Epigenetics as a new approach for biomarkers discovery

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23-27. September Frascati

Biomarker definition

"a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention (*Biomarkers Definitions Working Group, 2001*)"

„a measurable DNA and/or RNA characteristic that is an indicator of normal biologic processes, pathogenic processes, and/or response to therapeutic or other interventions (*European Medicines Agency, 2007*)"

Relations omarkers and int factors

Hemoglobin concentratio
as adaptation to high-altitud

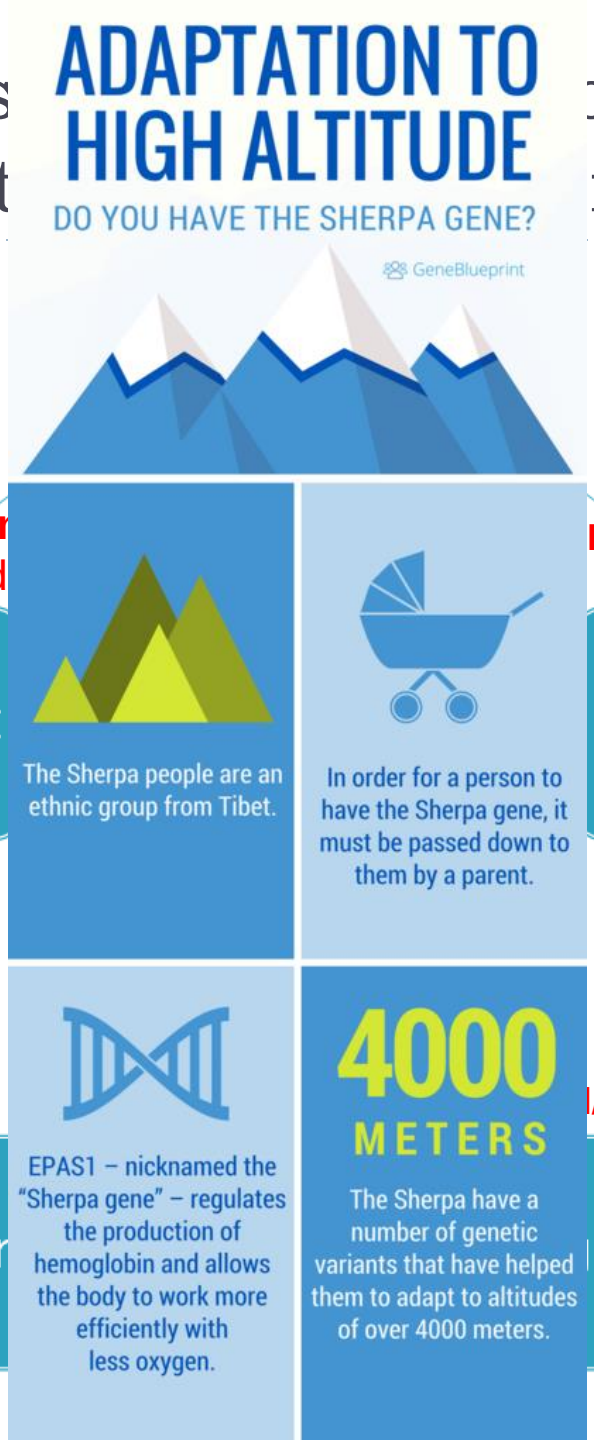
Elevated bilirubin concentration
in Gilbert's syndrome

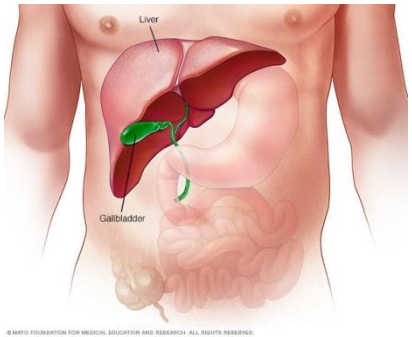
environment

genetic factors

ger e

l/L



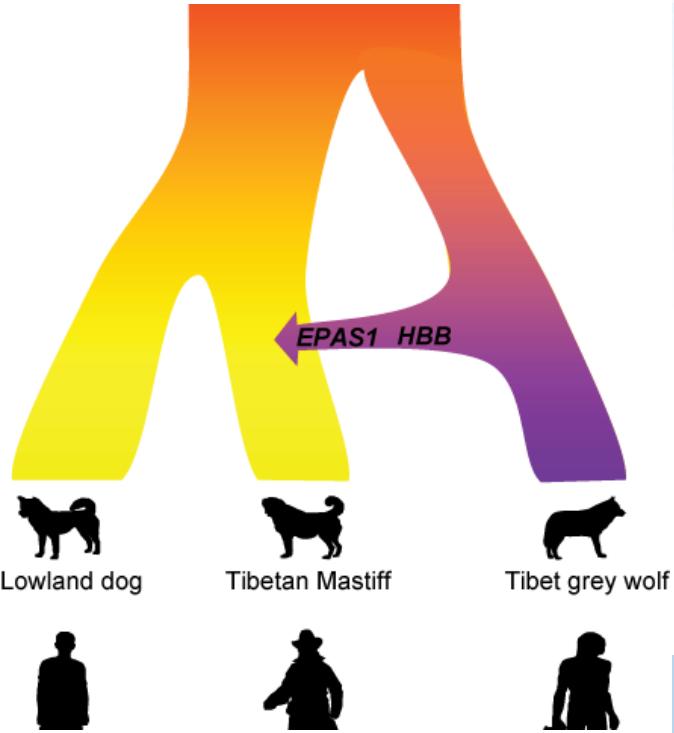


ADAPTATION TO HIGH ALTITUDE

DO YOU HAVE THE SHERPA GENE?

GeneBlueprint

GENETICS



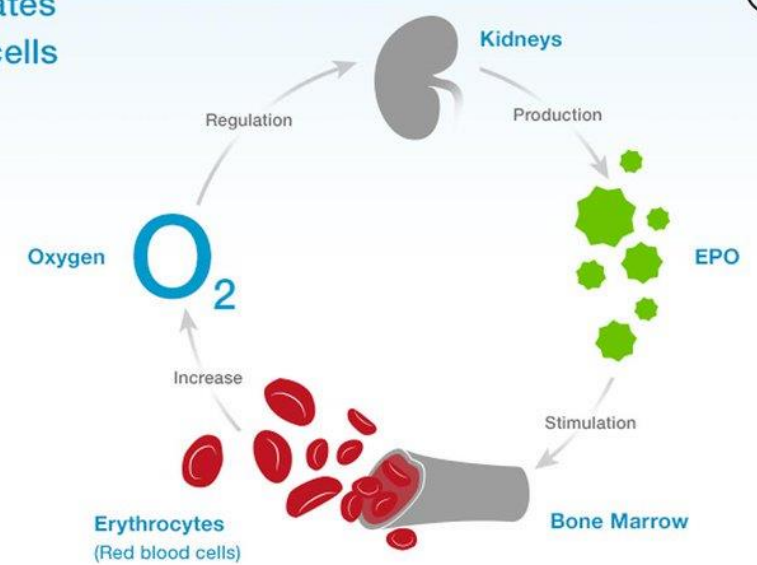
EPIGENETICS

Erythropoietin (EPO) stimulates the formation of red blood cells

Erythropoietin (EPO) is a naturally occurring glycoprotein hormone that controls the production of red blood cells.

The more red blood cells there are in the blood, the more oxygen can be absorbed. However, when someone is suffering from anemia or a lack of oxygen, less O_2 is absorbed and, as a result, the kidney is stimulated to produce more erythropoietin.

In patients with kidney disease, this adjustment does not work sufficiently well, and a lack of erythropoietin is usually the cause of the anemia.



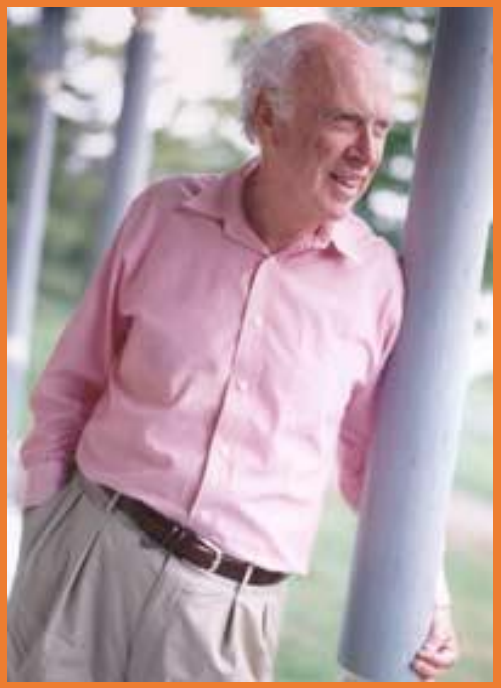
EPAS1 – nicknamed the "Sherpa gene" – regulates the production of hemoglobin and allows the body to work more efficiently with less oxygen.

4000 METERS

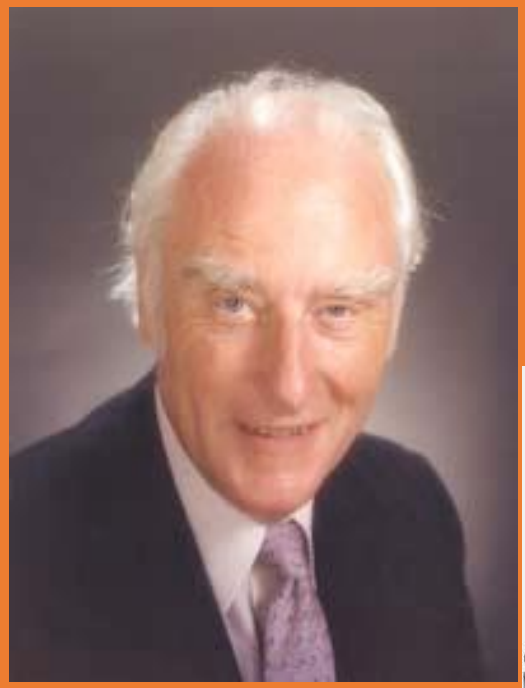
The Sherpa have a number of genetic variants that have helped them to adapt to altitudes of over 4000 meters.

The Watson-Crick DNA Model – 1953

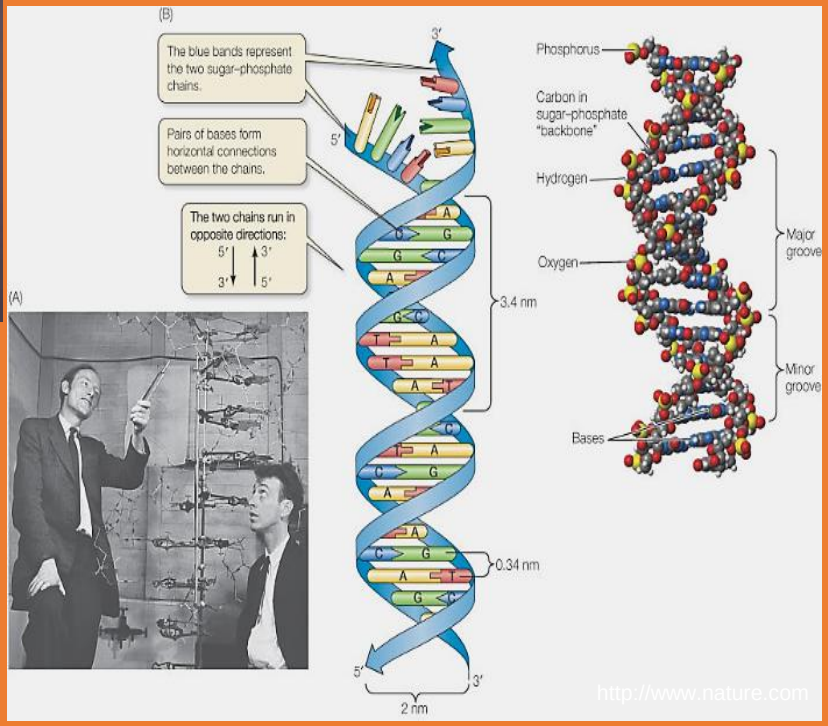
Nobel prize in Physiology or Medicine in 1962



James D. Watson

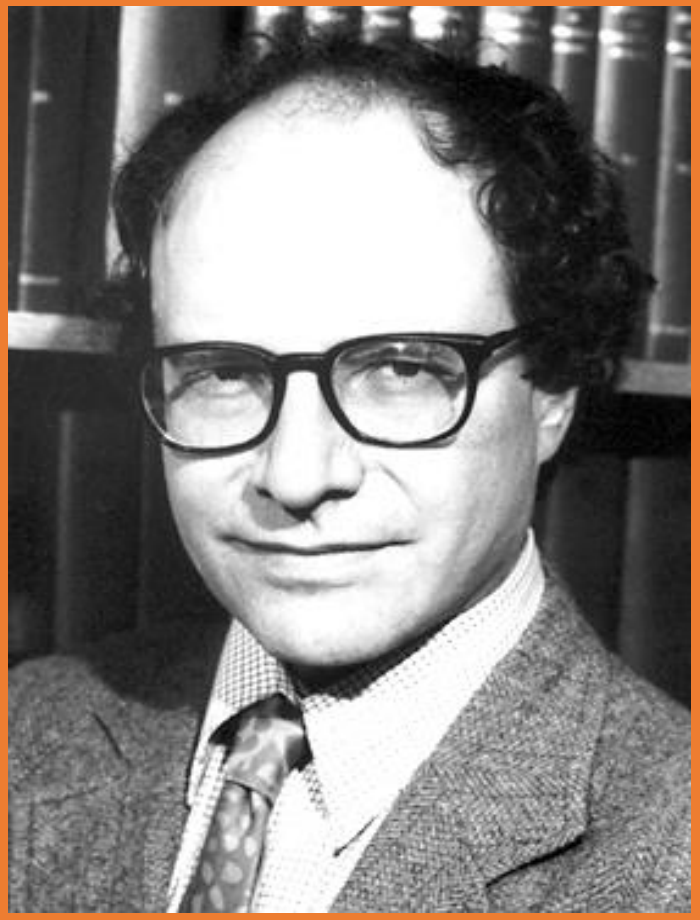


Francis H. C. Crick

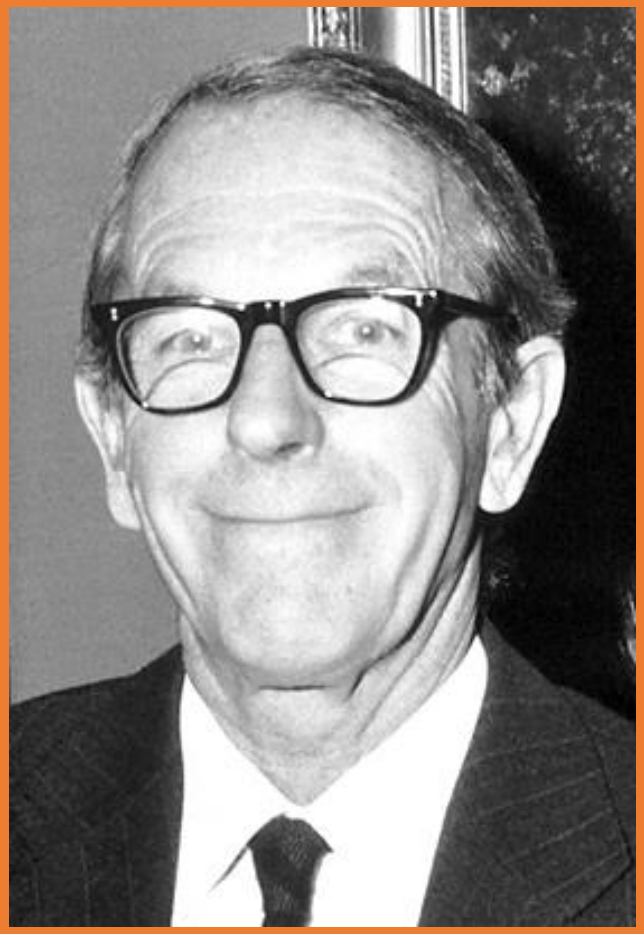


DNA Sequencing - 1977

- Gilbert and Sanger shared the Nobel Prize in Chemistry in 1980

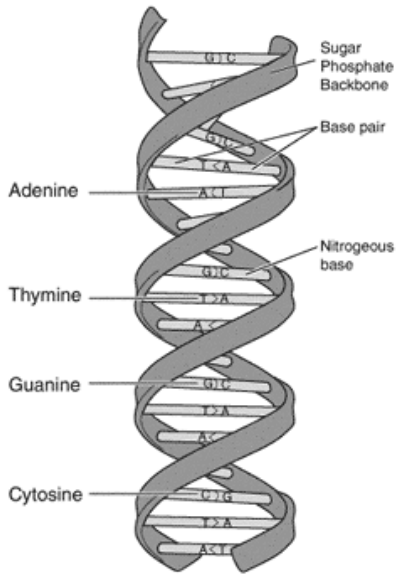


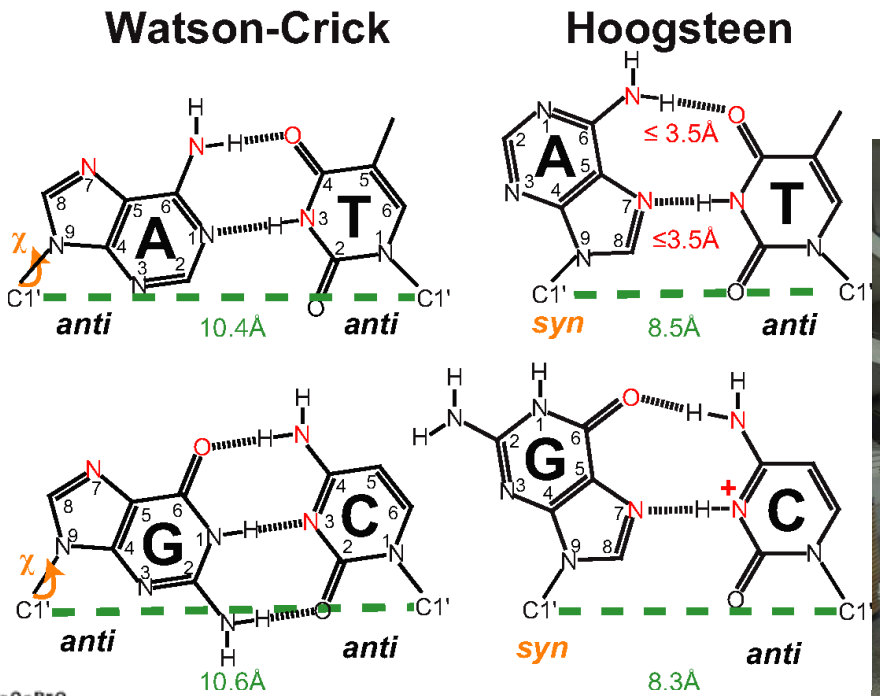
Walter Gilbert
(1932-; US Physicist and Biochemist)

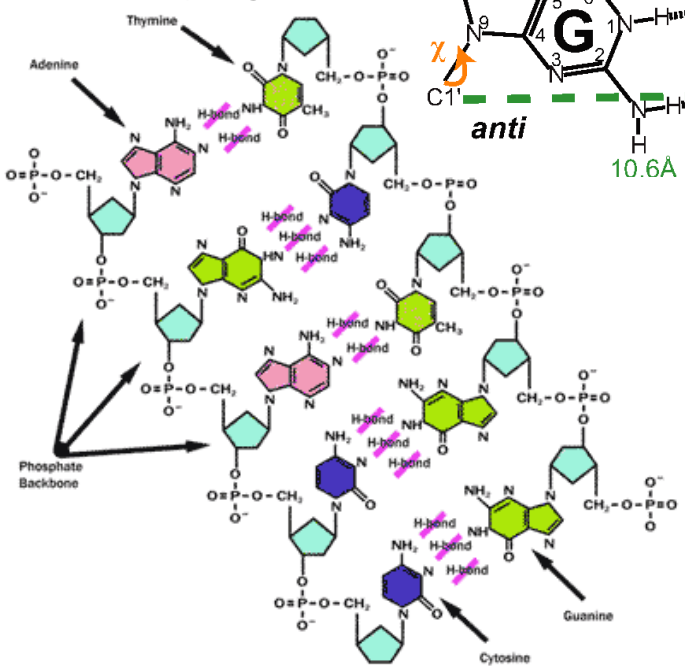


Frederick Sanger
(1918-2013; UK Biochemist)

Genome structure: DNA

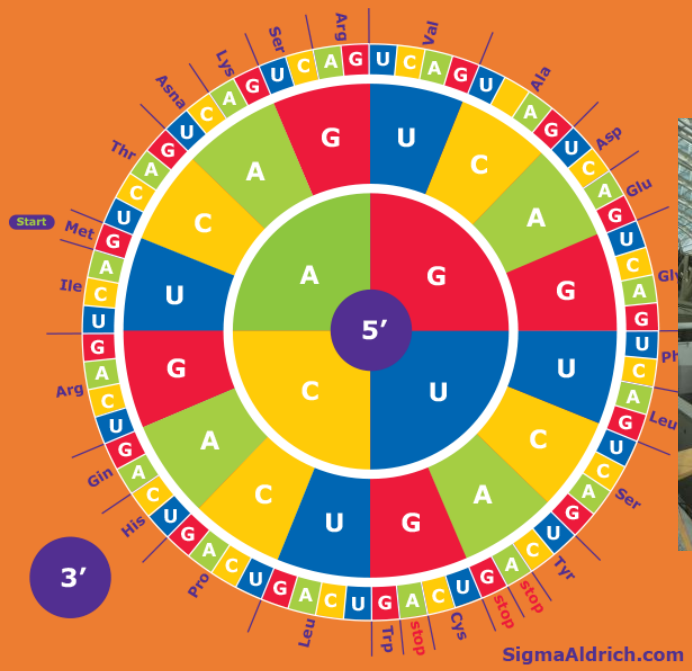


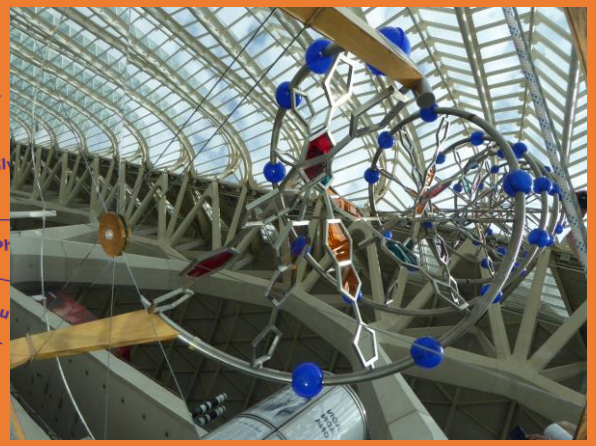




1959 Nobel Prize for Physiology or Medicine

for his work on the synthesis of RNA and deoxyribonucleic acid





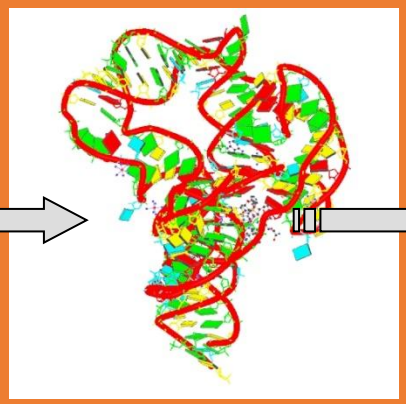
Severo Ochoa de Albornoz

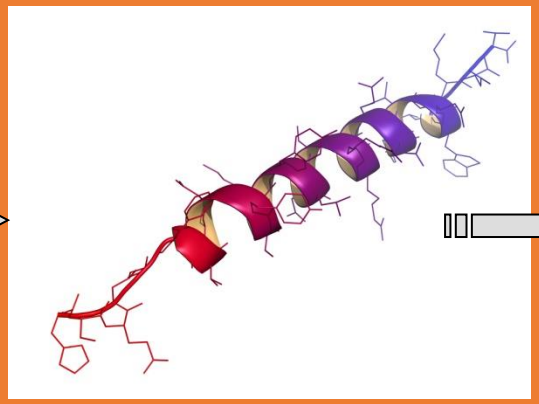
Biology dogma

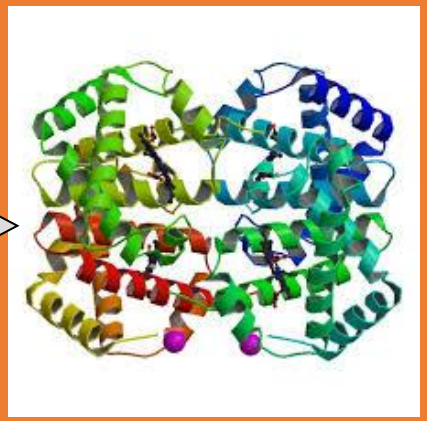
genetics

biochemistry

medicine







DNA

RNA

transcriptomics

Aminoacid sequence

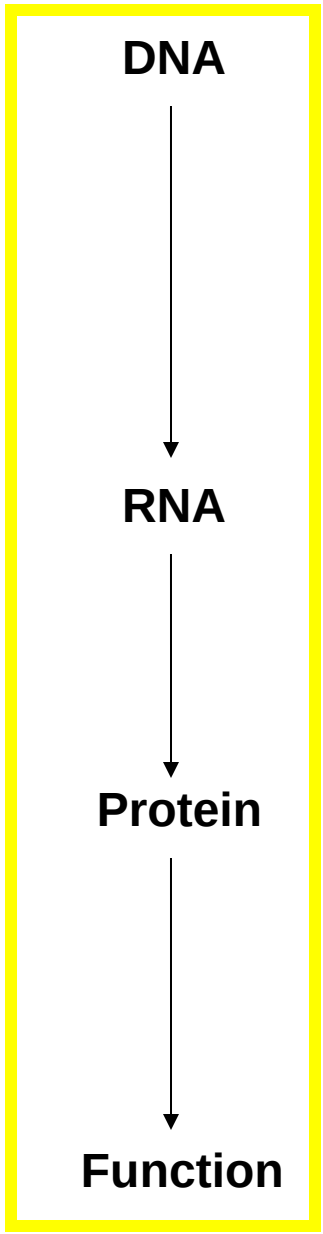
proteomics

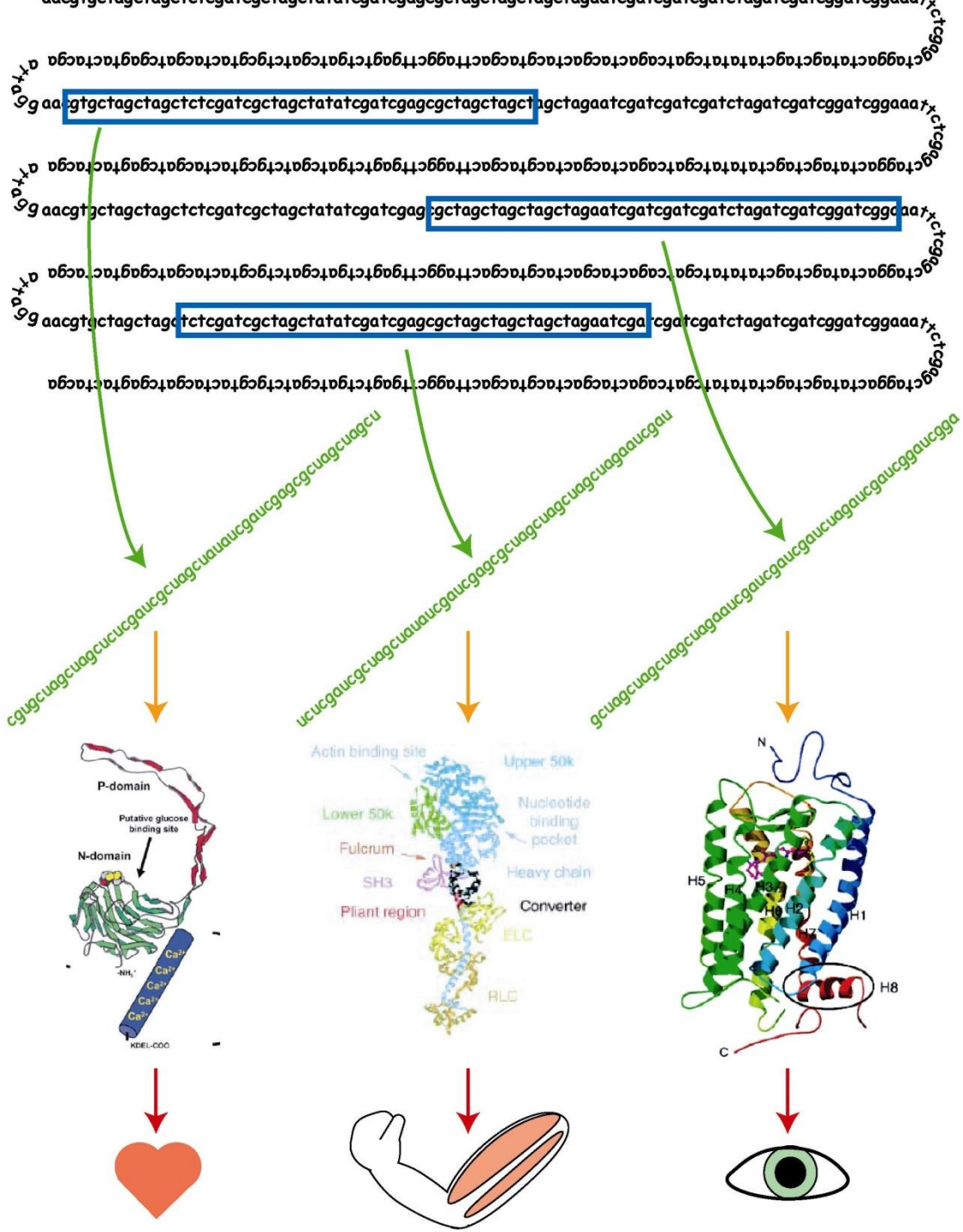
Protein structure and function

genomics

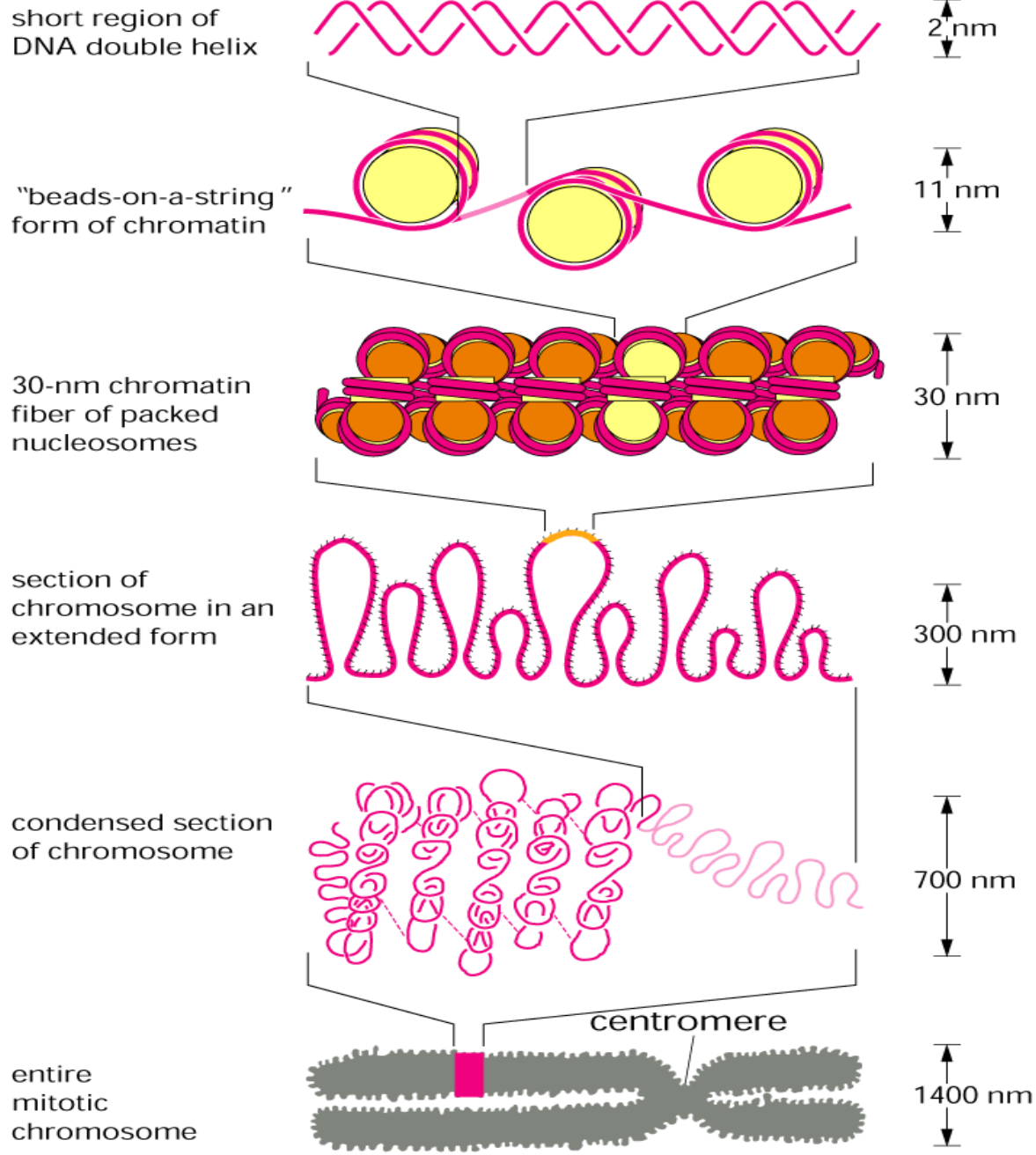
CADD

metabolomics

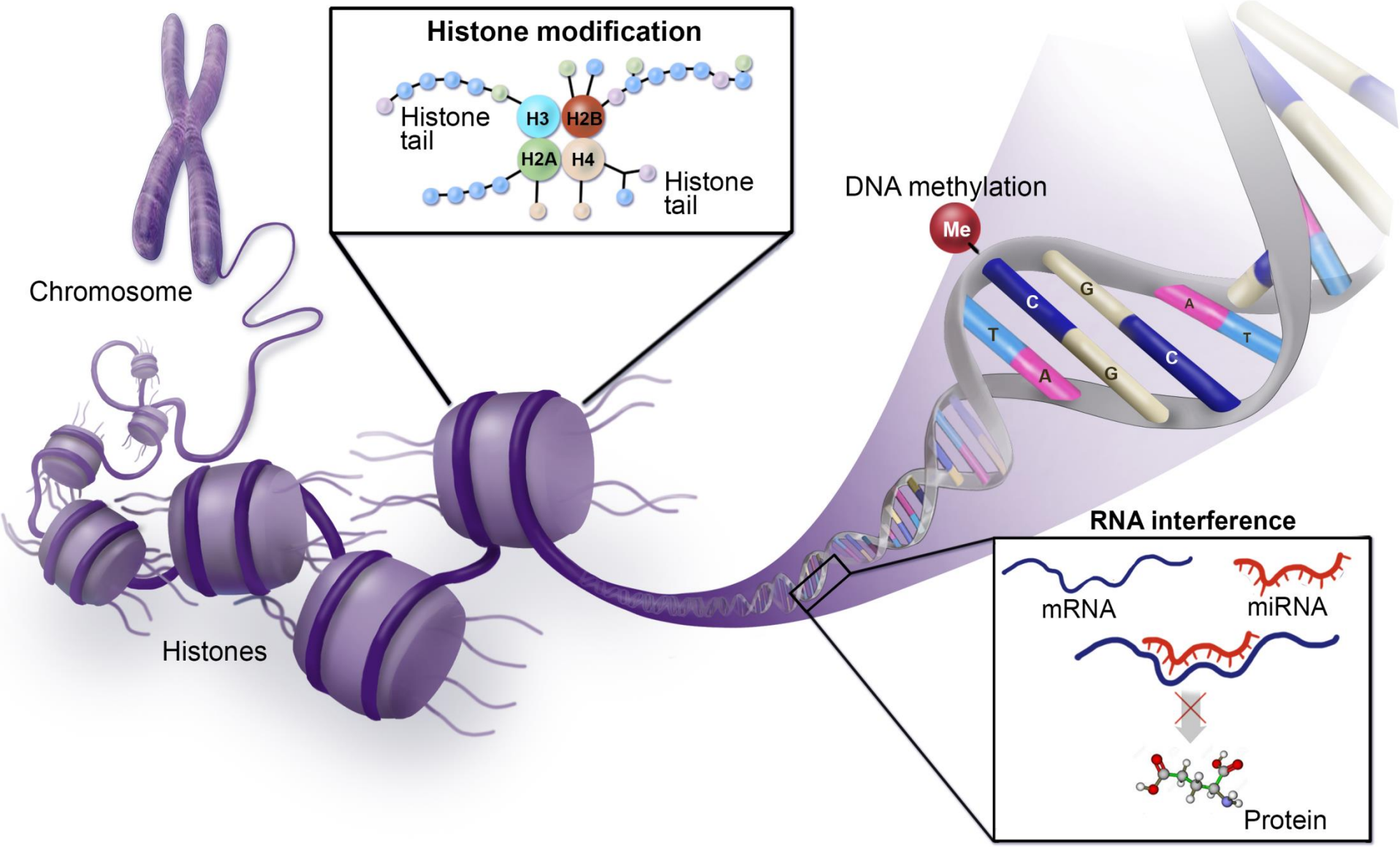

DNA
RNA
Protein
Function


P-domain
Putative glucose binding site
N-domain
Actin binding site
Upper 50k
Lower 50k
Nucleotide binding pocket
Fulcrum
SH3
Heavy chain
Pliant region
Converter
ELC
RLC
N
H5
H1
H8
C

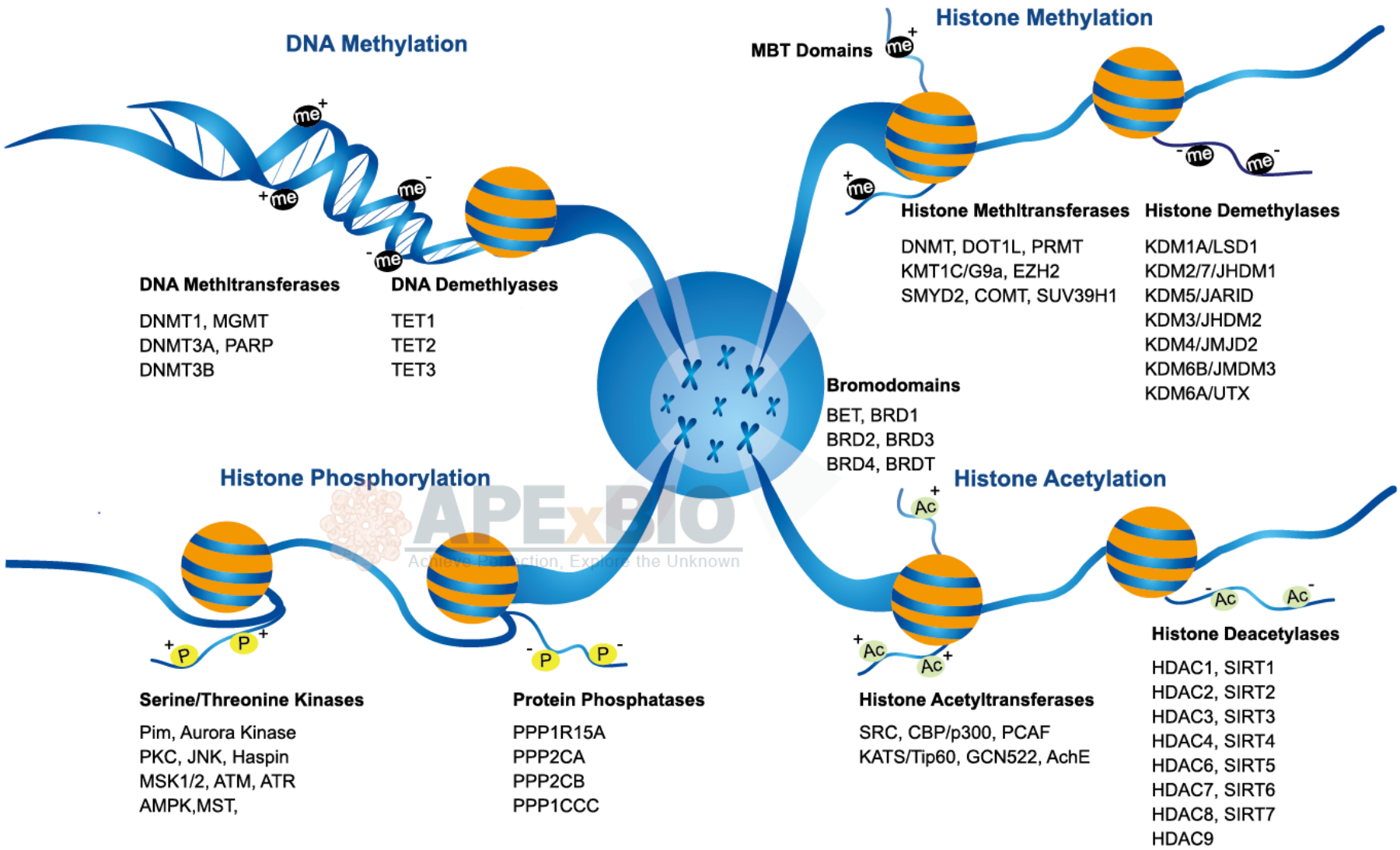
In a single human cell, the lenght of DNA strand is about 2 m



NET RESULT: EACH DNA MOLECULE HAS BEEN PACKAGED INTO A MITOTIC CHROMOSOME THAT IS 50,000x SHORTER THAN ITS EXTENDED LENGTH



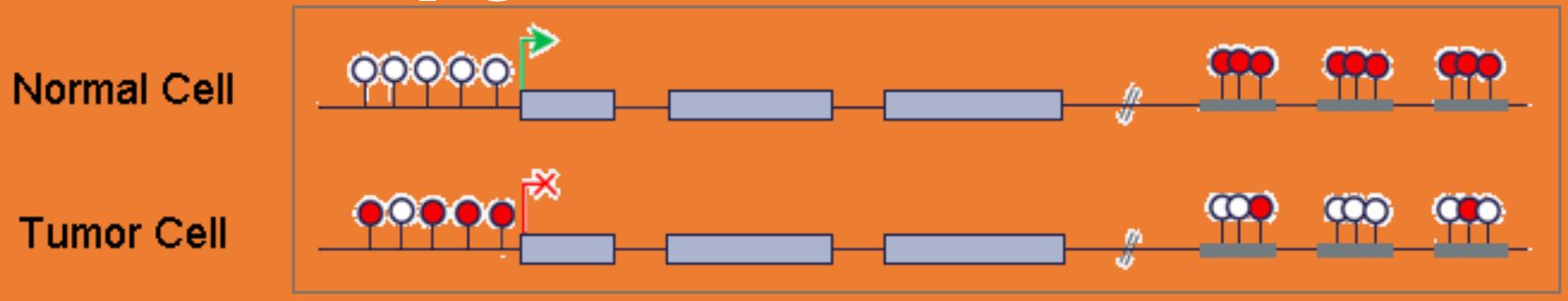
www.hematology.org



http://www.apexbt.com/signaling-pathways/chromatin-epigenetics.html

Methylation in cancer

epigenetic modification



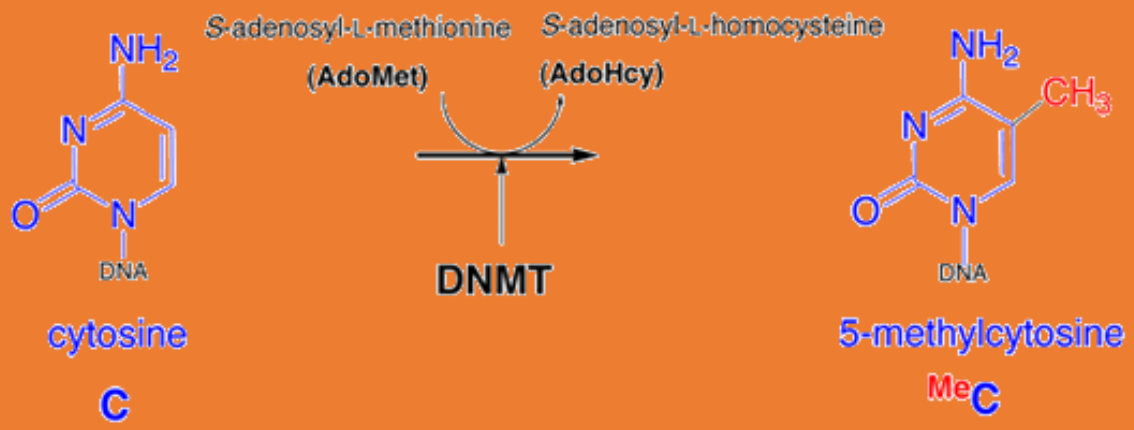
5 to 10% of promoters are **hypermethylated** in cancer leading to the silencing of downstream genes

CpG islands → Specific hypermethylation at gene promoters

Gene

Repeated sequences → Global hypomethylation of the genome

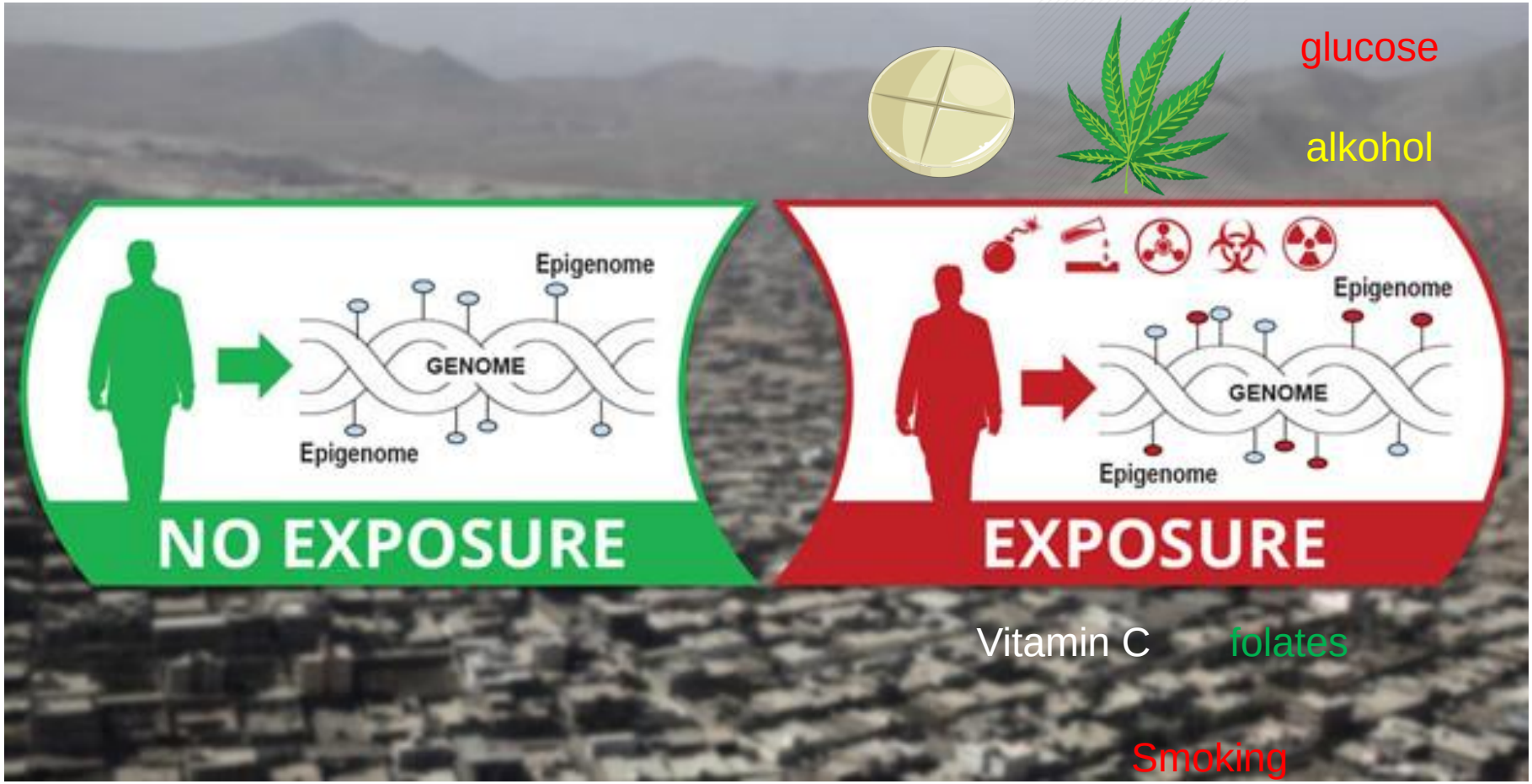
transcriptional re-activation of parasitic DNA sequences

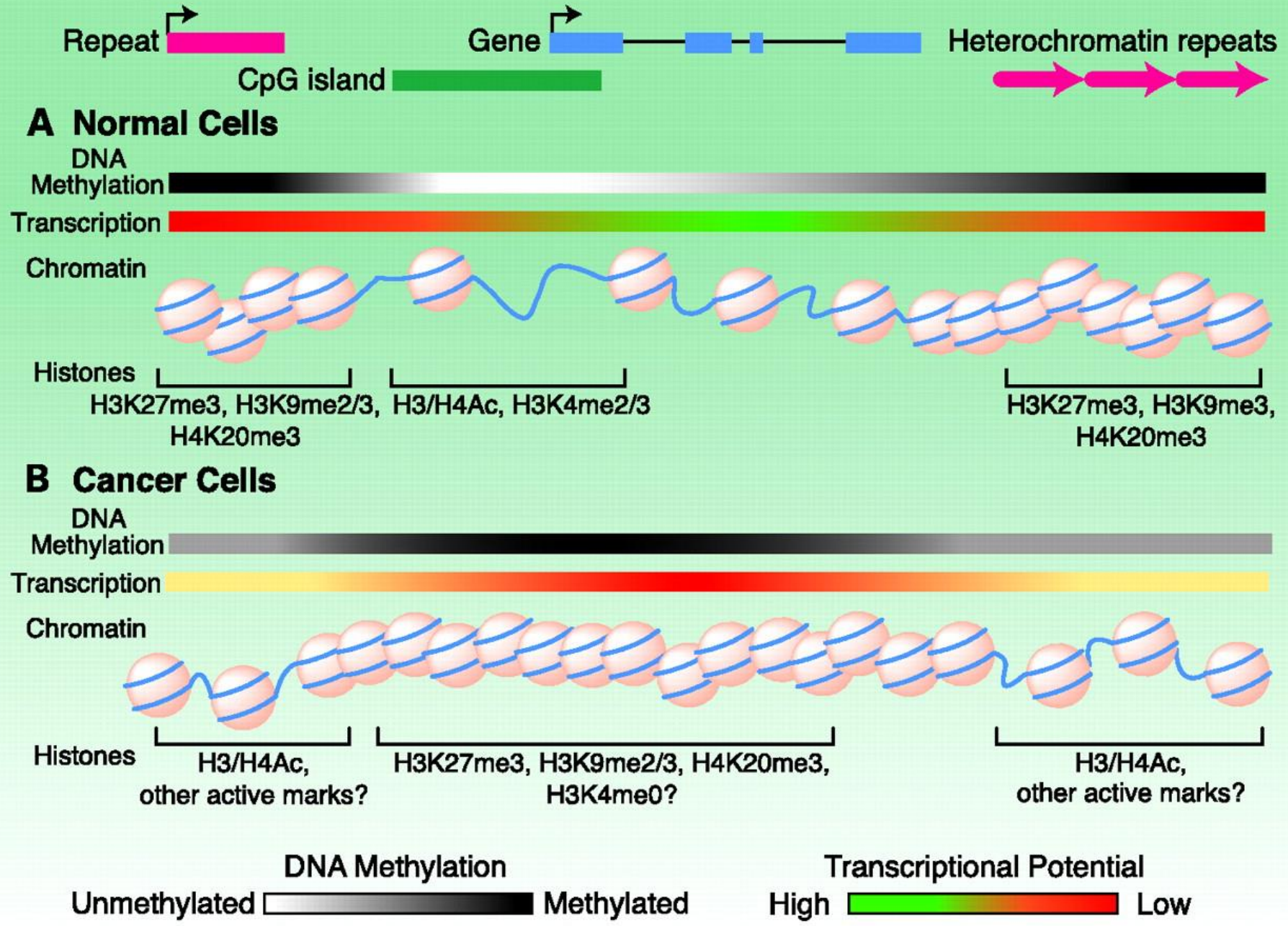


Moison C. Atlas of Genetics and Cytogenetics in Oncology and Haematology

Enviromental factors

epigenetic modifications





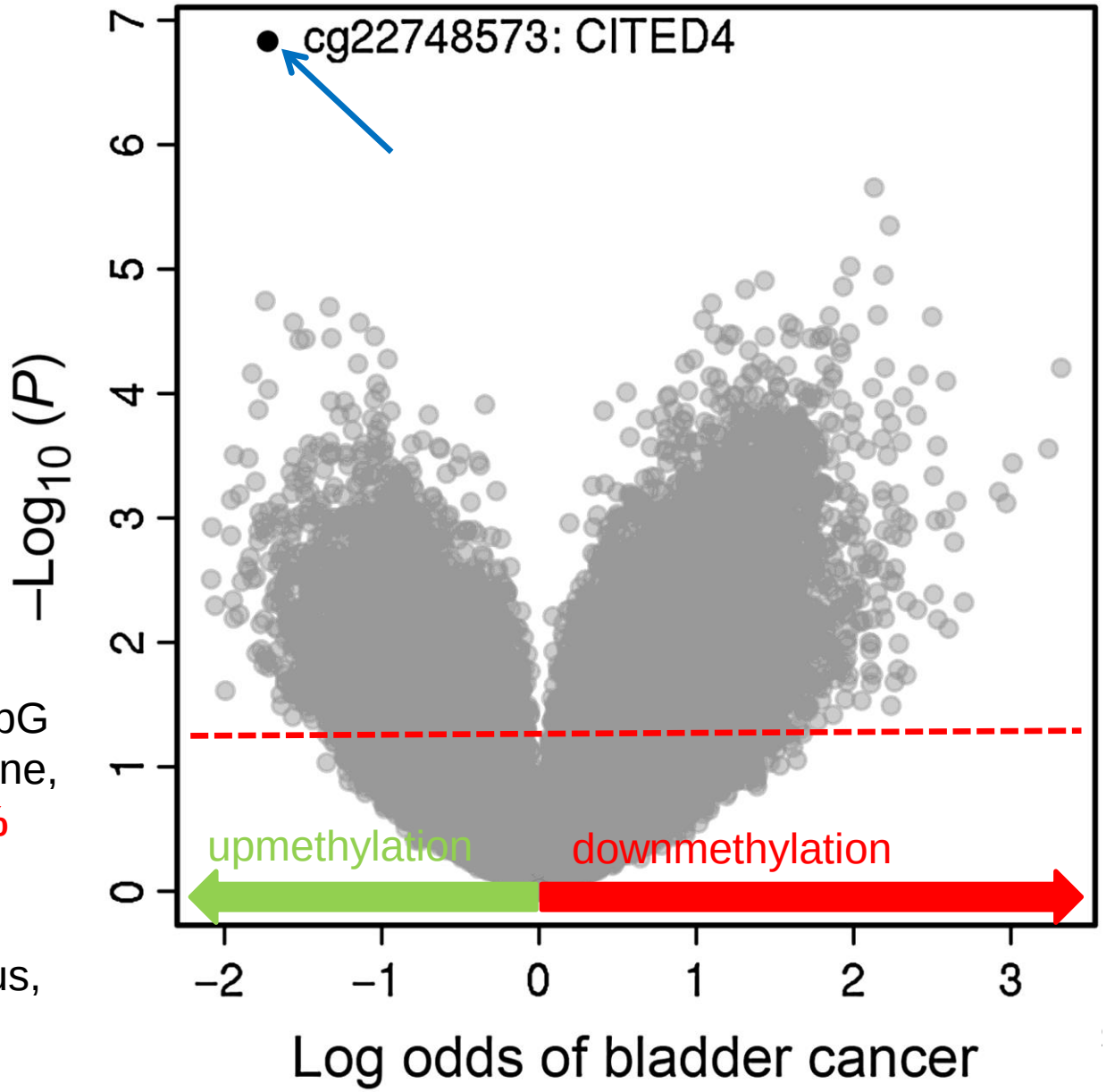
MT. McCabe https://doi.org/10.1158/1078-0432.CCR-08-2784

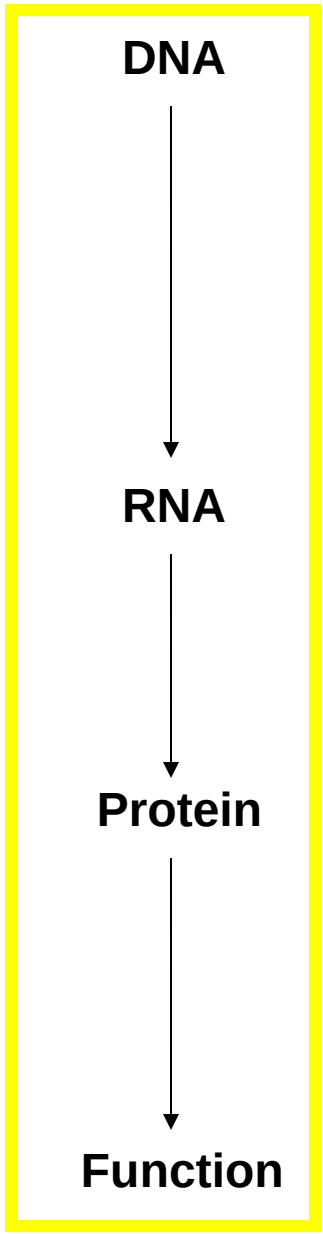
Genome-Wide DNA Methylation in Prediagnostic Blood and Bladder Cancer Risk in the Women's Health Initiative

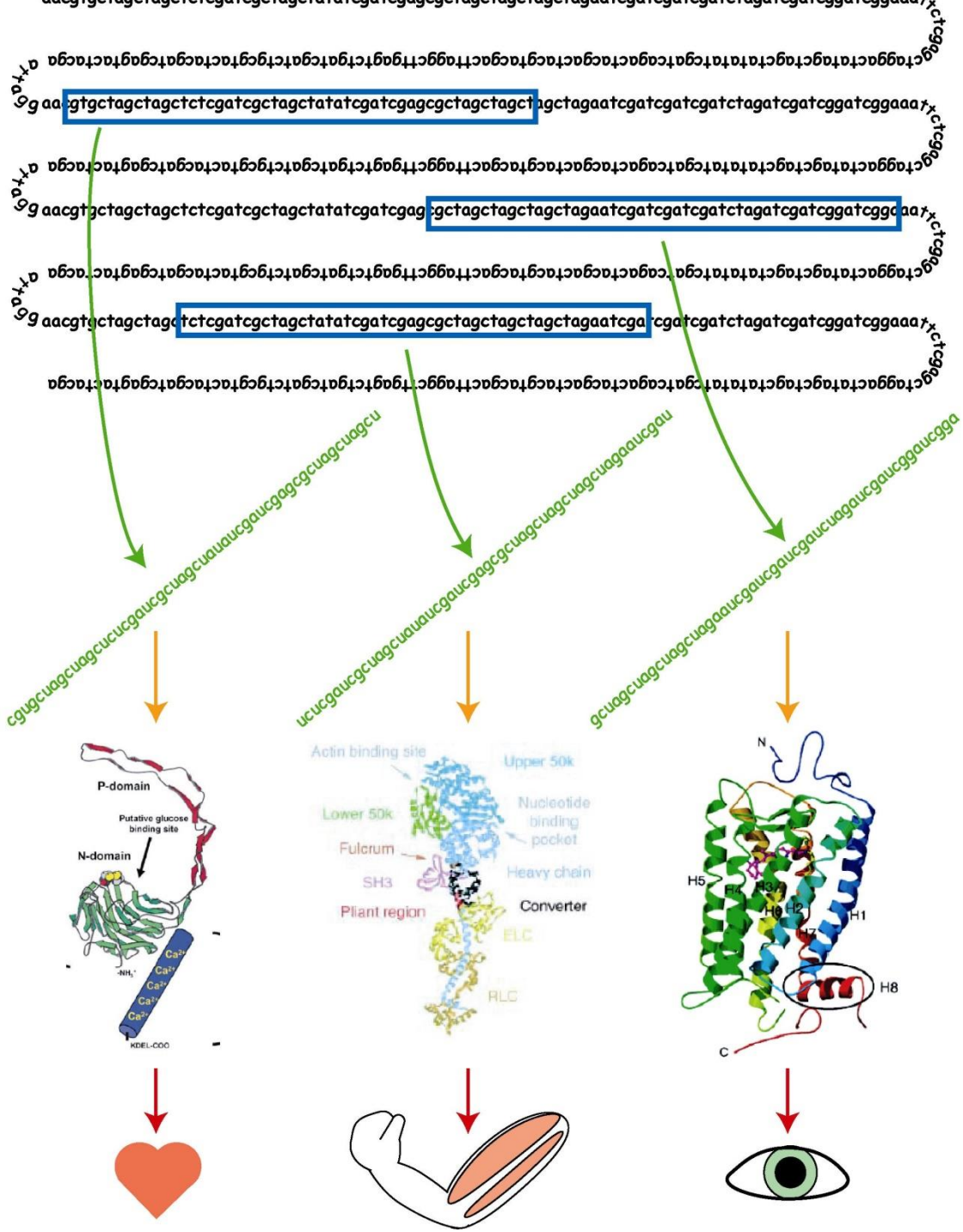
- 440 case–control pairs
- blood samples
- selected cases were followed until bladder cancer diagnosis
- methylation status at 485,577 CpG sites
- 17 CpG sites per gene

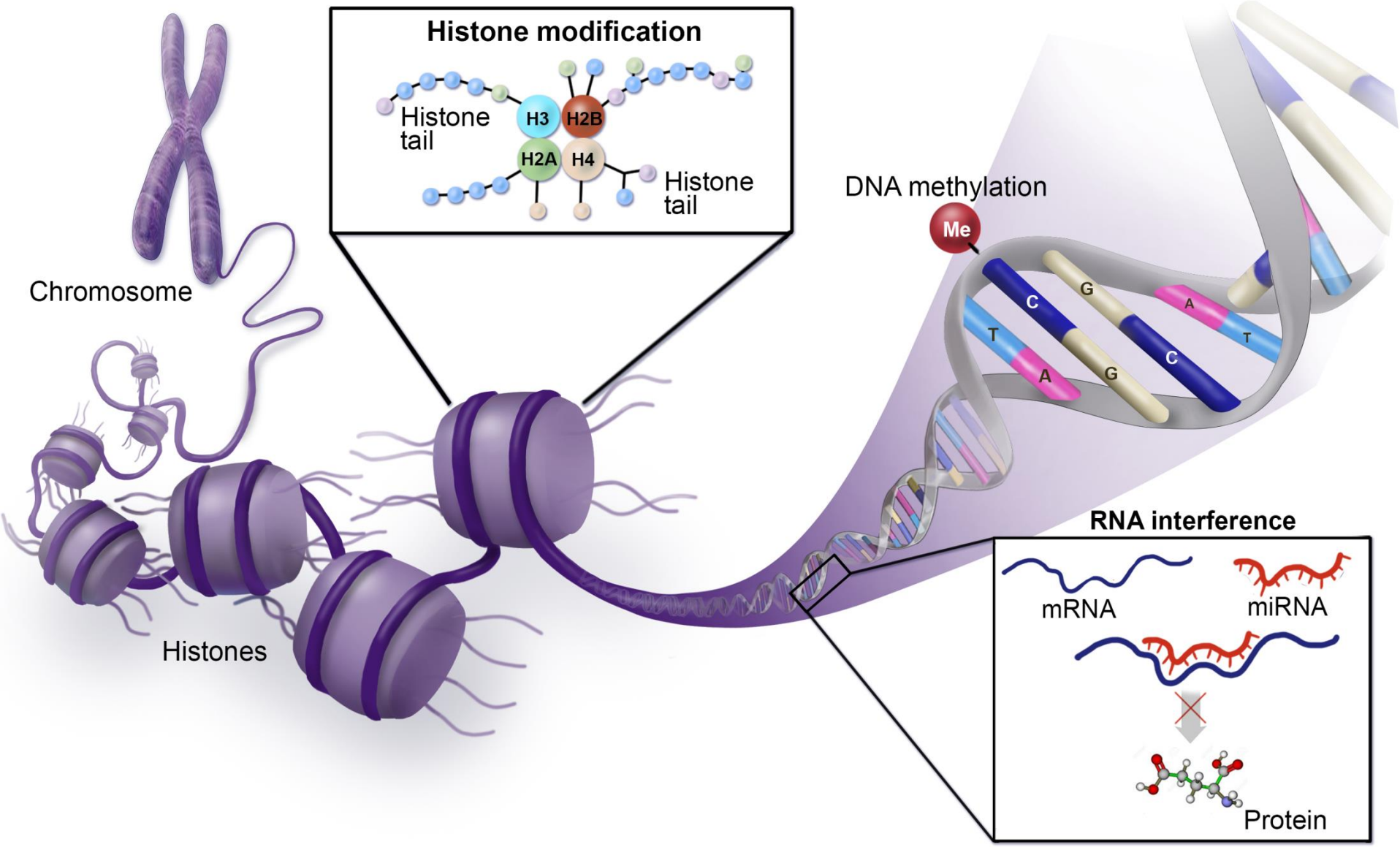
Jordahl et al. Cancer Epidemiol Biomarkers Prev 2018

increased methylation at cg22748573, located in a CpG island within the ***CITED4*** gene, was associated with an **82%** decreased risk of bladder cancer after adjusting for race/ethnicity, smoking status, pack-years of smoking




DNA
RNA
Protein
Function

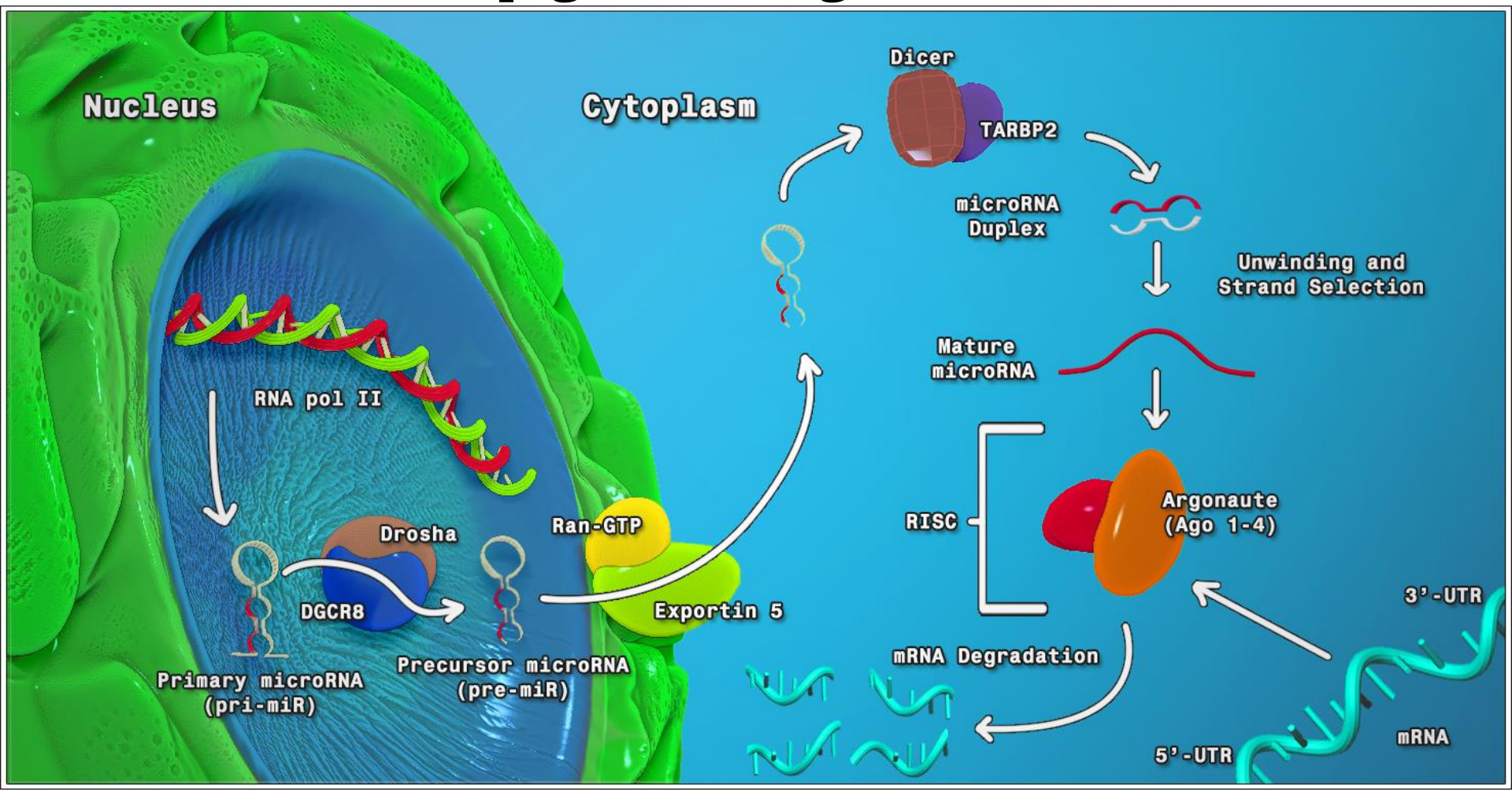

P-domain
Putative glucose binding site
N-domain
Actin binding site
Upper 50k
Lower 50k
Nucleotide binding pocket
Fulcrum
SH3
Heavy chain
Pliant region
Converter
ELC
RLC
N
H5
H1
H8
C



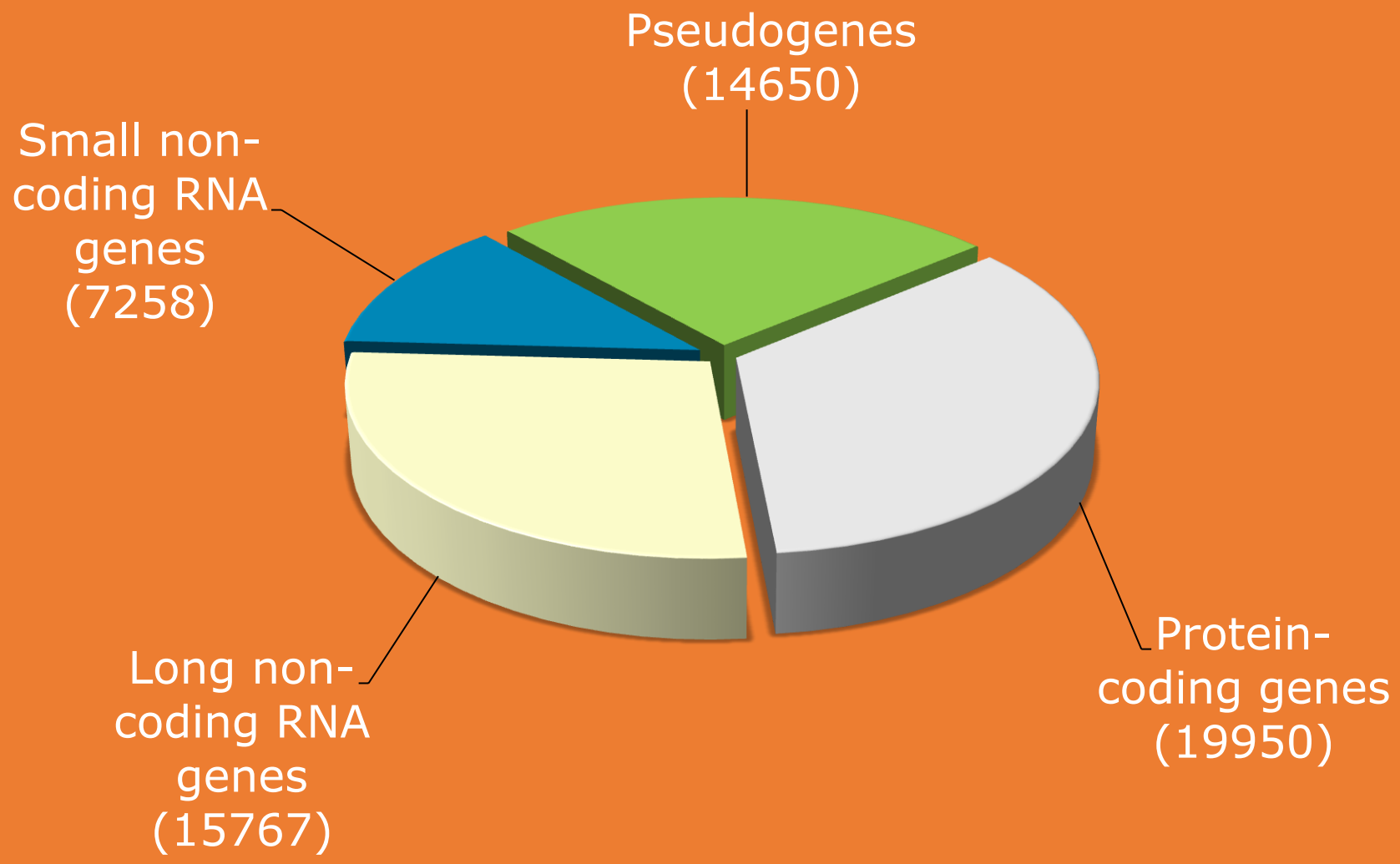
www.hematology.org

NoncodingRNA in cancer

epigenetic regulation



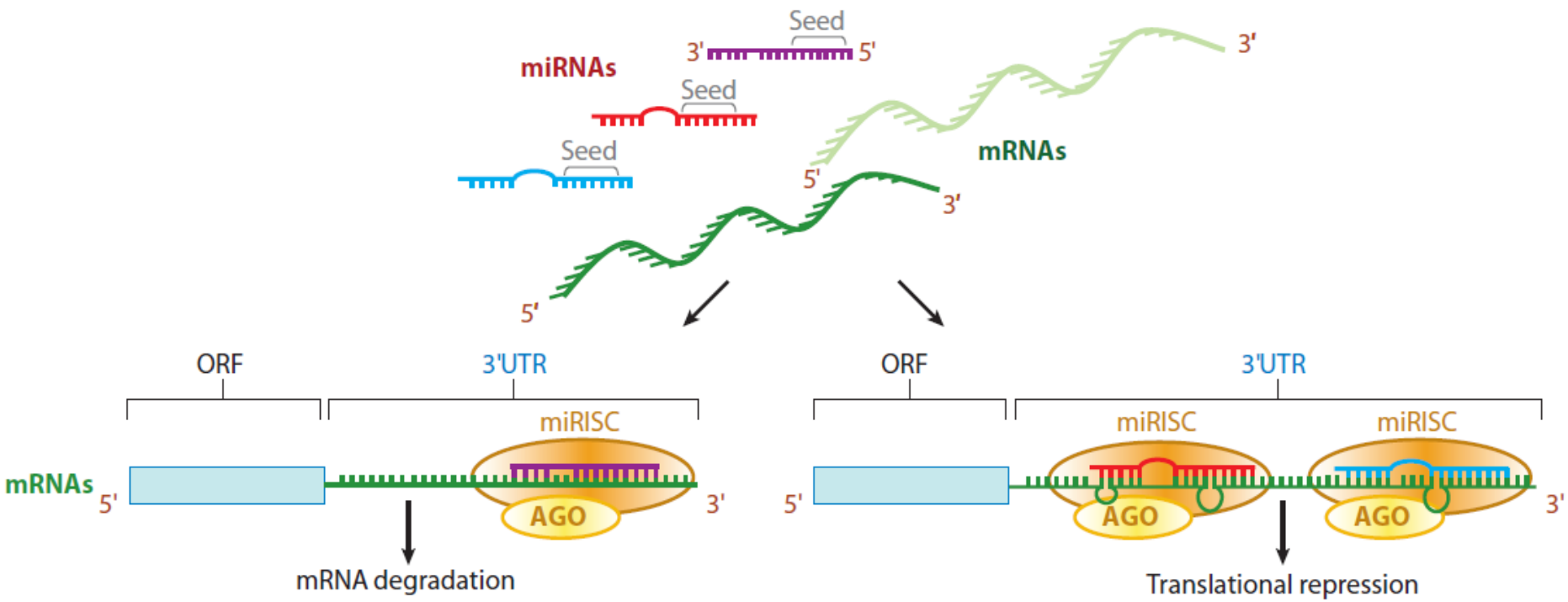
Human genome landscape (coding and non-coding)



GENCODE (www.gencodegenes.org)
Version 25 (March 2016 freeze, GRCh38) - Ensembl 85

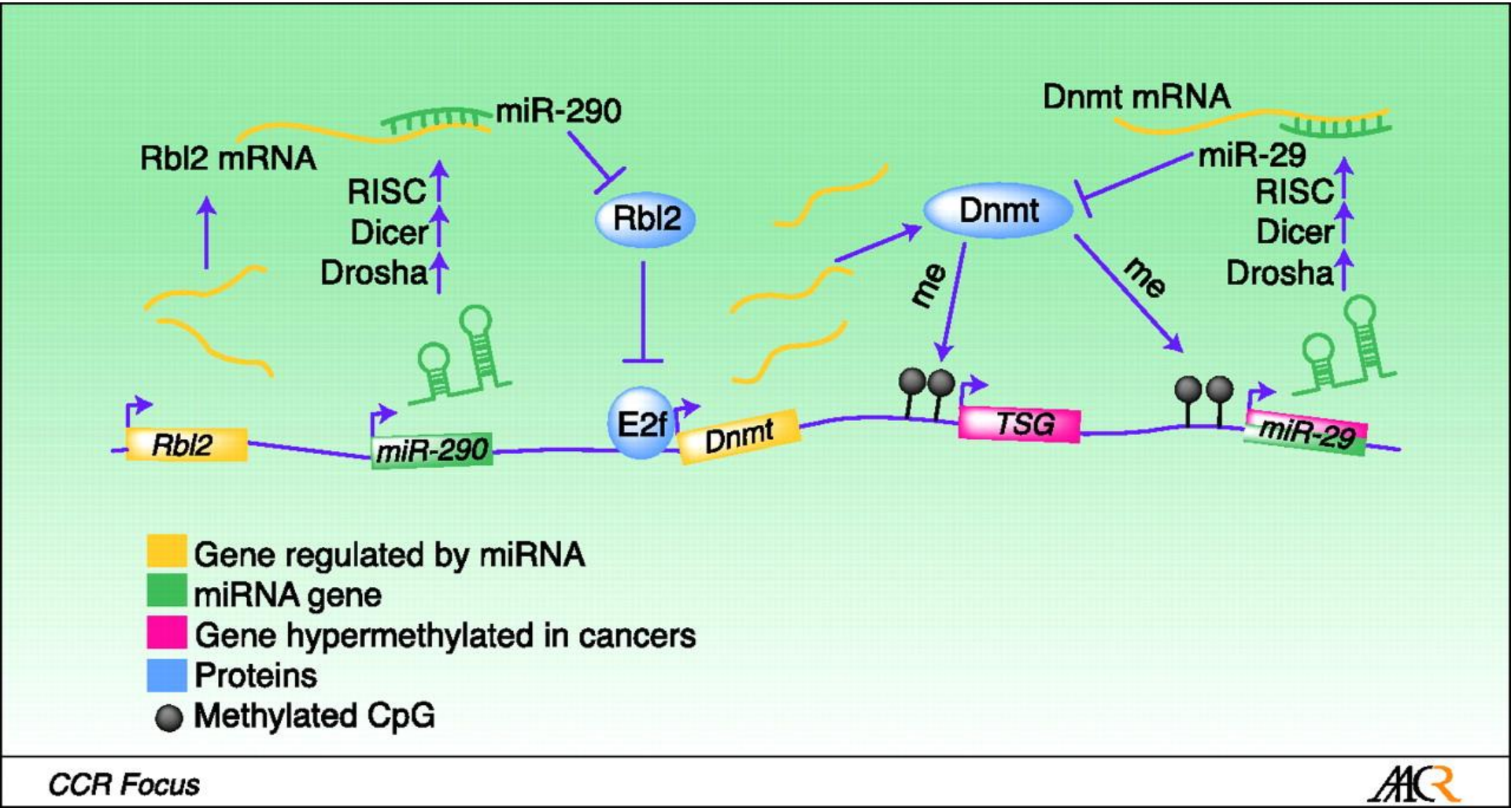
NoncodingRNA in cancer

epigenetic regulation



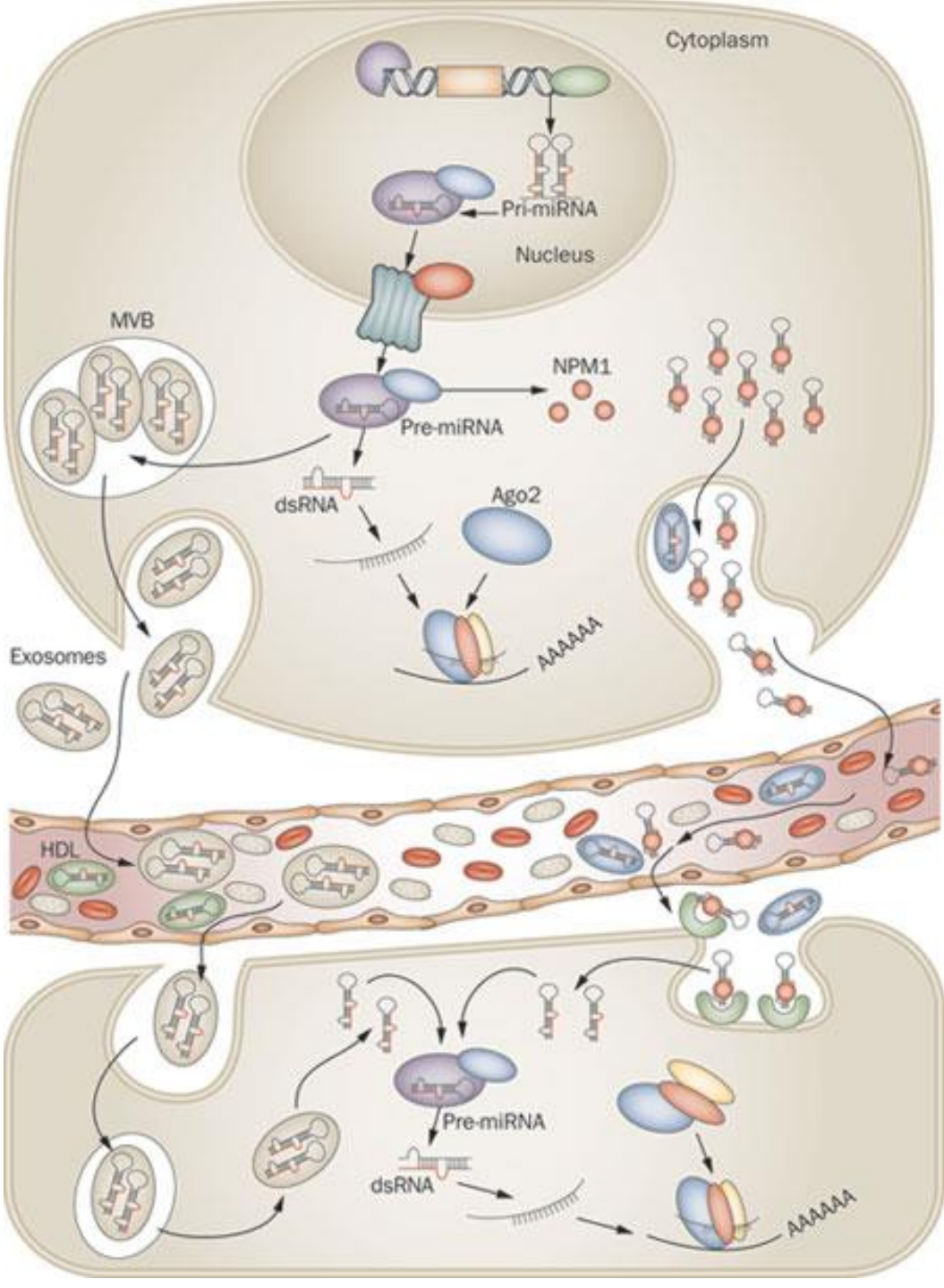
NoncodingRNA in cancer

epigenetic regulation



MT. McCabe https://doi.org/10.1158/1078-0432.CCR-08-2784

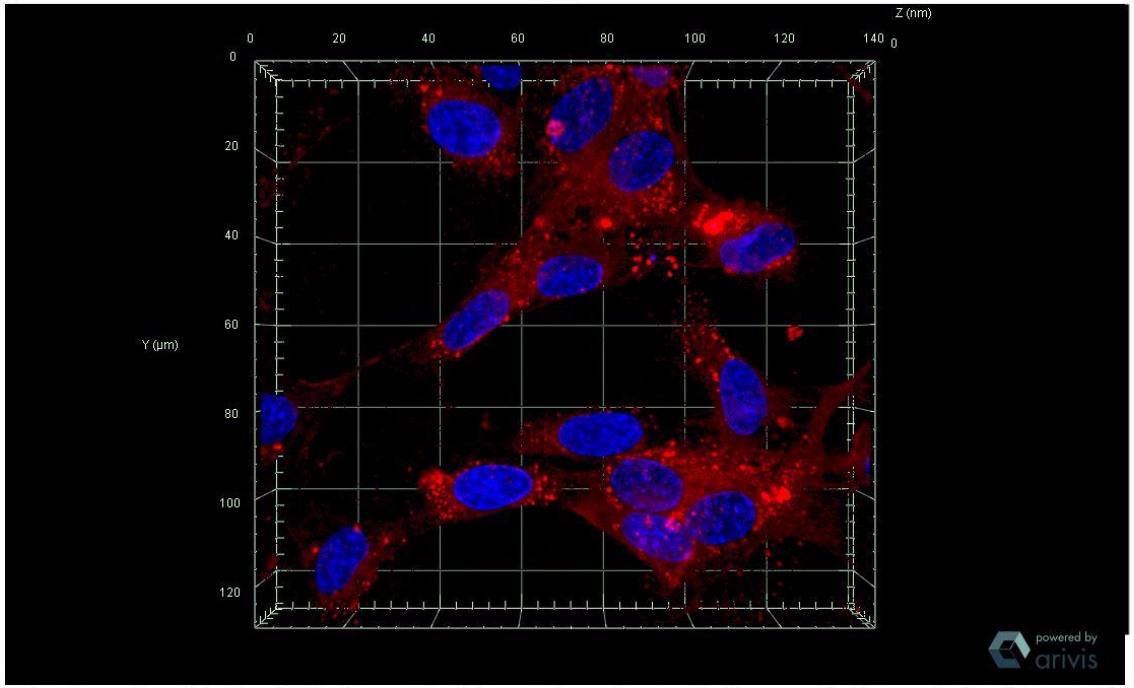
Role of microRNA in cell communication



Cortez, M. A. *et al.* (2011)
Nat. Rev. Clin. Oncol.
doi:10.1038/nrclinonc.2011.76

Cellular & Molecular Biology Letters

M.Durak-Kozica et al. 2018



Affiliated with

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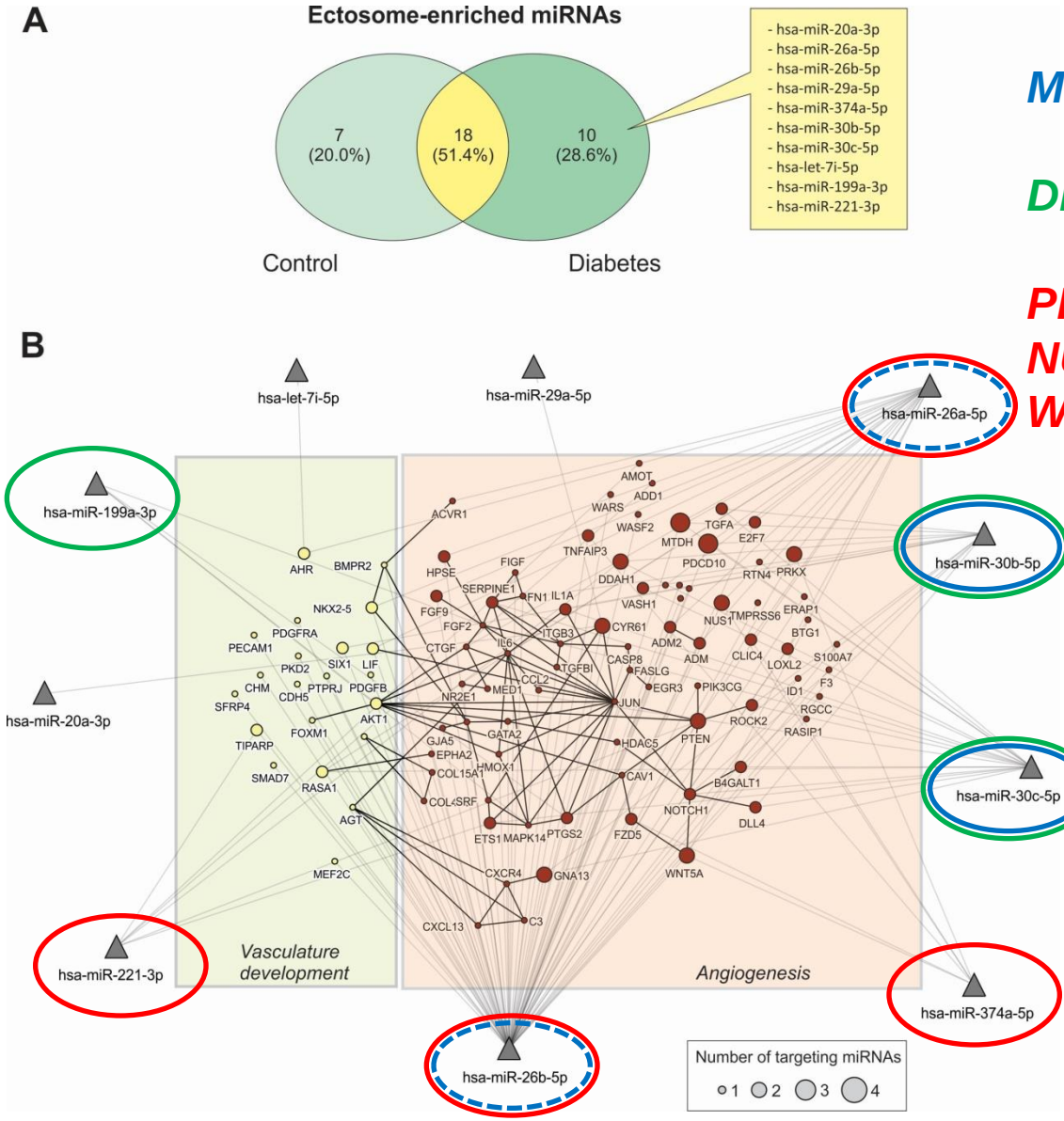
Featured article: 3D visualization of extracellular vesicle uptake by endothelial cells

Extracellular vesicles are small vesicles that contain cytoplasmic and membrane components from their paternal cells. They enter target cells through uptake to transfer their biological cargo. In this study, the authors investigated the process of endothelial EV internalization and created a 3D visualization of their intracellular distribution. The 3D visualization allows the determination of a more accurate location of EVs relative to the donor cell nucleus.

Circulating Ectosomes: Determination of Angiogenic MicroRNAs in Type 2 Diabetes



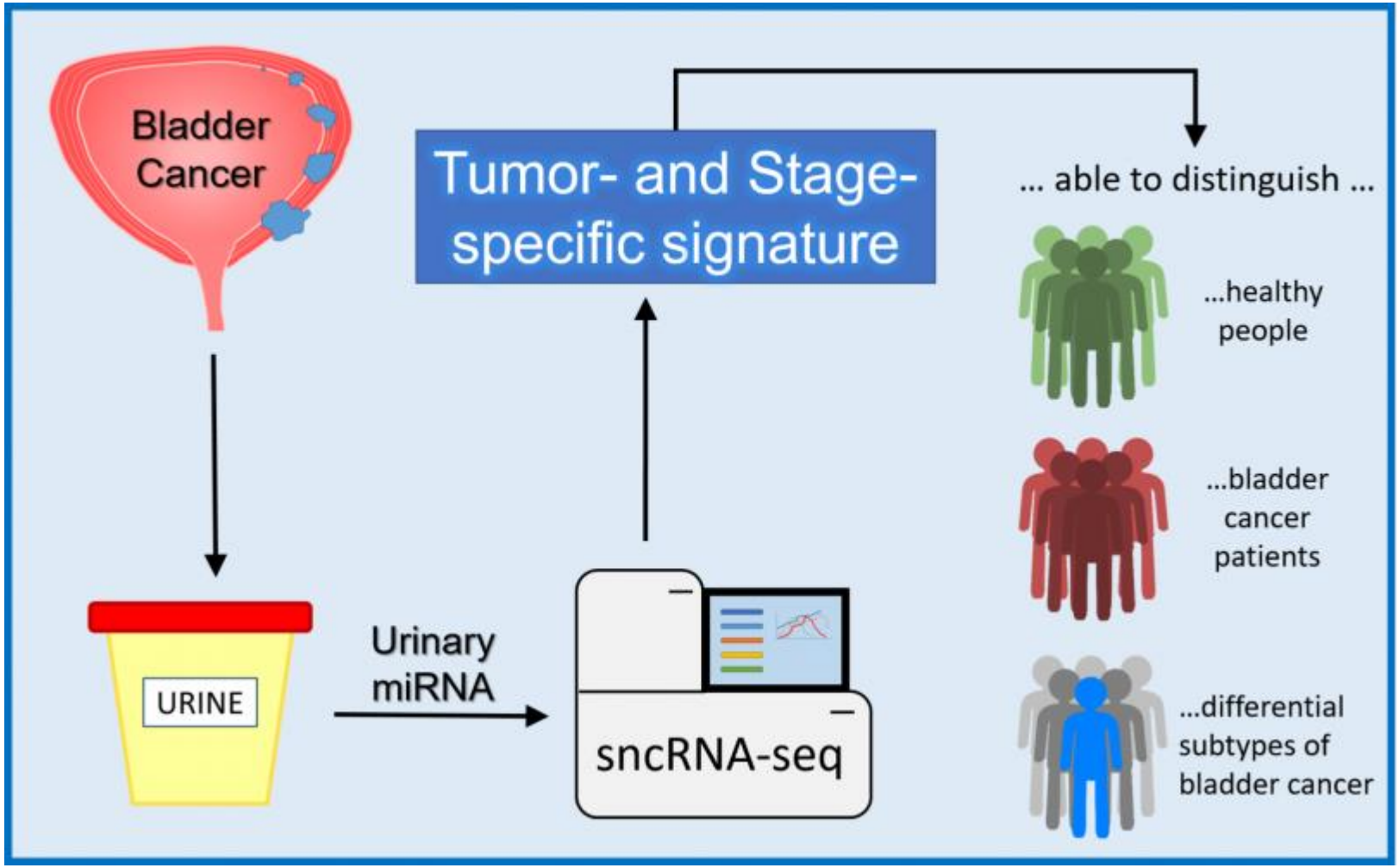
MTDH , PDCD10

DDAH, GNA13

PRX, CYR61, NUS1, PTEN, WNT5A

Stepien et al. *Theranostics. 2018*

UROMIRNA FOR A NON-INVASIVE DIAGNOSIS OF BLADDER CANCER

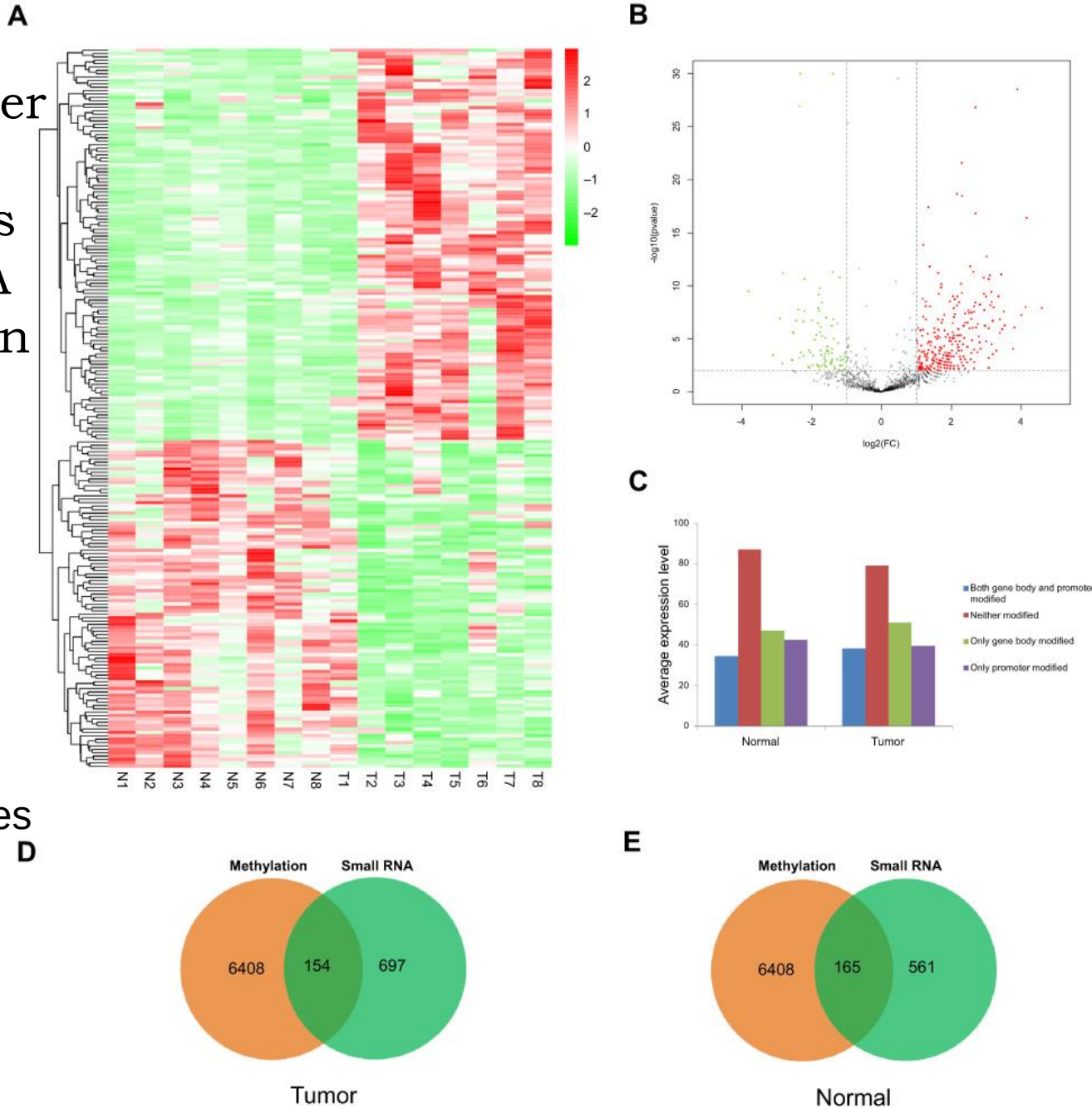


https://www.knowledge-share.eu/en/patent/uromirna-for-a-non-invasive-diagnosis-of-bladder-cancer/

Exploration of bladder cancer-associated methylated miRNAs by methylated DNA immunoprecipitation sequencing

X. Gao et al. OncoTargets and Therapy 2019

Differentially expressed miRNAs in BC tumor tissues are associated with methylation of miRNA-encoding genes.



Overlap of miRNA-encoding genes identified by MeDIP-Seq and sRNA-Seq in normal tissues

Epigenetics adds extra layers of complexity, turning this 2D puzzle into a Jenga board

Don’t blame grandparents yet, but your cancer may be their fault