Cancer epigenetics

Cancer Epigenetics

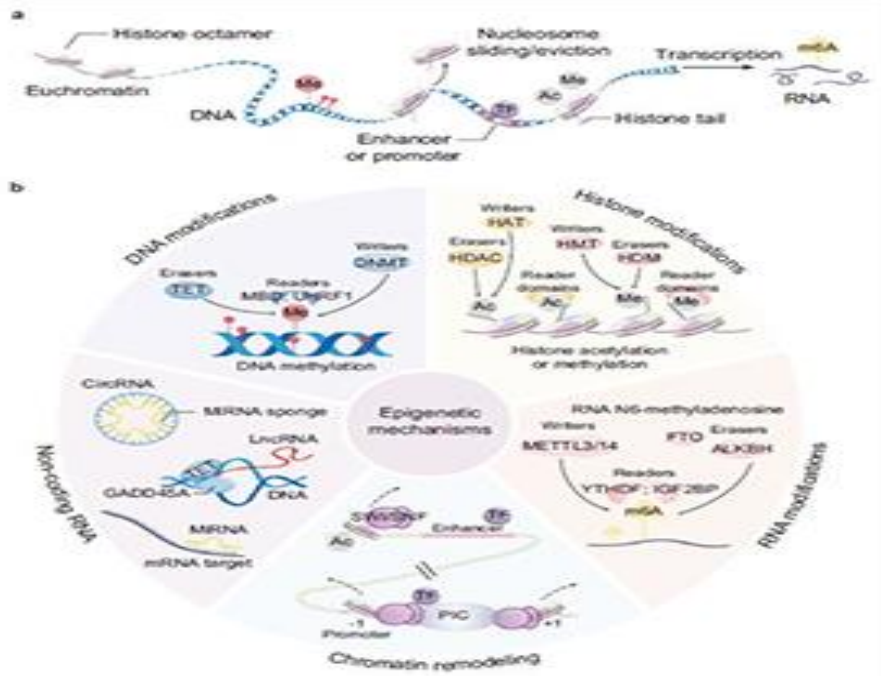
Mukesh Verma, PhD

Senior Scientific Advisor

and Program Director

Epidemiology and Genomics Research Program

NIH NATIONAL CANCER INSTITUTE



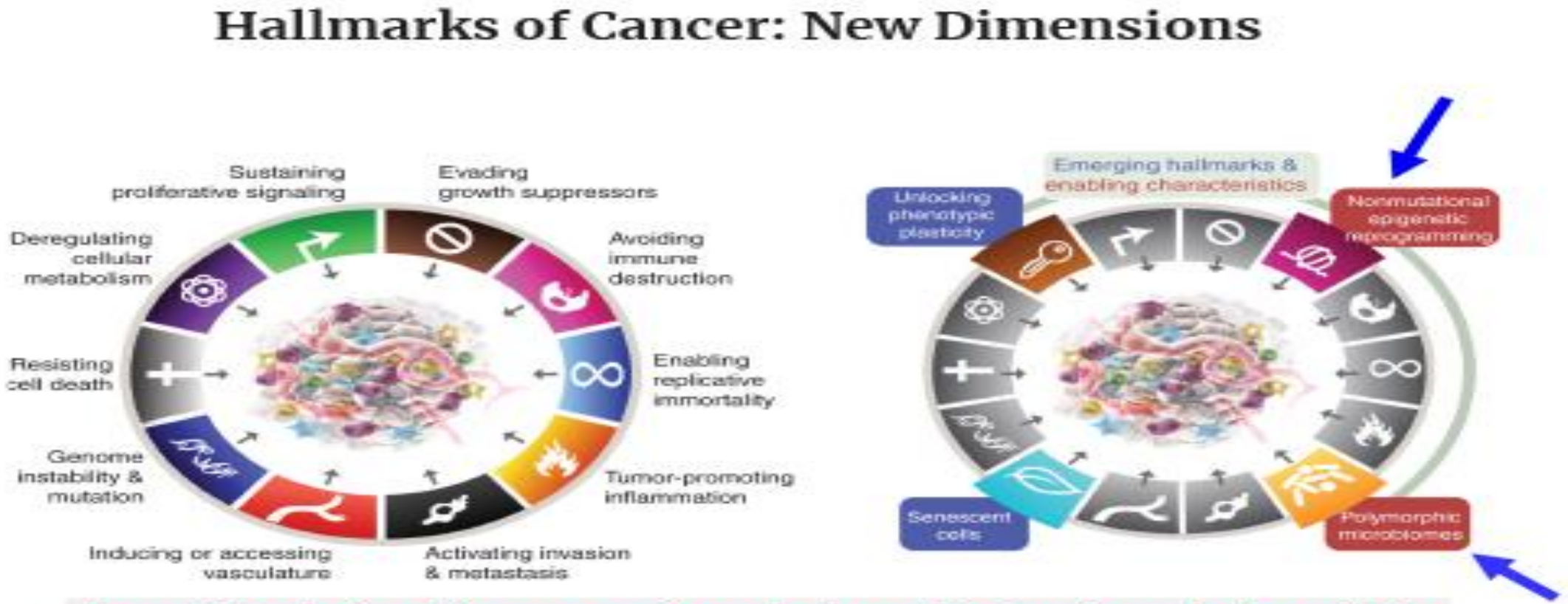
Outline

National Cancer Institute

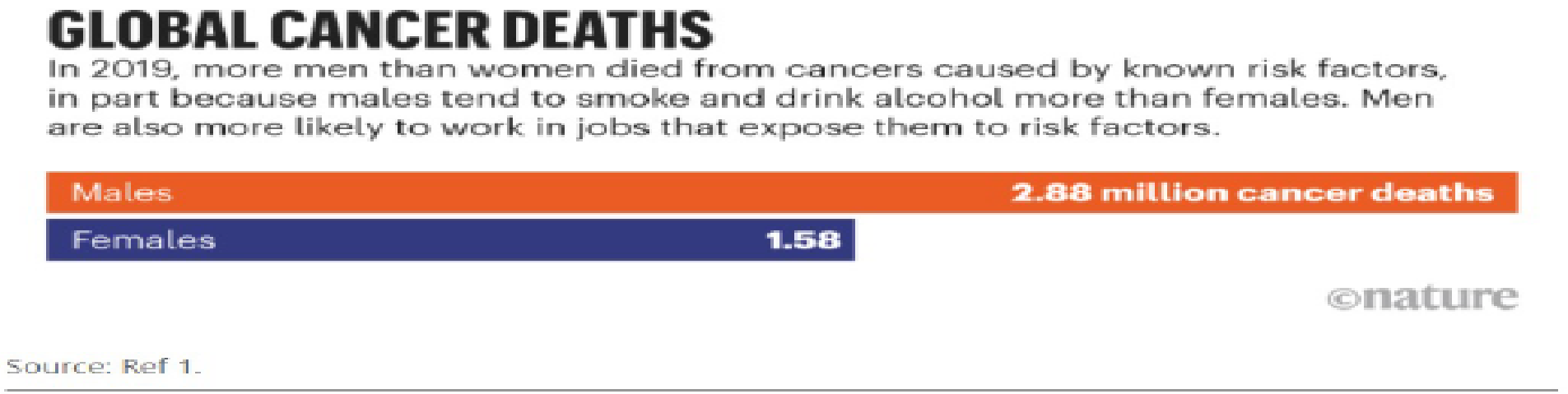
OUTLINE

- What is epigenetics
- Components of epigenome – methods to measure epigenetic changes
- Epigenetic reprogramming and epigenetic clock
- Epitranscriptomics
- Clinical implication of epigenetics- FDA approved epigenetic drugs
- NIH programs in epigenetics

Hallmarks of cancer



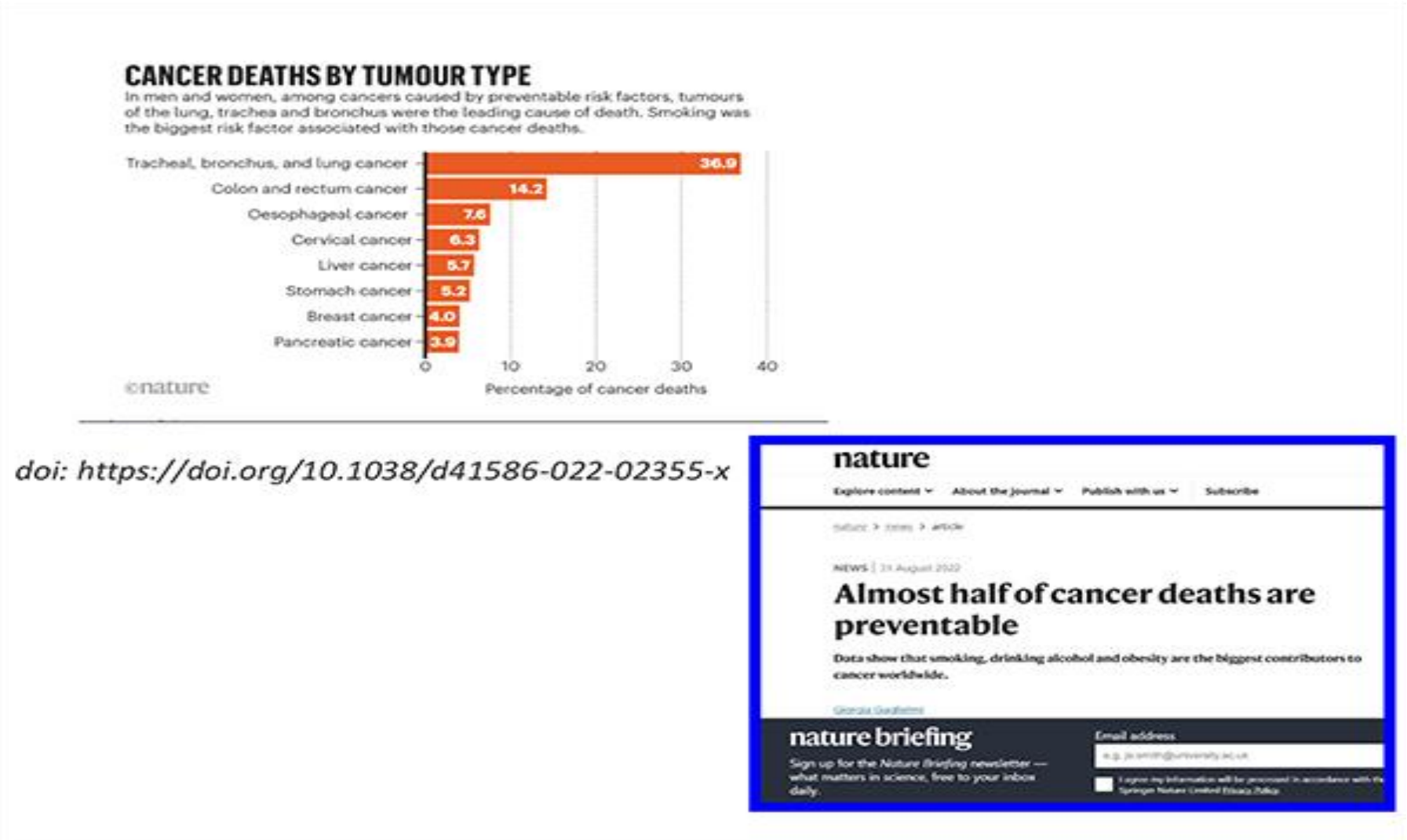
Global cancer deaths



https://www.nature.com/articles/d41586-022-02355-x

GBD 2019 Cancer Risk Factors Collaborators *Lancet* **400**, 563–591 (2022).

Cancer deaths by type



doi: https://doi.org/10.1038/d41586-022-02355-x

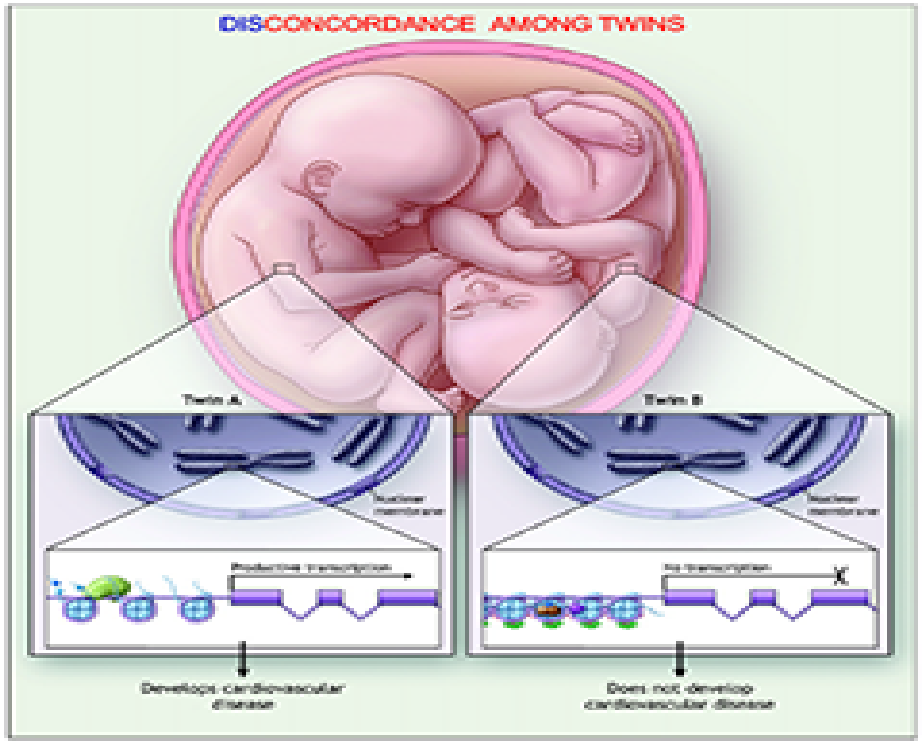
Epigenetics



DNA and destiny



The choices you make
can change your genes
-- and those of your kids.



Epigenetic predisposition to angiogenesneis? Individual? Populations?

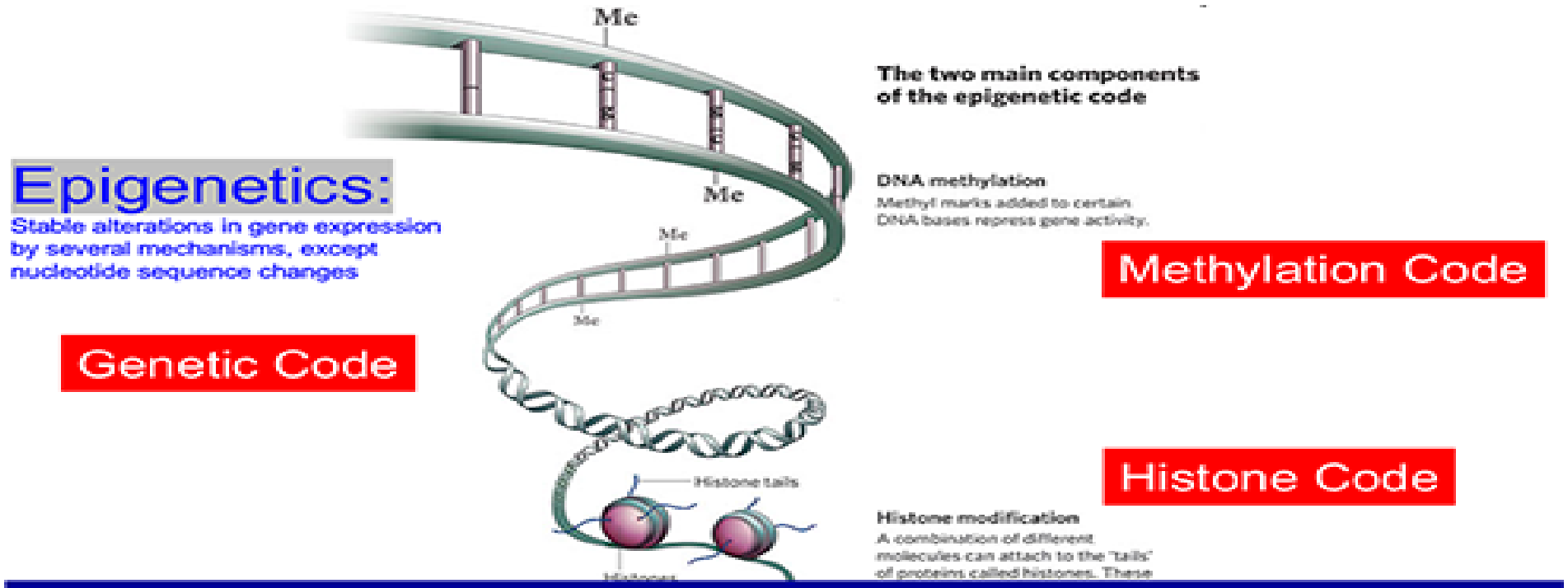
Pharmacogenomics and pharmacoepigenomics (personalized medicine)

Microenvironment, microbiome, and gene expression

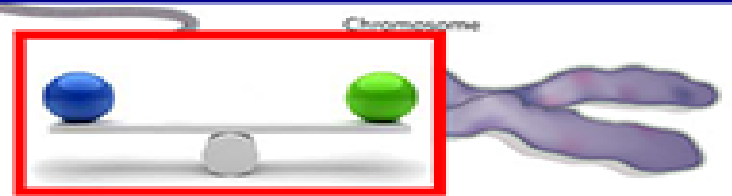
GWAS and EWAS

Adapted from Malouk and Marsden Cir Res 102:873

Epigenetics



The genetic information provides the blue print for the manufacture of all the proteins necessary to create a living organism, whereas the epigenetic information provides the instructions on how, where and when the genetic information will be used.

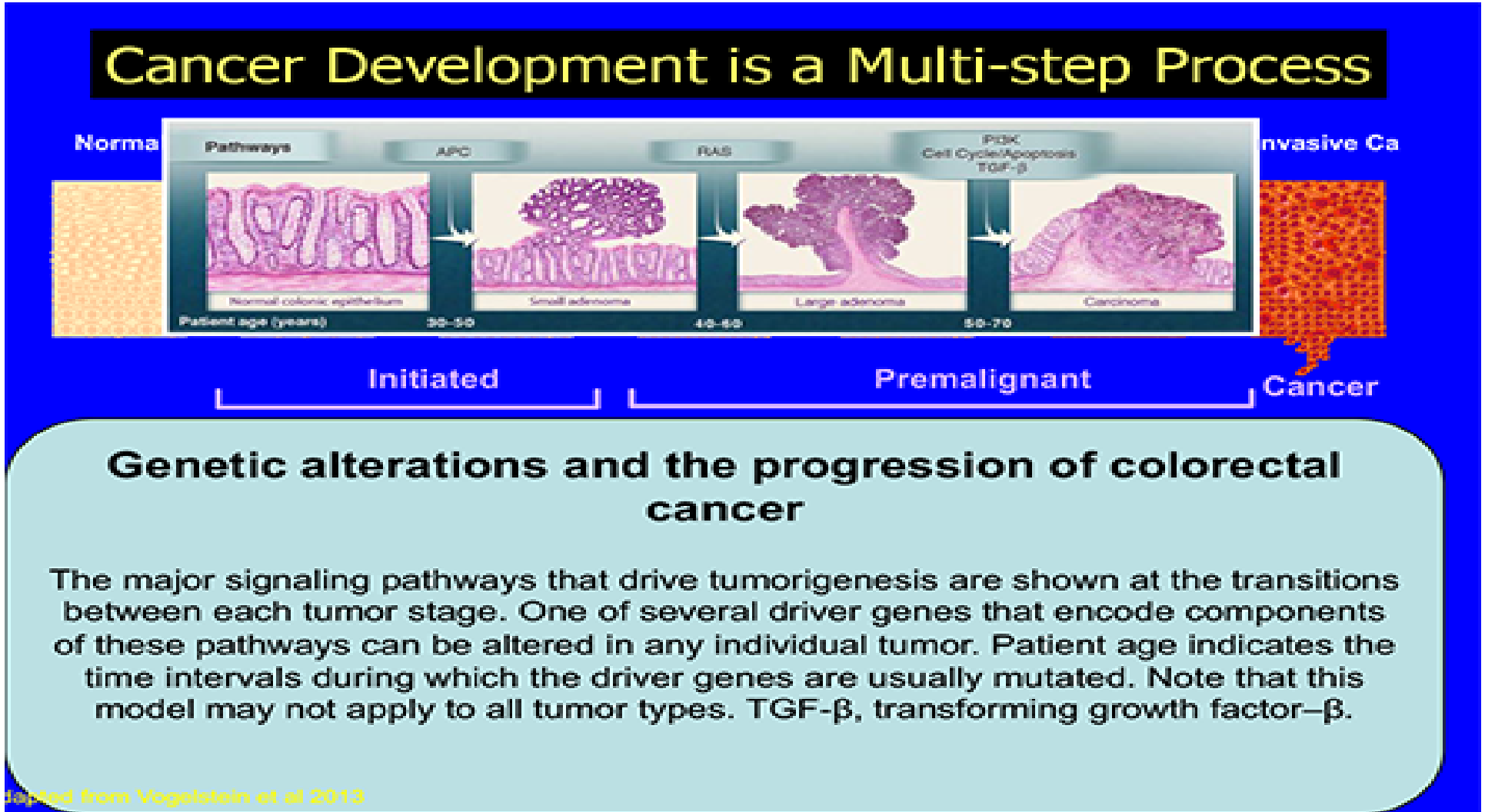


Qiu NATURE 441: 143

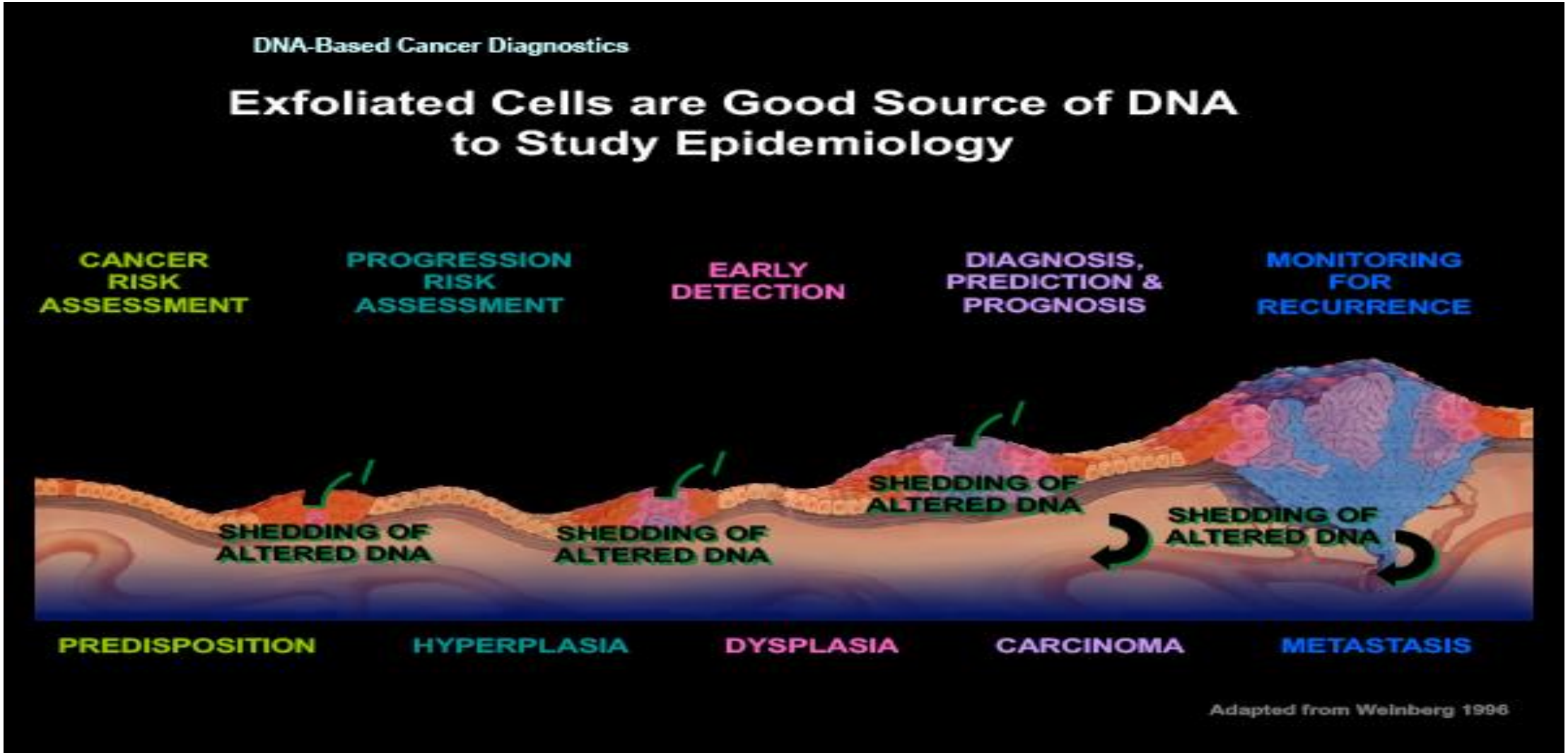
Cancer continuum



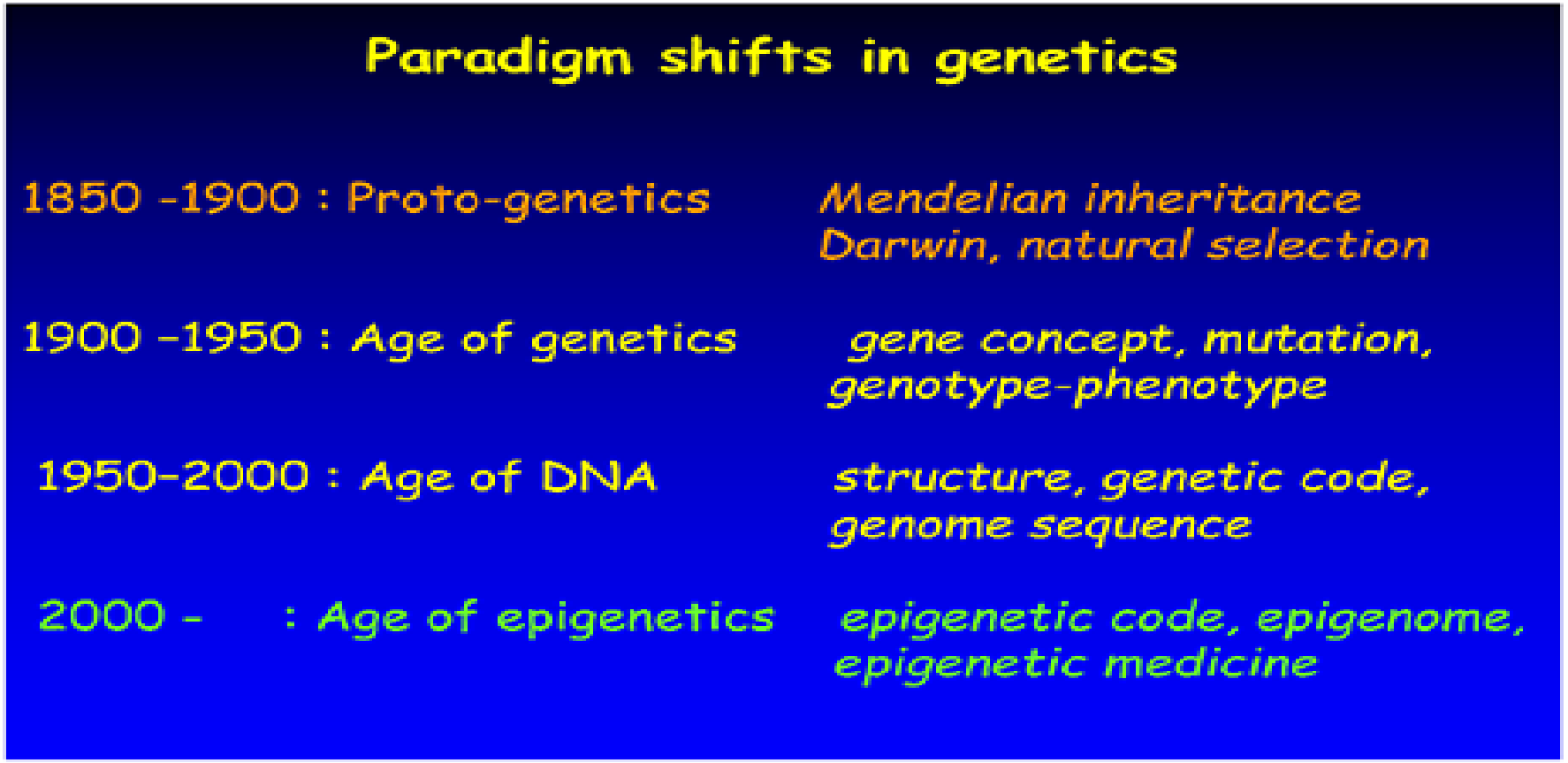
Cancer development



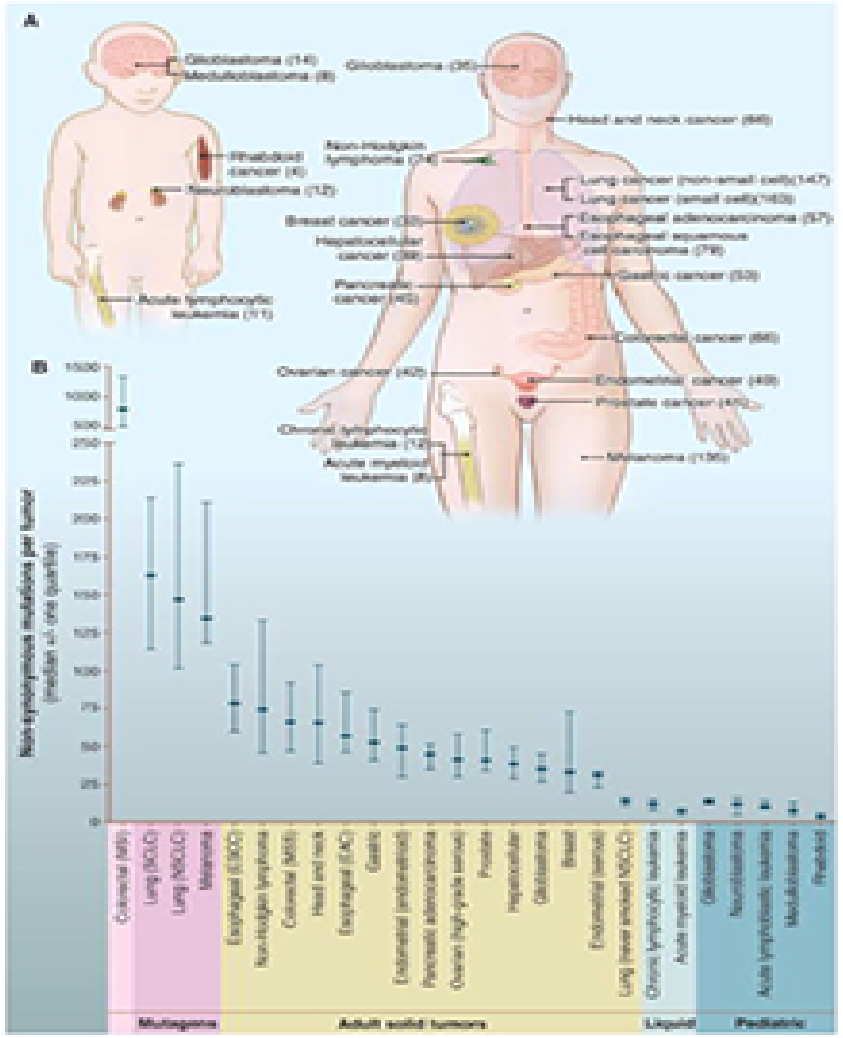
DNA sources


DNA-Based Cancer Diagnostics
Exfoliated Cells are Good Source of DNA to Study Epidemiology
CANCER RISK ASSESSMENT
PROGRESSION RISK ASSESSMENT
EARLY DETECTION
DIAGNOSIS, PREDICTION & PROGNOSIS
MONITORING FOR RECURRENCE
SHEDDING OF ALTERED DNA
SHEDDING OF ALTERED DNA
SHEDDING OF ALTERED DNA
SHEDDING OF ALTERED DNA
PREDISPOSITION
HYPERPLASIA
DYSPLASIA
CARCINOMA
METASTASIS
Adapted from Weinberg 1996

Paradigm shift

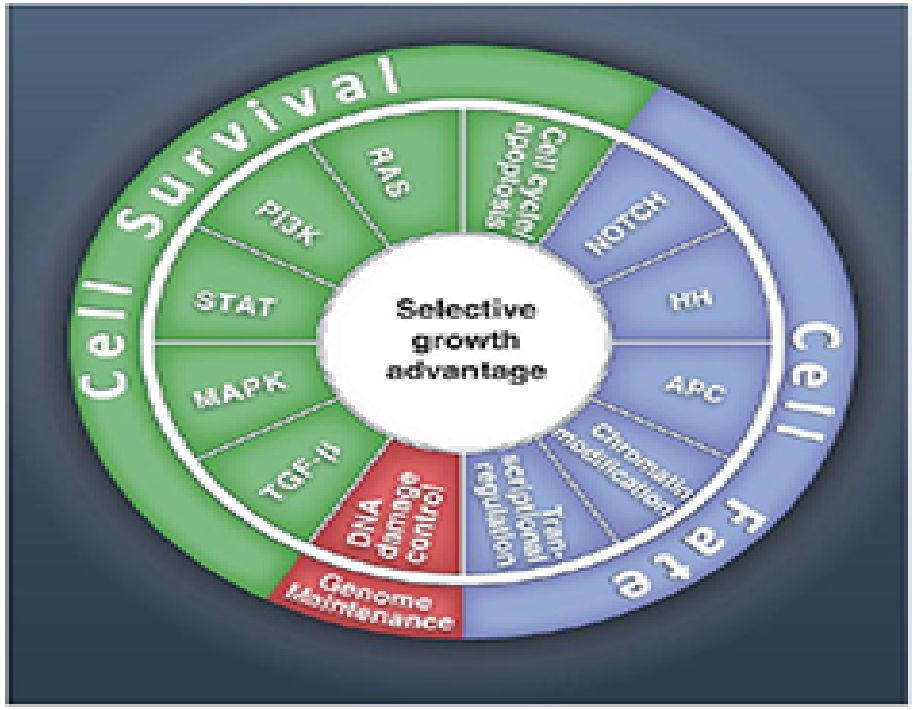


Genome landscape



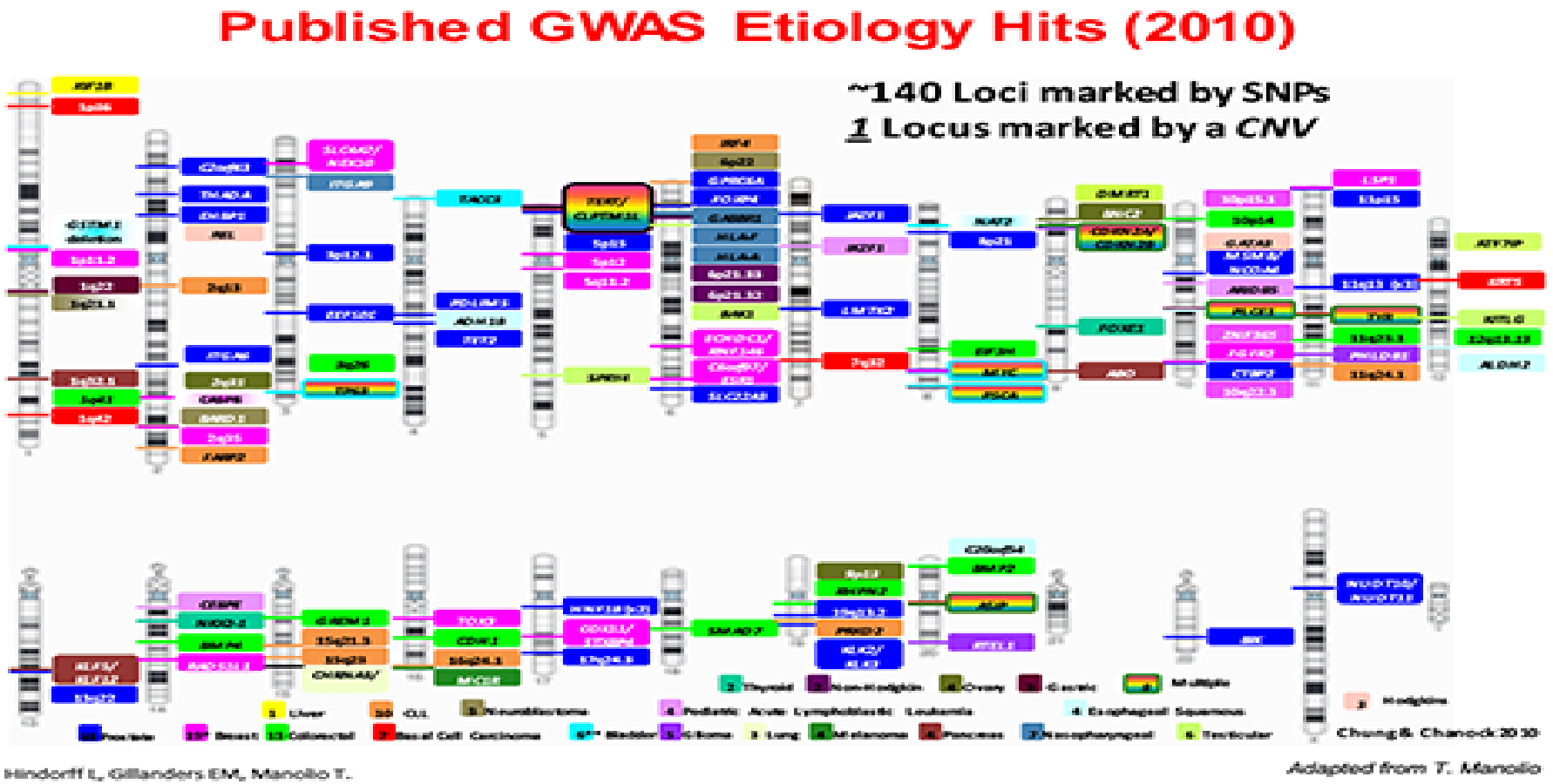
CANCER GENOME LANDSCAPE

Number of somatic mutations in representative human cancers, detected by genome-wide sequencing studies

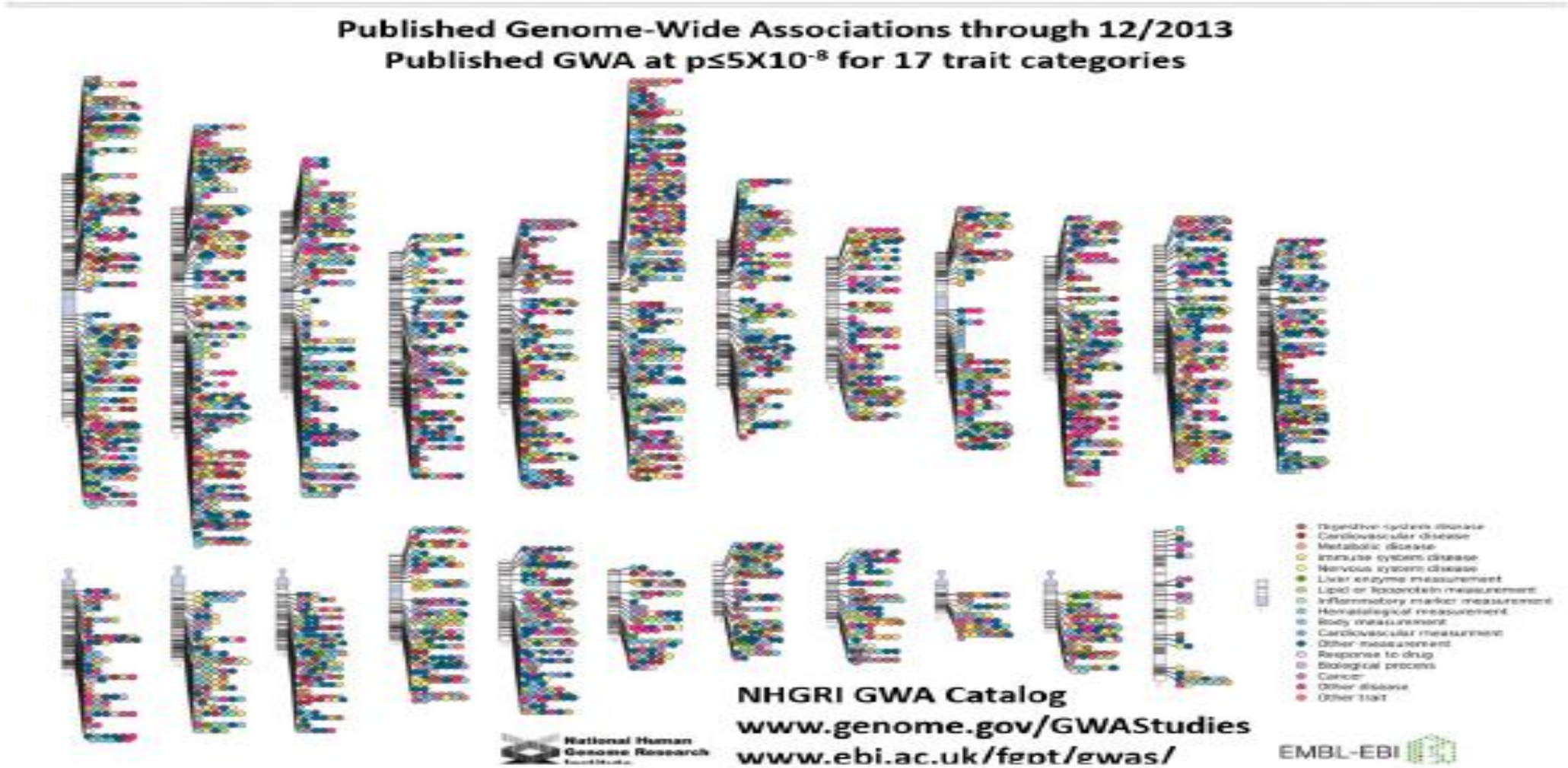


Adapted from Vogelstein and Kinzler (Science 2013)

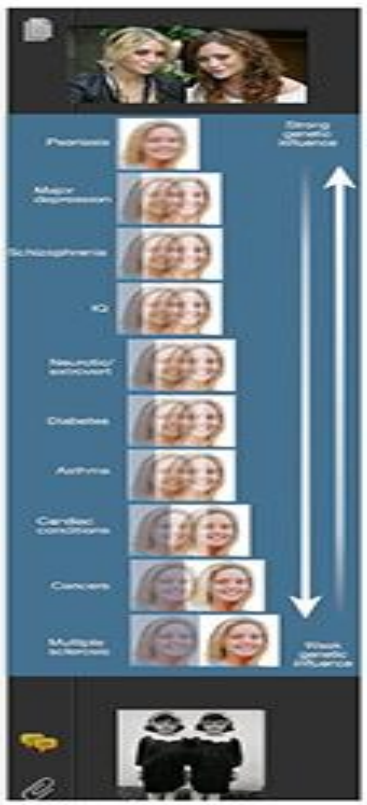
GWAS hits


Published GWAS Etiology Hits (2010)
~140 Loci marked by SNPs
1 Locus marked by a CNV
Hindorff L, Gillanders EM, Manolio T.
Adapted from T. Manolio

Genome associations



Genome versus epigenome



Genome vs. epigenome – why is it important?



- Genome is generally constant; epigenome changes
  - Age
  - Diet
  - Disease
  - Lifestyle
  - Environment



- Areas of interest:
  - Molecular basis of disease
  - Biomarker identification
  - Diagnostics development
  - Drug targeting





You only need to sequence your genome once, but you need to determine your epigenome multiple times…

https://www.youtube.com/watch?v=JMT6oRYgkTk

Nucleosomes

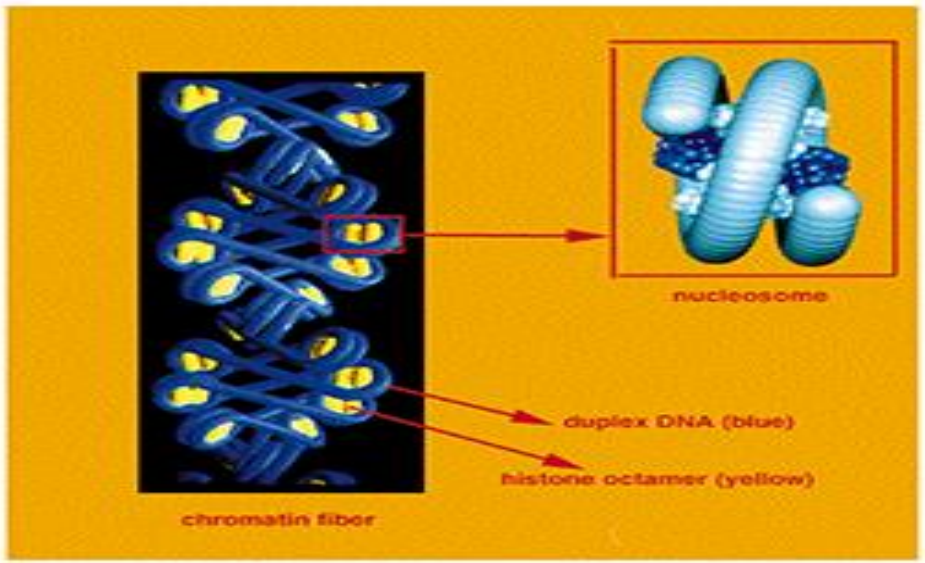
Nucleosomes (Units of Chromatin)

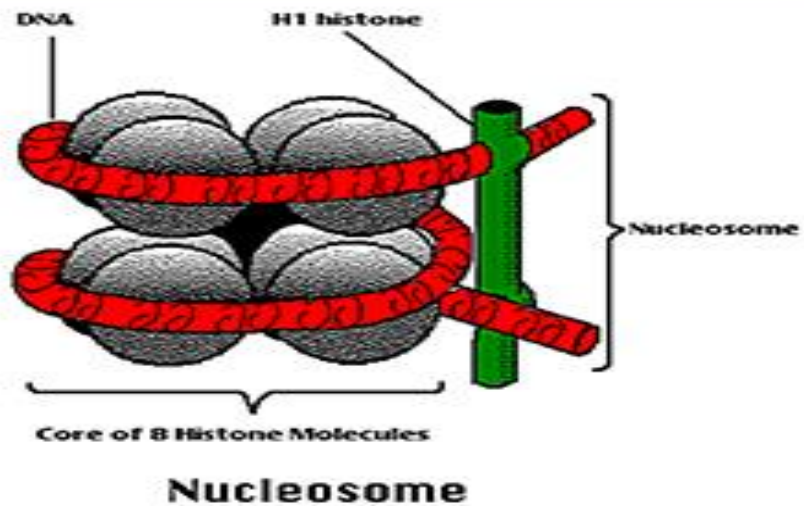
DNA
Histones H2a, H2b, H3, H4

} To neutralize charge and provide stability

H1 is a linker histone which binds to the DNA linking two adjacent nucleosomal cores

Nucleosome: two turns of DNA (146 base pairs) wrapped around an octomeric complex of two of each of histone types

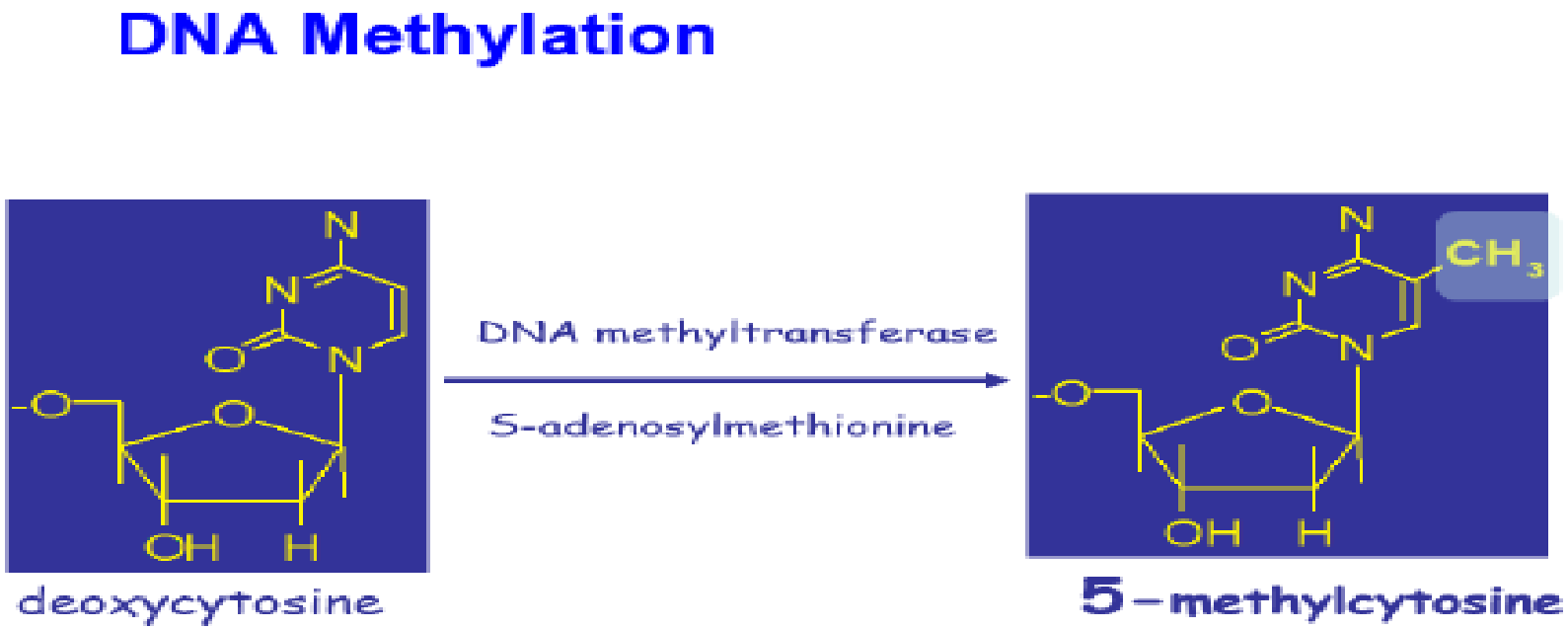




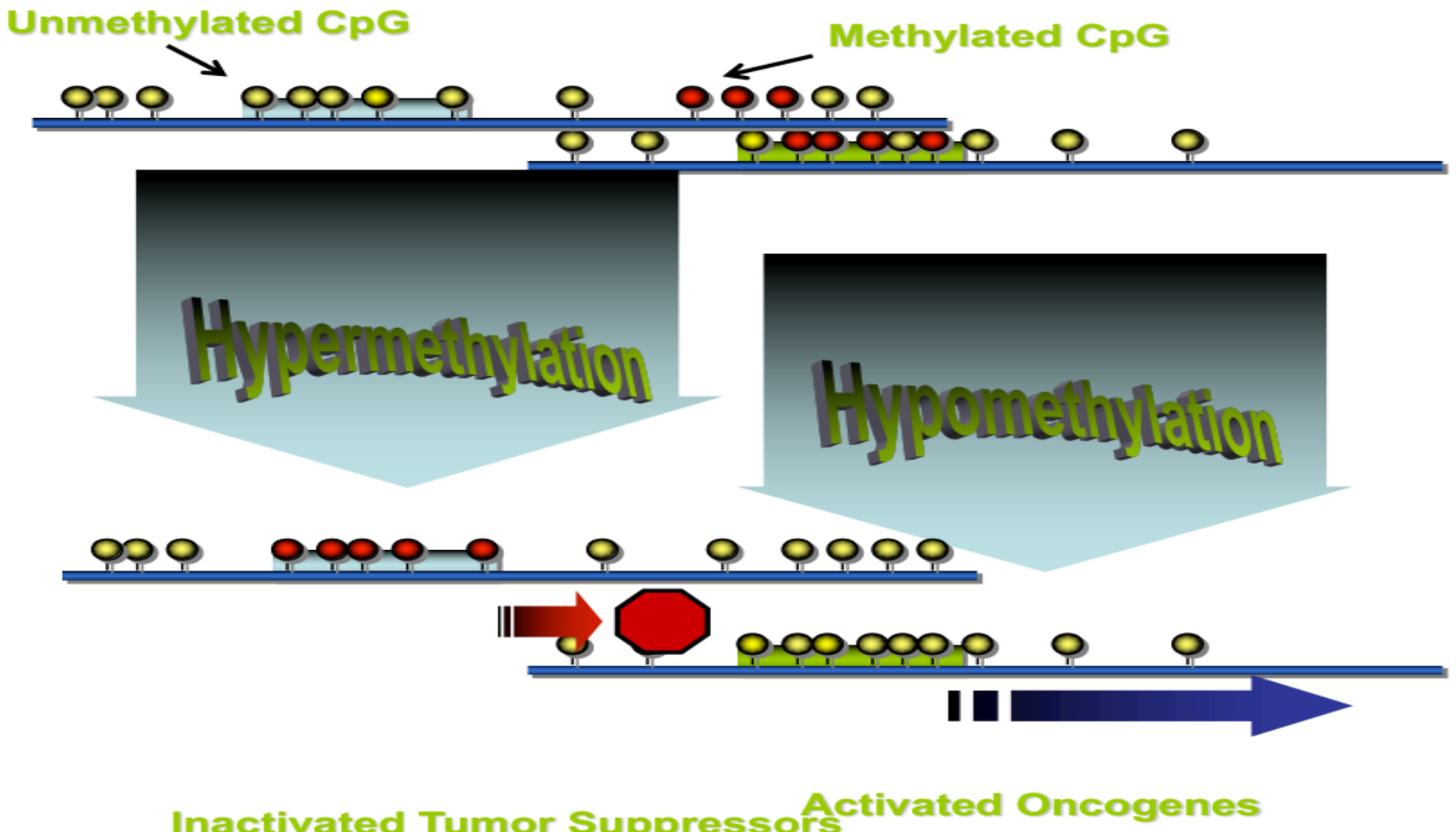
Nucleosome

Shores are 0-2kb from islands
Shelves are 2-4 kb and enhancers are beyond shelves

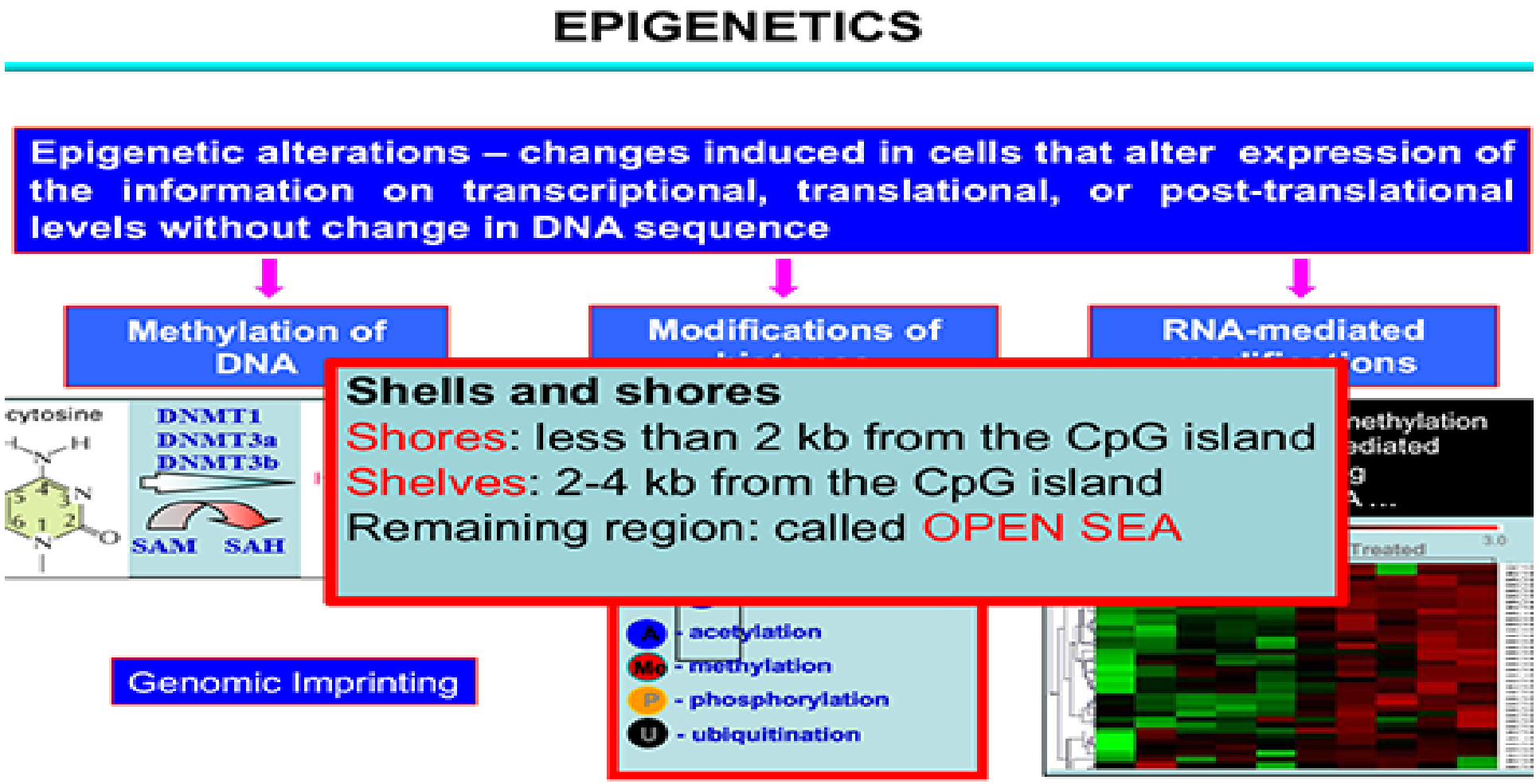
DNA methylation



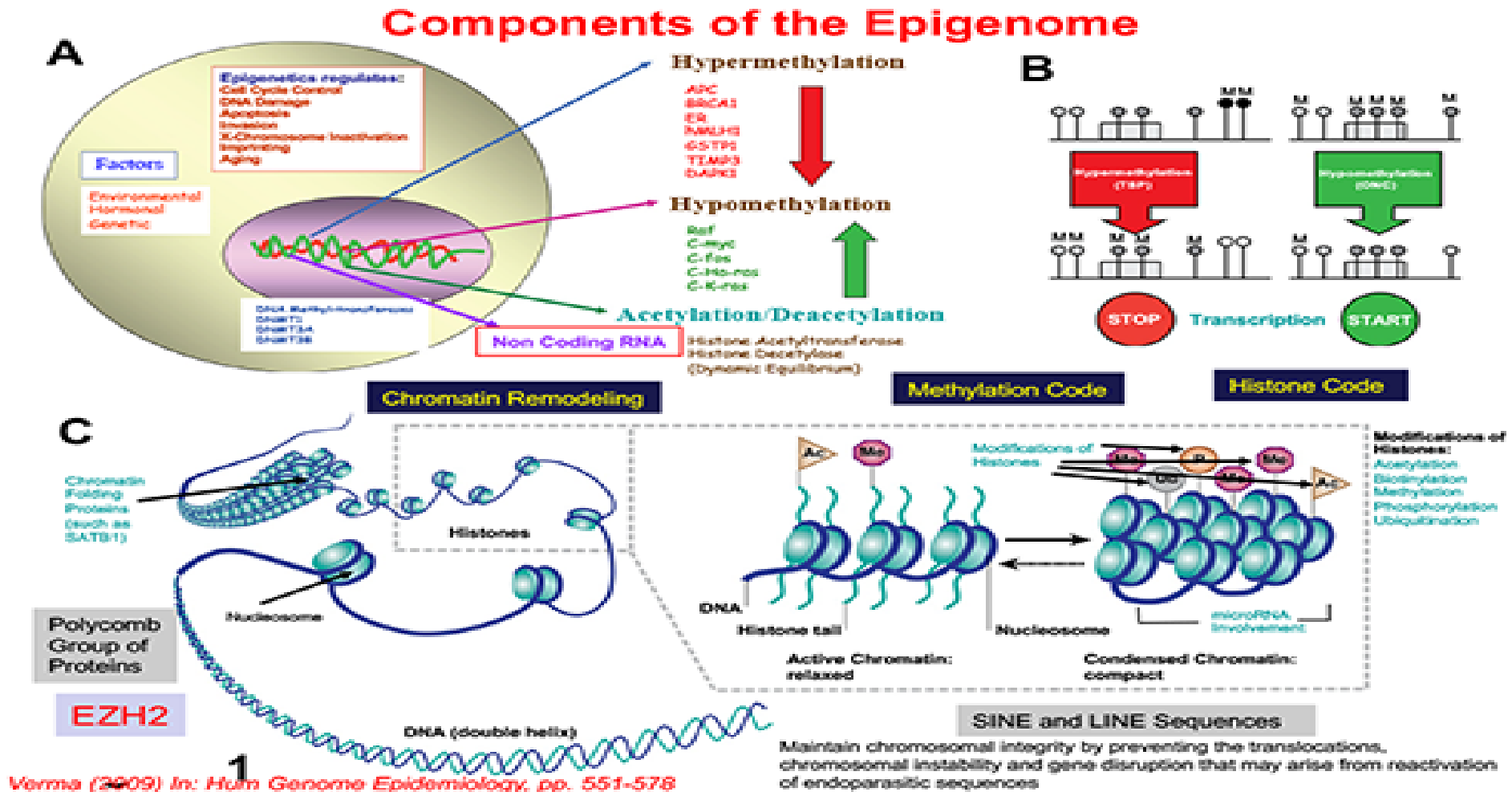
DNA methylation



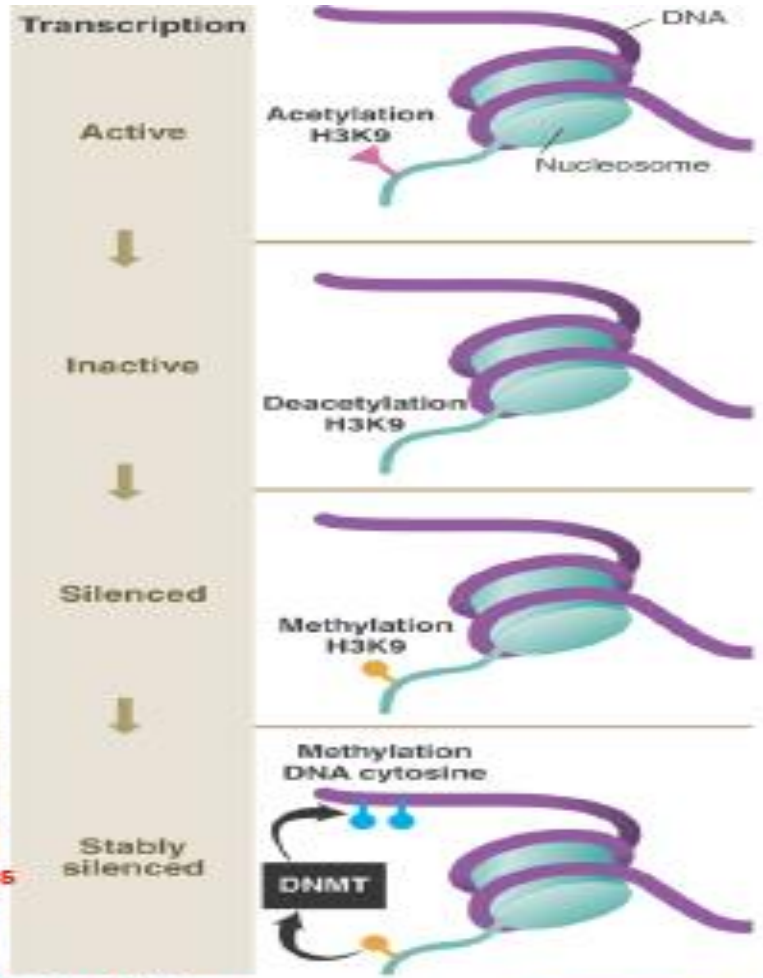
Epigenetics



Epigenome components

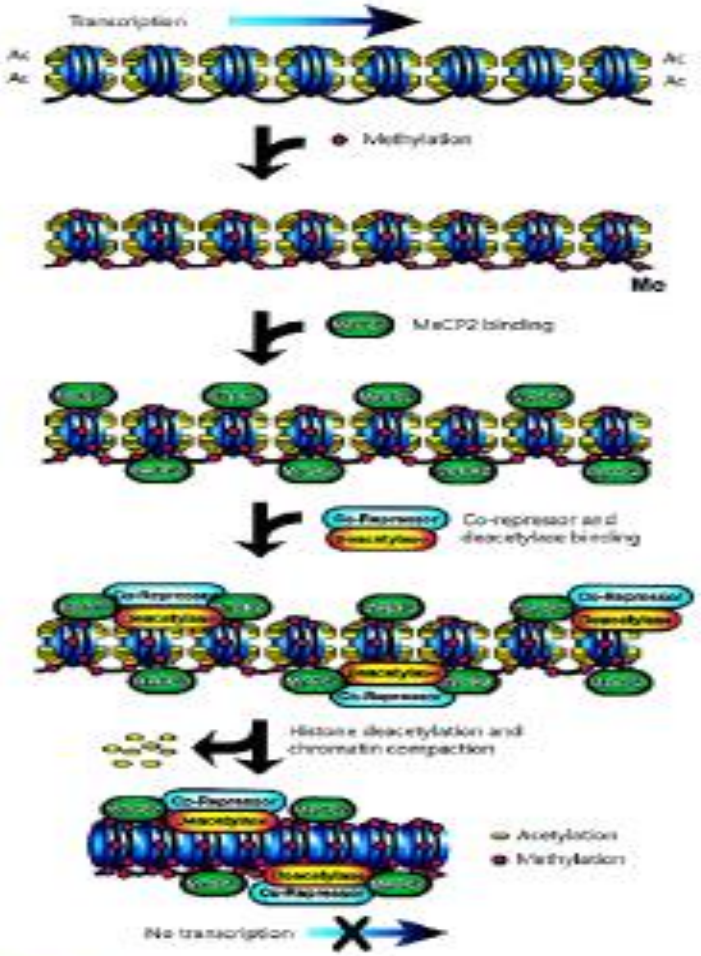


Methylation




Peter Jones


Andrew Feinberg

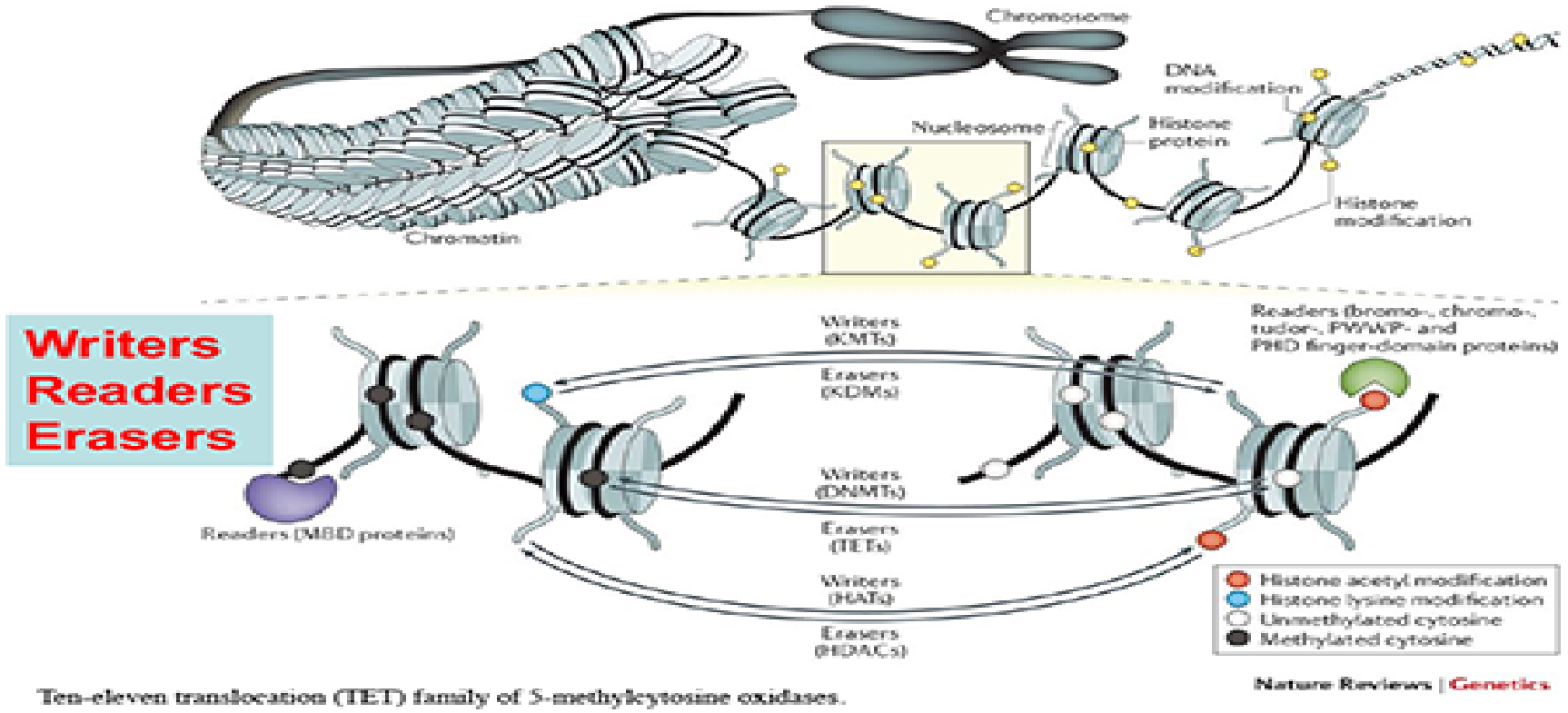


Jones and Laird. *Nat Rev Gen* 21: 163

Chromatin modifications

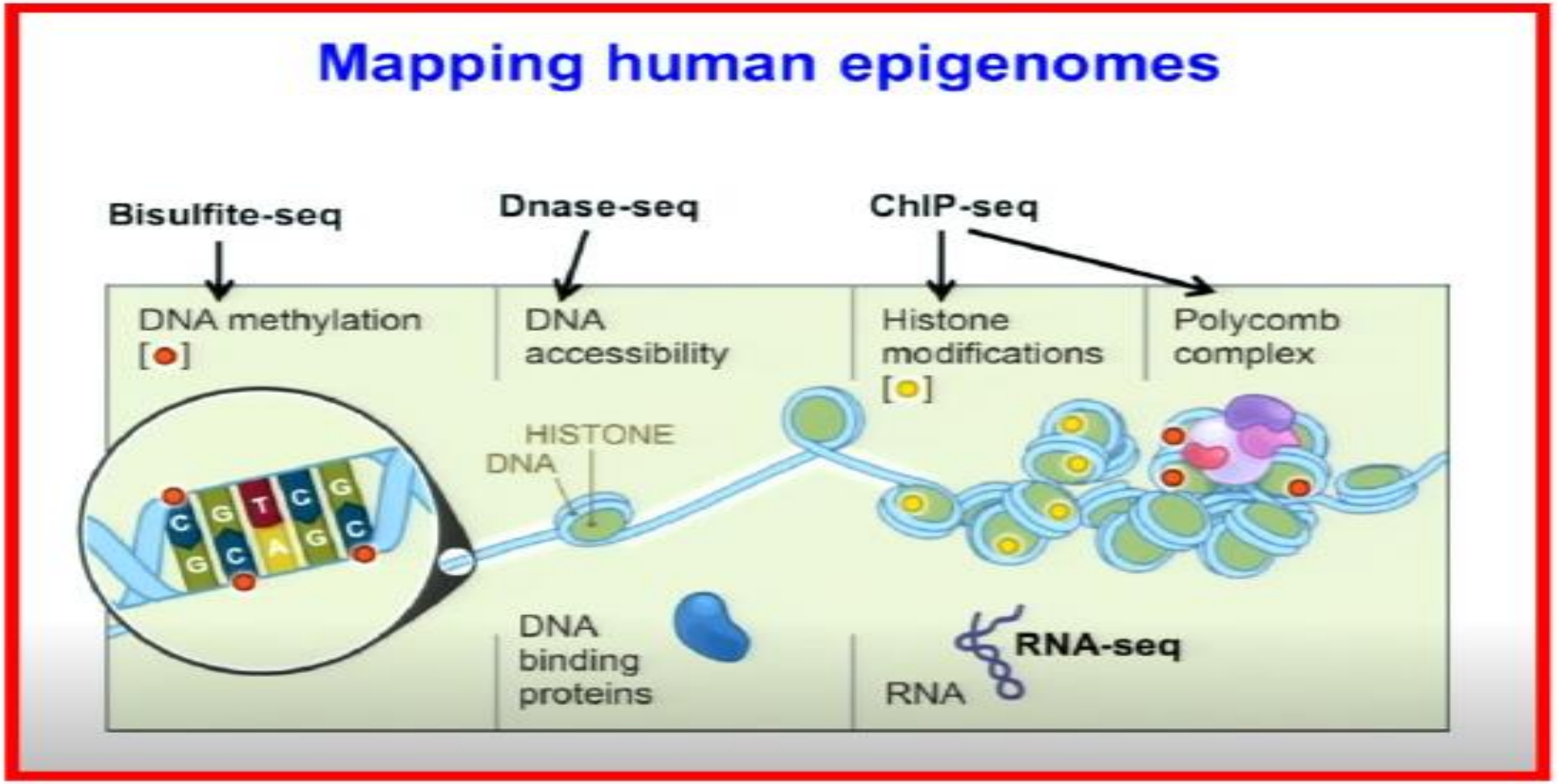
Figure 1 : Modulation of covalent modifications on chromatin.

From: Targeting the cancer epigenome for therapy

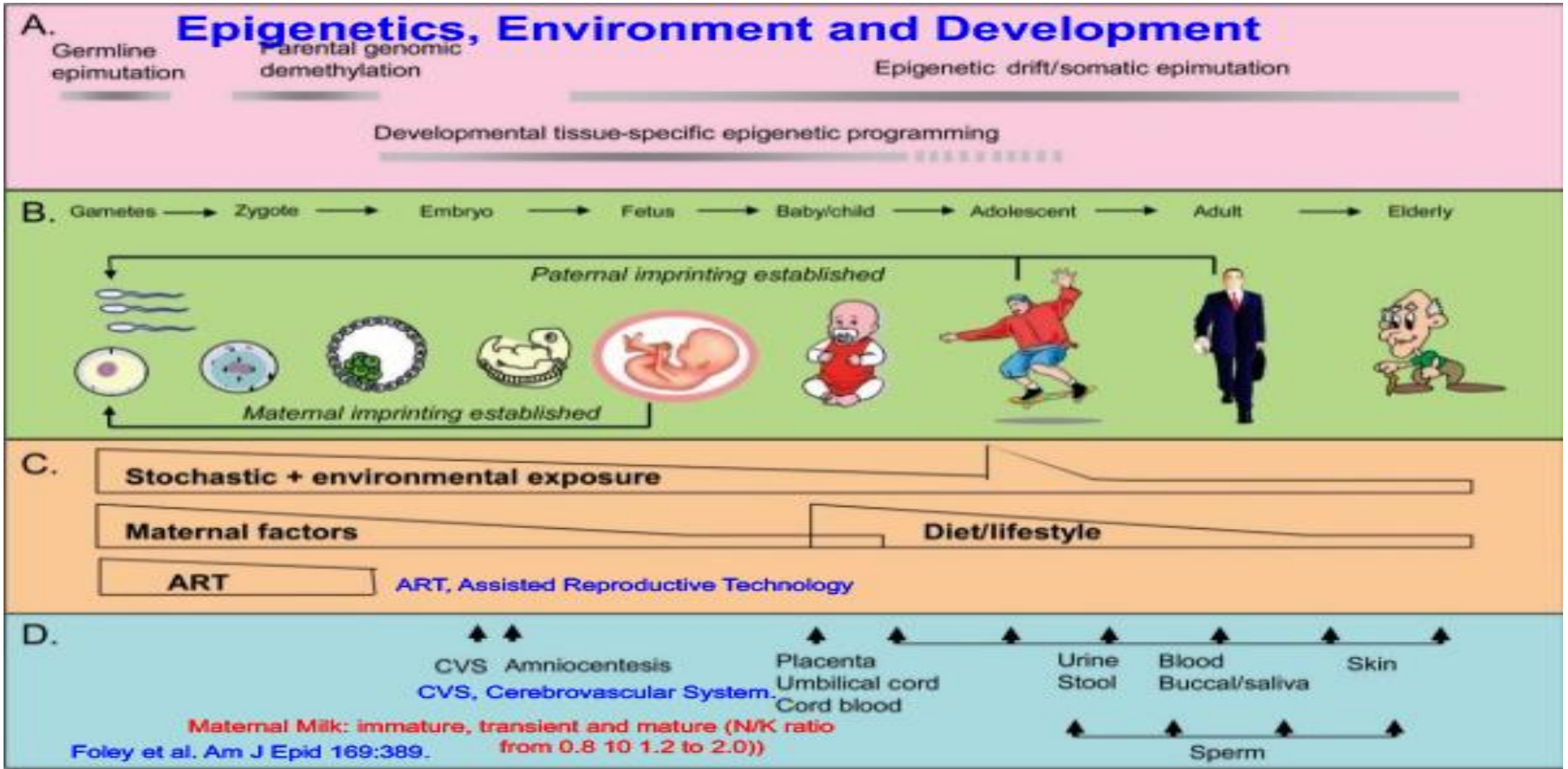


Ten-eleven translocation (TET) family of 5-methylcytosine oxidases.

Epigenomes


Mapping human epigenomes
Bisulfite-seq
Dnase-seq
ChIP-seq
DNA methylation
[●]
DNA
accessibility
Histone
modifications
[●]
Polycomb
complex
HISTONE
DNA
C G T C G
G C A G C
DNA
binding
proteins
RNA-seq
RNA

Epigenetics, environment and development



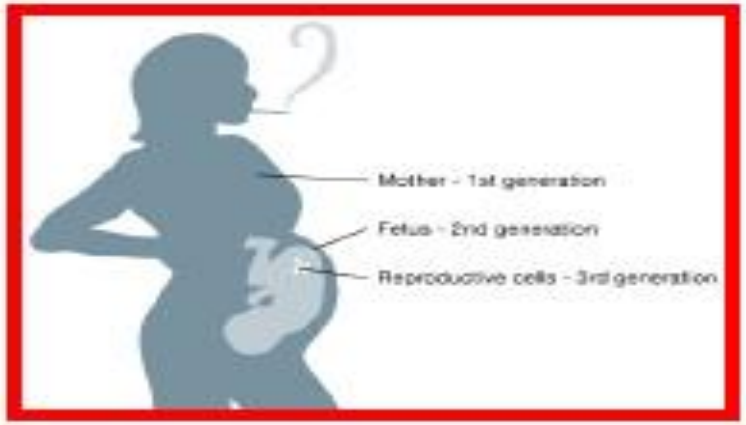
Toxic substances

Key toxic substances affecting the epigenome

Arsenic	Induces genetic and epigenetic changes
Benzene	Benzene and its metabolic product hydroquinone alter methylation profiles and contribute to leukemia
Cadmium	Induces hypermethylation of selected genes in lung cancer
Chromium	Induces hypermethylation in lung cancer
Nickel	Alters chromatin structure and induces histone acetylation
PFOS	Affects prenatal methylation and regulation of *GSTP1* and LINE/SINE sequences
PAHC	Alters histone H3 acetylation in breast cancer model
Uranium	Contributes to leukemia

PFOS, Perfluorooctane sulfonate
PAHC, Polycyclic aromatic and halogenated compounds

Histone phosphorylation





Aldehyde and nitric oxide, present in cigarette smoke induce phosphorylation of histones resulting in decreased histone deacetylase 2 activity



Viruses and bacteria

Oncogenic viruses, bacteria and epigenetics

Viruses:	p16 in HPV16/18 (Cervical Cancer)
	RASSF1a in SV40 (Mesothelioma)
	HBV and HCV genes (Liver Cancer)
	LANA in EBV (Nasopharyngeal Carcinoma)
Bacteria:	COX2 in H.pylori Infected Cells (Gastric Cancer)

Int. J. Cancer: **113**, 440–445 (2005)
© 2004 Wiley-Liss, Inc.

Frequent p16INK4a Promoter Hypermethylation in Human Papillomavirus-Infected Female Lung Cancer in Taiwan

LANA, Latency Associated Nuclear Antigen
EBNA, Epstein-Barr Virus Nuclear Antigen

Ming-Fang Wu[1,2], Ya-Wen Cheng[2,3], Ji-Ching Lai[4], Min-Chih Hsu[4], Jung-Ta Chen[5], Wen-Shan Liu[6], Ming-Chih Chiou[2,3], Chih-Yi Chen[7] and Huei Lee[3,4]*

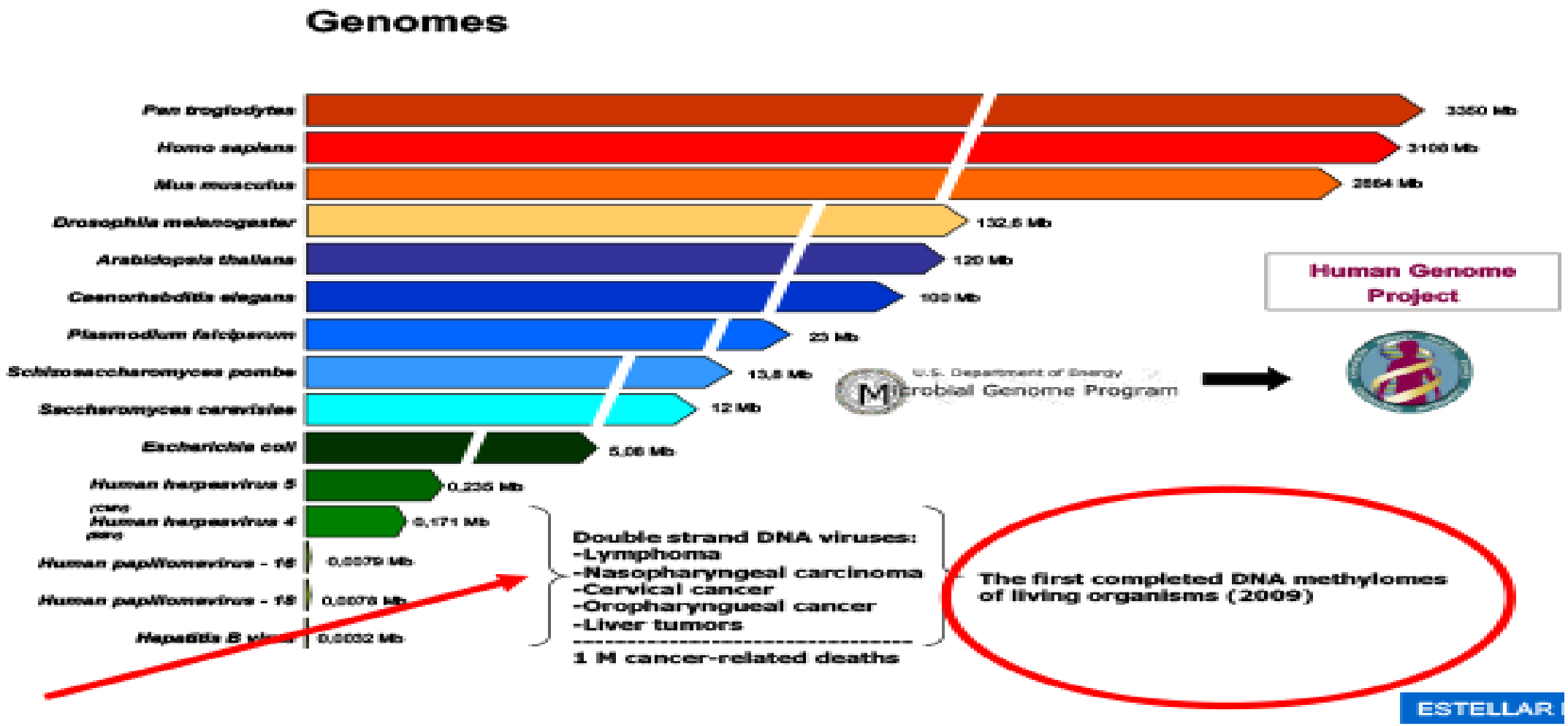
[1]Dep... of Internal Medicine, Chung Shan Medical University Hospital, Taichung, Taiwan

LANA

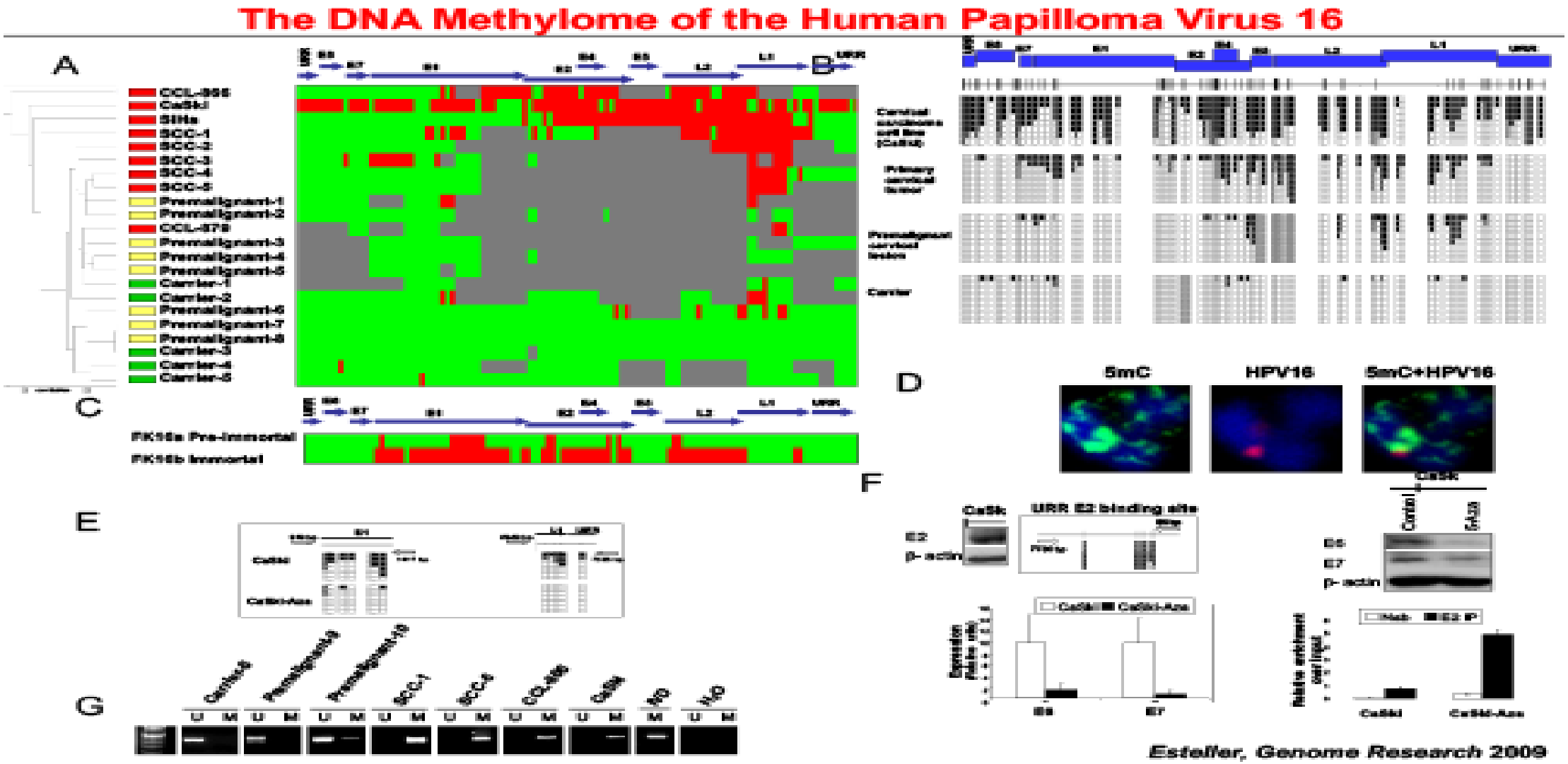
Complete methylome of HPV, EBV, and HBV.
Esteller M. Genome Research. 2009. 19: 438

EBNA

Genomes


Genomes
Pan troglodytes
3350 Mb
Homo sapiens
3100 Mb
Mus musculus
2654 Mb
Drosophila melanogaster
132.6 Mb
Arabidopsis thaliana
120 Mb
Caenorhabditis elegans
100 Mb
Plasmodium falciparum
23 Mb
Schizosaccharomyces pombe
13,8 Mb
Saccharomyces cerevisiae
12 Mb
Escherichia coli
5,06 Mb
Human herpesvirus 5
0,235 Mb
Human herpesvirus 4
0,171 Mb
Human papillomavirus - 16
0,0079 Mb
Human papillomavirus - 18
0,0078 Mb
0,0032 Mb
Human Genome Project
U.S. Department of Energy
Microbial Genome Program
Double strand DNA viruses:
-Lymphoma
-Nasopharyngeal carcinoma
-Cervical cancer
-Oropharyngeal cancer
-Liver tumors
1 M cancer-related deaths
The first completed DNA methylomes of living organisms (2009)
ESTELLAR

DNA methylome



Infection and cancer

Infection and Cancer: New and Emerging Associations

Infectious Agent	Cancer
Merkel cell polyomavirus (MCV)	Merkel cell carcinoma
Plasmodium falciparum	Endemic Burkitt's lymphoma
Cytomegalovirus	Brain
Salmonella typhi	Gallbladder
Streptococcus bovis	Colorectal
Chlamydia pneumoniae	Lung
Others?	???



Special populations

93

Special Populations in EGRP

African-American men & women

South American women

Asian-American & Asian men & women

Latin-American/Hispanics

African men & women

Alaskan & Hawaiian Natives

Middle-Eastern populations

American-Indian, incl. Navajo

Rural South

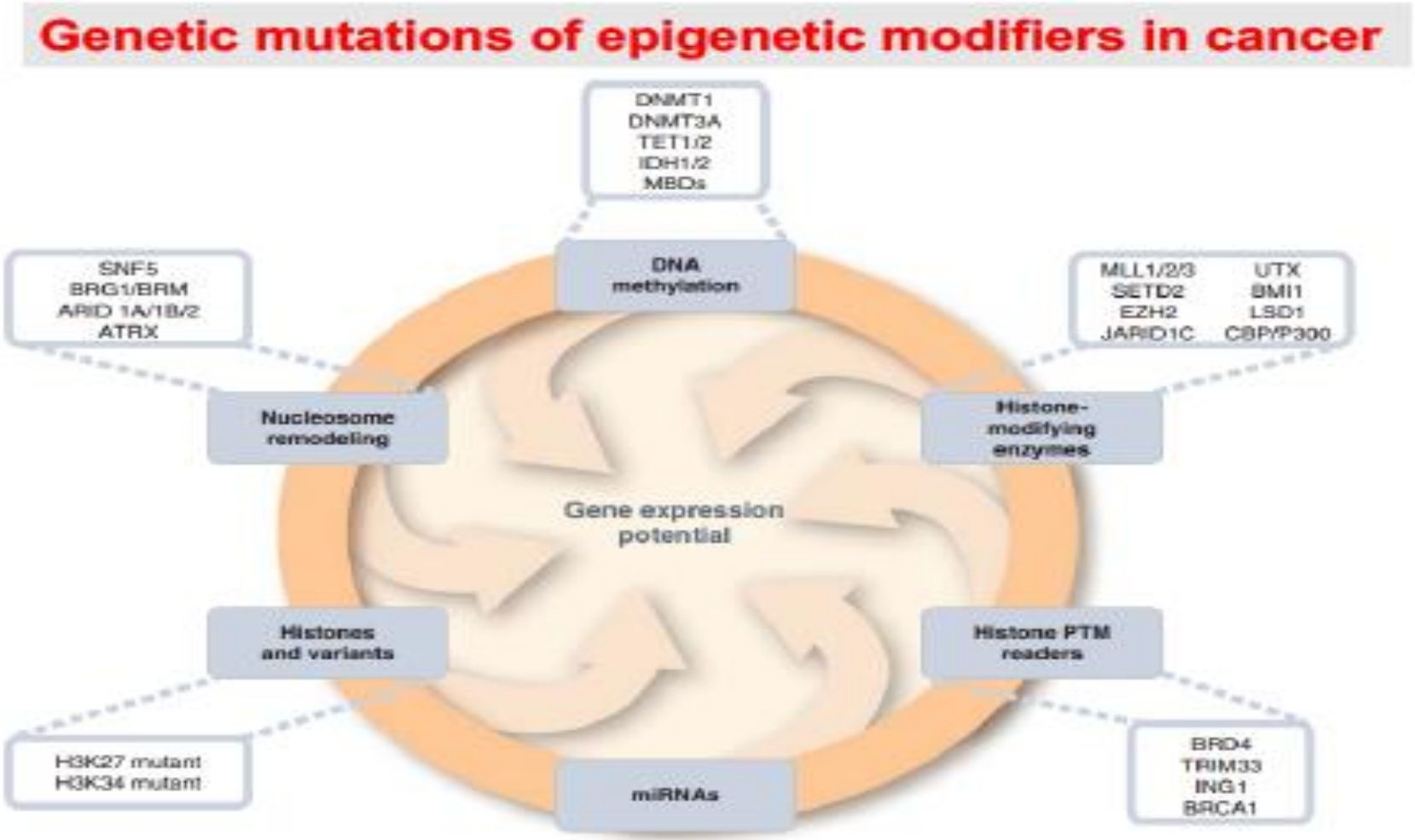
Chinese

EGRP Studies Are Everywhere

- Senegal
- Malawi
- The Zambia
- China
- Japan
- Egypt
- Israel
- Brazil
- Colombia
- England
- Canada
- Sweden
- Denmark
- France
- Costa Rica
- Singapore
- Poland
- Australia
- U.S., including Alaska & Hawaii

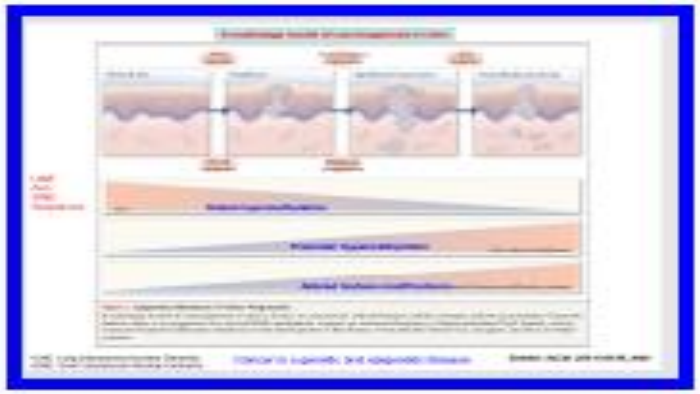
2.3 Million Subjects
Cohorts, CGN and Family Registries

Genetic mutations

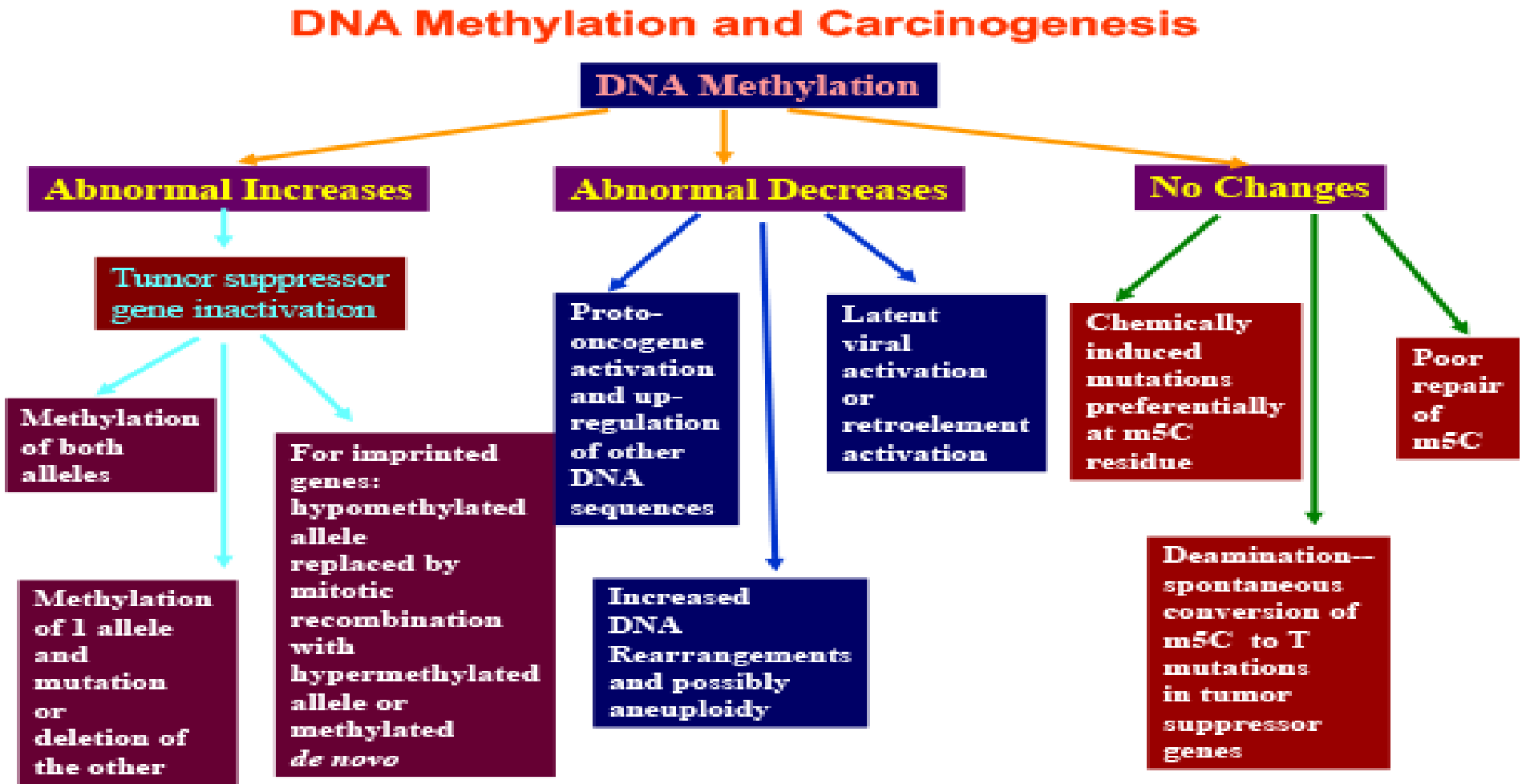


Hypomethylation

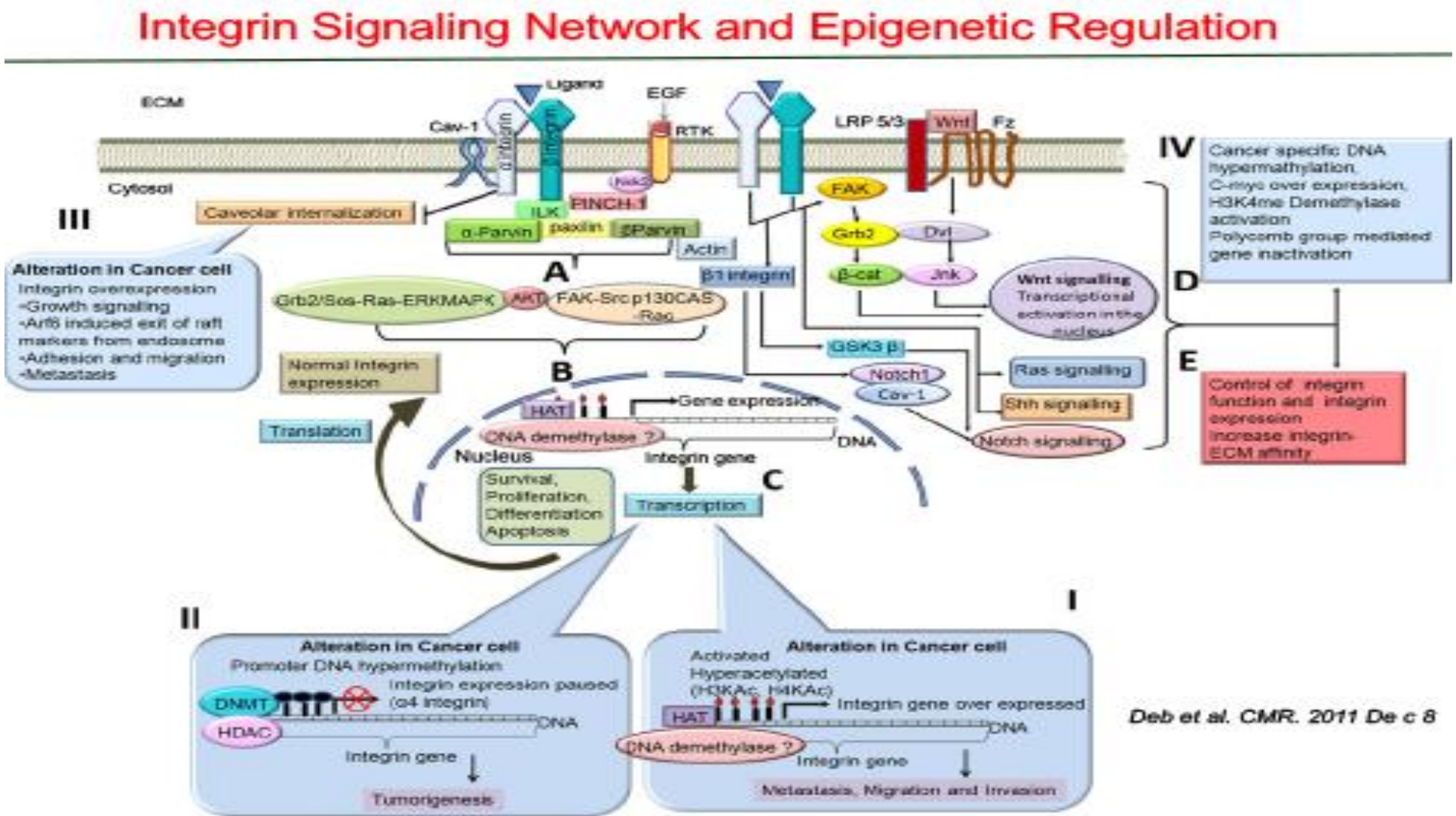




DNA methylation and carcinogenesis

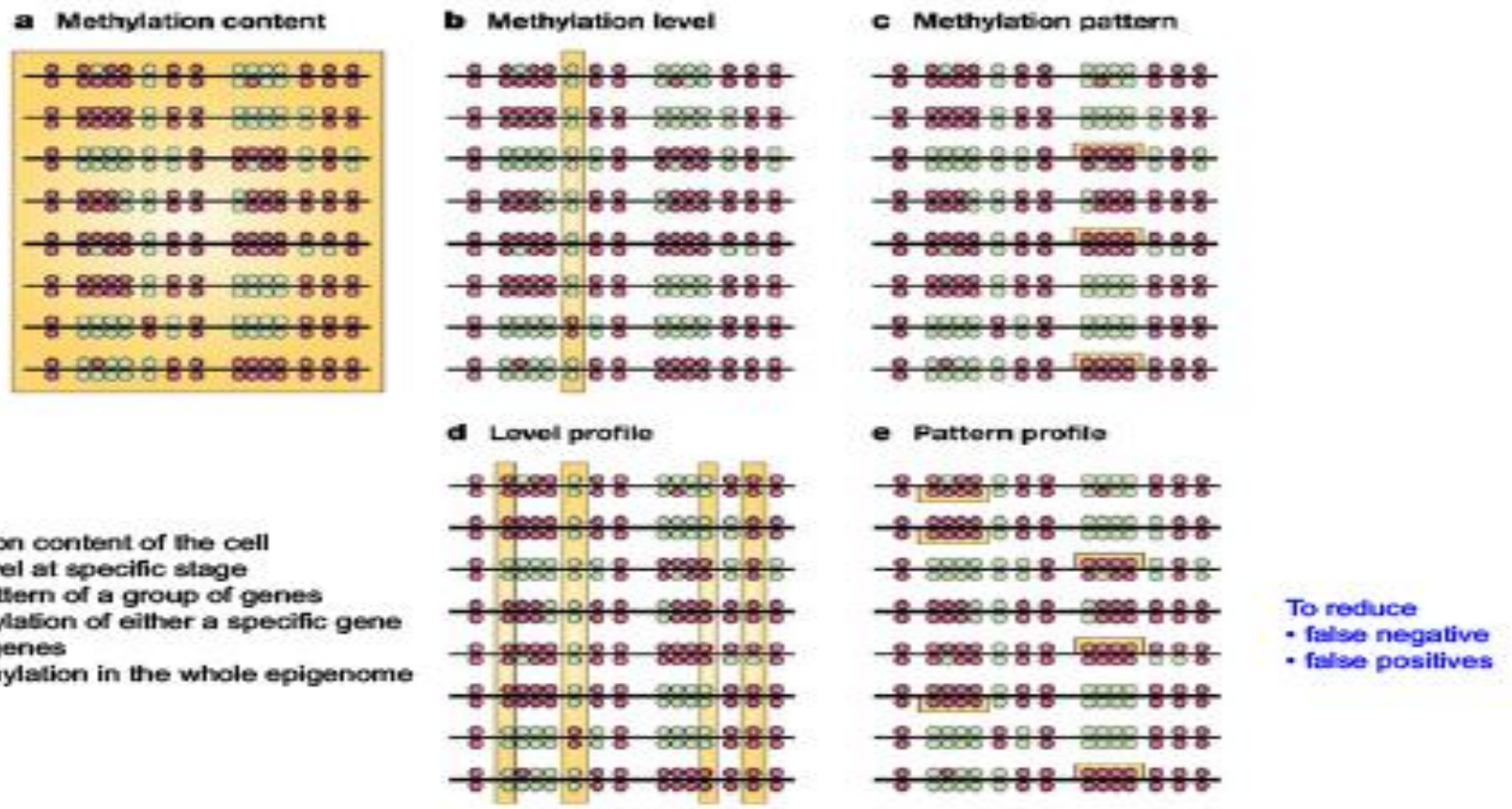


Integrin signaling



Deb et al. CMR. 2011 De c 8

Methylation

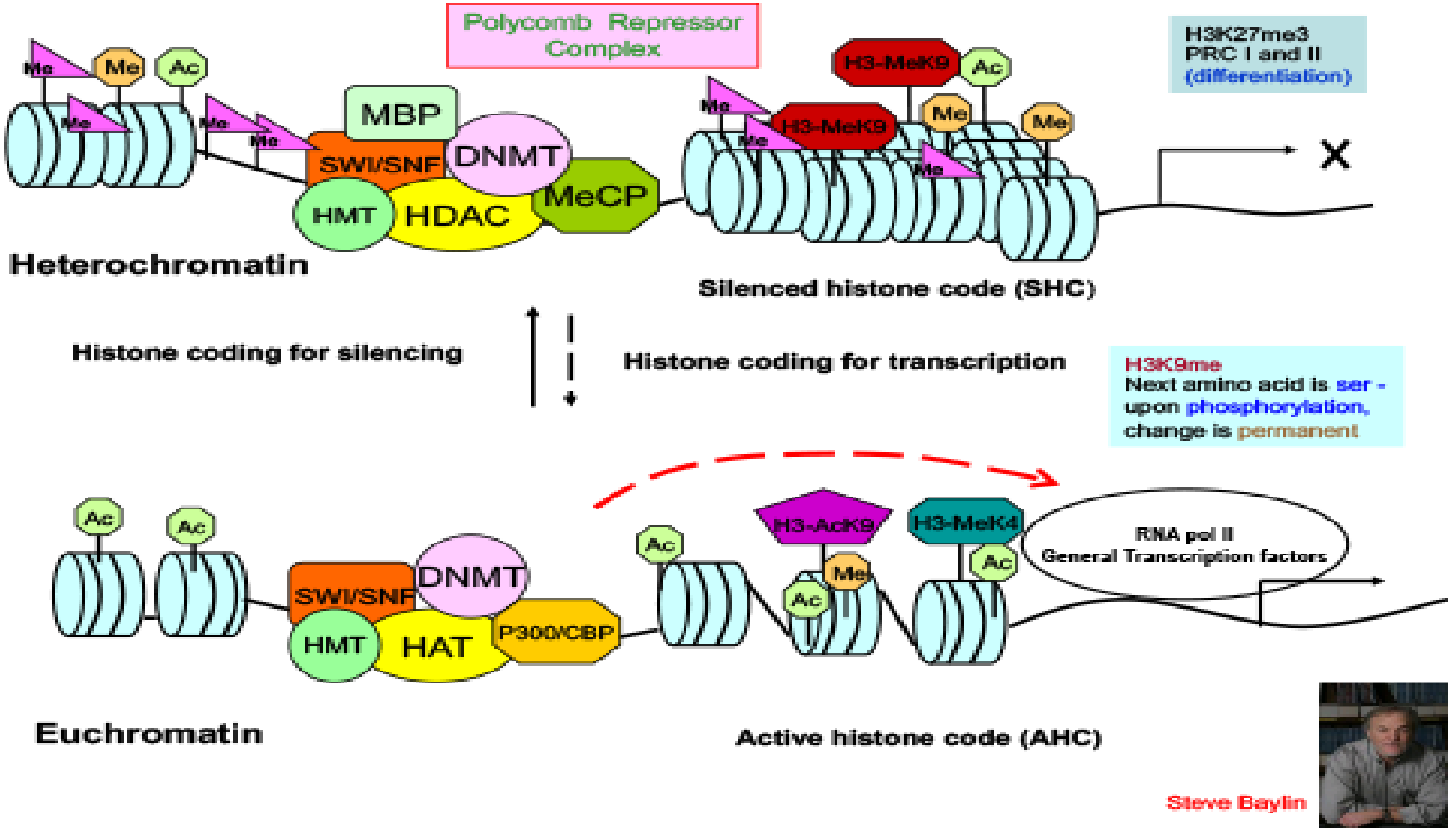


- Total methylation content of the cell
- methylation level at specific stage
- methylation pattern of a group of genes
- profile of methylation of either a specific gene or a number of genes
- pattern of methylation in the whole epigenome

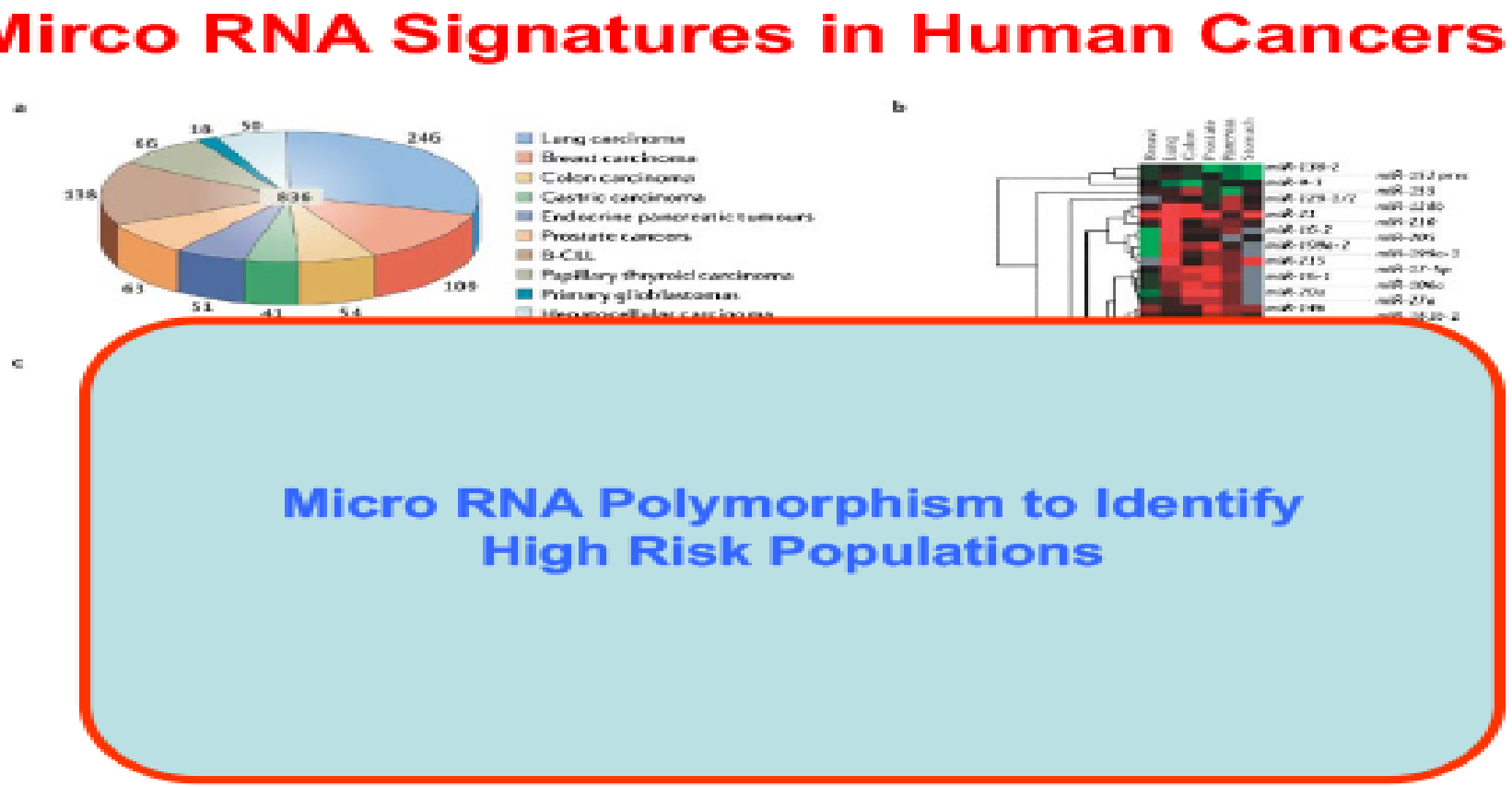
To reduce
- false negative
- false positives

Laird *Nat Rev Cancer* 3:253

Histone acetylation



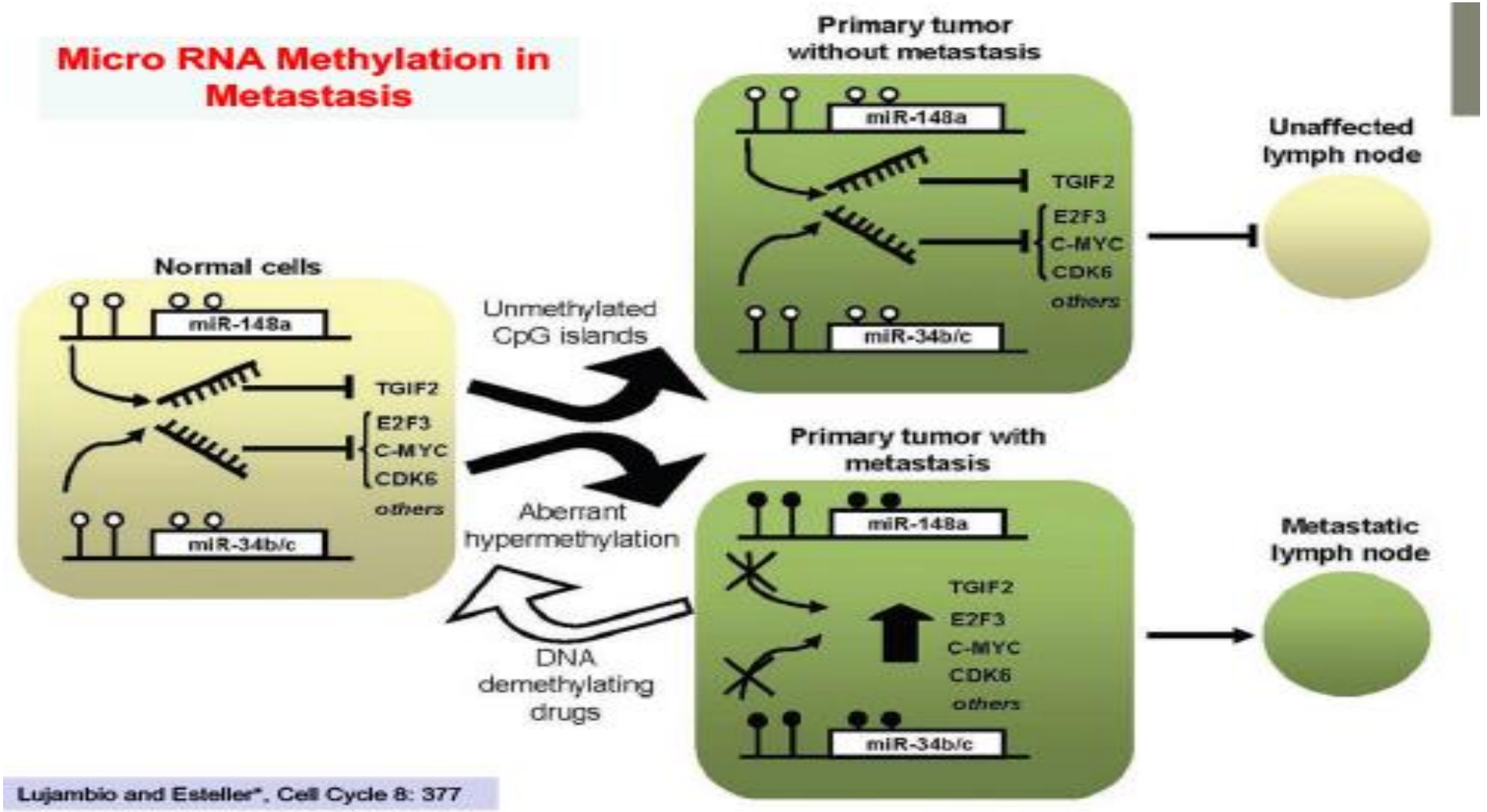
Micro RNA signatures



Mir-31 inhibits metastasis in breast cancer

nature REVIEWS CANCER

Micro RNA methylation



RNA epigenetics

Epitranscriptomics or RNA Epigenetics

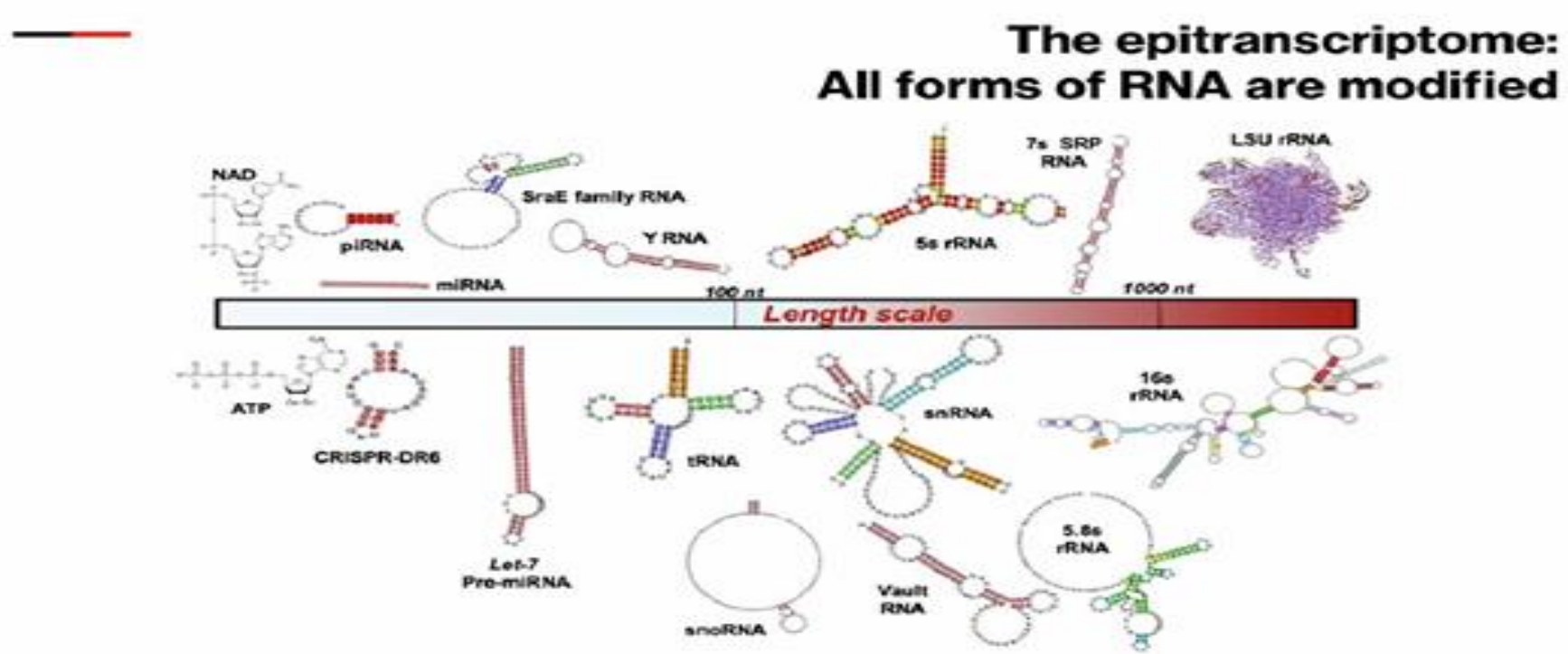
- Epitranscriptomics, also known as RNA epigenetics, is the study of chemical modifications to RNA molecules that occur after transcription.
- Can affect the structure of RNA, its stability, and how it's translated.
- Can also impact gene expression and regulation.

Some examples of RNA modifications include:

- N6-methyladenosine (m6A),
- N1-methyladenosine (m1A),
- 7-methylguanosine (m7G), Pseudouridine (Ψ),
- 5-methylcytidine (m5C).

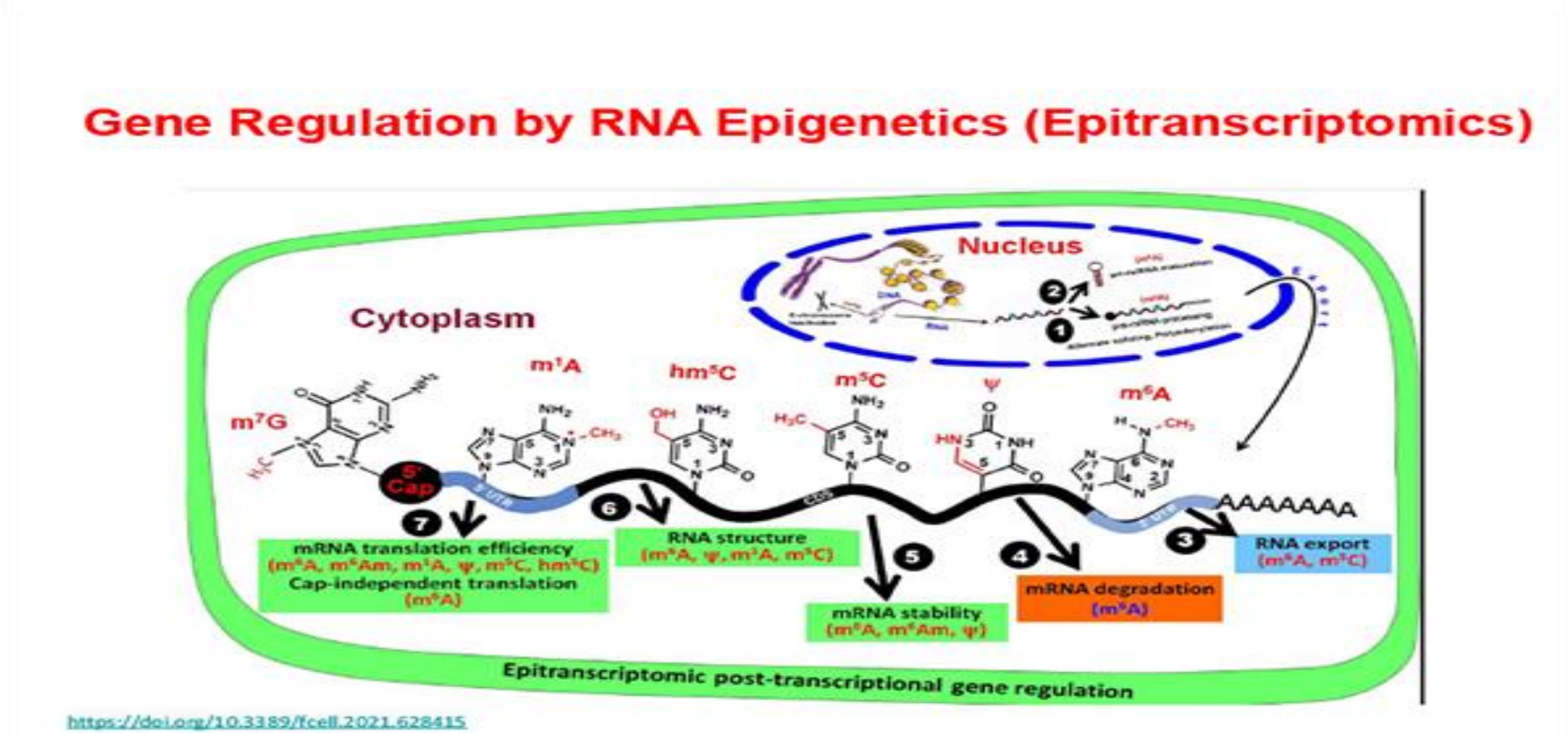
Int. J. Mol. Sci. 2020, *21*(18), 6578; https://doi.org/10.3390/ijms21186578

Epitranscriptome

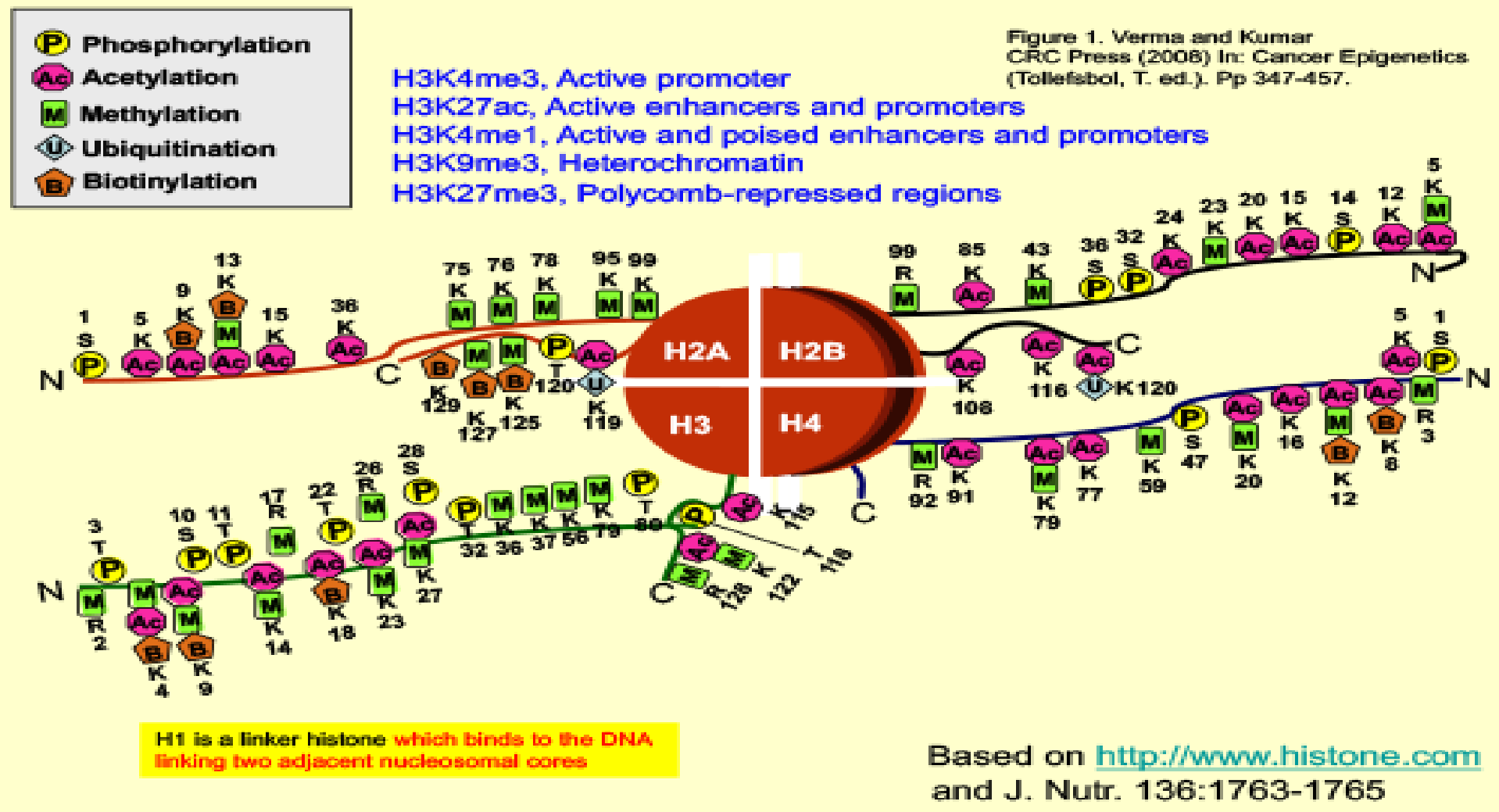


Int. J. Mol. Sci. **2020**, *21*(18), 6578; https://doi.org/10.3390/ijms21186578

RNA epigenetics



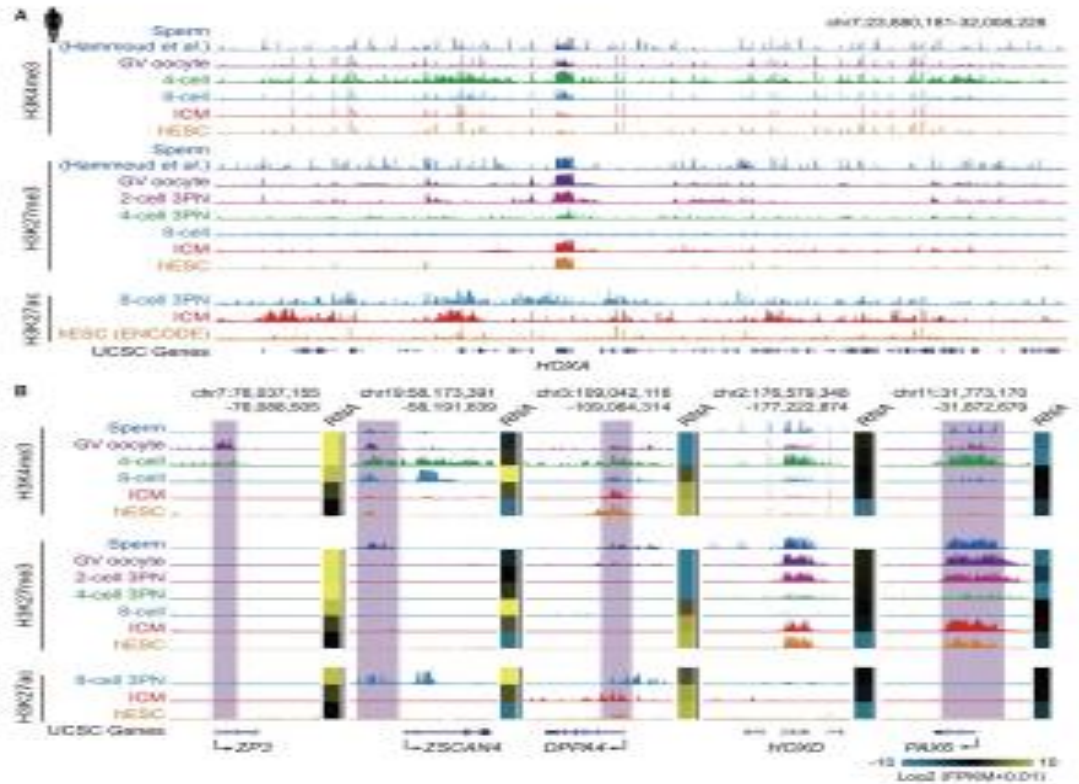
Histone modifications



Histone modifications

Fig. 1 Mapping histone modifications in human gametes and preimplantation embryos.

Histone mapping

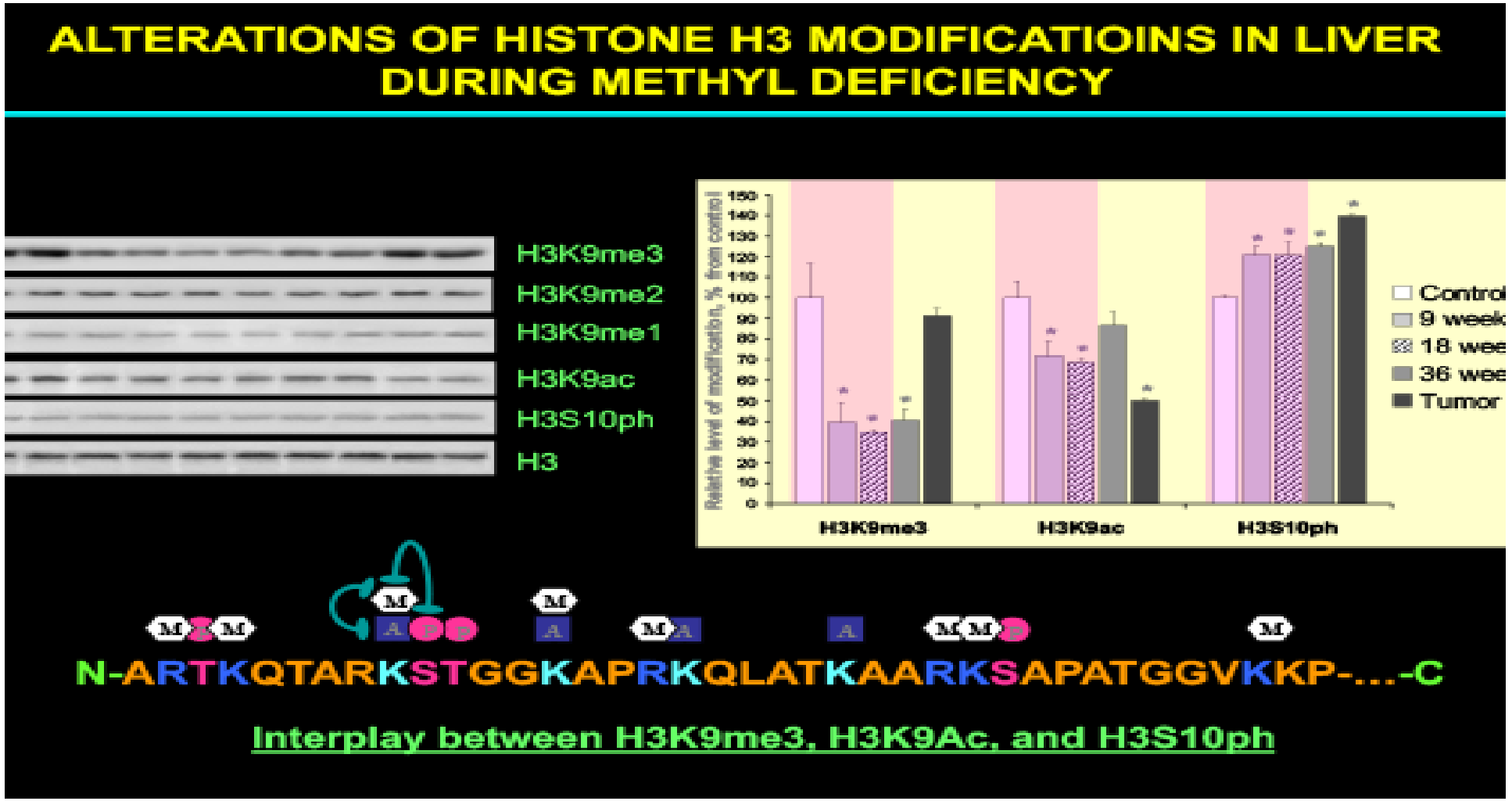


Weikun Xia et al. Science 2019;365:353-360

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Science AAAS

Histone H3 modifications



Epigenetic regulation

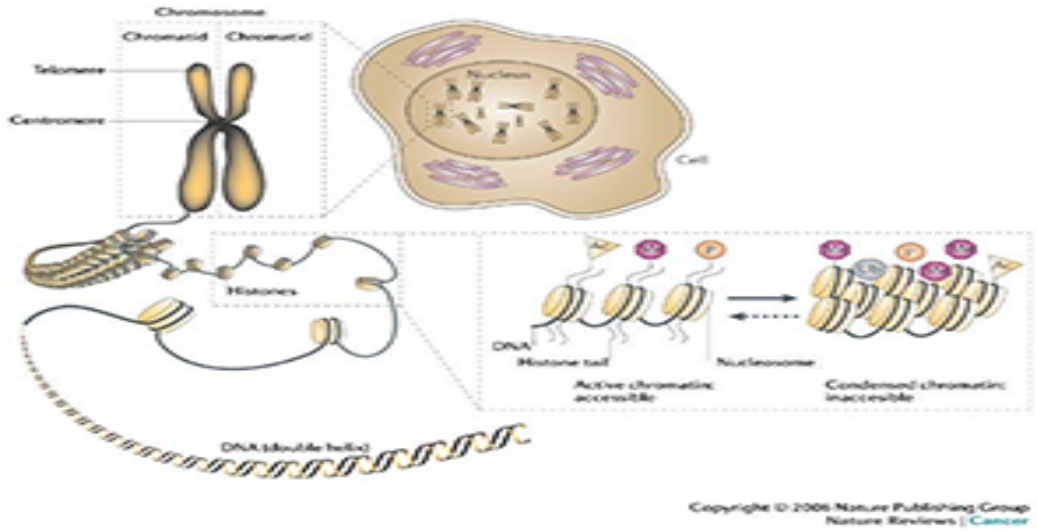
Epigenetic Gene Regulation:

Modification		Methylation			Acetylation
		Mono-methylation	Di-methylation	Tri-methylation	
DNA		Repression	--	--	--
Histone	H3K4	Activation	Activation	Activation	--
	H3K9	Activation	Repression	Repression	Activation
	H3K27	Activation	Repression	Repression	--
	H3K36	--	Repair	Activation	Activation
	H3K79	Activation	Activation	Activation Repression	--
	H3R17	--	Activation	--	--
	H4K5	--	--	--	Activation
	H4K8	--	--	--	Activation
	H4K12	--	--	--	Activation
	H4K16	--	--	--	Activation
	H4K20	Activation	Activation	Repression	--
	H4K16	--	--	--	Activation

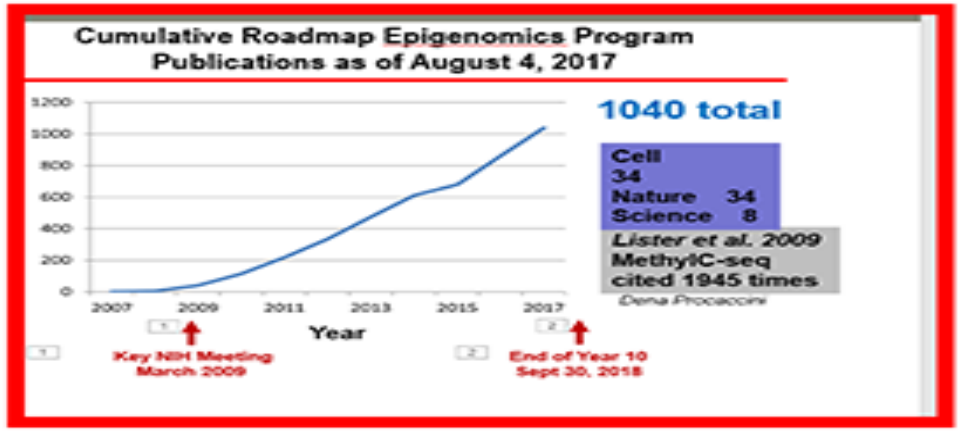


Epigenetics roadmap

Epigenetics Roadmap



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Nature Reviews | Cancer



Epigenetically Regulated Diseases:
Several cancers, autoimmune disorders, reproductive disorders, and neurobehavioral and cognitive dysfunctions

The NIH Roadmap Epigenomics Mapping Consortium was launched with the goal of producing a public resource of human epigenomic data to catalyze basic biology and disease-oriented research.

http://nihroadmap.nih.gov/epigenomics/

Epigenetics roadmap





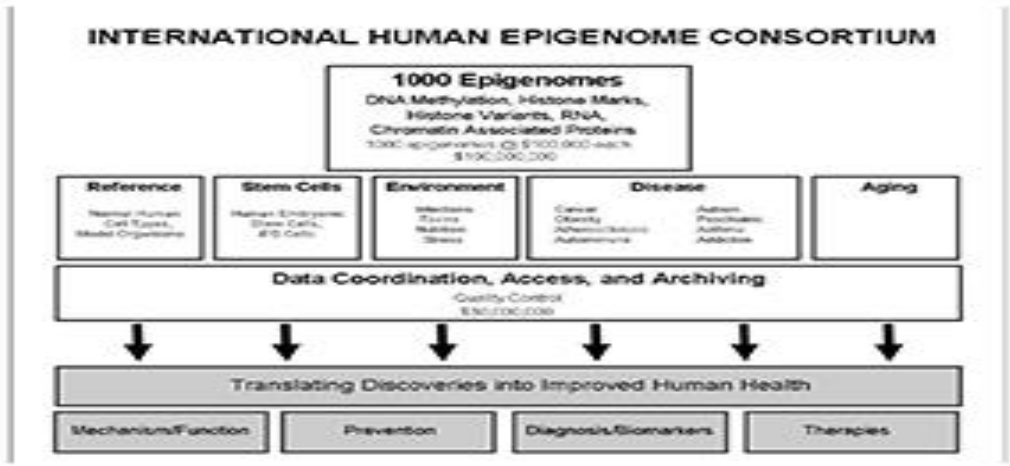
Epigenomics Program Budget

Component	FY08	FY09	FY10	FY11	FY12	FY13	FY14	FY15	Total
RFA 1: Mapping Centers	10	10	10	10	10				50
RFA 2: RM/IC Projects		4	8	12	16	20	16	12	88
RFA 3: Data Analysis/Coord	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	12
RFA 4: Tech Development	3.5	3.5	7	7	7	7	7		42
RFA 5: Discovery of Novel Marks	3.5	3.5	4	2	2				15
NCBI: Public access	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	12

= RFA released

8-Year Total $219 M
(plus $3M JUMPSTART)

Epigenome consortium







Participants in IHEC Meeting: Paris, Jan. 25-26, 2010

Australia
Austria
Canada
China
Euro. Comm. (EU)
France
Germany
Israel
Italy
Japan
Korea
Netherlands
Norway
Poland
Singapore
Spain
Sweden
Switzerland
UK
USA

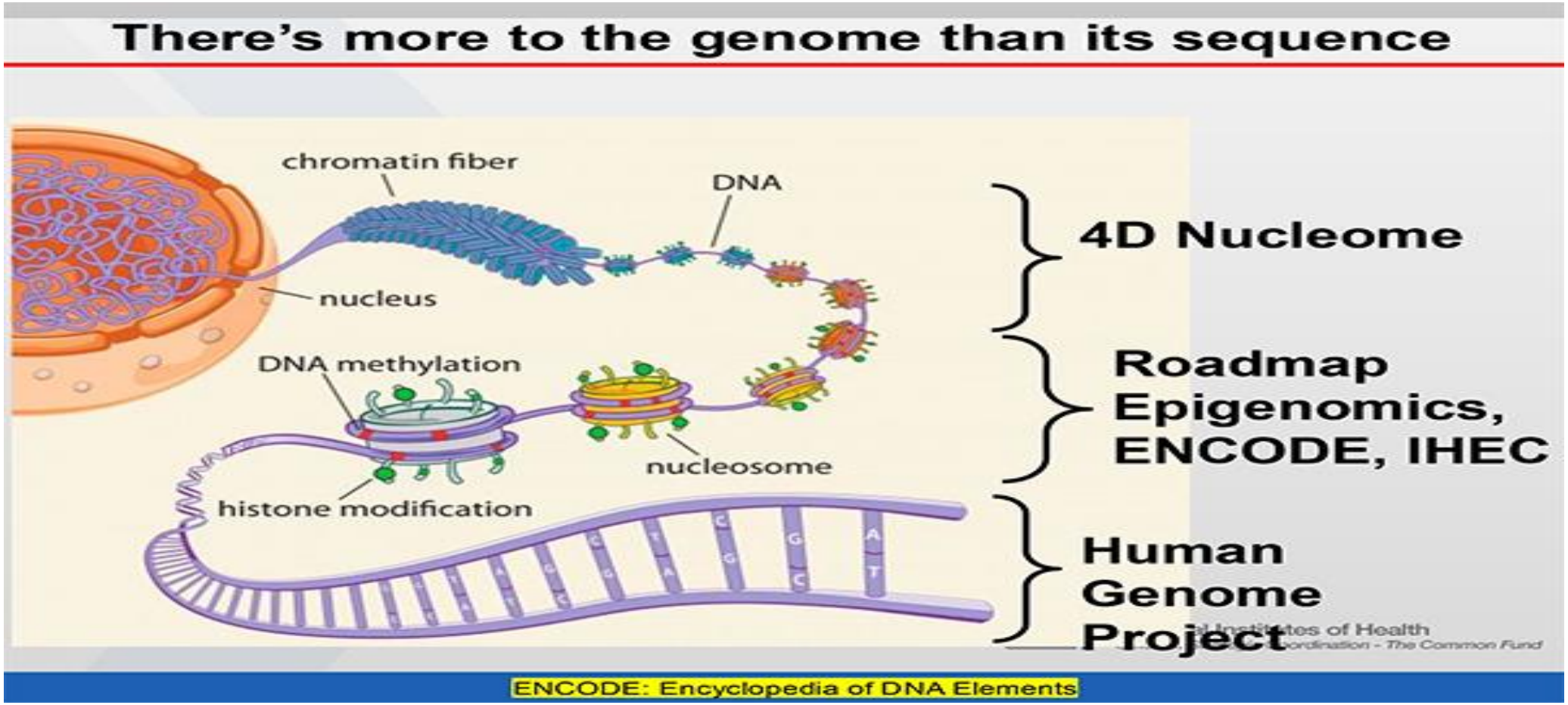
Funding Agencies
Consiglio Nazionale delle Ricerche, Italy
European Science Foundation
Genome British Columbia, Canada
German Research Foundation, Germany
National Natural Science Foundation, China
Netherlands Genomic Initiative, Netherlands
NIH, USA
Wellcome Trust, UK

Industrial Participants
Affymetrix
Genoscope
Novartis

Other
AACR

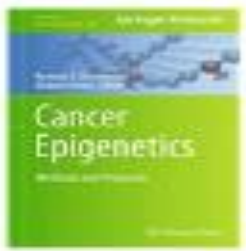
Publishers
Nature
Science

Genome sequence



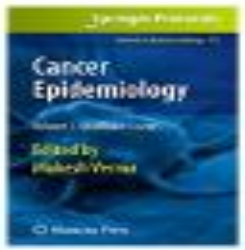
Books

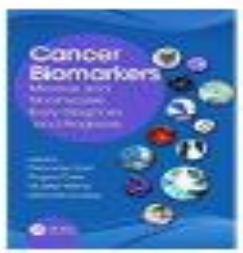








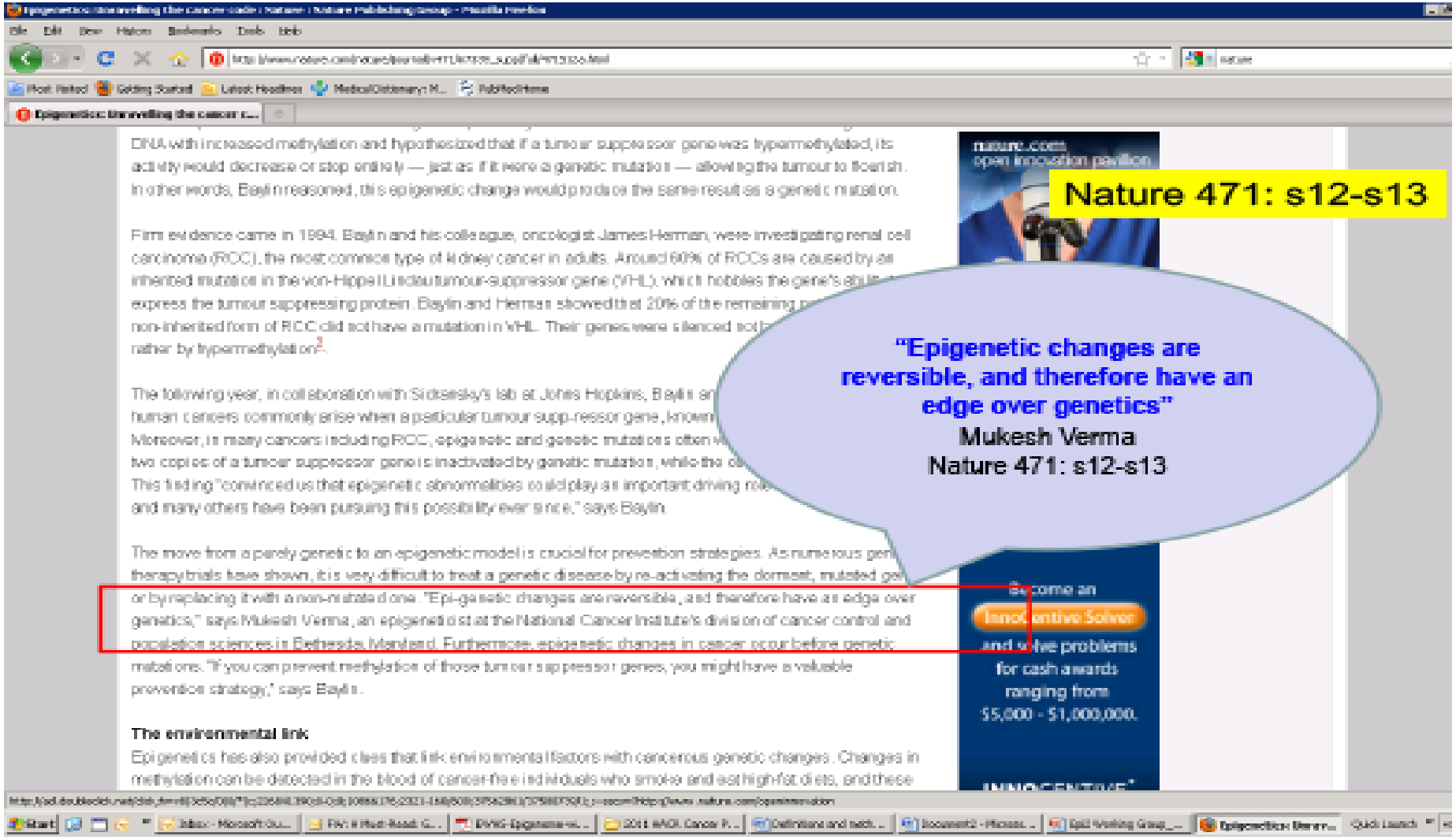




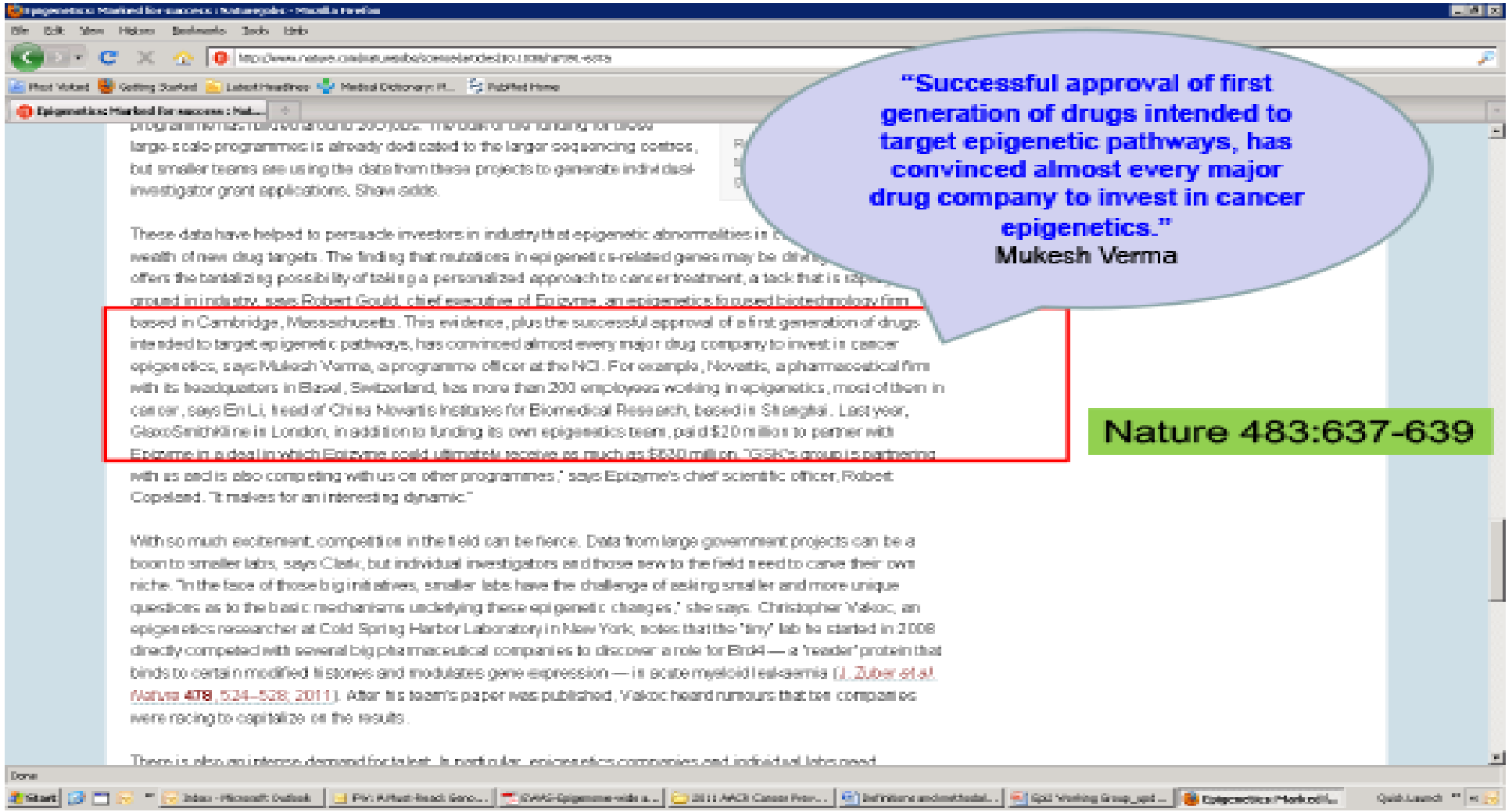


Books edited by Mukesh Verma

Epigenetic changes



Epigenetic drugs



Tumors and epigenetics

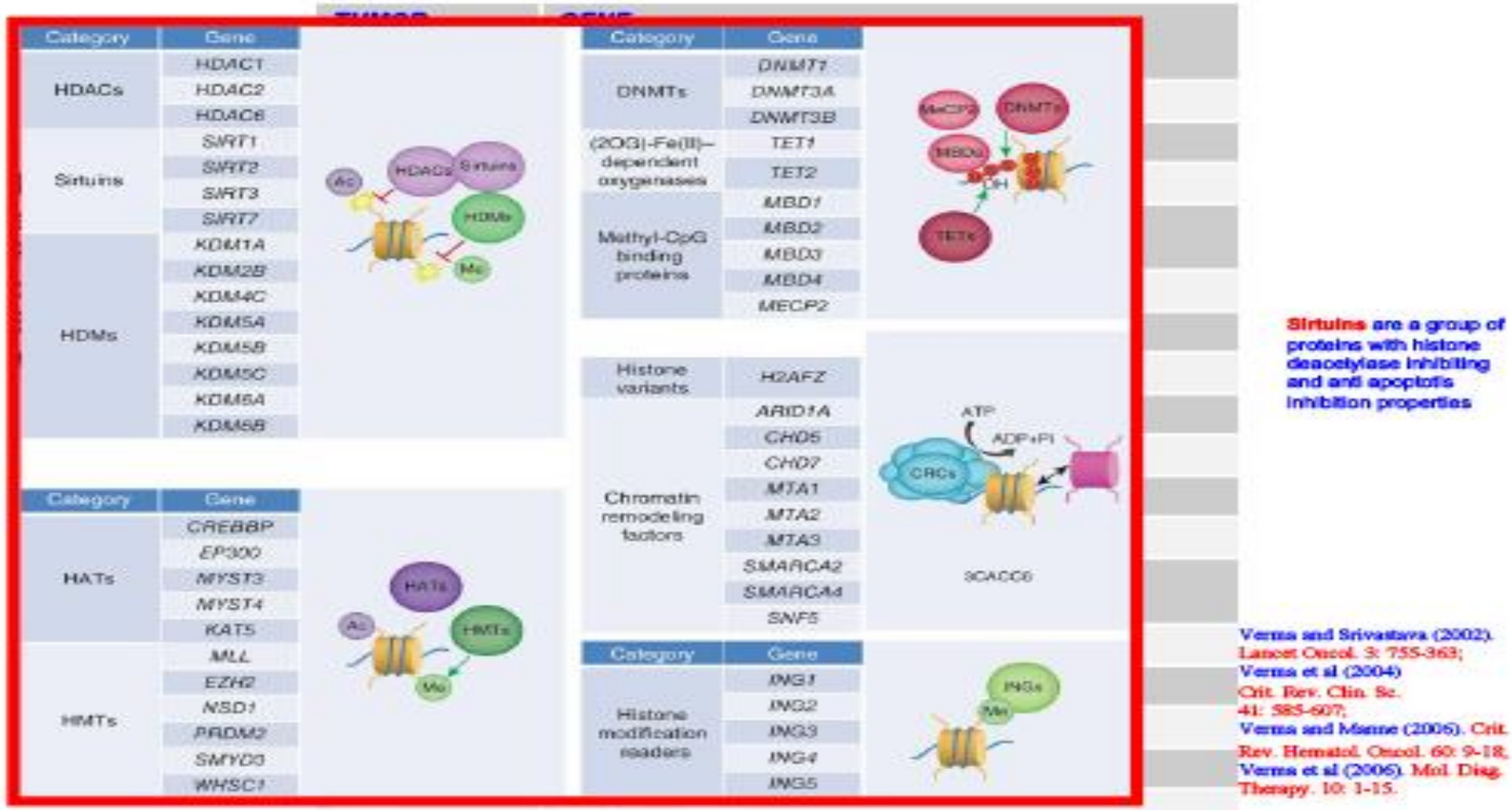
Tumor Types and Genes Regulated by Epigenetic Mechanism

TUMOR LOCATION	*GENE*
Breast	p16, BRCA1, GSTP1, DAPK, CDH1, TIMP-3
Brain	p16, p14^{ARF}, MGMT, TIMP-3
Bladder	p16, DAPK, APC
Colon	p16, p14^{ARF}, CRBP1, MGMT, hMLH1, DAPK, TIMP-3, APC
Endometrium	hMLH1
Esophagus	p16, p14^{ARF}, GSTP1, CDH1, APC
Head and Neck	p16, MGMT, DAPK
Kidney	p16, p14^{ARF}, MGMT, GSTP1, TIMP-3, APC
Leukemia	p15, MGMT, DAPK1, CDH1, p73
Liver	p16, CRBP1, GSTP1, APC
Lymphoma	p16, p15, CRBP1, MGMT, DAPK, p73
Lung	p16, p14^{ARF}, CRBP1, MGMT, GSTP1, DAPK, FHIT, TIMP-3, RARbeta, RASSF1A
Ovary	p16, BRCA1, DAPK
Pancreas	p16, MGMT, APC
Prostate	GSTP1, p27(kip1)
Stomach	p14^{ARF}, P16, APC, hMLH1, MGMT
Uterus	p16, p14^{ARF}, hMLH1

Silmitasertib is a group of procaine with histone deacetylase inhibitors and cytotoxic properties

Verma and Srivastava (2002) Lancet Oncol 3: 755-763
Verma et al (2004) Curr Rev Clin Sci 41: 585-607
Verma and Moore (2000) Curr Rev Biomed Oncol 00:9-18
Verma et al (2000) Mol Diag Therapy 10:1-15

Histone enzymes



Sirtuins are a group of proteins with histone deacetylase inhibiting and anti apoptotic inhibition properties

Verma and Srivastava (2002). Lancet Oncol. 3: 755-363;
Verma et al (2004) Crit. Rev. Clin. Sc. 41: 585-607;
Verma and Mamne (2006). Crit. Rev. Hematol. Oncol. 60: 9-18,
Verma et al (2006). Mol. Diag. Therapy. 10: 1-15.

Epigenetic drugs

Target	Drug	Clinical Trial
DNA Methylation	5-Azacytidine	Phase I/II
	5-Aza-2'deoxycytidine	Phase I/II
	FCD R	
	Zebularine	
	Procainamide	
	EGCG	Phase I
	Psamaplin A	
	Antisense Oligomers	Phase I
Histone deacetylase	Phenylbutyric acid	Phase I/II
Stimulates production of proteins with histone acetylase inhibiting and cell cycle inhibitor properties	SAHA (Suberoylanilide hydroxamic acid) or Vorinostat	Phase II
	Depsipeptide	Phase I/II
	Valproic Acid	Phase I/II

Adverse Experiences
SAHA
[illegible] .2007.
[illegible] 109:31.

- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible]

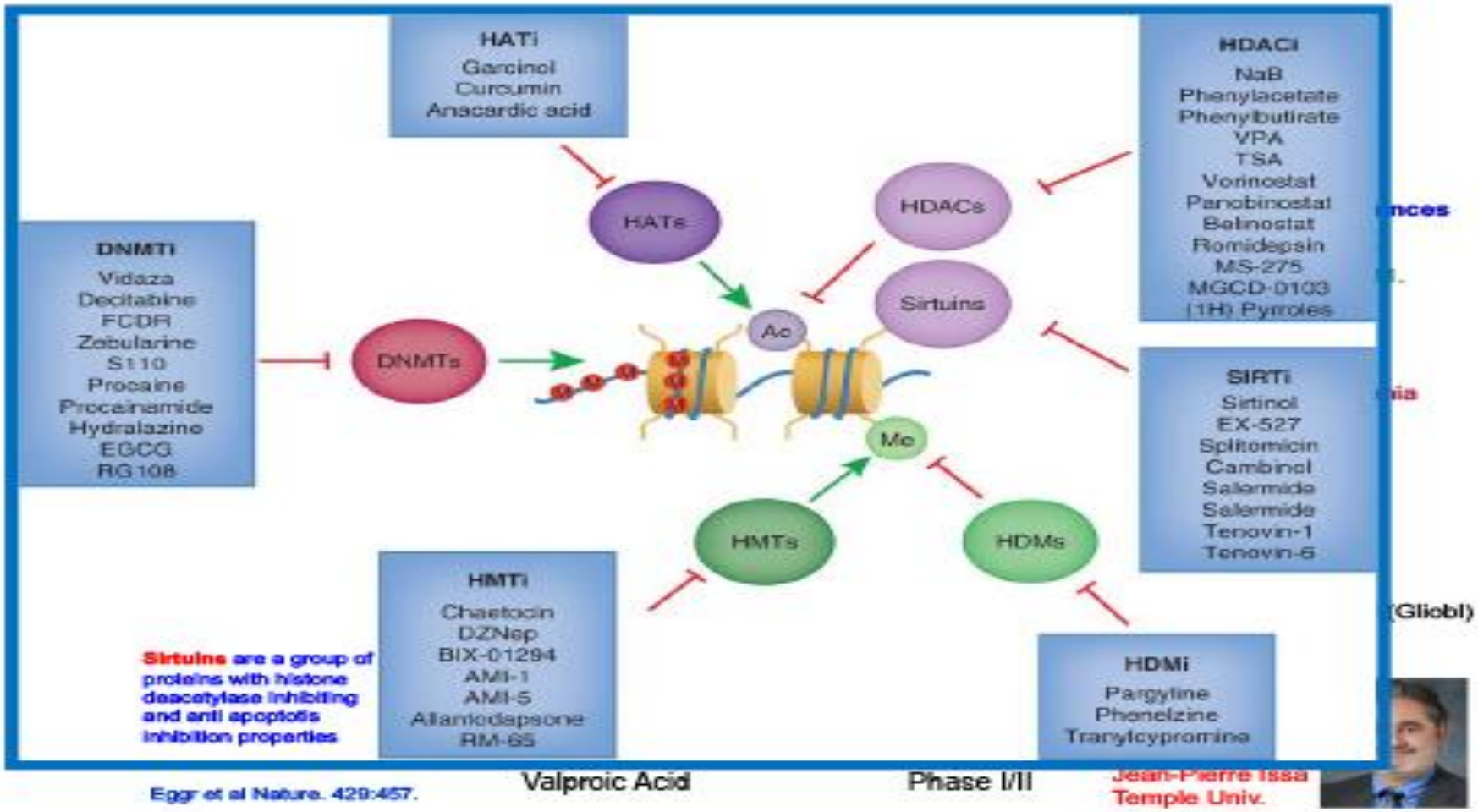
[illegible]

Nature 429:457

[illegible]
[illegible]



Methylation and acetylation enzymes



Histone deacetylase inhibitors

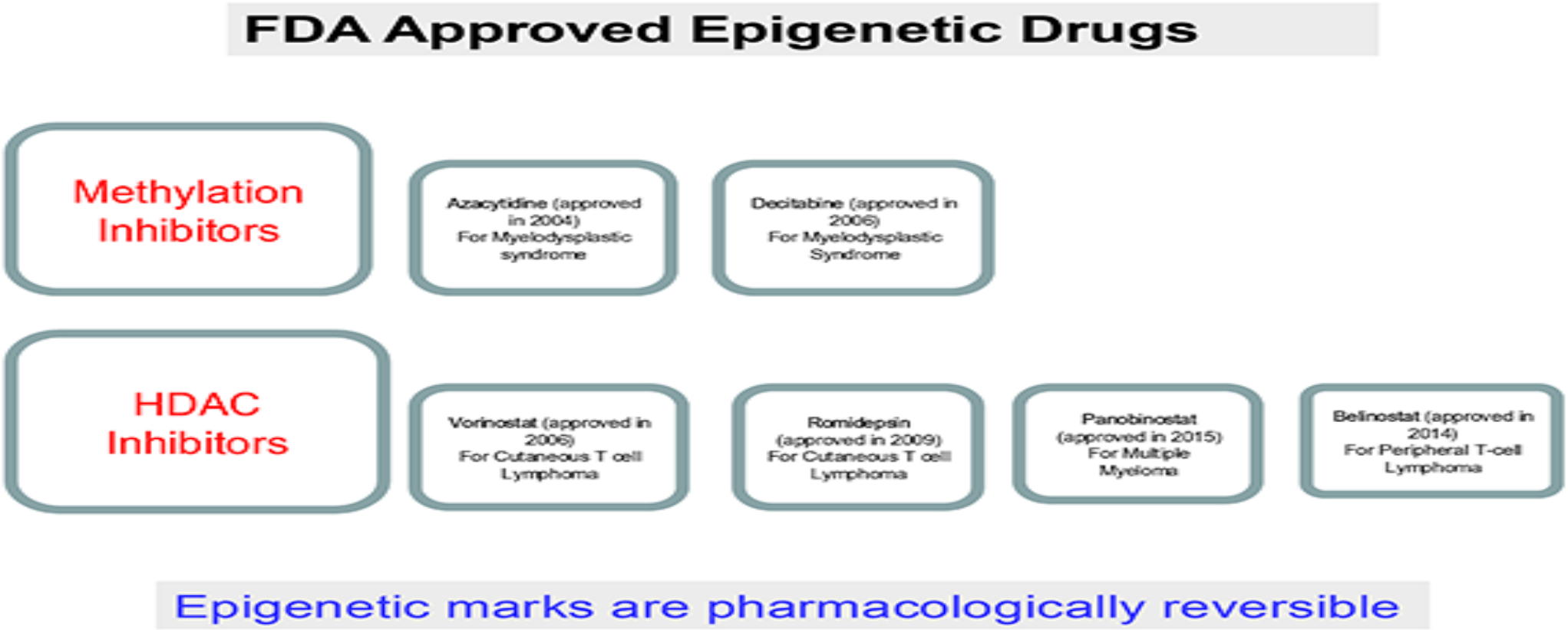
Table 4. Classification of Histone Deacetylase Inhibitors

Class	Compounds	Concentration needed for inhibition of histone deacetylase	Clinical trials	Notes
Short chain fatty acids	Phenylbutyrate	Milli-mole	Yes	Not ideal drug because of high dose requirement
Aliphatic compounds with hydroxamic acid	Trichostatin A, Suberoylanilide hydroxamic acid	Nano-mole Micro-mole	No Yes	Chelate Zn ion at catalytic site of HDAC.
Cyclic tetrapeptides	Trapoxin B, FK 228	Nano-molar Nano-molar	No Yes	FK228, a natural prodrug
Benzamides	MS-27-275	Micro-mole	Yes	Strong anti-tumor activity

Current Medicinal Chemistry, 2006, *13*, 2909-2919

HDAC 1, 2, 3, 8, 11 have been characterized (Khan, I , 2007)

FDA approved drugs



Phase I study

Phase I study of epigenetic modulation with 5-azacytidine and valproic acid in patients with advanced cancers.

Braiteh F, Soriano AO, Garcia-Manero G, Hong D, Johnson MM, Silva Lde P, Yang H, Alexander S, Wolff J, Kurzrock R. Clin Cancer Res.14(19):6296-301. (colorectal cancer, melanoma and breast cancer)

5 Azacytidine
S.C. daily for 10 days

+

Valproic Acid
Orally daily to titrate to 75-100 ug/ml

28 Days Cycle

55 people with Advanced cancer Median age 60

Peripheral blood
- Pyrosequencing
- Chip

Analysis Day 1, 10 and 28

- **The maximum tolerated dose was 75 mg/m(2) of 5-AZA in combination with valproic acid.**
- **Dose-limiting toxicities were neutropenic fever and thrombocytopenia, which occurred at a dose of 94 mg/m(2) of 5-AZA.**
- **Stable disease lasting 4 to 12 months (median, 6 months) was observed in 14 patients (25%).**

A significant decrease in global DNA methylation and induction of histone acetylation were observed.

The combination of 5-AZA and valproic acid is safe at doses up to 75 mg/m(2) for 5-AZA in patients with advanced malignancies.

5-azacytidine, valproic acid and ATRA

Safety and clinical activity of the combination of 5-azacytidine, valproic acid, and all-trans retinoic acid in acute myeloid leukemia and myelodysplastic syndrome.

Soriano et al. Blood. 110(7):2302-8.

- **Combination of 5-azacitidine (5-AZA), valproic acid (VPA), and ATRA in patients with acute myeloid leukemia or high-risk myelodysplastic syndrome.**
- **A total of 53 patients were treated.**
- **The overall response rate was 42%.**
- **A significant decrease in global DNA methylation and induction of histone acetylation were achieved.**
- **VPA blood levels were higher in responders.**
- **The combination studied is safe and has significant clinical activity.**

This clinical trial was registered at www.clinicaltrials.gov as no. NCT00326170.

Histone inhibitors

Histone Inhibitors in Clinical Trials (Clinicaltrials.gov)

STATUS	STUDY
Recruiting	Safety Study of the Histone Deacetylase Inhibitor, CHR-3996, in Patients With Advanced Solid Tumours
Recruiting	Phase II Study of Histone-Deacetylase Inhibitor ITF2357 in Refractory/Relapsed Lymphocytic Leukemia
Recruiting	phII Study of an HDAC Inhibitor in Very High-Risk Relapsed/Refractory Hodgkin's Lymphoma Patients
Recruiting	Phase IIA Study of the HDAC Inhibitor ITF2357 in Patients With JAK-2 V617F Positive Chronic Myeloproliferative Diseases
Recruiting	Phase II Trial of the Histone-Deacetylase Inhibitor ITF2357 Followed by Mechlorethamine in Relapsed/Refractory Hodgkin's Lymphoma Patients
Recruiting	HDAC Inhibitor Vorinostat (SAHA) With Capecitabine (Xeloda) Using a New Weekly Dose Regimen for Advanced Breast Cancer
Recruiting	Valproic Acid, Temozolomide, and Radiation Therapy in Treating Patients With Glioblastoma Multiforme
Recruiting	Study of Vorinostat (MK0683) an HDAC Inhibitor, or Placebo in Combination With Bortezomib in Patients With Multiple Myeloma
Recruiting	Study of Vorinostat (MK0683), an HDAC Inhibitor, in Combination With Bortezomib in Patients With Relapsed or Refractory Multiple Myeloma
Completed	A Phase II Study of Epigenetic Therapy to Overcome Chemotherapy Resistance in Refractory Solid Tumors
Recruiting	Sorafenib and LBH589 in Hepatocellular Carcinoma (HCC)
Recruiting	Phase II Study of Valproic Acid With FEC100 for Patients With Locally Advanced Breast Cancer

Total : 84 studies

http://clinicaltrials.gov/ct2/results?term=histone+inhibitors&pg=4

Methylation inhibitors

Methylation Inhibitors in Clinical Trials (Clinicaltrials.gov)

STATUS	STUDY
Completed	A Phase II Study of Epigenetic Therapy to Overcome Chemotherapy Resistance in Refractory Solid Tumors
Active Not Recruiting	Azacitidine and Valproic Acid in Patients With Advanced Cancers
Recruiting	Azacitidine With MS-275 in Treating Patients With Myelodysplastic Syndromes, Chronic Myelomonocytic Leukemia, or Acute Myeloid Leukemia
Active Not Recruiting	PhIII-Azacitidine Plus Valproic Acid and Eventually Arsenic in Intermediate II and High Risk MDS
Recruiting	Decitabine With or Without Interferon Alfa-2b in Treating Patients With Unresectable or Metastatic Solid Tumors
Recruiting	Hydralazine Valproate for Cervical Cancer
Recruiting	Hydralazine Valproate for Ovarian Cancer
Recruiting	Decitabine in Treating Patients With Previously Untreated Acute Myeloid Leukemia
Recruiting	Chronic Hepatitis C Non-Responder Study With Ada Met and Ribavirin
Recruiting	Azacitidine, Docetaxel, and Prednisone in Treating Patients With Metastatic Prostate Cancer That Did Not Respond to Hormone Therapy
Recruiting	Low Dose Decitabine + Interferon Alfa-2b in Advanced Renal Cell Carcinoma

Total : 51 studies

http://clinicaltrials.gov/ct2/results?term=methylation+inhibitors

Schering-Plough (Decitabine (5-aza-Deoxycytadine) Trial for melanoma) (8 hrs to inactivate DNMT1)
Bristol-Myers Squibb (other compounds)

Three-drug combination



Novel drug combination shows promise in advanced HER2-negative breast cancer treatment

A novel three-drug combination achieved notable responses in patients with advanced HER2-negative breast cancer, according to new research directed by investigators from the Johns Hopkins Kimmel Cancer Center.

The treatment included a histone deacetylase inhibitor, a drug that causes a chemical change to stop tumor cells from dividing, with two types of immunotherapy known as checkpoint inhibitors, which unharness the power of the immune response against cancer.

The multicenter phase IB study, which aimed to improve response to checkpoint inhibitors by sensitizing the tumor microenvironment, found that the combination therapy resulted in a 25%

Three-drug combination achieved notable responses in patients with advanced HER2-negative breast cancer

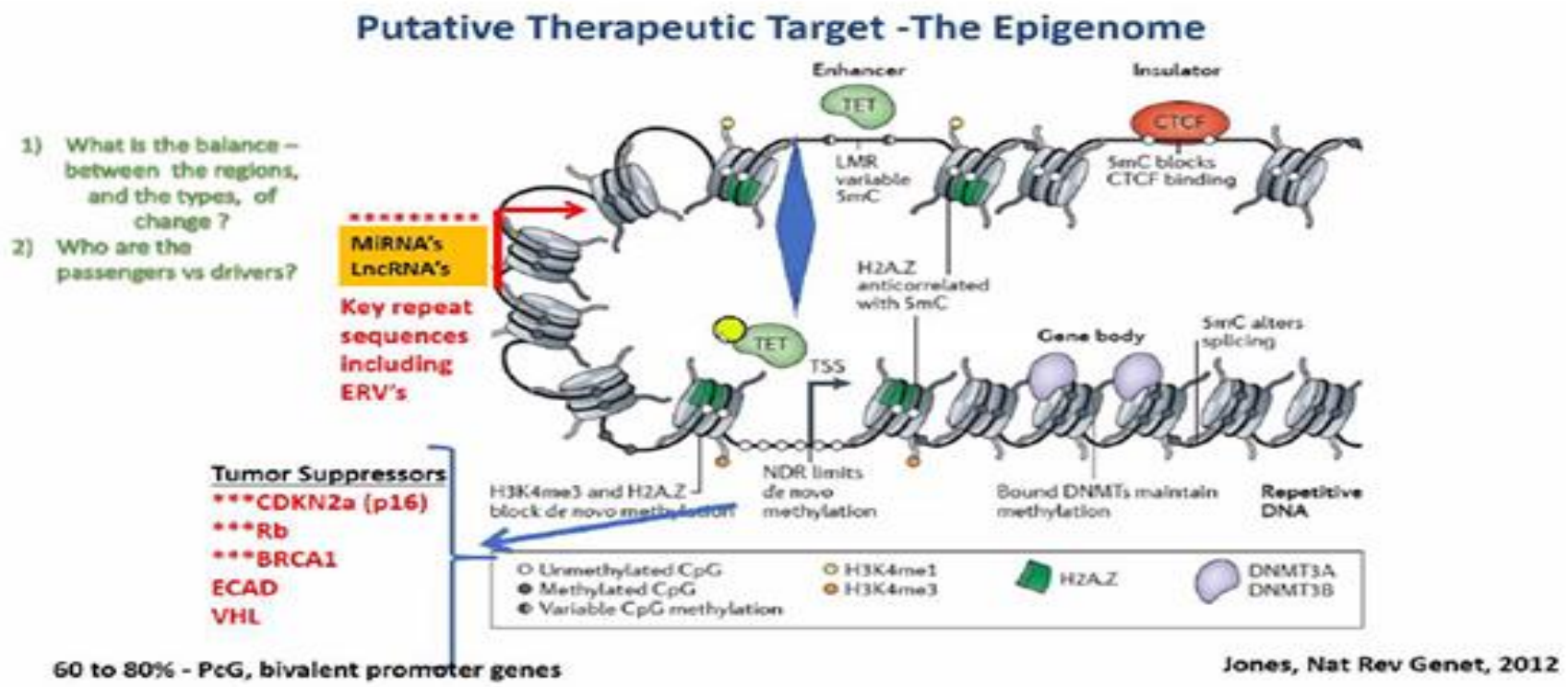
HDAC (entinostat)
Drug causing chemical change to stop tumor cell from dividing
Checkpoint inhibitors
PD-1/PD-L1 inhibitor nivolumab
CTLA-4 inhibitor ipilimumab

25% reduction in response rate in advanced breast cancer patients for 6 months (tumor either destroyed or reduced)

HER-2. Human Epidermal Growth Factor Receptor

Nature Cancer. February 2024

Therapeutic target



Epigenetics of cancer type

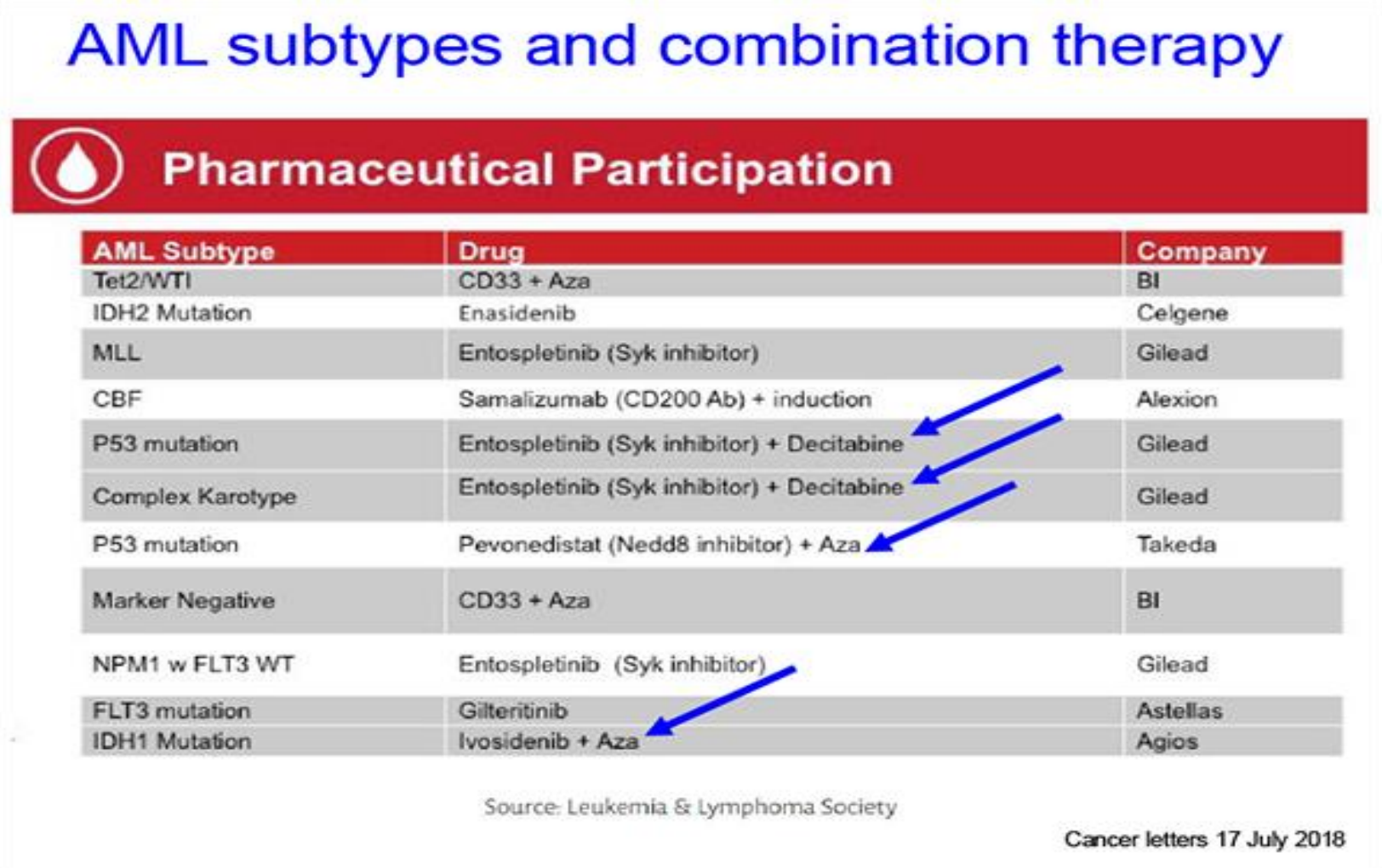
Tumor Types and Genes Regulated by Epigenetic Mechanism

TUMOR LOCATION	GENE
Breast	p16, BRCA1, GSTP1, DAPK, CDH1, TIMP-3
Brain	p16, $p14^{ARF}$, MGMT, TIMP-3
Bladder	p16, DAPK, APC
Colon	p16, $p14^{ARF}$, CRBP1, MGMT, hMLH1, DAPK, TIMP-3, APC
Endometrium	hMLH1
Esophagus	p16, $p14^{ARF}$, GSTP1, CDH1APC
Head and Neck	p16, MGMT, DAPK
Kidney	p16, $p14^{ARF}$, MGMT, GSTP1, TIMP-3, APC
Leukemia	p15, MGMT, DAPK1, CDH1, p73
Liver	p16, CRBP1, GSTP1, APC
Lymphoma	p16, p15, CRBP1, MGMT, DAPK, p73
Lung	p16, $p14^{ARF}$, CRBP1, MGMT, GSTP1, DAPK, FHIT, TIMP-3, RARbeta, RASSF1A
Ovary	p16, BRCA1, DAPK
Pancreas	p16, MGMT, APC
Prostate	GSTP1, p27(kip1)
Stomach	$p14^{ARF}$, P16, APC, hMLH1, MGMT

Sirtuins are a group of proteins with histone deacetylase inhibiting and anti apoptotis inhibition properties

Verma and Srivastava (2002). Lancet Oncol. 3: 755-363;
Verma et al (2004) Crit. Rev. Clin. Sc. 41: 585-607;
Verma and Manne (2006). Crit. Rev. Hematol Oncol. 60: 9-18;
Verma et al (2006). Mol. Diag. Therapy. 10: 1-15.

AML subtypes and combination therapy



Combination epigenetic therapy



Combination epigenetic therapy has efficacy in patients with refractory advanced non-small cell lung cancer.

Juergens RA, Wrangle J, Vendetti FP, Murphy SC, Zhao M, Coleman B, Sebree R, Rodgers K, Hooker CM, Franco N, Lee B, Tsai S, Delgado IE, Rudek MA, Belinsky SA, Herman JG, Baylin SB, Brock MV, Rudin CM.

Department of Oncology, Johns Hopkins University, Baltimore, Maryland 21231, USA.

Abstract

Epigenetic alterations are strongly associated with the development of cancer. We conducted a phase II trial of combined epigenetic therapy with azacitidine and entinostat, inhibitors of DNA methylation and histone deacetylation, respectively, in extensively pretreated patients with recurrent metastatic non-small cell lung cancer. This therapy is well tolerated, and objective responses were observed, including a complete response and a partial response in a patient who remains alive and without disease progression approximately 2 years after completing protocol therapy. Median survival in the entire cohort was 6.4 months (95% CI 3.8–9.2), comparing favorably with existing therapeutic options. Demethylation of a set of 4 epigenetically silenced genes known to be associated with lung cancer was detectable in serial blood samples in these patients and was associated with improved progression-free (P = 0.034) and overall survival (P = 0.035). Four of 19 patients had major objective responses to subsequent anticancer therapies given immediately after epigenetic therapy. Significance: This study demonstrates that combined epigenetic therapy with low-dose azacitidine and entinostat results in objective, durable responses in patients with solid tumors and defines a blood-based biomarker that correlates with clinical benefit.

Comment in

A combined epigenetic therapy equals the efficacy of conventional chemotherapy in refractory advanced non-small cell lung cancer. [Cancer Discov. 2011]

Publication Types, MeSH Terms, Substances, Grant Support

Epigenetic Therapy for Colorectal Cancer

Vivek Vaish, Tripti Khare, Mukesh Verma, and Sharad Khare

Methods Mol Biol. 2015;1238:771-82. doi: 10.1007/978-1-4939-1804-1_40

Epigenetic alterations

Epigenome Reprogramming and Epigenetic Editing

Table. Selected epigenomic editing companies

Company, Year Founded	Recent Funding Events	Selected ASGCT 2023 Presentations[b]
Chroma Medicine, 2021	$125M Series A (November 2021) $135M Series B (March 2023)	Development of a Human PCSK9-Targeting Epigenetic Editor with Durable, Near-Complete In Vivo Silencing Efficiency Multiplexed Editing without Chromosomal Rearrangements Using Epigenetic Editors
Epic Bio, 2022	$55M Series A (July 2022)	EPI-321: A Potential Cure for FSHD
Modalis Therapeutics, 2016[a]		Advancing Epigenetic Editing with CRISPR-GNDM: Novel Muscle-Tropic AAV Vectors Deliver Promising Single-Dose Treatment for LAMA2-CMD
Navega Therapeutics, 2018	$3.8M SBIR/NCI (September 2019) $2M NINDS (June 2021)	N/A
Tune Therapeutics, 2020	$40M Series A (December 2021)	Transient Delivery of Epigenome Editors Stably Represses PCSK9 and Lowers LDL Cholesterol in Nonhuman Primates
Rejuvenate Bio, 2017	$10M Series A (April 2021)	Relevance of Animal Data for Human Health Programs

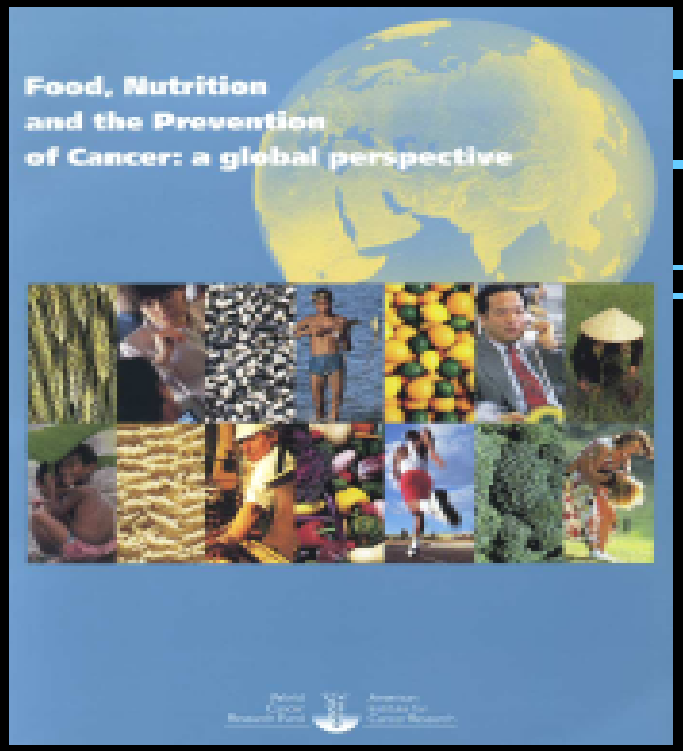
[a]Named EdiGene when founded in 2016 and renamed Modalis Therapeutics in 2019.
[b]Oral abstract session or scientific symposium.

Epigenetic reprogramming refers to the locus-specific targeting of epigenetic enzymes to rewrite the local epigenetic landscape of an endogenous genomic site, often with the aim of transscriptional reprogramming.

FSHD: Facioscapulohumeral muscular dystrophy; CRISPR: clustered regularly interspaced short palindromic repeats; CMD: congenital muscular dystrophy

Diet and cancer

DIET AND CANCER: FOCUS ON PREVENTION



Cancer is principally caused by environmental factors, of which the most important are tobacco, diet and factors related to diet, including body mass and physical activity, and exposures in the workplace and elsewhere.

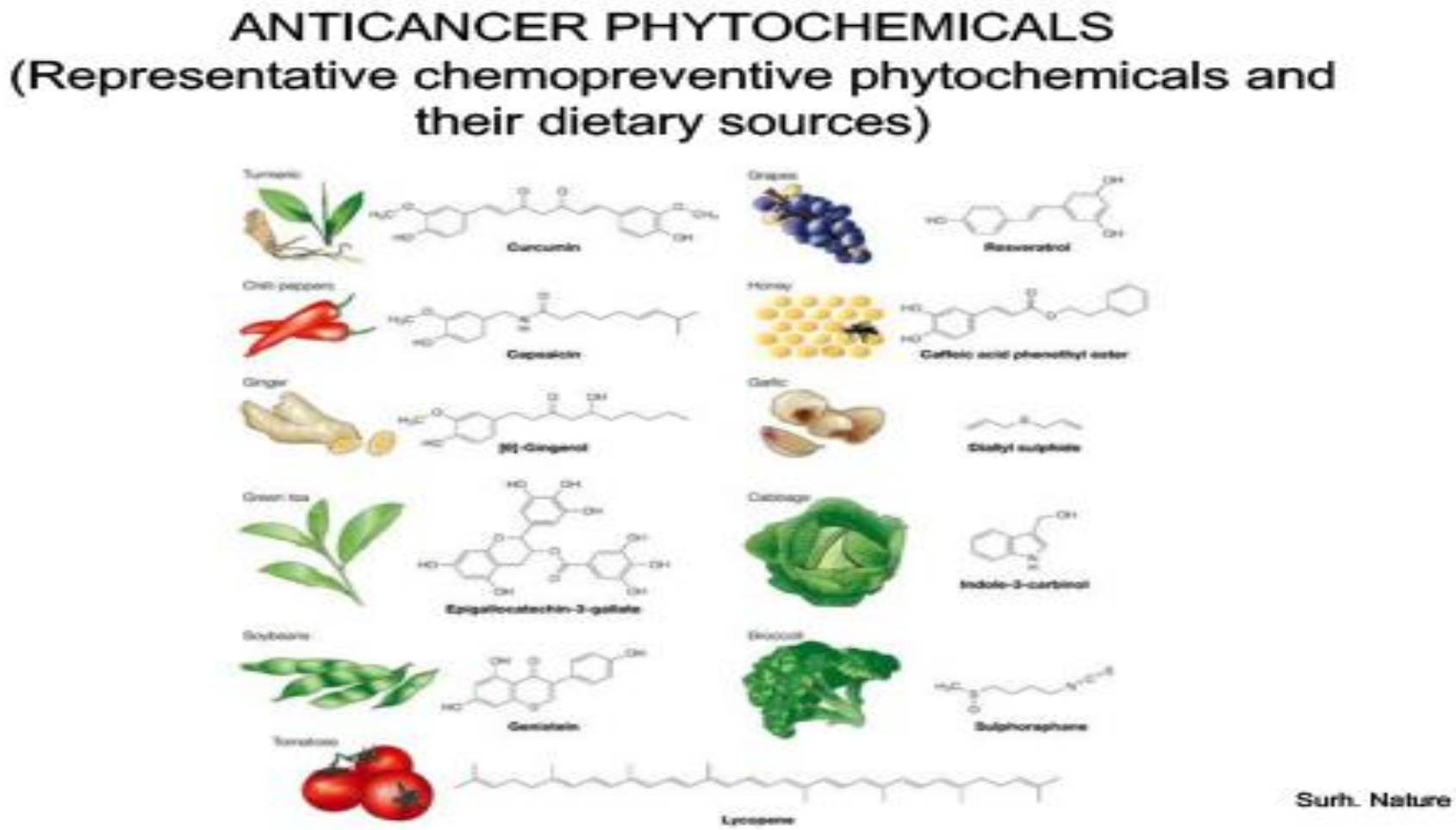
Between 30% and 40% of cancer cases throughout the world are preventable by feasible dietary means.

- Understanding the determinants of the earliest detectable phenotypes in initiated cells
- Uncovering the molecular mechanisms of action of dietary nutrients leading to cancer formation and prevention
- Defining effects of dietary compounds not only on cancer cells but on normal and precancerous cells
- Determining factors that can modulate effect of diet

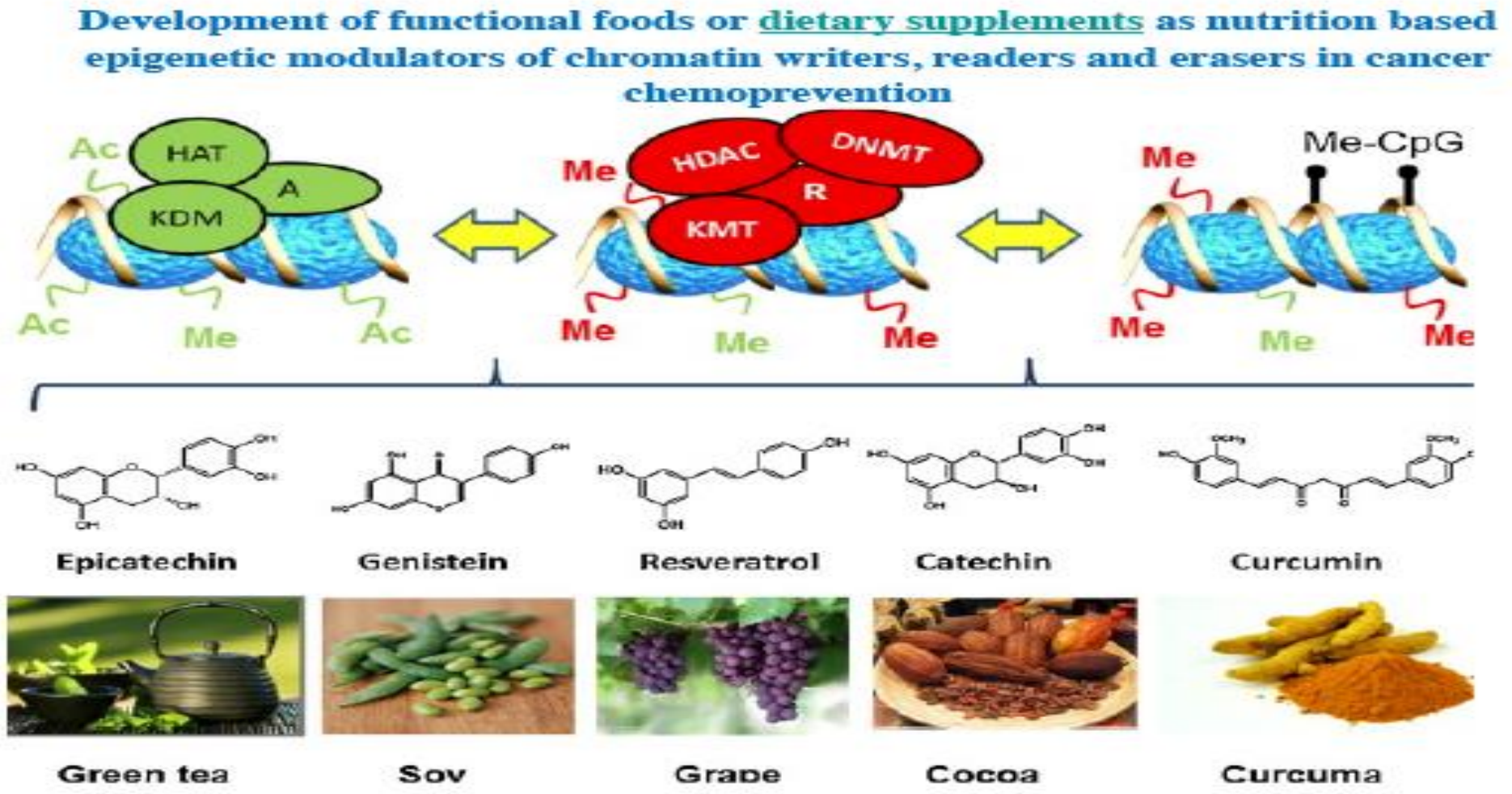
Methyl deficiency



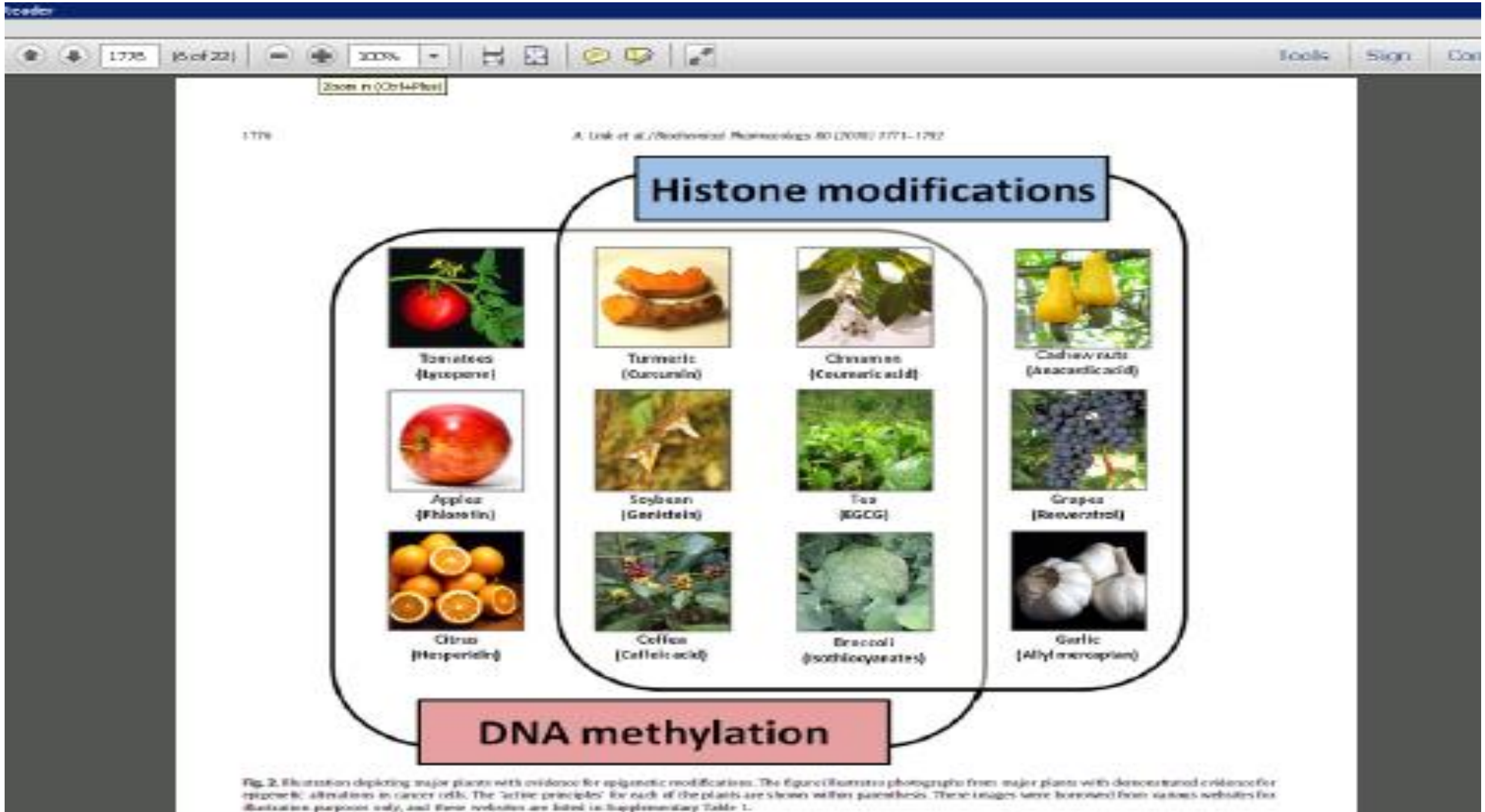
Anticancer phytochemicals



Dietary supplements



Epigenetic foods



Myplate







https://www.myplate.gov/

Mobile food record



Conclusions

Conclusions

- Epigenetic regulation is needed for normal development.
- External and internal environment contribute to alterations in epigenetic components and gene expression resulting in disease initiation and development.
- Epigenetic changes are reversible.
- Epigenetic inhibitors have been used successfully in combination therapy.

