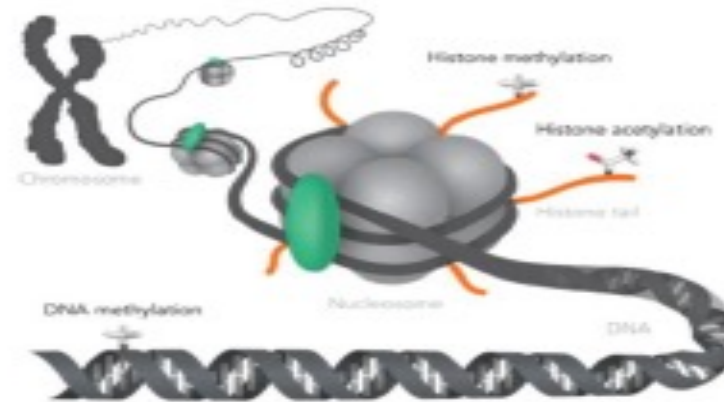


Epigenetics and cancer

Epigenetics and Cancer



Mukesh Verma, Ph.D.

Chief, Methods and Technologies Branch
Program Director,
Epidemiology and Genomics Research Program
DCCPS, NCI, NIH

Epigenetics

Epigenetics:

Stable alterations in gene expression by several mechanisms, except nucleotide sequence changes

Genetic Code

The two main components of the epigenetic code

DNA methylation

Methyl marks added to certain DNA bases repress gene activity.

Methylation Code

Histone Code

Histone modification

A combination of different molecules can attach to the 'tails' of proteins called histones. These

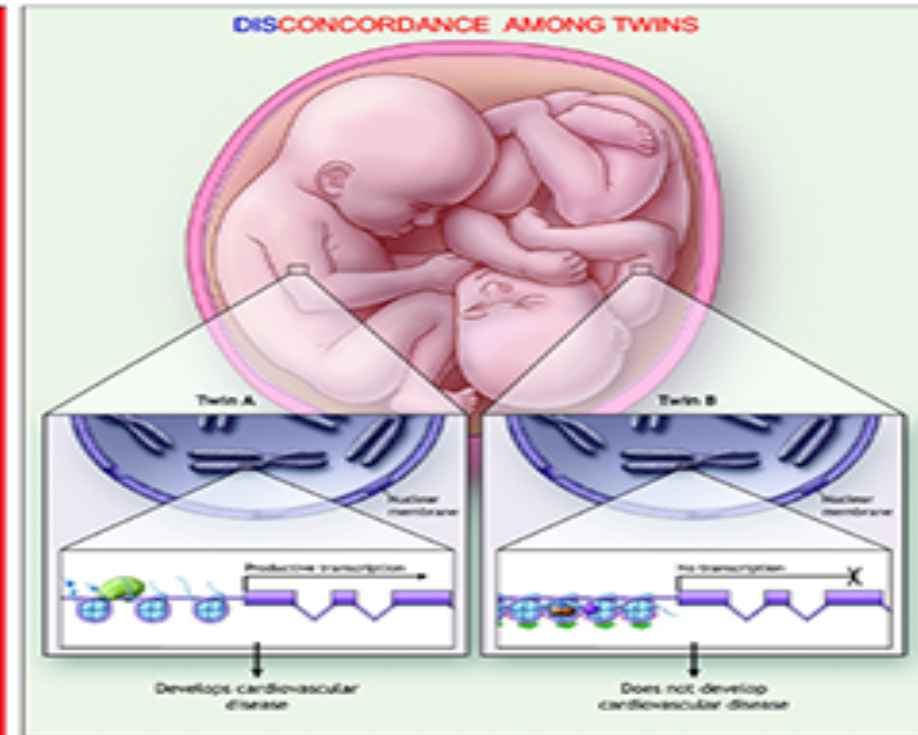
The genetic information provides the blue print for the manufacture of all the proteins necessary to create a living organism, whereas the epigenetic information provides the instructions on how, where and when the genetic information will be used.



DNA and destiny



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



Epigenetic predisposition to angiogenesis? Individual? Populations?

Pharmacogenomics and pharmacoepigonomics (personalized medicine)

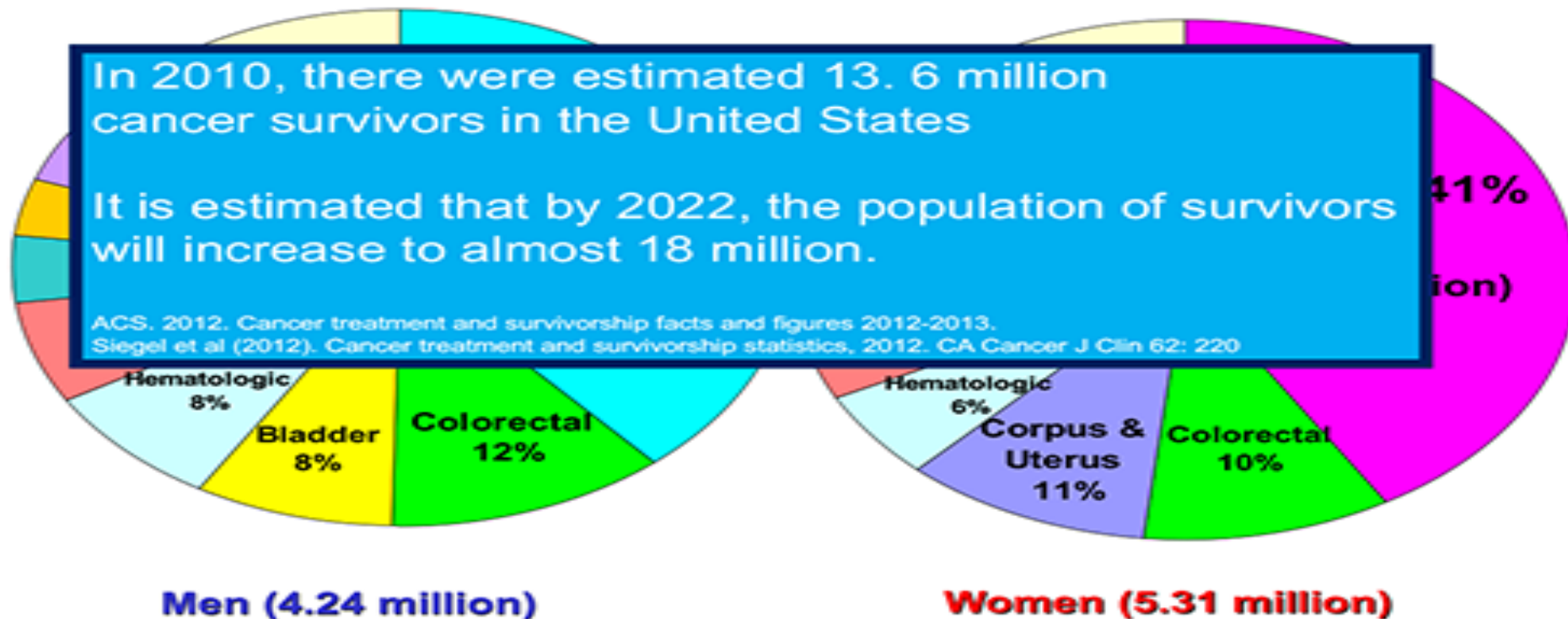
Microenvironment, microbiome, and gene expression

GWAS and EWAS

Adapted from Matouk and Marsden *Cir Res* 102:873

Cancer Survivors

Estimated Number of Persons Alive in the U.S. Diagnosed with Cancer by Site



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

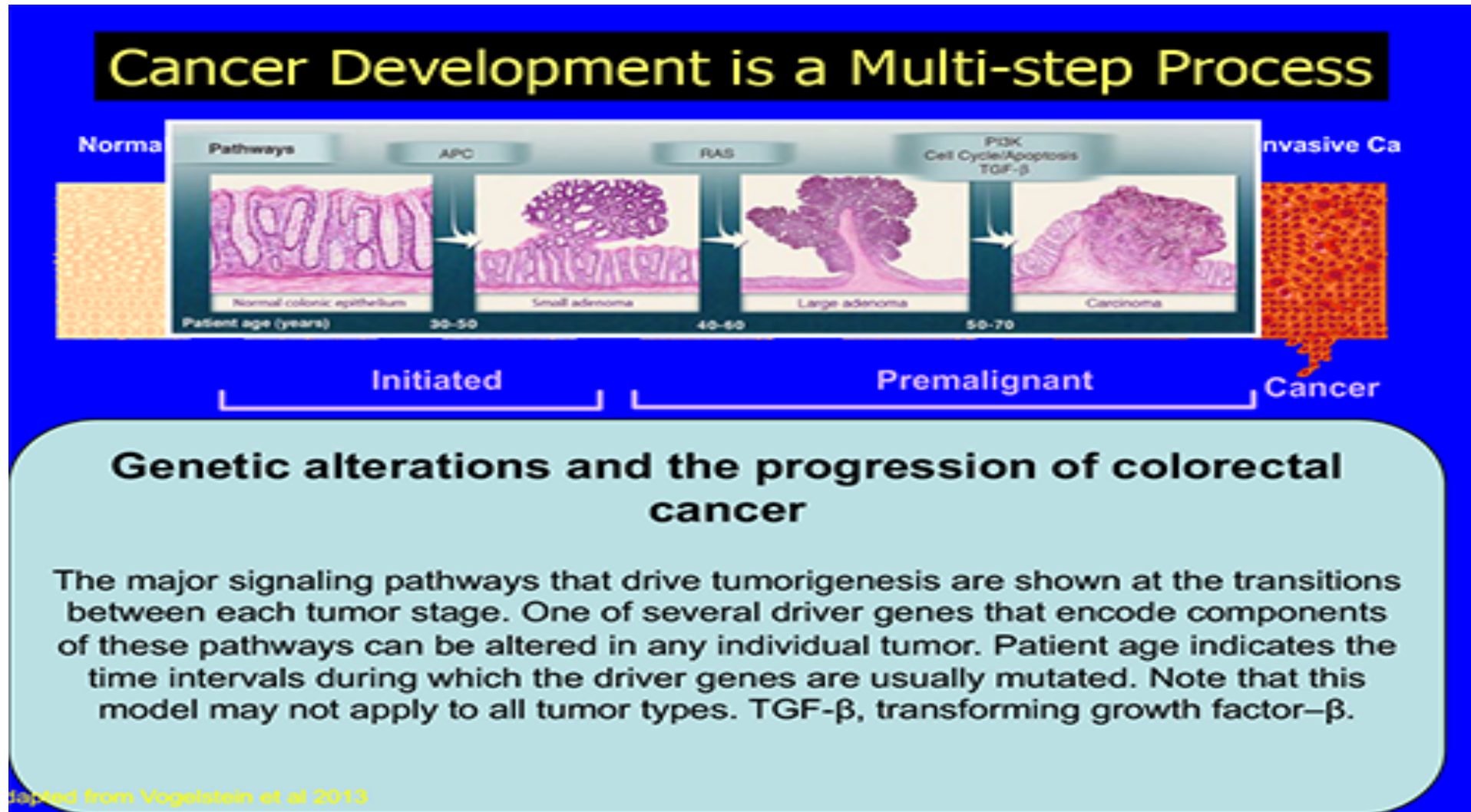
Prevention



Cancer recurrence
Secondary cancer

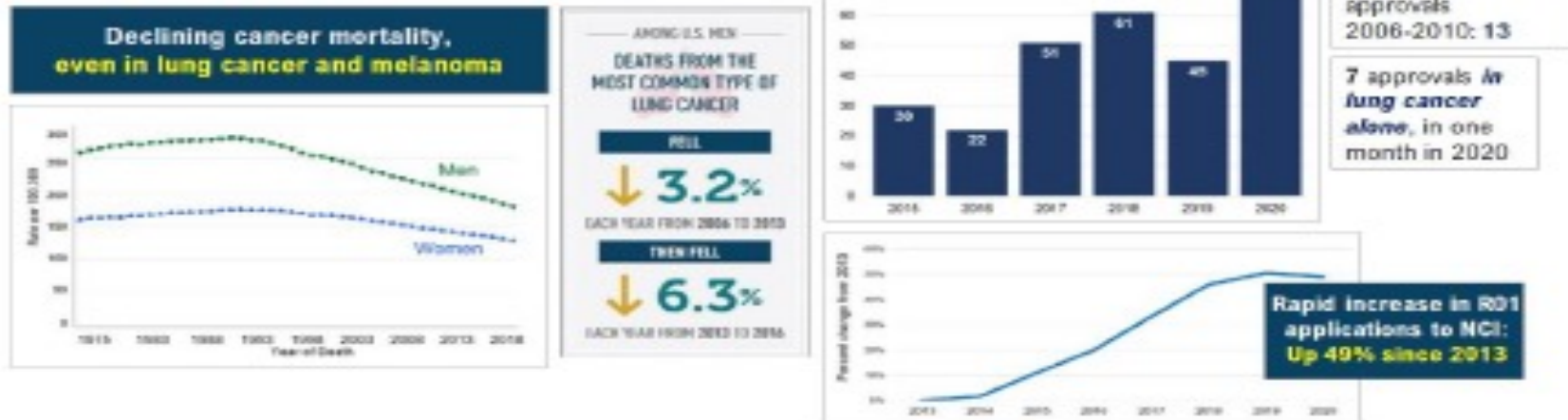
Prevention: restoring transcription,
halting progression, or stopping
metastasis

Cancer development



Cancer research progress

Remarkable progress in cancer research

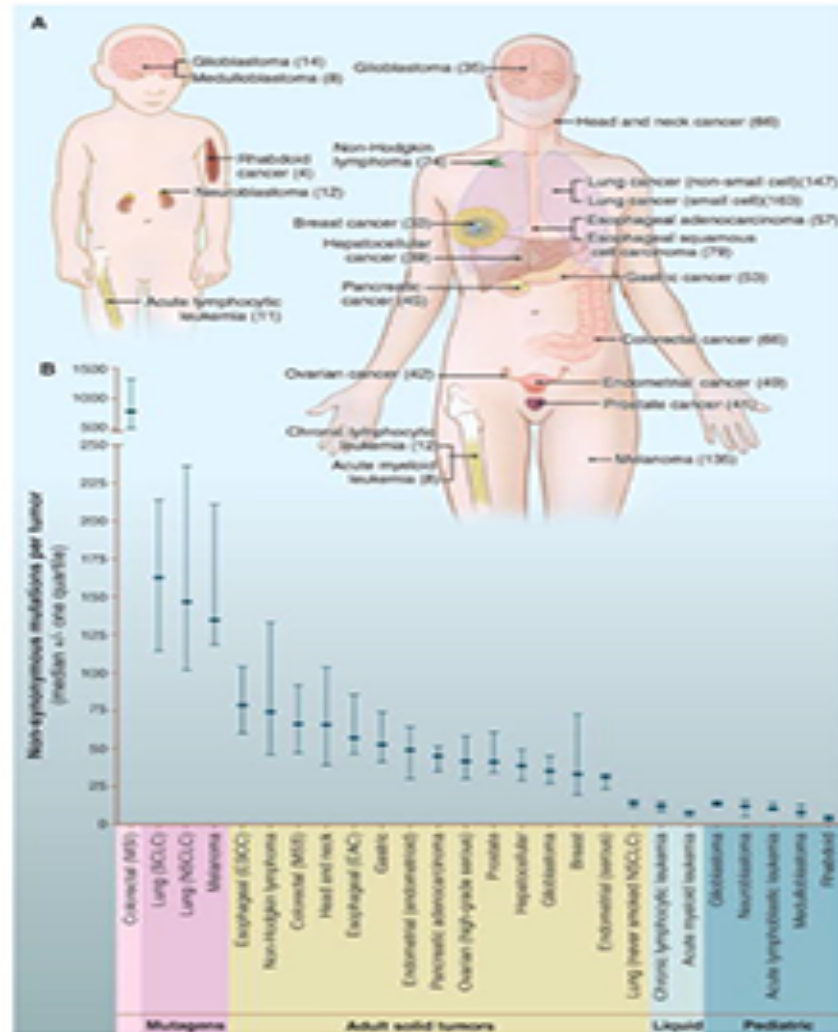


Paradigm shift

Paradigm shifts in genetics

| | |
|------------------------------|--|
| 1850 -1900 : Proto-genetics | <i>Mendelian inheritance Darwin, natural selection</i> |
| 1900 -1950 : Age of genetics | <i>gene concept, mutation, genotype-phenotype</i> |
| 1950-2000 : Age of DNA | <i>structure, genetic code, genome sequence</i> |
| 2000 - : Age of epigenetics | <i>epigenetic code, epigenome, epigenetic medicine</i> |

Genome landscape



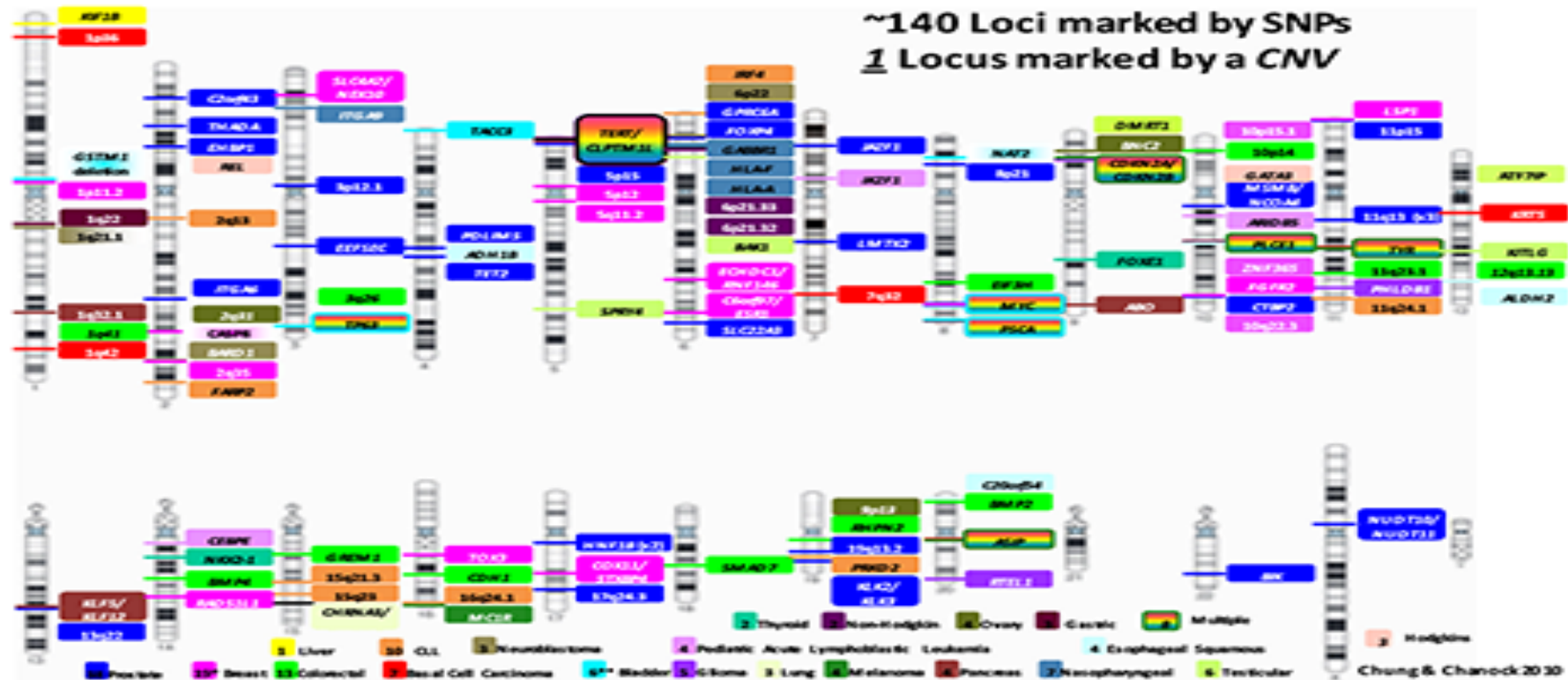
CANCER GENOME LANDSCAPE
 Number of somatic mutations in representative human cancers, detected by genome-wide sequencing studies



Adapted from Vogelstein and Kinzler (Science 2013)

GWAS hits

Published GWAS Etiology Hits (2010)



Hindorf L, Gillanders EM, Manolio T.

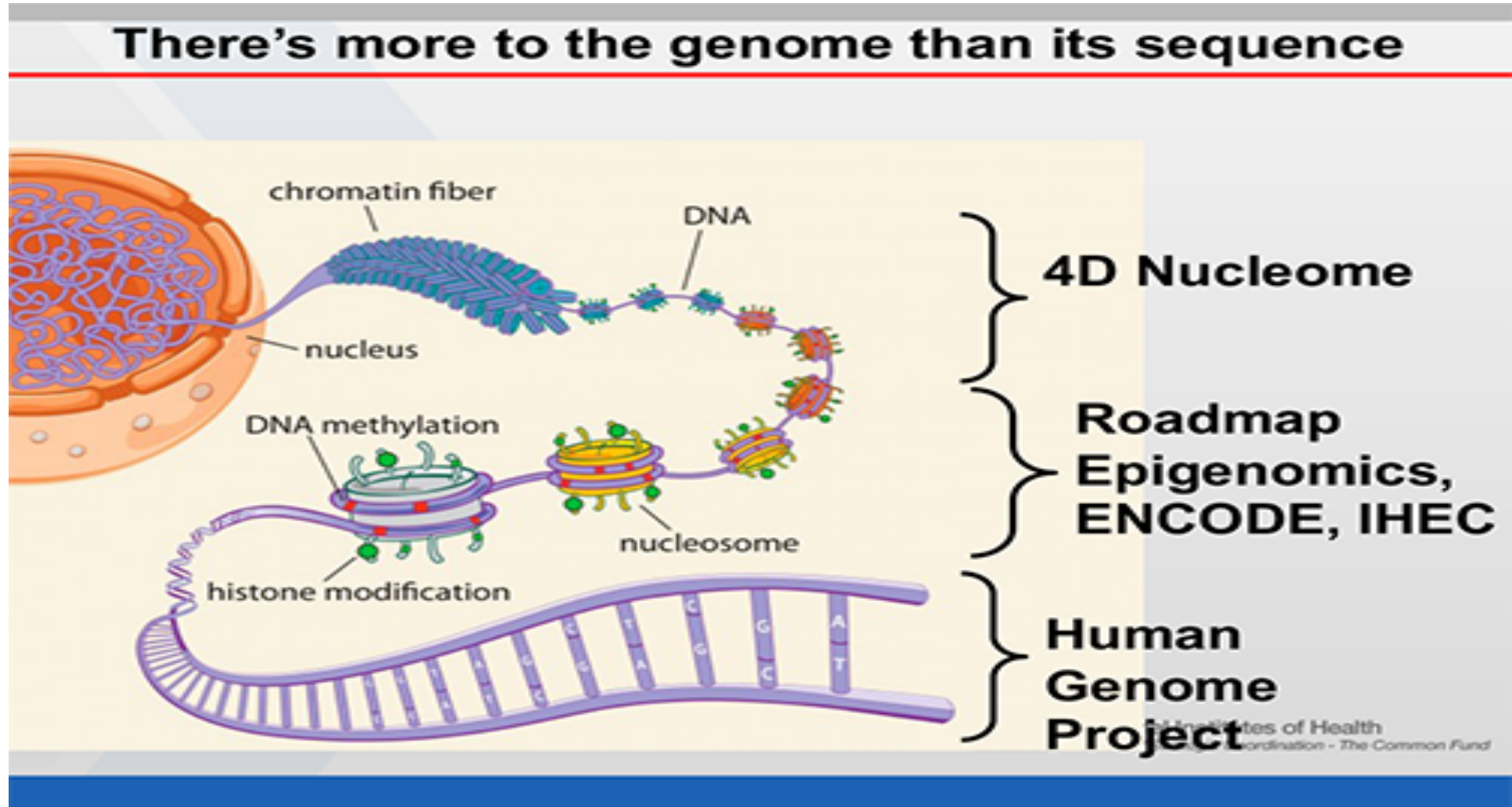
Adapted from T. Manolio

Cancer genes



Adapted from T. Manolio

Genome sequence



Kornberg and nucleosome

Nucleosomes (Units of Chromatin)

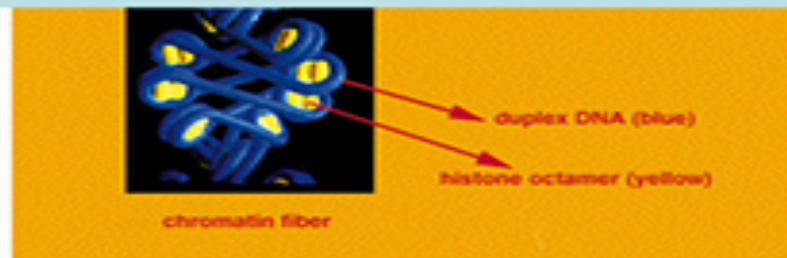
DNA
Histones H2a, H2b, H3, H4

To neutralize charge and provide stability

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

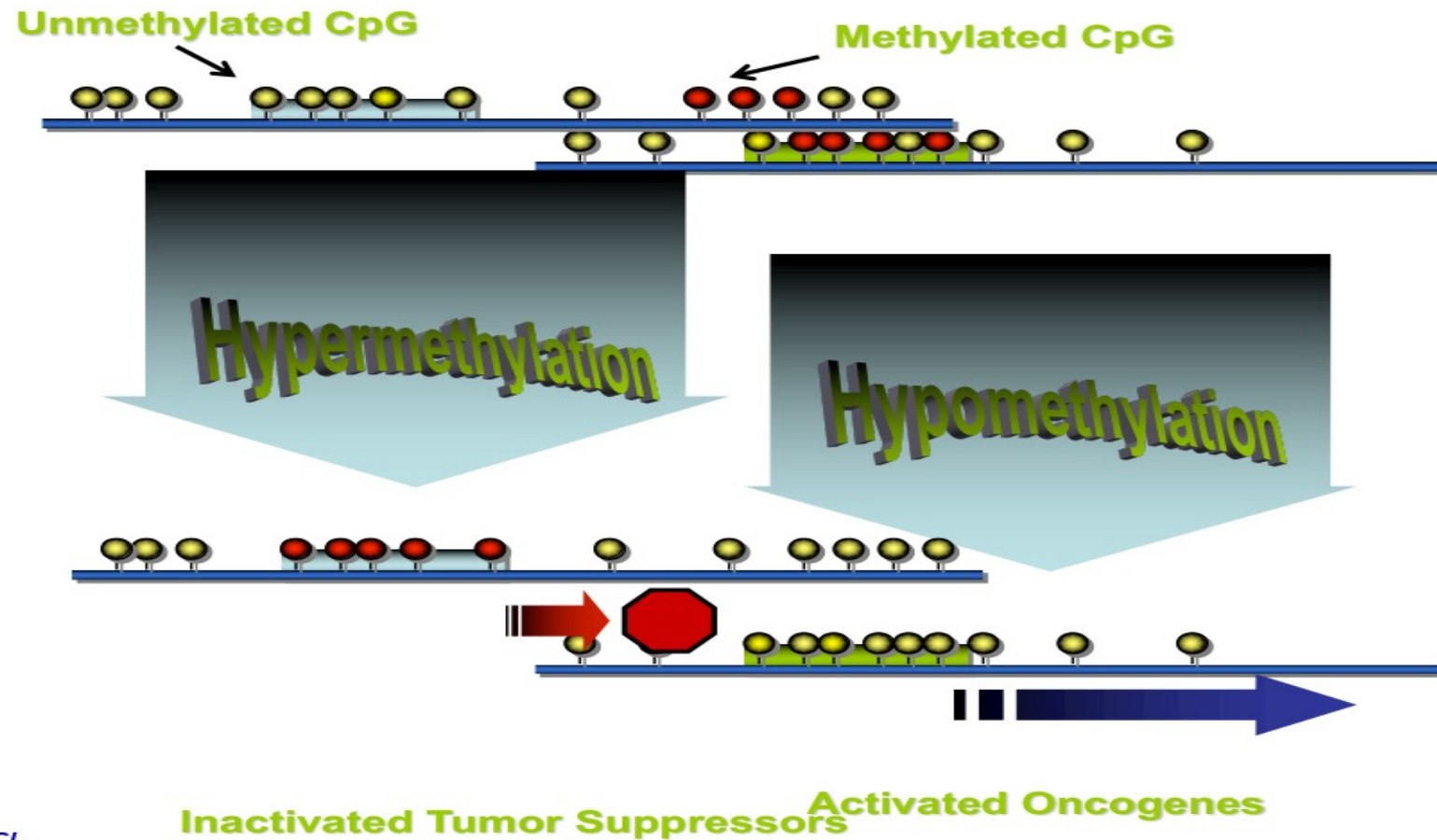
Nucleosome: two turns of DNA (146 base pairs) wrapped around an octomeric complex of two of each of histone types

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

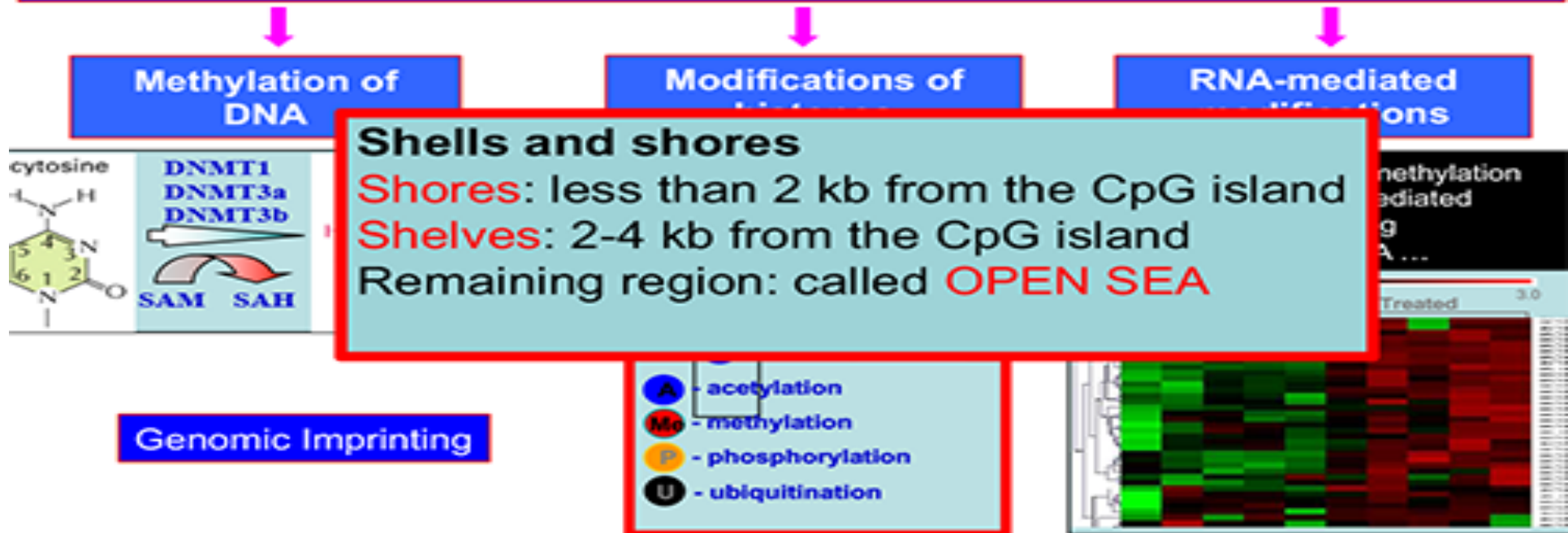
DNA methylation



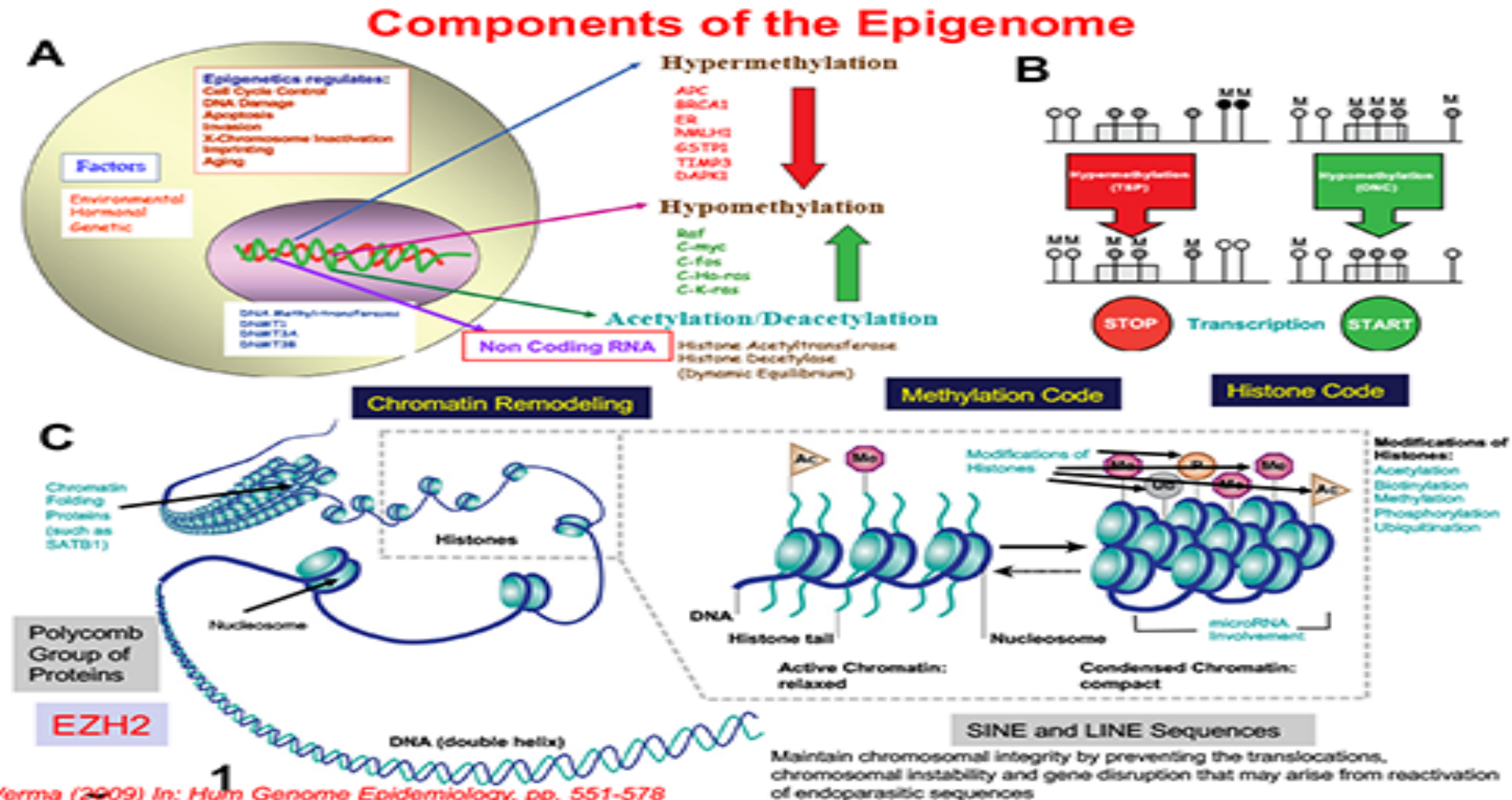
Epigenetics

EPIGENETICS

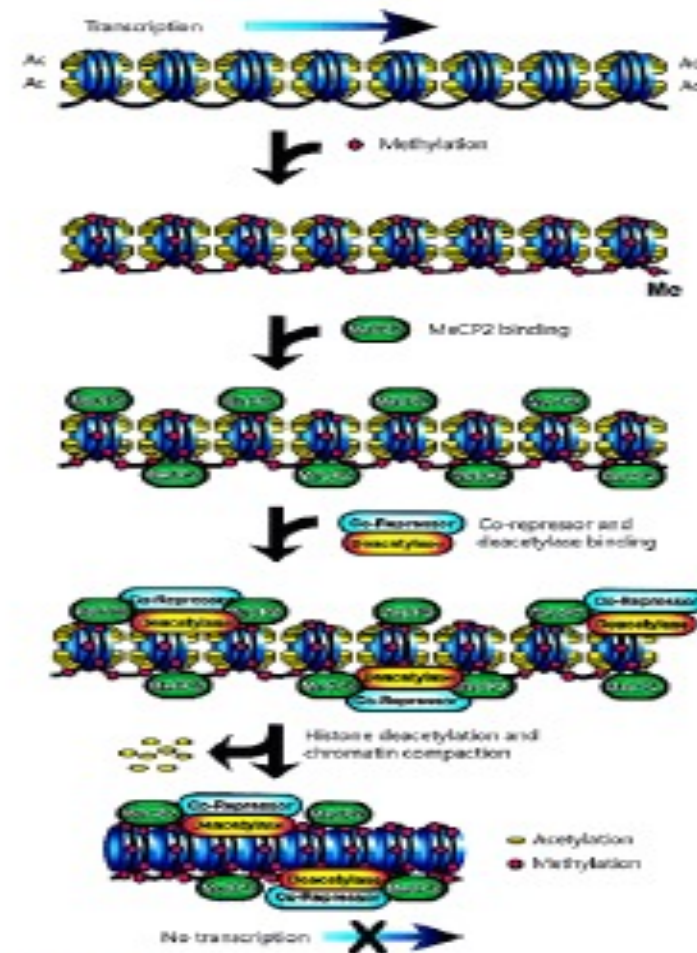
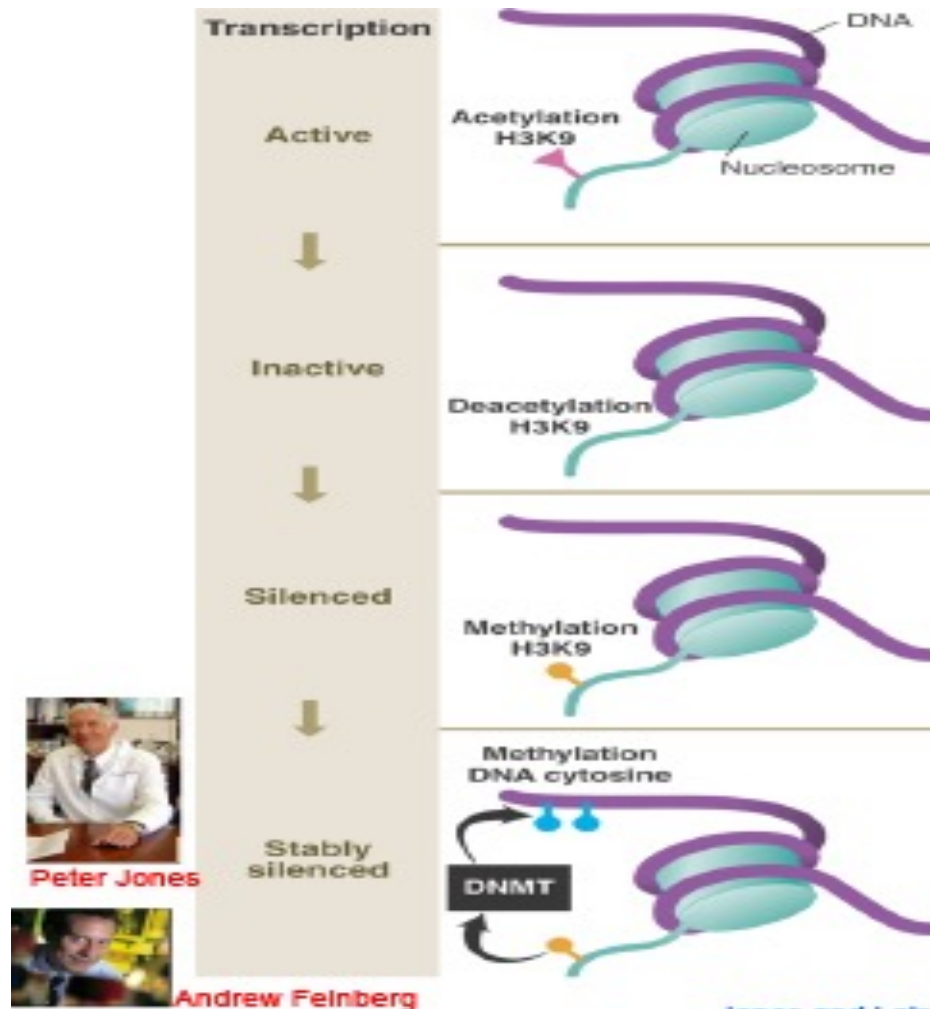
Epigenetic alterations – changes induced in cells that alter expression of the information on transcriptional, translational, or post-translational levels without change in DNA sequence



Epigenome components



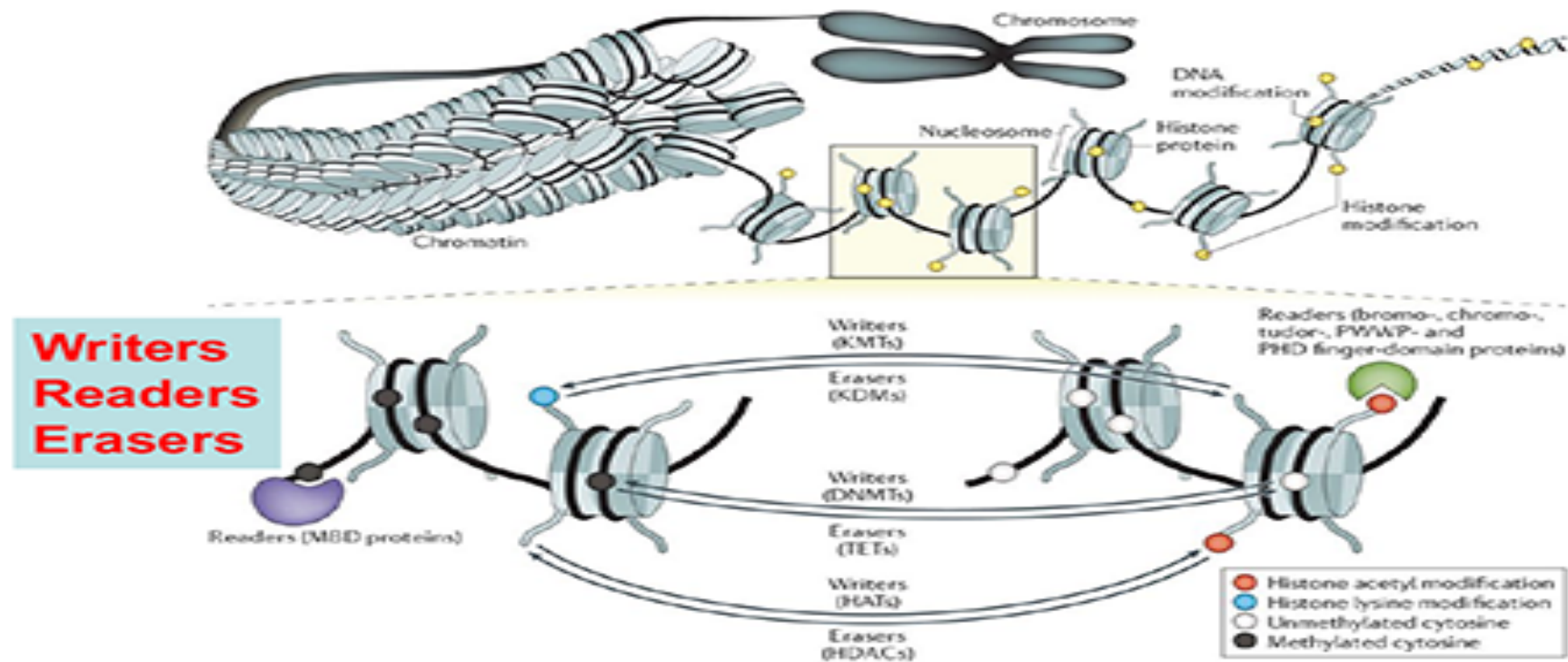
Methylation



Chromatin modifications

Figure 1 : Modulation of covalent modifications on chromatin.

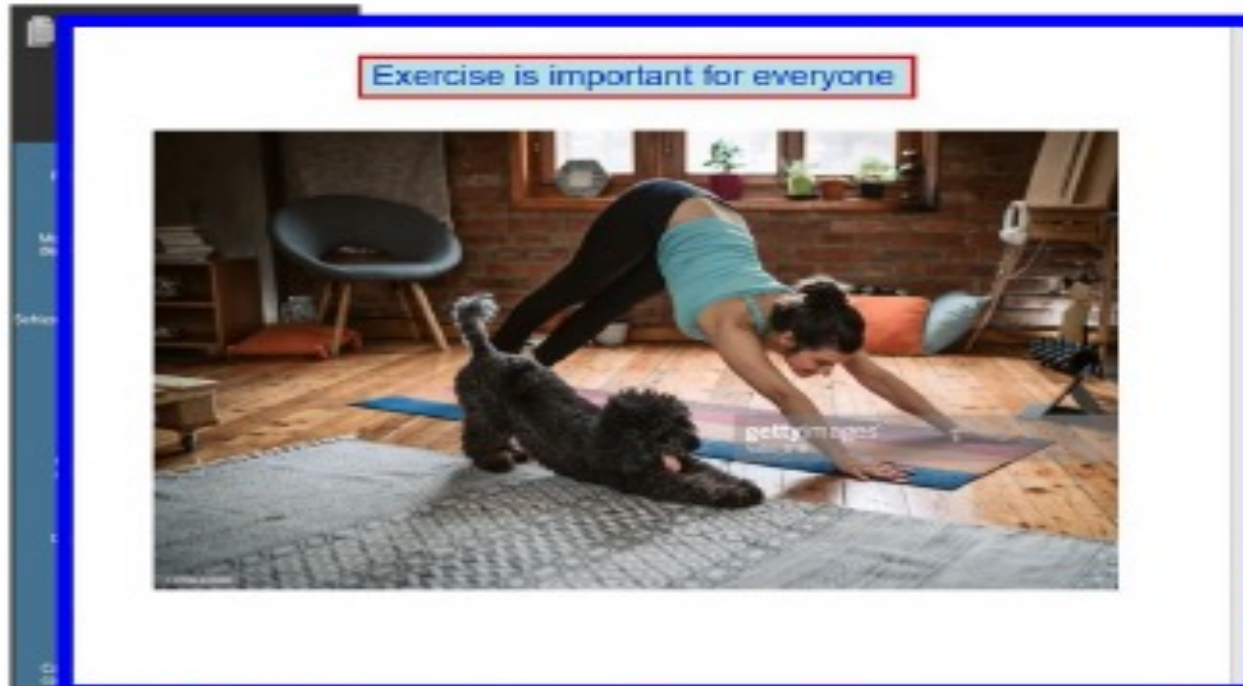
From: Targeting the cancer epigenome for therapy



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

Nature Reviews | Genetics

Exercise



important?



changes

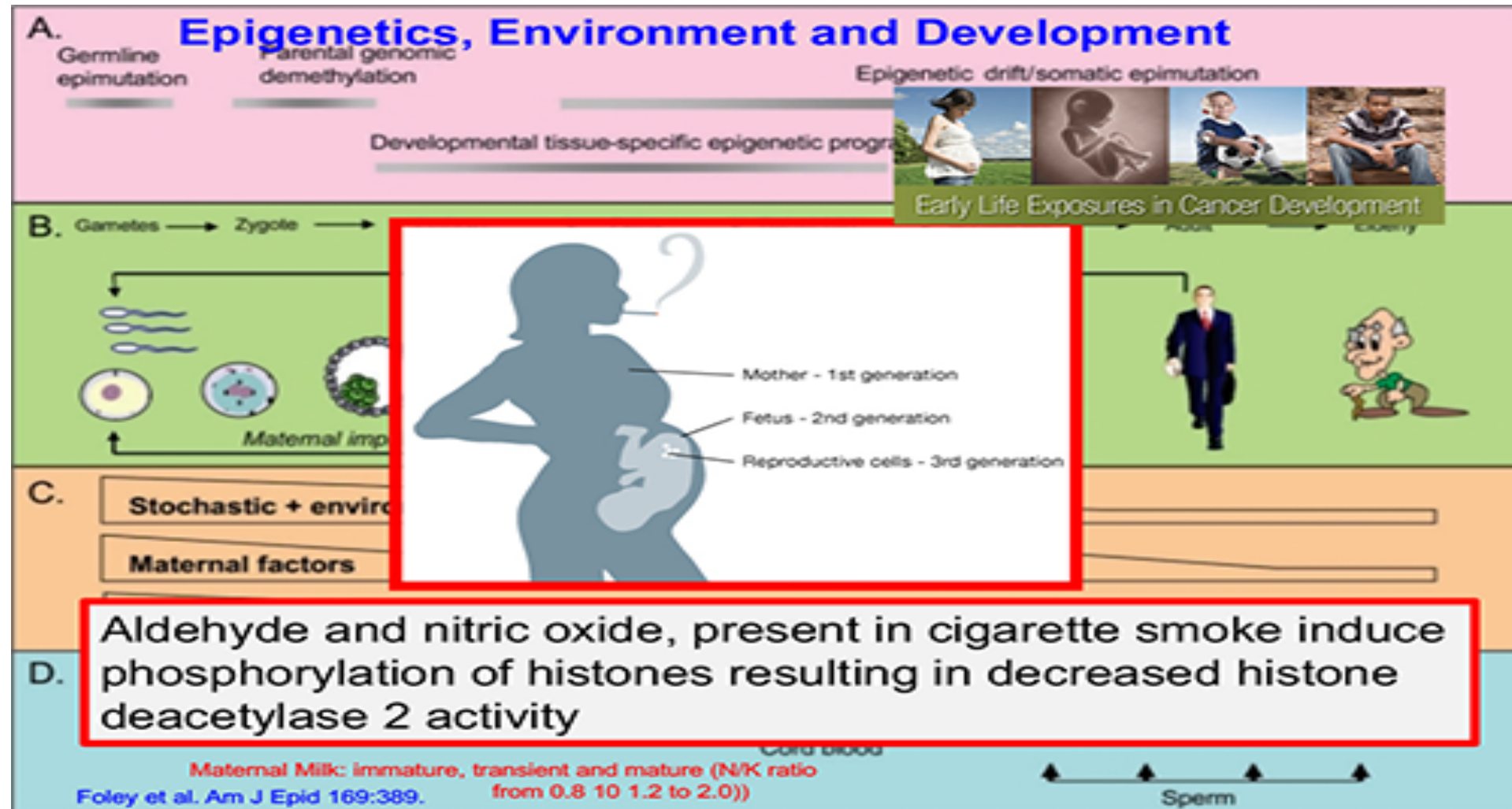


- Drug targeting

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

<https://www.youtube.com/watch?v=JMT6oRYqkTk>

Environment and development



Histone phosphorylation



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



Endogenous factors

PLoS One. 2016 May 12;11(5):e0155554. doi: 10.1371/journal.pone.0155554. eCollection 2016.

Maternal Smoking during Pregnancy and DNA-Methylation in Children at Age 5.5 Years: Epigenome-Wide-Analysis in the European Childhood Obesity Project (CHOP)-Study.

Rzehak P¹, Saffery B²,
Verdaci E³, Rava E⁴.

⊕ Author information

Abstract

Mounting evidence
profile in the blood
assessed by Epige
DNAm signatures
of children at age 5
biological role by e
children of the mul

Transl 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}, Noyakovic B^{1,2}, Meyer B^{1,2}, Rzehak P^{1,3}, Vulliamin P^{1,2,4,5}, Ponsonby AL^{1,2}, Collier F^{4,6}, Burdett D^{1,2}, Saffery B^{1,2}, Ryan J^{1,2,6,7}; BIS investigator team.

⊕ Collaborators

⊕ Author information

Abstract

Compelling evidence
genes, insulin-like
methylation. This

Epigenetic Biomarkers

- Environmentally inducible :
- Tissue- and cell-specific
- Factors that may affect the plasticity of human epigenome

Exogenous risk factors

- Lifestyle factors
 - Smoking
 - Alcohol consumption
 - Physical activity
 - Diet
- Environmental Pollutants

Endogenous factors

- Aging
- Oxidative stress
- Inflammation
- Metabolic disorders
- Hormone disorders

Cancer etiology

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

2
4

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)



- 62 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.

Toxic substances

Key toxic substances affecting the epigenome

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

PFOS, Perfluorooctane sulfonate

PAHC, Polycyclic aromatic and halogenated compounds

Environment and child health outcomes

The image is a screenshot of the ECHO (Environmental Influences on Child Health Outcomes) program website. At the top, the NIH logo is on the left, and the ECHO logo is in the center. Below the NIH logo is the text "National Institutes of Health" and "Turning Discovery Into Health". A search bar is on the right. A URL bar in the center shows "https://www.nih.gov/echo". Below the URL bar is a navigation menu with links: "Health Information", "Grants & Funding", "News & Events", "Research & Training", "Institutes at NIH", and "About NIH". The main header is a blue banner with the text "ENVIRONMENTAL INFLUENCES ON CHILD HEALTH OUTCOMES (ECHO) PROGRAM". On the left side, there is a sidebar with links: "Environmental influences on Child Health Outcomes (ECHO) Program", "Director's Page", "About ECHO", "Governance", "Program Components", "Funding", "Announcements", and "Contact Us". The main content area features a large article titled "Early-life exposures to infectious agents and later cancer development" by Vioya Vedham, Mahesh Verma, and Soondet Mahabir. The article is categorized under "Cancer Medicine" and "REVIEW". It includes an abstract, keywords, and a correspondence section. A red box highlights the article content. On the right side, there is a sidebar with links: "Information", "ECHO", "Environmental influences on Child Health Outcomes", "A program supported by the NIH", "Creating Center of Excellence", "Information about environmental influences on child health outcomes (ECHO)", "Visit the Center website", "Environmental Influences on Child Health Outcomes (ECHO) Program", "Short Data Collection", "View PDF", "NIH is", "document so that it".

NIH National Institutes of Health
Turning Discovery Into Health

Search NIH

https://www.nih.gov/echo

NIH Employee Intranet | Staff Directory | En Español

Health Information | Grants & Funding | News & Events | Research & Training | Institutes at NIH | About NIH

Home » Research & Training

ENVIRONMENTAL INFLUENCES ON CHILD HEALTH OUTCOMES (ECHO) PROGRAM

Environmental influences on Child Health Outcomes (ECHO) Program

Director's Page
About ECHO
Governance
Program Components
Funding
Announcements
Contact Us

NIH officially launches with more than \$150 million

About the ECHO Program

Understanding the environment as a priority for the National Institutes of Health launched a new series of Environmental Influences on Child Health Outcomes (ECHO) program

Cancer Medicine

REVIEW

Early-life exposures to infectious agents and later cancer development

Vioya Vedham¹, Mahesh Verma² & Soondet Mahabir²

¹Telemedicine and Technology Branch, National Cancer Institute, National Institutes of Health, 3500 Research Triangle Drive, Rockville, Maryland 20855
²Environmental Epidemiology Branch, Epidemiology and Genomics Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, National Institutes of Health, 3500 Research Triangle Drive, Rockville, Maryland 20855

Keywords
Cancer; early-life exposures; infectious agents; personal transmission

Correspondence
Soondet Mahabir, Environmental Epidemiology Branch, Epidemiology and Genomics Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, National Institutes of Health, 3500 Research Triangle Drive, Rockville, MD 20855. Tel: 301-210-6885. E-mail: mahabir@dcf.hhs.gov

Abstract
There is a growing understanding that several infectious agents are acquired in early life and this is the subset who probably receives target the new born, infants, and adolescents. Infectious agents are associated with cancer development and it is estimated that about 20% of the world's cancer burden is attributed to infectious agents. There is a growing evidence that certain infectious agents acquired in early life can give rise to cancer development, but outcomes of the cancer burden from this early-life acquisition is unknown. In this article, we have selected five cancers (cervical, liver, Burkitt's lymphoma-leukemia, nasopharyngeal carcinoma, and adult T-cell leukemia-lymphoma) and examine their links to infectious agents (HPV, HBV, HCV, EBV, and HTLV-1) acquired in early life. For these agents, the acquisition in early life is from mother-to-child transmission, perinatal contact with genital tract secretions, saliva, blood, urine, and breast milk, saliva, sexual intercourse, and blood transfusion. The

Cancer Med. 2015; Dec; 4(12):1985-22

Information
ECHO
Environmental influences on Child Health Outcomes
A program supported by the NIH
Creating Center of Excellence
Information about environmental influences on child health outcomes (ECHO)
Visit the Center website
Environmental Influences on Child Health Outcomes (ECHO) Program
Short Data Collection
View PDF
NIH is
document so that it

Scientific goal

ECHO Scientific Goal

Answer crucial questions about the effects of a **broad** range of **early environmental influences** on child health and development.



<https://www.nih.gov/echo/pediatric-cohorts>

From
society
to
biology



Health outcomes throughout
childhood and adolescence

Developmental Life Stages

Developmental Life Stages

| | |
|------------------------|---|
| Preconception/Prenatal | Anything prior to labor |
| Perinatal | Labor through discharge (or < 1 month?) |
| Infancy | 1 month through 11 months, 30 days |
| Early Childhood | 12 months through 59 months |
| Middle Childhood | 60 months through 11 years, 11 months |
| Adolescence | 12 years through 18 (or 21?) years |

[RFP FY17]

Placenta, cord blood, nail, hair, saliva, urine
Maternal blood, milk before and after pregnancy

ECHO advantages

Developmental Life Stages

Advantages of ECHO Research Design

- Longitudinal cohorts – opportunity to examine repeated measures
 - in utero
 - early in life
 - other transition periods
- Look across multiple tissues in same person
- Unifying/harmonizing epigenetic data with other data (including other omics data)
- Potential for single cell analysis
- Across generation

Adolescence

12 years through 18 (or 21?) years

Placenta, cord blood, nail, hair, saliva, urine
Maternal blood, milk before and after pregnancy

Epigenetics and behavior

Epigenetics and
behavior (including
emotions)



[Transl Psychiatry](#), 2016 Mar 29;6:e785. 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](#)^{1,3}, [Vulliamin 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

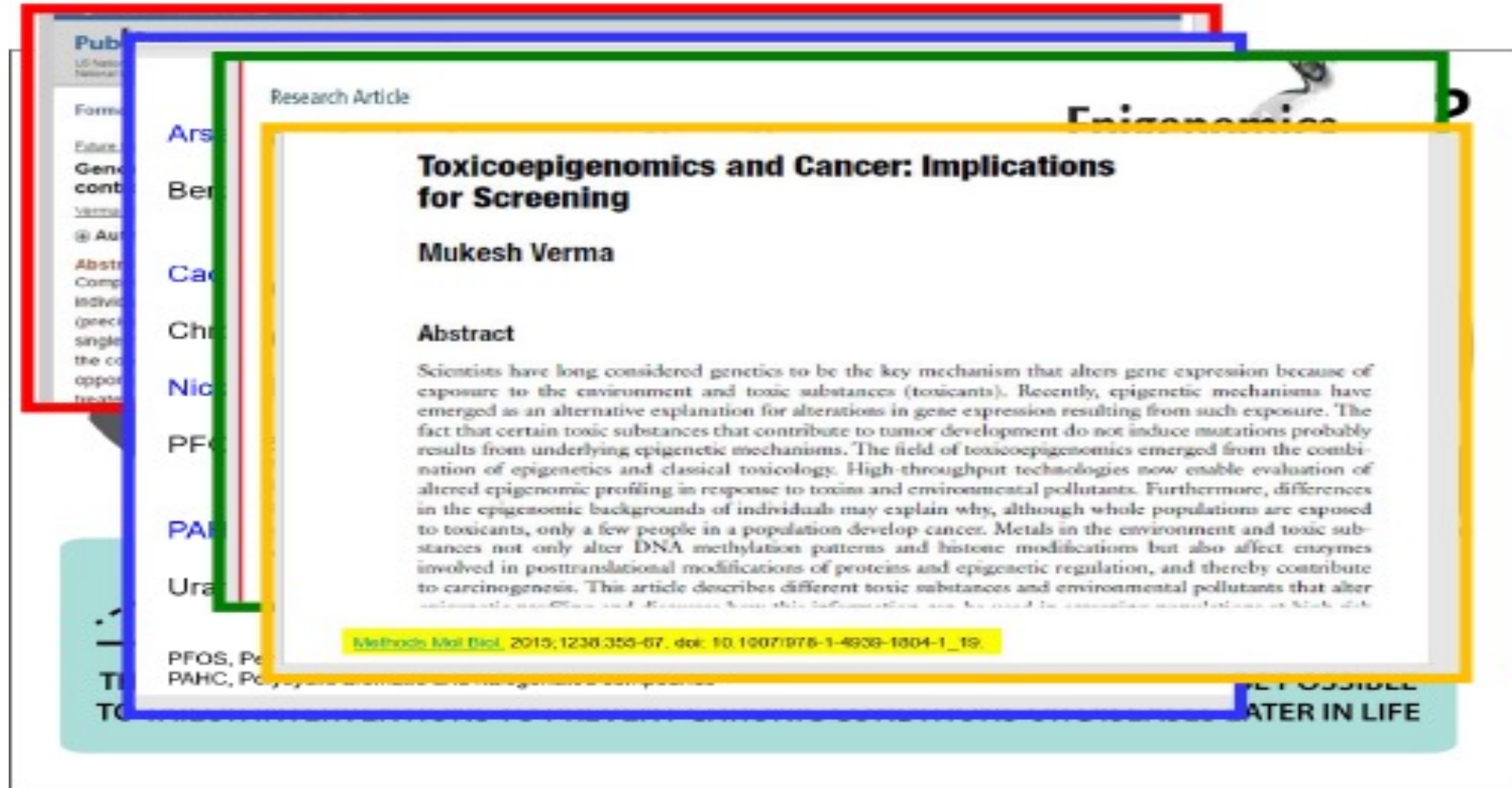
[Open/close author information list](#)

Abstract

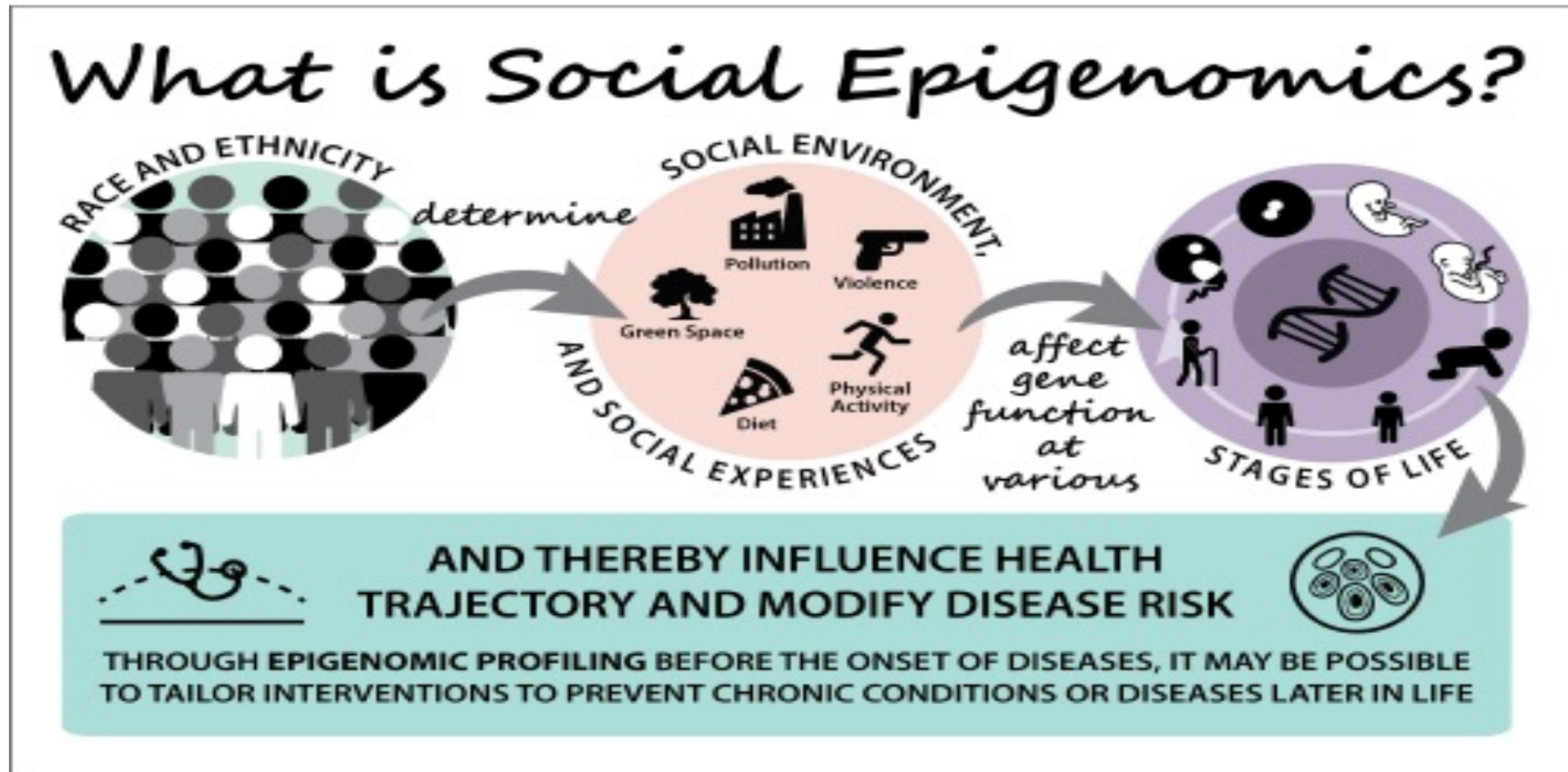
Compelling evidence suggests that maternal mental health in pregnancy can influence fetal development. The imprinted genes, insulin-like growth factor 2 (IGF2) and H19, are involved in fetal growth and each is regulated by DNA methylation. This study aimed to determine the association between maternal mental well-being during pregnancy and differentially methylated regions (DMRs) of IGF2 (DMR0) and the IGF2/H19 imprinting control region (ICR) in newborn offspring. Maternal depression, anxiety and perceived stress were assessed at 28 weeks of pregnancy in the Barwon Infant Study (n=576). DNA methylation was measured in purified cord blood mononuclear cells using the Sequenom

within your DNA that can be controlled by you, by your emotions, beliefs and behavioral choices."

Toxico epigenomics



Social epigenomics



Epigenomics

Research Article

For reprint orders, please contact: reprints@futuremedicine.com

Epigenomics

CROSS-GENERATIONAL EFFECTS

Cross-generational effects of alcohol dependence in humans on *HRAS* and *TP53* methylation in offspring

Shirley Y Hill^{1,*}, G...

¹Department of Psychiatry, U...

²Center for Neuroscience, U...

³Departments of Anesthesi...

15213, USA

* Author for correspondence

Toxicoepigenomics and Cancer: Implications for Screening

Mukesh Verma

Abstract

Scientists have long considered genetics to be the key mechanism that alters gene expression because of exposure to the environment and toxic substances (toxicants). Recently, epigenetic mechanisms have emerged as an alternative explanation for alterations in gene expression resulting from such exposure. The fact that certain toxic substances that contribute to tumor development do not induce mutations probably results from underlying epigenetic mechanisms. The field of toxicoepigenomics emerged from the combination of epigenetics and classical toxicology. High-throughput technologies now enable evaluation of altered epigenomic profiling in response to toxins and environmental pollutants. Furthermore, differences in the epigenomic backgrounds of individuals may explain why, although whole populations are exposed to toxicants, only a few people in a population develop cancer. Metals in the environment and toxic substances not only alter DNA methylation patterns and histone modifications but also affect enzymes involved in posttranslational modifications of proteins and epigenetic regulation, and thereby contribute to carcinogenesis. This article describes different toxic substances and environmental pollutants that alter

Loss (or gain) of gene function in cancer



Dr. Shih

Loss (or Gain) of gene function in cancer

Most permanent

Most dynamic

Deletion Point mutations
Amplification
Chromosomal
Translocation
(Ig rearrangement)

Genetic

Chromatin
Changes
Promoter
Methylation
Silencing

Epigenetic

Transcription
Factor
Changes

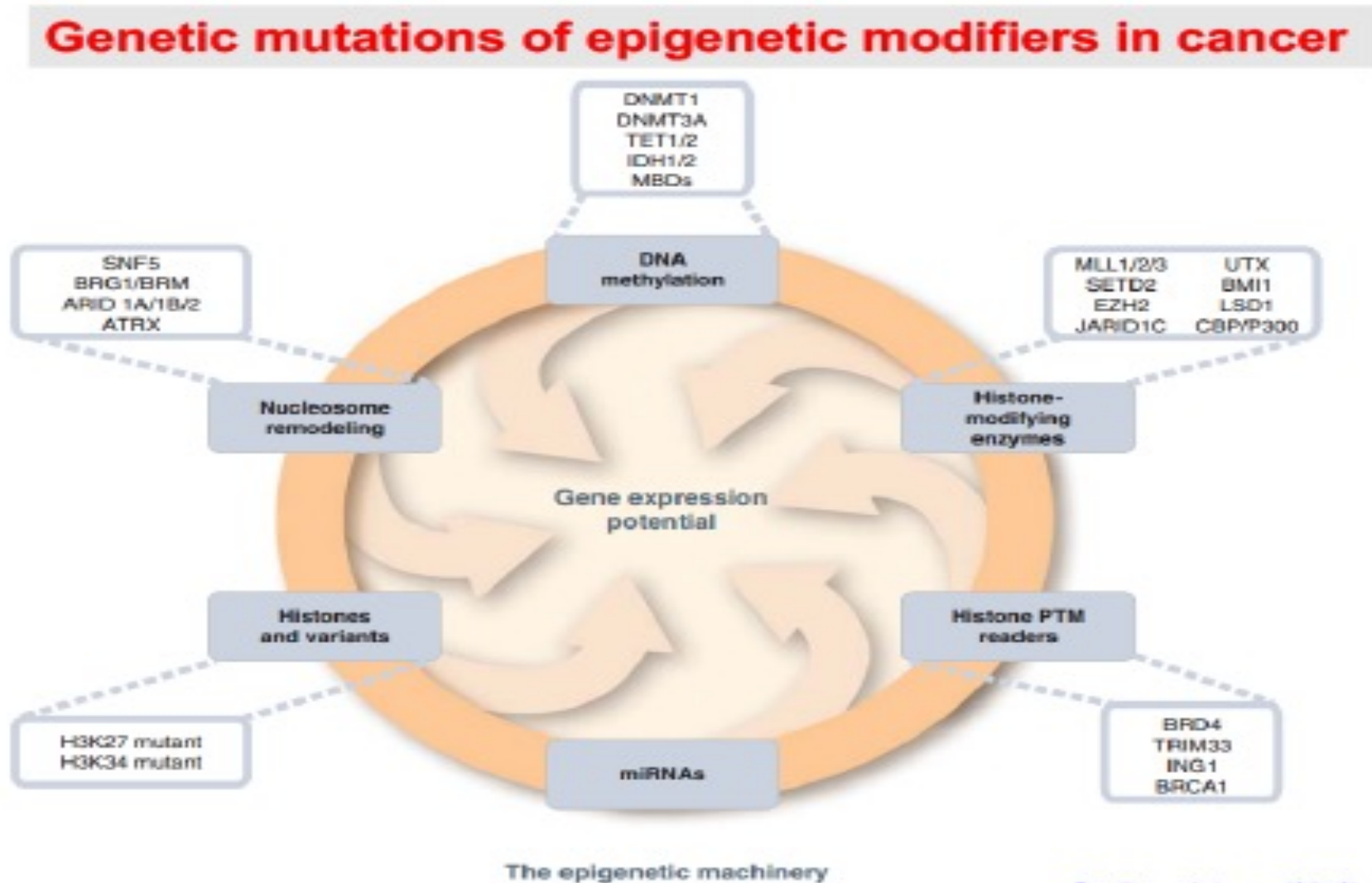
Cell-cycle
Regulated
Changes

Lerman Chw 125:1193-1223

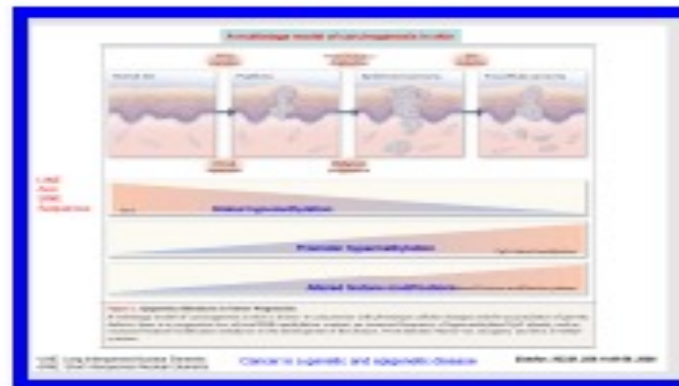


James Lerman

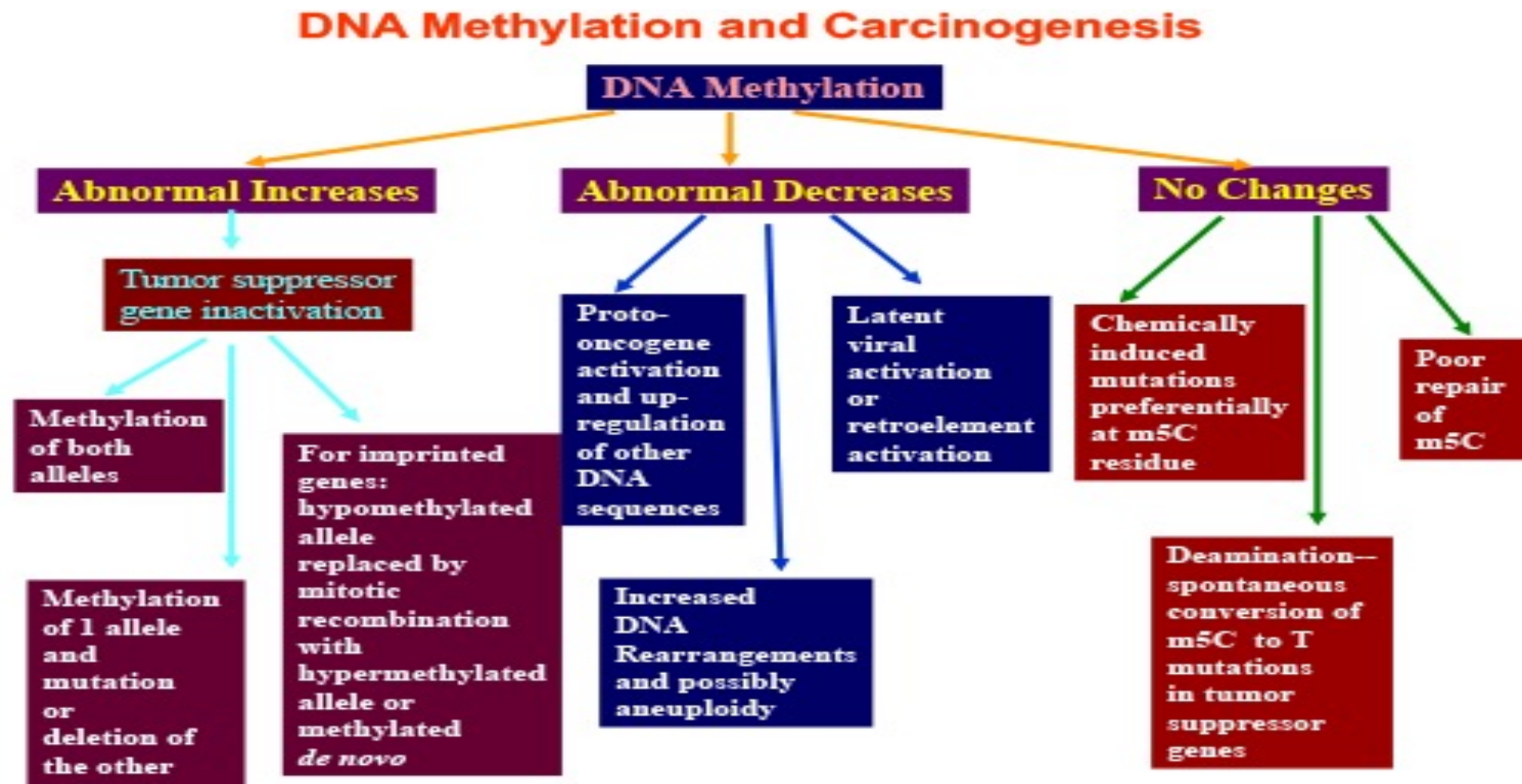
Genetic mutations



Hypomethylation

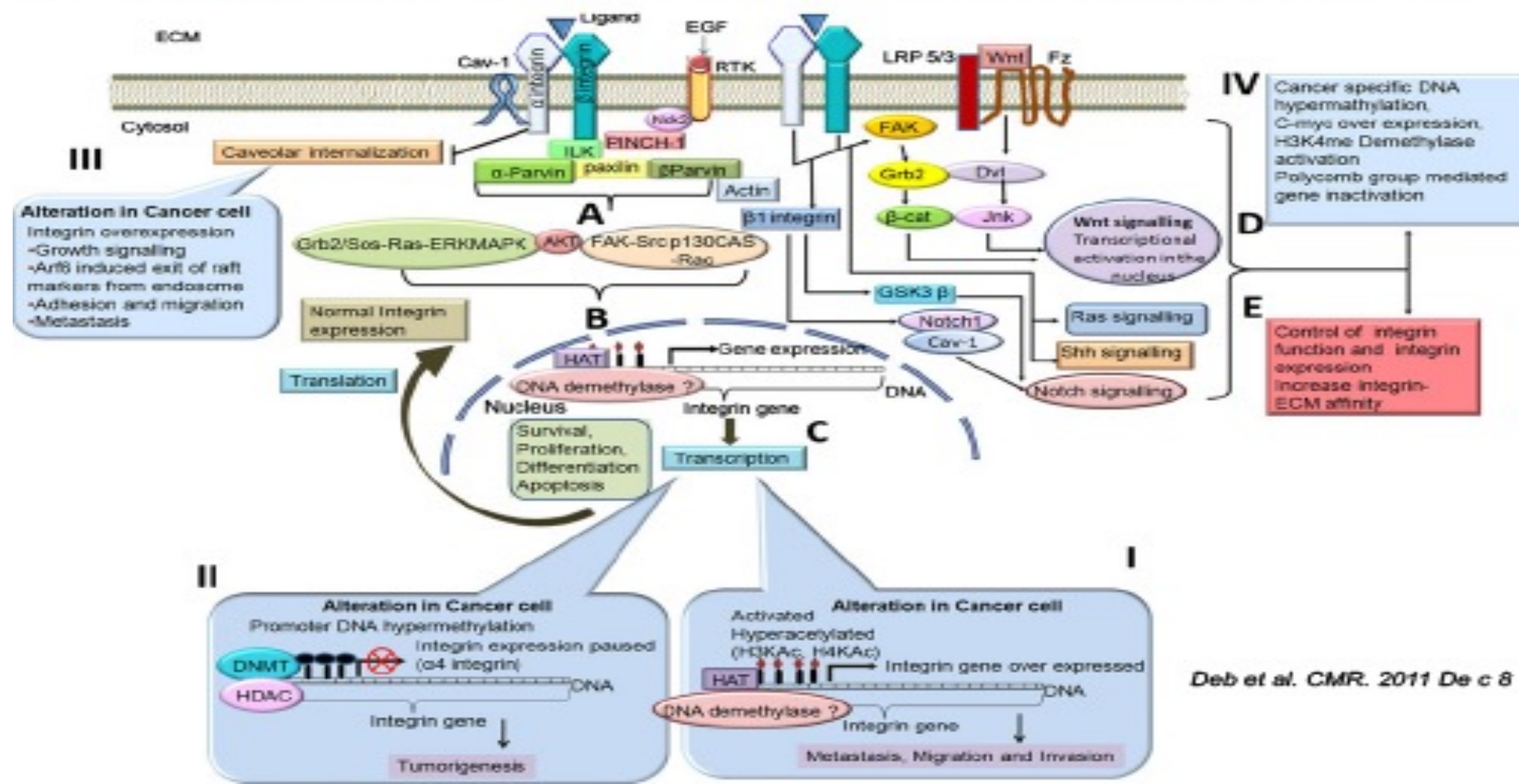


DNA methylation and carcinogenesis



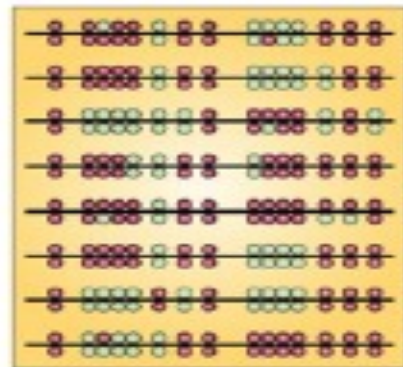
Integrin signaling

Integrin Signaling Network and Epigenetic Regulation

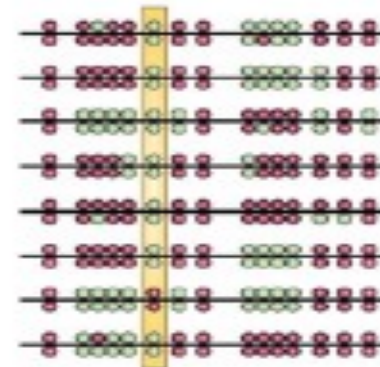


Methylation

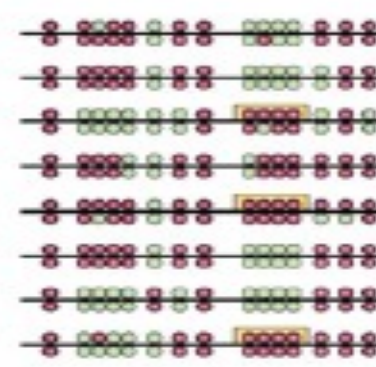
a Methylation content



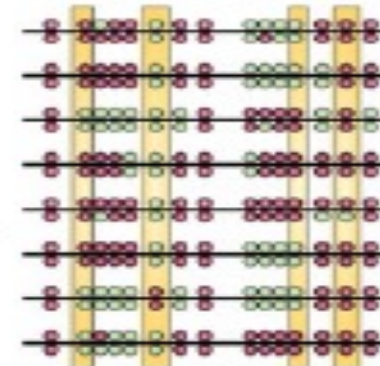
b Methylation level



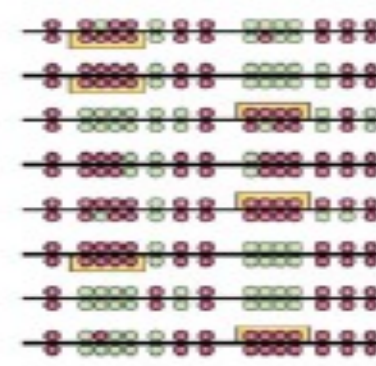
c Methylation pattern



d Level profile



e Pattern profile

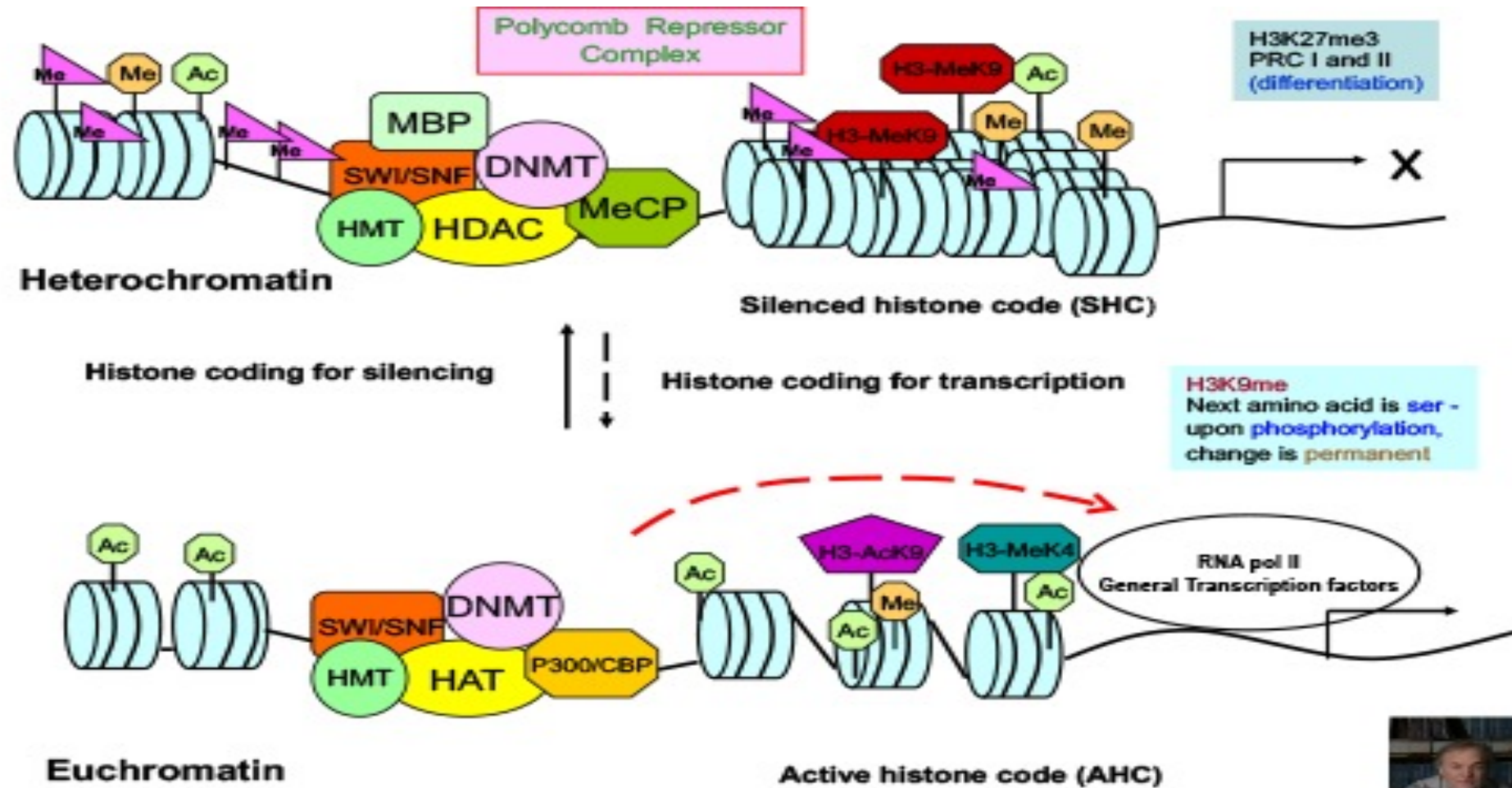


- Total methylation content of the cell
- methylation level at specific stage
- methylation pattern of a group of genes
- profile of methylation of either a specific gene or a number of genes
- pattern of methylation in the whole epigenome

To reduce

- false negative
- false positives

Histone acetylation



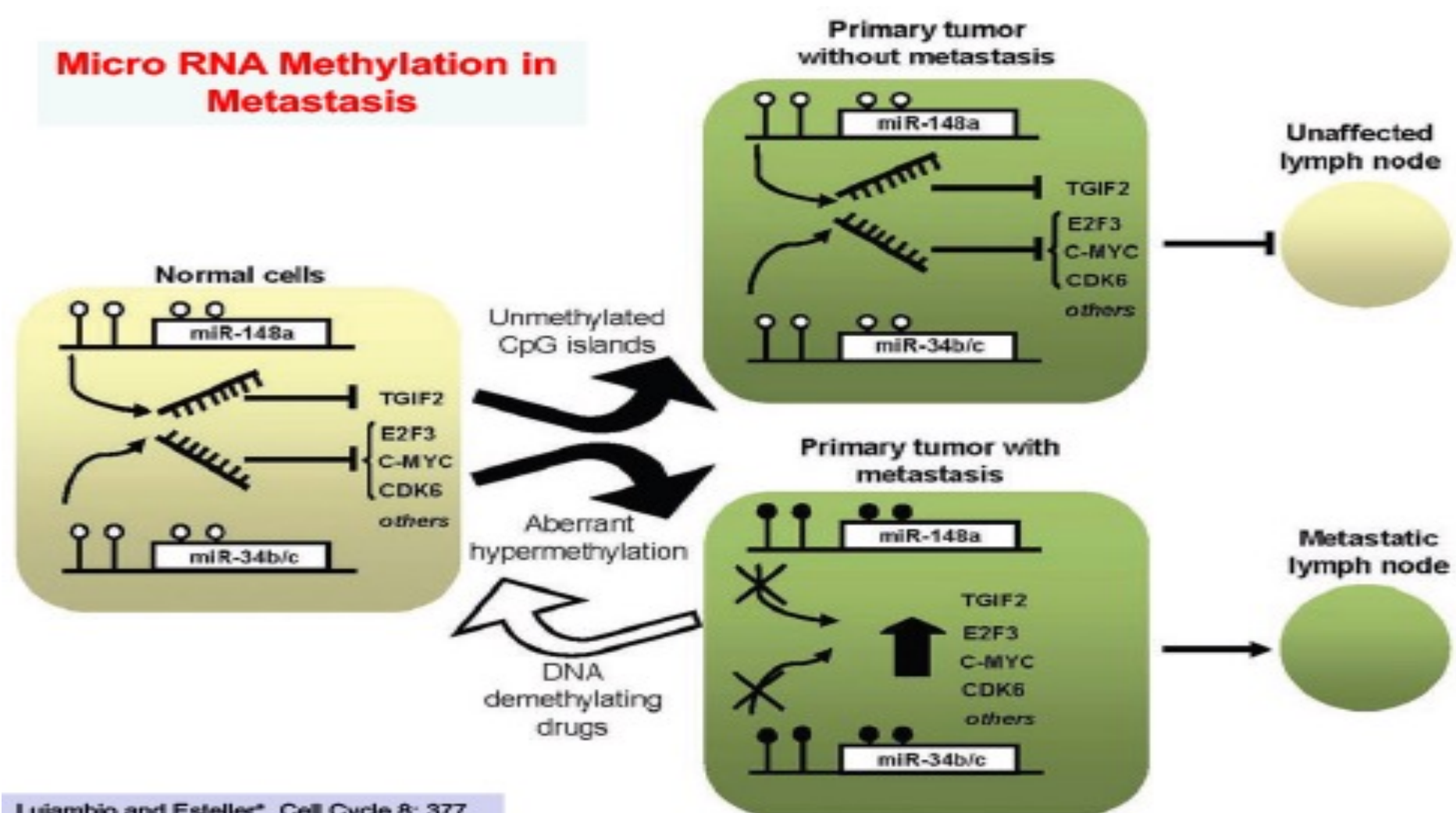
Micro RNA signatures

Mirco RNA Signatures in Human Cancers



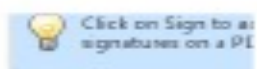
Micro RNA Polymorphism to Identify High Risk Populations

Micro RNA methylation



Extracellular vesicles

in BMC Clinical Pathology (2015) 15:6
186/v12907-015-0005-5



VIEW

Open Access

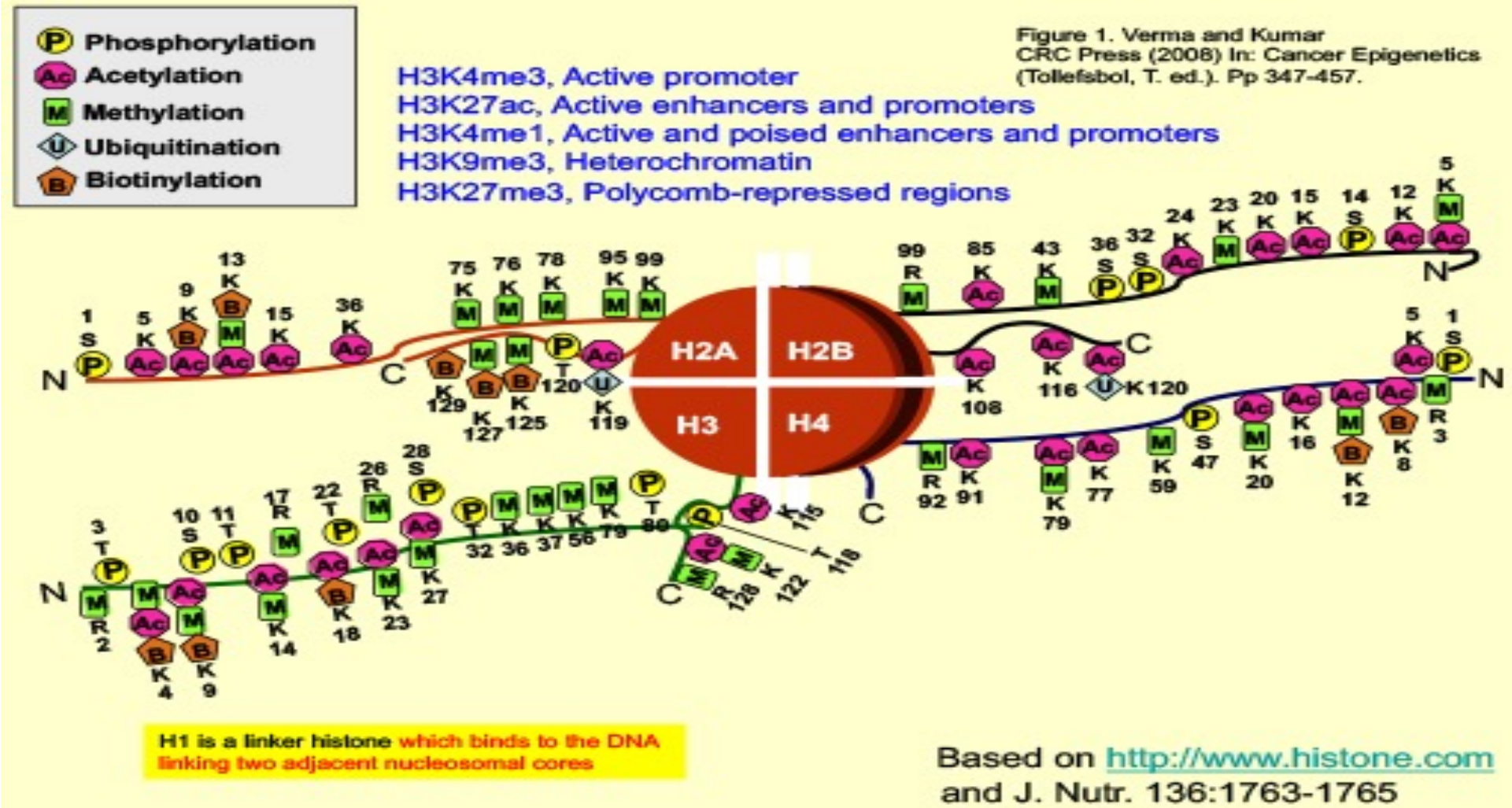
Extracellular vesicles: potential applications in cancer diagnosis, prognosis, and epidemiology

Raj Verma¹, Tram Kim Lam, Elizabeth Hebert and Rao L Divi

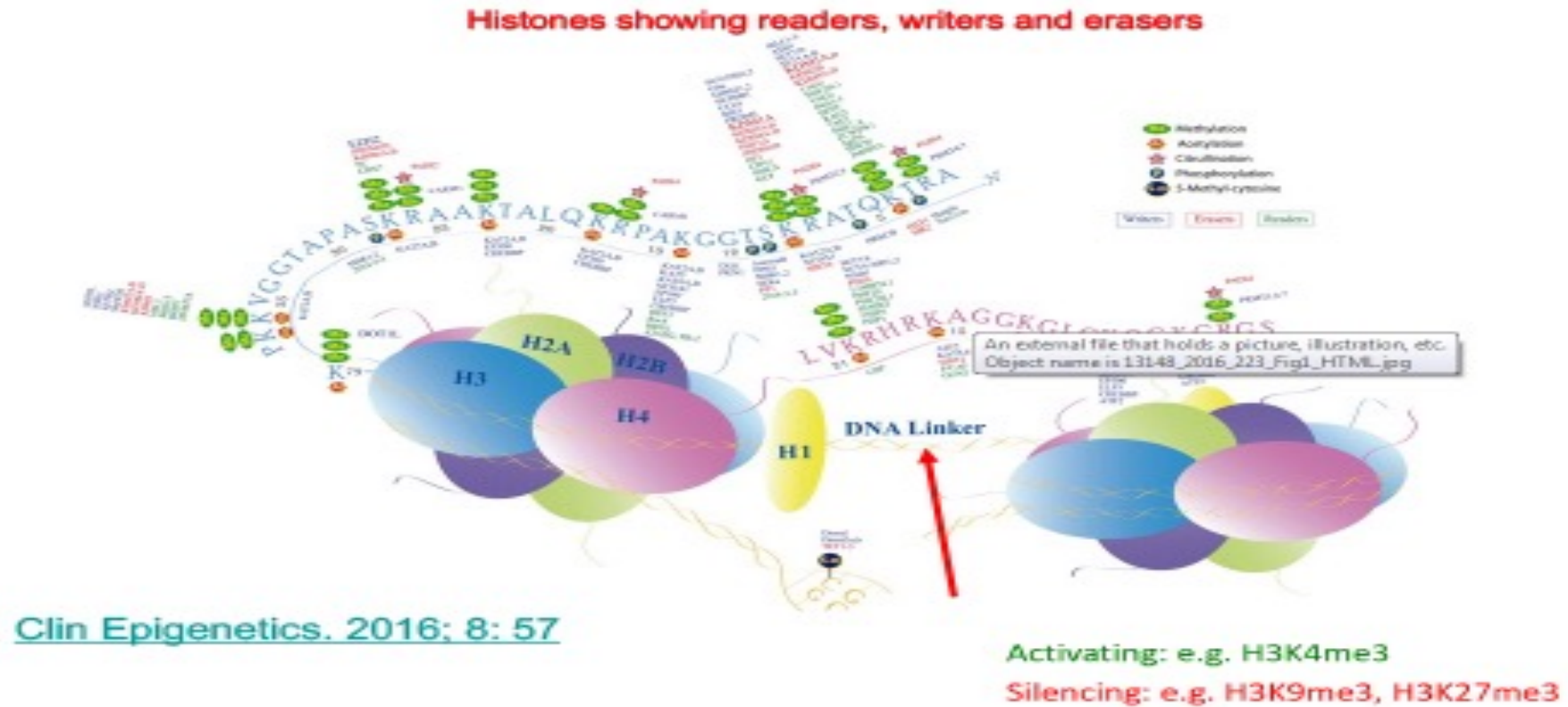
Abstract

Normal and diseased cells continuously shed extracellular vesicles (EVs) into extracellular space, and the EVs molecular signatures and effectors of both health and disease. EVs reflect dynamic changes that are occurring in cells and tissue microenvironment in health and at a different stage of a disease. EVs are capable of altering the function of the recipient cells. Trafficking and reciprocal exchange of molecular information by EVs among different cell types and cell types have been shown to contribute to horizontal cellular transformation, cellular reprogramming, phenotypic alterations, and metastasis. EV contents may include tumor suppressors, phosphoproteins, proteases,

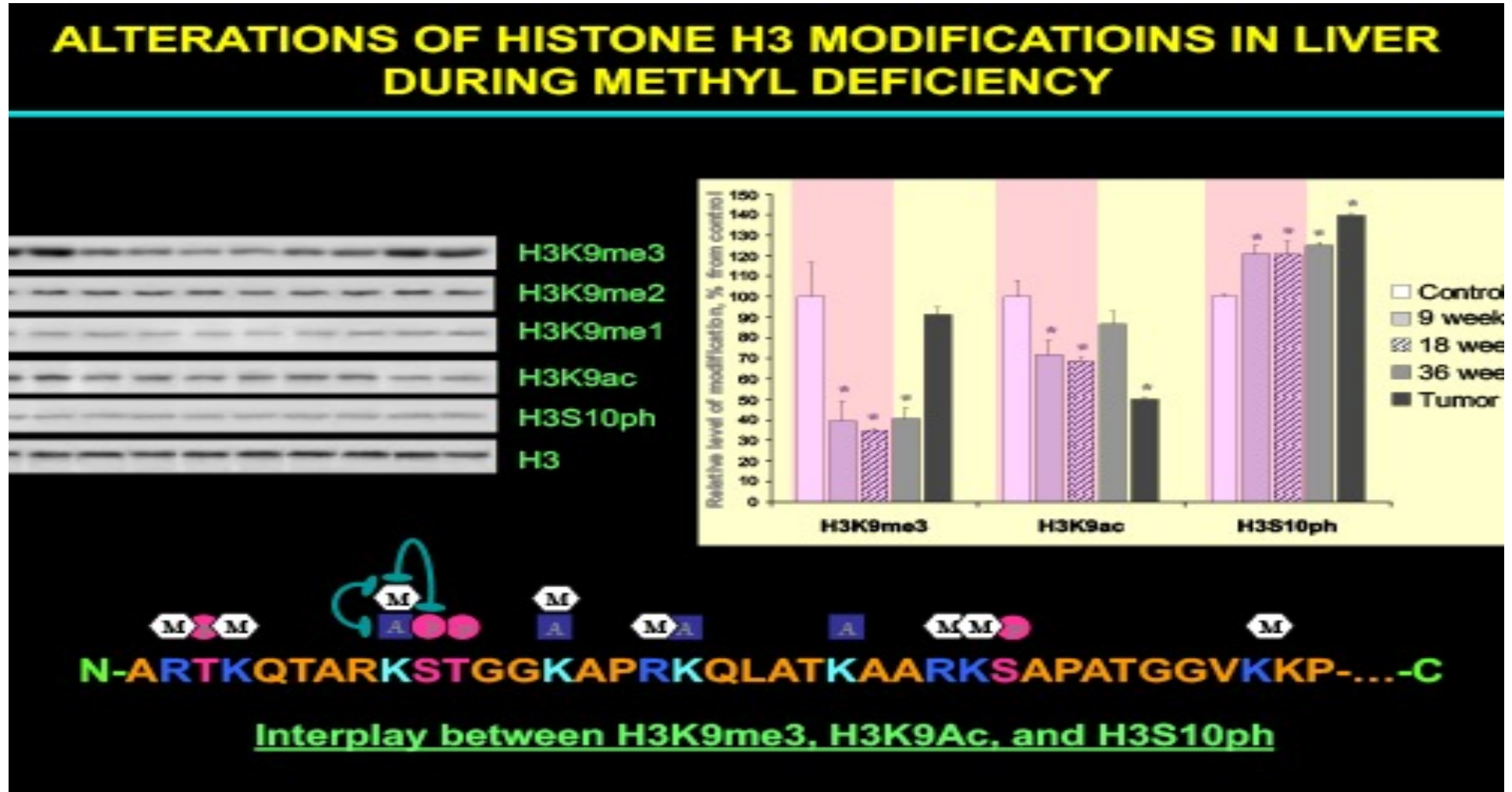
Histone modifications



Histones



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 |



Single cell epigenomics

SINGLE CELL EPIGENOMICS

Single cells isolated from

- Blood
- Breast milk
- Exfoliated cells
- Hair
- Oral swab
- Pancreatic fluid
- Saliva
- Skin
- Tissue
- Urine

1. Methylation profiling
2. Histone modifications
3. miRNA profiling
4. Chromatin Accessibility

Single Cell
Epigenomics

Identify open and closed chromatin

Identify cell-specific transcription factors

Determine nucleosome position

Identify active and repressive
transcription state

Implications of single cell epigenomics

Risk Assessment to identify high-risk individuals
Diagnosis
Prognosis
Screening
Follow up treatment and co-morbidity

Histone modifications

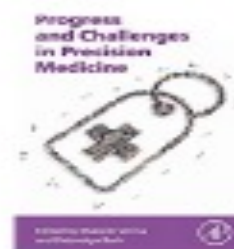
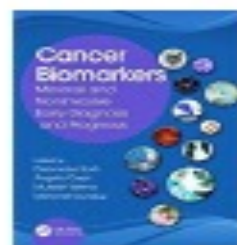
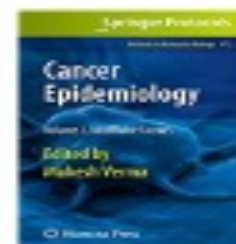
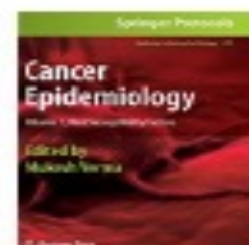
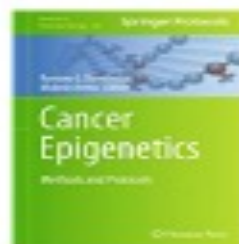
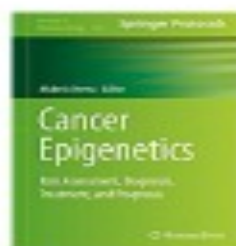
20 Diagnosing Cancer Using Histone Modification Analysis

Mukesh Verma and Deepak Kumar

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Books



Books edited by Mukesh Verma

Epigenetic drugs

The image is a screenshot of a web browser displaying a Nature magazine article. The browser's address bar shows the URL: <http://www.nature.com/news/epigenetics/2011/01/110101a.html>. The article title is "Epigenetics: Marked for success". A large blue speech bubble callout contains the text: "Successful approval of first generation of drugs intended to target epigenetic pathways, has convinced almost every major drug company to invest in cancer epigenetics." followed by "Mukesh Verma". A red rectangular box highlights a paragraph in the article. To the right of the box, a green label reads "Nature 483:637-639". The article text includes the following paragraphs:

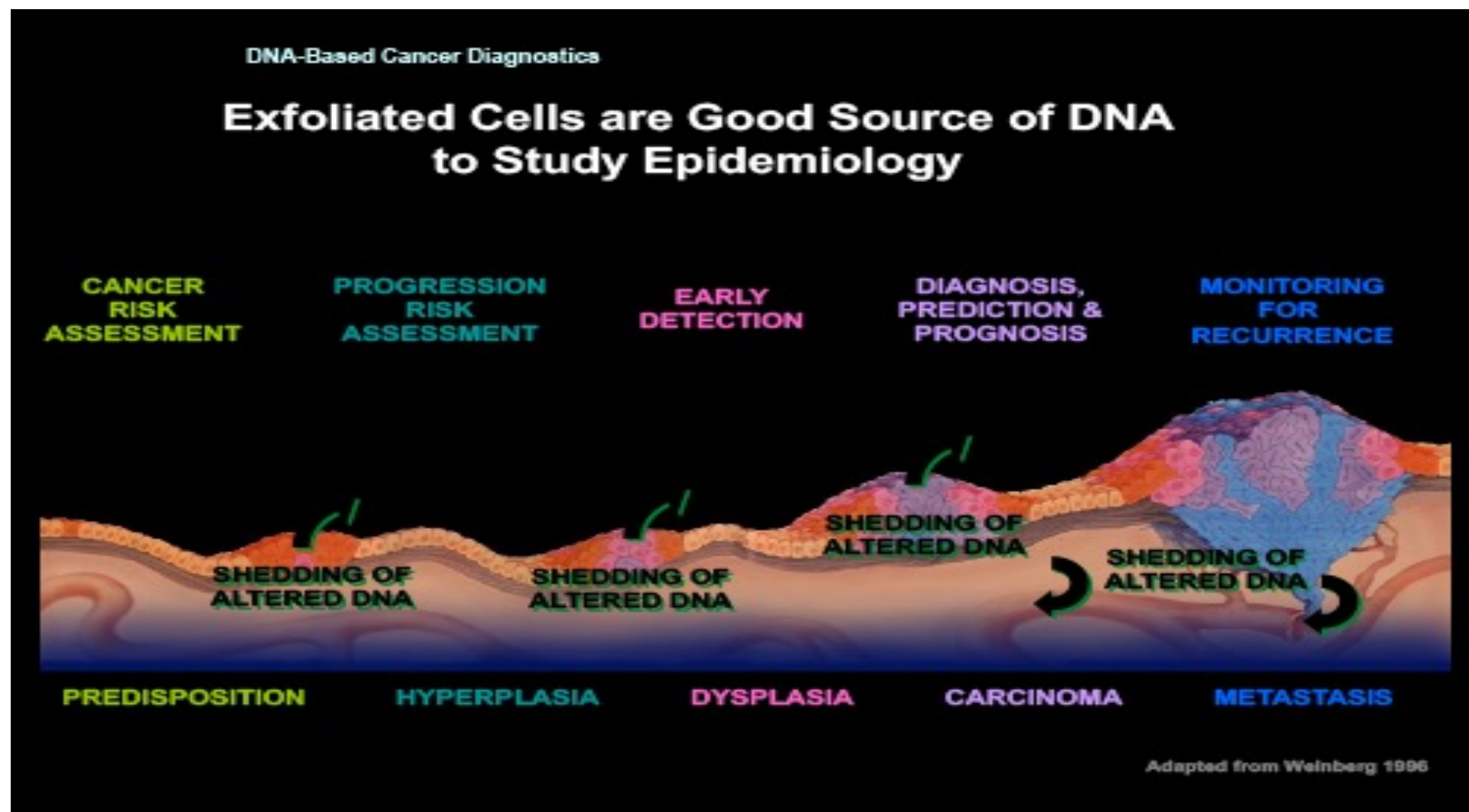
programmes intended to do so. The UK's Cancer Research UK, for example, has already dedicated to the larger sequencing centres, but smaller teams are using the data from these projects to generate individual investigator grant applications, Shaw adds.

These data have helped to persuade investors in industry that epigenetic abnormalities in cancer are a wealth of new drug targets. The finding that mutations in epigenetic-related genes may be driving cancer offers the tantalizing possibility of taking a personalized approach to cancer treatment, a tack that is rapidly gaining ground in industry, says Robert Gould, chief executive of Epizyme, an epigenetics-focused biotechnology firm based in Cambridge, Massachusetts. This evidence, plus the successful approval of a first generation of drugs intended to target epigenetic pathways, has convinced almost every major drug company to invest in cancer epigenetics, says Mukesh Verma, a programme officer at the NCI. For example, Novartis, a pharmaceutical firm with its headquarters in Basel, Switzerland, has more than 200 employees working in epigenetics, most of them in cancer, says En Li, head of China Novartis Institutes for Biomedical Research, based in Shanghai. Last year, GlaxoSmithKline in London, in addition to funding its own epigenetics team, paid \$20 million to partner with Epizyme in a deal in which Epizyme could ultimately receive as much as \$600 million. "GSK's group is partnering with us and is also competing with us on other programmes," says Epizyme's chief scientific officer, Robert Copeland. "It makes for an interesting dynamic."

With so much excitement, competition in the field can be fierce. Data from large government projects can be a boon to smaller labs, says Clark, but individual investigators and those new to the field need to carve their own niche. "In the face of those big initiatives, smaller labs have the challenge of asking smaller and more unique questions as to the basic mechanisms underlying these epigenetic changes," she says. Christopher Vakoc, an epigenetics researcher at Cold Spring Harbor Laboratory in New York, notes that the "tiny" lab he started in 2008 directly competed with several big pharmaceutical companies to discover a role for Bmi-1 — a "repressor" protein that binds to certain modified histones and modulates gene expression — in acute myeloid leukaemia (J. Zuber *et al.*, *Nature* **478**, 534–538, 2011). After his team's paper was published, Vakoc heard rumours that two companies were racing to capitalize on the results.

There is also an intense demand for talent. In particular, epigenetics companies and individual labs need

Exfoliated cells



Tumors and epigenetics




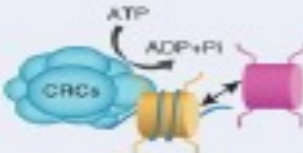

Tumor Types and Genes Regulated by Epigenetic Mechanism

| TUMOR LOCATION | GENE |
|----------------|---|
| Breast1 | p16, BRCA1, GSTP1, DAPK, CDH1, TIMP-3 |
| Brain | p16, p14 ^{ME} , MGMT, TIMP-3 |
| Bladder | p16, DAPK, APC |
| Colon | p16, p14 ^{ME} , CREP1, MGMT, hMLH1, DAPK, TIMP-3, APC |
| Endometrium | hMLH1 |
| Esophagus | p16, p14 ^{ME} , GSTP1, CDH1/APC |
| Head and Neck | p16, MGMT, DAPK |
| Kidney | p16, p14 ^{ME} , MGMT, GSTP1, TIMP-3, APC |
| Leukemia | p15, MGMT, DAPK1, CDH1, p78 |
| Liver | p16, CREP1, GSTP1, APC |
| Lymphoma | p16, p15, CREP1, MGMT, DAPK, p78 |
| Lung | p16, p14 ^{ME} , CREP1, MGMT, GSTP1, DAPK, FHT, TIMP-3, RARb α , RASSF1A |
| Ovary | p16, BRCA1, DAPK |
| Pancreas | p16, MGMT, APC |
| Prostate | GSTP1, p27 ^{kip1} |
| Stomach | p14 ^{ME} , P16, APC, hMLH1, MGMT |
| Uterus | p16, p14 ^{ME} , hMLH1 |

SIMULins are a group of proteins with histone deacetylase inhibiting and/or apoptosis inhibition properties

Venkov and Savova (2002)
 Leukemia, Oncol 3: 355-363
 Venkov et al (2004)
 Crit Rev Clin Sci
 41: 585-607
 Venkov and Mavrouk (2006) Crit
 Rev Hematol Oncol 60: 9-18
 Venkov et al (2006) Mol Diag
 Therapy 10: 1-15

Histone enzymes

| TUMORS | | GENES | |
|---|--------|--|---------|
| Category | Gene | Category | Gene |
| HDACs | HDAC1 | DNMTs | DNMT1 |
| | HDAC2 | | DNMT3A |
| | HDAC8 | | DNMT3B |
| Sirtuins | SIRT1 | (2OG)-Fe(II)-dependent oxygenases | TET1 |
| | SIRT2 | | TET2 |
| | SIRT3 | Methyl-CpG binding proteins | MBD1 |
| | SIRT7 | | MBD2 |
| HDMs | KDM1A | | MBD3 |
| | KDM2B | | MBD4 |
| | KDM4C | | MECP2 |
| | KDM5A | | |
| | KDM5B | | |
| | KDM5C | | |
| KDM6A | | | |
| KDM6B | | | |
|  | |  | |
| Category | Gene | Category | Gene |
| HATs | CREBBP | Histone variants | H2AFZ |
| | EP300 | | ARID1A |
| | MYST3 | | CHD5 |
| | MYST4 | | CHD7 |
| | KAT5 | | MTA1 |
| HMTs | MLL | Chromatin remodeling factors | MTA2 |
| | EZH2 | | MTA3 |
| | NSD1 | | SMARCA2 |
| | PRDM2 | | SMARCA4 |
| | SMYD3 | | SNF5 |
| | WHSC1 | | |
|  | |  | |
| Category | Gene | Category | Gene |
| Histone modification readers | ING1 | Histone modification readers | ING1 |
| | ING2 | | ING2 |
| | ING3 | | ING3 |
| | ING4 | | ING4 |
| | ING5 | | ING5 |
|  | | | |

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

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

Epigenetic drugs

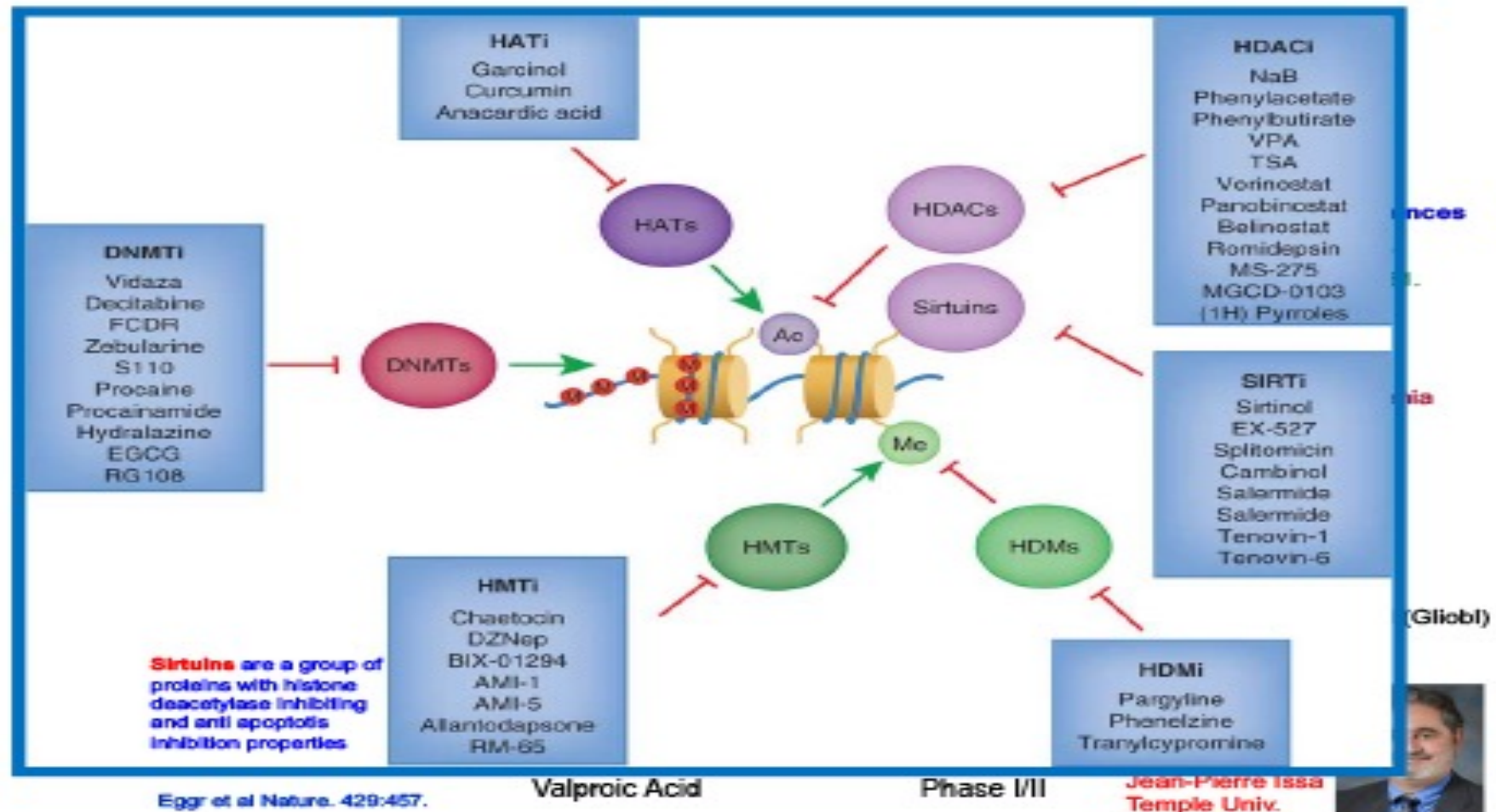
| Target | Drug | Clinical Trial | |
|---------------------|--|----------------|---|
| DNA Methylation | 5-Azacytidine | Phase I/II/III | |
| | 5-Aza-2'deoxyctidine | Phase I/II/III | |
| | FCD R | | |
| | Zebularine | | Adverse Experiences SAHA Duro et al. 2007. Ann. N.Y. Acad. 109:31. |
| | Procainamide | | • Dizziness • Diarrhea • Nausea |
| | EGCG | Phase I | • Thrombocytopenia • Vomiting |
| | Psamaplin A | | |
| Histone deacetylase | Antisense Oligomers | Phase I | |
| | Phenylbutyric acid | Phase I/II | Vanniasari, Phil H; Gupta; |
| | SAHA (Suberoylanilide hydroxamic acid) or Vorinostat | Phase I/II | |
| | Depsipeptide | Phase I/II | |
| | Valproic Acid | Phase I/II | Jean-Pierre Issa Temple Univ. |

SAHAs are a group of proteins with histone deacetylase inhibiting and and apoptosis inhibitor properties

Epigenetics Nature 429:457



Methylation and acetylation enzymes



HDAC inhibitors

- HDAC inhibitors are a novel class of anticancer drugs that mainly leads to an accumulation of acetylated proteins

Thereby inducing

- Cell cycle arrest
- Differentiation
- Migration
- apoptosis in cancer and transformed cells

- Few HDAC inhibitors act as radiation-sensitizing drugs resulting in better radiation therapy (head and neck cancer) responsiveness

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.

Braithe 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



Peripheral blood
• Pyrosequencing
• Chip

Analysis
Day 1, 10 and 28

28 Days Cycle

55 people with
Advanced cancer
Median age 60

- The maximum tolerated dose was 75 mg/m² of 5-AZA in combination with valproic acid.

- Dose-limiting toxicities were neutropenic fever and thrombocytopenia, which occurred at a dose of 94 mg/m² 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/m² 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-azacytidine (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 Cancer |
| Recruiting | Azacitidine With or Without Decitabine or 5-Aza-2-Deoxycytidine in Treating Patients With Myelodysplastic Syndromes, Chronic Myelomonocytic Leukemia, or Acute Myeloid Leukemia |
| Active Not Recruiting | PhIL1-Azacitidine Plus Valproic Acid and Etoposide in Intermediate and High Risk MDS |
| Recruiting | Decitabine With or Without Interferon Alfa-2b in Treating Patients With Unresectable or Metastatic Solid Tumors |
| Recruiting | Hydroxyurea Monotherapy for Cervical Cancer |
| Recruiting | Hydroxyurea Monotherapy for Ovarian Cancer |
| Recruiting | Decitabine in Treating Patients With Previously Untreated Acute Myeloid Leukemia |
| Recruiting | Chronic Hepatitis C Non-Responder Study With Adefovir and Peginterferon |
| 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 |

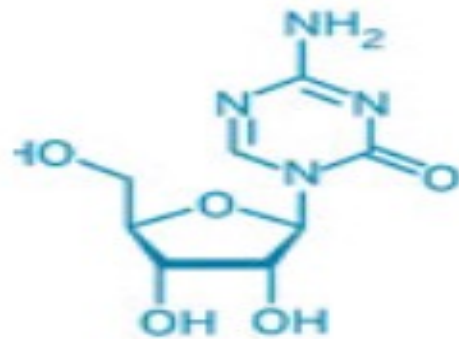
Total : 51 studies

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

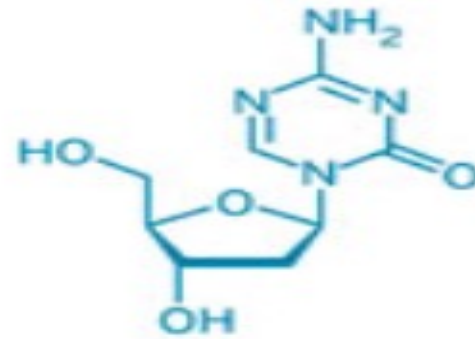
Schering-Plough (Decitabine (5-aza-Deoxycytidine) Trial for melanoma) (8 hrs to inactivate DNMT1)
Bristol-Myers Squibb (other compounds)

Epigenetic inhibitors

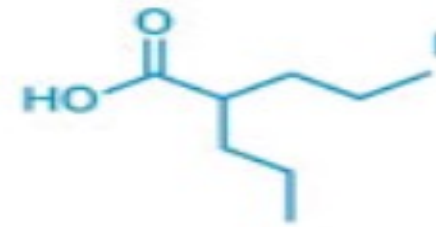
FDA Approved Epigenetic Inhibitors



5-Azacitidine



Decitabine

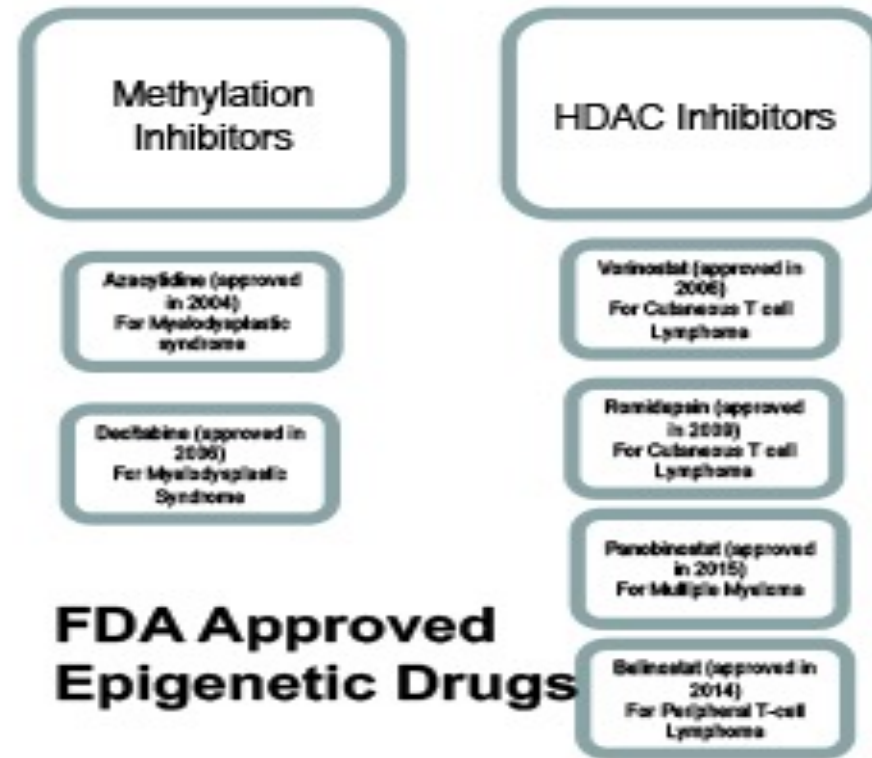


Valproic acid



SAHA

Approved epigenetic drugs



Epigenetic drugs

| Cancer type | Epigenetic therapy | Drug combination | Patient selection | Response | Pharmacodynamic target validation ^{†*} | Refs [‡] |
|---|---|---|--|--|---|-------------------|
| Gastrointestinal stromal tumours | Paritumumab (pan-EGFR inhibitor) | Paritumumab and imatinib | Patients with metastatic gastrointestinal stromal tumours refractory to imatinib and sunitinib | 1 of 11 partial response; 7 of 11 stable disease; 3 of 11 progressive disease | Yes | 87 |
| Wild-type KRAS metastatic colorectal cancer | Decitabine (demethylating agent) | Decitabine and panitumumab (monoclonal antibody against EGFR) | Patients with progressive disease on standard therapy and previously treated with cetuximab | 2 of 20 partial response; 11 of 20 stable disease; 7 of 20 progressive disease | No | 88 |
| Advanced solid tumours | Azacitidine (demethylating agent); Valproic acid (pan-EGFR inhibitor) | Azacitidine, valproic acid and carboplatin | Advanced cancer and progression following standard therapy (platinum-based) or no standard effective therapy available | 6 of 32 stable disease; 26 of 32 progressive disease | Yes | 89 |
| Epithelial ovarian cancer | Decitabine (demethylating agent) | Decitabine and carboplatin | Initial response by RECIST and/or CA125 criteria then progressing 6–12 months after previous platinum therapy | 3 of 15 CA125 partial response; 1 of 15 RECIST partial response | Yes | 78 |
| Epithelial ovarian cancer | Decitabine (demethylating agent) | Decitabine and carboplatin | Progression or recurrence within 6 months of platinum-based compound | 1 of 17 complete response; 5 of 17 partial response | Yes | 77 |
| Epithelial ovarian cancer | Azacitidine (demethylating agent) | Azacitidine and carboplatin | Progression or recurrence within 6 months of platinum-based compound | 1 of 29 complete response; 3 of 29 partial response | Yes | 90 |
| Prostate cancer | Azacitidine (demethylating agent) | Azacitidine, LHRH analogue and anti-androgens | Progression on combined androgen blockade | 19 of 34 PSADT >3 months; 11 of 34 PSADT >6 months; 9 of 34 PSADT >9 months | Yes | 91 |
| ER- and PR-positive breast cancer | Vorinostat (pan-EGFR inhibitor) | Vorinostat and tamoxifen | Progression or recurrence on any aromatase inhibitors or completed tamoxifen for 1 year | 8 of 34 partial response | Yes | 92 |
| Epithelial ovarian cancer | Belinostat (pan-EGFR inhibitor) | Belinostat and carboplatin | Recurrence at ≤6 months of last platinum and taxol treatment | 2 of 27 objective response | No | 93 |
| Epithelial ovarian cancer | Belinostat (pan-EGFR inhibitor) | Belinostat, carboplatin and paclitaxel | Platinum-refractory or -resistant disease | 15 of 35 objective response | No | 94 |

EGFR, epidermal growth factor receptor; ER, estrogen receptor; LHRH, luteinizing hormone-releasing hormone; PR, progesterone receptor; PSADT, prostate specific antigen doubling time; RECIST, response evaluation criteria in solid tumors. [†]Pharmacodynamic validation refers to whether there was evidence of epigenetic responses in surrogate or tumour tissue from patients. [‡]Publications were identified using PubMed. Search terms: HDAC inhibitors, decitabine or 5-azacytidine or azacitidine or 5-azacytidine or demethylating agent and cancer. Only clinical trials of solid tumours that used a chemotherapy agent that patients are already known to be resistant to are included.

Combination therapy

AML subtypes and combination therapy



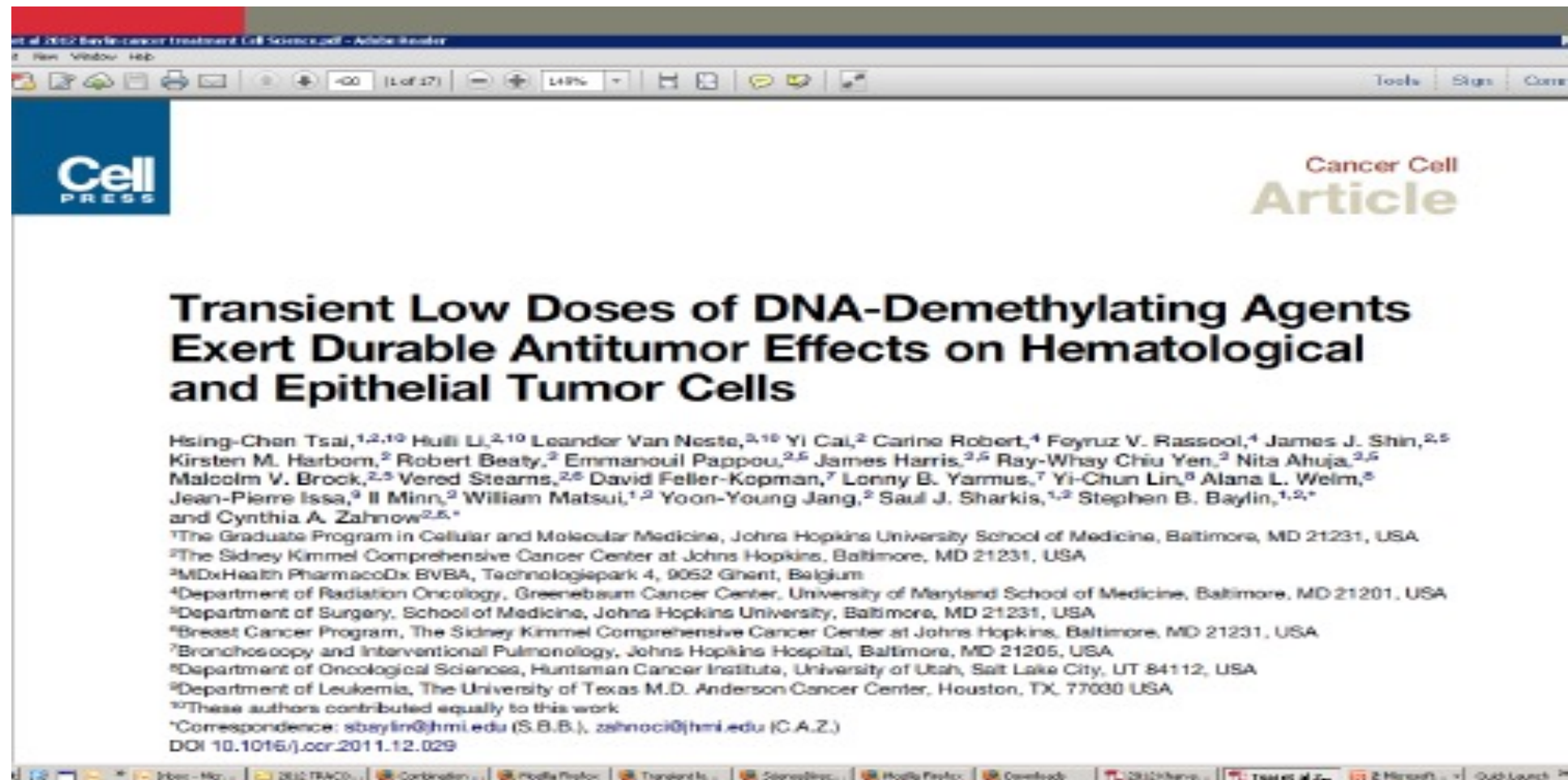
Pharmaceutical Participation

| AML Subtype | Drug | Company |
|------------------|--|----------|
| Tet2/WT1 | CD33 + Aza | BI |
| IDH2 Mutation | Enasidenib | Celgene |
| MLL | Entospletinib (Syk inhibitor) | Gilead |
| CBF | Samalizumab (CD200 Ab) + induction | Alexion |
| P53 mutation | Entospletinib (Syk inhibitor) + Decitabine | Gilead |
| Complex Karotype | Entospletinib (Syk inhibitor) + Decitabine | Gilead |
| P53 mutation | Pevonedistat (Nedd8 inhibitor) + Aza | Takeda |
| Marker Negative | CD33 + Aza | BI |
| NPM1 w FLT3 WT | Entospletinib (Syk inhibitor) | Gilead |
| FLT3 mutation | Gilteritinib | Astellas |
| IDH1 Mutation | Ivosidenib + Aza | Agios |

Source: Leukemia & Lymphoma Society

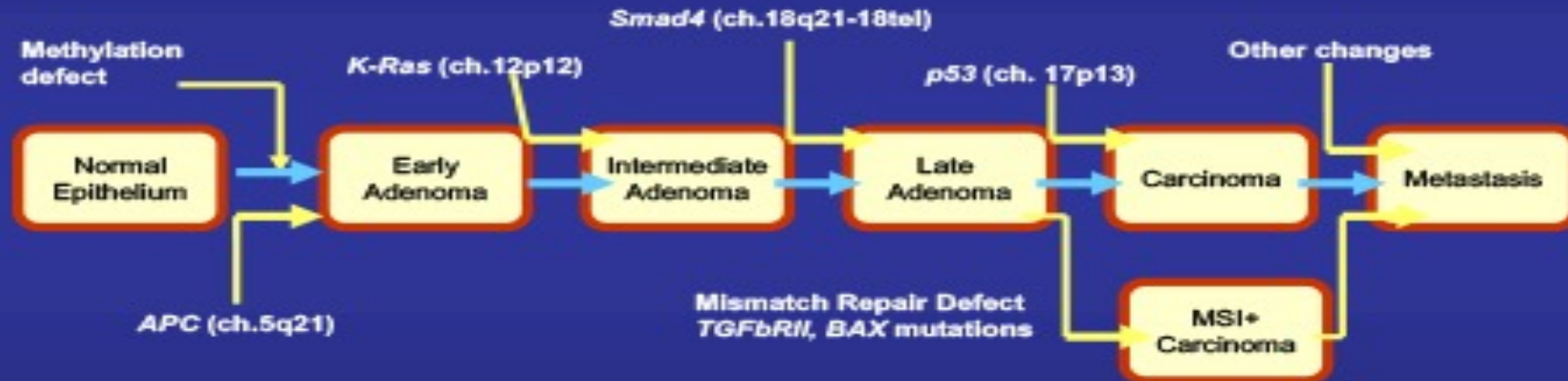
Cancer letters 17 July 2018

Low doses of DNA-demethylating agents



Intervention

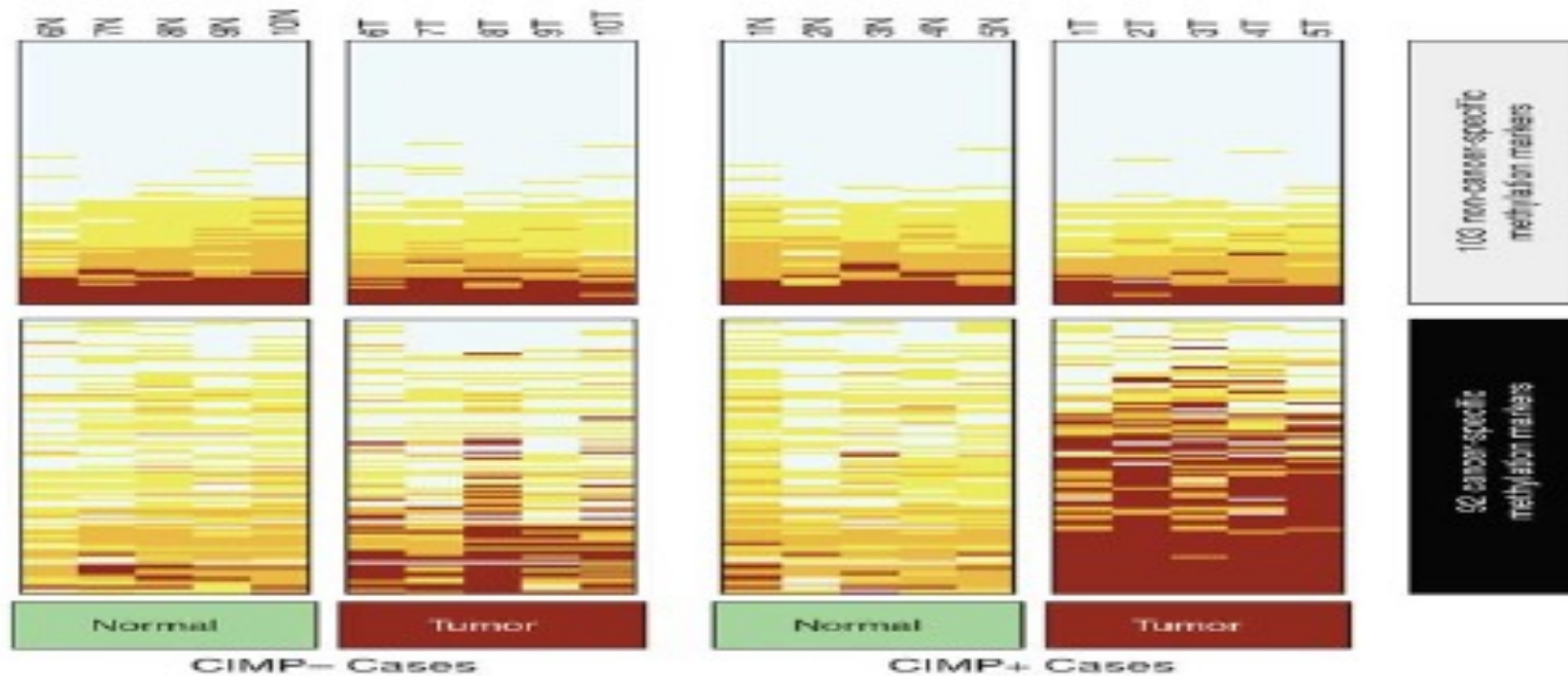
Potential Steps for Intervention



A Model for Colorectal Tumorigenesis

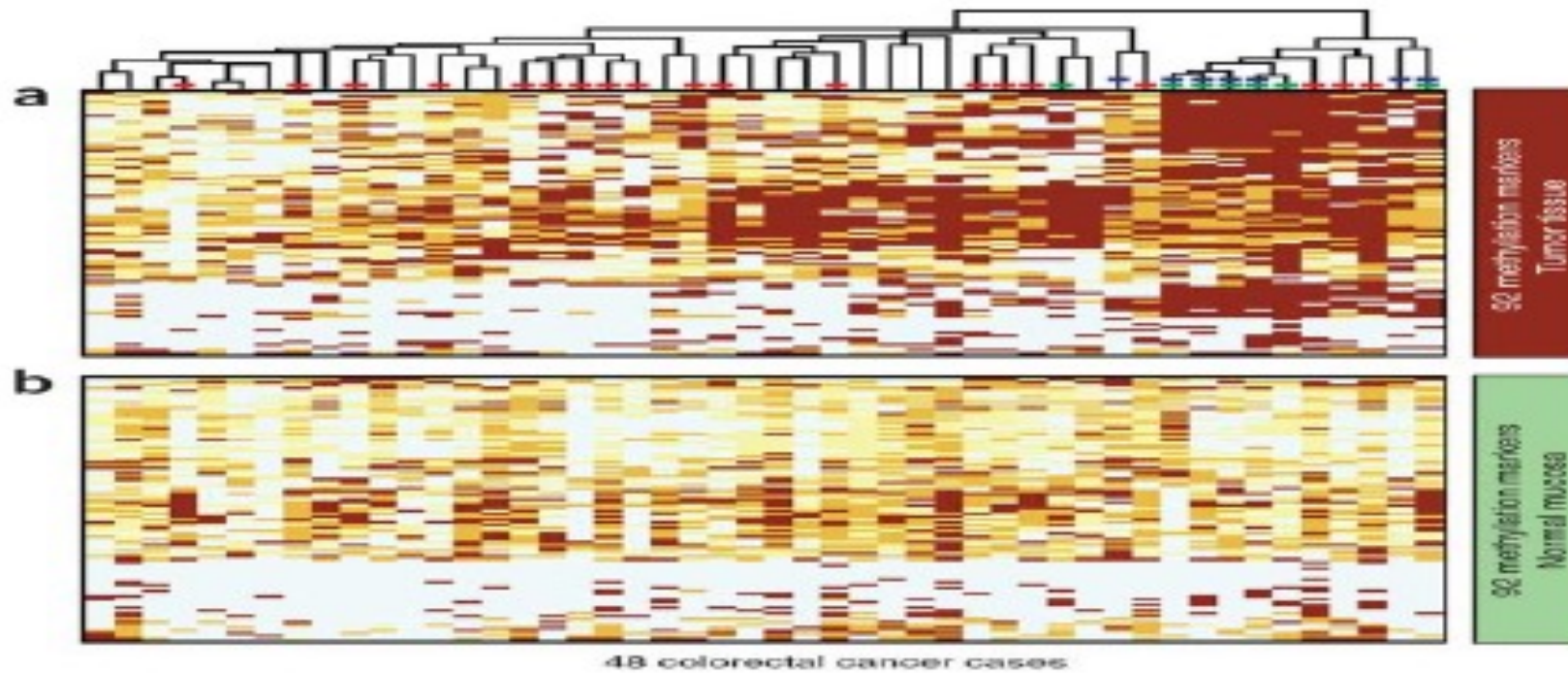
Microsatellite instability

CpG island methylator phenotype underlies sporadic microsatellite instability and is tightly associated with BRAF mutation in colorectal cancer



Tumor clusters

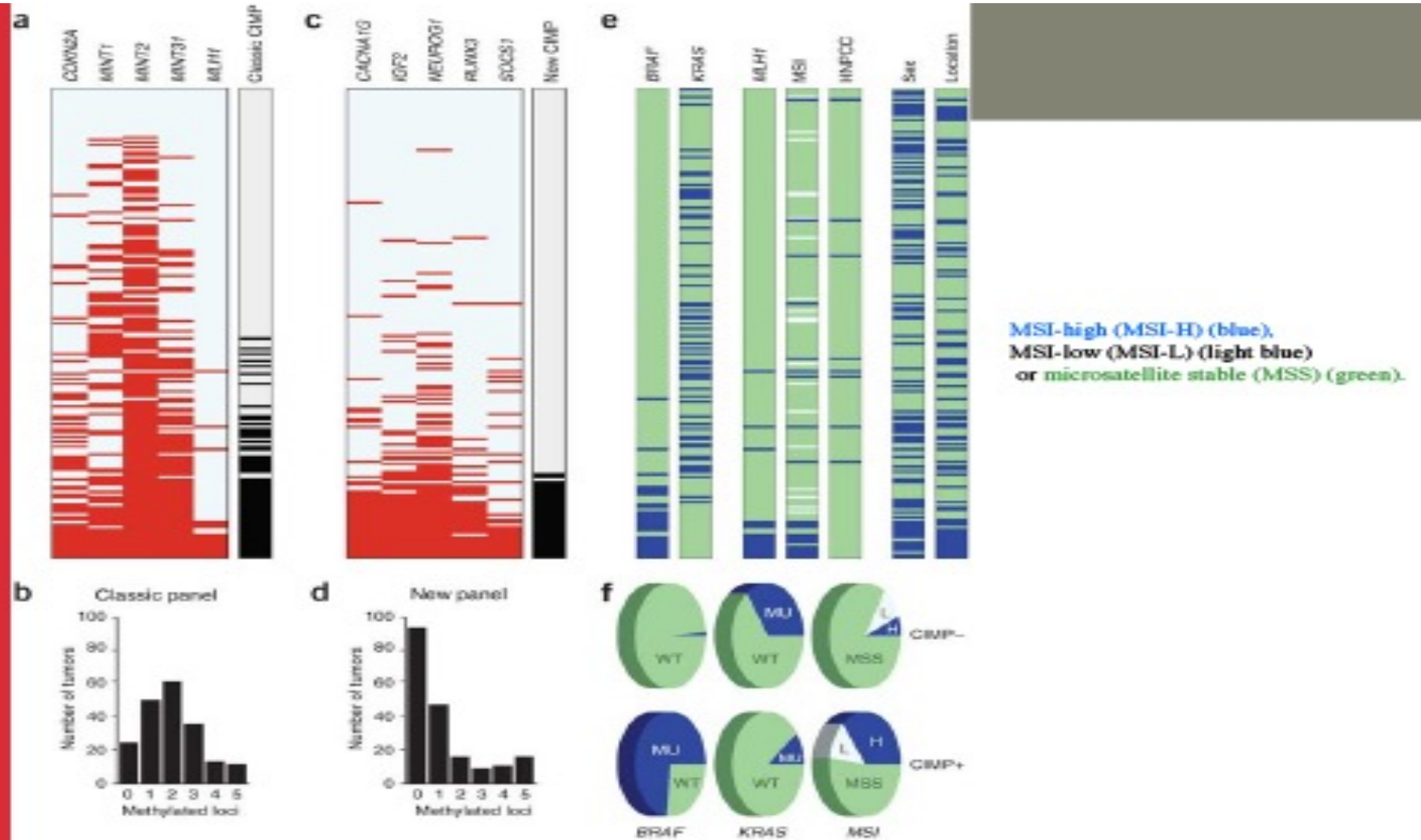
Identification of tumor clusters.



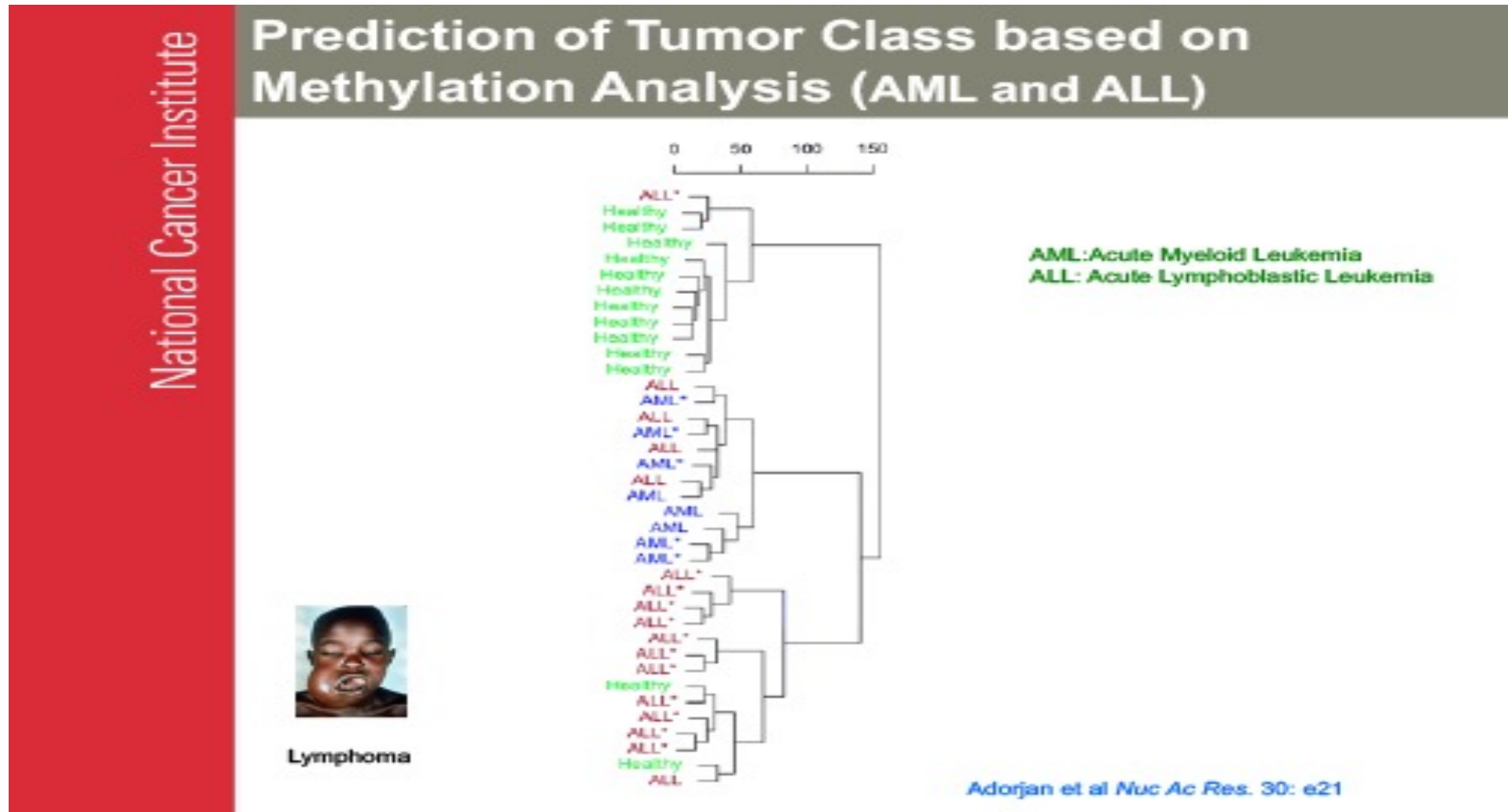
KRAS mutation indicated by a red rectangle overlaying the branch,
BRAF mutations indicated by a green rectangle
MSI-H cases designated with a blue rectangle.

48 Colorectal tumors

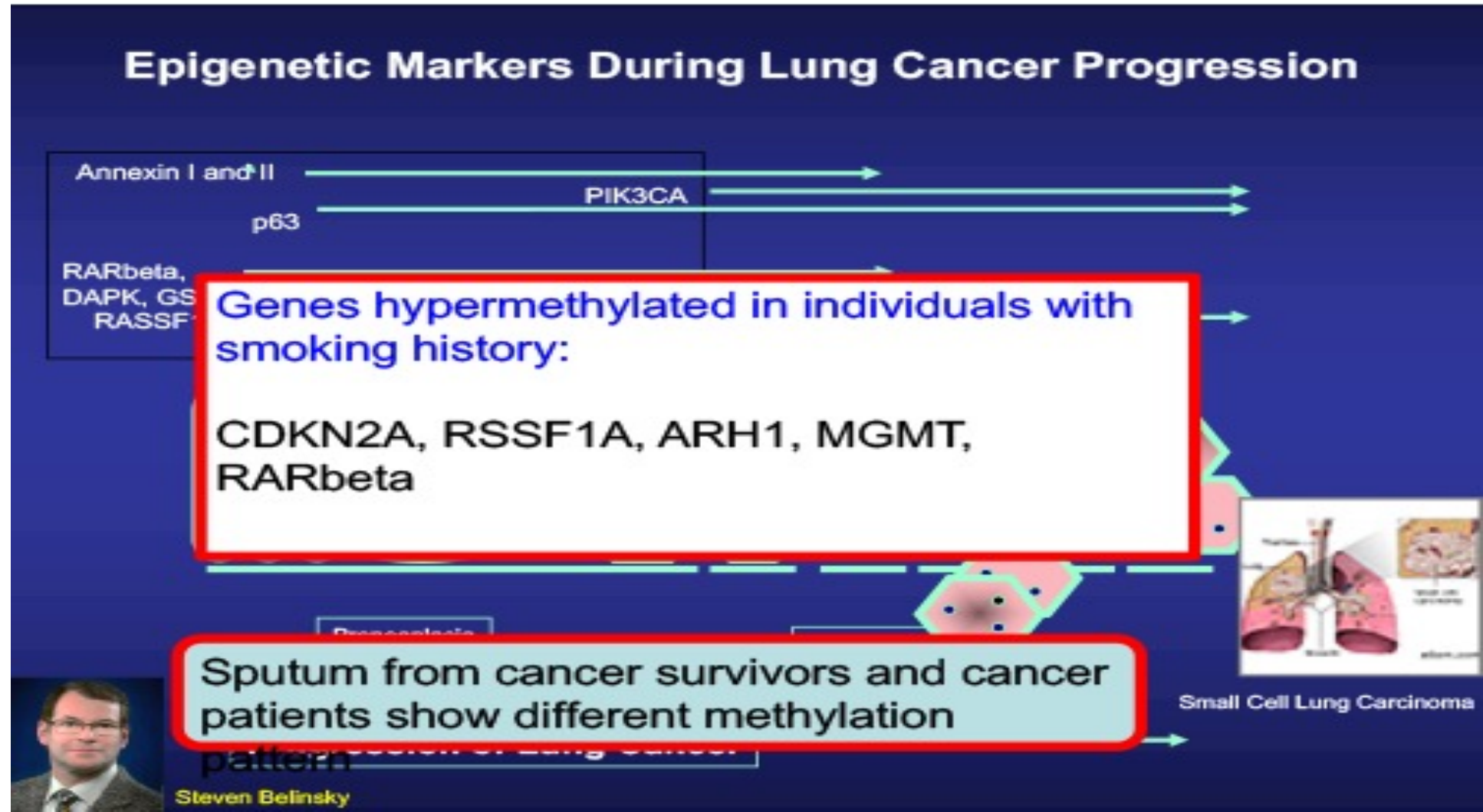
Genetic analysis



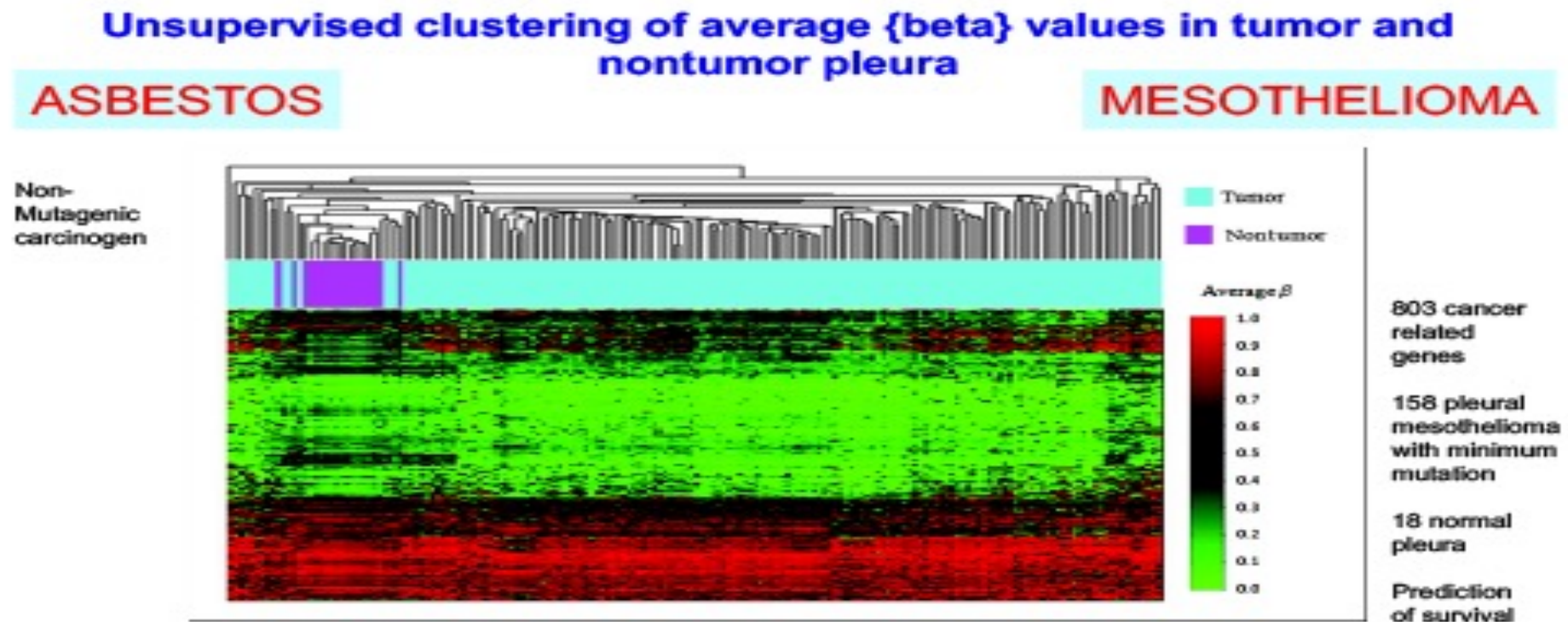
Methylation analysis



Epigenetic markers



Mesothelioma



Christensen, B. C. et al. Cancer Res 2009;69:227-234

Epigenetic Profiles Distinguish Pleural Mesothelioma from Normal Pleura and Predict Lung Asbestos Burden and Clinical Outcome

Cancer Research

Epigenetic pattern

Epigenetic Patterns in the Progression of Esophageal Adenocarcinoma

Cancer Research

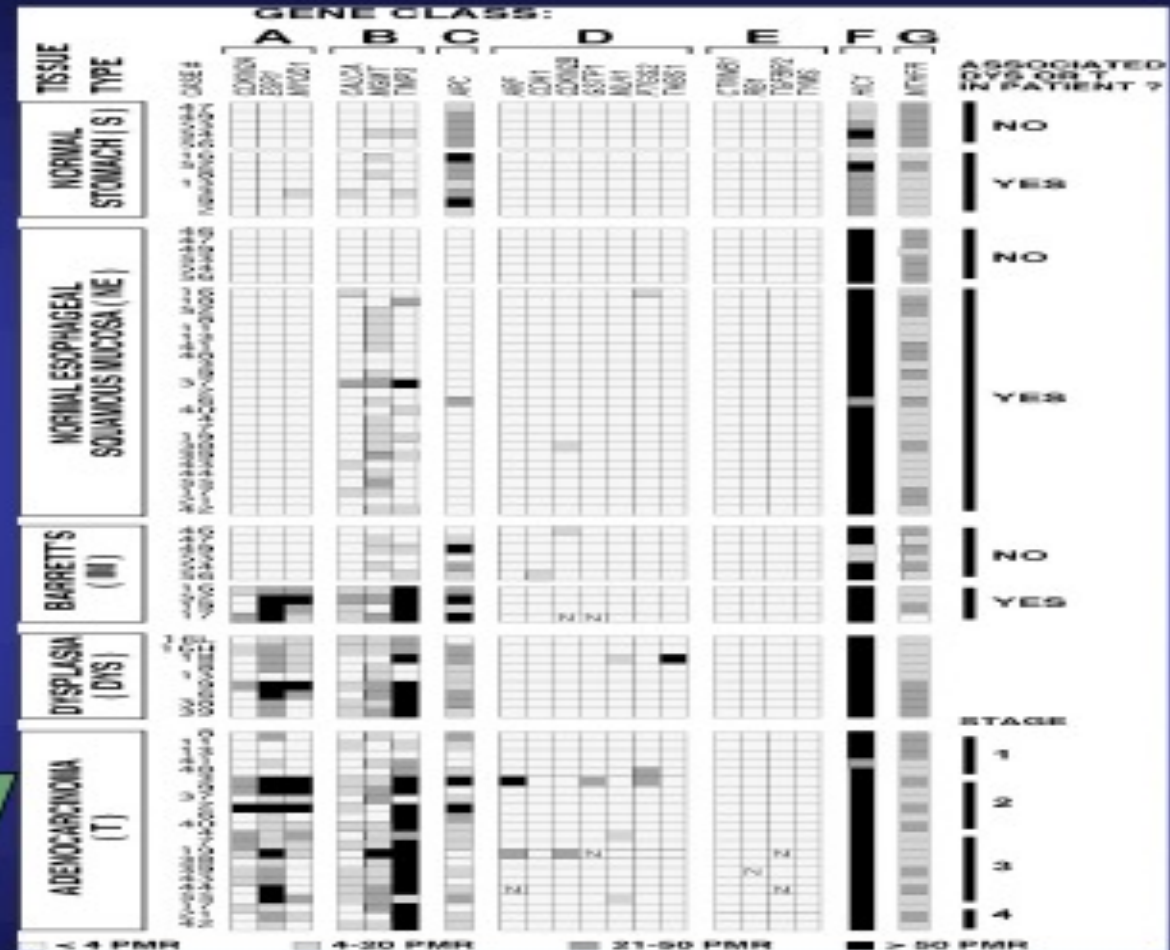
61:3410



Cancer Progression

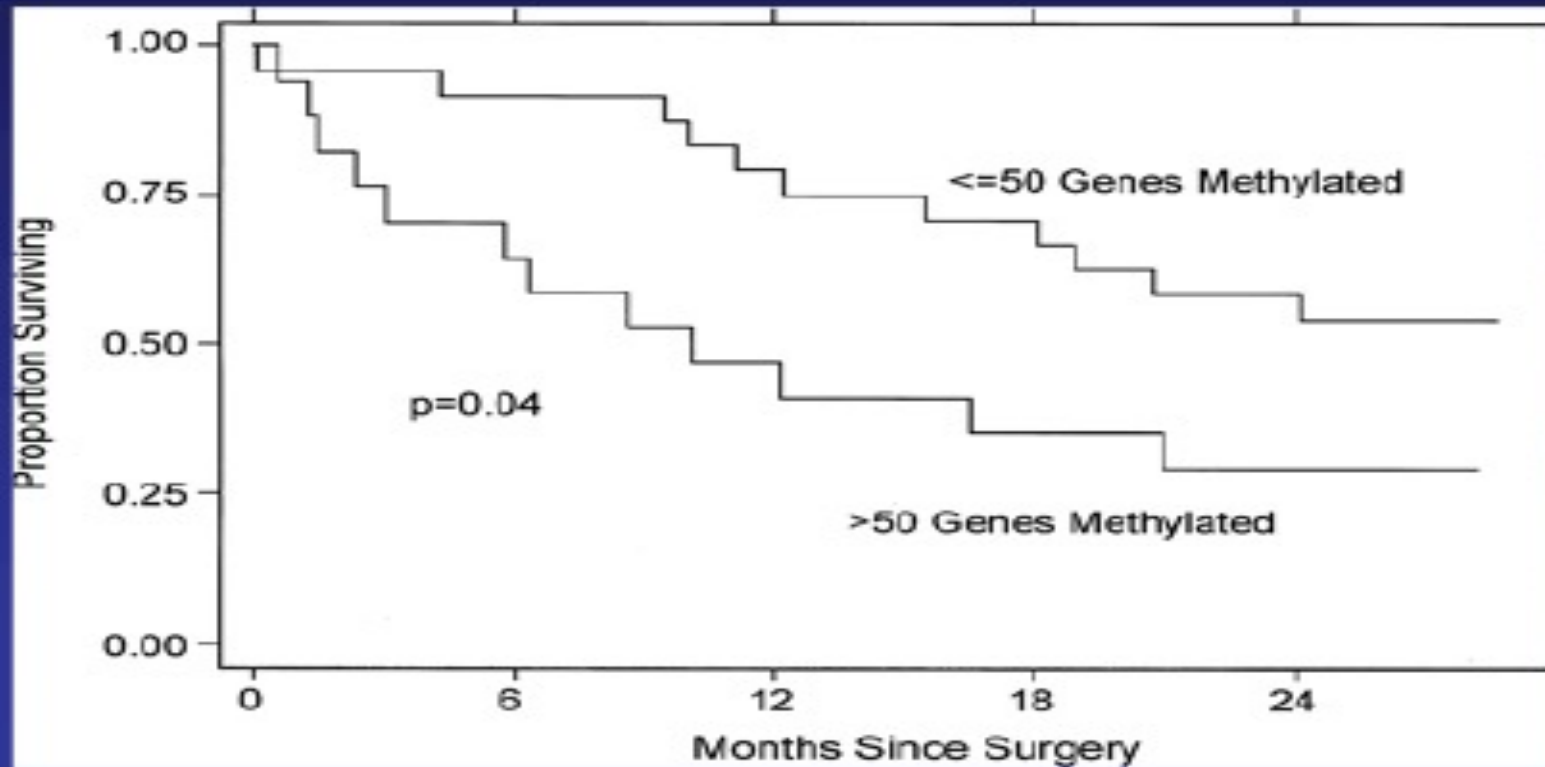
Risk factors

- Gastroesophageal Reflex Disease (GERD)
- Smoking
- Higher Body Mass Index (BMI) or obesity



Esophageal cancer

Esophageal Cancer: Probability of Survival



Pancreatic cancer

Pancreatic Cancer: Methylation of p14ARF and p16INK4a

Pancreatic Carcinoma (PCA) : 39

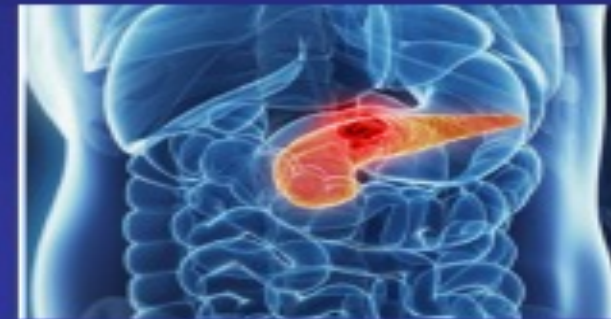
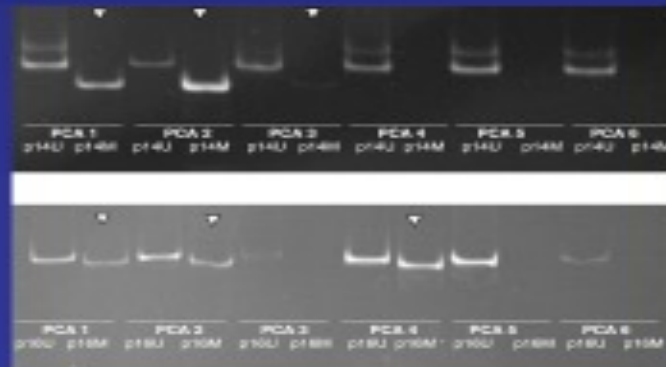
19/39 p16INK4a

Chronic Pancreatitis (CP) : 16

0/16 p16INK4a

Normal Pancreatogram (NAD) : 6

0/6 p16INK4a

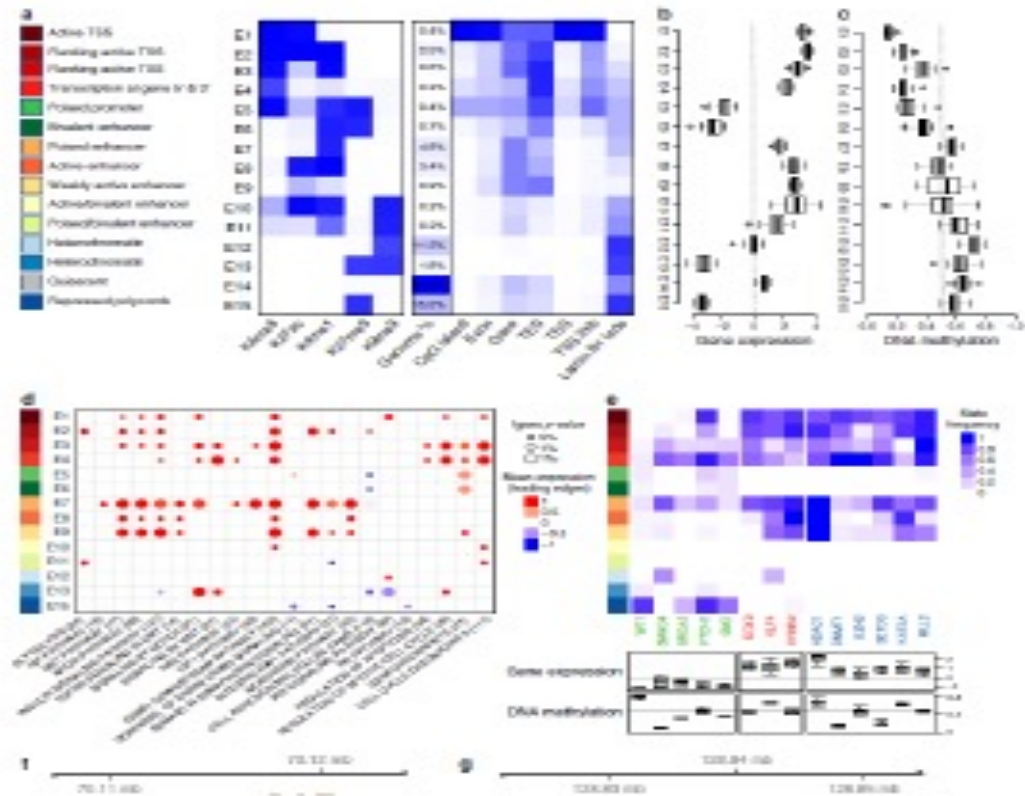


Sample: Pancreatic Fluid

(Klump et al. *Mol Cell Path* 88: 217)

Chromatin states

Distinct chromatin states of human PDAC



Breast cancer

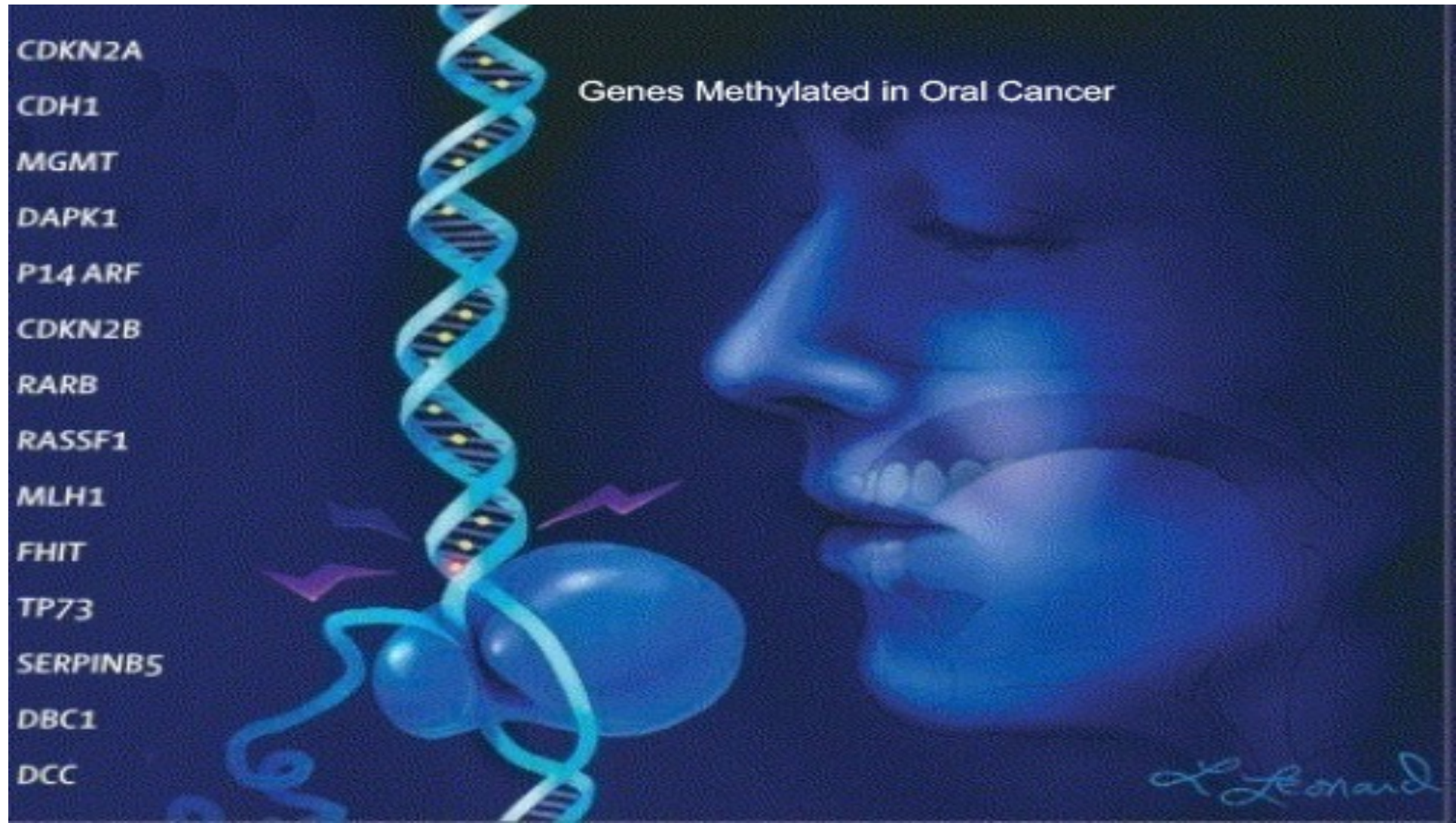
Breast Cancer Response to Tamoxifen Treatment by ESR1 Methylation

Preinvasive lesions, often designated as “in situ” or “intraepithelial neoplasia” falls in the domain of prevention.

Ductal carcinoma in situ (DCIS) lesions, detected in screening are generally treated aggressively, although all DCIS do not lead to breast cancer (over treatment).

Methylation profiling of DCIS lesions can distinguish aggressive from indolent DCIS.

Methylated genes



Immune system and epigenetics

Immune System and Epigenetics

[Shin HJ et al.](#)

Links STAT4 expression in human **T cells** is regulated by DNA methylation but not by promoter polymorphism.

J Immunol. 175(11):7143-50.

[Espinoza CR, Feeney AJ.](#)

The extent of **histone acetylation** correlates with the differential rearrangement frequency of individual **VH genes in pro-B cells**.

J Immunol. 175(10):6668-75.

[Gasche JA, Hoffmann J, Boland CR, Goel A.](#)

Interleukin-6 promotes tumorigenesis by altering DNA methylation in oral cancer cells.

Int J Cancer. 2011 Sep 1;129(5):1053-63.

[Fujisawa T, Joshi BH, Puri RK.](#)

Histone modification enhances the effectiveness of IL-13 receptor targeted immunotoxin in murine models of human pancreatic cancer.

J Transl Med. 2011 Apr 8;9:37.

[Tahara T et al.](#)

Association between IL-17A, -17F and MIF polymorphisms predispose to CpG island hyper-methylation in gastric cancer.

Int J Mol Med. 2010 Mar;25(3):471-7.

Biomarkers

Epigenomics Grants Predictive Biosciences Rights to Use a Biomarker in a Prostate Cancer Test

Epigenomics (www.epigenomics.com) granted Predictive Biosciences (www.predictivebiosci.com) a nonexclusive license to use its prostate cancer DNA methylation biomarker, mGSTP1, for the development and commercialization of a laboratory test to help in the diagnosis and management of prostate cancer. The agreement follows a similar deal covering mGSTP1 signed with Quest Diagnostics (www.questdiagnostics.com) in February 2009.

Quest Diagnostics Incorporates
leading provider of diagnostic
services.

ion in Prostate Cancer

drug detoxification enzyme which

Seattle, WA, U.S.A., February 25,
G (Frankfurt, Prime Standard: ECX),
diagnostics company, today announced
a non-exclusive licensing agreement

marker

Methyl-Profiler™ DNA Methylation PCR ARRAYS

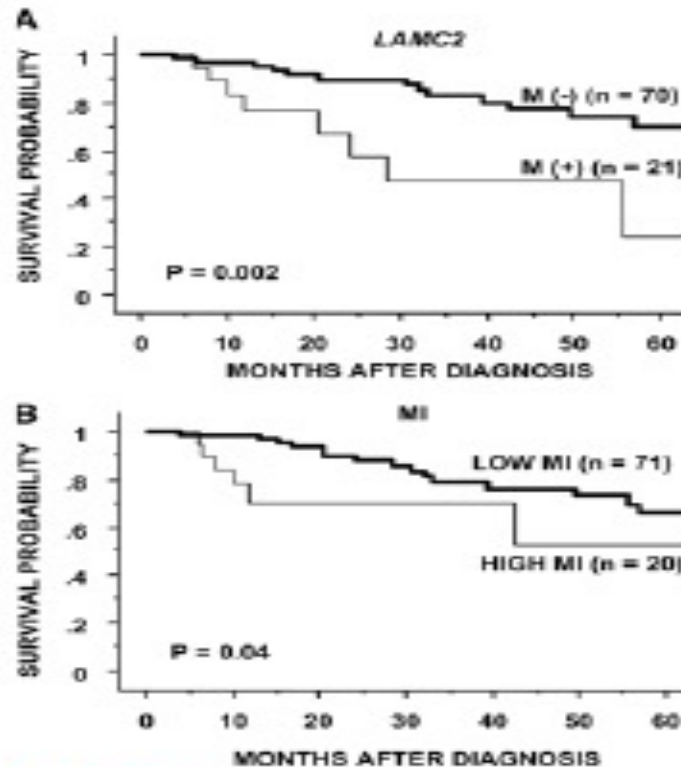
| Product* | Catalog # | Price* |
|---|-----------|---------|
| Human Breast Cancer - Signature Panel | MeAH-011 | \$ 499 |
| Human Gastric Cancer - Signature Panel | MeAH-021 | \$ 499 |
| Human Liver Cancer - Signature Panel | MeAH-031 | \$ 499 |
| Human Lung Cancer - Signature Panel | MeAH-041 | \$ 499 |
| Human Prostate Cancer - Signature Panel | MeAH-051 | \$ 499 |
| Human Stem Cell Transcription Factors - Signature | MeAH-511 | \$ 499 |
| Human Inflammatory Response - Signature Panel | MeAH-521 | \$ 499 |
| Human T Cell Activation - Signature Panel | MeAH-531 | \$ 499 |
| Human Cytokine Production - Signature Panel | MeAH-541 | \$ 499 |
| Custom Methyl-Profiler PCR Arrays | Inquire | Inquire |

* Methyl-Profiler PCR Arrays are available in Signature Panels (24 genes) & Complete Panels (96 genes).

Bladder cancer methylation

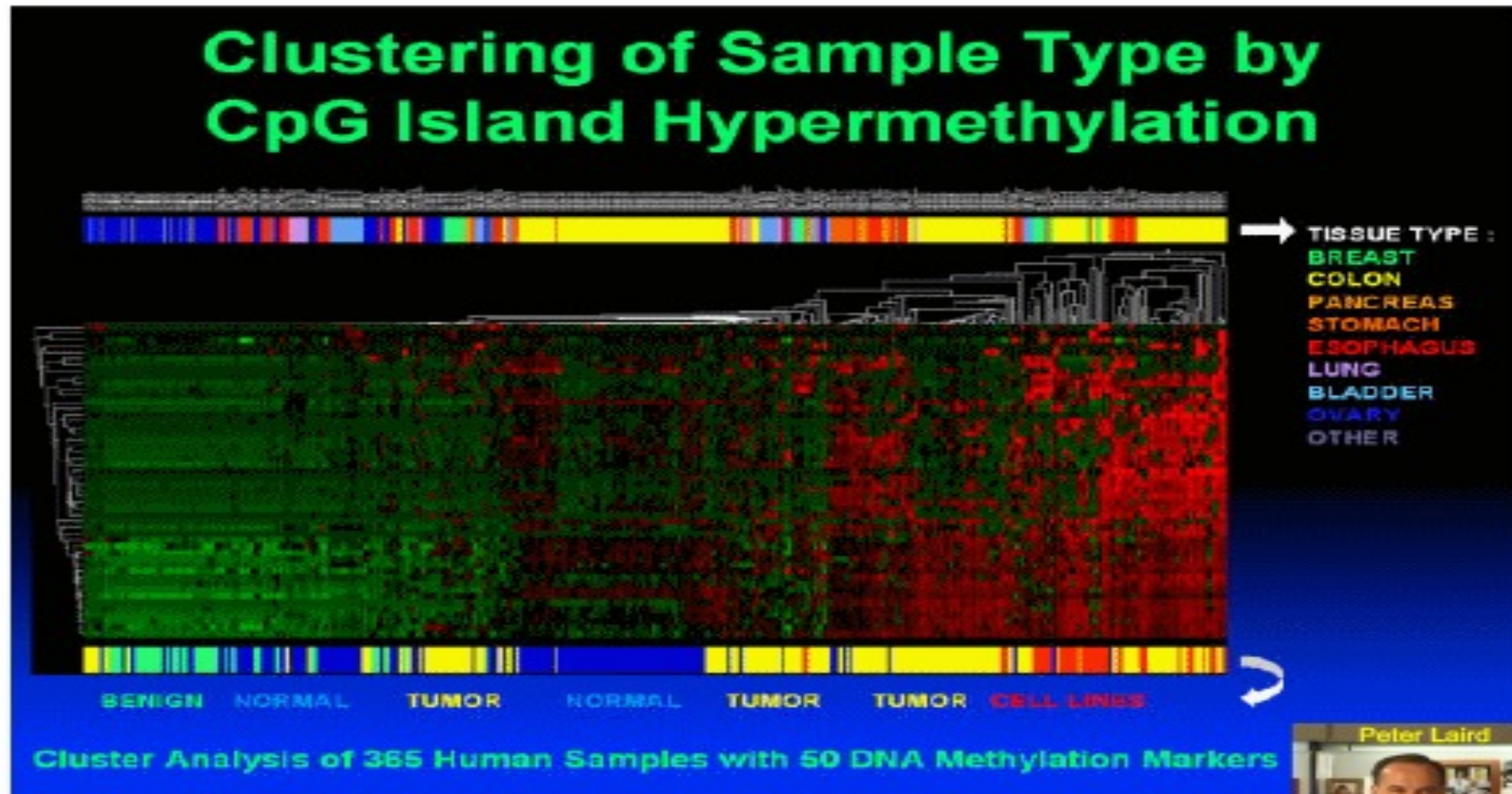


Bladder Cancer Methylation of LAMC2 in Exfoliated Cells Isolated from Urine



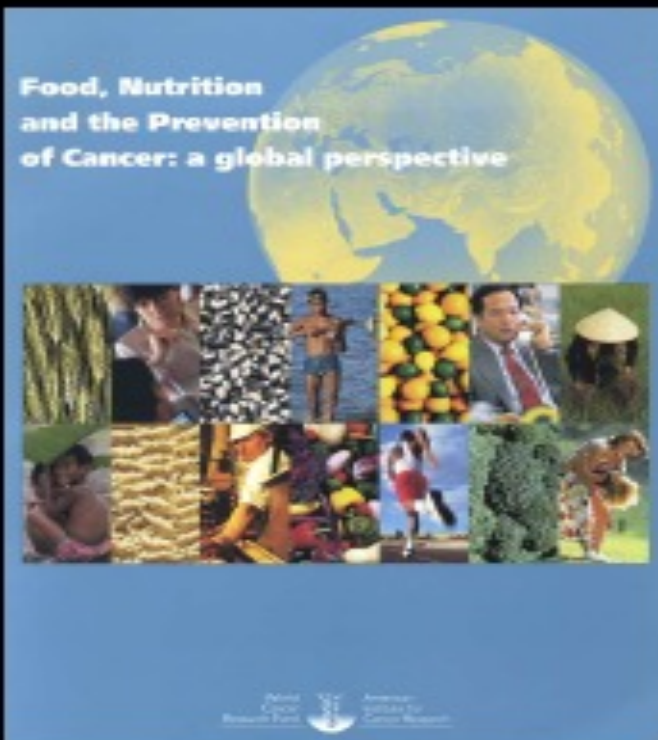
Another Study:
Schistosomes and Bladder Cancer

CpG island hypermethylation



Diet and cancer

DIET AND CANCER: FOCUS ON PREVENTION



Ignat Pagnanly

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

METHYL-DEFICIENT MODEL OF ENDOGENOUS HEPATOCARCINOGENESIS

- Chronic deficiency in the methyl donors methionine, choline, folic acid and vitamin B₁₂
- No exogenous carcinogens added
- No genetic manipulation
- Hepatocellular carcinoma in 14-16 months in male rats and certain mouse strains
- Sequence of pathological changes similar to the development of hepatocellular carcinoma in humans

Normal tissue

36 weeks, G8Tr-foci ≥54 weeks, G8Tr-tumor

Liver tumor



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[illegible]

Nutritional Epigenetics and the Prevention of Hepatocellular Carcinoma with Bioactive Food Constituents.

Alvarez, FJ¹, Martin, S¹, Parsons, MJ²

(ii) *Additional information*

all days the month

Hepatocellular carcinoma (HCC) is an aggressive and life-threatening disease often diagnosed at intermediate or advanced stages, with substantially limited therapeutic approaches to its successful treatment. This indicates that the prevention of HCC may be the most promising strategy in reducing its incidence and mortality. Emerging evidence indicates that numerous nutrients and non-nutrient dietary bioactive components can reduce the occurrence and/or delay the development of HCC through modifications of deregulated carcinogenic mechanisms. This review examines the evidence associated with diet and chemoprevention, based on epidemiologic data and *in vitro* and *in vivo* models of HCC on the

chemopreventive potential of epigenetic food components, including dietary methyl-group donors, epigenetic histone deacetylase, sodium butyrate, resveratrol, curcumin, and sulforaphane, on liver carcinogenesis. Future direction and potential challenges in the effective use of bioactive food constituents in the prevention of HCC are highlighted and discussed.

Downloaded At: 11:53 11 September 2009

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Positive, Accurate –

Figure 1

First Received: 2008 Jan 8; 10:08 AM; doi: 10.1002/ajim.20910; eCollection 2009 Jul 15.

Association of TNRSP12A Methylation With Prognosis in Hepatocellular Carcinoma With History of Alcohol Consumption.

PROXYTM, STENOSM, HXSM, STENOSM, HXSM, HXSM, STENOSM, HXSM, STENOSM, HXSM

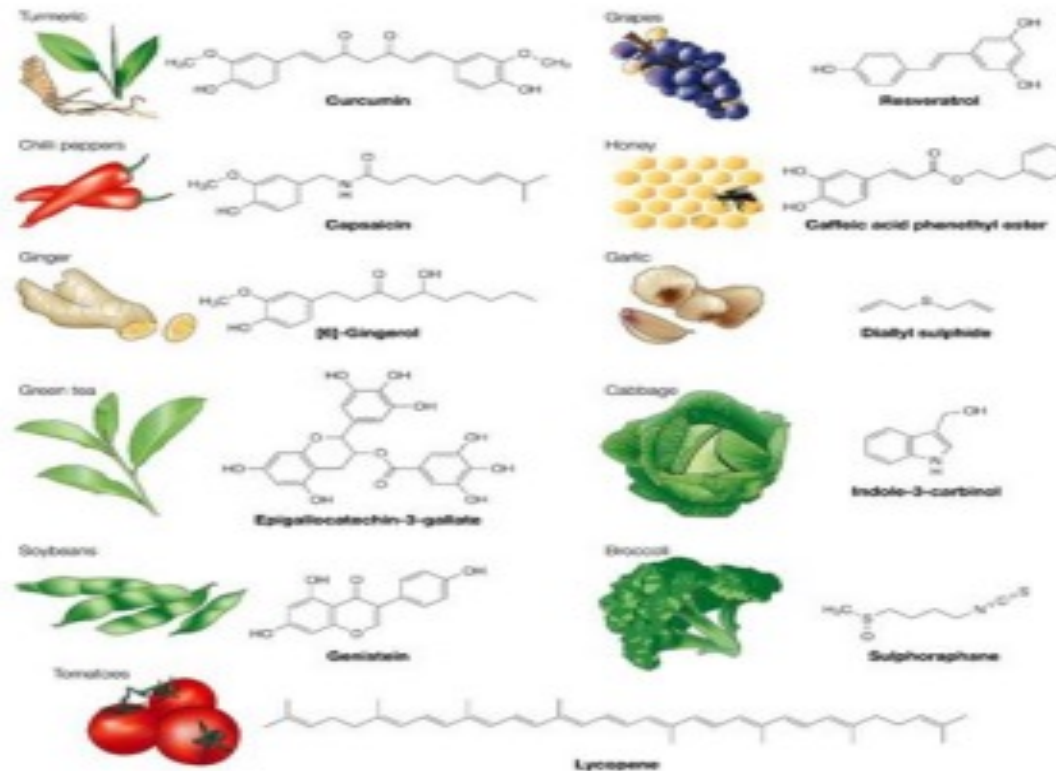
(4) *Ascaris lumbricoides*

Abstract

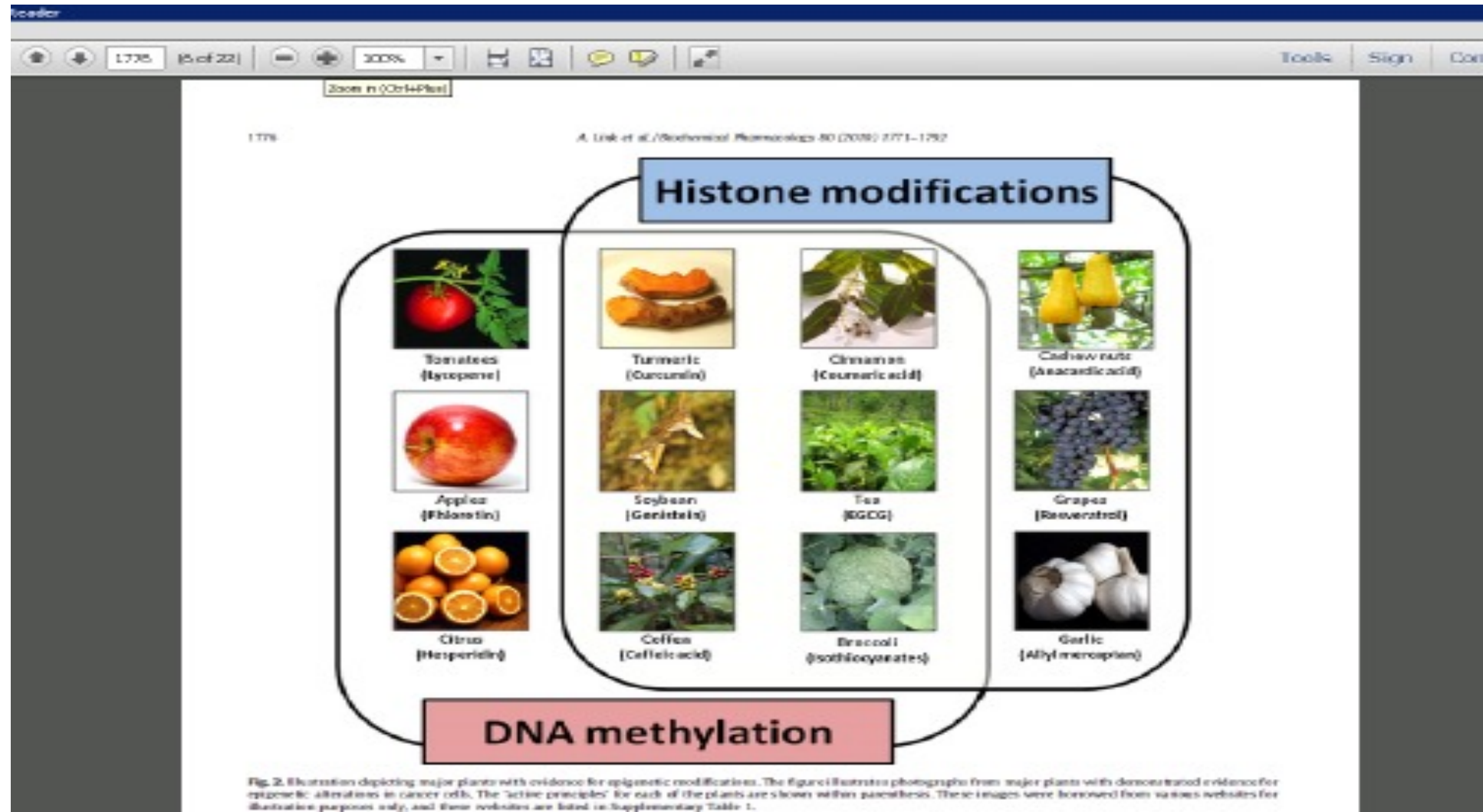
Hepatocellular carcinoma (HCC) is the third leading cause of cancer in HCC-endemic worldwide with a poor prognosis. Alcohol is the second-most common etiological factor for HCC, accounting for approximately one-third of all HCC cases. Current evidence proved that aberrant over-expression of TP53P123 correlates with the severity of disease, making it a highly indicator of disease a more aggressive and worse prognosis outcome. Emerging studies have confirmed that epigenetic changes are critical events in the development and progression of liver cancer. The study to investigate the mechanisms by which alcohol abuse mediated changes in the methylation level of TP53P123 affect the occurrence, development and prognosis of HCC were under-undertaken. Thus, in this study are aimed to publicly available datasets to detect the association between DNA methylation level of CpG sites in gene TP53P123 and the development of HCC in those with alcohol abuse history. Finally, we determined that the hypomethylation of two methylation sites cg26079447 and cg26080020 could identify HCC from other non-HCC liver diseases. Also, hypomethylation of these two sites could identify alcoholic cirrhosis from other non-hepatocellular carcinoma liver diseases. Most important, the prognostic analysis revealed that the hypomethylation of cg26079447 and cg26080020 in HCC patients with alcohol abuse history could predict poor prognosis. Further, survival analysis by gender and location in HCC patients with alcohol abuse history. The results of the present study indicate that the methylation of CpG sites in the TP53P123 gene could be used as a biomarker for the diagnosis and prognosis of HCC. The further researches need to confirm that this DNA methylation marker DNMT3L might regulate TP53P123 methylation and affect the occurrence, development and prognosis of HCC, especially in patients with a history of alcohol abuse. These findings provide new insights into the role of epigenetic mechanisms in the transformation of alcoholic liver disease into HCC.

Anticancer phytochemicals

ANTICANCER PHYTOCHEMICALS (Representative chemopreventive phytochemicals and their dietary sources)



Epigenetic foods



Research opportunities

Research Opportunities and Challenges

Will inclusion of epigenetic markers help in identification of new risk factors (modifiable factors and host factors) in different races and ethnic groups?

Will epigenetic markers in cohort and case-control studies improve sensitivity and specificity of markers and help in identifying high-risk populations?

Are genetic and epigenetic events correlated during cancer development?

Are there race/ethnicity specific miRNAs and noncoding RNAs?

How can we use this information for better define cancer subcategories?

How can we overcome EWAS technical challenges?



Christopher Plass (Heidelberg)



Nancy Kiviat (Seattle)



Christine Ambertson
(Roswell Park, Buffalo)

Research challenges

National Cancer Institute

Research Opportunities and Challenges

Can we predict cancer recurrence or secondary cancer development based on epigenetics marks (or in combination with other omics marks)?

Why is it difficult to harmonize epigenetic data with other omics data sets?

Is there a window of susceptibility of exposure? How can we develop epigenetic approaches to intervene?

How to avoid activity of DNMT and HDAC inhibitors on normal cell functions?

What is the role of non-histone proteins in gene regulation?

How to target cancer stem cells using epigenetic approaches?

How much microbiome-specific metabolites can affect epigenetic regulation? How effective are probiotics in cancer prevention?

How to address challenges

National Cancer Institute



How are we addressing these challenges?



NIH common fund

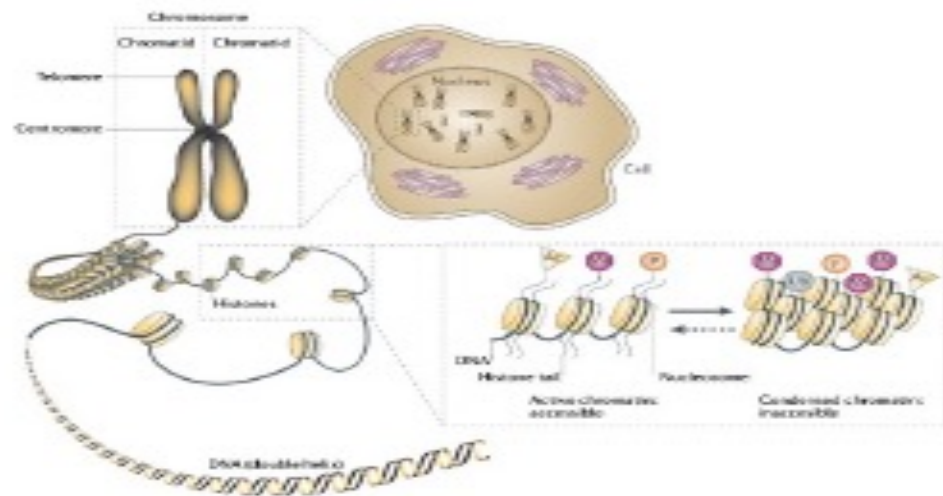


Personalized medicine

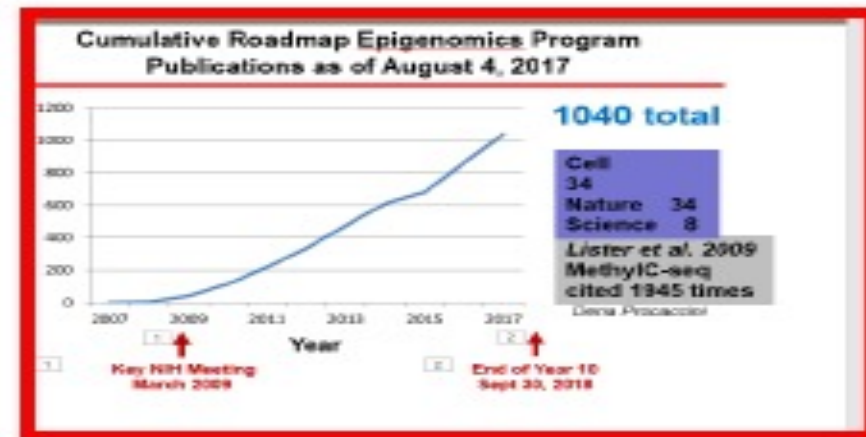


Epigenetics roadmap

Epigenetics Roadmap



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Nature Reviews | Cancer

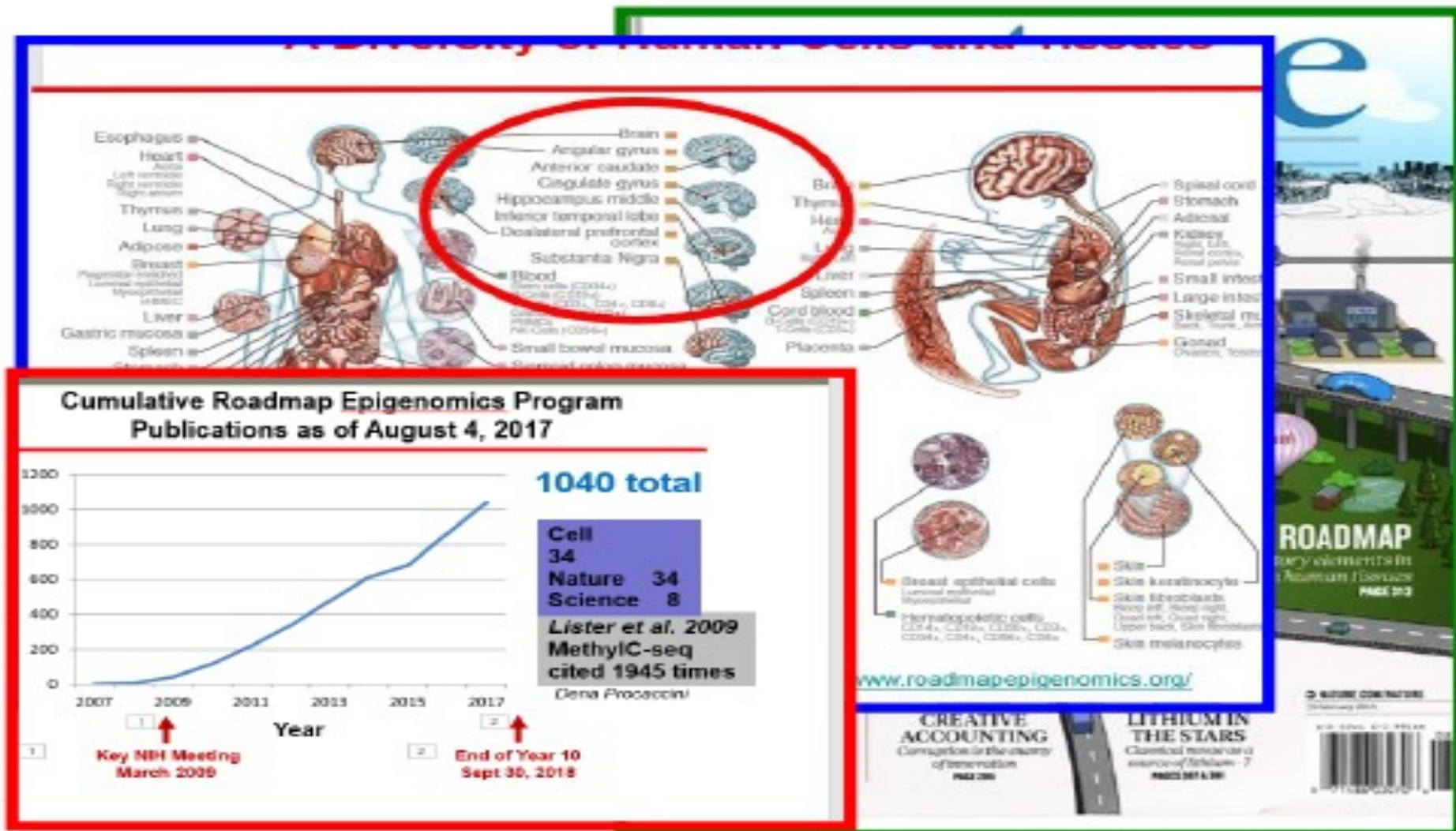


Epigenetically Regulated Diseases:

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.

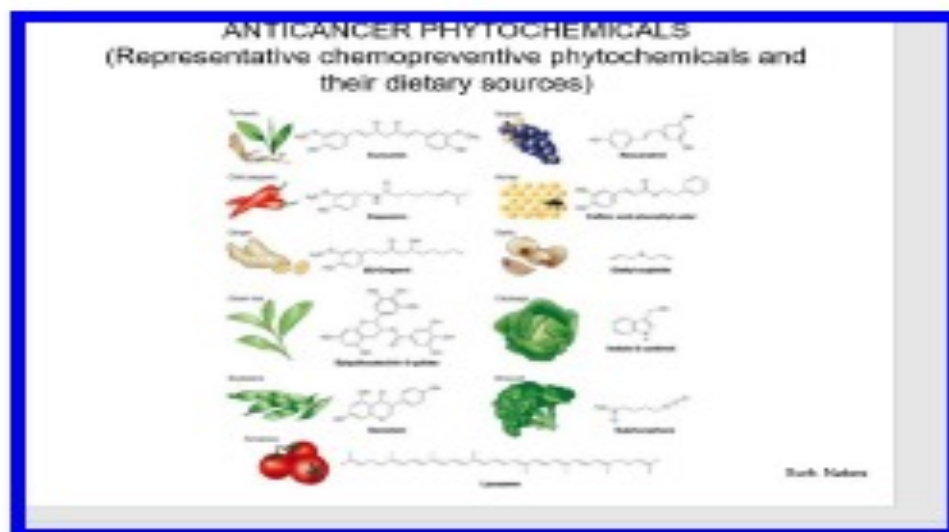
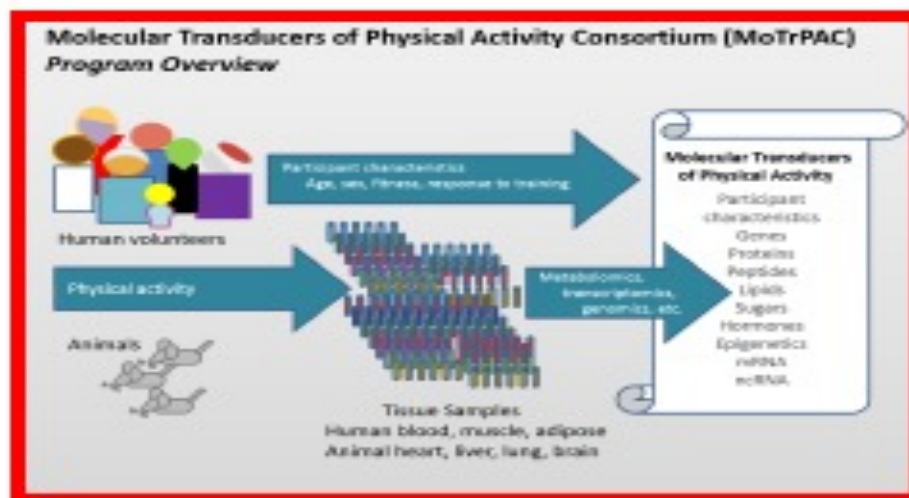
Roadmap



IHEC



Miscellaneous



Common fund

Common fund data ecosystem

An **online portal** that will allow researchers to access and work across multiple Common Fund program data sets within a **digital cloud environment**.

Follow **FAIR** principles

F = Findable

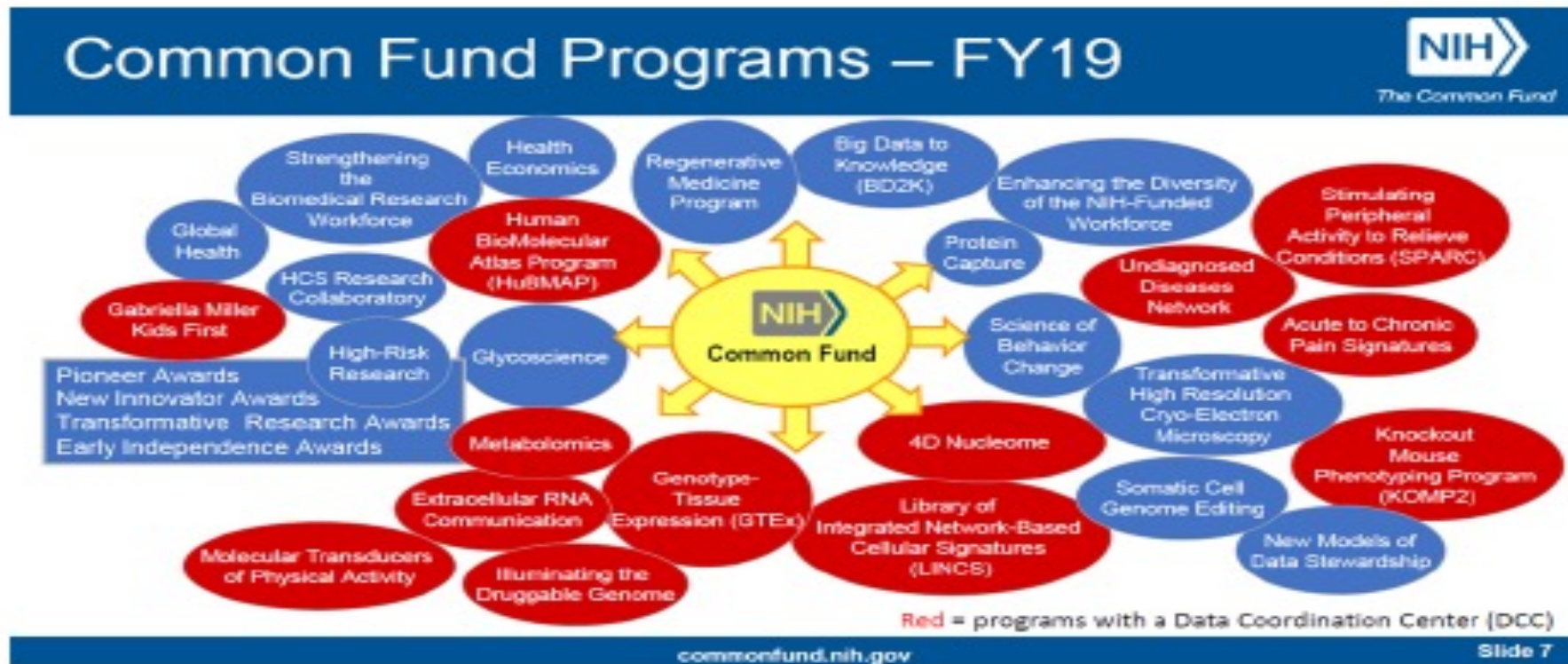
A = Accessible

I = Interoperable

R = Reusable

commonfund.nih.gov/dataecosystem

Common fund programs



CFDE projects

Status of CFDE Project activities



- Funded the CFDE Coordinating Center (Owen White, PI)
 - The CFDE Coordinating Center had "Deep Dive" in-person visits to 8 Common Fund DCCs.
 - Kids First
 - GTEx
 - HMP
 - LINCS
 - SPARC
 - MoTrPAC
 - HuBMAP
 - 4D Nucleome
 - Metabolomics (Nov)
 - Plan to evaluate "success" of the CFDE both impact on CF Programs and project process.
 - Fund the next set of CFDE activities, such as addressing data storage and single-sign on.
-

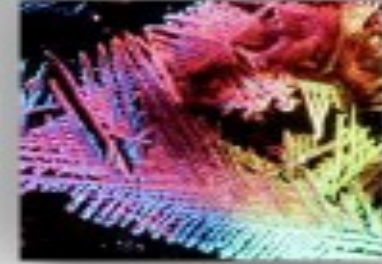
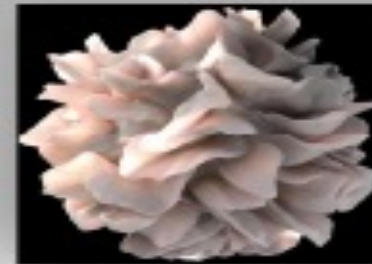
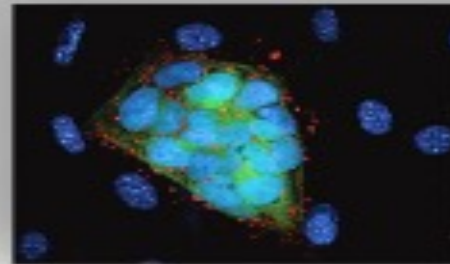
NIH



NIH...

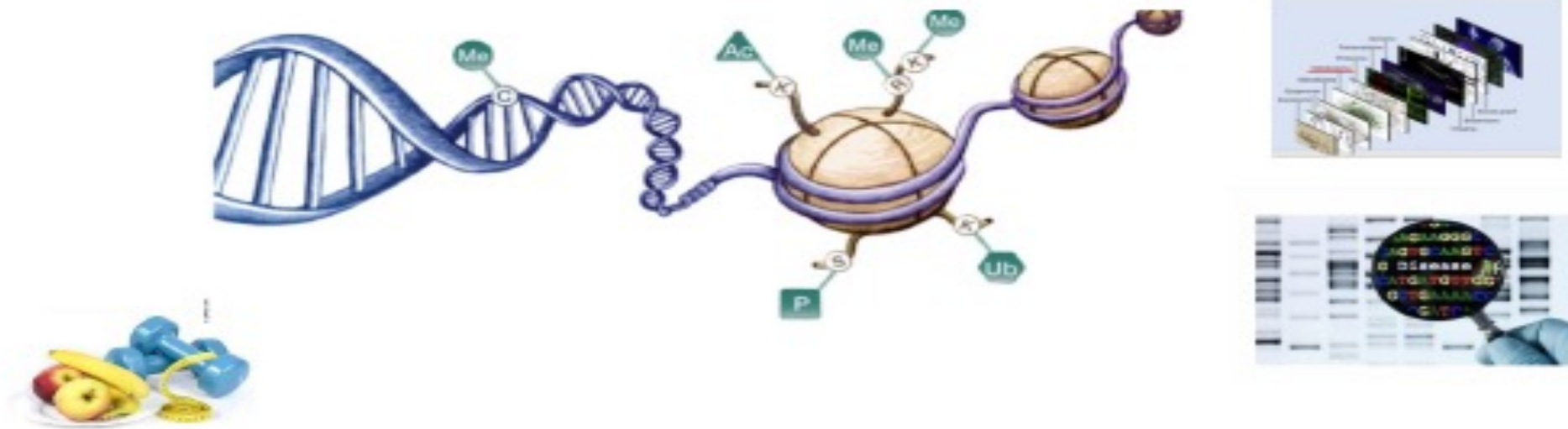
Mukesh Verma, PhD
vermam@mail.nih.gov

Turning Discovery Into Health



Epigenetic approaches

EPIGENETIC APPROACHES IN CANCER CONTROL AND TREATMENT



Mukesh Verma, Ph.D.

Chief, Methods and Technologies Branch
Program Director,
Epidemiology and Genomics Research Program
DCCPS, NCI, NIH