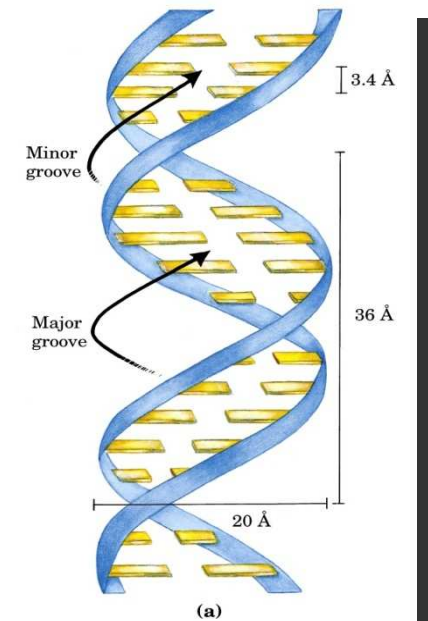


FROM GENETICS TO EPIGENETICS AND EPIGENOMICS: CHALLENGES AND APPLICATIONS

Prof. Athanasios Tsiftaris



GENETICS



GENETICS



GENOMICS

Automated sequencing



Software

Base calling
Sequence quality
Vector trimming
Assembling

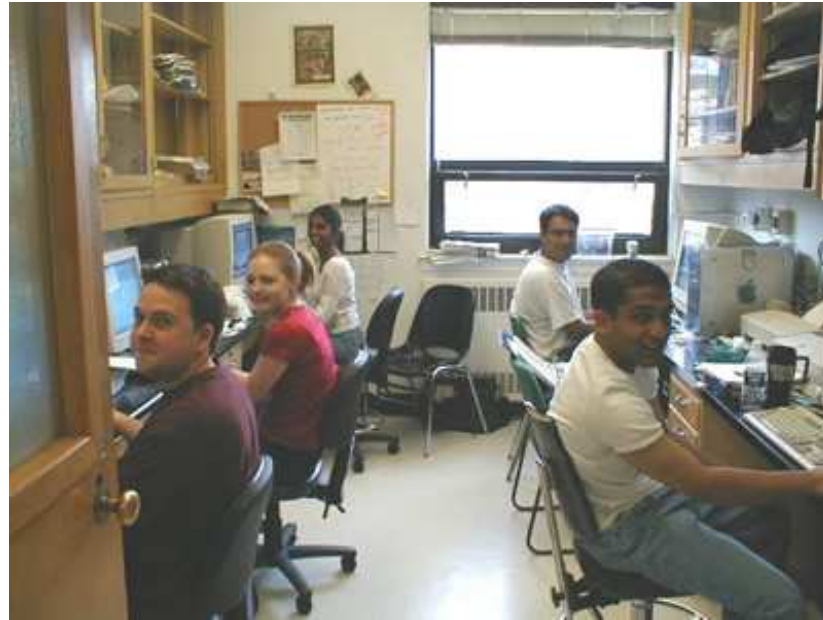
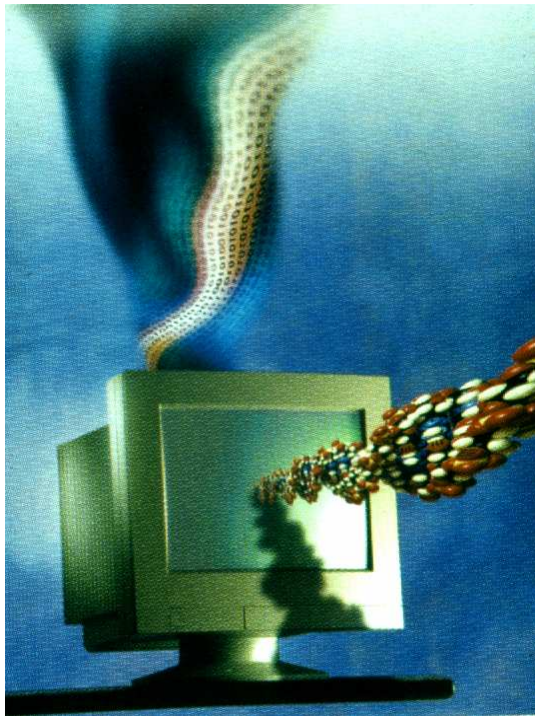
Οι Ολυμπιακοί ήταν οι παλαιότεροι και πιο σημαντικοί από όλους τους ελληνικούς αγώνες. Ήταν η μεγαλύτερη θρησκευτική γιορτή, ανάμεσα στις γιορτές τις αφιερωμένες στο Δία, τον ανώτατο θεό. Το ιερό της Ολυμπίας επέβαλλε το κύρος του σε ολόκληρο τον ελληνικό κόσμο.

```
>Gene  
ACCTGTCAGTGTCAACTGCTTCAATAGC  
TAATGCTAGGCTCGATAATCGCTGGCCT  
CAGCTCAGTCTGCTCGATAATCGCTGG  
CCCGATAATCGC
```

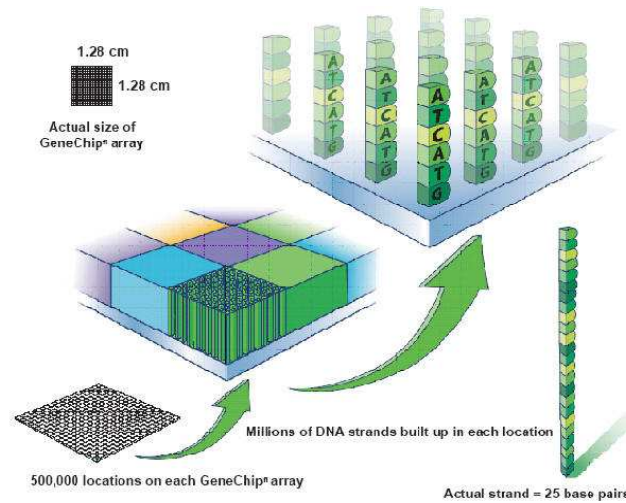
```
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01010100100100000  
0000000000000011  
0000000000000000  
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0000000000000000  
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000000011000000000000001000001100000000011111  
000000000000010000000100000001000001000000110  
0000000011000100001100000000000000110011000000  
000110000001000000100000010000000100000100000  
000010001000000001000000100000100000001000000  
001100000000110000000010001110101100000000001  
1100000000000100001011101001011011000000100111  
11100000000010100000111011001000000101000001111  
001101100000000000000000000000000000000011100  
0101010100111000000001010101000000000000010  
000001111111100000000000111000000110000000
```



BIOINFORMATICS



NANOTECHNOLOGY



*Heritable changes in gene expression or cellular phenotype that **entail changes** in the DNA sequence*

GENETICS

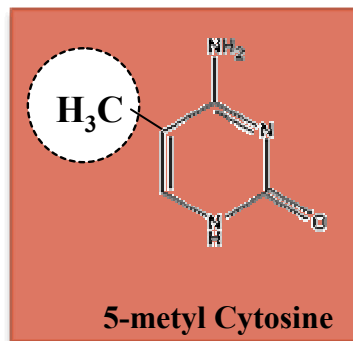
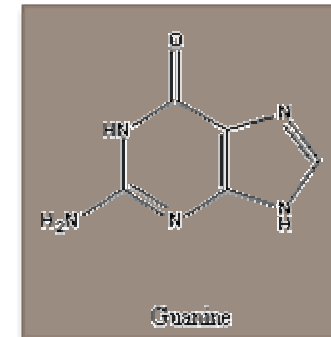
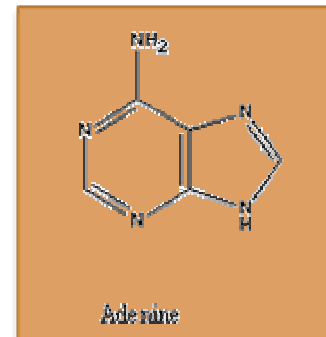
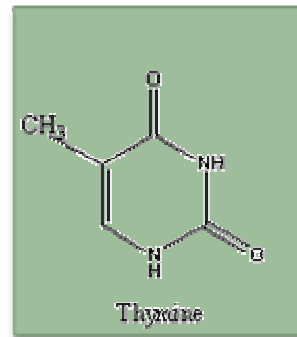
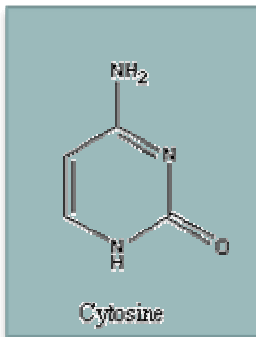


EPIGENETICS

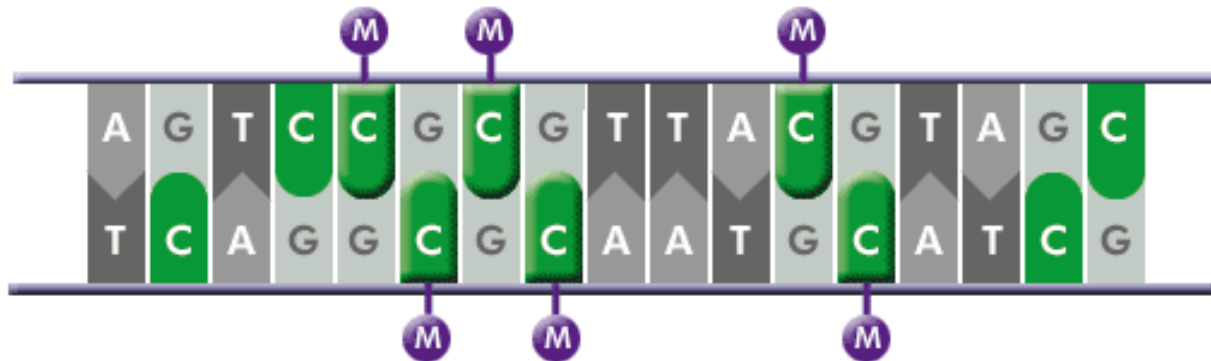
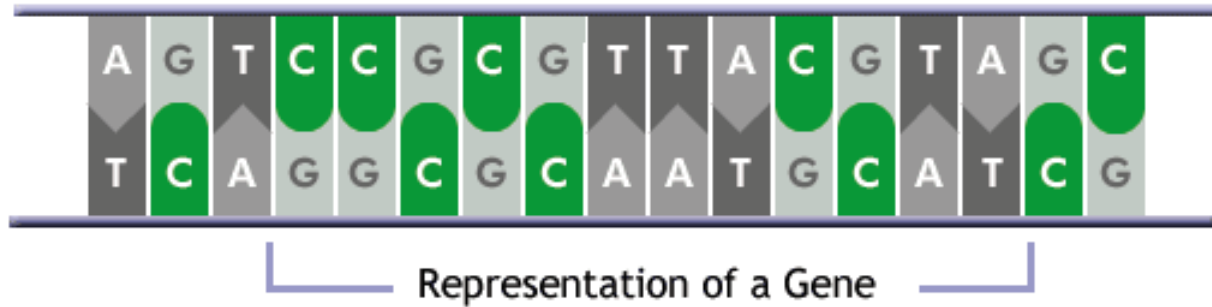
*Heritable changes in gene expression or cellular phenotype that **do not entail changes** in the DNA sequence*

**DNA
methylation**

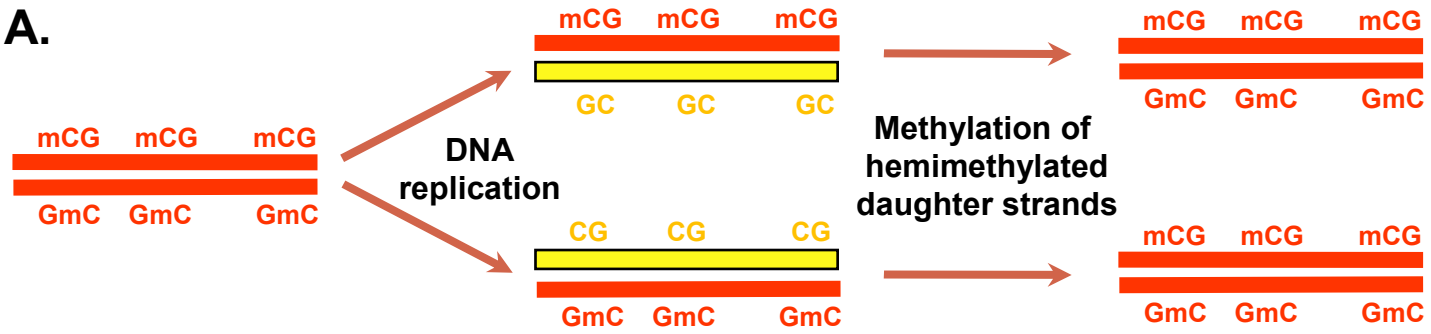
METHYLATION OF CYTOSINE



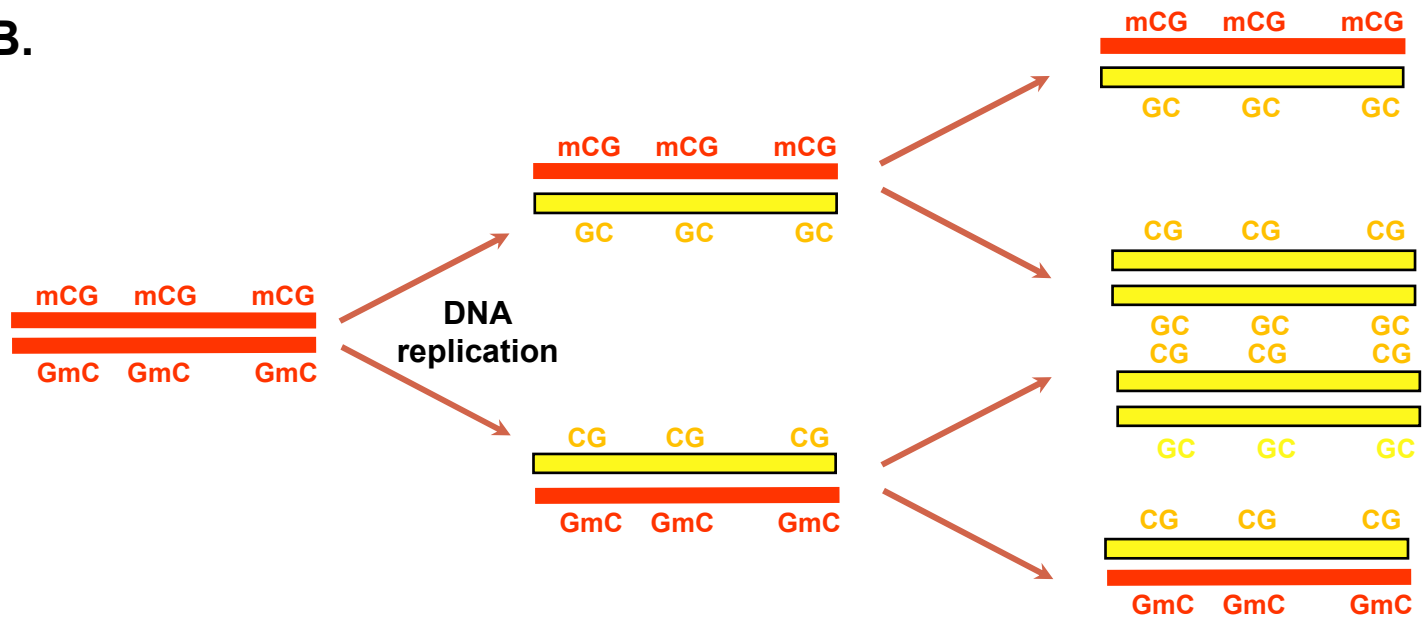
DNA METHYLATION



A.



B.

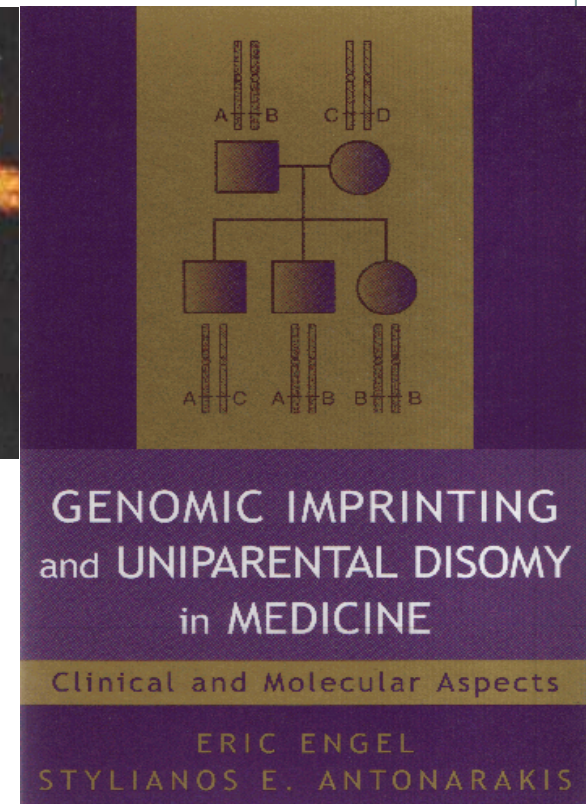


PARENTAL IMPRINTING



Μικρός καρπός

Μεγάλος καρπός





LTR Hypomethylated

When to Intervene??

LTR Hypermethylated

Yellow
Mouse



Agouti
Mouse

High risk cancer, diabetes,
obesity & reduced lifespan



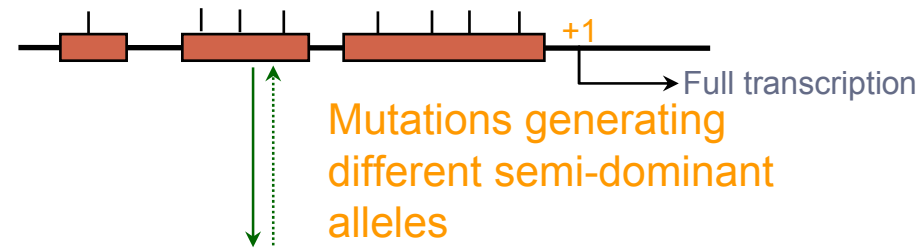
Lower risk of cancer,
diabetes, obesity and

Maternal Supplements with zinc prolonged life
methionine betaine choline, folate B₁₂

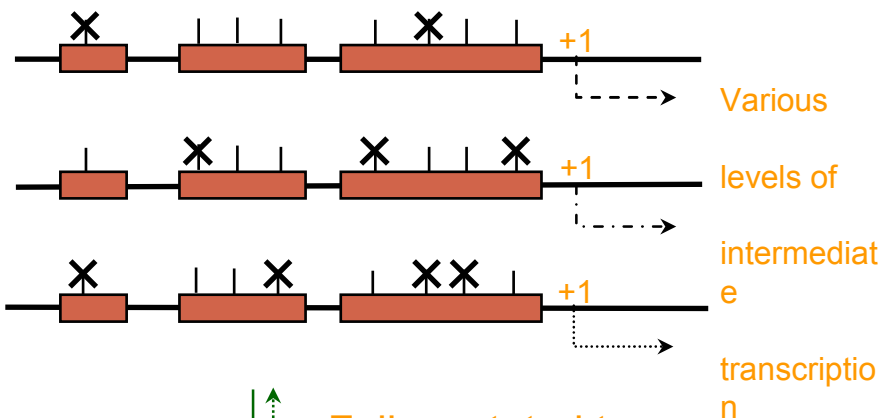
Cooney et al. J Nutr 132:2393S (2002)

A. MUTATIONS

A positive dominant gene

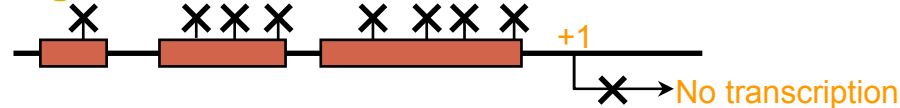


Different semi-dominant alleles



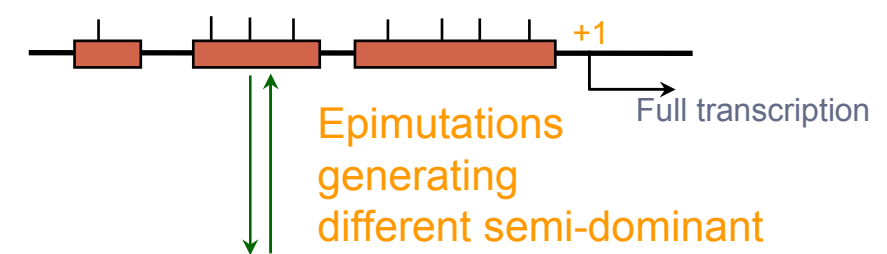
Fully mutated to a degenerative inactive recessive

Degenerative recessive

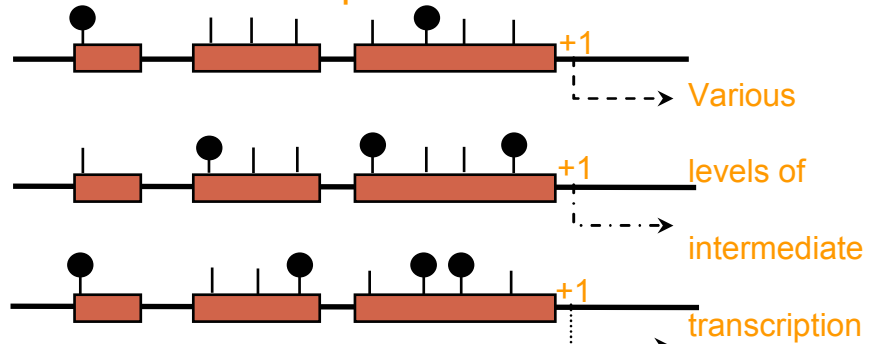


B. EPIMUTATIONS

A positive dominant gene

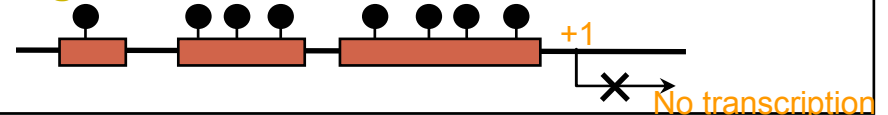


Different semi-dominant alleles



Fully epimutated to a degenerative inactive recessive

Degenerative recessive



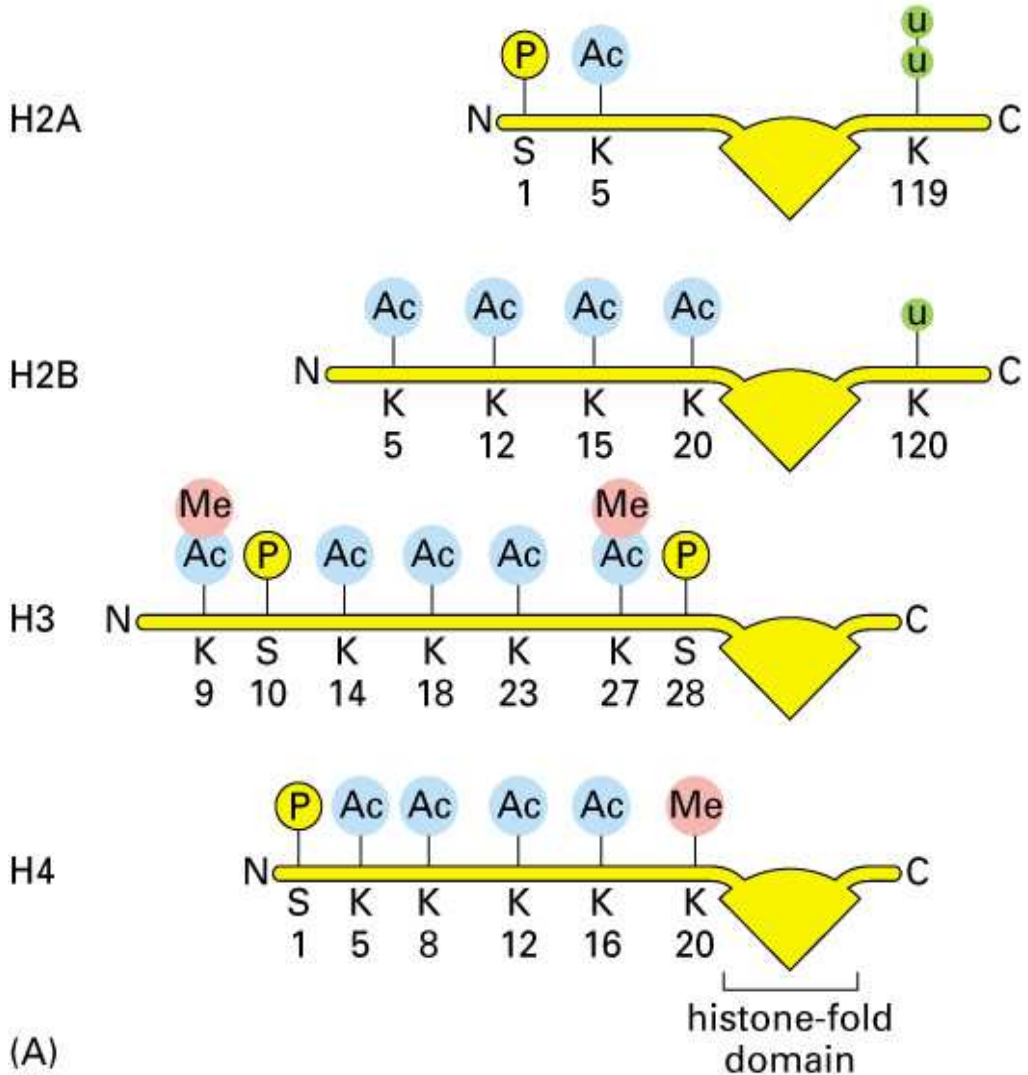
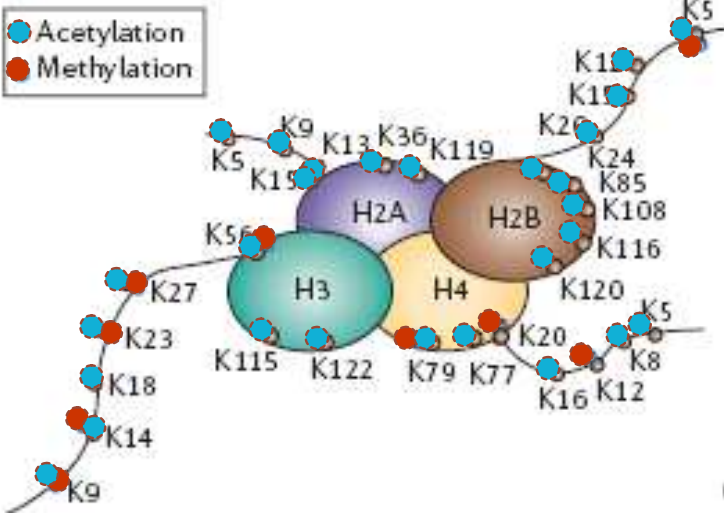


**Histone
modification**



HISTONE CODE

- Acetylation
- Methylation
- Phosphorylation
- Ubiquitinylation



Methylation

H3K9 H3K27 H3K79

H4K20

Deacetylation

Heterochromatin

compact inactive state

Gene silencing

Methylation

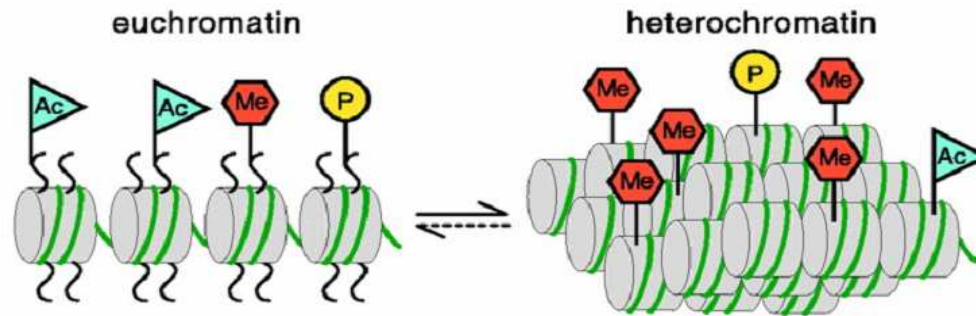
H3K4

Acetylation

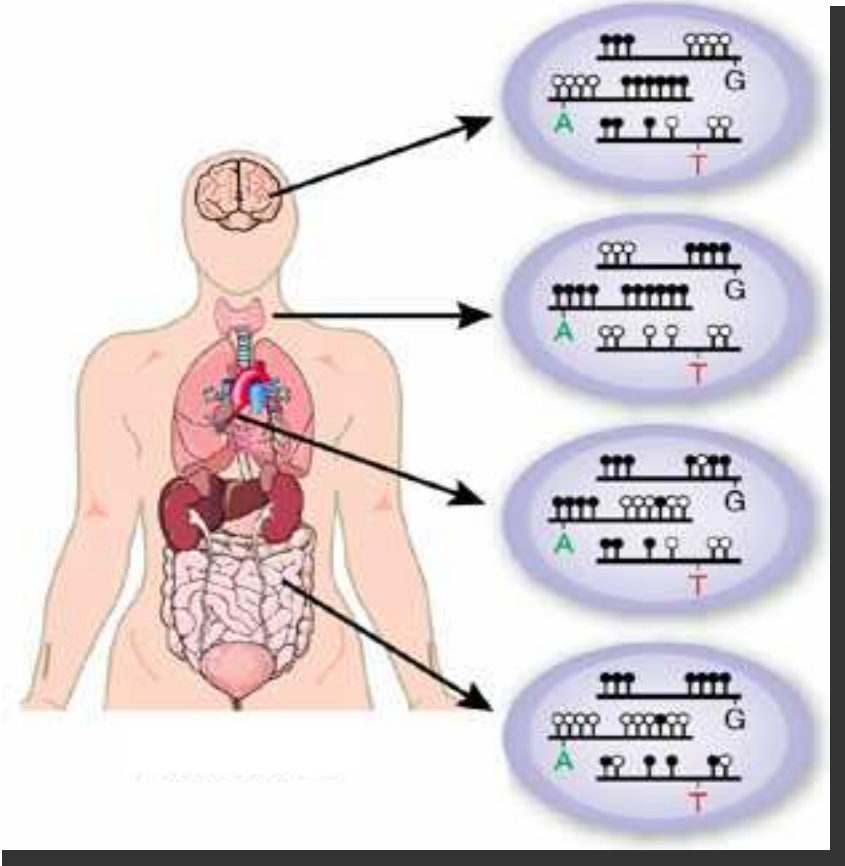
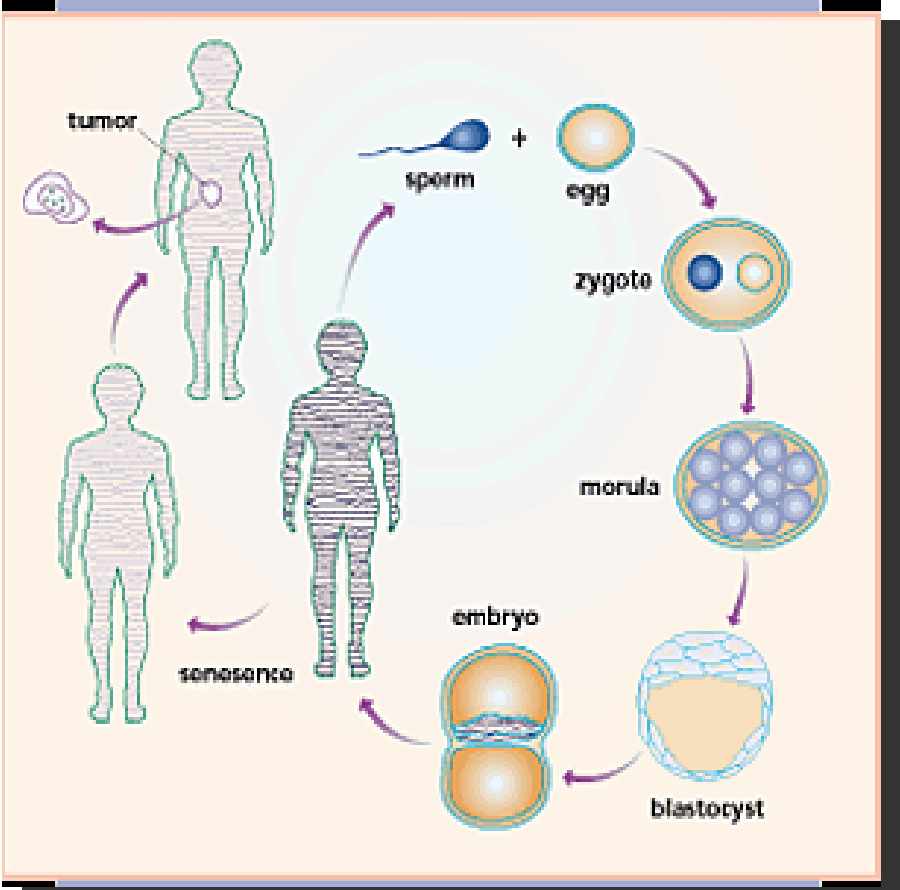
Euchromatin

active state

Gene expression

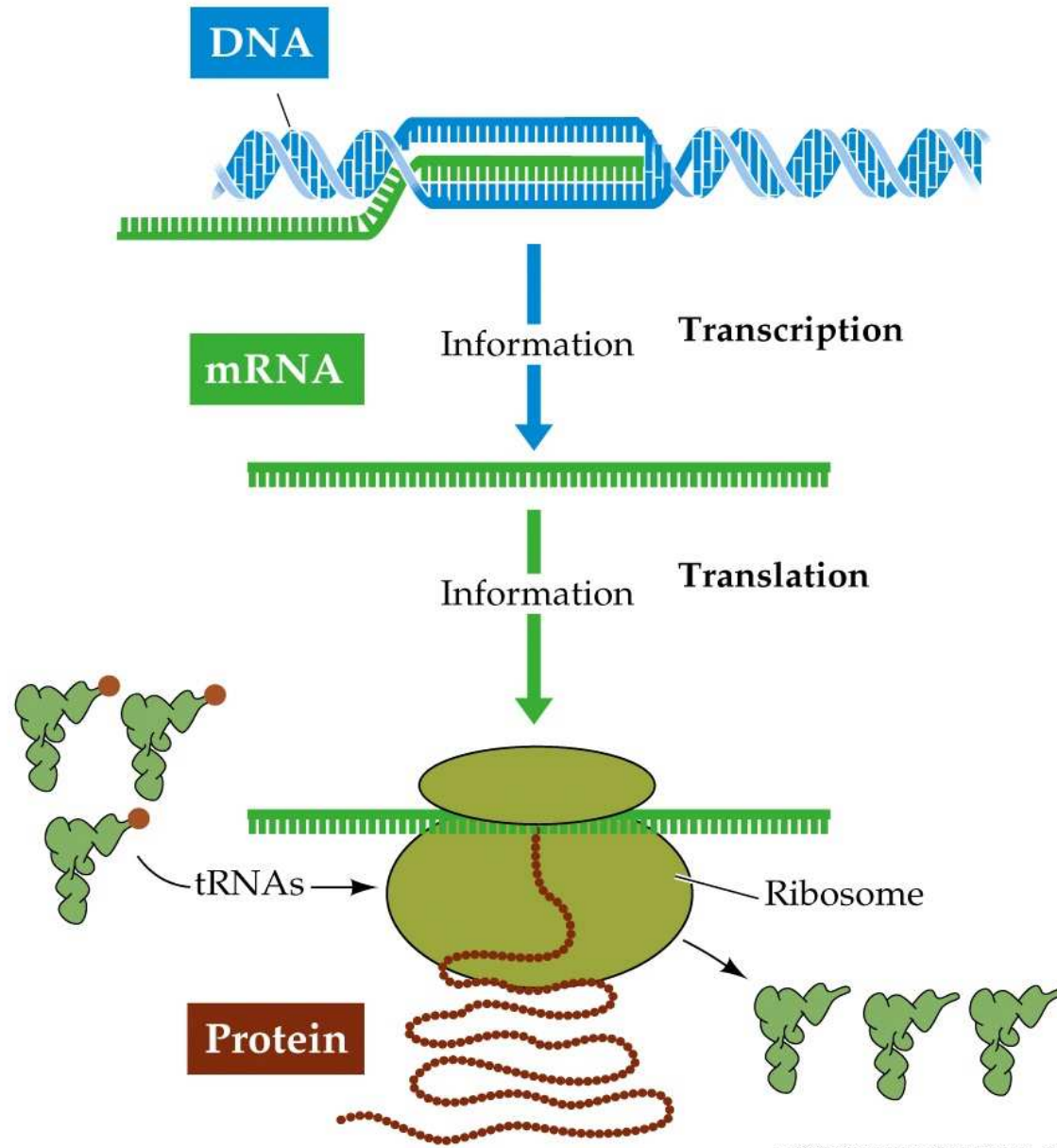


METHYLATION PATTERNS IN HUMAN DEVELOPMENT AND TISSUES

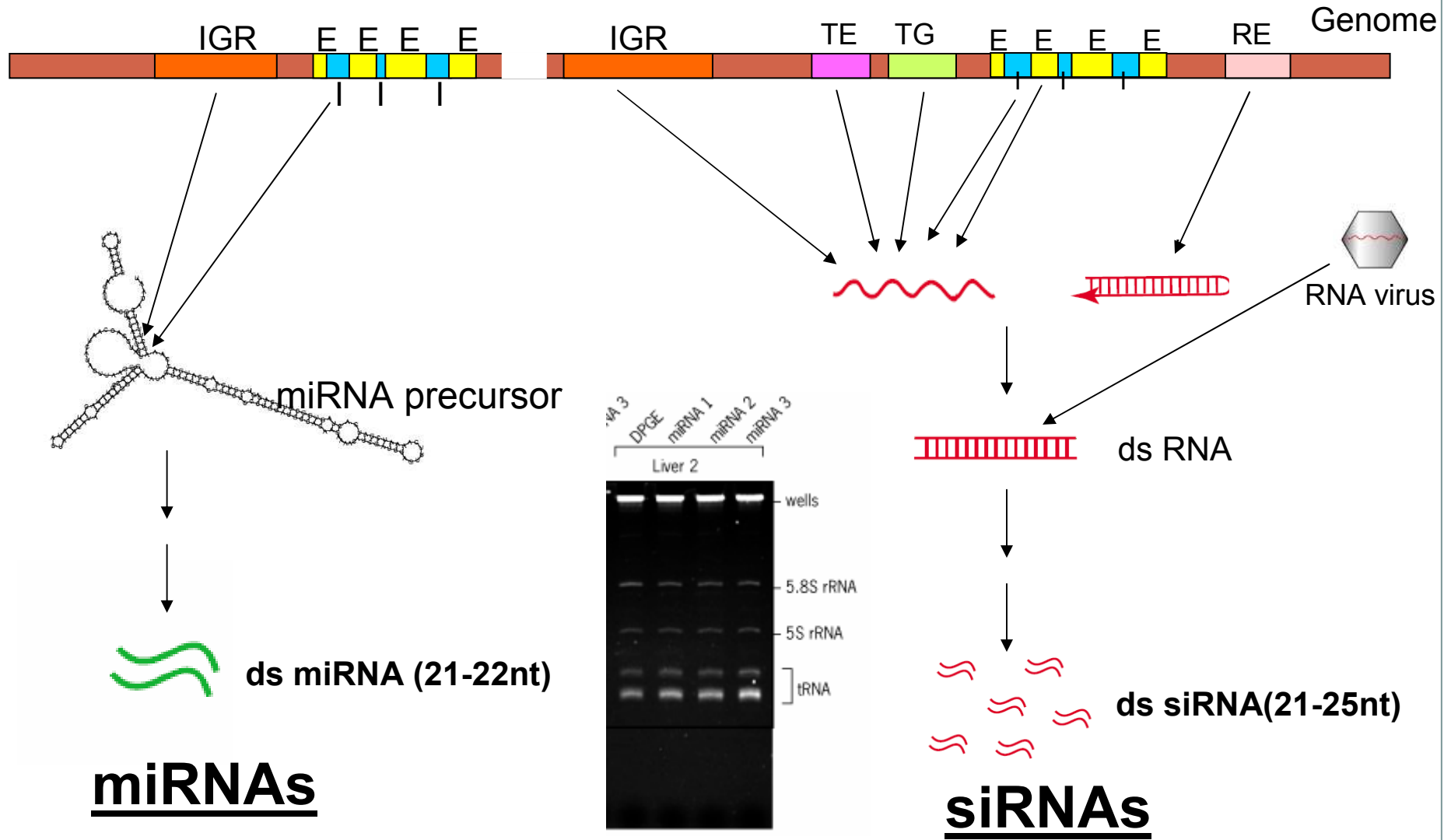




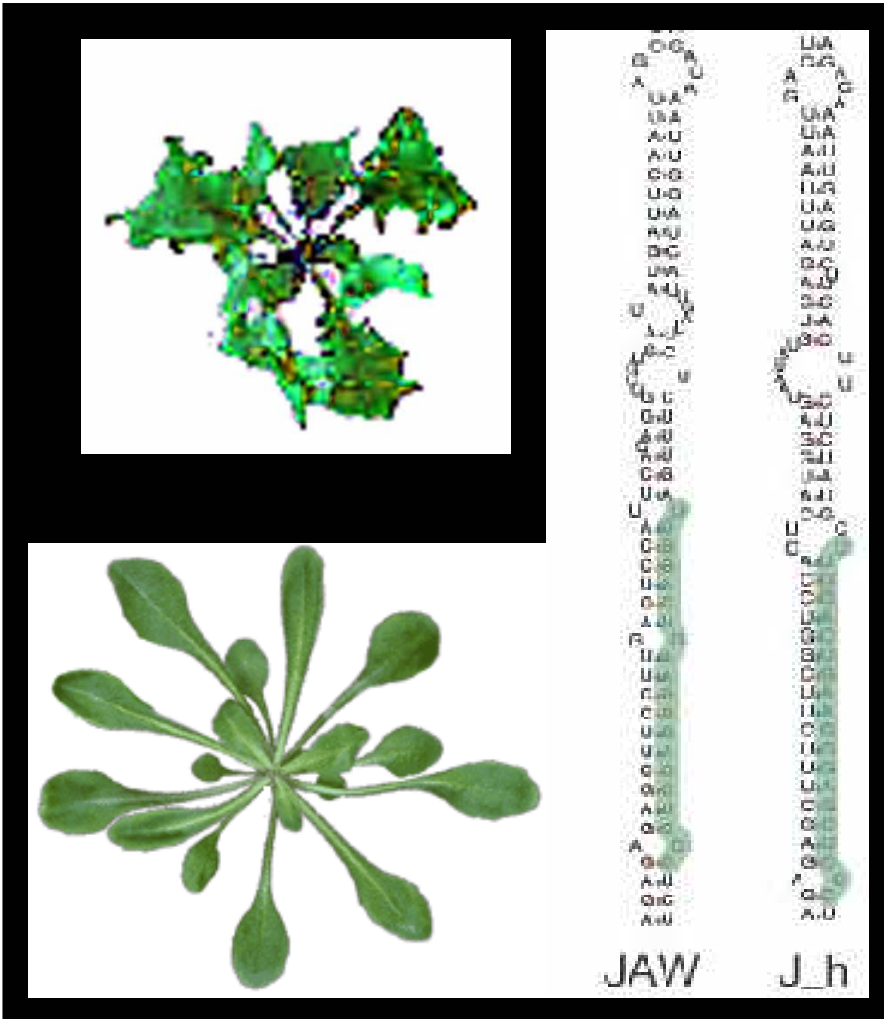
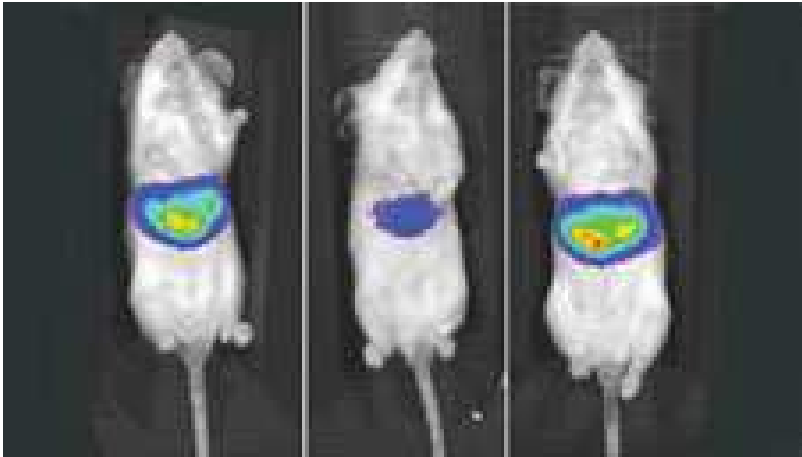
**RNA
Interference**

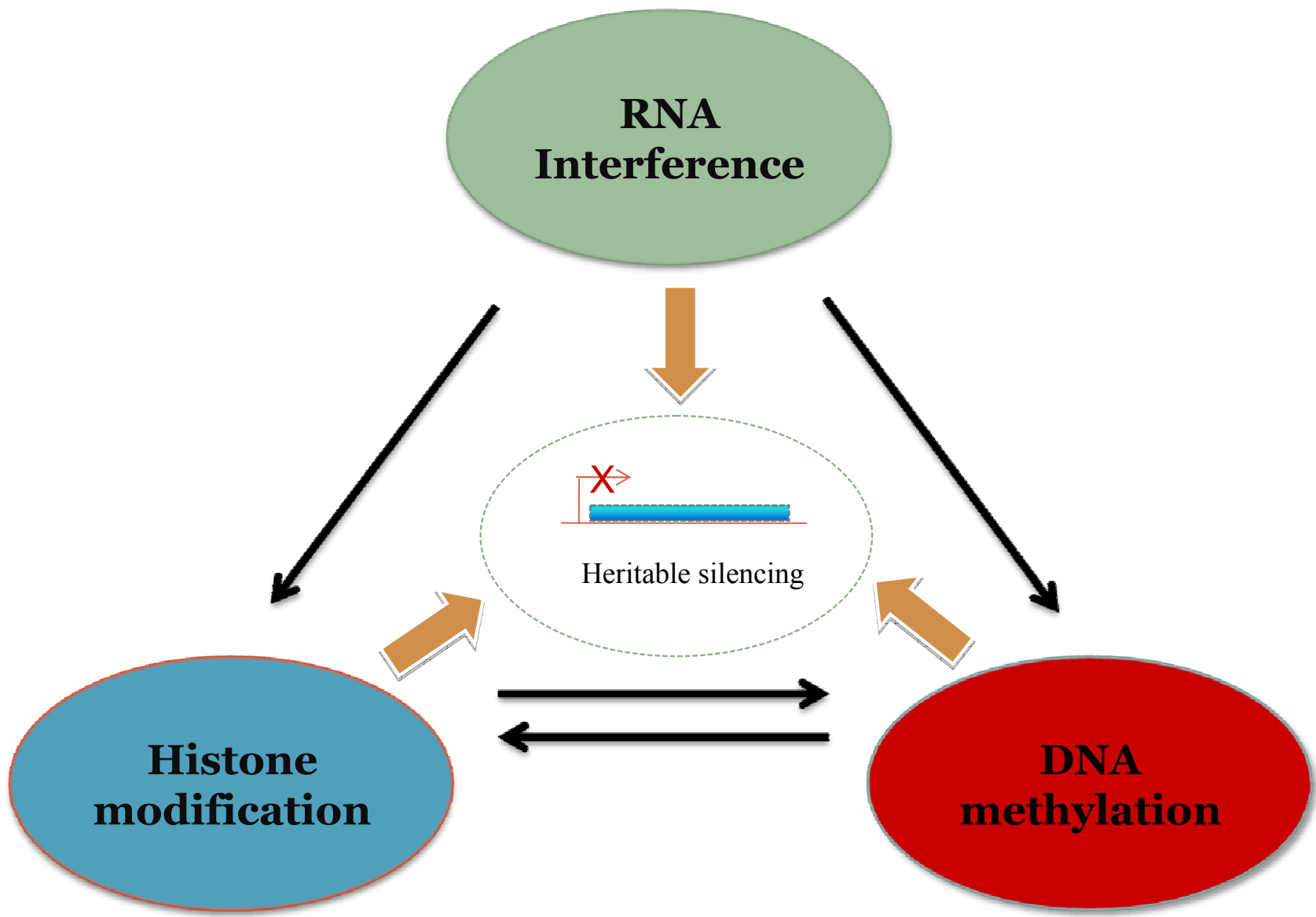


SMALL RNAS (SRNAs)

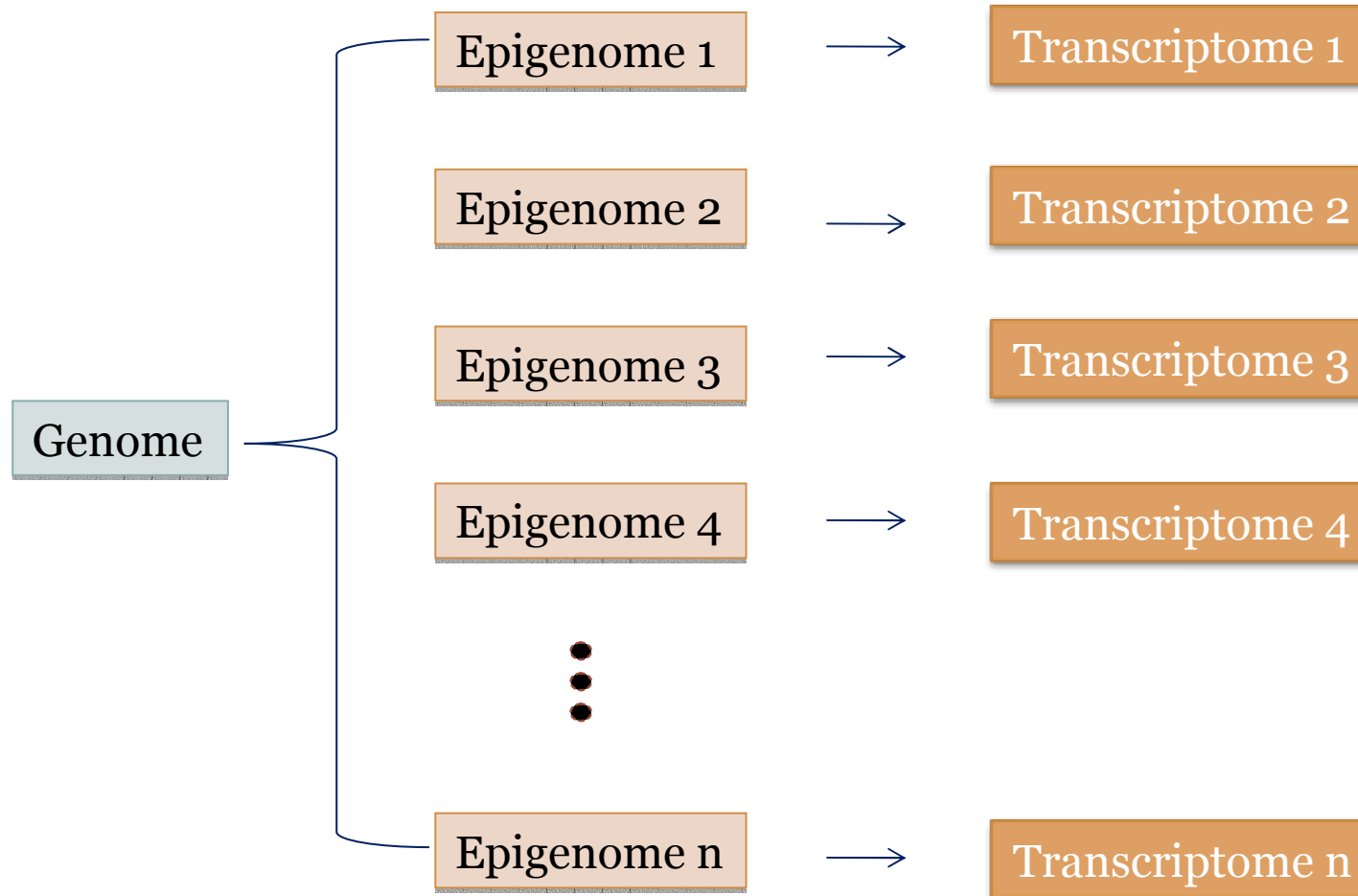


GENE SILENCING

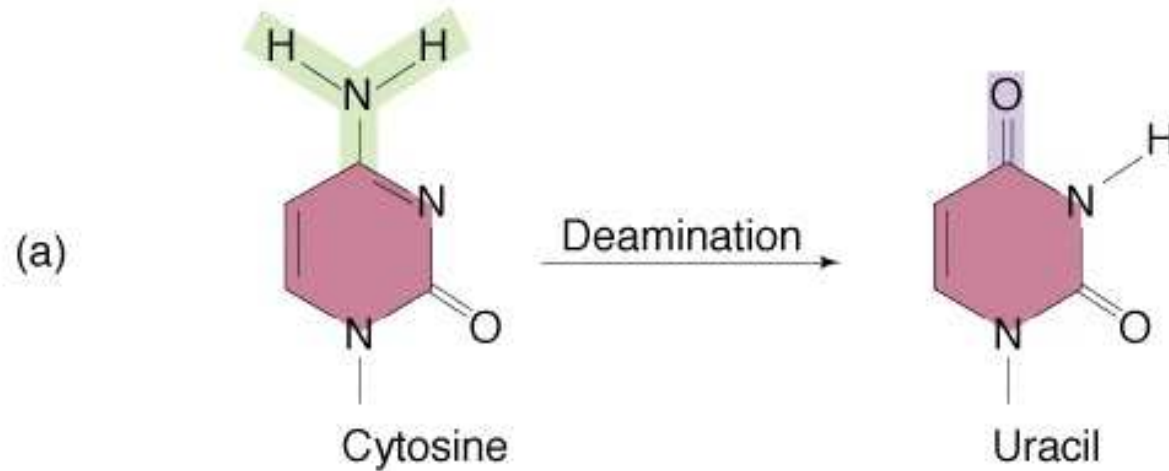




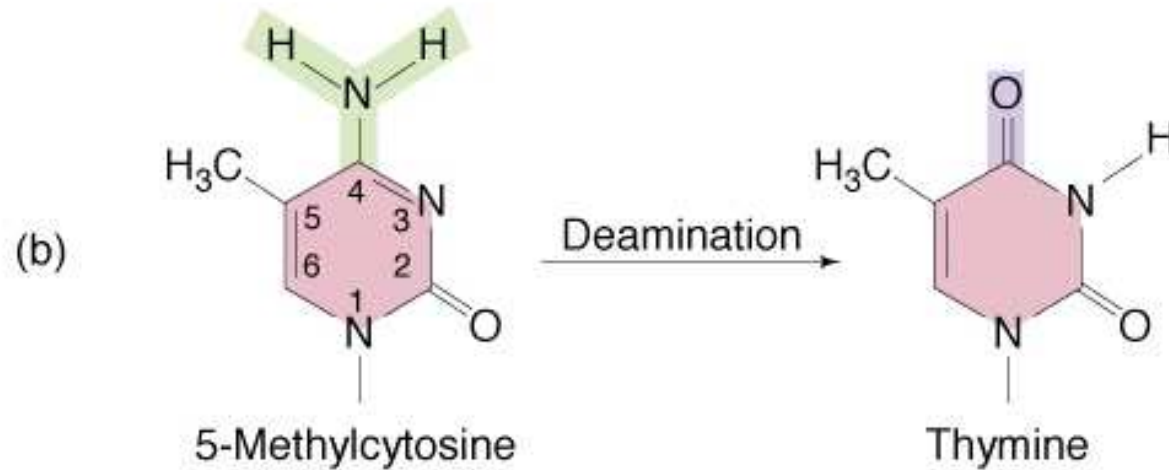
ONE GENOME VERSUS MULTIPLE EPIGENOMES



DNA METHYLATION IS A “HOTSPOT” FOR MUTATIONS

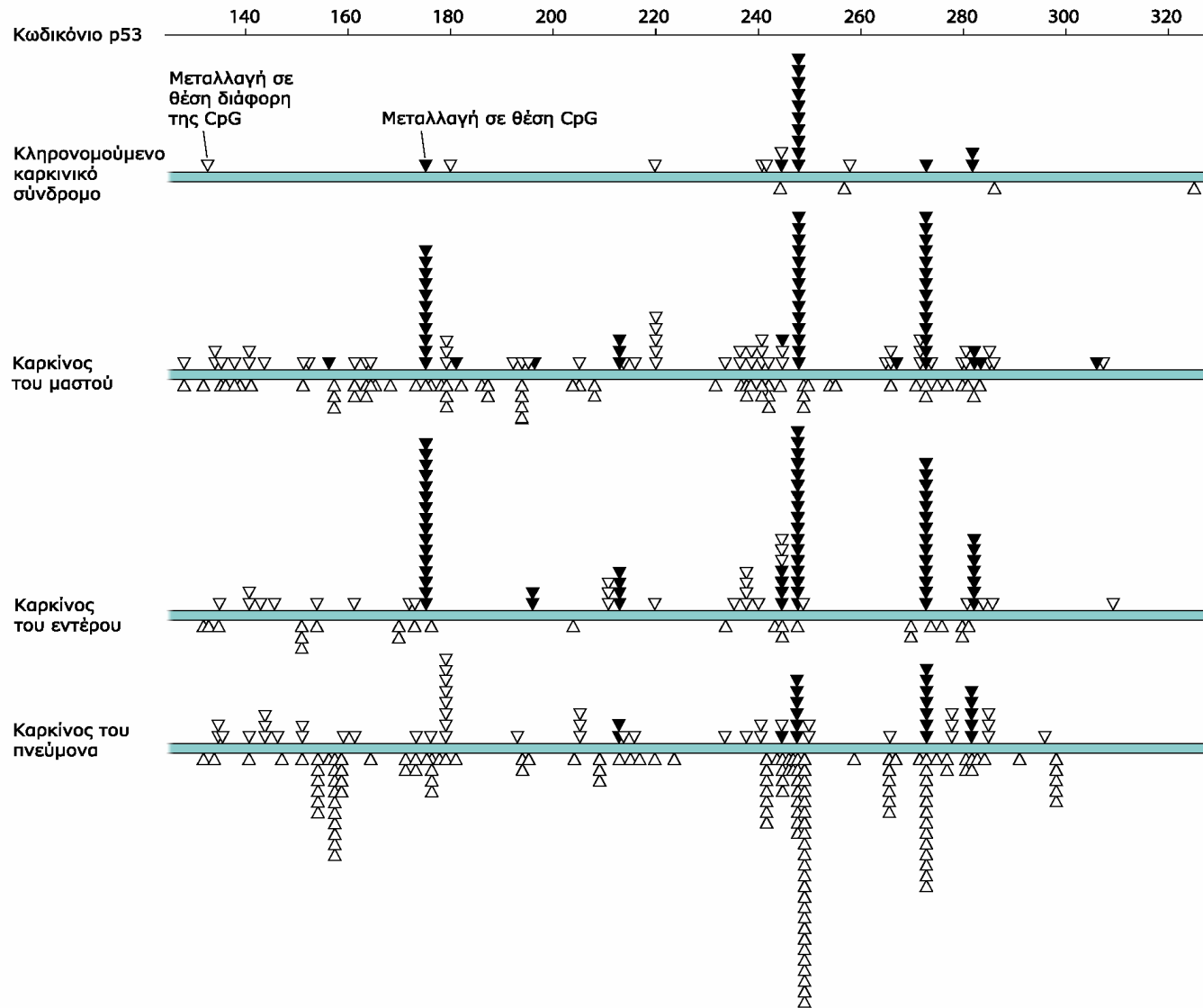


Not a DNA base
Error correction

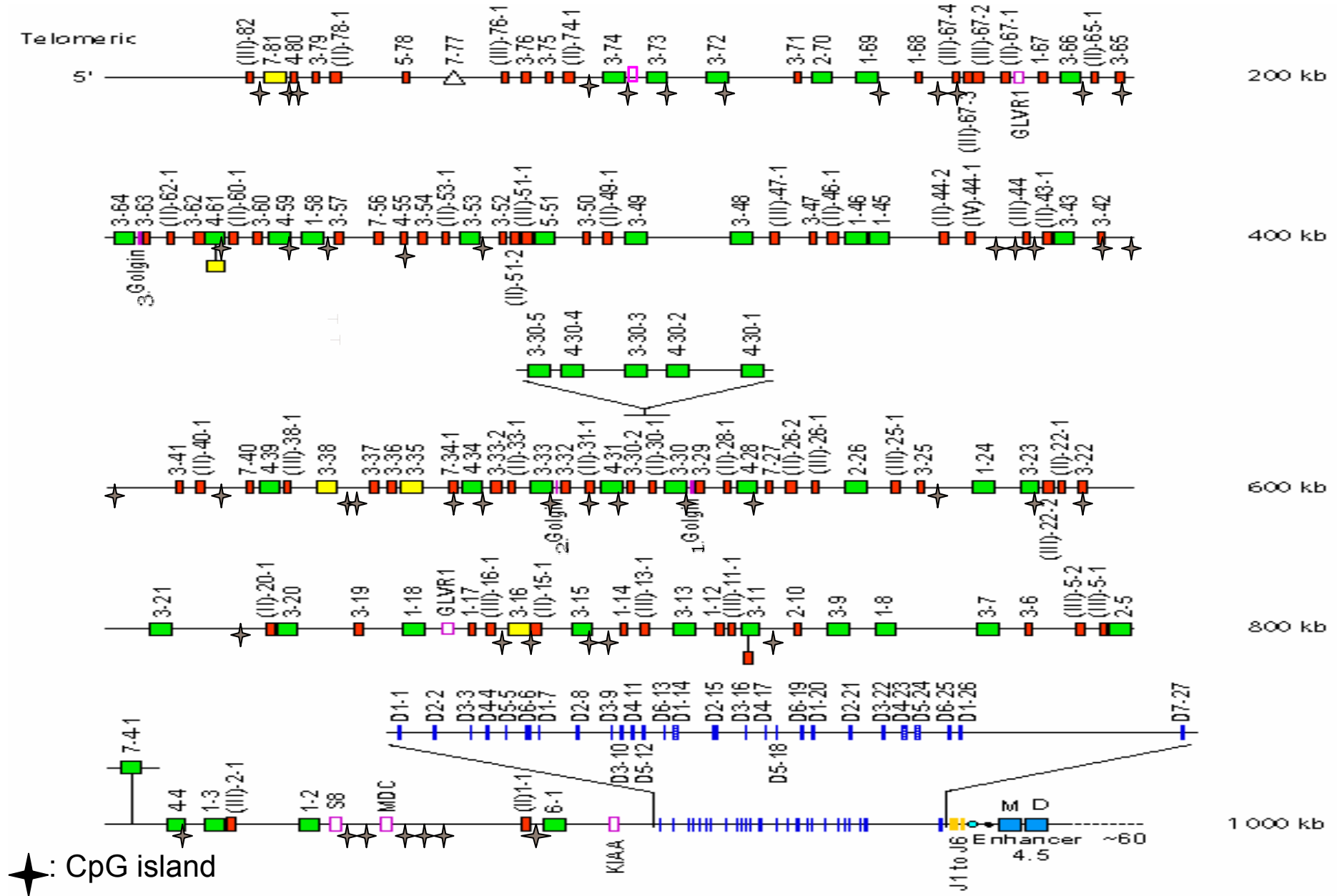


Normal DNA base
No correction

THE TRANSITION C > T, THAT PROBABLY IS A RESULT OF 5-METHYL-CYTOSINE DEAMMINATION, IS FREQUENT IN TUMORS.

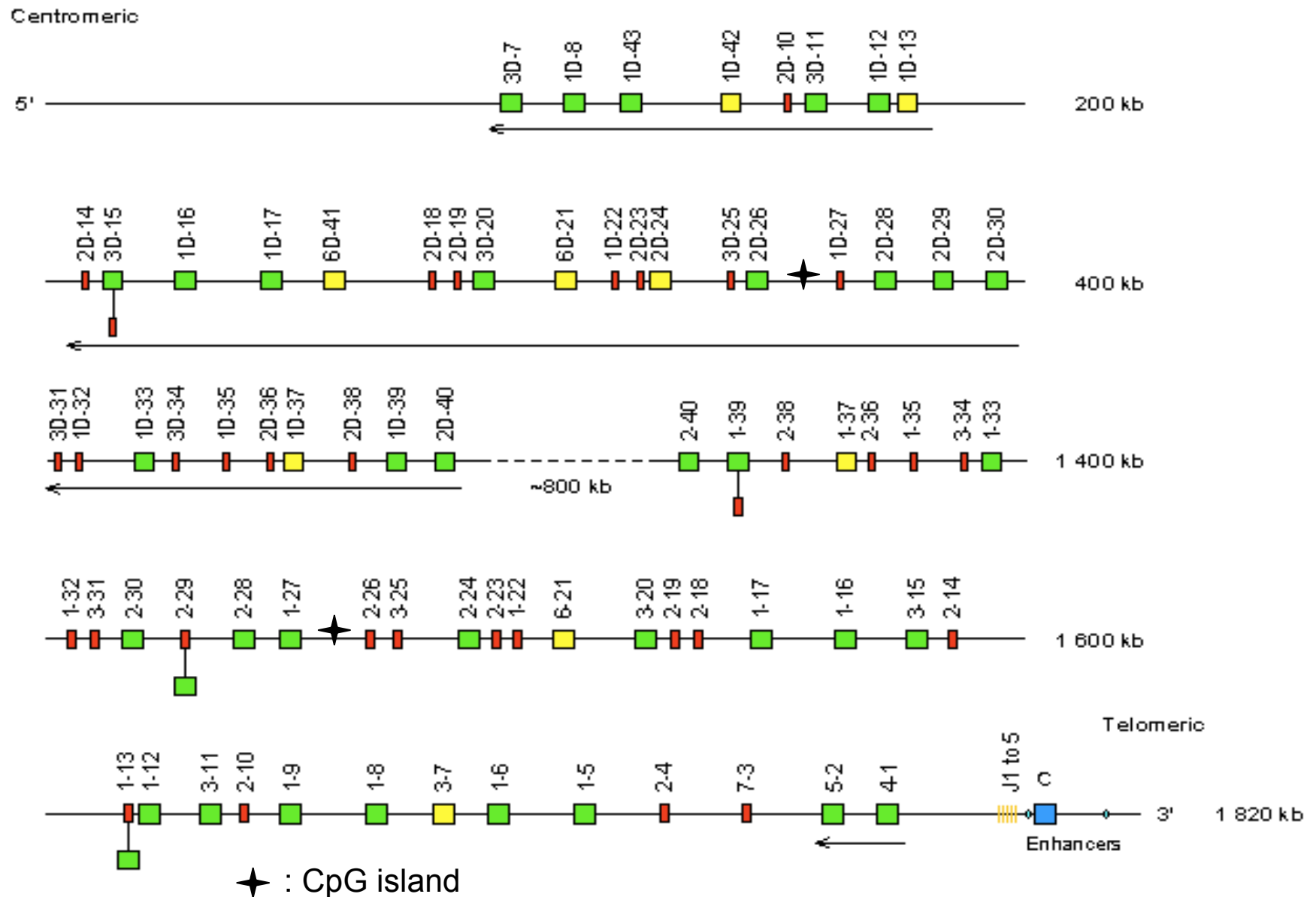


Human (homo sapiens) IGH locus chromosome 14 (14q32.33)



Human (*Homo sapiens*) IGK locus on chromosome 2 (2p11.2)

- Locus representation: Human IGK DNA fragment containing the 5 IGK/OR22 orphans

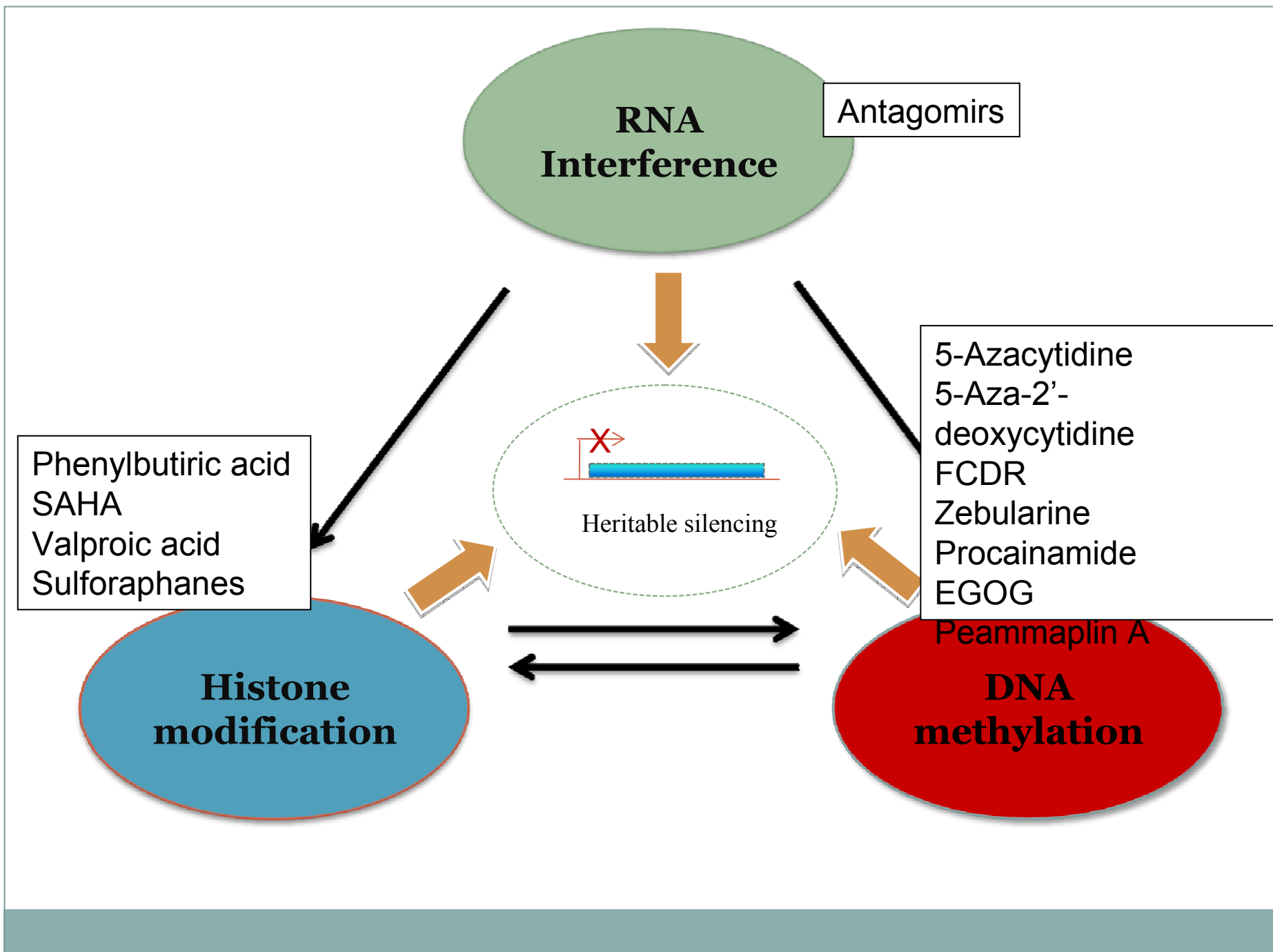




EPI-THERAPY

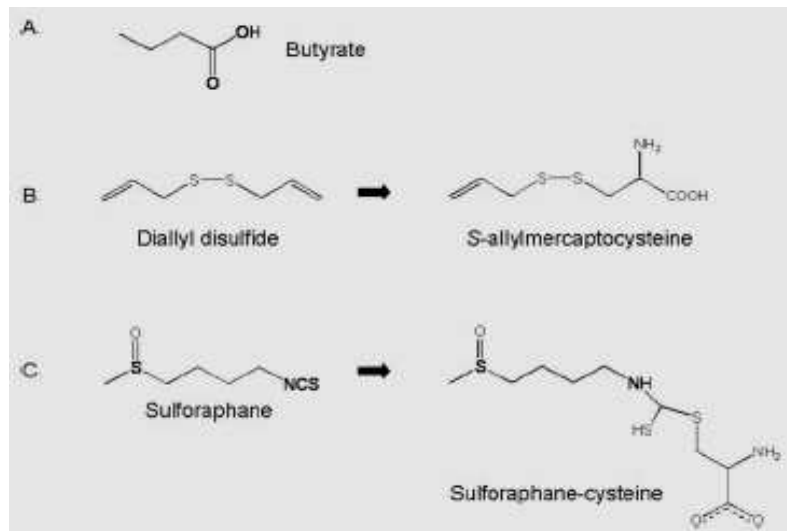
EPIGENETIC DISEASES AND DIAGNOSIS

Disease	Aetiology	Diagnostic Method
Fragile X syndrome	Expansion of CGG repeat in FMR1 5'UTR	PCR, Sequencing
Angelman's syndrome	Deregulation of one or more imprinted genes	Bisulfite method, sequencing
Rett syndrome	MeCP2 mutations	Sequencing, RFLP
Leukemia	Chromosomal translocations involving HATs and HMTs	RT-PCR, sequencing
Various cancers	De novo methylation of various promoters	Bisulfite method, sequencing, PCR

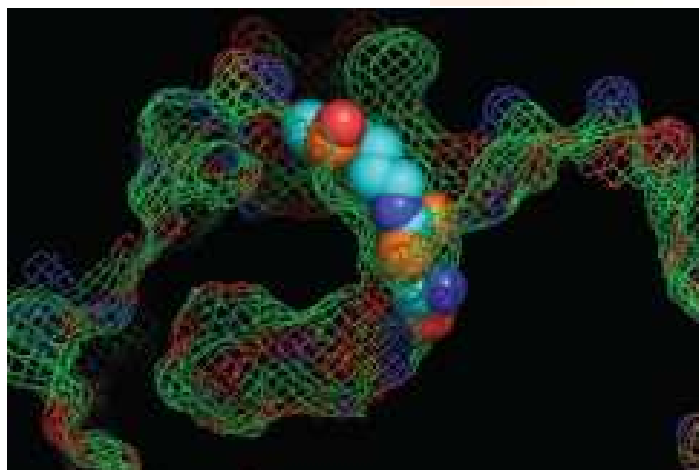
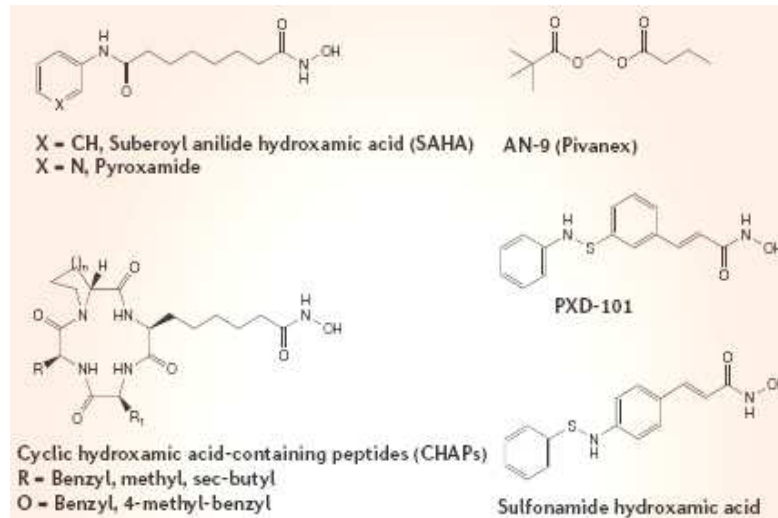


HISTONE ACETYLASE INHIBITORS

Natural inhibitors



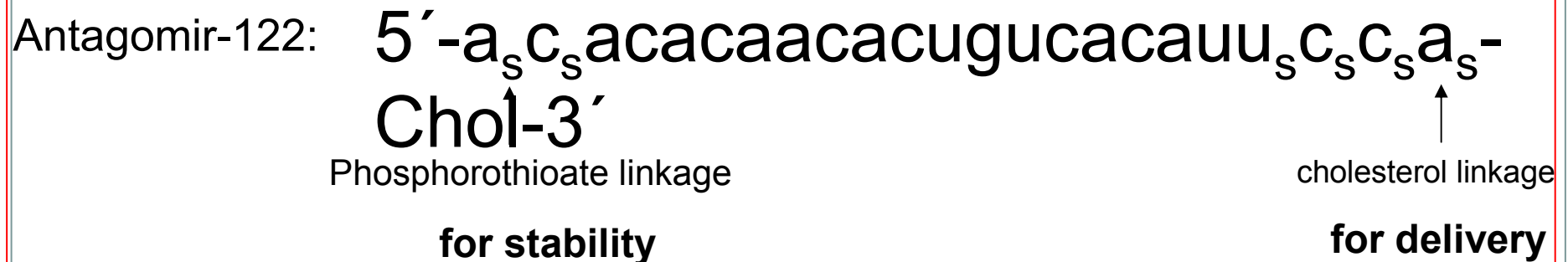
Synthetic inhibitors



ANTAGOMIRS

Can silence miRNAs *in vivo*

Chemically modified ss RNA analogues complementary to miRNAs



Antagomir-16

Antagomir-122

Antagomir-192

Antagomir-194

Intravenous administration



Silencing of the endogenous

miR16

miR122

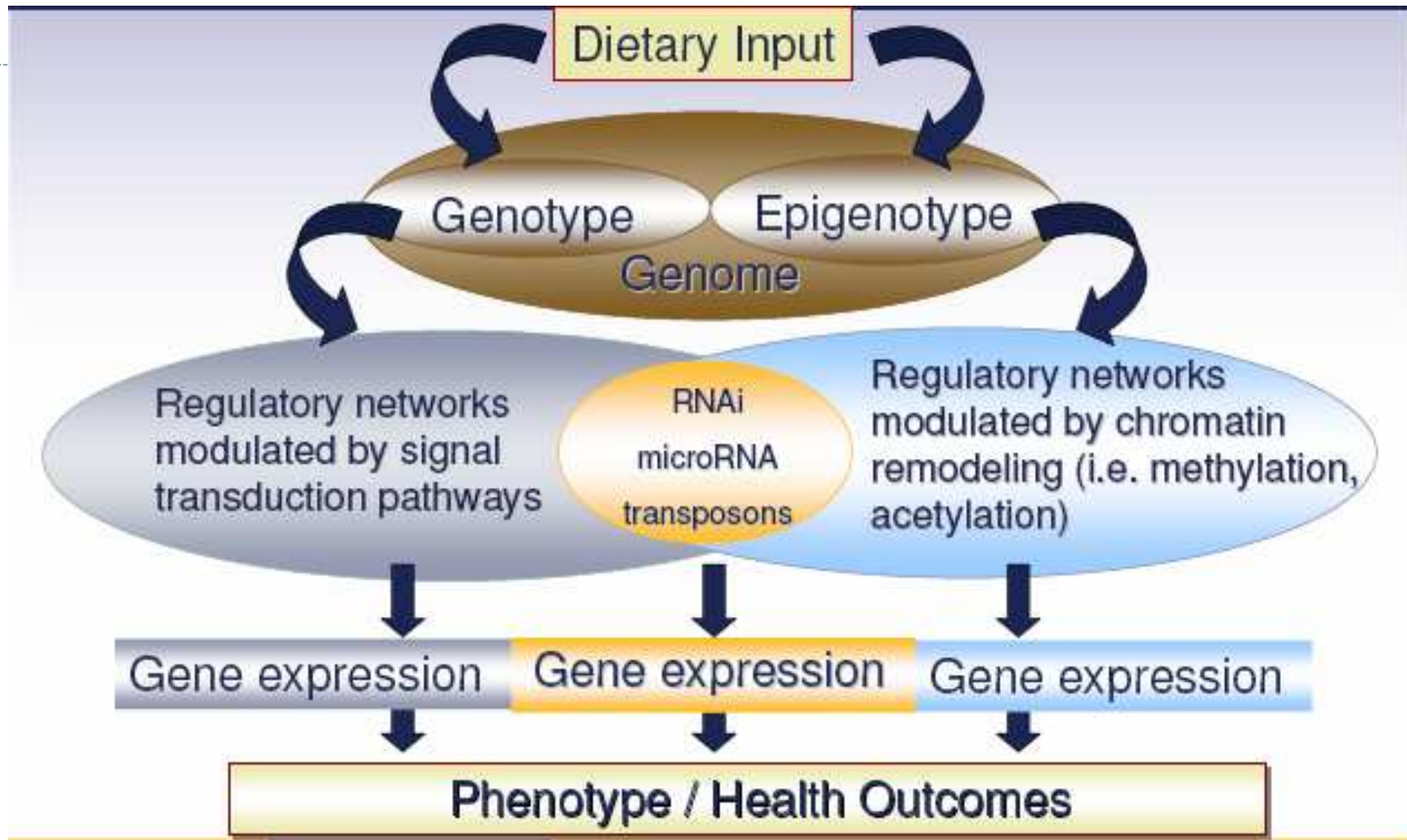
miR192

miR194

•Very promising therapeutic potential



EPI-NUTRITION



LTR Hypomethylated

When to Intervene??

LTR Hypermethylated

Yellow
Mouse



Agouti
Mouse

High risk cancer, diabetes,
obesity & reduced lifespan

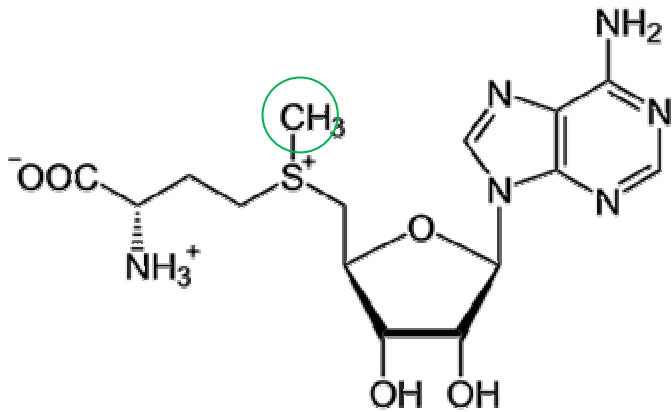


Lower risk of cancer,
diabetes, obesity and

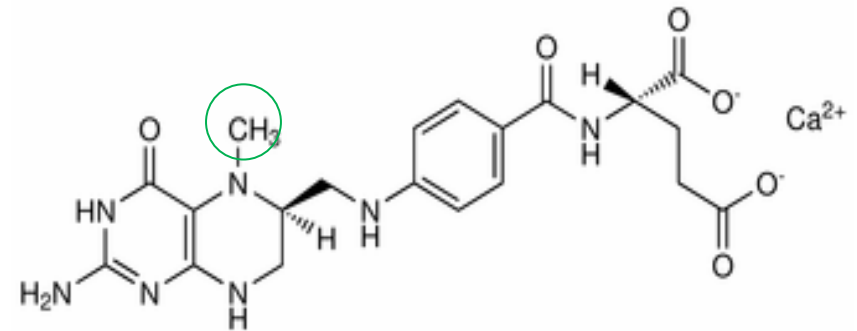
Maternal Supplements with zinc prolonged life
methionine betaine choline, folate B₁₂

Cooney et al. J Nutr 132:2393S (2002)

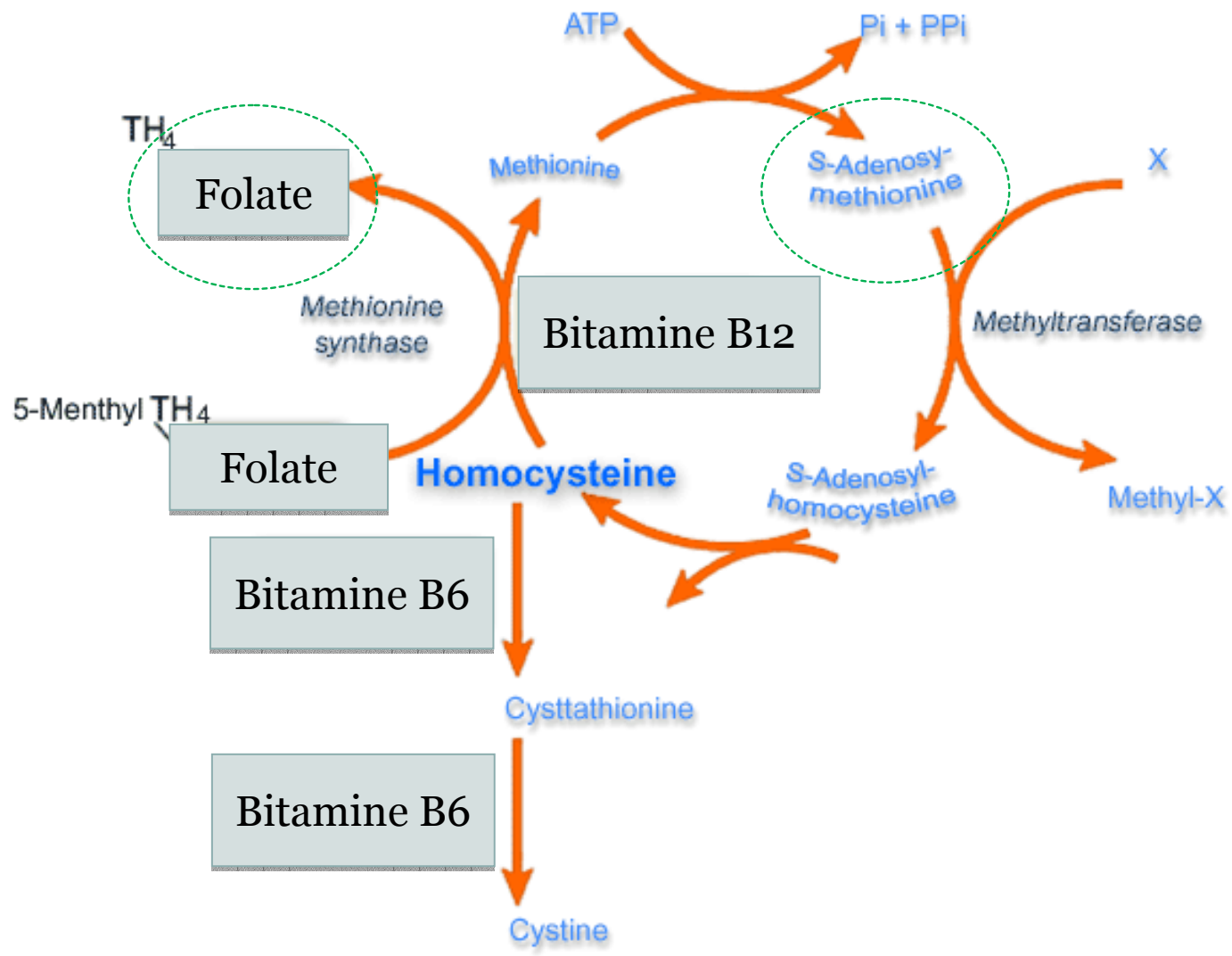
METABOLISM OF METHYLS



S-Adenosyl methionine



Methyltetrahydrofolate



EPIGENETIC BIOACTIVE COMPOUNDS IN PLANTS



Artichoke
(Silymarin)



Oleander
(Oleanderin)



Tomato
(Lycopene)



Garlic
(Diallyl sulfide, ajoene,
S-allyl cysteine, allicin)



Carrots
(β -carotenes)



Tea
(Catechins)



Red grapes
(Resveratrol)



Red chilli
(Capsaicin)



Turmeric
(Curcumin)



Cloves
(Eugenol &
isoeugenol)



Honey-bee propolis
(Caffeic acid, CAPE)



**Cruciferous
vegetables**
(Sulforaphane)



Pomegranate
(Ellagic acid)



Ginger
(6-Gingerol)



Basil
(Ursolic acid)



Fennel,
(Anethol)



Soybean
(Genistein)



Aloe
(Emodin)

NUTRITIONAL CONTROL OF REPRODUCTIVE STATUS IN HONEY BEES



R. Kucharski, J. Maleszka, S. Foret, R. Maleszka *Science* **319**, 1827 (2008) pag. 1827-1830

EPIGENETIC MODIFIERS IN BARLEY SEED DEVELOPMENT



Caresse



Kos

Ippolytos

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[St Clair D](#), [Xu M](#), [Wang P](#), [Yu Y](#), [Fang Y](#), [Zhang F](#), [Zheng X](#), [Gu N](#), [Feng G](#), [Sham P](#), [He L](#)

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Annu Rev Genomics Hum Genet. 2004;5:479-510

THANK YOU



- **My collaborators at AUTH and CERTH**
- **All of you for your attention**