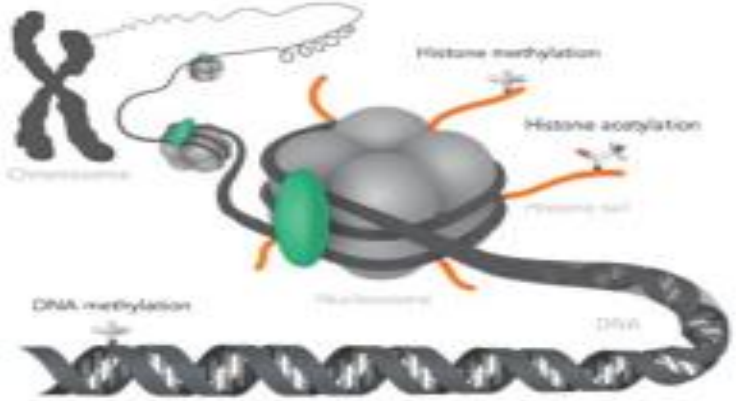
Epigenetics and cancer

National Cancer Institute

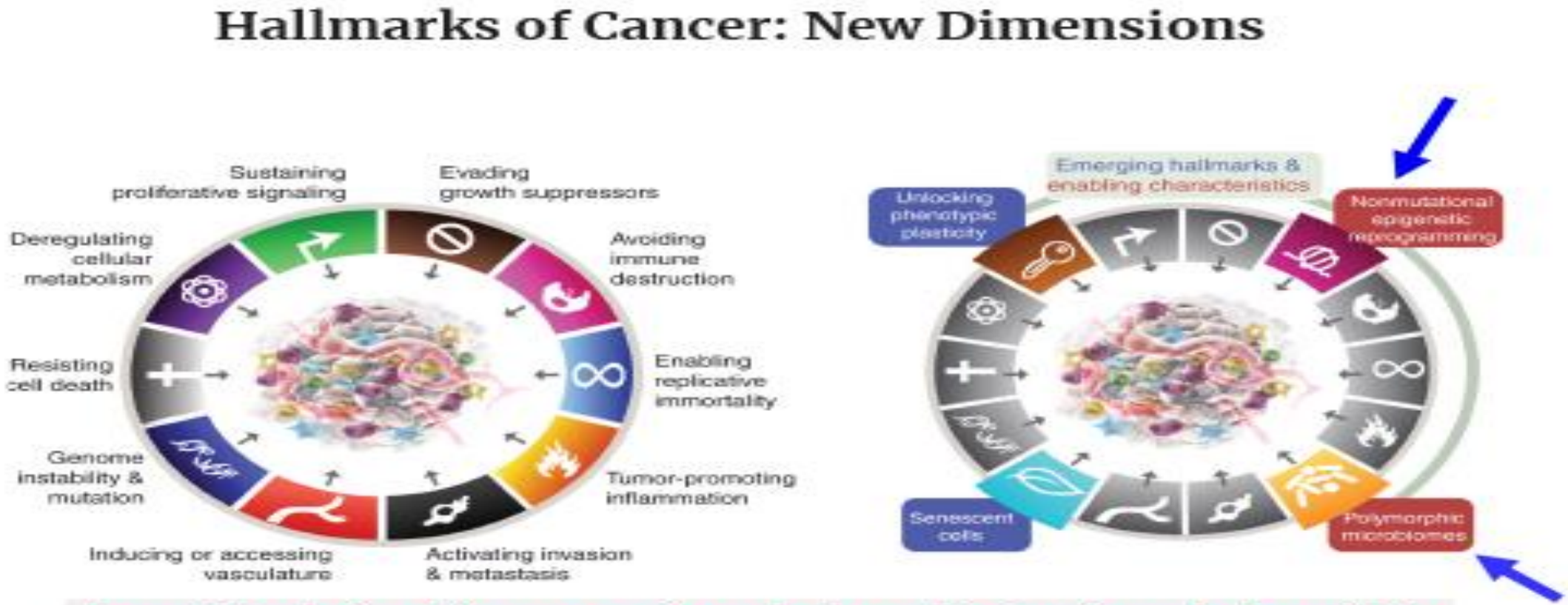
Epigenetics and Cancer



Mukesh Verma, Ph.D.
Chief, Methods and Technologies Branch
Program Director,
Epidemiology and Genomics Research Program
DCCPS, NCI, NIH

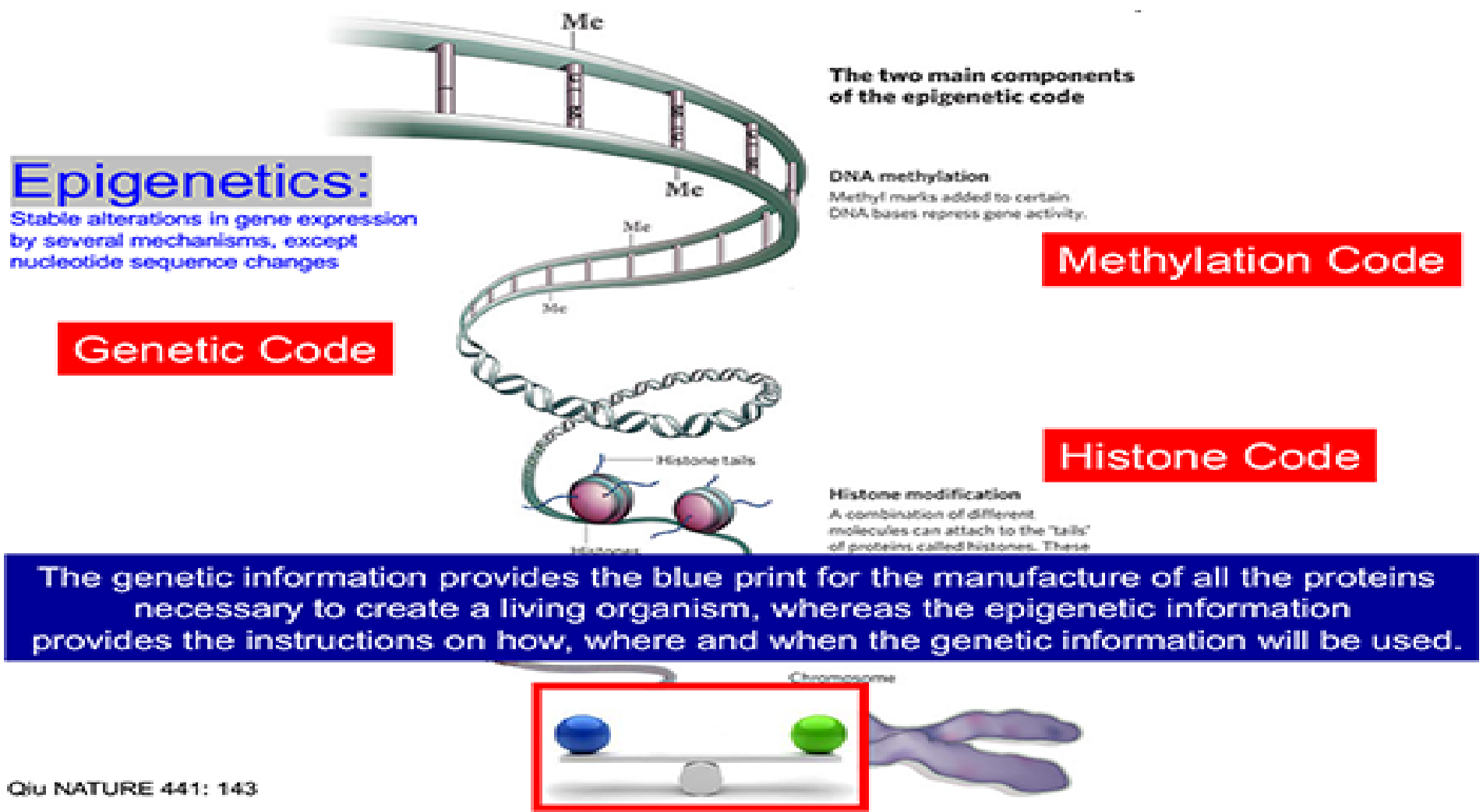
Fig. Credit: https://horizondiscovery.com/en/applications/cell-line/epigenetics

Hallmarks of cancer



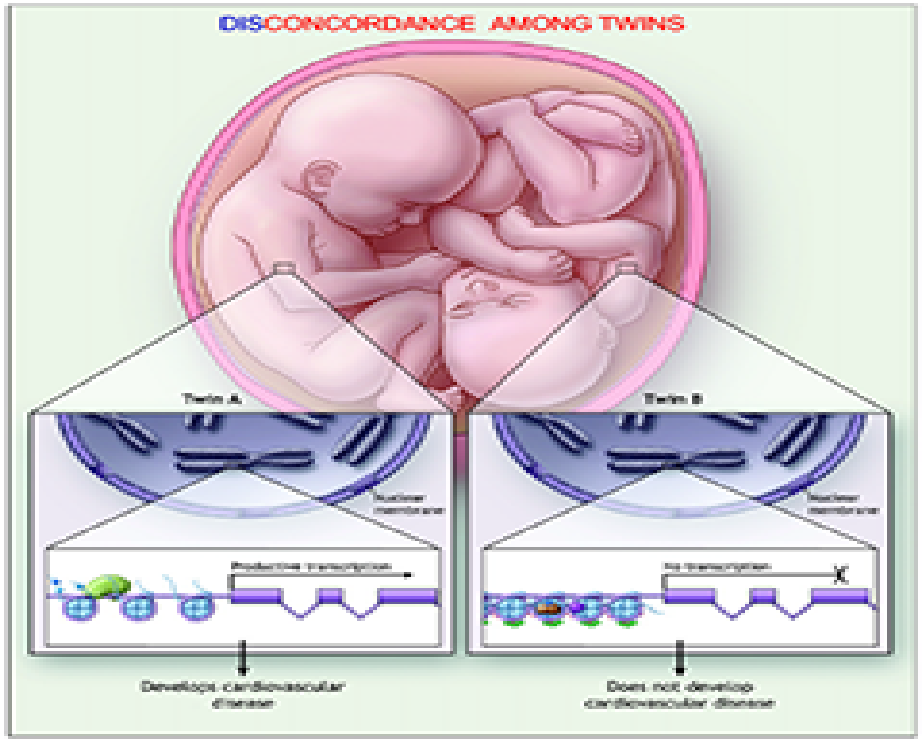
Epigenetics

Epigenetics



DNA and destiny

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



Epigenetic predisposition to angiogenesesis? Individual? Populations?

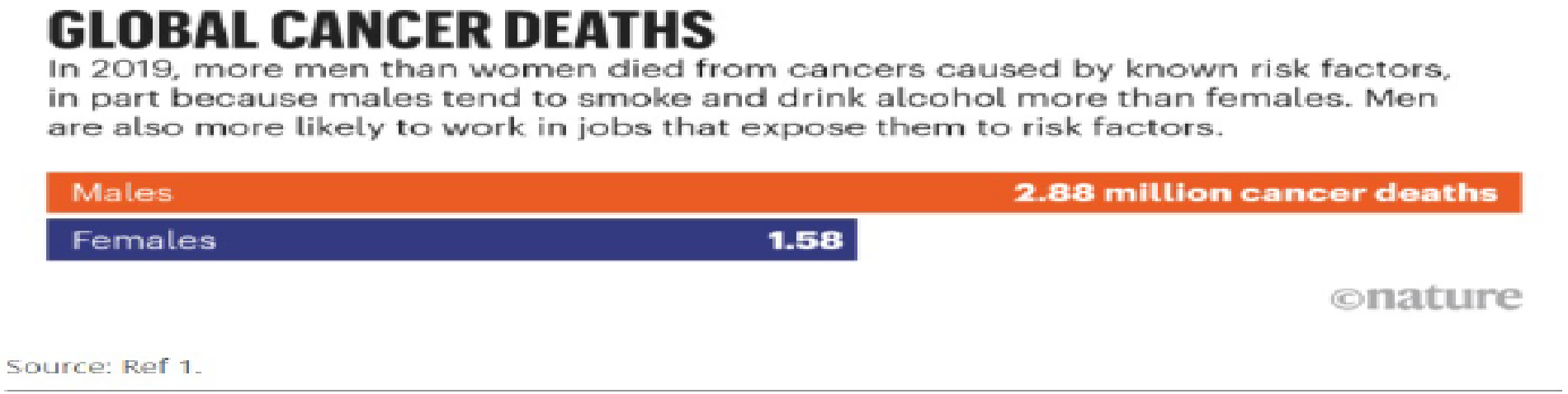
Pharmacogenomics and pharmacoepigenomics (personalized medicine)

Microenvironment, microbiome, and gene expression

GWAS and EWAS

Adapted from Matouk and Marsden Circ Res 102:873

Global cancer deaths

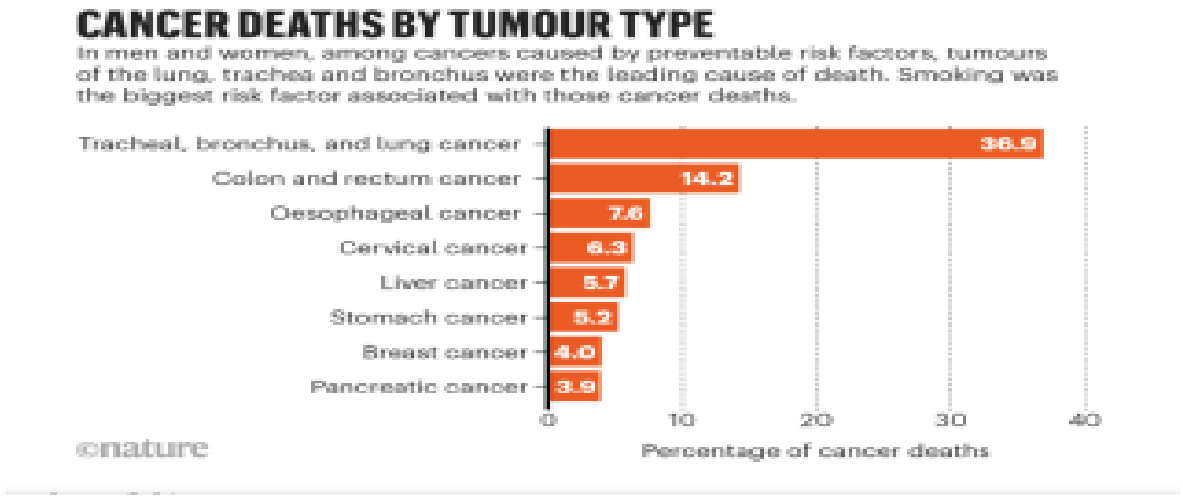


Source: Ref 1.

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

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

Cancer tumor deaths



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

Cancer continuum

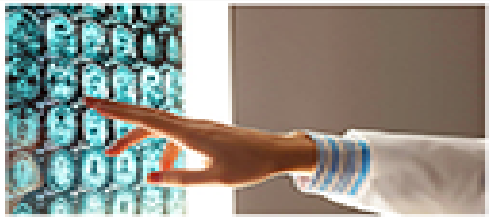
DCCPS covers cancer continuum

Prevention

Tobacco, physical activity, diet, sun, environment, HPV immunization

Early Detection

Breast, cervical, colorectal cancer screening



Diagnosis

Incidence, Stage at diagnosis

Treatment

Trends in cancer treatment

Life After Cancer

Financial burden of cancer care, Cancer survivorship

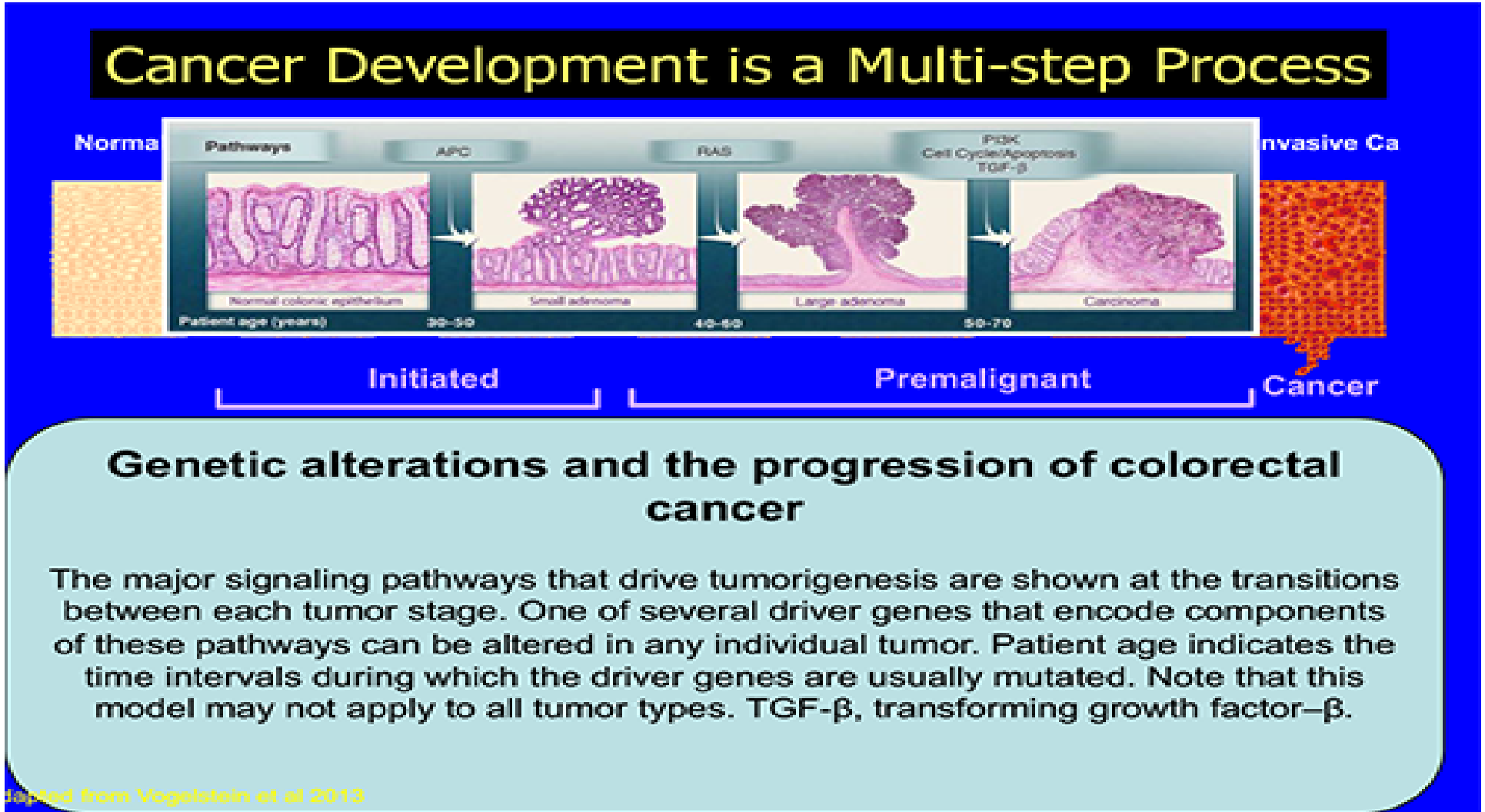
End of Life

Mortality, Person – years of life lost

Prevention → Cancer recurrence, Secondary cancer

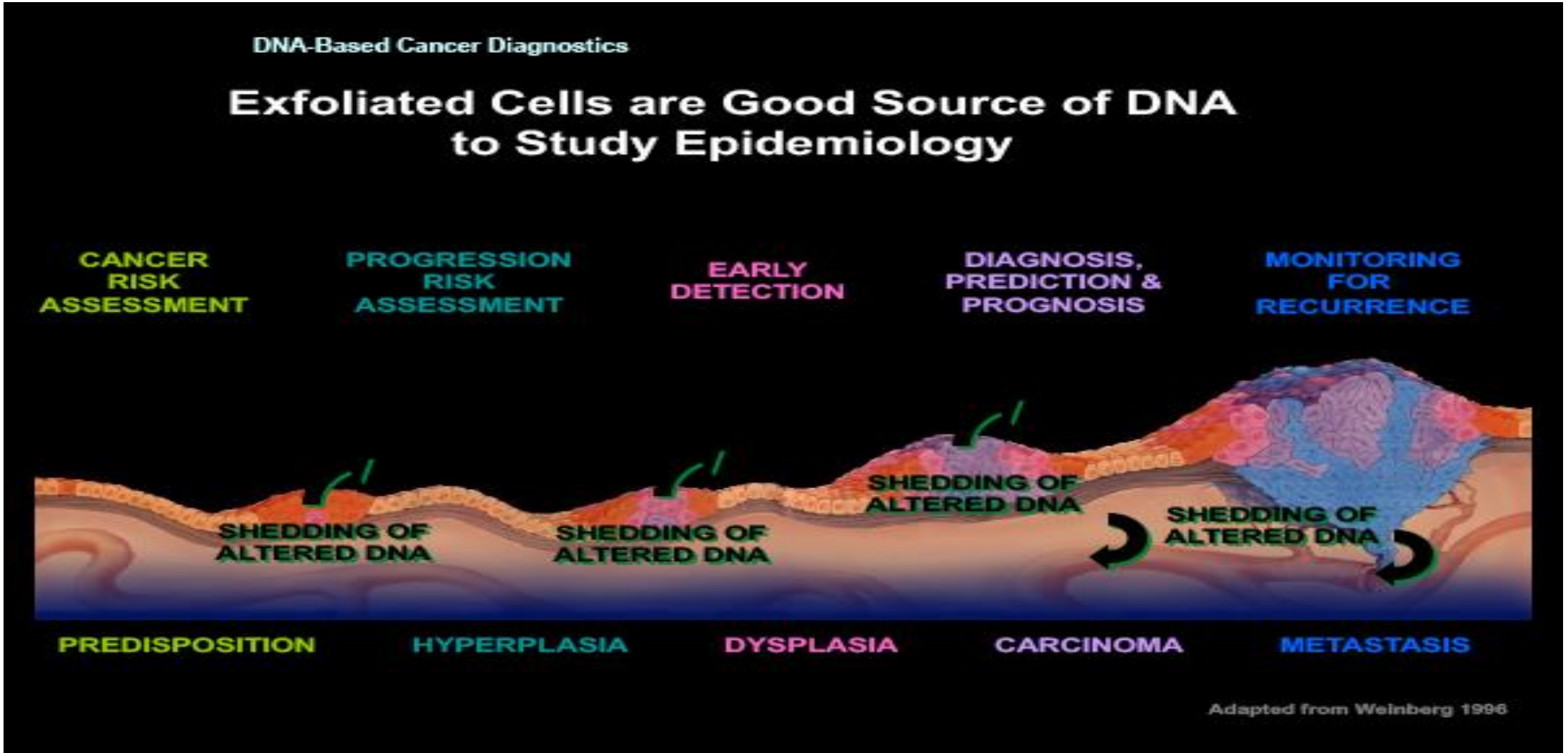
Prevention: restoring transcription, halting progression, or stopping metastasis

Cancer development

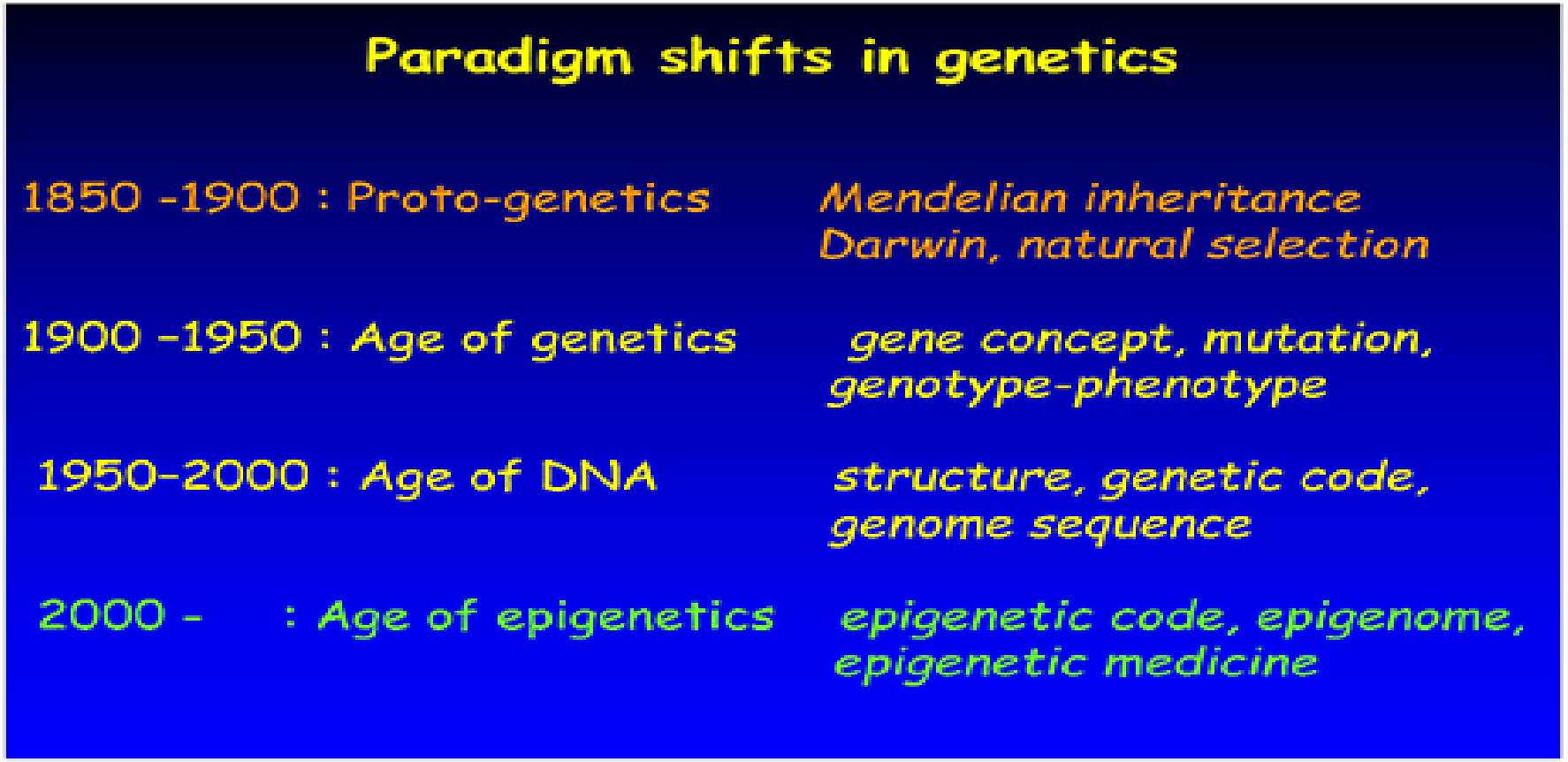


Adapted from Vogelstein et al 2013

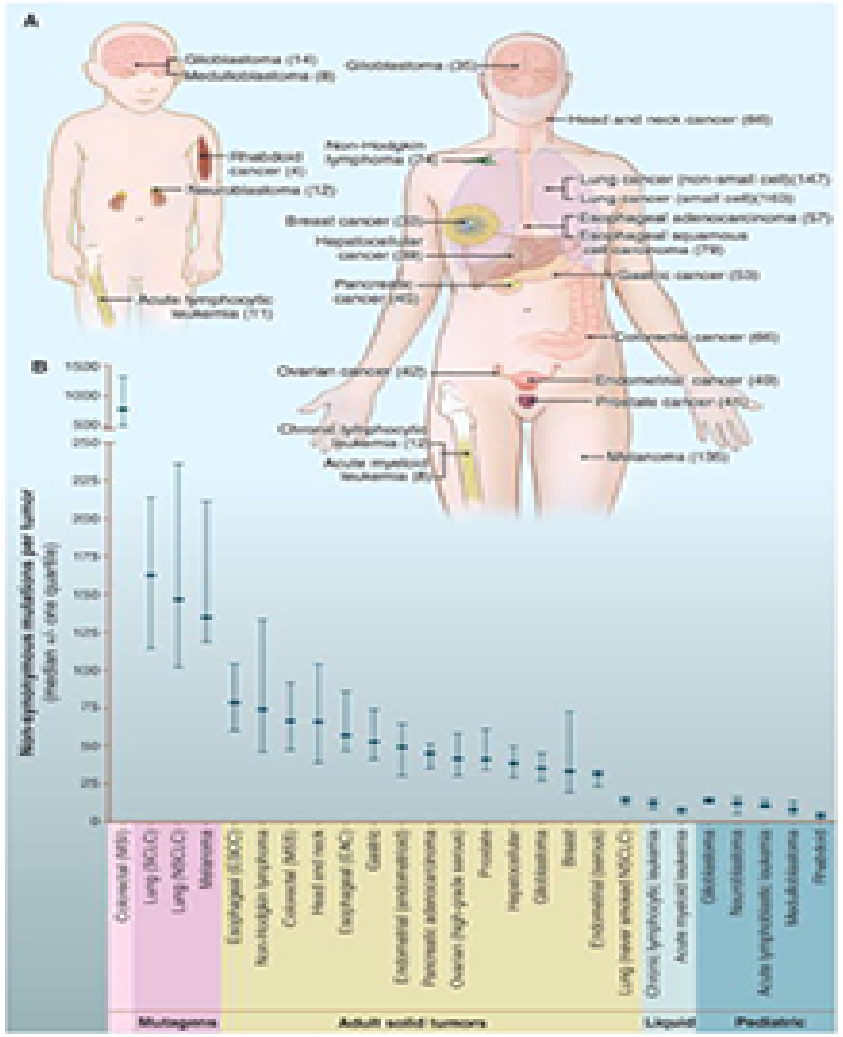
DNA sources


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

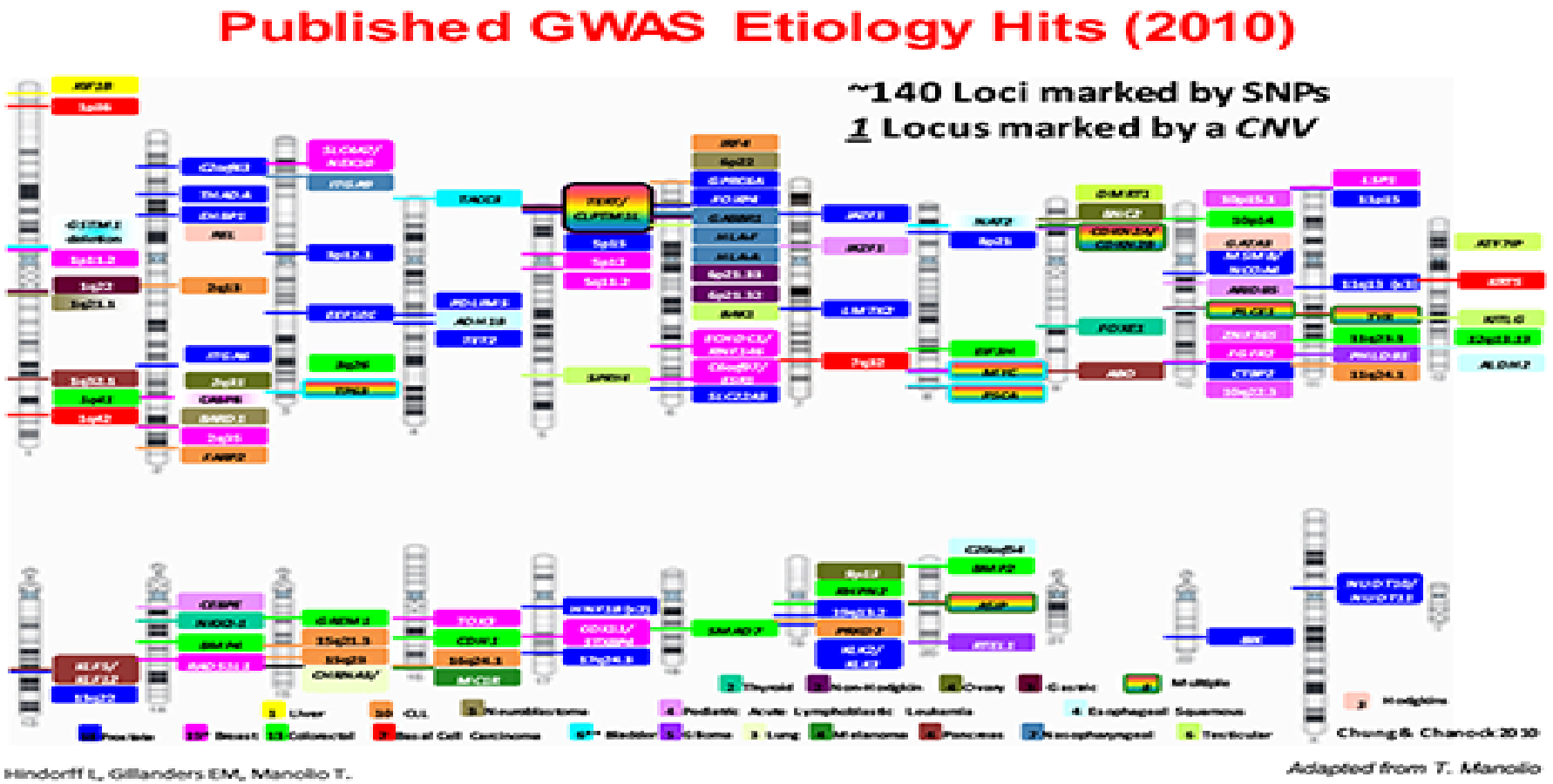


CANCER GENOME LANDSCAPE

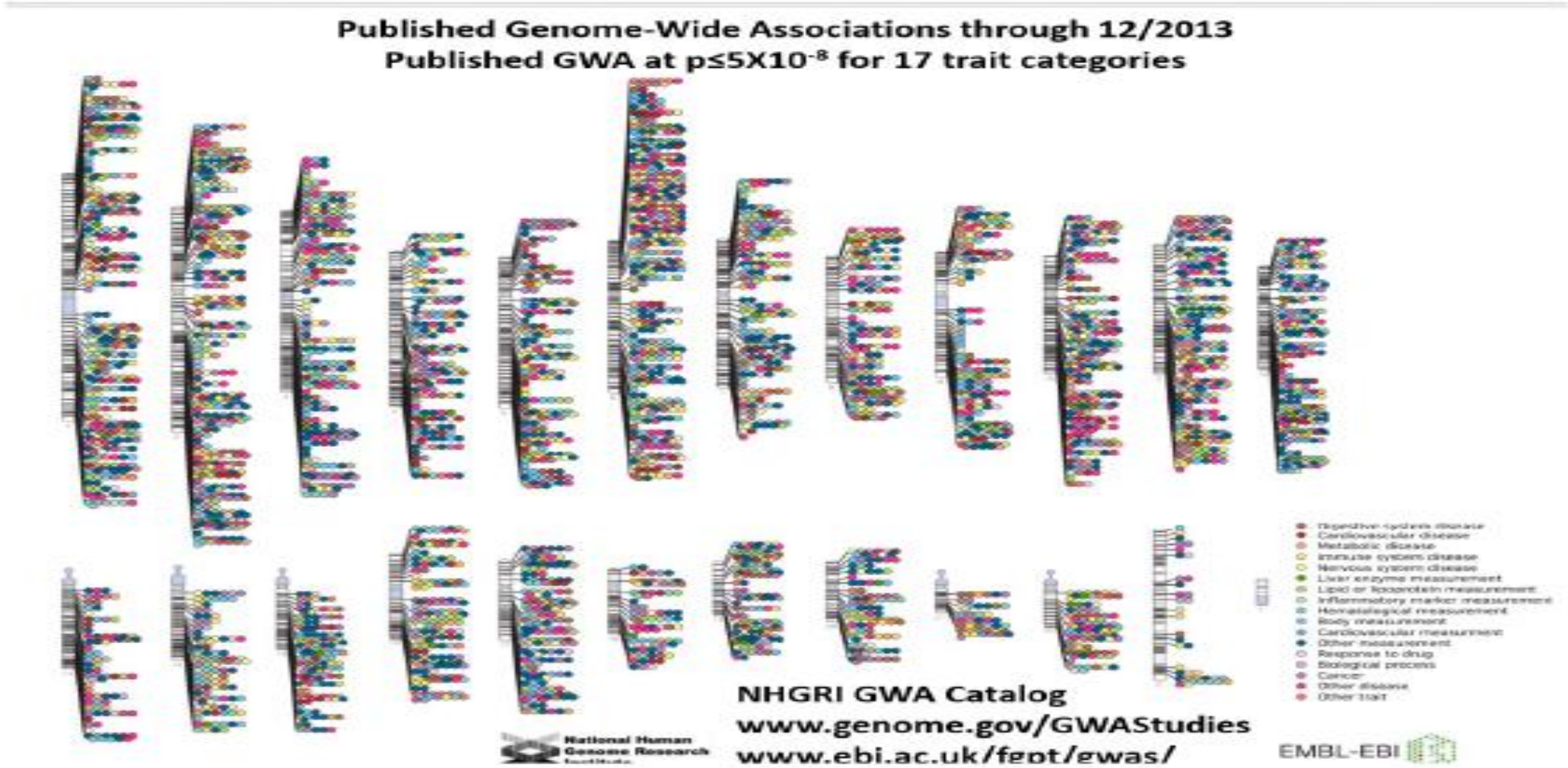
Number of somatic mutations in representative human cancers, detected by genome-wide sequencing studies

Adapted from Vogelstein and Kinzler (Science 2013)

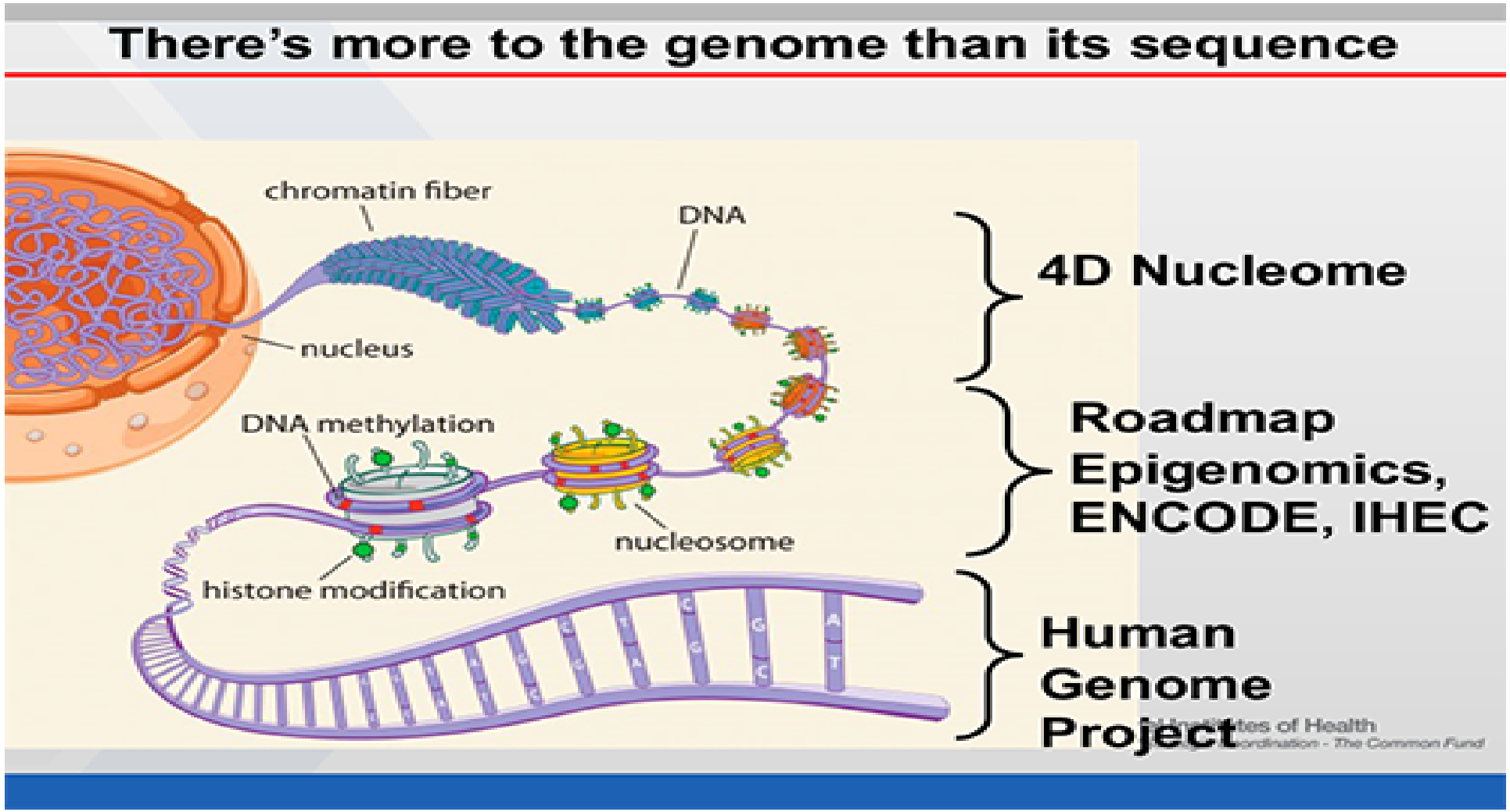
GWAS hits


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 sequence



Kornberg and nucleosome

Nucleosomes (Units of Chromatin)

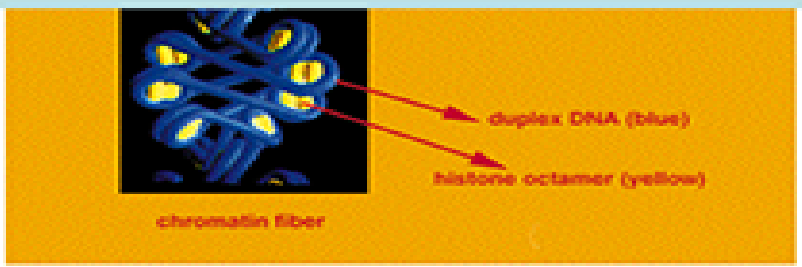
DNA
Histones H2a, H2b, H3, H4

} To neutralize charge and provide stability

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

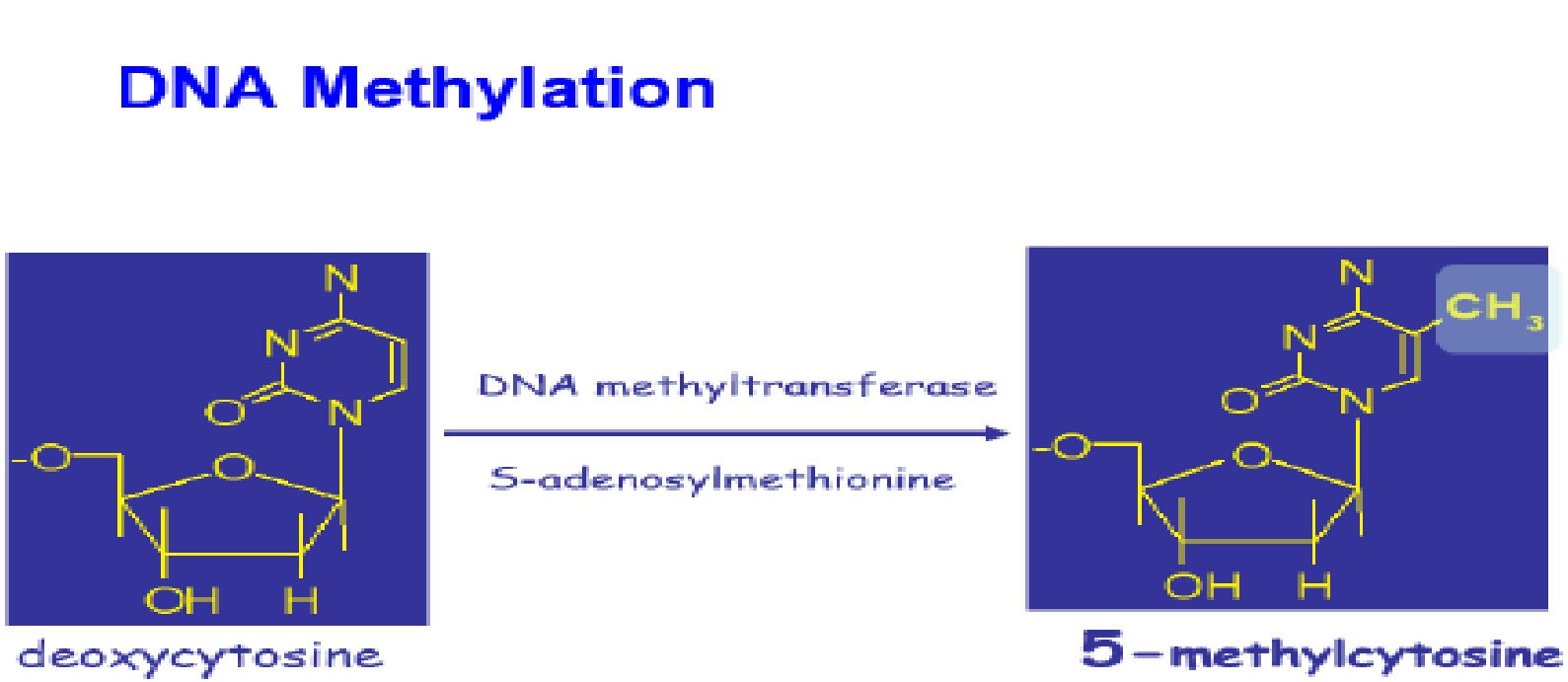
Nucleosome: two turns of DNA (146 base pairs) wrapped around an octomeric complex of two of each of histone types

1974: Roger Kornberg discovers nucleosome who won Nobel Prize in 2006.

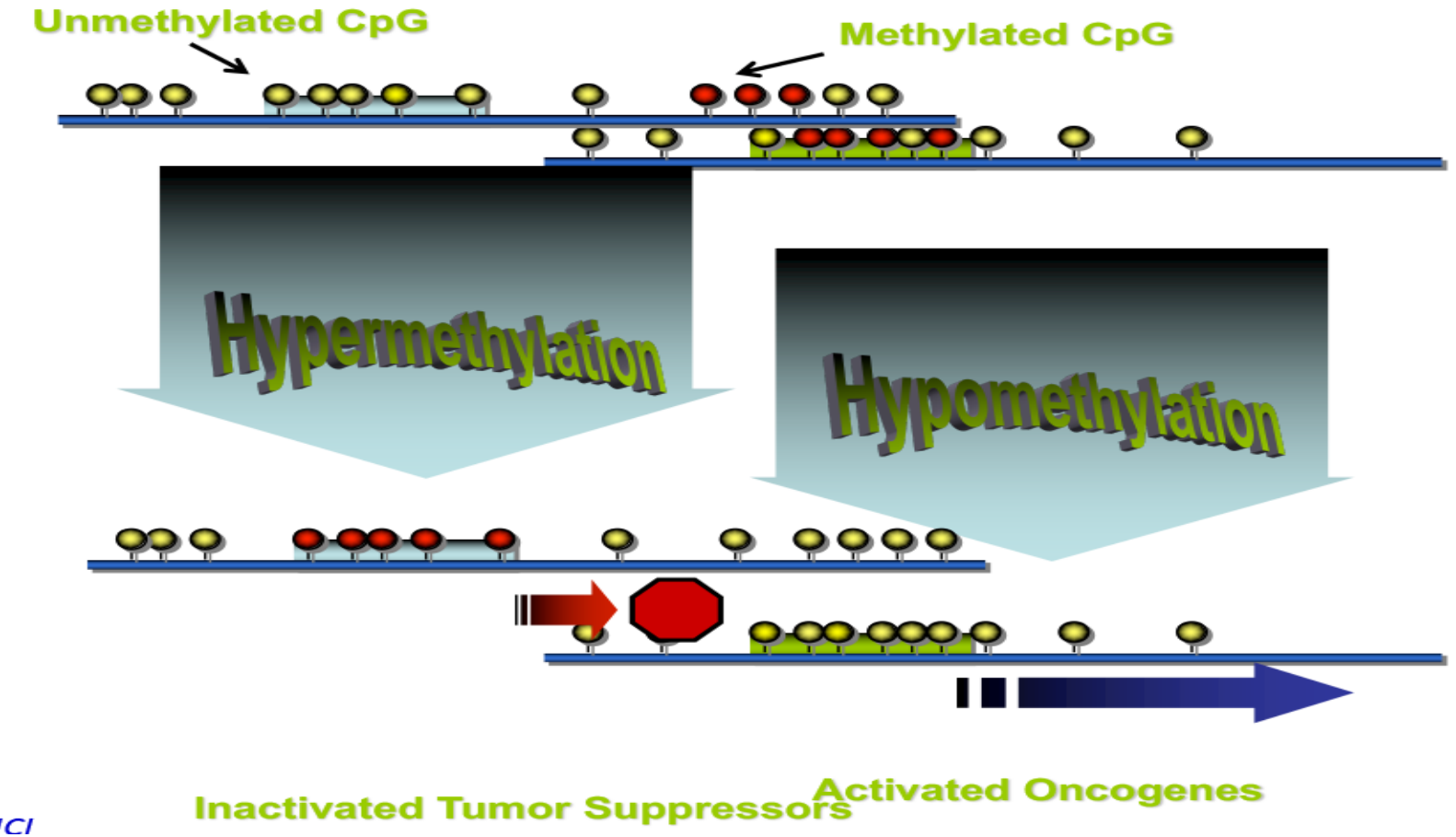


Shores are 0-2kb from islands
Shelves are 2-4 kb and enhancers are beyond shelves

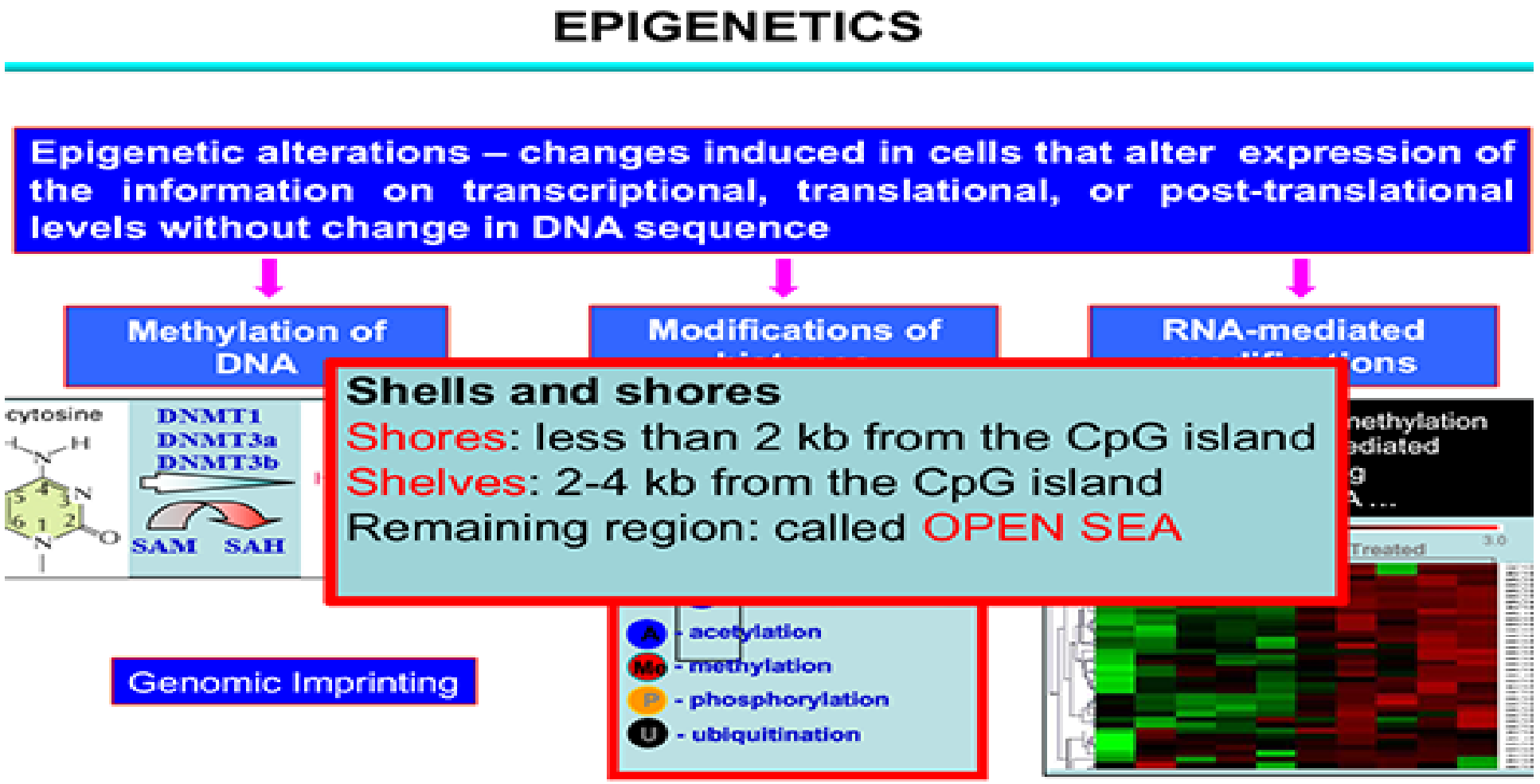
DNA methylation



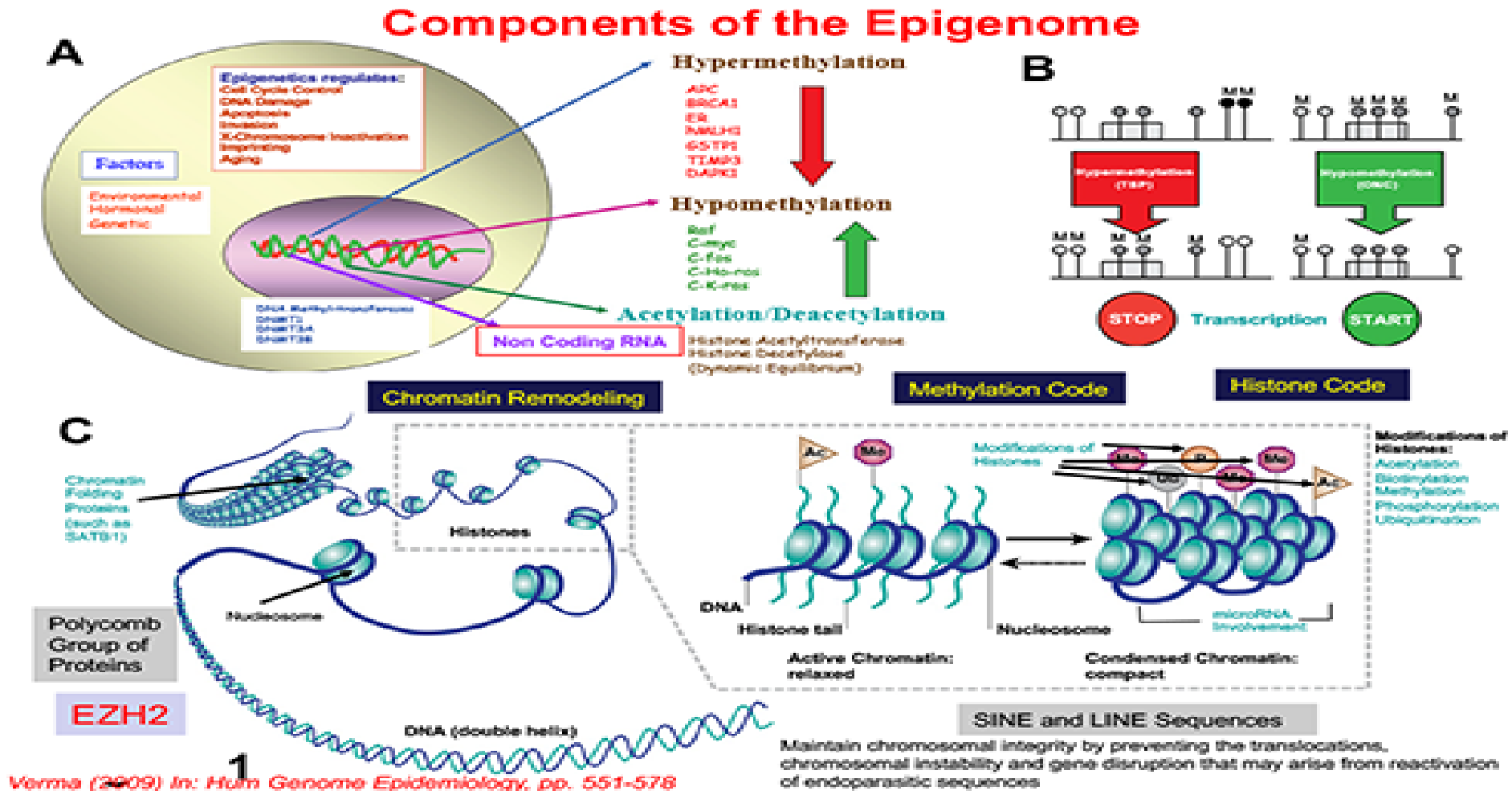
DNA methylation



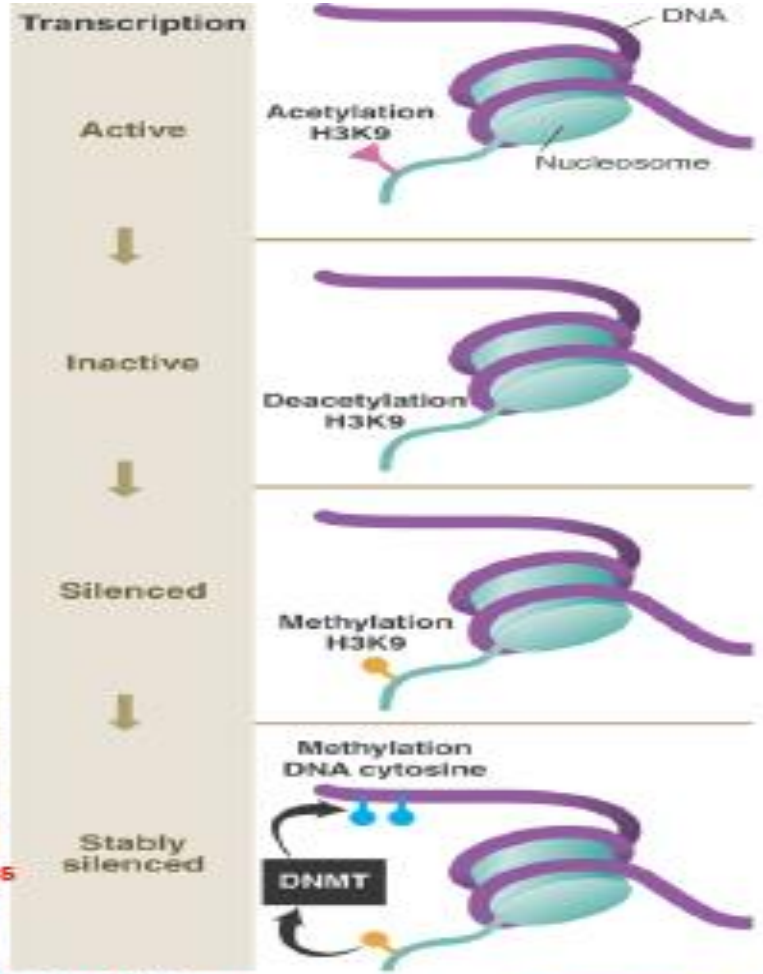
Epigenetics



Epigenome components

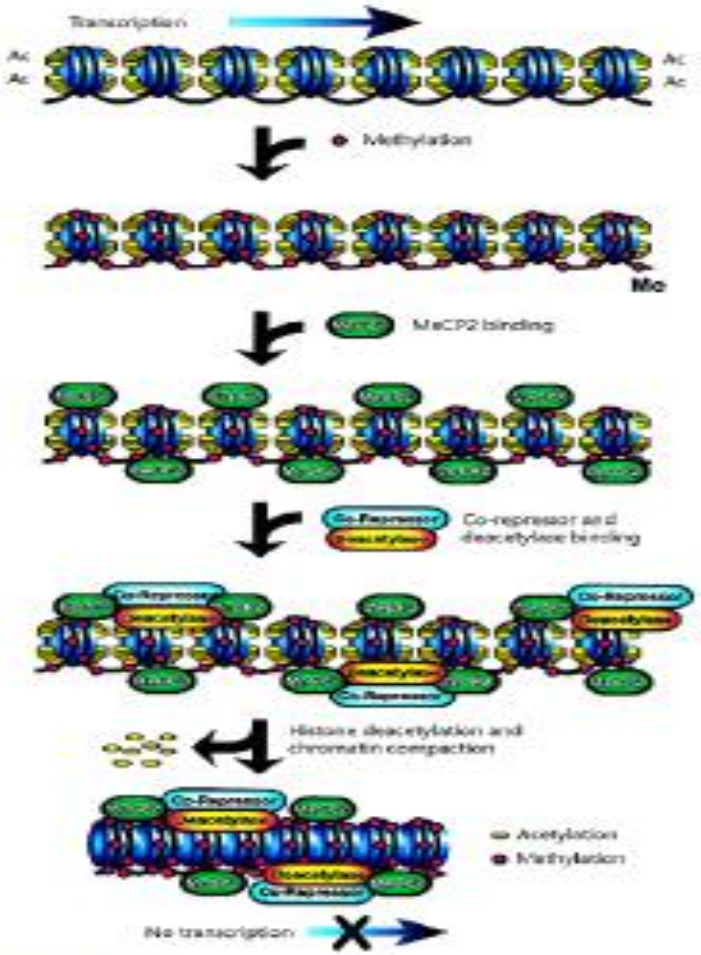


Methylation




Peter Jones


Andrew Feinberg

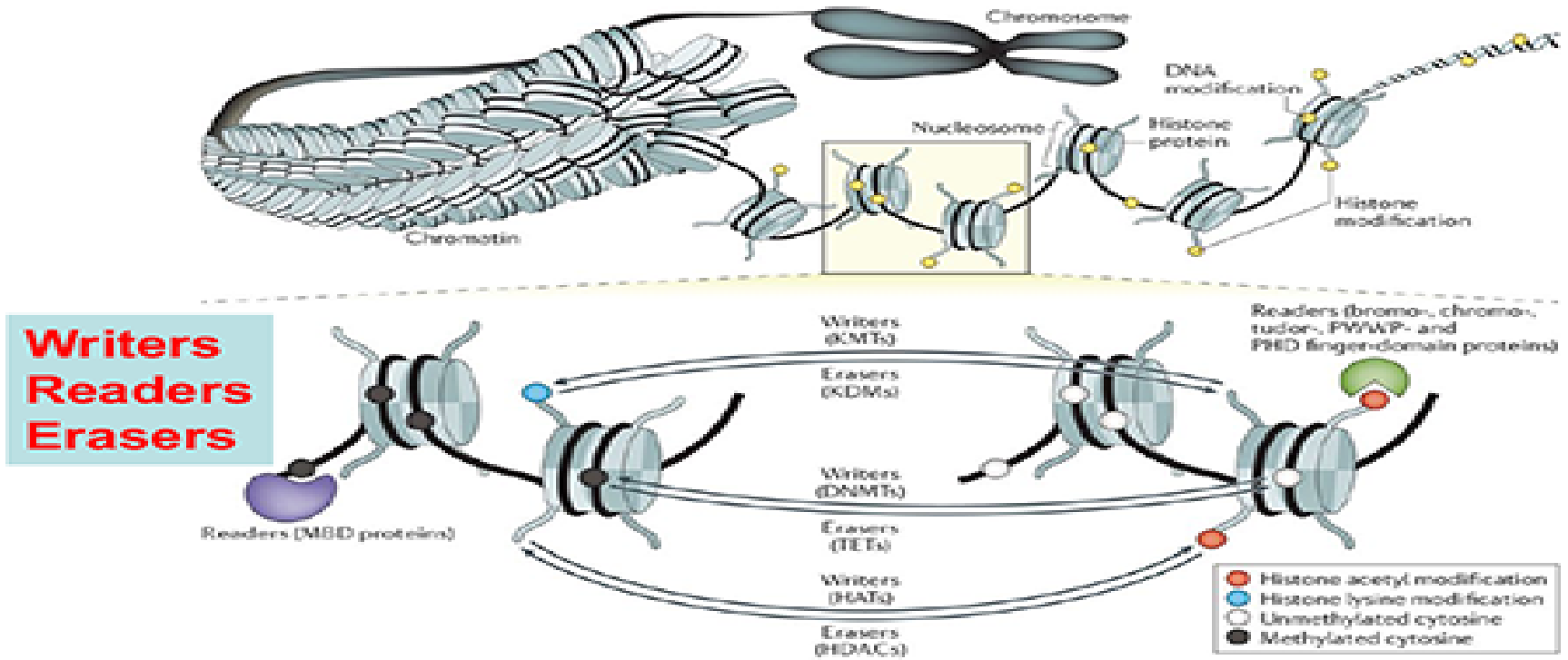


Jones and Laird. *Nat Rev Gen* 21: 163

Chromatin modifications

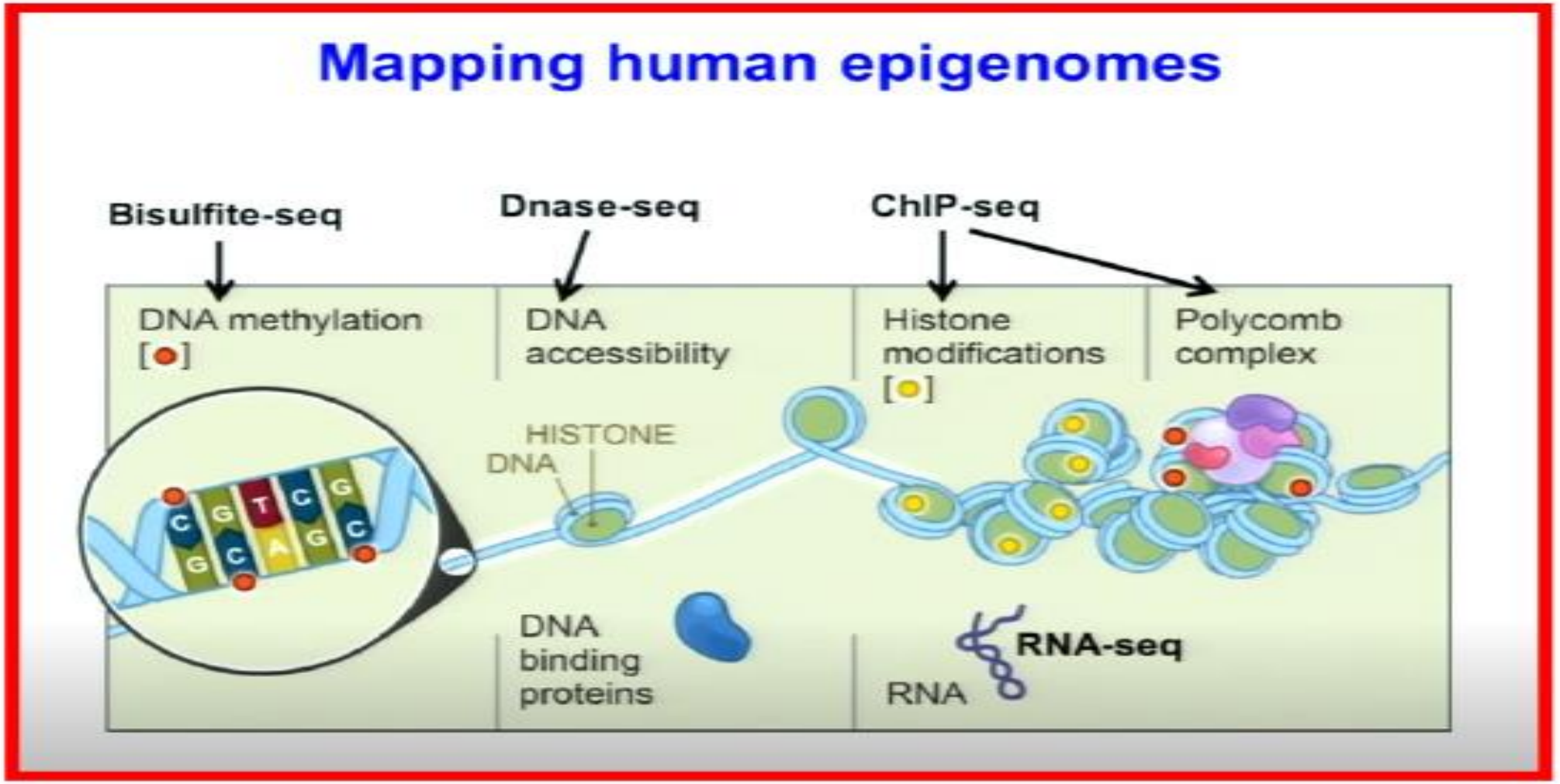
Figure 1 : Modulation of covalent modifications on chromatin.

From: Targeting the cancer epigenome for therapy

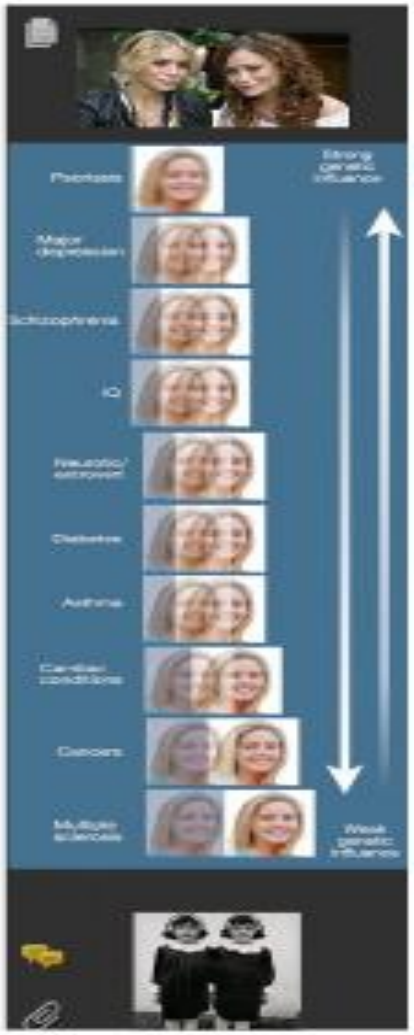


Ten-eleven translocation (TET) family of 5-methylcytosine oxidases.

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

Genome versus epigenome



Genome vs. epigenome – why is it important?

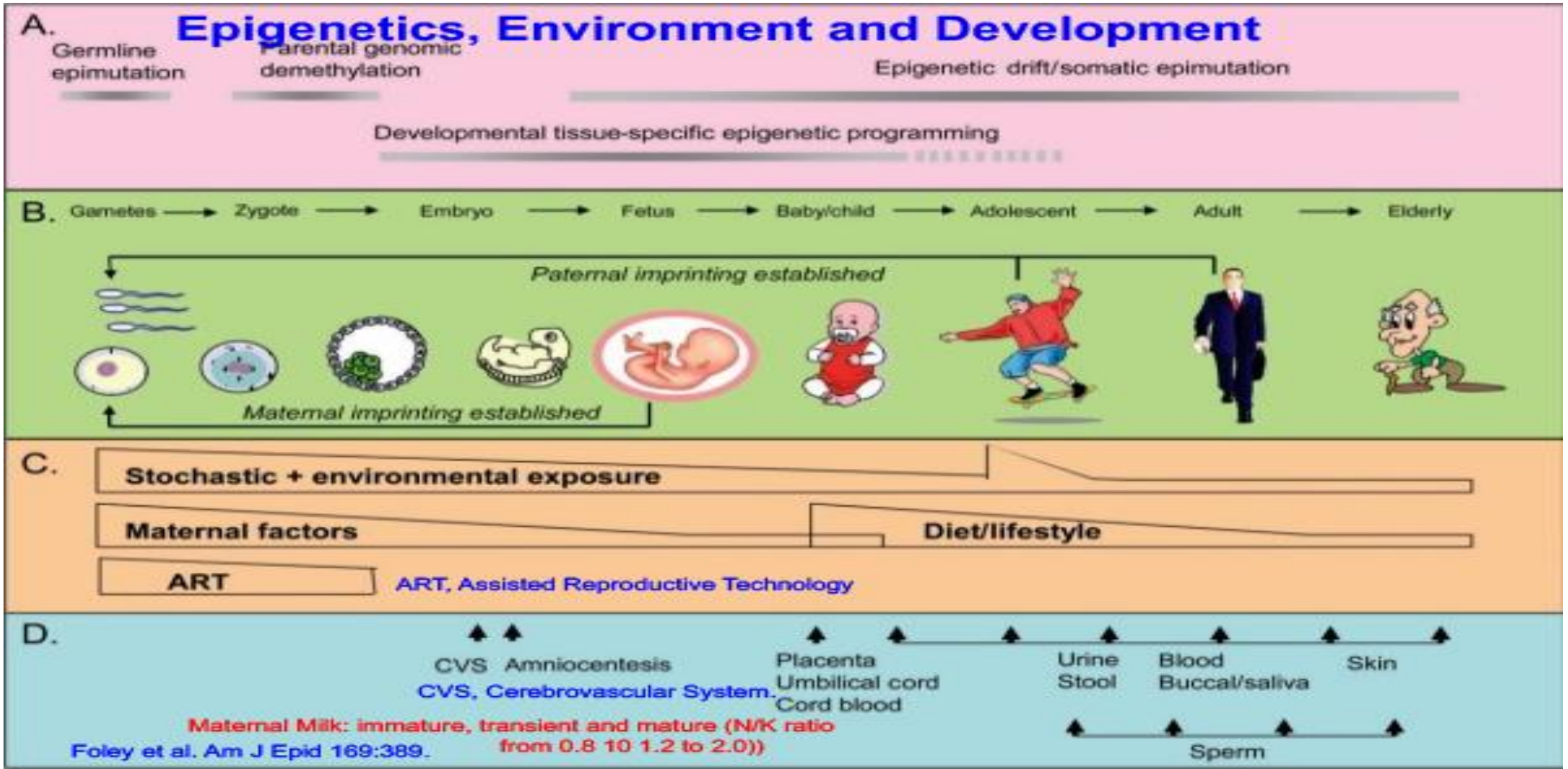
- **Genome is generally constant; epigenome changes**
  - Age
  - Diet
  - Disease
  - Lifestyle
  - Environment

- **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

Epigenetics, environment and development



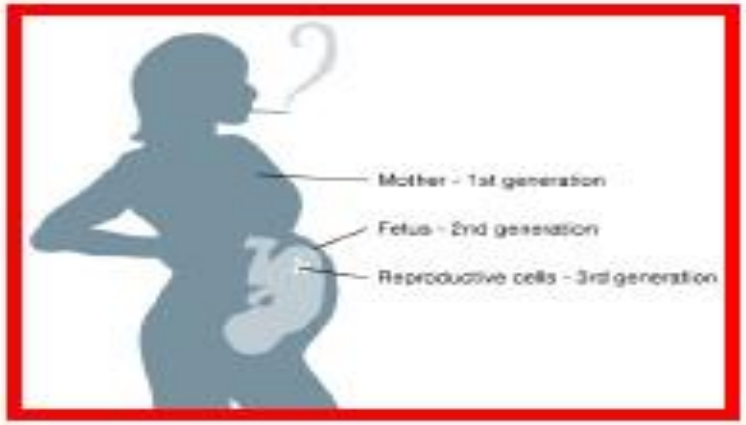
Toxic substances

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

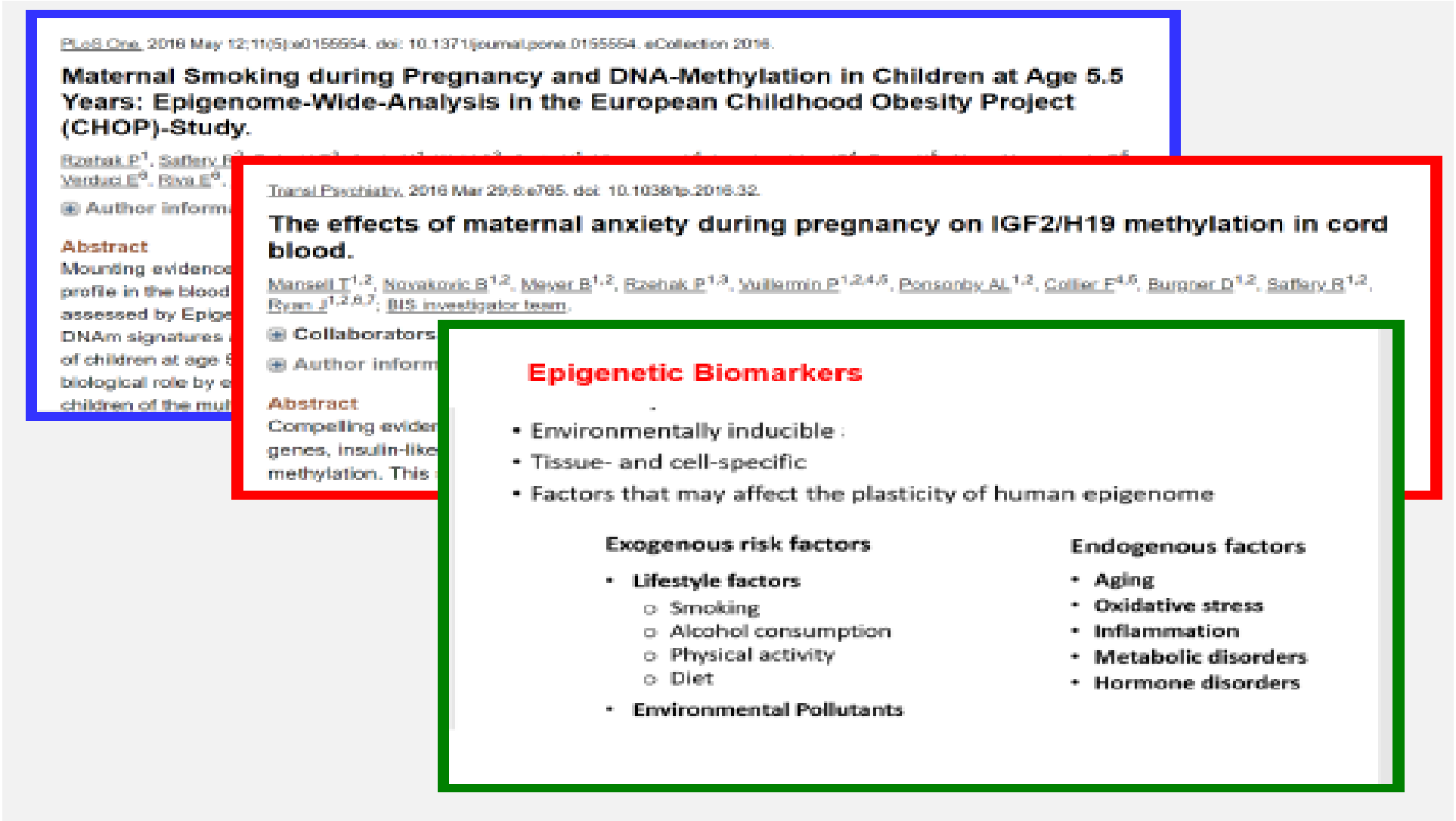
PFOS, Perfluorooctane sulfonate
PAHC, Polycyclic aromatic and halogenated compounds

Histone phosphorylation



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

Endogenous factors



Epigenetics and behavior

Epigenome-Wide Association Study of Aggressive Behavior

Translational Psychiatry, 2016 Mar 29;6:e765. doi: 10.1038/tp.2016.32.

The effects of maternal anxiety during pregnancy on IGF2/H19 methylation in cord blood.

Mansell T[1,2], Novakovic B[1,2], Meyer B[1,2], Rzehak P[1,2], Vuillermin P[1,2,4,5], Ponsonby AL[1,2], Collier F[4,5], Burgner D[1,2], Saffery R[1,2], Ryan J[1,2,6,7]; BIS investigator team.

Collaborators (11)

Author information

Abstract

Compelling evidence suggests that maternal mental hea
genes, insulin-like growth factor 2 (IGF2) and H19, are i
methylation. This study aimed to determine the associat
differentially methylated regions (DMRs) of IGF2 (DMR0
offspring. Maternal depression, anxiety and perceived st
Infant Study (n=576). DNA methylation was measured in

Chapter 29

Epigenetic Regulation in Biopsychosocial Pathways

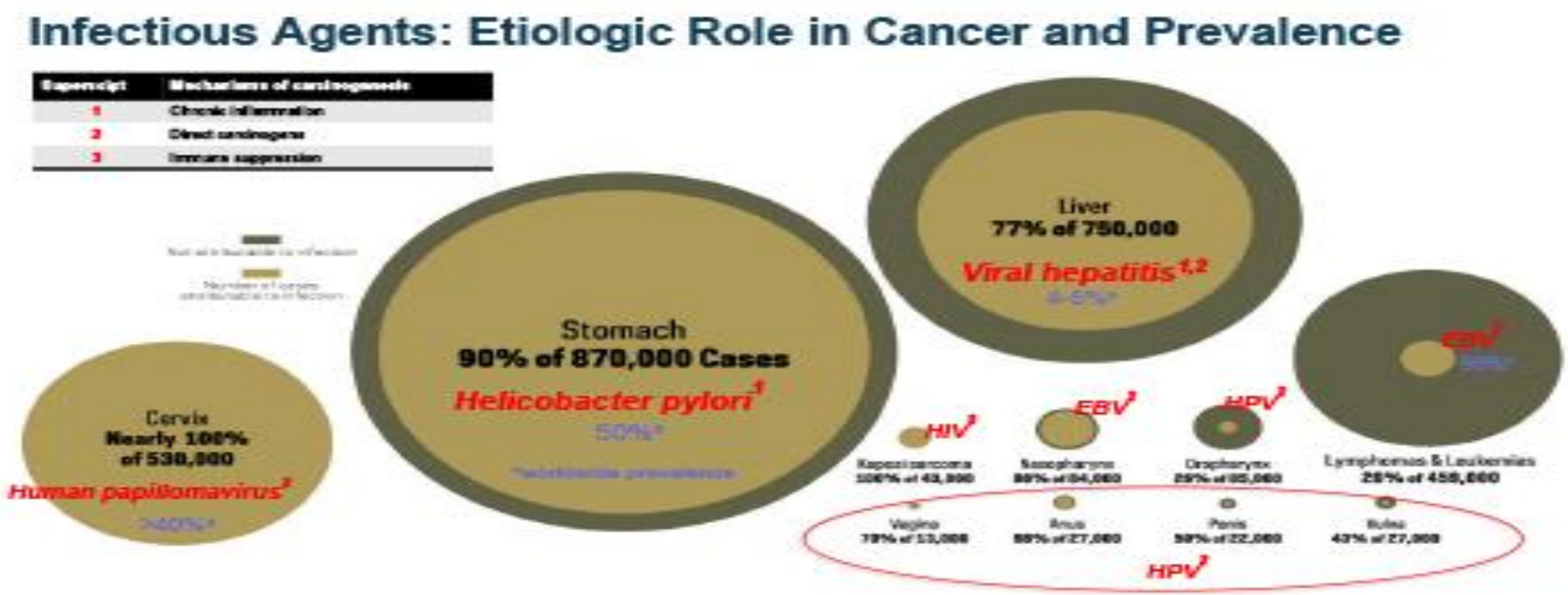
Kristin Litzelman and Mukesh Verma

Cancer Prevention Fellow

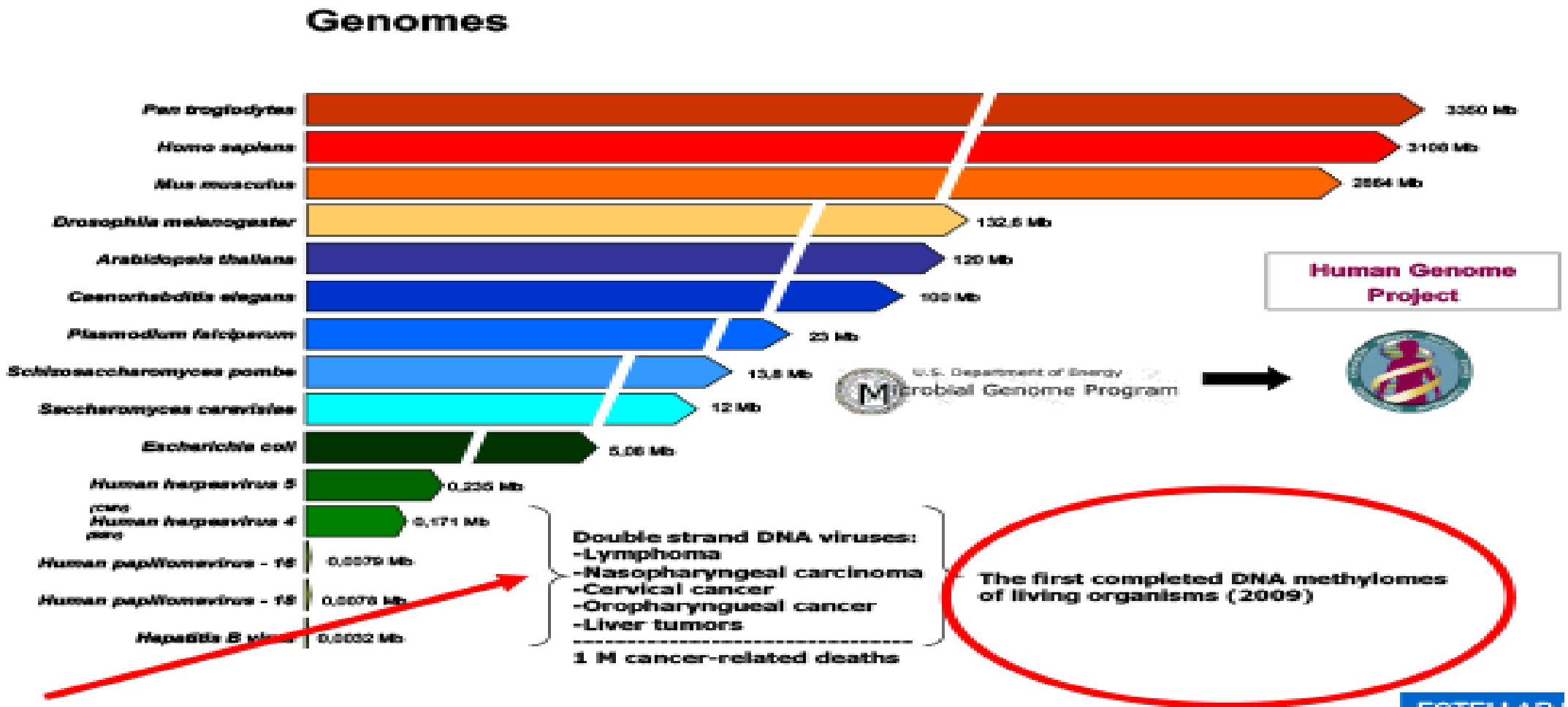
Abstract

Theory and empirical evidence suggest that psychological stress and other adverse psychosocial experiences can contribute to cancer progression. Research has begun to explore the potential role of epigenetic changes in these pathways. In basic, animal and human models, exposure to stressors or to the products of

Infectious agents



Genomes



Oncogenic 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)

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... Internal Medicine, Chung Shan Medical University Hospital, Taichung, Taiwan*

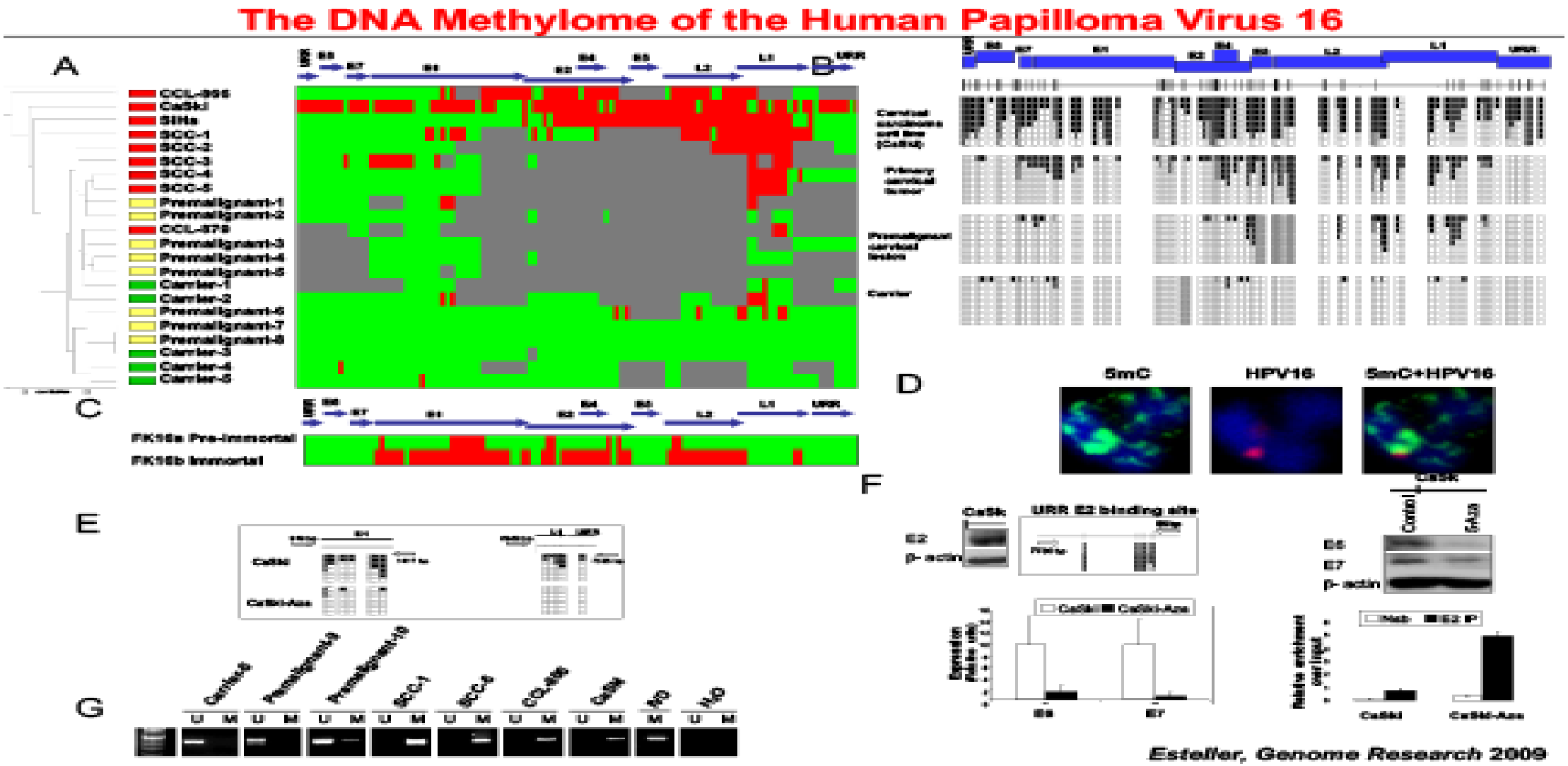
LANA

Complete methylome of HPV, EBV, and HBV.

Esteller M. Genome Research. 2009. 19: 438

EBNA

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?	???

Risk Assessment

Understanding Cancer Etiology and Risk Assessment

Need healthy population (pathologically disease free) (cohort) with information about

- Exposure (Chemicals, Radiations, Infectious Agents, Toxic substance)
- Family History
- Diet and Life Style
- Medication

Need easily collected biospecimens (non-invasive technologies) and analytic tools

Need follow up (for longitudinal studies) for several years

Challenge: Expensive, data sharing

Advantage: Essential to identify risk factors for cancer

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

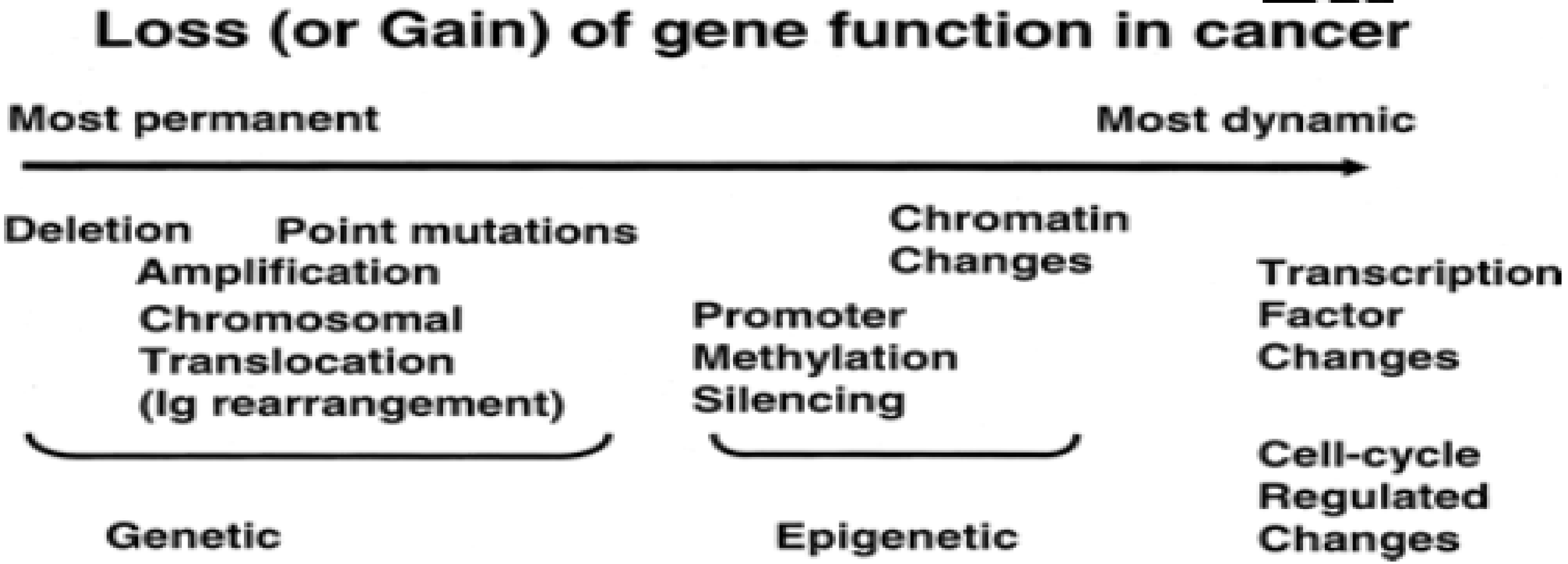
Cohort consortium

The Cohort Consortium (CoCo)

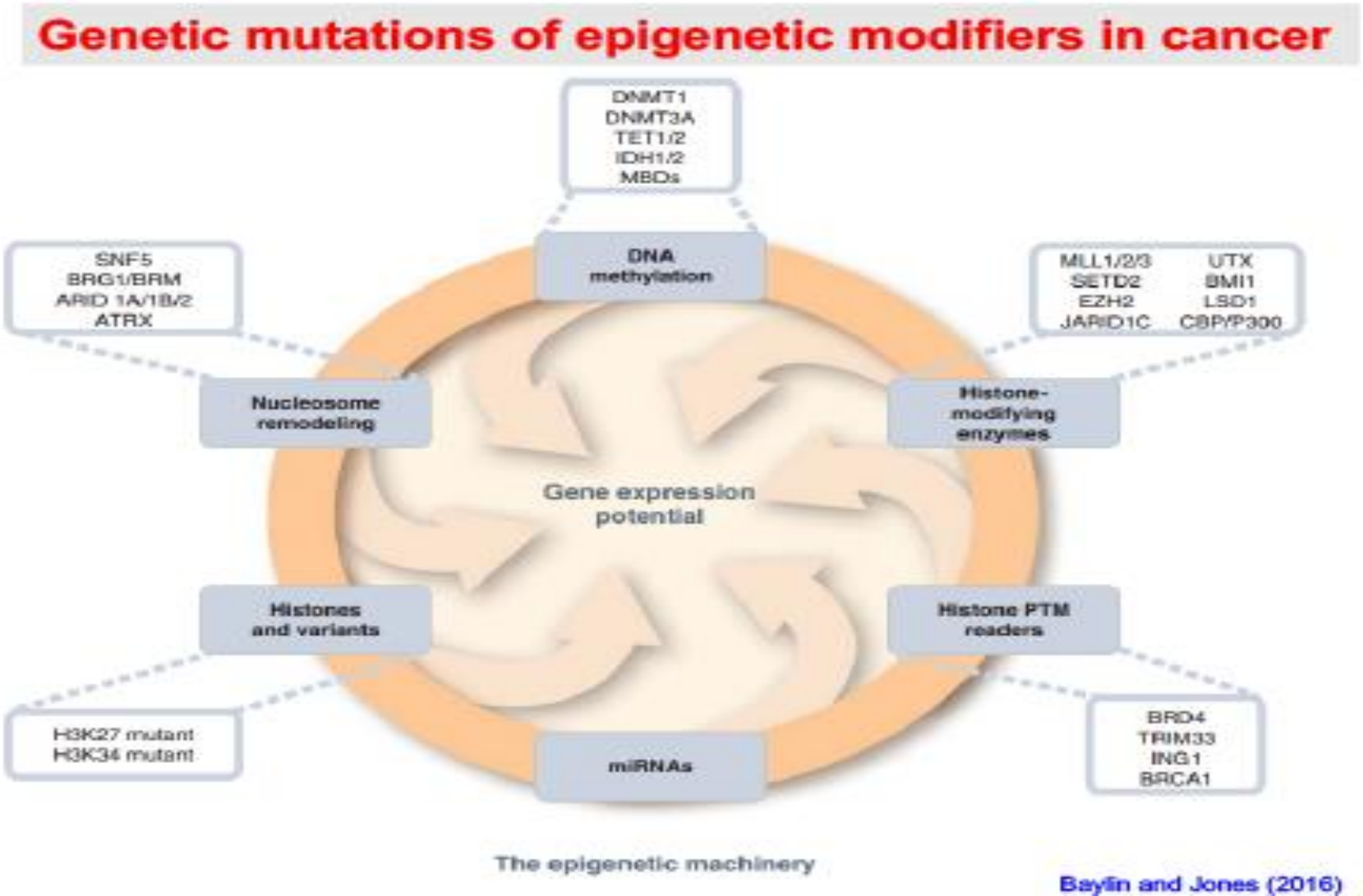
- 73 cohorts, over 4 million individuals
- Membership: cohort studies worldwide with >10,000 subjects, blood samples and questionnaire data on important cancer risk factors
- The Cohort Consortium was formed by NCI to address the need for large-scale collaborations for
  - Rapid identification and confirmation of common polymorphisms and cancer susceptibility (GWAS)
  - Studies of GxG and GxE interactions in the etiology of cancer.

https://epi.grants.cancer.gov/cohort-consortium/members/#members

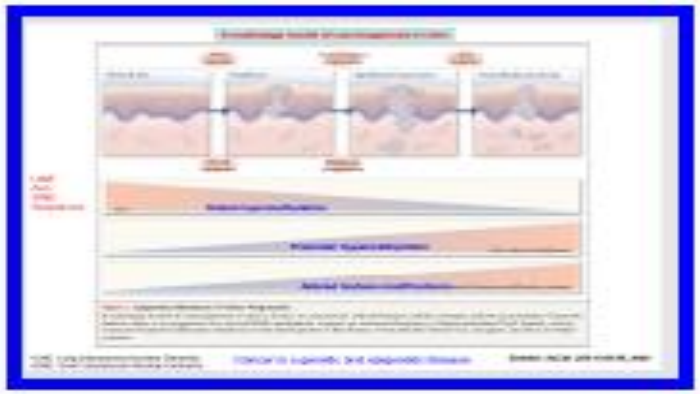
Loss (or gain) of gene function in cancer



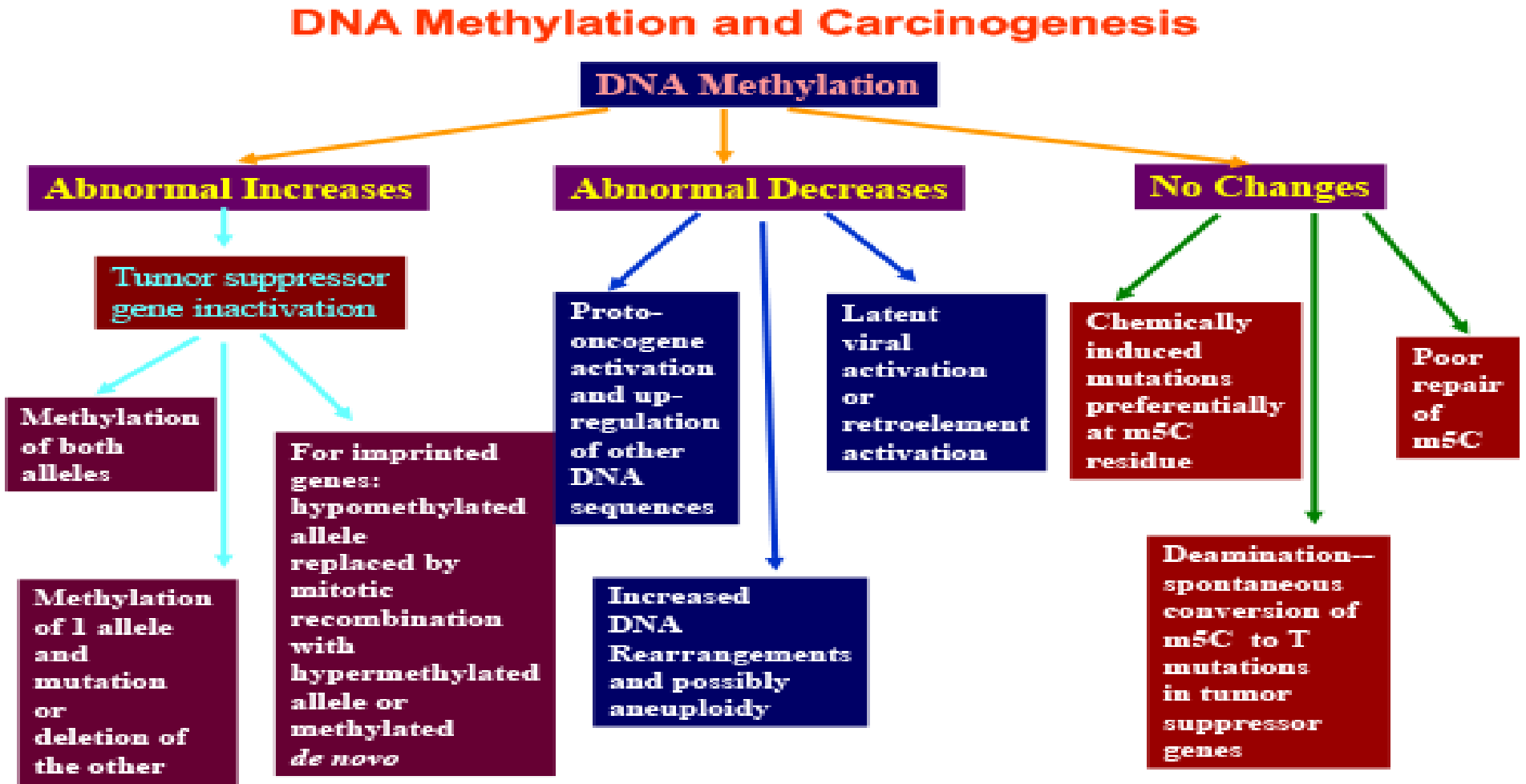
Genetic mutations



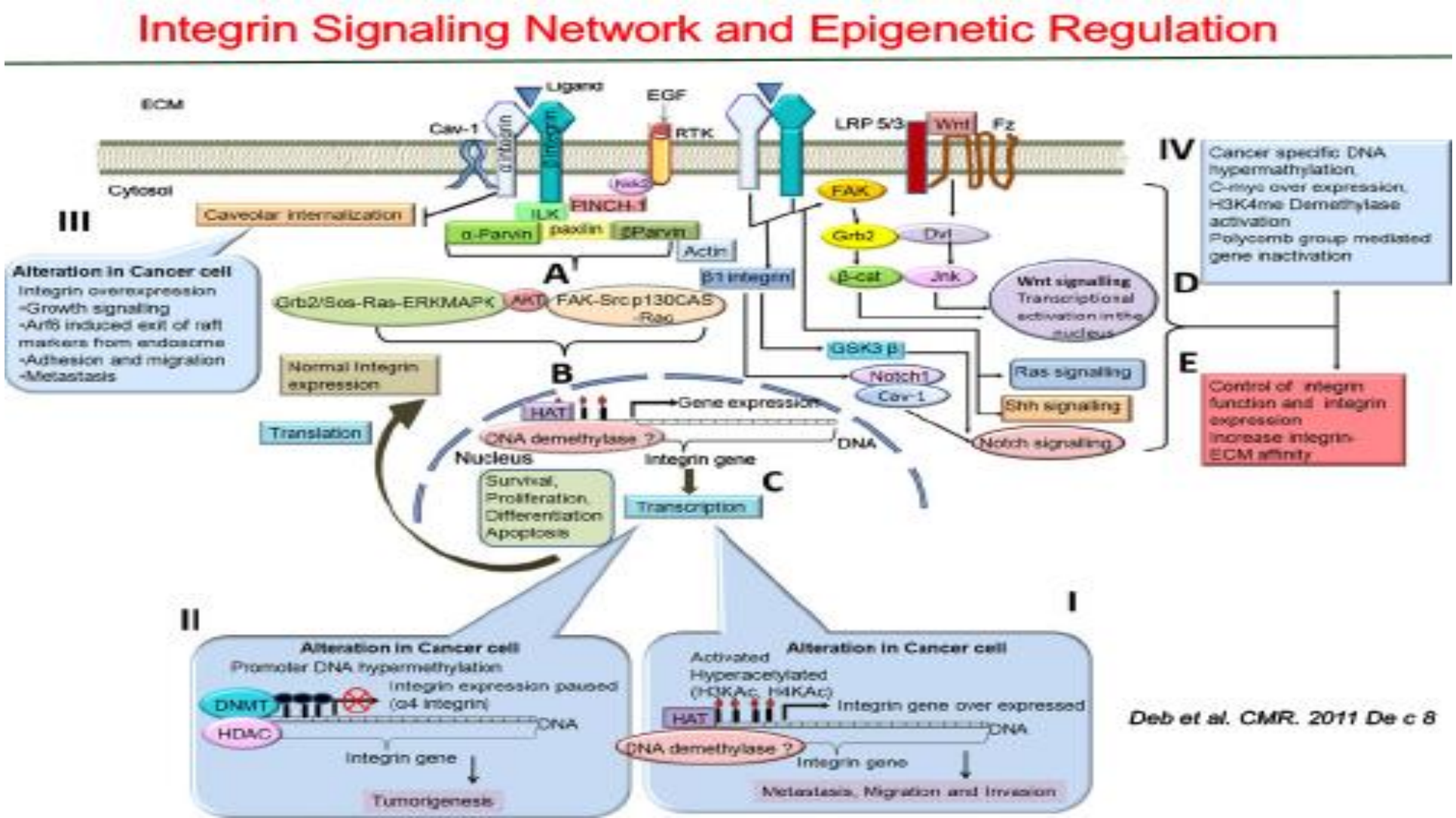
Hypomethylation



DNA methylation and carcinogenesis

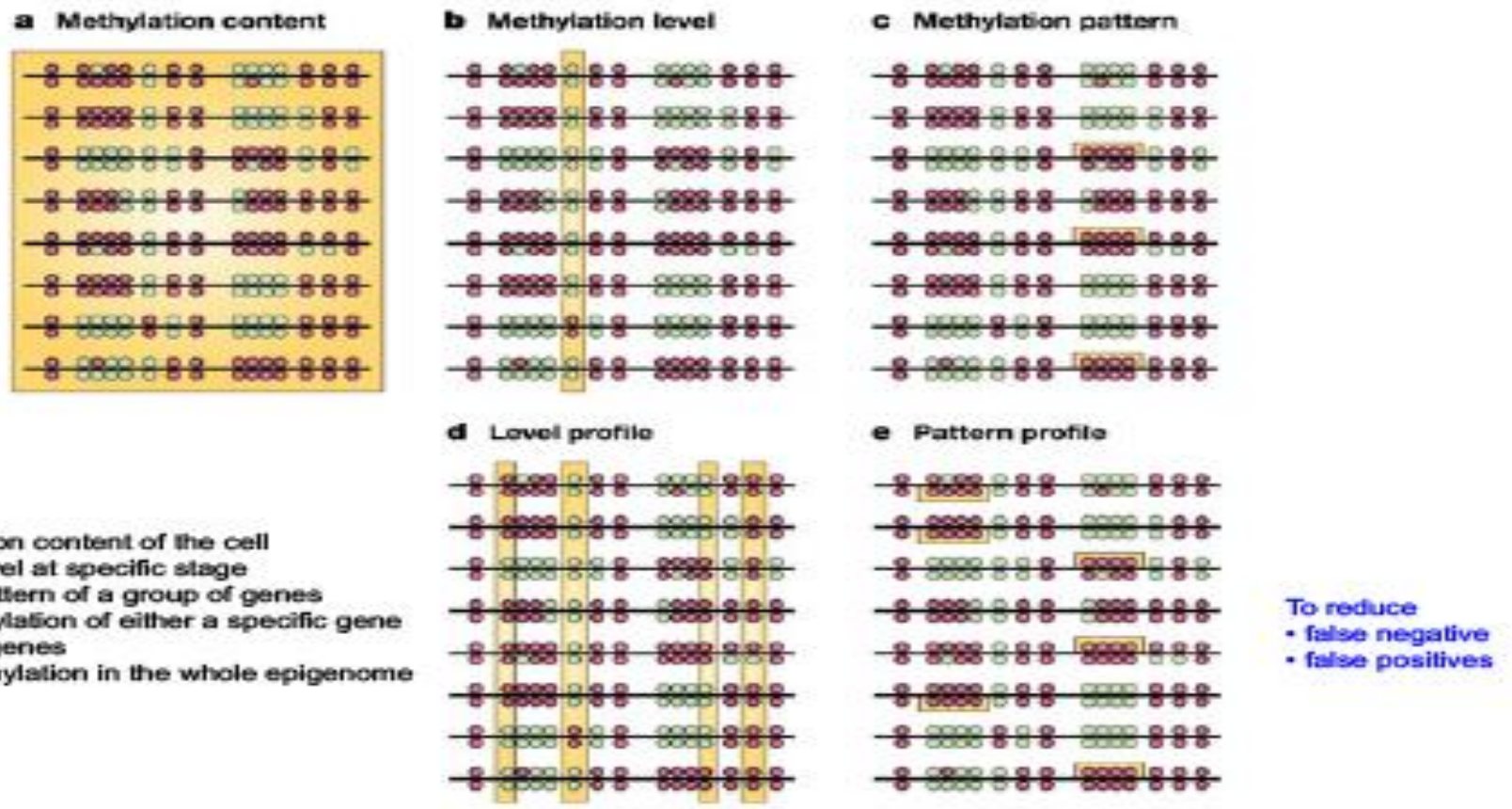


Integrin signaling

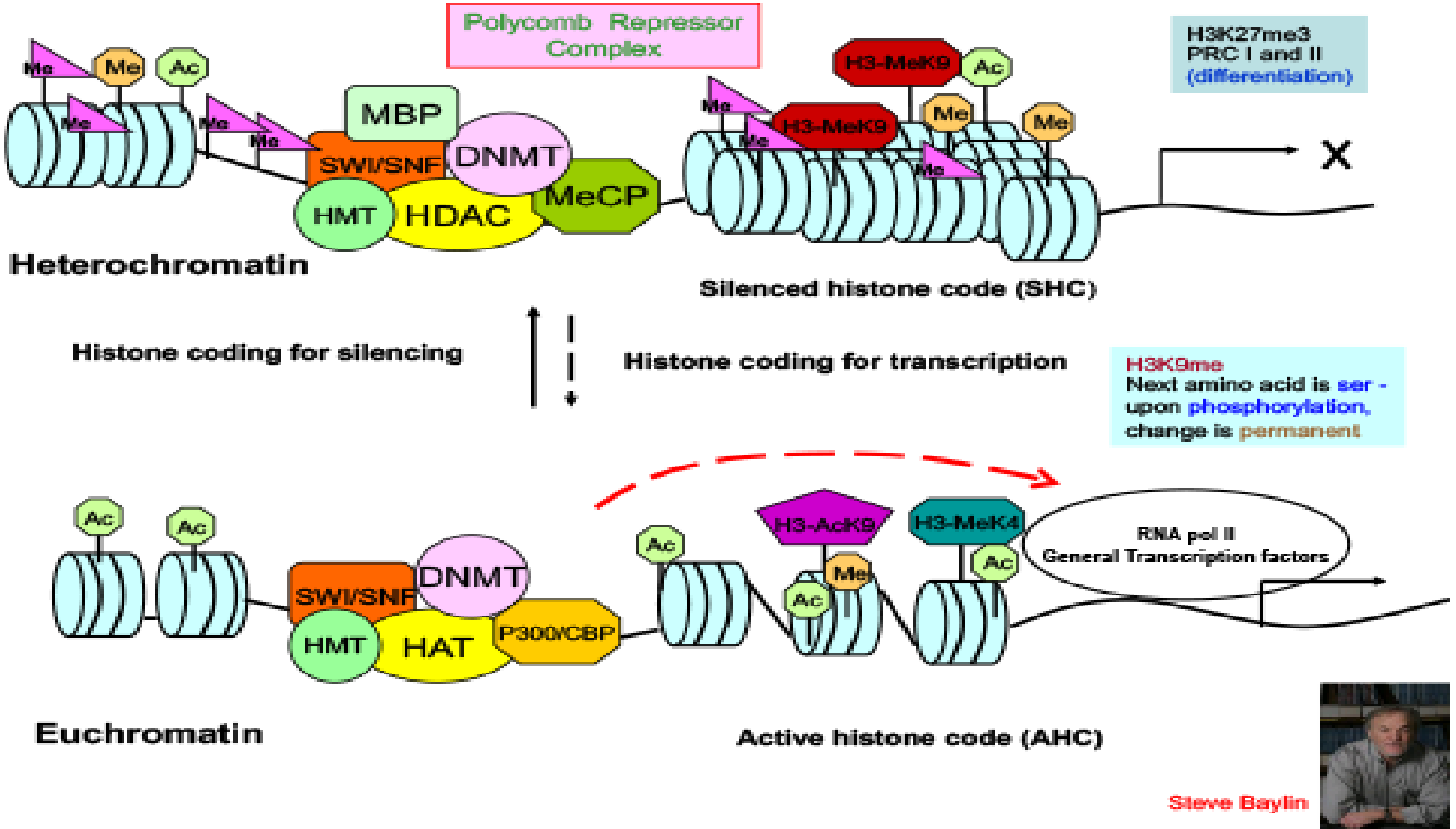


Deb et al. CMR. 2011 De c 8

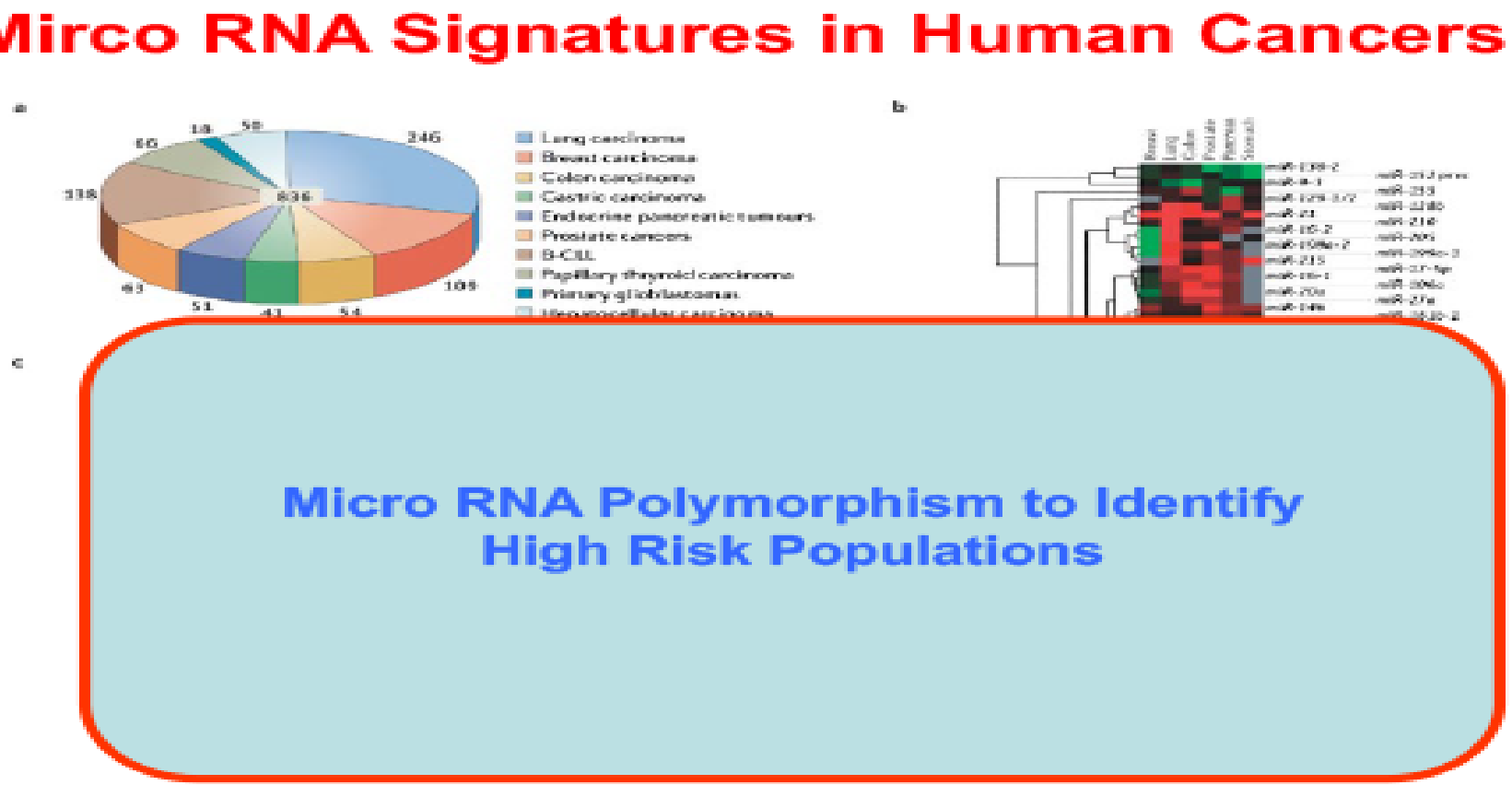
Methylation



Histone acetylation



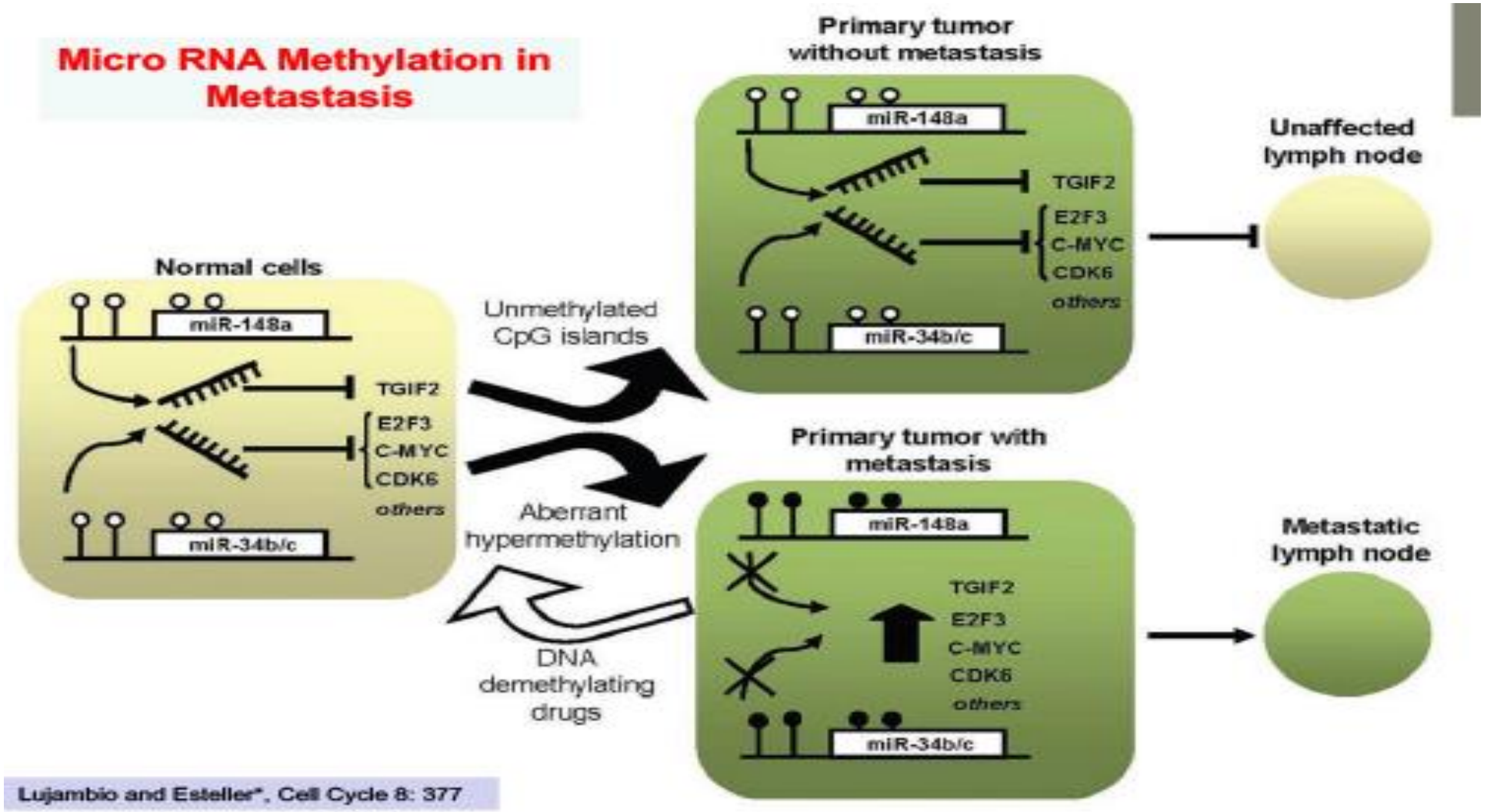
Micro RNA signatures



Mir-31 inhibits metastasis in breast cancer

nature REVIEWS CANCER

Micro RNA methylation



Methylation of microRNAs

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-019-11826-1 OPEN

Distinct methylation levels of mature microRNAs in gastrointestinal cancers

Masamitsu Konno[1,10], Jun Koseki[2,10], Ayumu Asai[1,2,10], Akira Yamagata[3,10], Teppei Shimamura[4], Daisuke Motooka[5], Daisuke Okuzaki[5], Koichi Kawamoto[6], Tsunekazu Mizushima[6], Hidetoshi Eguchi[6], Shuji Takiguchi[6,7], Taroh Satoh[1], Koshi Mimori[8], Takahiro Ochiya[9], Yuichiro Doki[6], Ken Ofusa[3], Masaki Mori[6] & Hideshi Ishii[2]

The biological significance of micro (mi)RNAs has traditionally been evaluated according to their RNA expression levels based on the assumption that miRNAs recognize and regulate their targets in an unvarying fashion. Here we show that a fraction of mature miRNAs including miR-17-5p, -21-5p, and -200c-3p and let-7a-5p harbor methyl marks that potentially alter their stability and target recognition. Importantly, methylation of these miRNAs was significantly increased in cancer tissues as compared to paired normal tissues. Furthermore, miR-17-5p methylation level in serum samples distinguished early pancreatic cancer patients from healthy controls with extremely high sensitivity and specificity. These findings provide a

RNA epigenetics

Epitranscriptomics or RNA Epigenetics

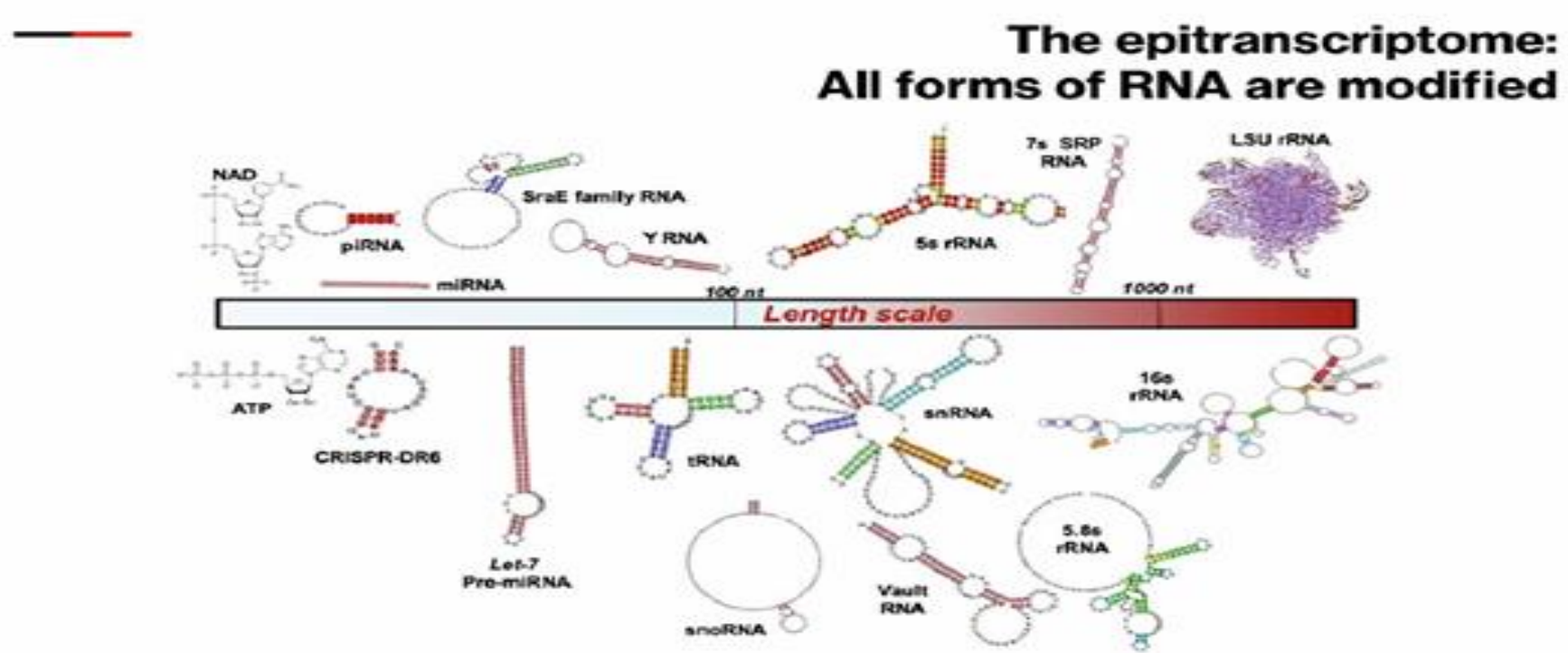
- Epitranscriptomics, also known as RNA epigenetics, is the study of chemical modifications to RNA molecules that occur after transcription.
- Can affect the structure of RNA, its stability, and how it's translated.
- Can also impact gene expression and regulation.

Some examples of RNA modifications include:

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

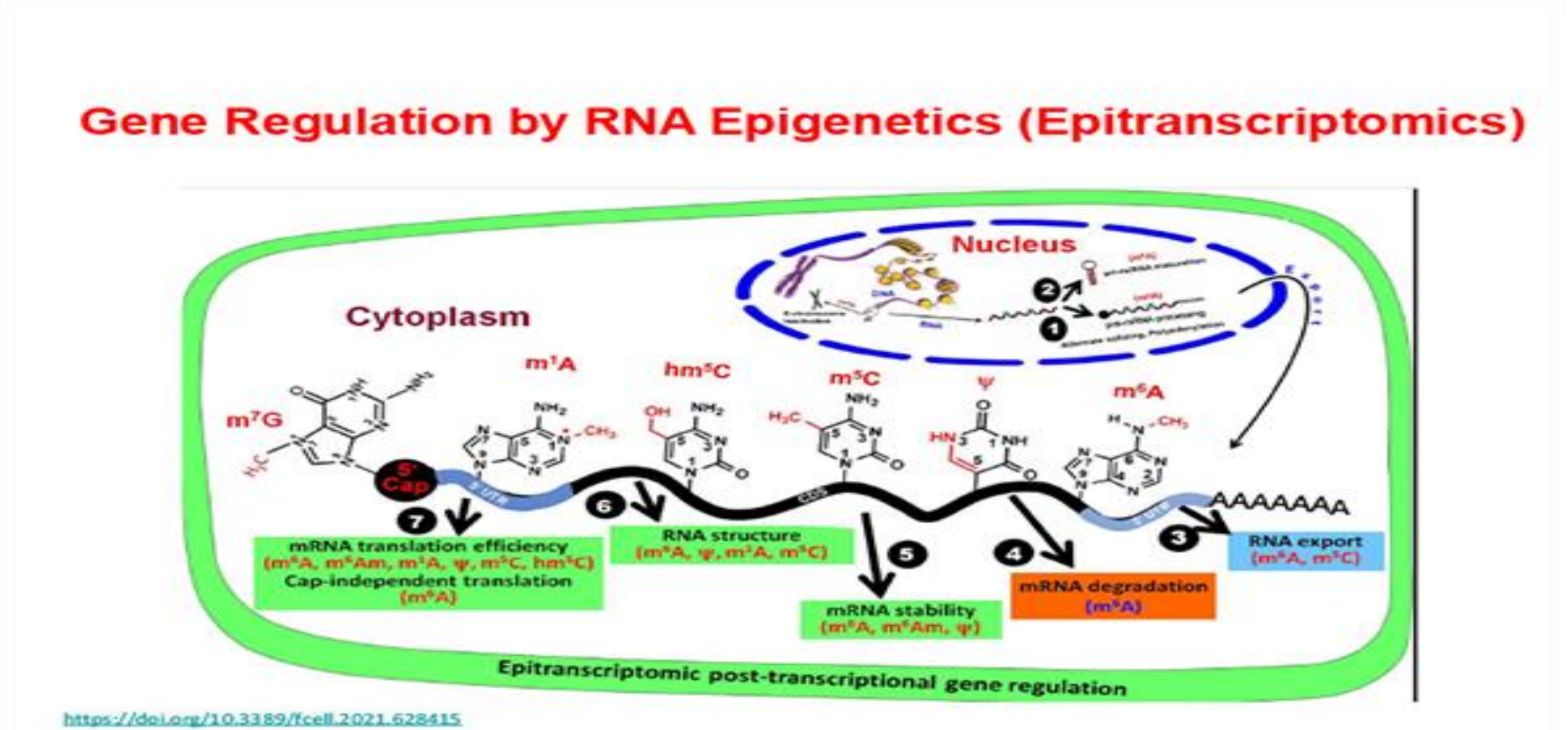
Int. J. Mol. Sci. 2020, *21*(18), 6578; https://doi.org/10.3390/ijms21186578

Epitranscriptome

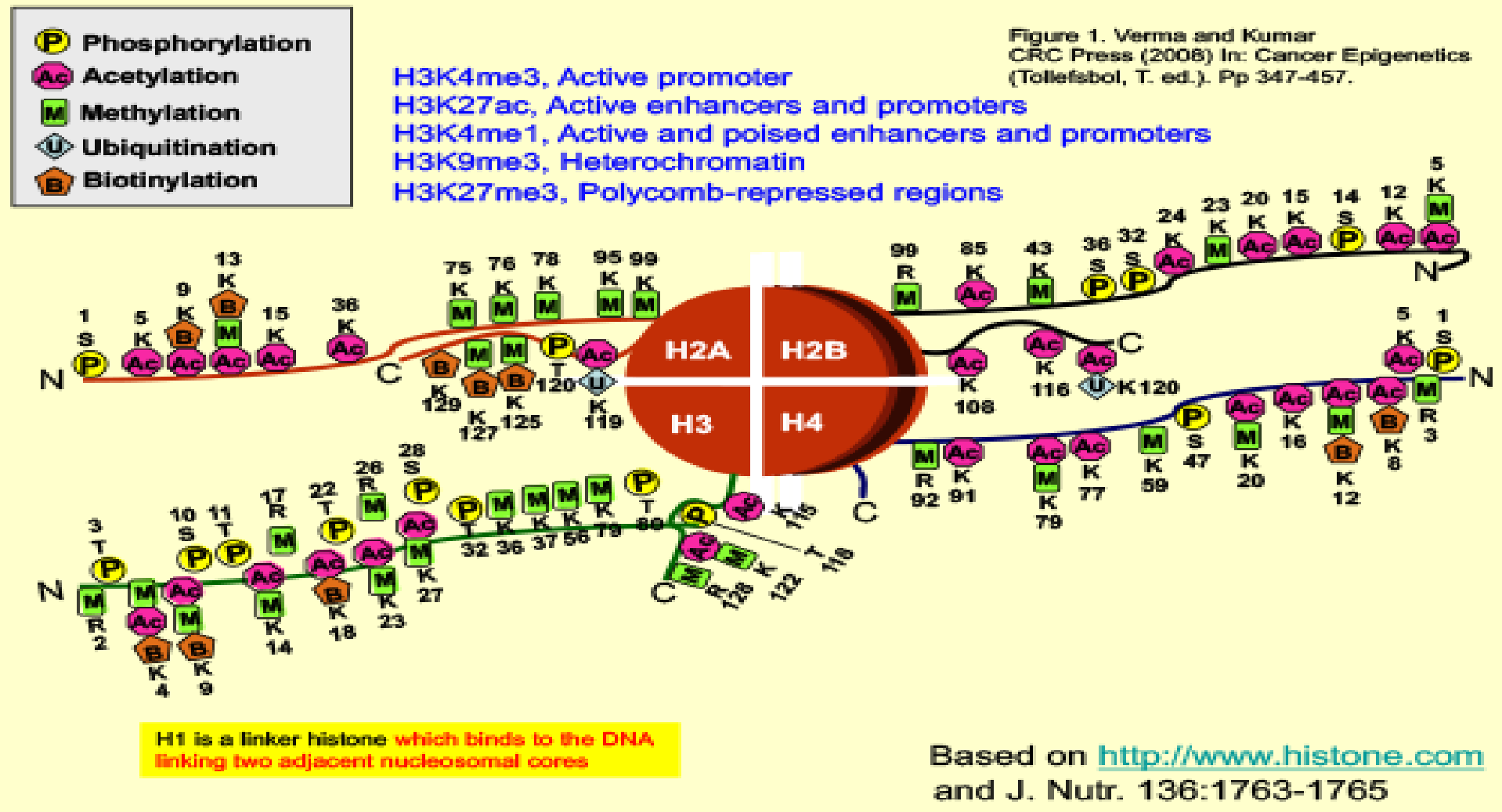


Int. J. Mol. Sci. **2020**, *21*(18), 6578; https://doi.org/10.3390/ijms21186578

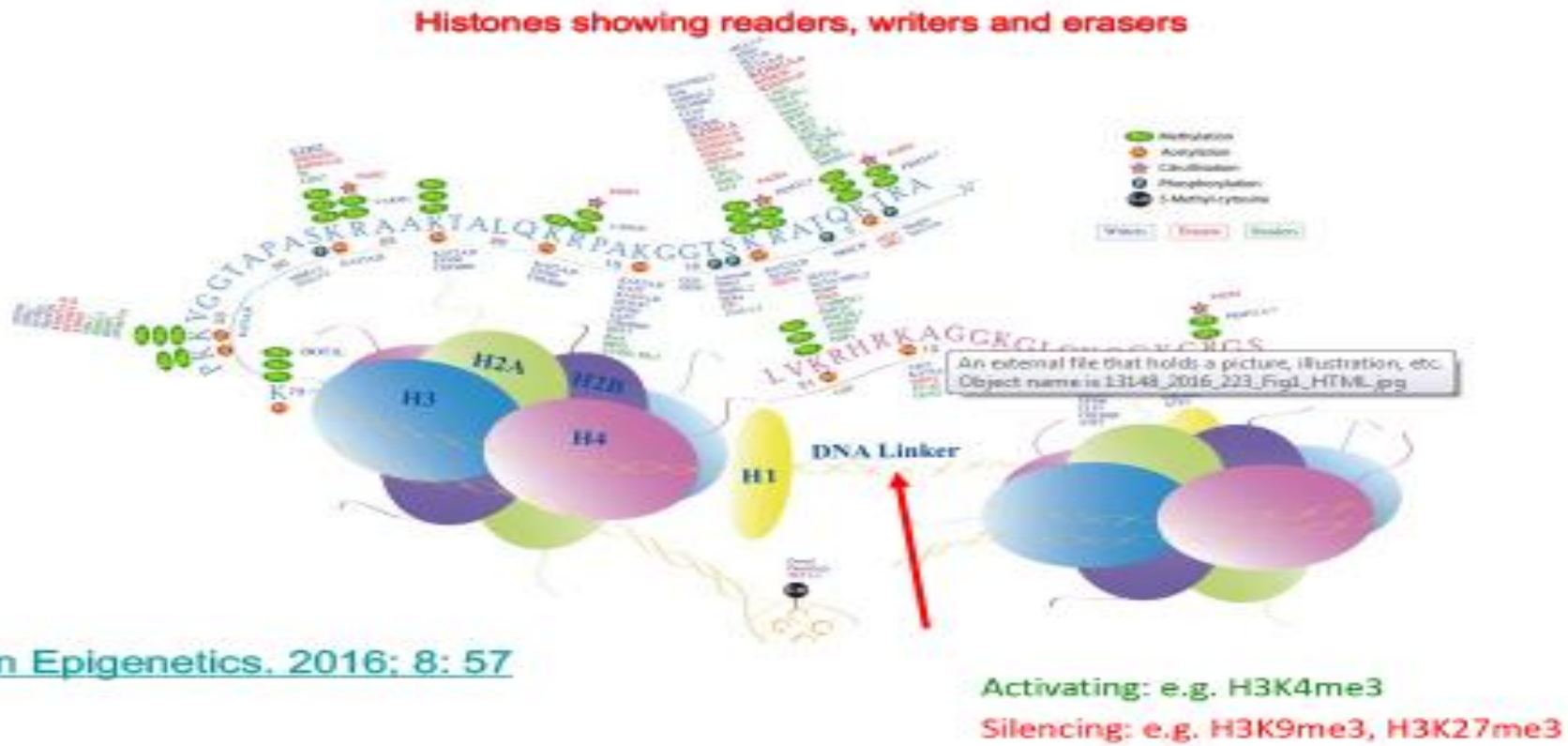
RNA epigenetics



Histone modifications



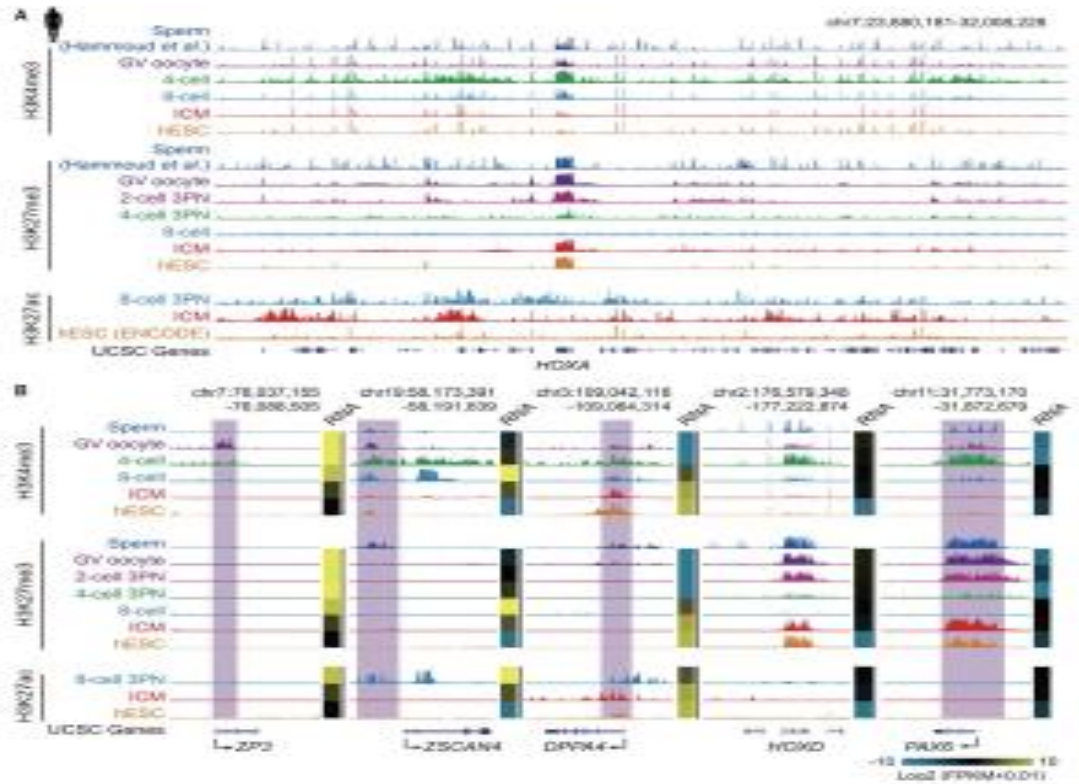
Histones


Histones showing readers, writers and erasers
H2A
H2B
H3
H4
H1
DNA Linker
An external file that holds a picture, illustration, etc.
Object name is 13148_2016_223_Fig1_HTML.jpg
Clin Epigenetics. 2016; 8: 57
Activating: e.g. H3K4me3
Silencing: e.g. H3K9me3, H3K27me3

Histone modifications

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

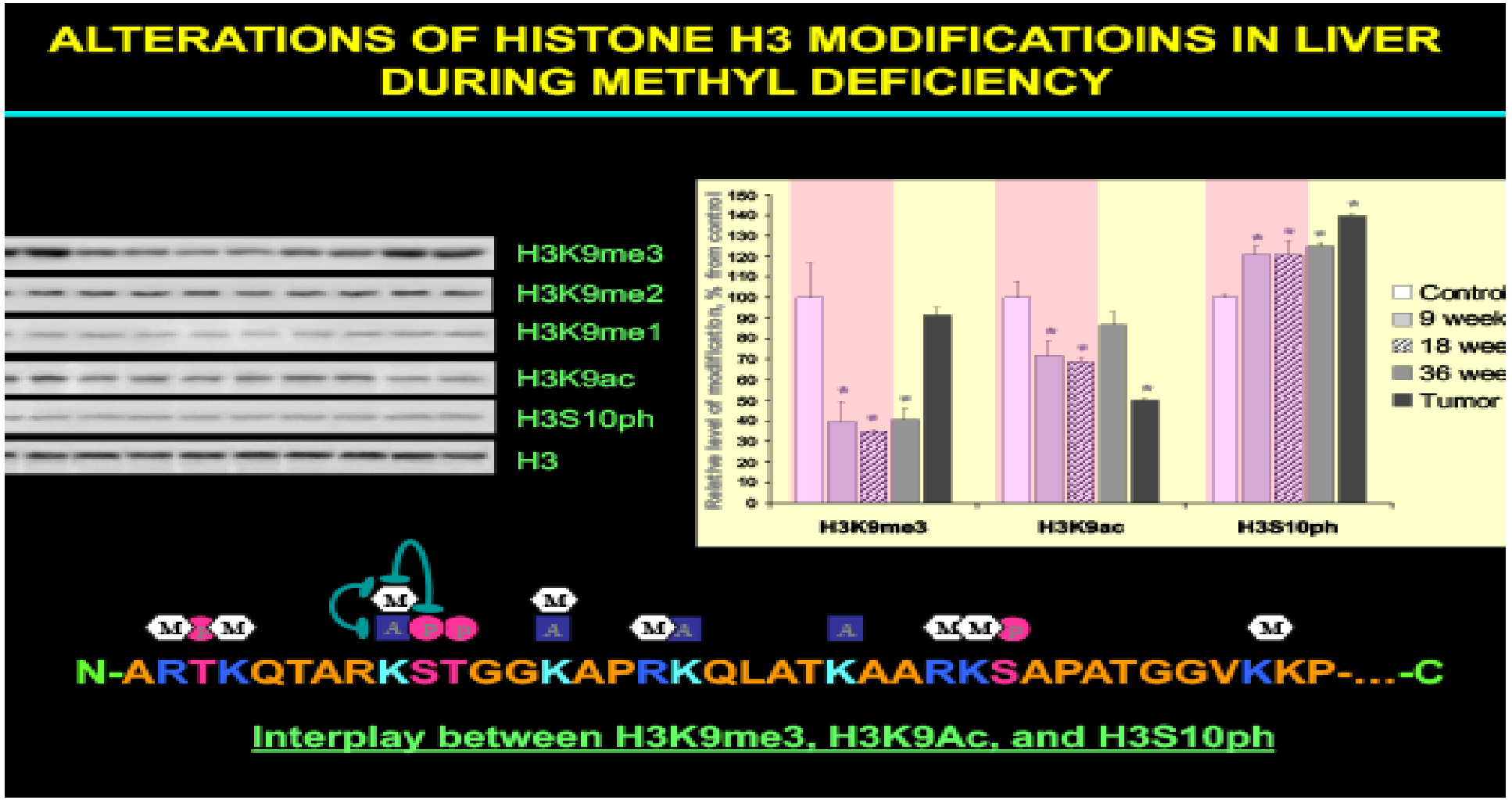
Histone mapping



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

Science AAAS

Histone H3 modifications



Epigenetic regulation

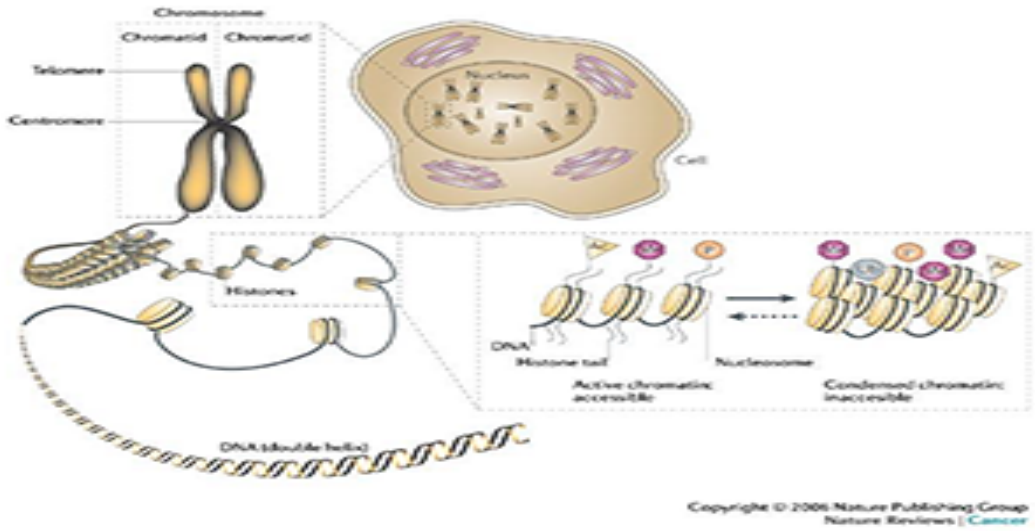
Epigenetic Gene Regulation:

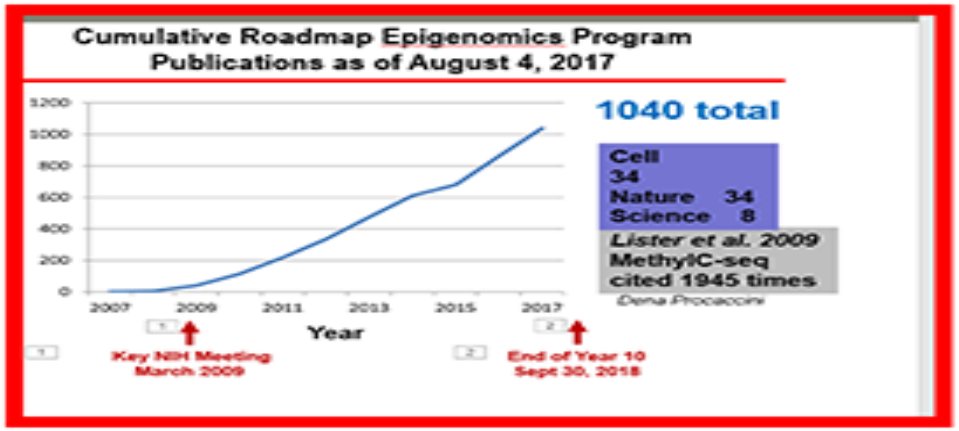
Modification		Methylation			Acetylation
		Mono-methylation	Di-methylation	Tri-methylation	
DNA		Repression	--	--	--
Histone	H3K4	Activation	Activation	Activation	--
	H3K9	Activation	Repression	Repression	Activation
	H3K27	Activation	Repression	Repression	--
	H3K36	--	Repair	Activation	Activation
	H3K79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

Abnova

Epigenetics roadmap

Epigenetics Roadmap





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

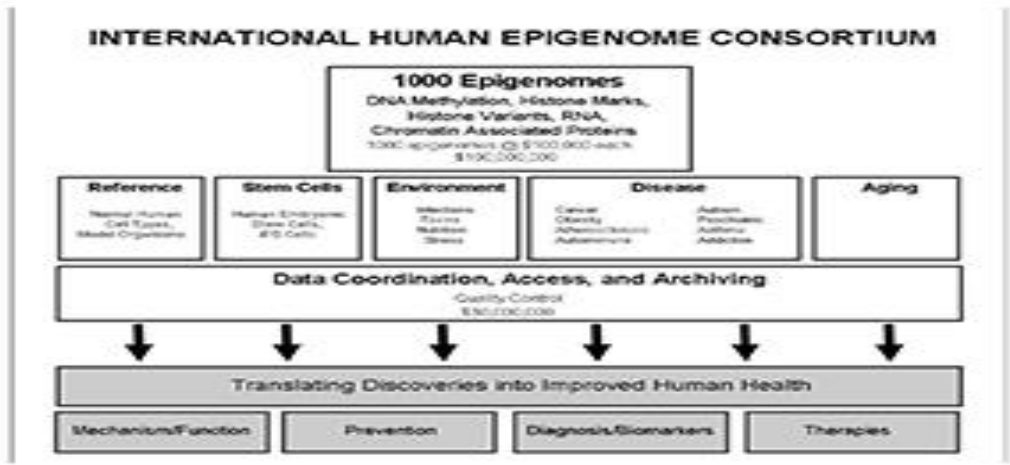
Epigenomics Program Budget

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



http://ihec-epigenomes.org/

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

Histone modifications

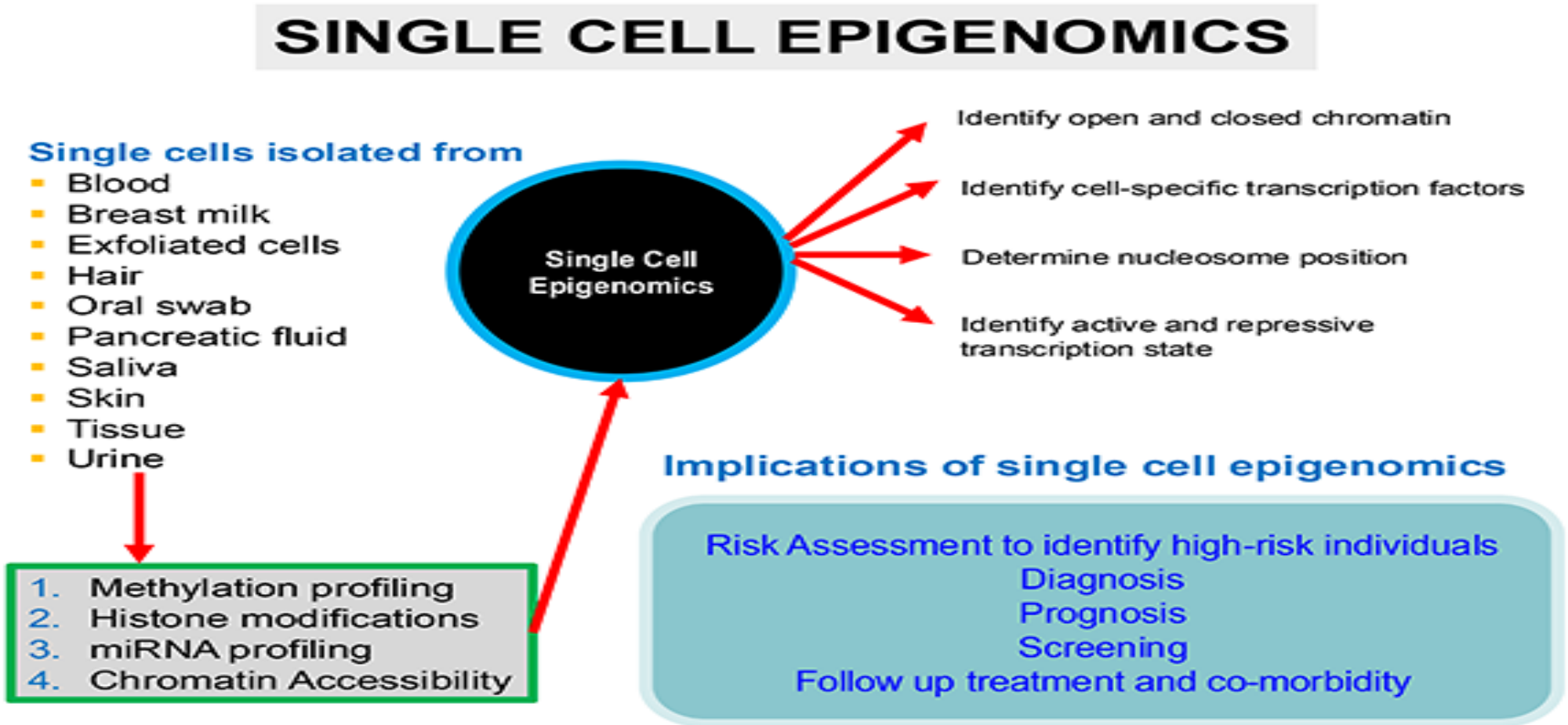
20 Diagnosing Cancer Using Histone Modification Analysis

Mukesh Verma and Deepak Kumar

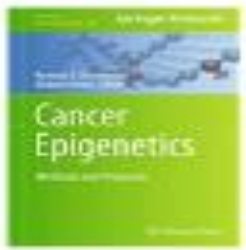
CONTENTS

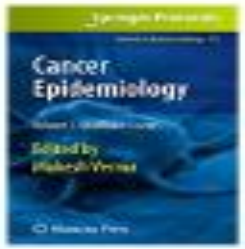
ISBN 9781420045796 - CAT# 45792

Single cell epigenomics



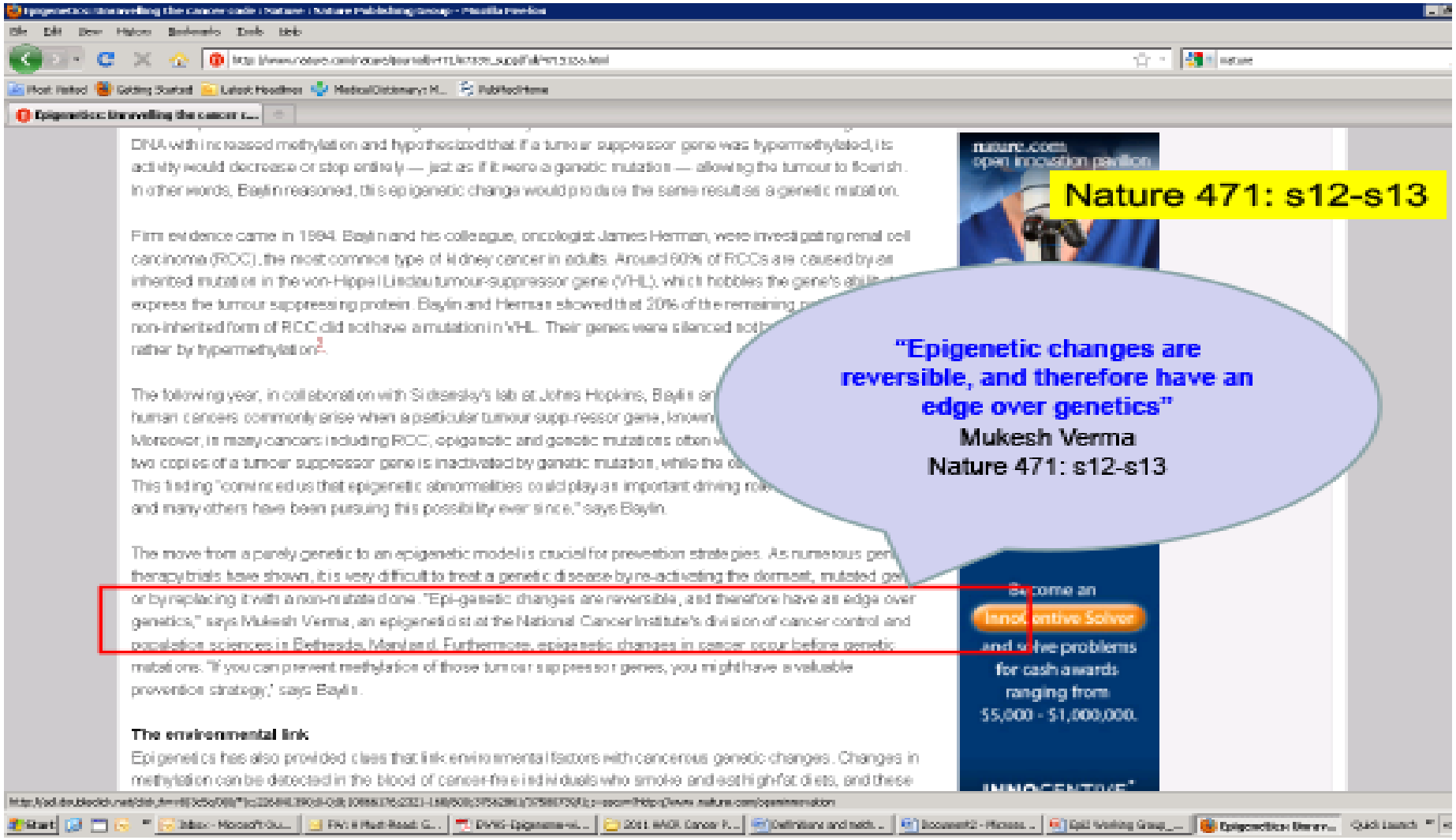
Books



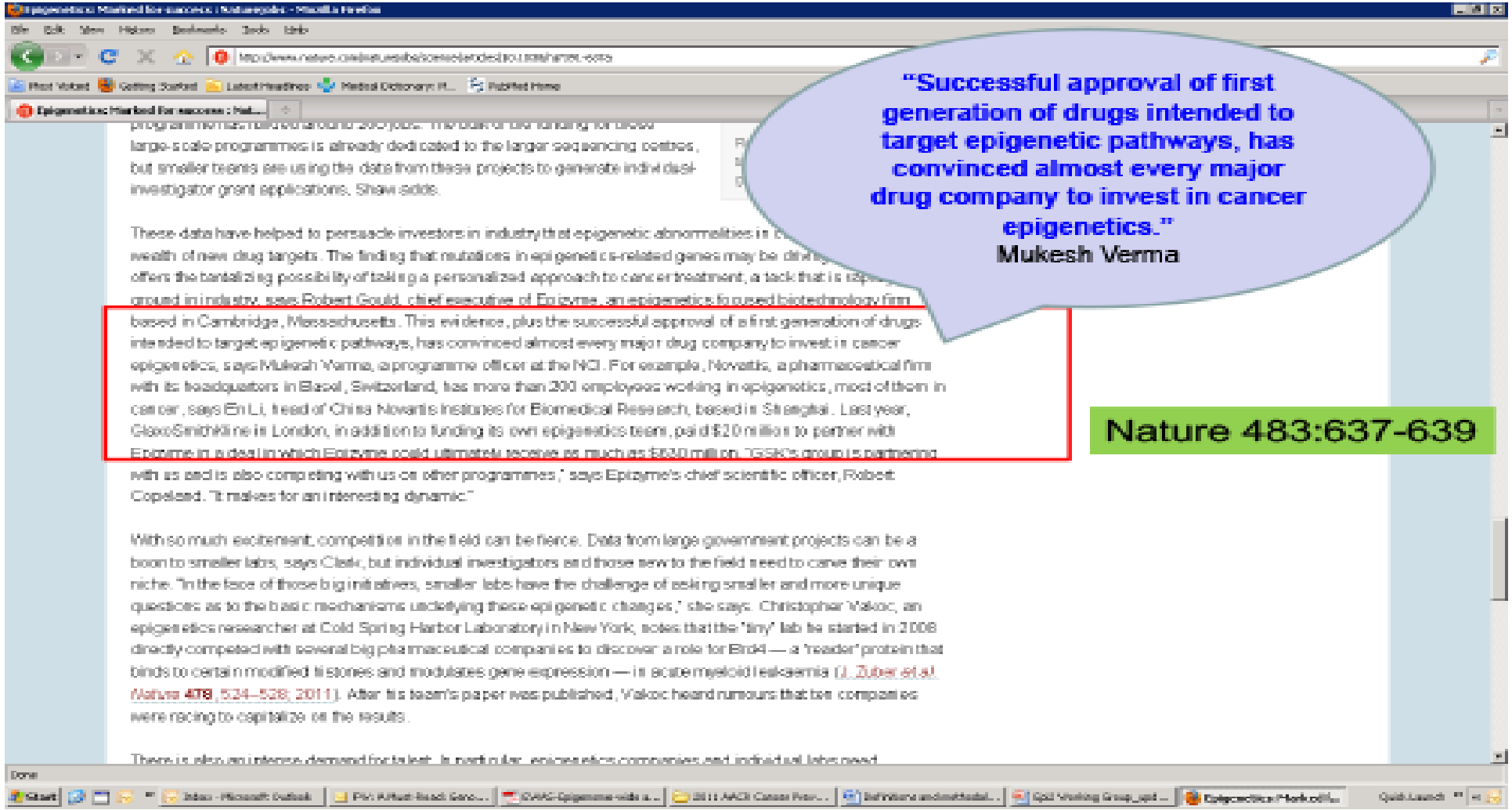


Books edited by Mukesh Verma

Epigenetic changes



Epigenetic drugs



Tumors and epigenetics

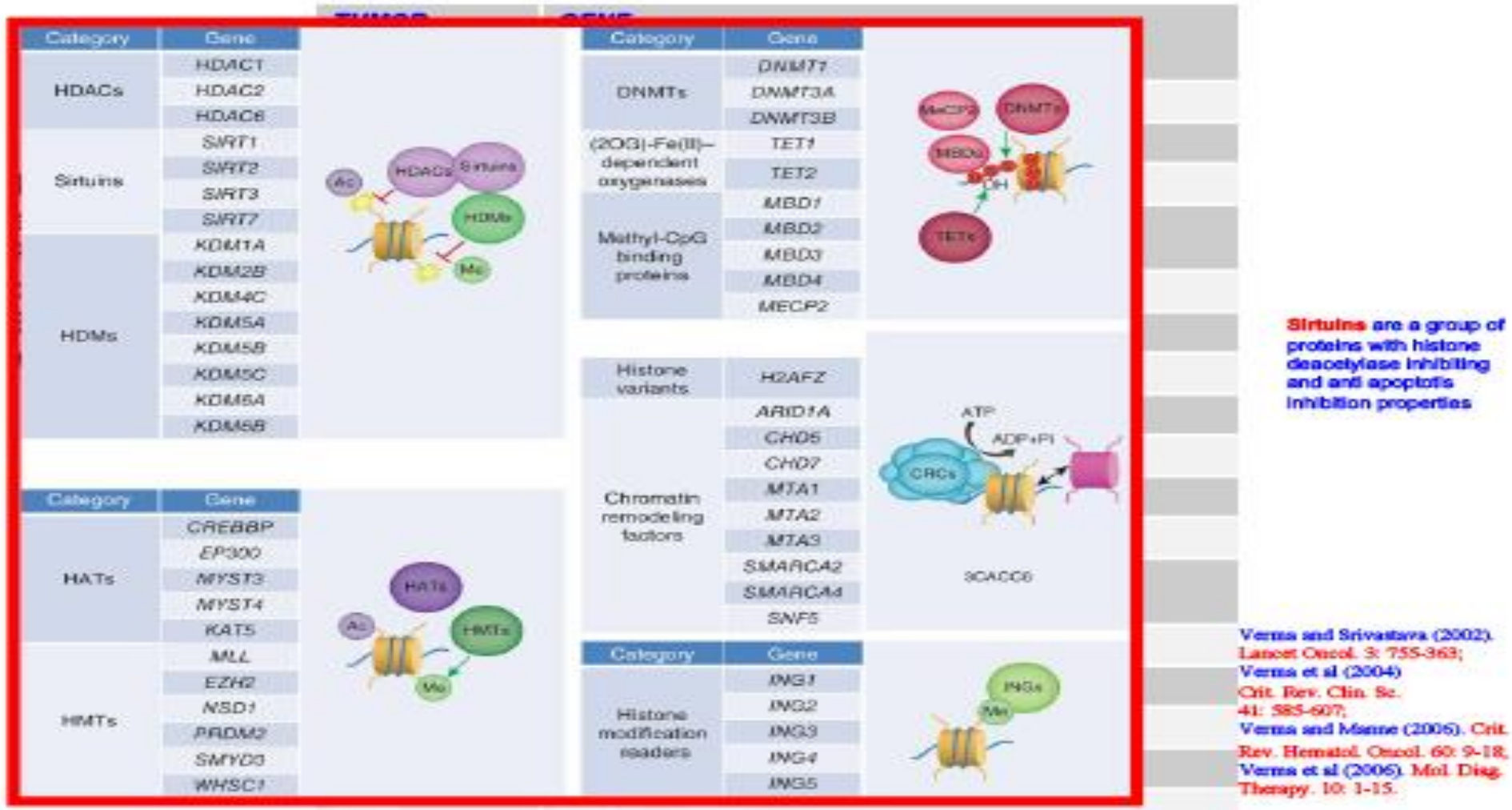
Tumor Types and Genes Regulated by Epigenetic Mechanism

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

Silencing of a group of promoters with histone deacetylase inhibitors and cytidine analog inhibitor properties

Yoo and Snyder (2002) Cancer Cell 1: 235-240
Yoo et al (2004) Cell Res Clin Sci 41: 565-607
Yoo and Moore (2000) Clin Rev Neurosci Oncol 60:9-18
Yoo et al (2000) Mol Diag Therapy 10:1-15

Histone enzymes



Epigenetic drugs

Target	Drug	Clinical Trial
DNA Methylation	5-Azacytidine	Phase I/II/III
	5-Aza-2'deoxycytidine	Phase I/II/III
	FCDR	
	Zebularine	
	Procainamide	
	EGCG	Phase I
	Psamaplin A	
	Antisense Oligomers	Phase I
Histone deacetylase	Phenylbutyric acid	Phase I/II
	SAHA (Suberoylanilide hydroxamic acid) or Vorinostat	Phase I/II
	Depsipeptide	Phase I/II
	Valproic Acid	Phase I/II

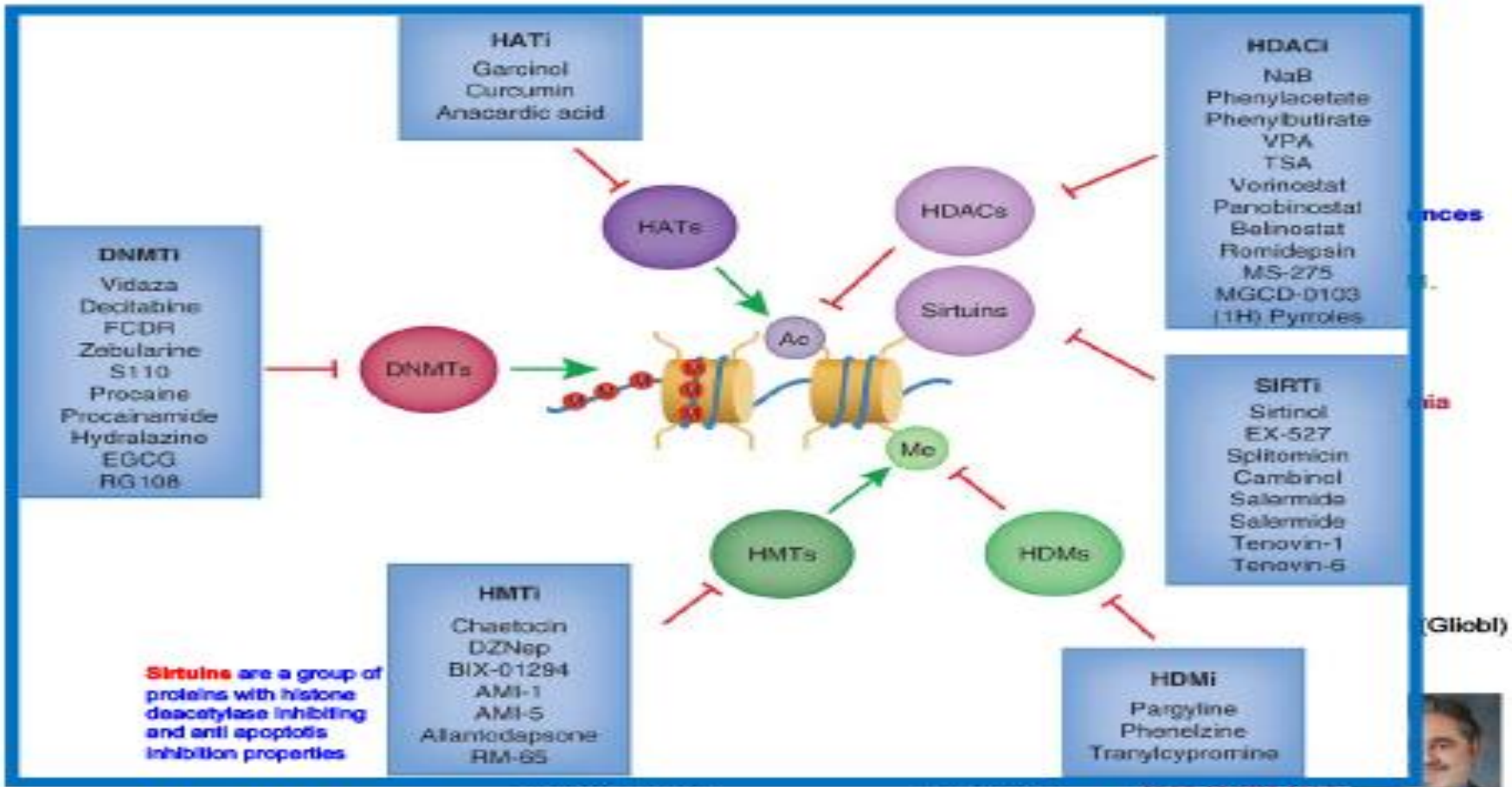
Adverse Experiences
SAHA
[illegible] 2007.
[illegible] 109:31.

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

[illegible]

[illegible]
Temple Univ.

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)

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)
Recriting	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)

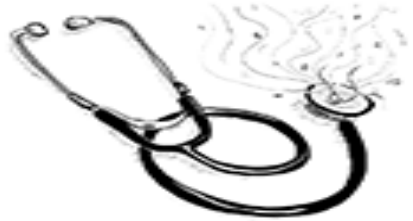
STATUS	STUDY
Completed	A Phase II Study of Epigenetic Therapy to Overcome Chemotherapy Resistance in Refractory Solid Tumors
Active Not Recruiting	Azacitidine and Valproic Acid in Patients With Advanced Cancers
Recruiting	Azacitidine With MGCD0103 or MS-275 in Treating Patients With Myelodysplastic Syndromes, Chronic Myelomonocytic Leukemia, or Acute Myeloid Leukemia
Active Not Recruiting	PhIII-Azacitidine Plus Valproic Acid and Preantelbe Beta 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 Ado Met and Peginx
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

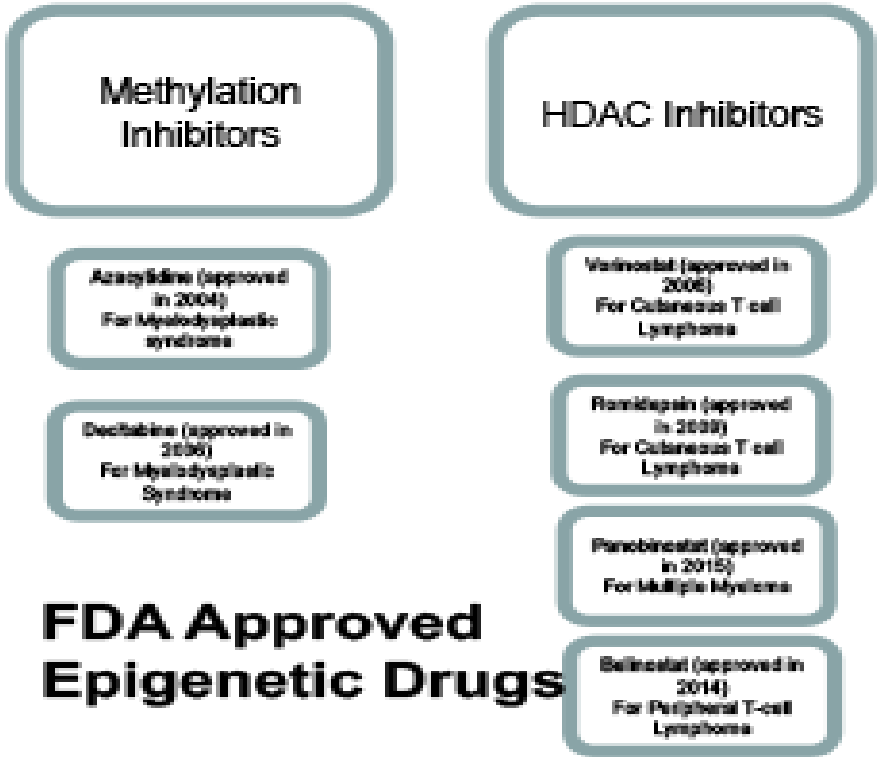
HDAC (entinostat)
Drug causing chemical change to stop tumor cell from dividing
Checkpoint inhibitors
PD-1/PD-L1 inhibitor nivolumab
CTLA-4 inhibitor ipilimumab

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

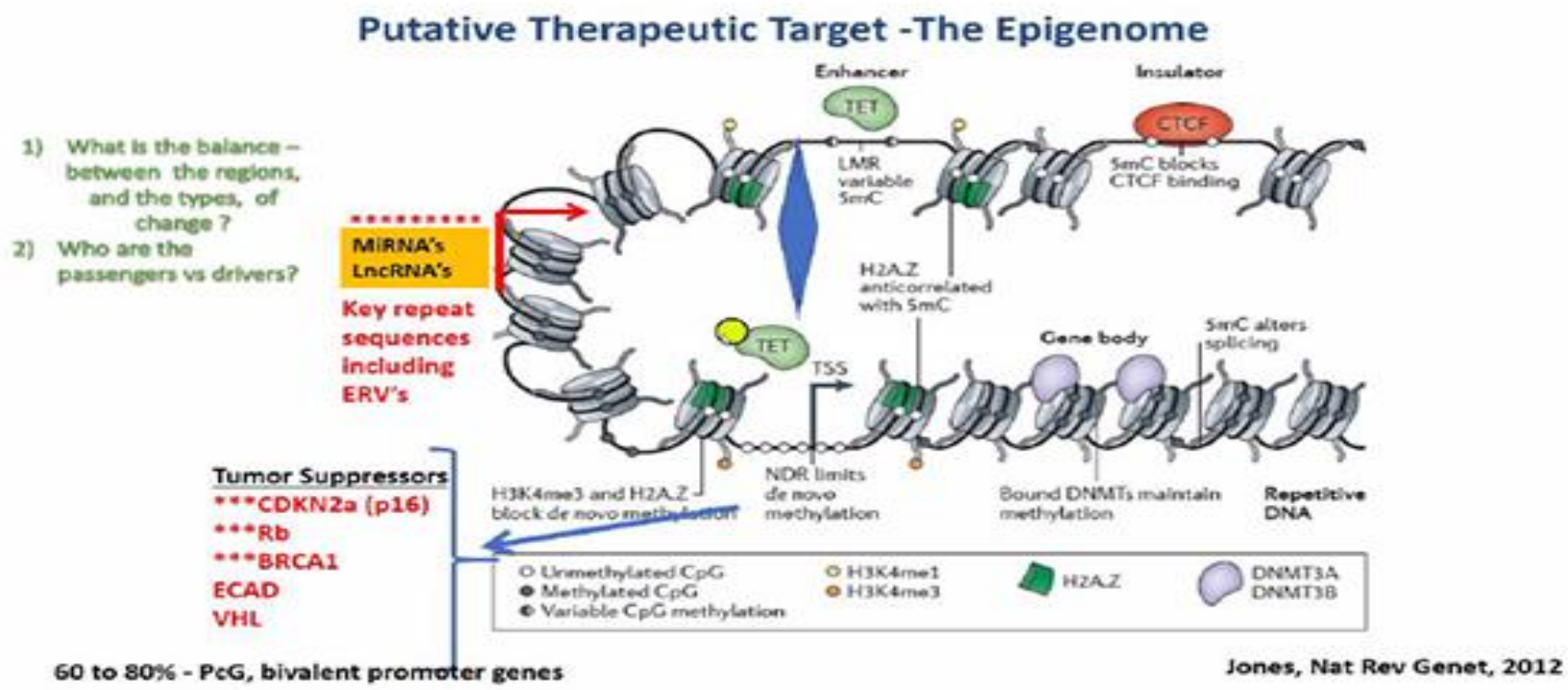
HER-2. Human Epidermal Growth Factor Receptor

Nature Cancer. February 2024

Approved epigenetic drugs



Therapeutic target



Epigenetics of cancer type

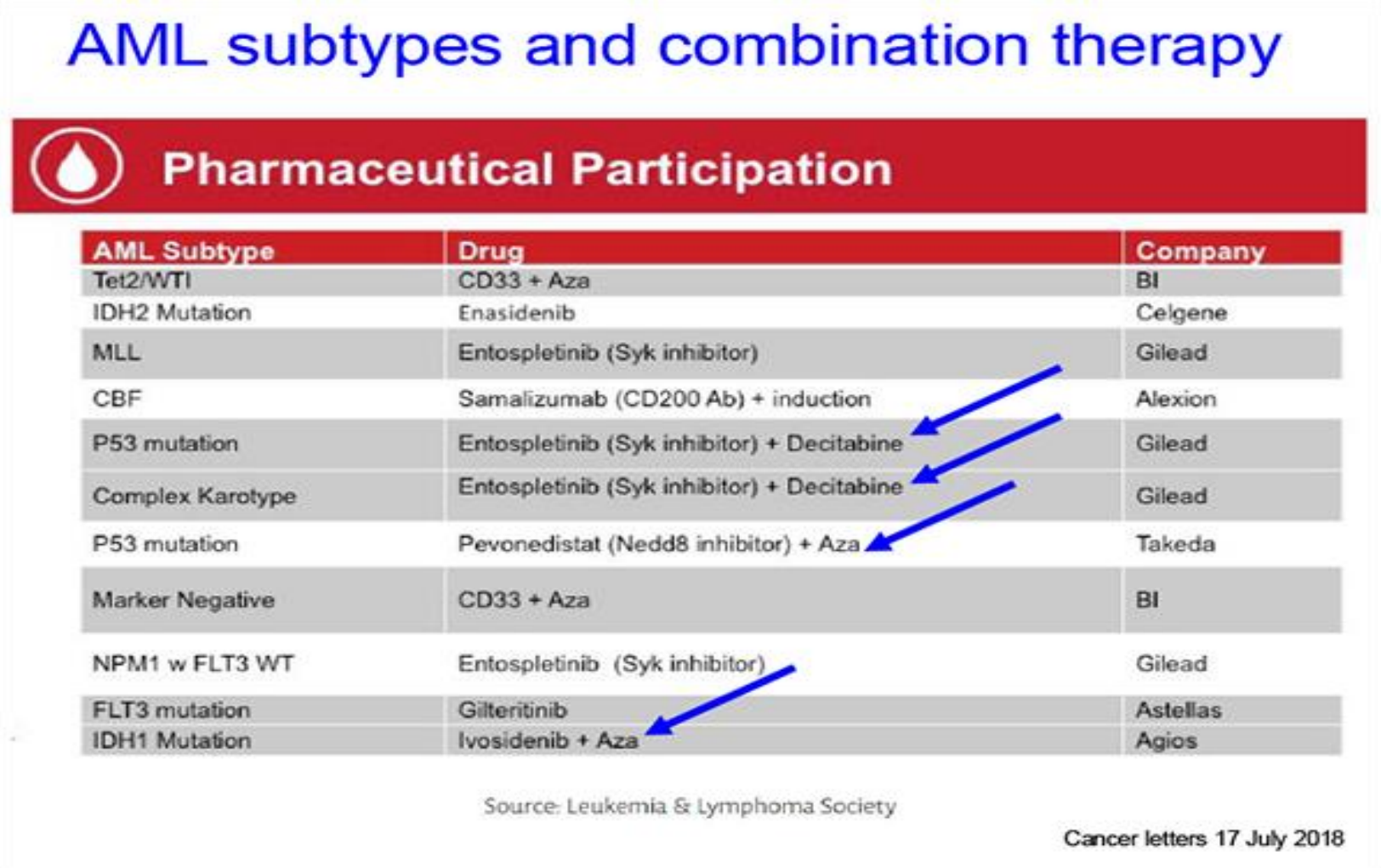
Tumor Types and Genes Regulated by Epigenetic Mechanism

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

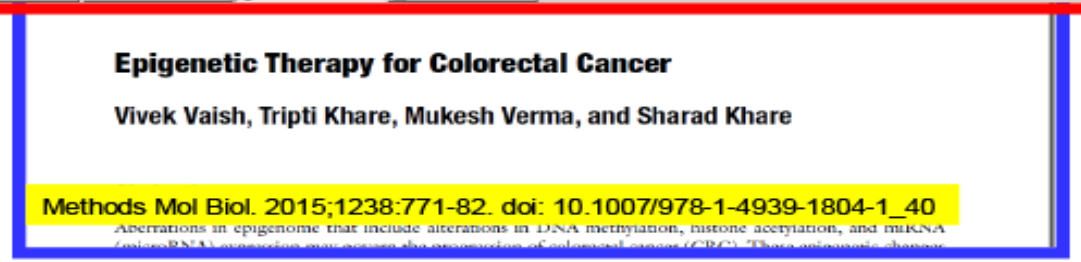


Combination epigenetic therapy

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.

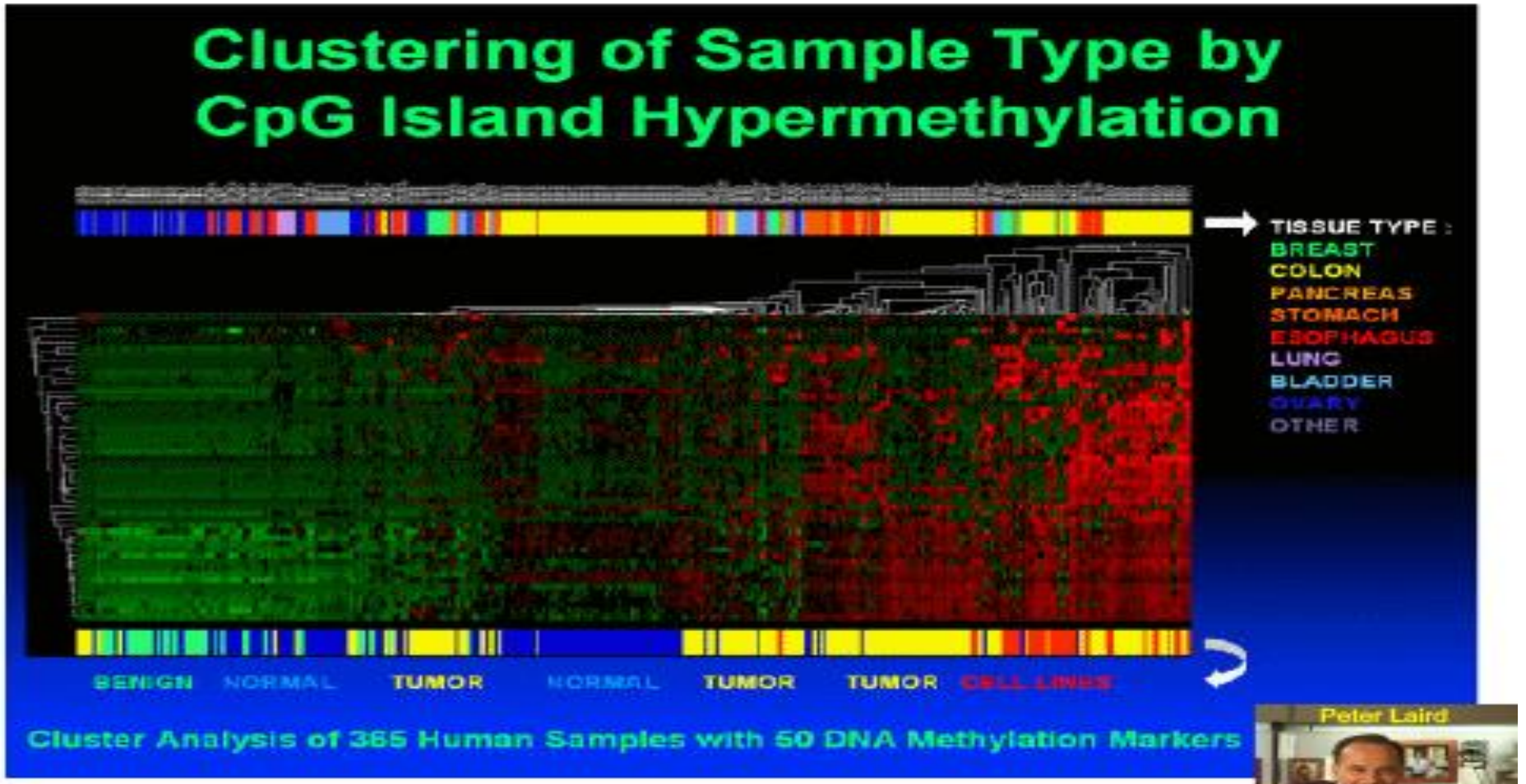


Epigenetic Therapy for Colorectal Cancer

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

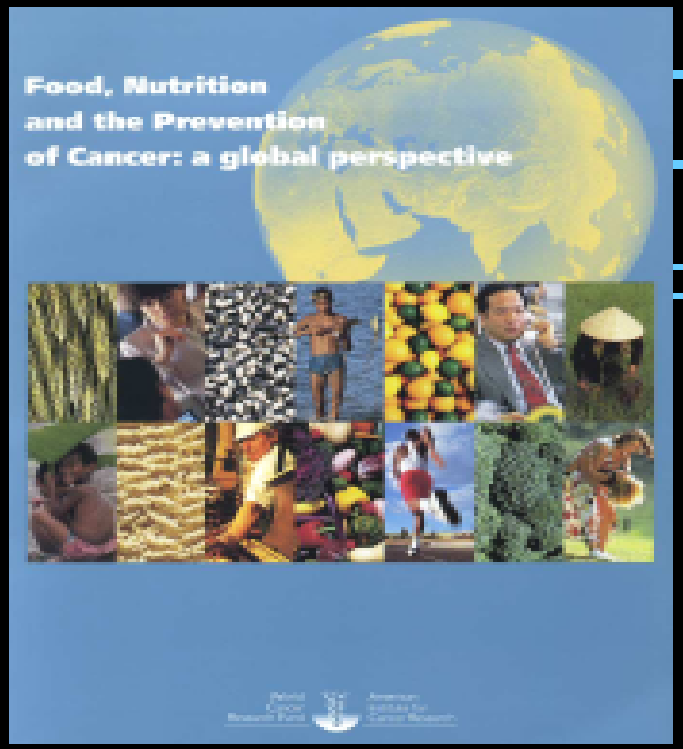
Methods Mol Biol. 2015;1238:771-82. doi: 10.1007/978-1-4939-1804-1_40

CpG island hypermethylation



Diet and cancer

DIET AND CANCER: FOCUS ON PREVENTION

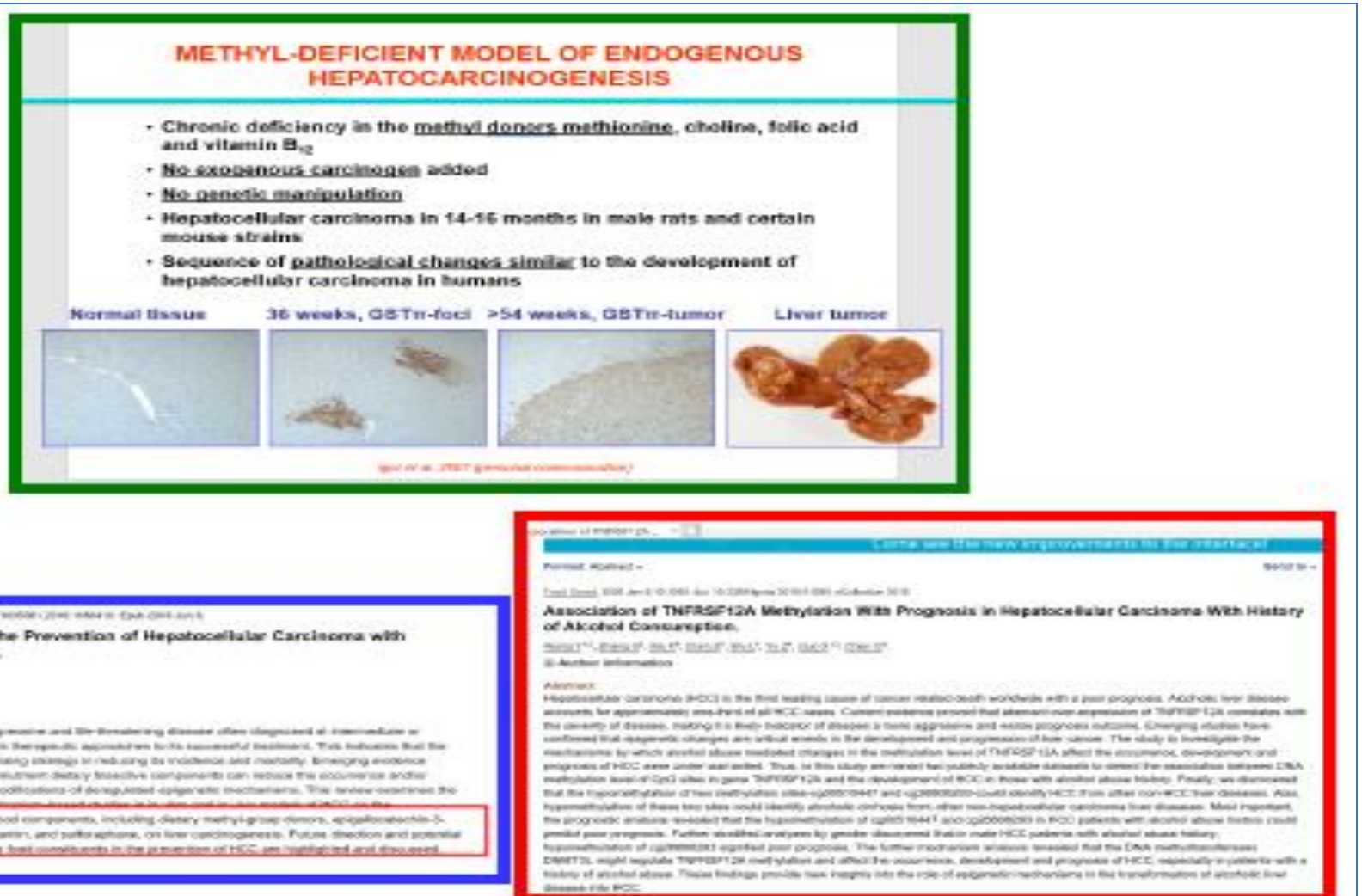


Cancer is principally caused by environmental factors, of which the most important are tobacco, diet and factors related to diet, including body mass and physical activity, and exposures in the workplace and elsewhere.

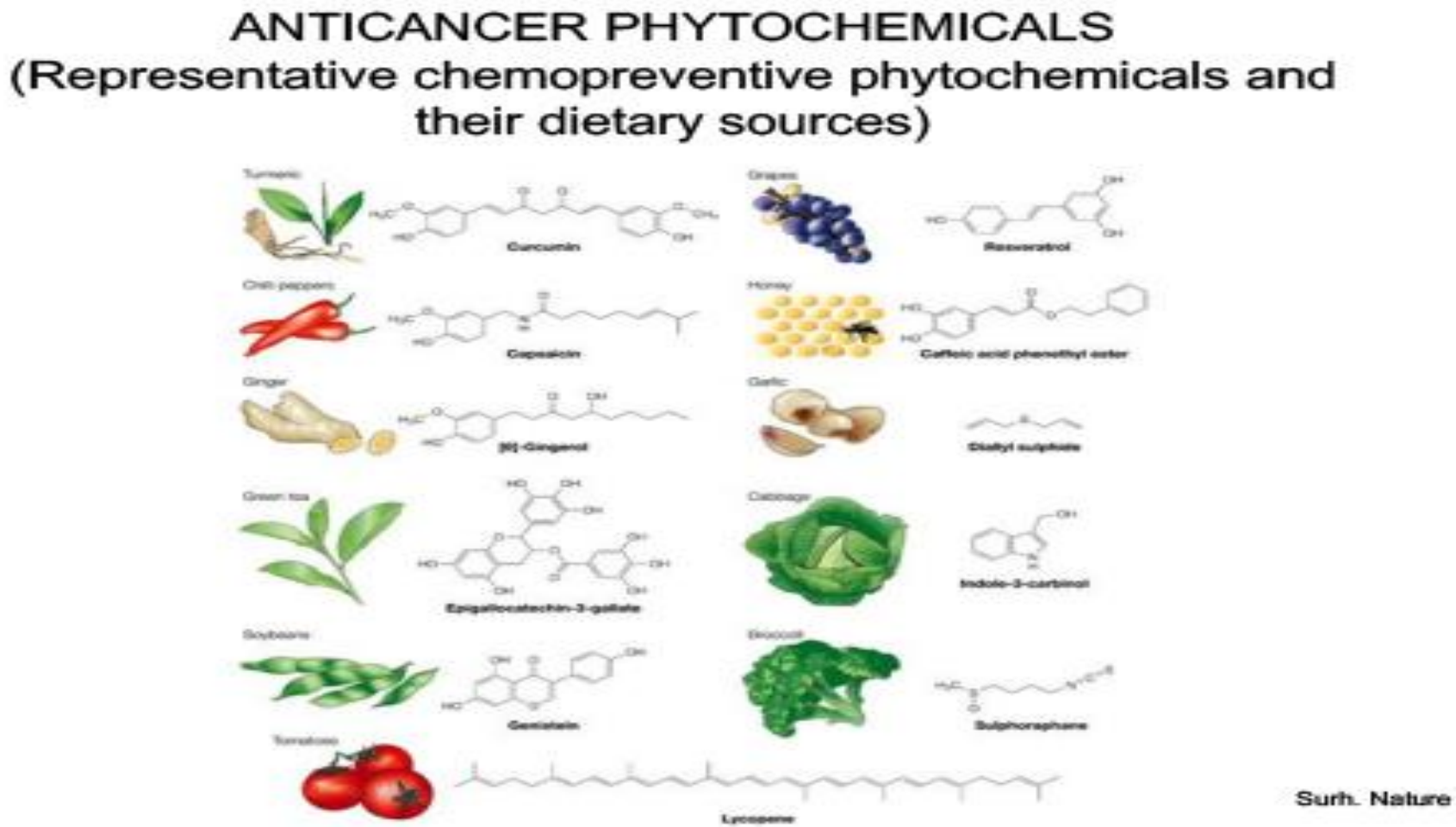
Between 30% and 40% of cancer cases throughout the world are preventable by feasible dietary means.

- 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 preneoplastic cells
- Determining factors that can modulate effect of diet

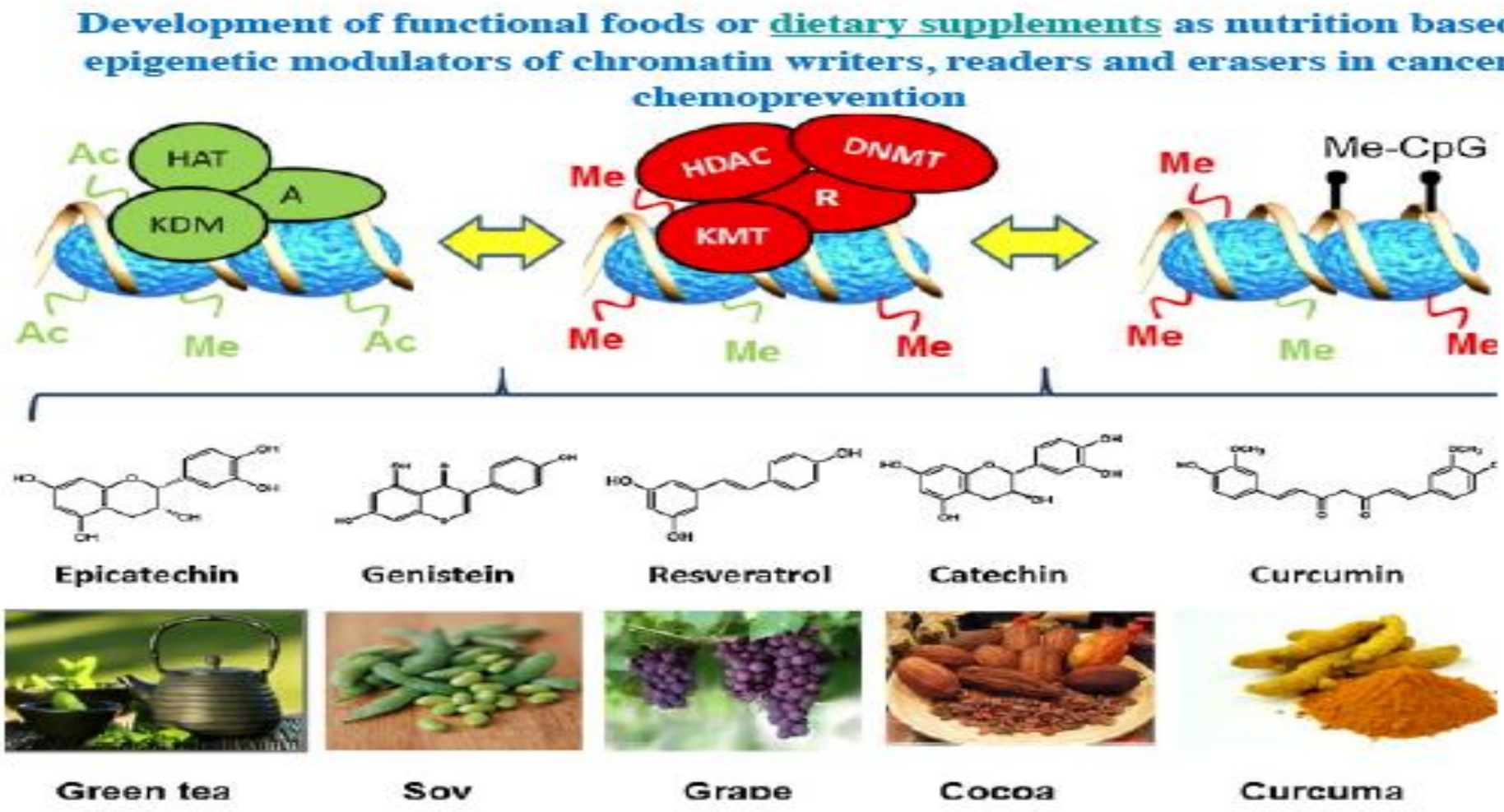
Methyl deficiency



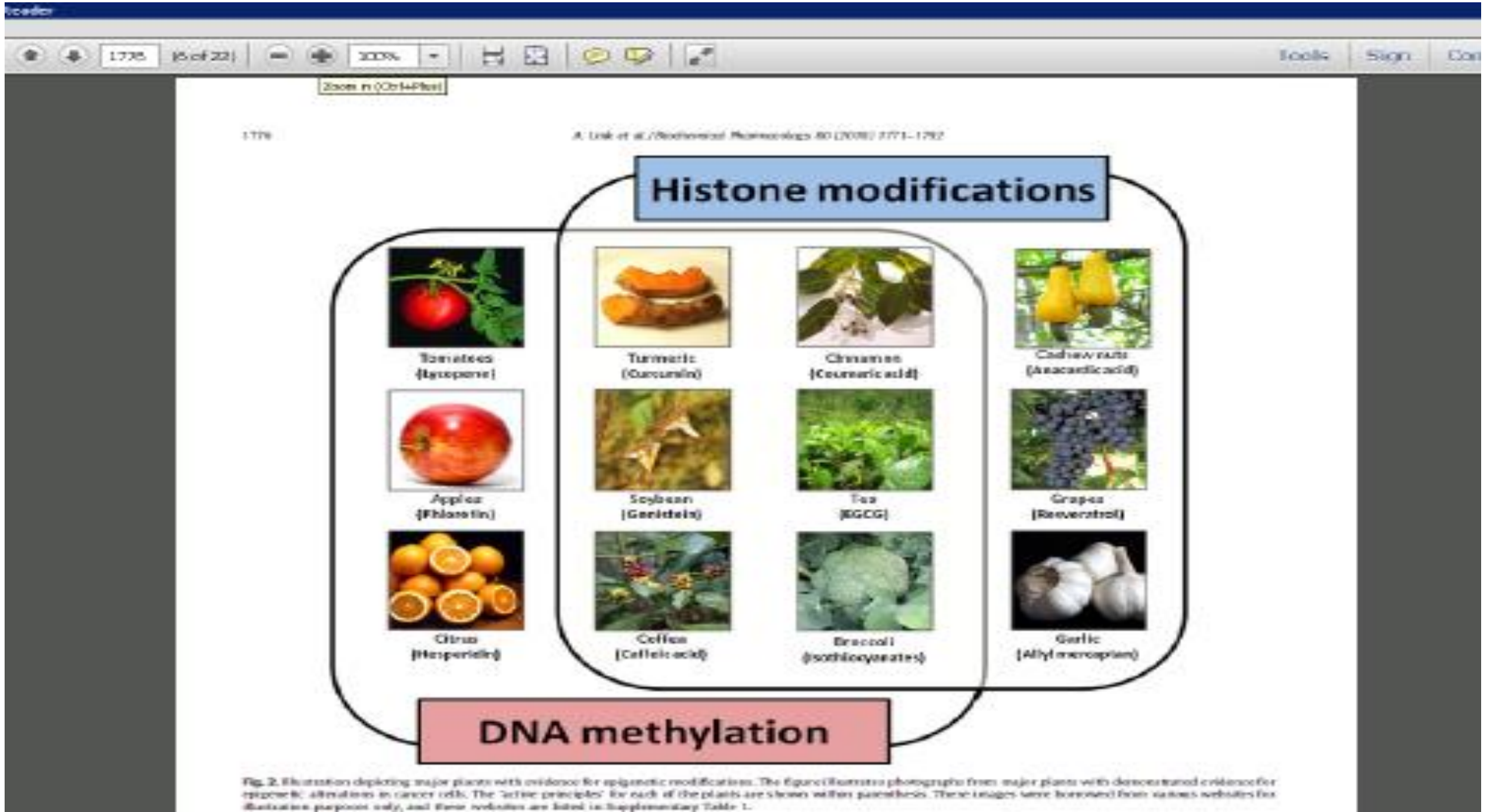
Anticancer phytochemicals



Dietary supplements



Epigenetic foods



Myplate

https://www.myplate.gov/

Mobile food record

Ahmad et al doi: 10.1145/2986035.2986038; (Zhu et al 2022)

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.**