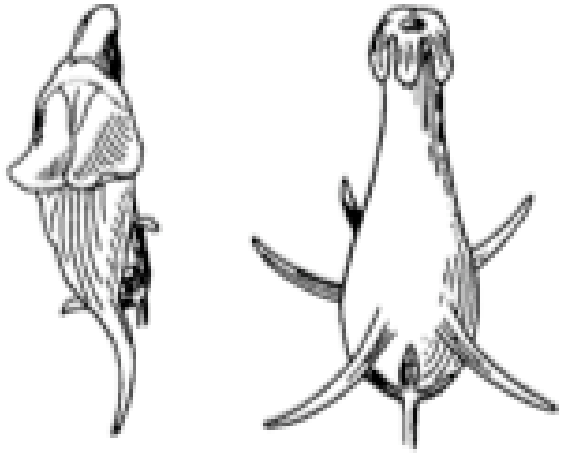
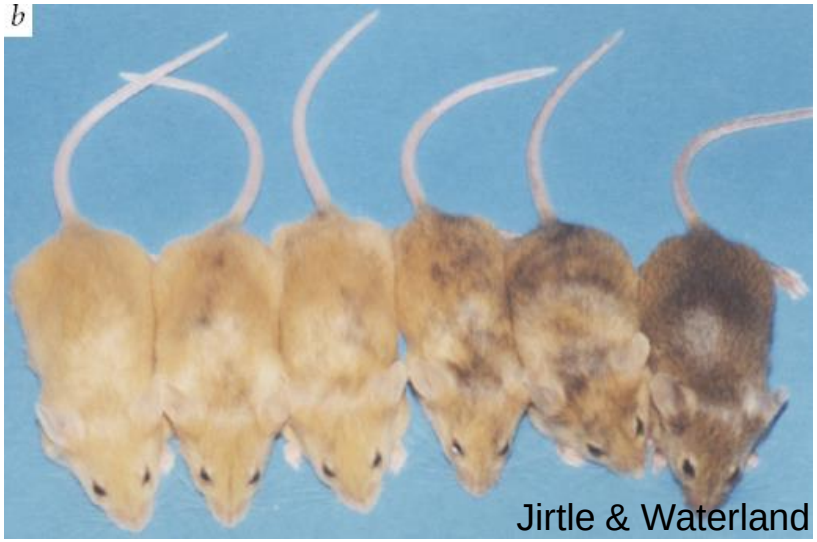


Fig. 2. Goethes illustration of normal-flowering *Linaria vulgaris* (left) and his view of the five-spurred Peloria (right)

Inheritance of the mutant phenotype of the „Peloria mutant“ over 200 years with no detectable genetic alteration
(but DNA-methylation changes at the promoter)

Epigenetic changes and Nutrition

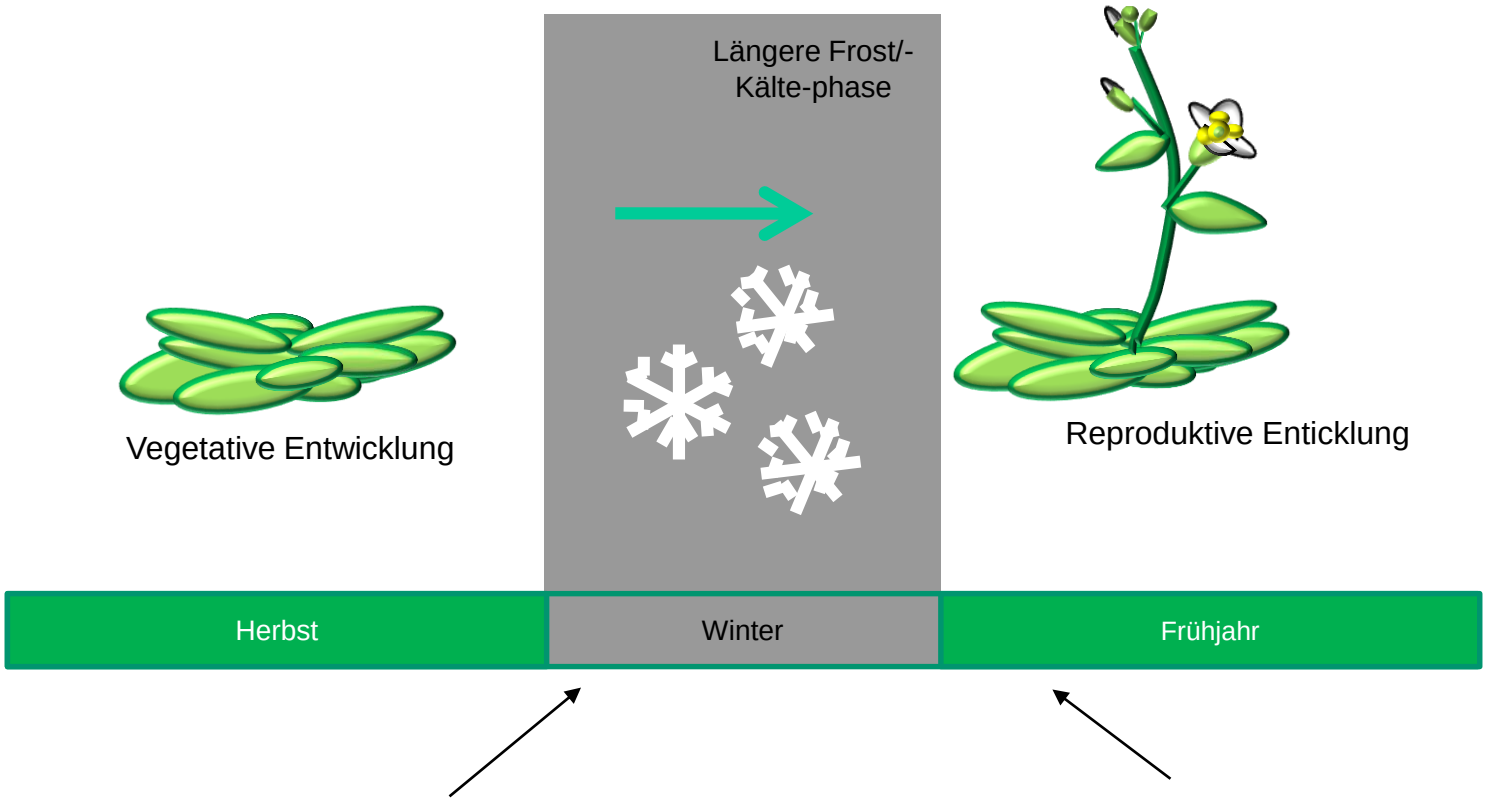
Supplementation of folic acid and vitamin B12



ON OFF

Increase of DNA-Methylation at the Agouti Gene

Temperature induced epigenetic memory



Epigenetics

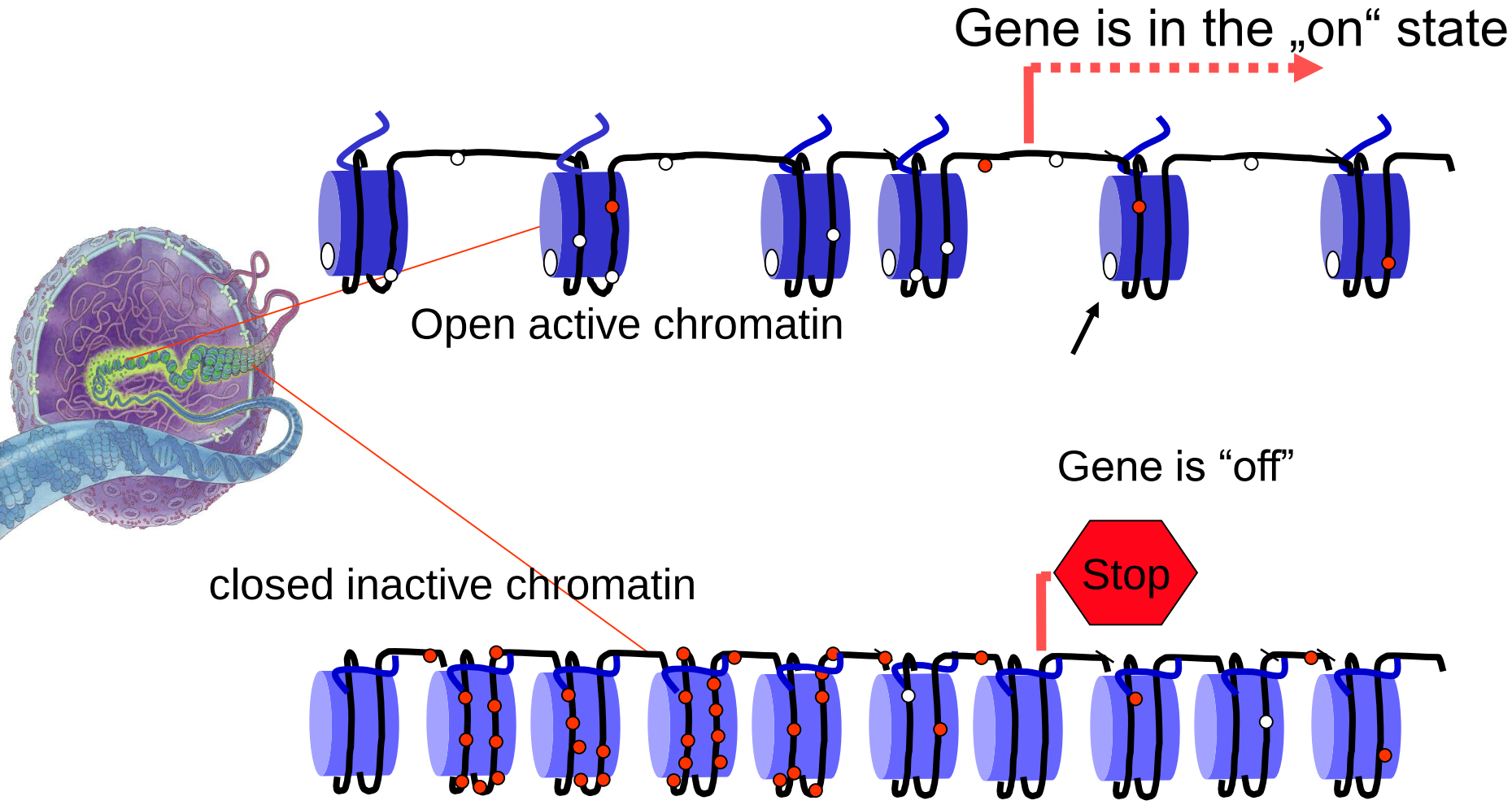
"Molecular/Biochemical Definition:

Reversible modifications of DNA or chromatin that affect the functions of the genome/chromosomes in a heritable way"

What are epigenetic modifications?

- alter the chemical structure of proteins and/or DNA bases in chromosomes
- are transmissible/heritable across cell divsions (during mitosis and in some cases also during meiosis)
- can be deleted/reset/reprogrammed at certain stages during development and cellular differentiation.
- are established in multiple „layers“ forming a cell type specific „epigenome“
- cell specific epigenomes change with development, age and in diseases.

The epigenetic control of gene operates in chromatin



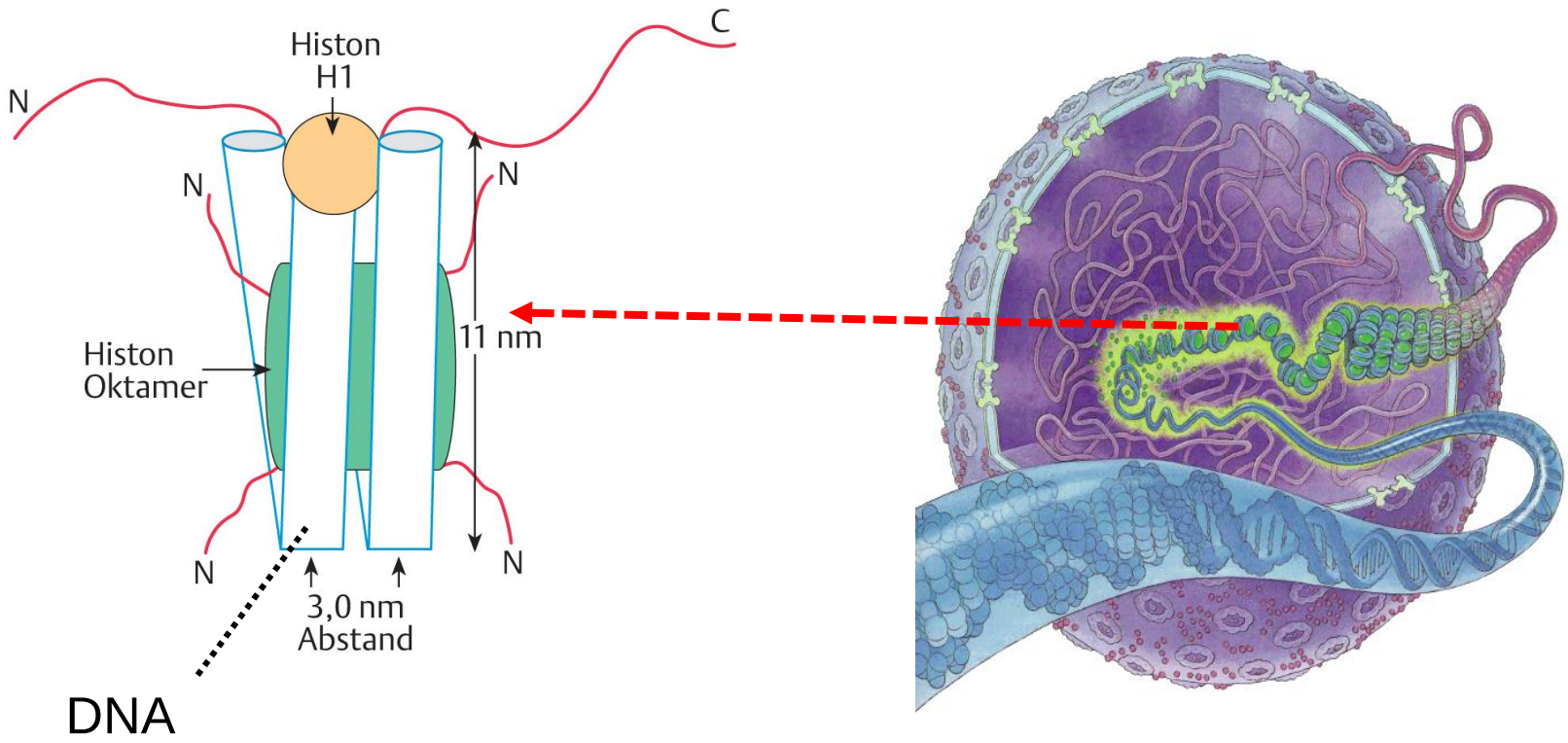
Chromatin:
the „playground for epigenetic control“

The basic building unit of chromatin (chromosomes) is a nucleosome

Nucleosomes are formed by histones and DNA

The density (= nucleosome packaging) of chromosomes is controlled by DNA- and histone modifications

Nucleosomes: the basic structure of chromatin

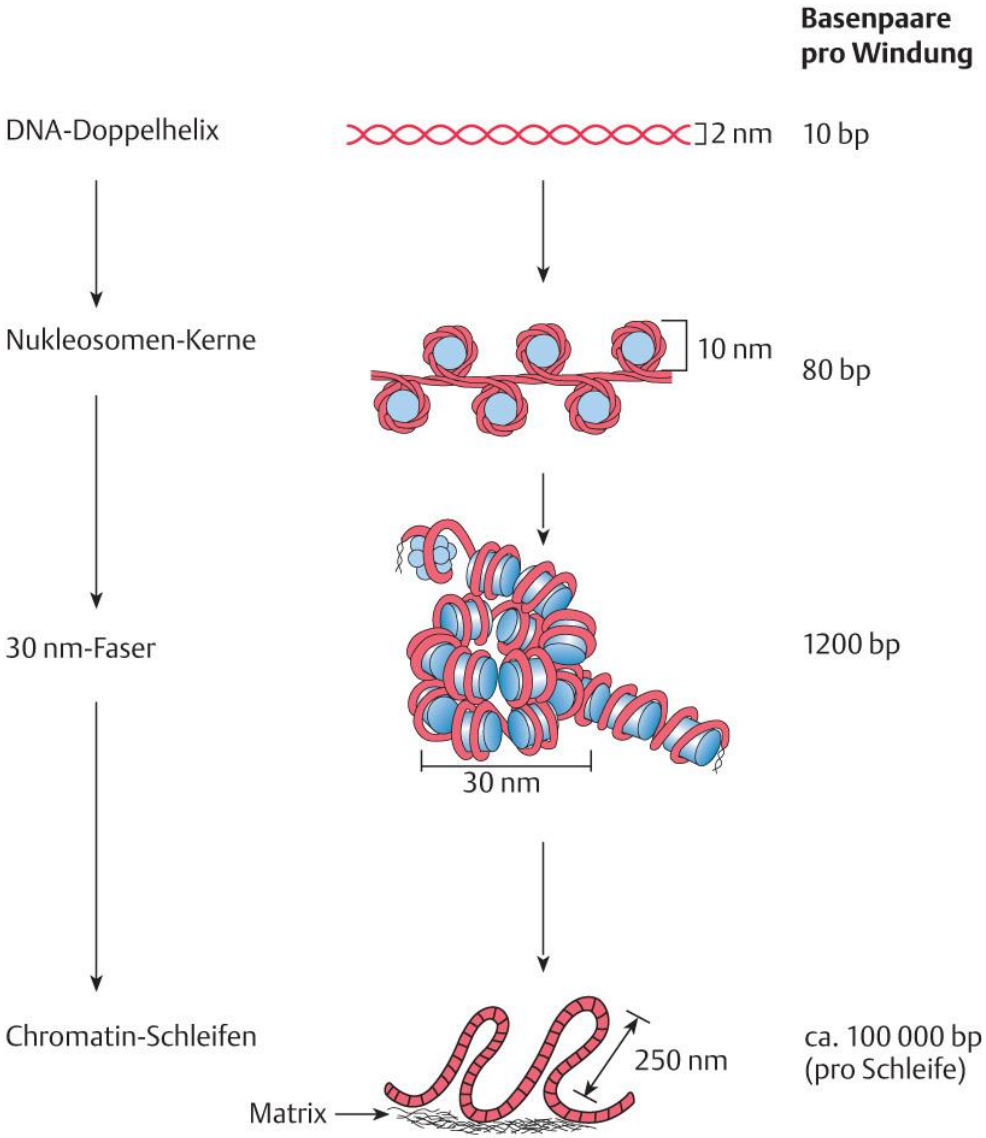


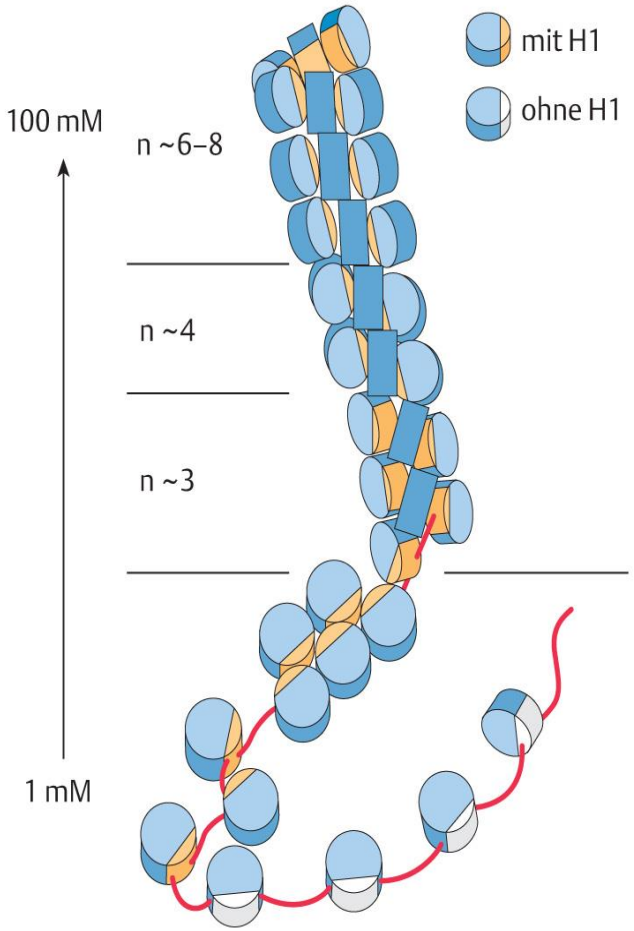
A nucleosome consists of a histone octamer (= 8 histones, 2x 4 different types) and 146-150 bp DNA (white ribbon) wrapped around the octamer

Nucleosomes: the basic structure of chromatin

- Consists of a histone octamer (2 x (H3 + H4 dimer) + 2x (H2A+H2B dimer).
- The DNA-Double-helix is wound twice around the octamer (146-150bp) (with linker Histons H1, approx. 200bp).
- DNA on nucleosoms is more tighly wound with 10,2 bp/helical turn as compared to „naked“ B-DNA (10,4 – 10,6bp/turn).

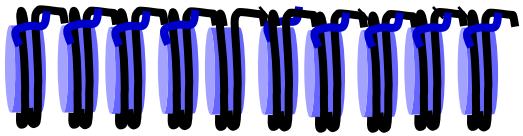
Chromatin is packages into different stages of condensation





Epigenetic control through chromatin regulation:
The main players.....

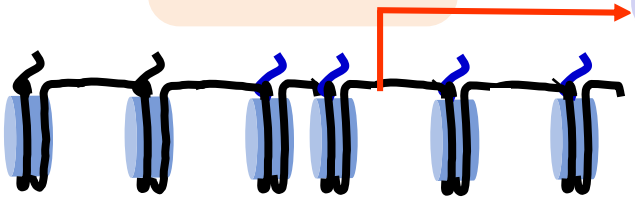
Closed, inaccessible chromatin



DNA-methylation

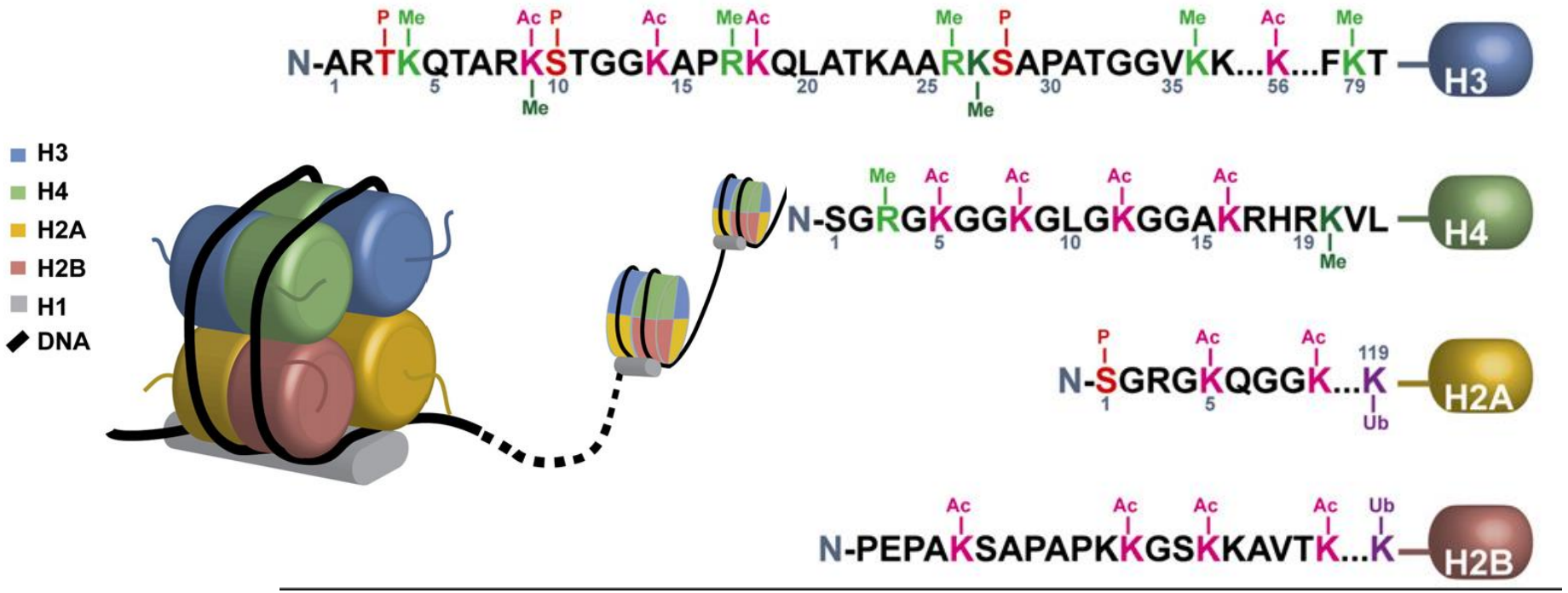
ncRNAs

Histone Modifications



Open, transcriptionally competent chromatin

Epigenetic modifications at the N-termini of Histones



Histone-modifications

- The packaging of Chromatin is modulated by modifications of specific amino acids in the N- and C- termini of histones. The four major histone modifications types are:

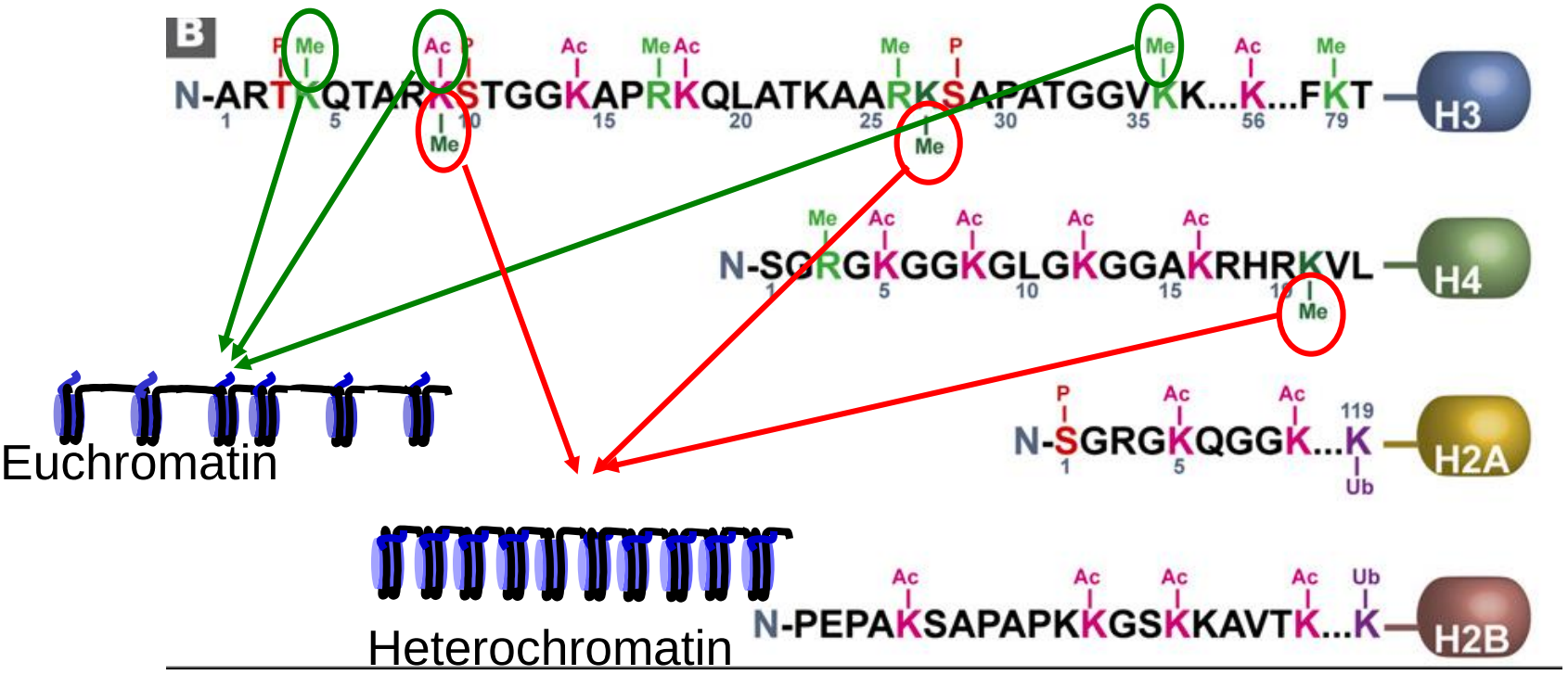
- Acetylation (Ac) of the amino acid lysine (K)

- Methylation (Me) = addition of methyl group(s) to the amino acids arginine (R) and lysine (K)

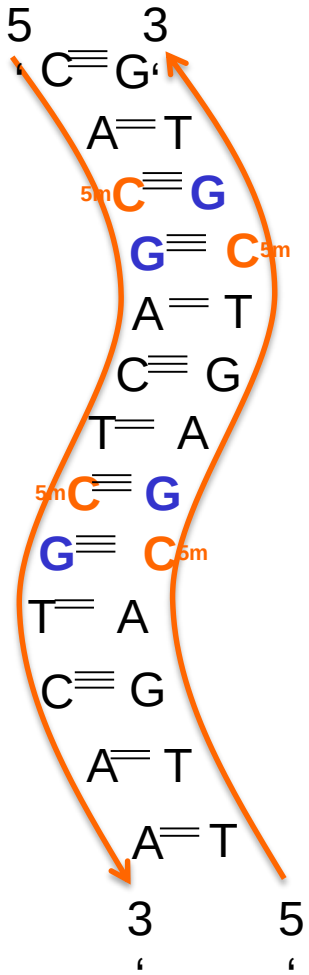
- Ubiquitination (Ub) of the amino acid lysine (K)

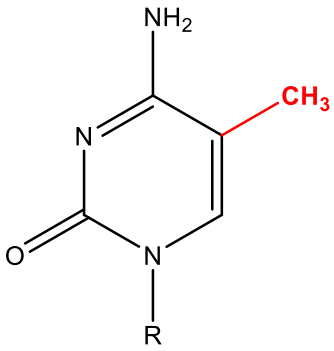
- Phosphorylation(P) of the amino acids serine and/or threonine (S/T)

Histone modifications are specific for open and closed chromatin structures



DNA-methylation

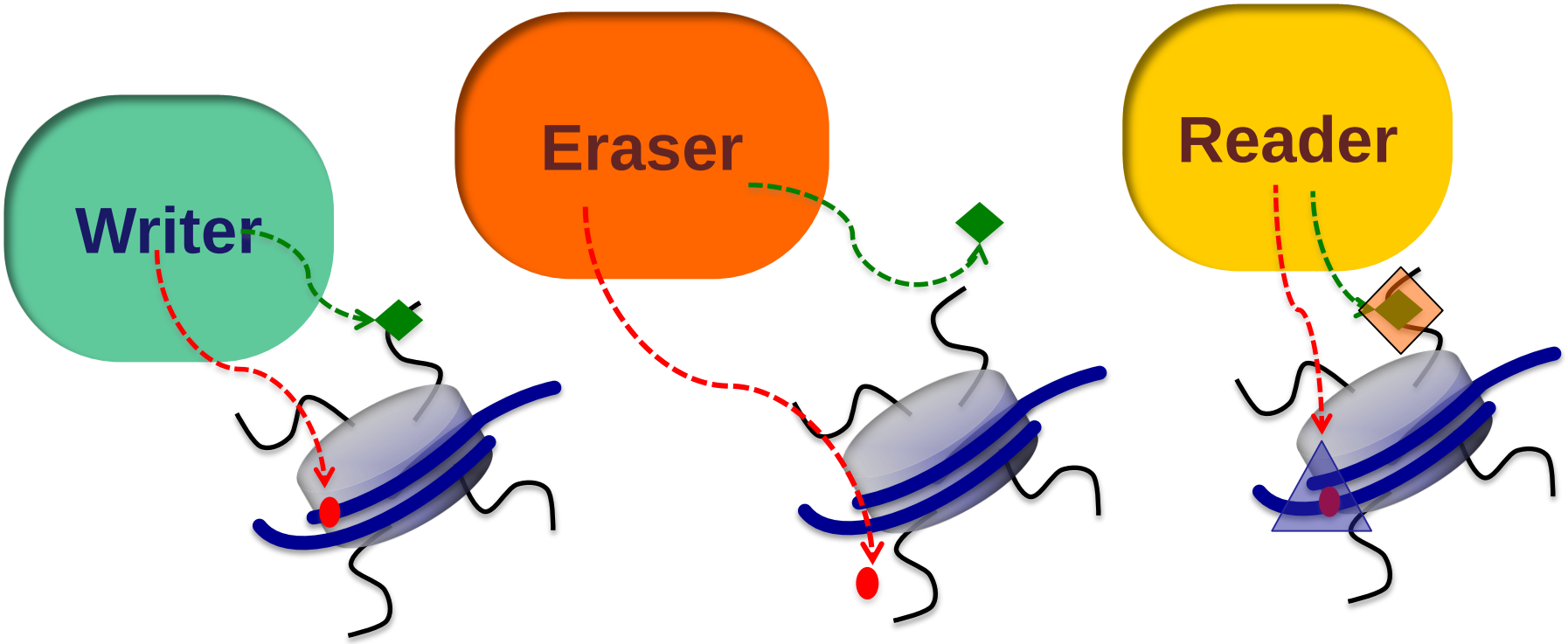




5-Methylcytosin (5mC)

DNA-Methylation is established „postreplicative“ by DNA-Methylatransferases (DNMT‘s)

Epigenetic modifications are **set and erased** by specific enzymes with antagonisitc specificity



DNA-methylation & Histone modifcations are **read** by specific proteins

Key characteristics of epigenetics

DNA of chromosomes is packed by histones in nucleosome units.

Histones and DNA contain secondary epigenetic modifications which are reversible.

Modifications are locus and gene specific – they change the expression of genes

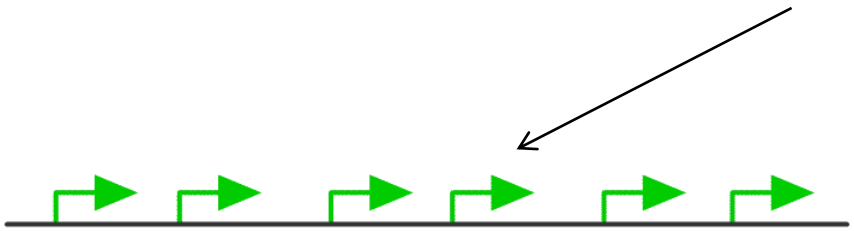
Cells can be distinguished by gene and cell type specific „epigenetic“ modifications.

Epigenetics and development: Regulation of cell specific programs

stem cell

Differentiation:

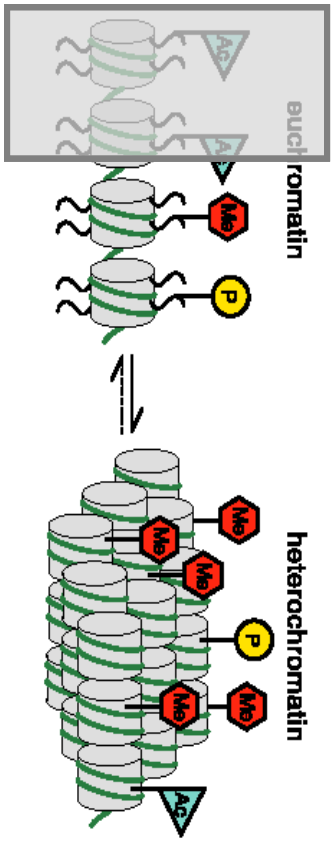
genetic & epigenetis programs



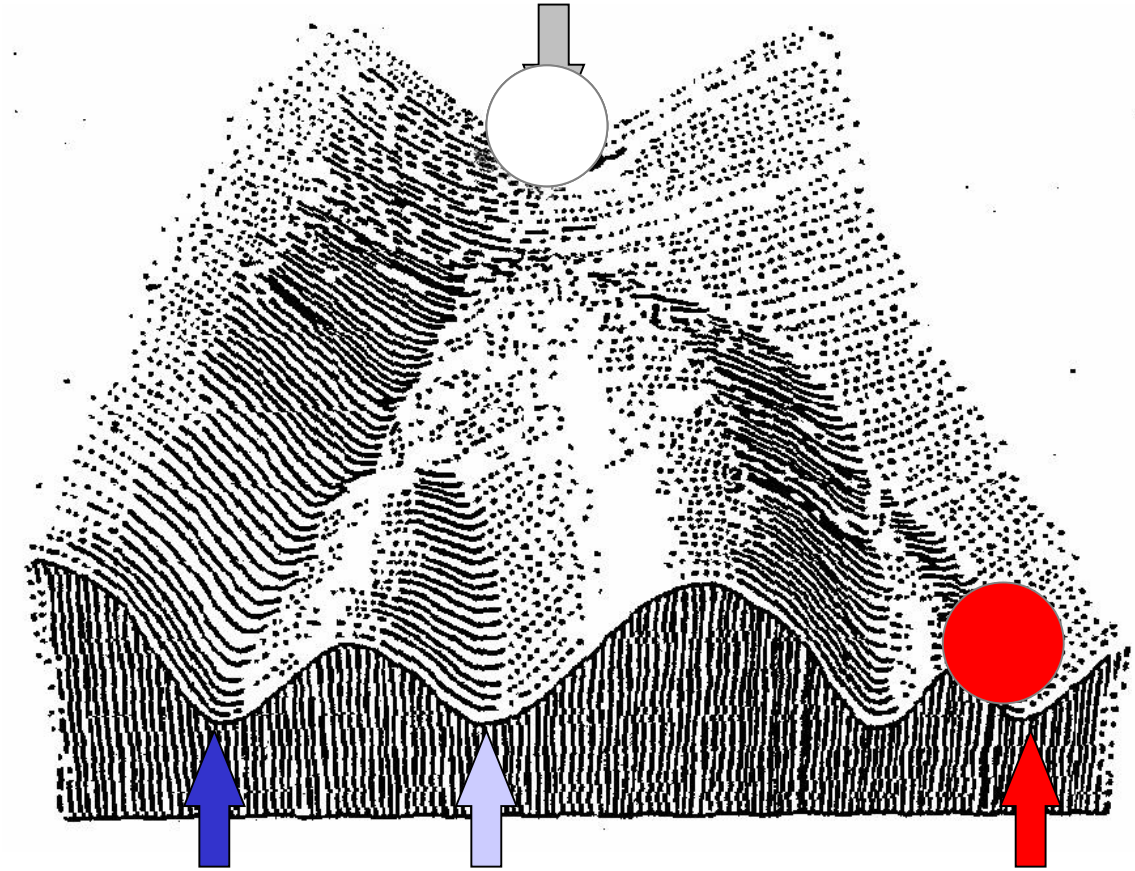
some genes on, some off

some genes on, some off

Epigenetics and „Epigenesis“



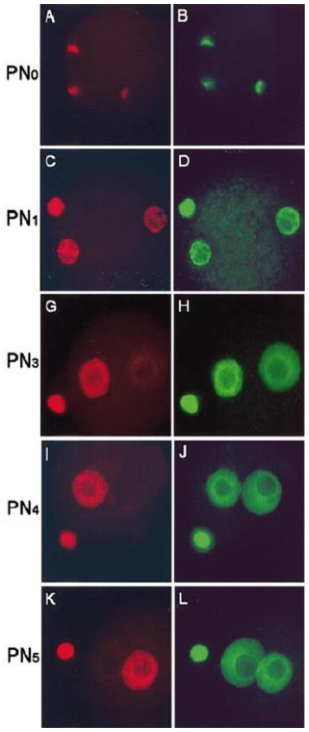
Pluripotency

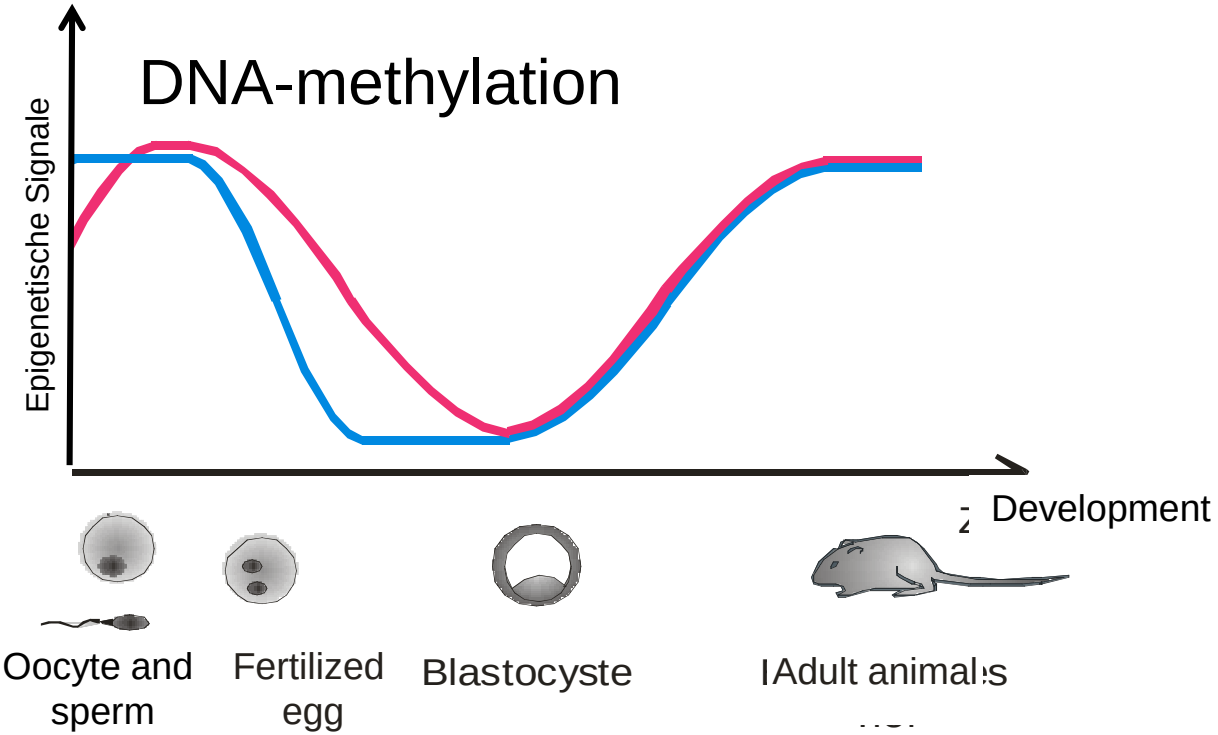


Conrad Waddington: Epigenetic landscape & "Canalization"
Modified: Timo C. Dinger & Albrecht Müller

Following differentiation cells adopt different epigenomic states – reprogramming allows to revert this process

Epigenetische Programme und Entwicklung

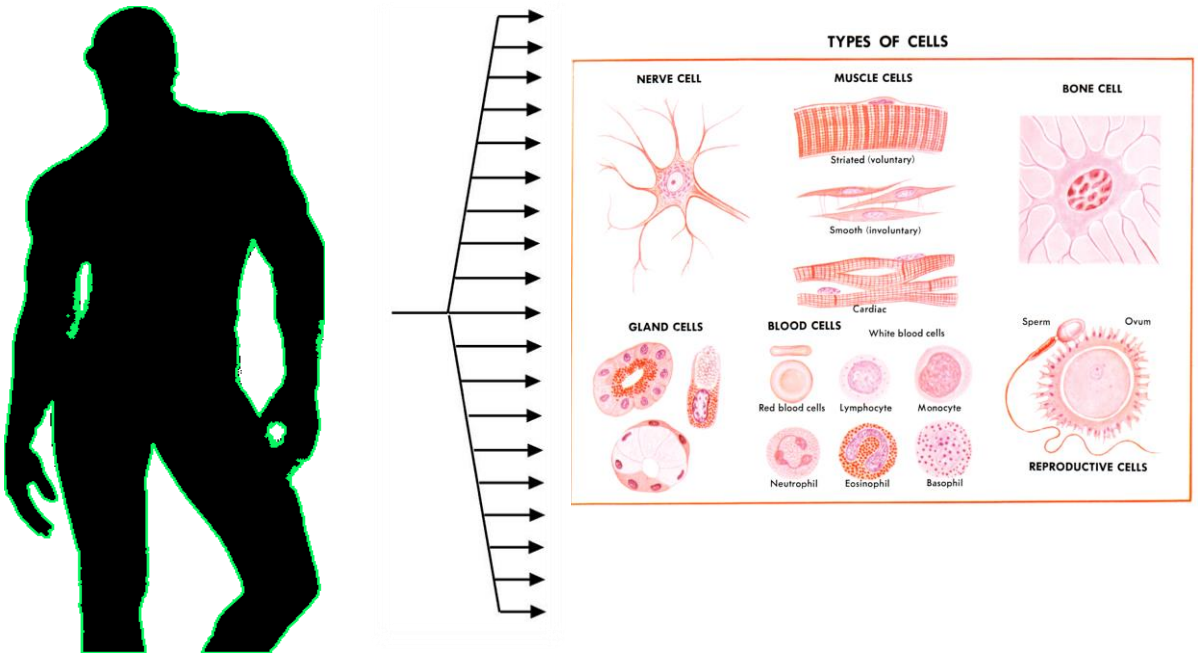




Epigenetic modifications are earsed and „re-established„ during early development!

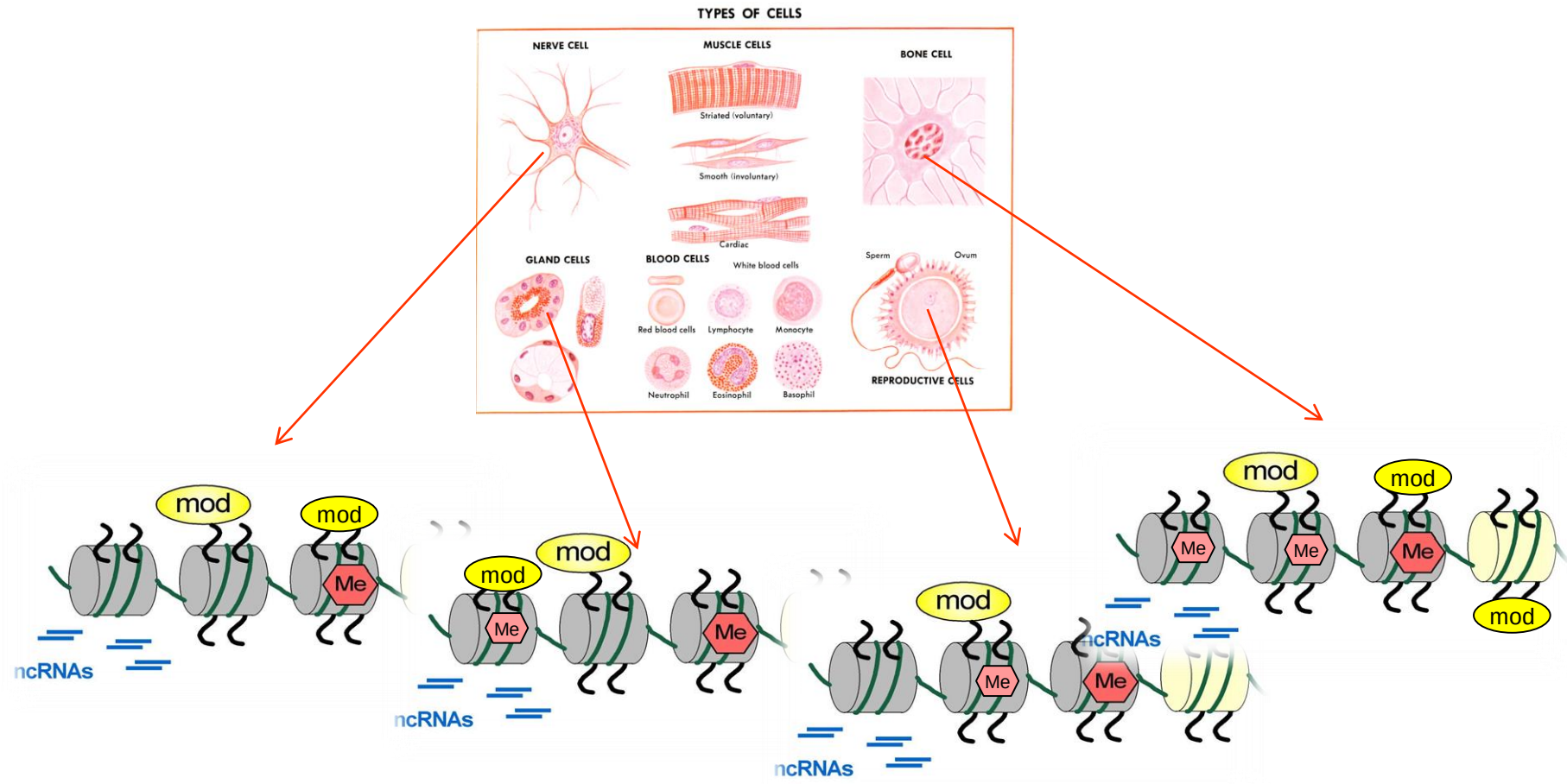
Epigenetic and cell diversity: THE EPIGENOME

One genome in many different cell types of our body



estimations 35 Billion cells and > 250 cell-types (probably many more)

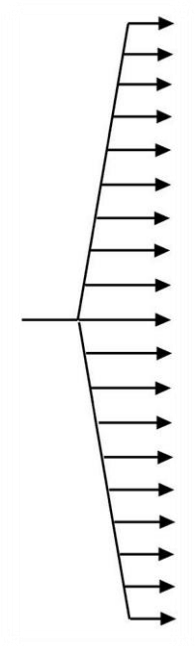
Cell type specific epigenomes

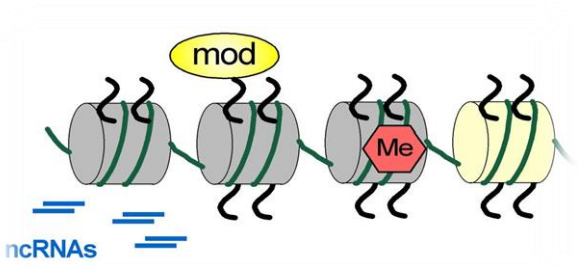


Each cell type develops a characteristic pattern of epigenetic modifications along chromosomes

Epigenetics helps to understand cell diversity: THE EPIGENOME

1 Genome → *>250 EpiGenomes*



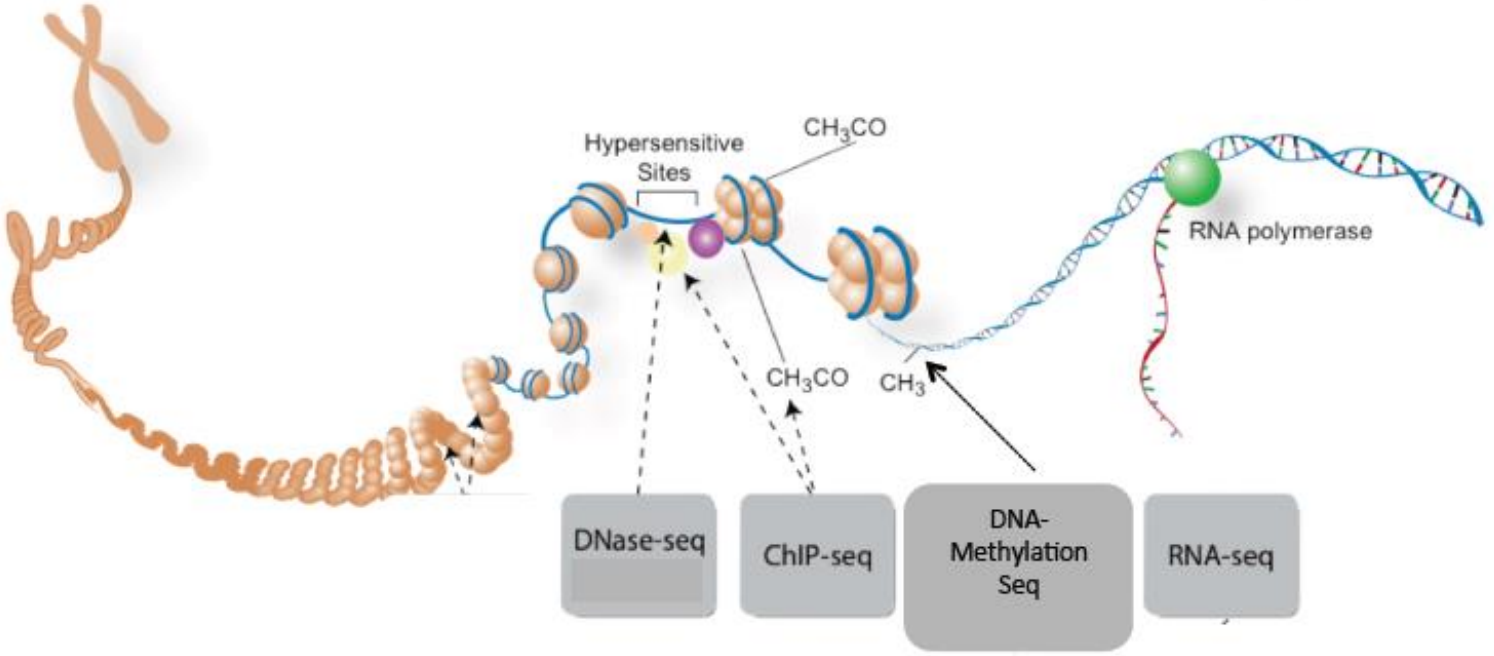


Epigenetic profiles of individual cell types

Methoden der Epigenom-Kartierung

Epigenomic mapping

IHEC
International Human Epigenome Consortium



www.ihec-epigenomes.org/

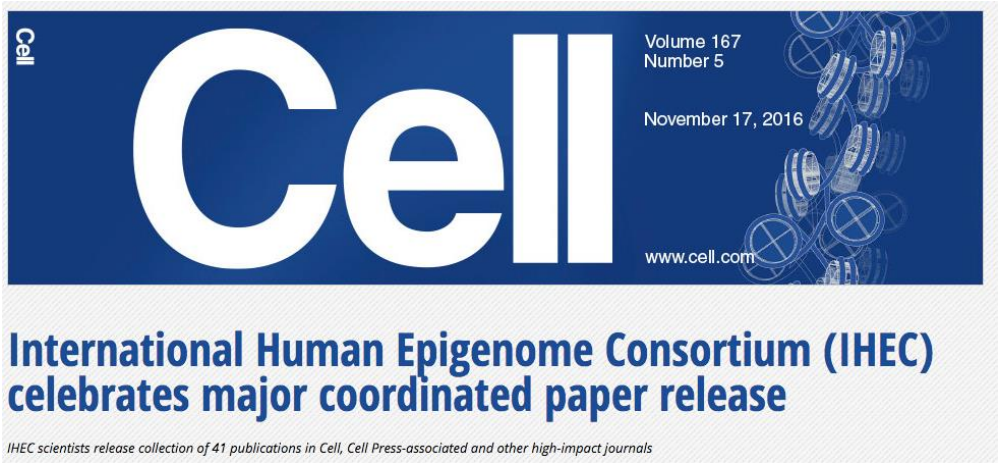
Understanding the EPIGENOME

IHEC
International Human Epigenome Consortium

The goal of the international human epigenome consortium IHEC

"Mapping and decoding of the landscape of chromosomal modifications associated with the cell type specific regulation of human genes"

http://www.cell.com/consortium/IHEC



Mapping of cell specific epigenomes

Sequencing on
NGS machines

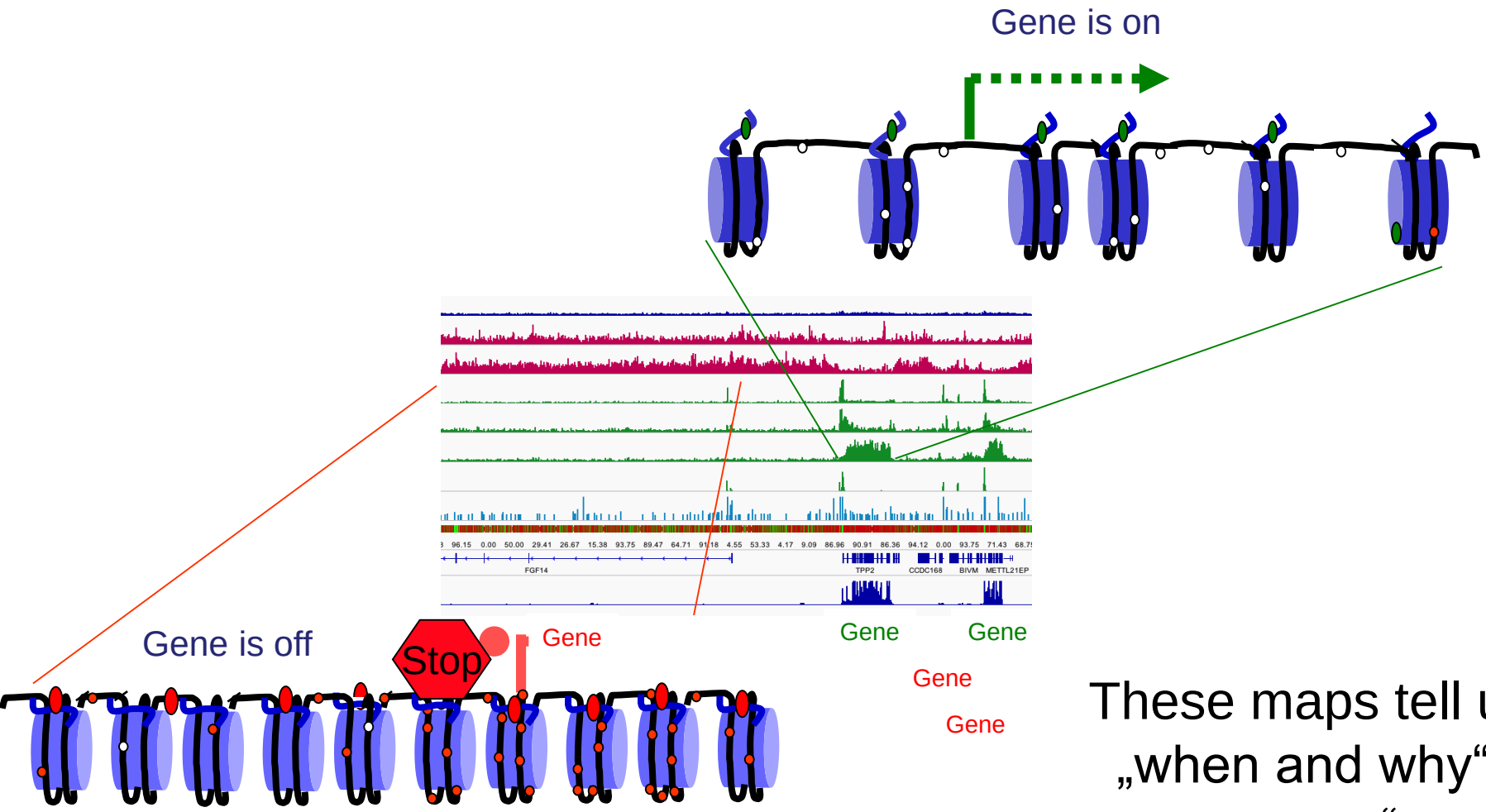
Cell Isolation

Retrieval of
fresh tissue

Isolation of RNA,
DNA or Chromatin.
Application of epigenomic
sequencing techniques

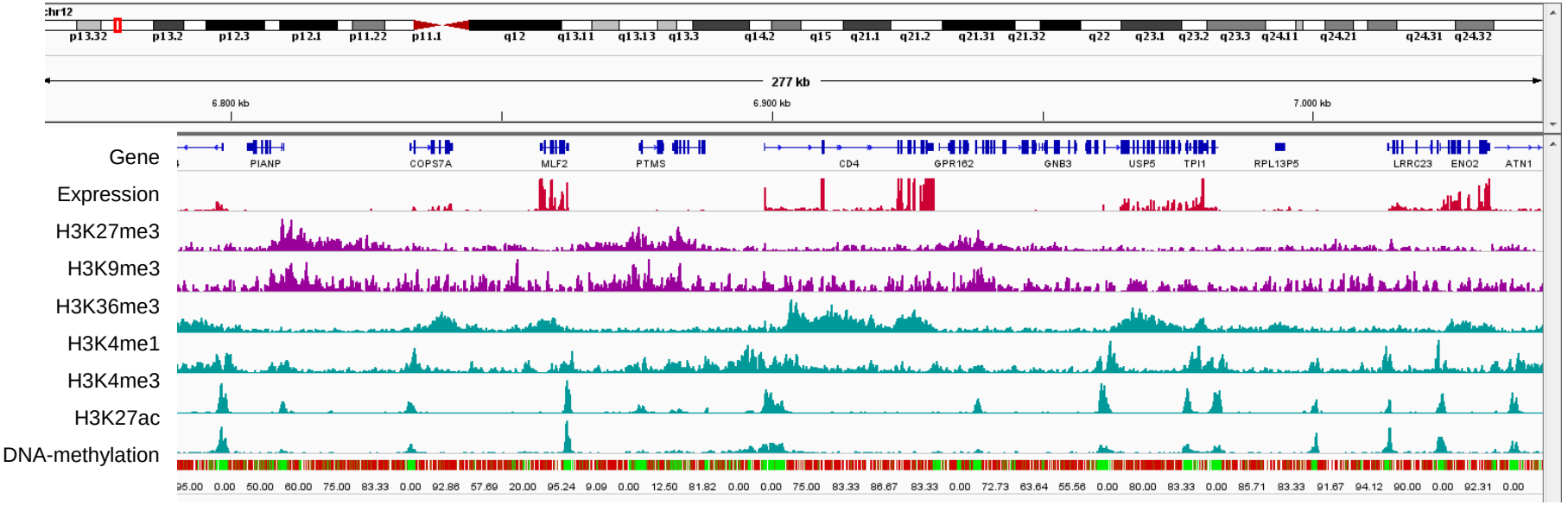
Data analysis

Reading of cell specific epigenomes



These maps tell us „when and why“ genes are „on“ or „off“ and what goes wrong in diseases

Integrated epigenomic maps: assignment of landmarks for gene regulation: Promoters (P), Enhancer (E), Silencer (S), Chromatin loop boundaries(B),.....



P P P P P P EP E P P P

Cell specific epigenomes

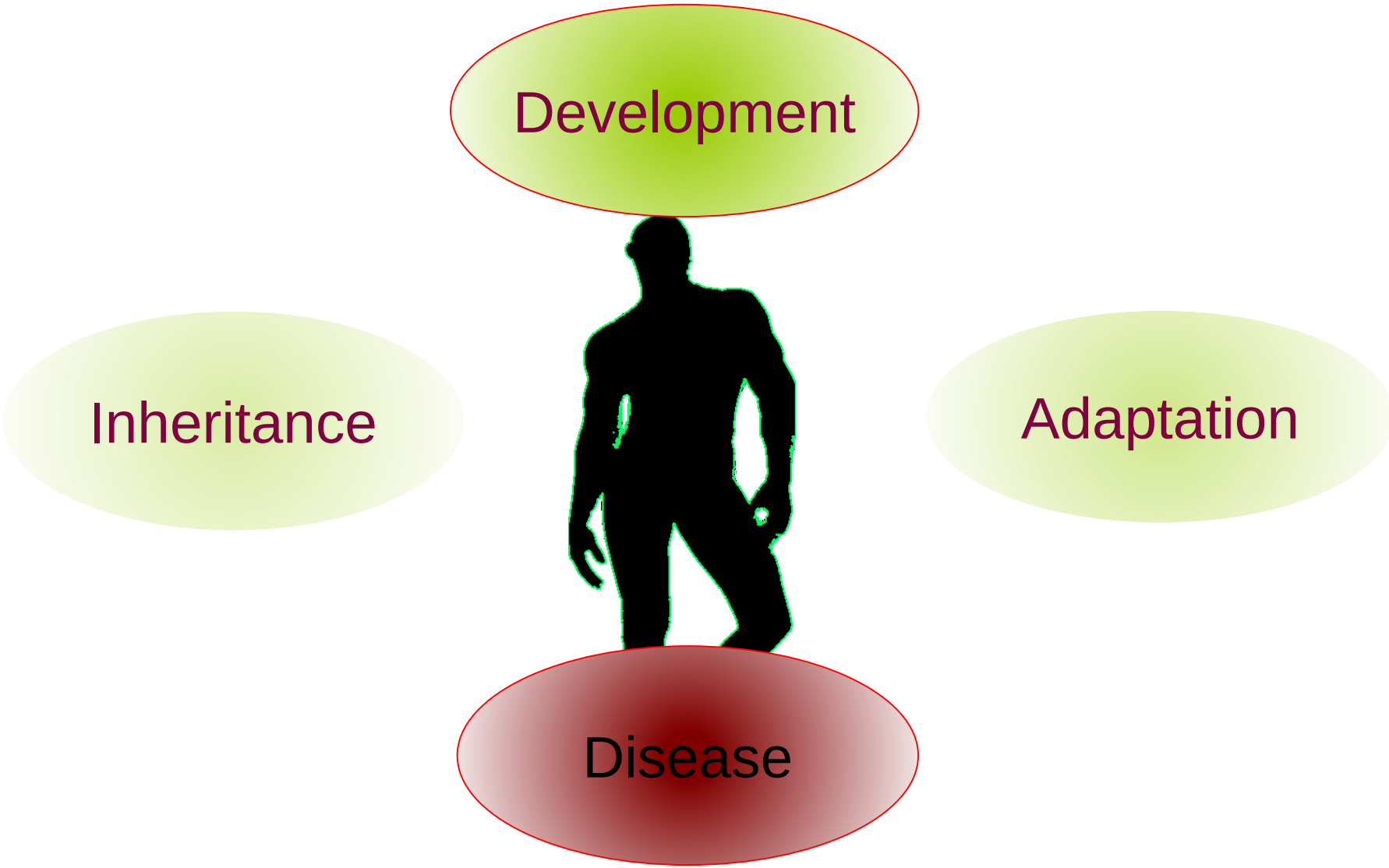
- Each cell type of our body has a specific epigenomic signature(landscape)
- Comprehensive Epigenomes are composed of a series of „epigenetic sequencing“ approaches:
  - DNA-methylation, Chromatin modifications, Chromatin openess and the Gene expression
- The integration of such data can be used to identfy epigenetic changes that are linked to development, aging or disease

Epigenetics and disease

Epigenetic changes provide new molecular insights into the cell specific basis of human diseases:

- Autoimmune diseases (Rheuma), Chronic Inflammation (Morbus Crohn,)
- Leukemias: CLL, AML, ALL,....) and all solid tumors
- Age and immune related disease (Alzheimer, Parkinson, MS, ALS .....)
- Complex genetic syndromatic diseases (imprinting),
- Prenatal development & Reproductive problems (environmental influences, aging, reprogramming)
- Metabolic diseases (Adipositas, T2D)

Epigenetics in Biology



Epigenetic differentiation between types of brain tumors (Glioblastom)