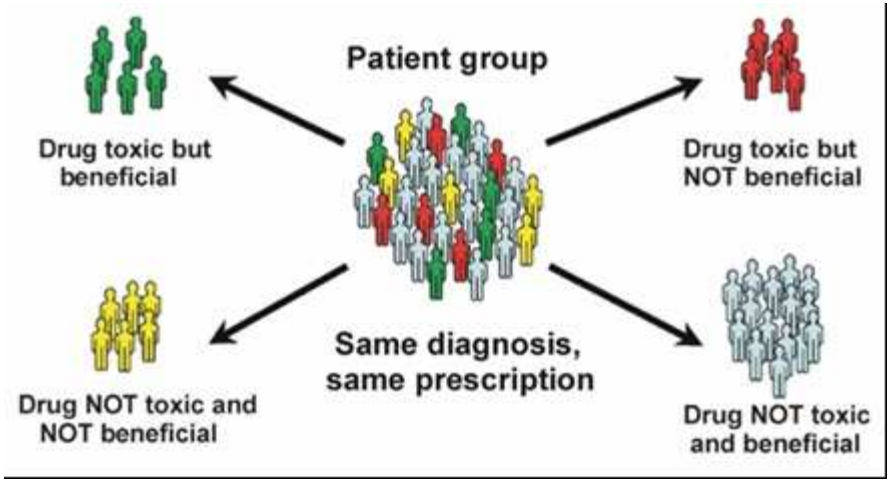


Mukesh Verma, Ph.D.

Chief, Methods and Technology Branch
Program Director,
Epidemiology and Genomics Res. Program
DCCPS, NCI, NIH



Epigenetic and genetic approaches in personalized medicine in cancer



Mukesh Verma, Ph.D.

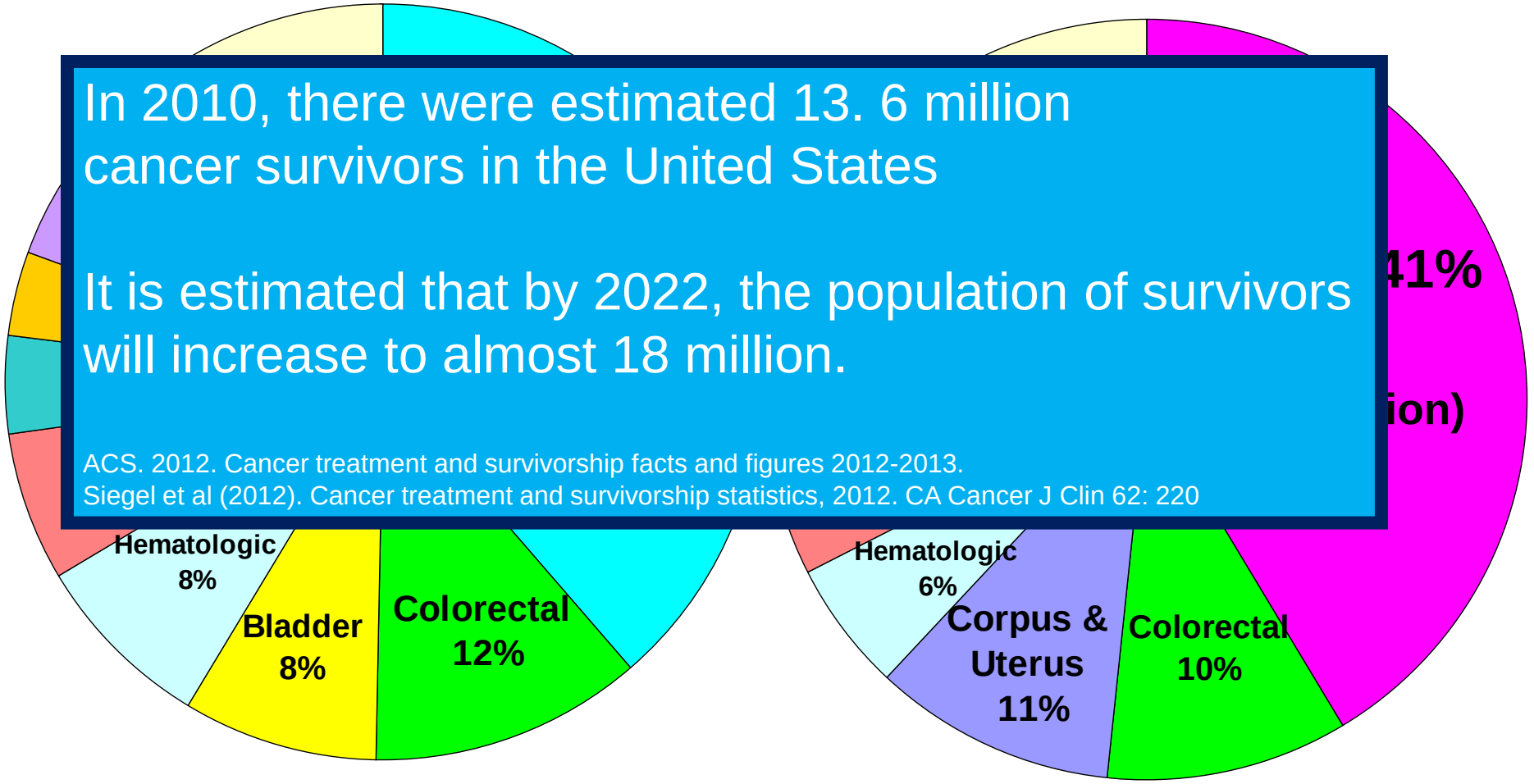
Chief, Methods and Technology Branch
Program Director,
Epidemiology and Genomics Res. Program
DCCPS, NCI, NIH

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

In 2010, there were estimated 13. 6 million cancer survivors in the United States

It is estimated that by 2022, the population of survivors will increase to almost 18 million.

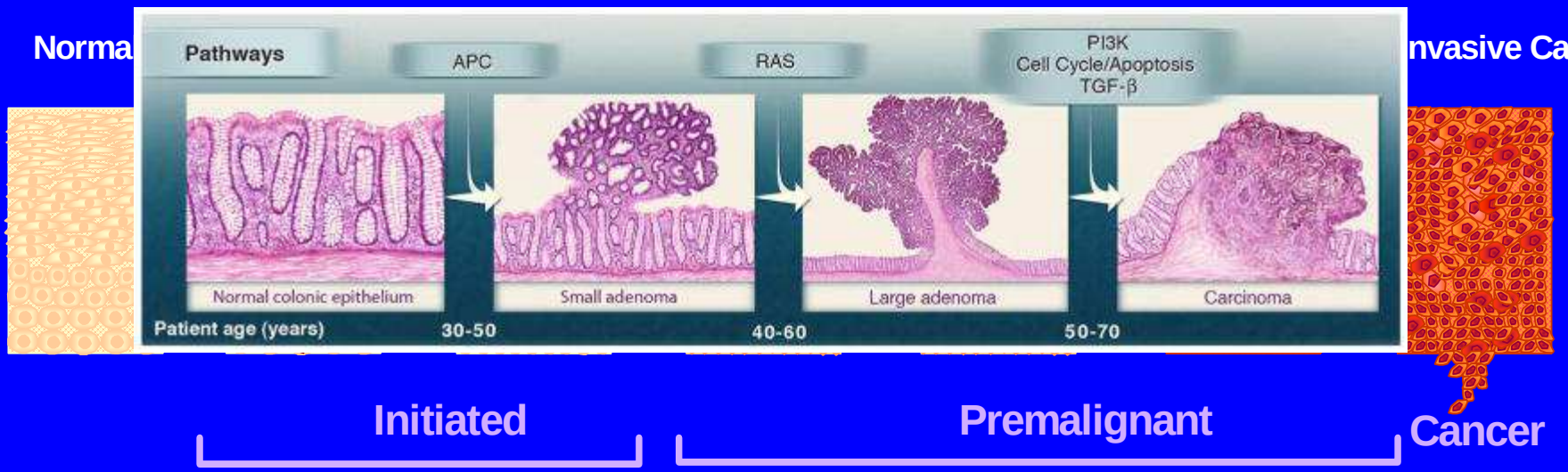
ACS. 2012. Cancer treatment and survivorship facts and figures 2012-2013.
Siegel et al (2012). Cancer treatment and survivorship statistics, 2012. CA Cancer J Clin 62: 220



Men (4.24 million)

Women (5.31 million)

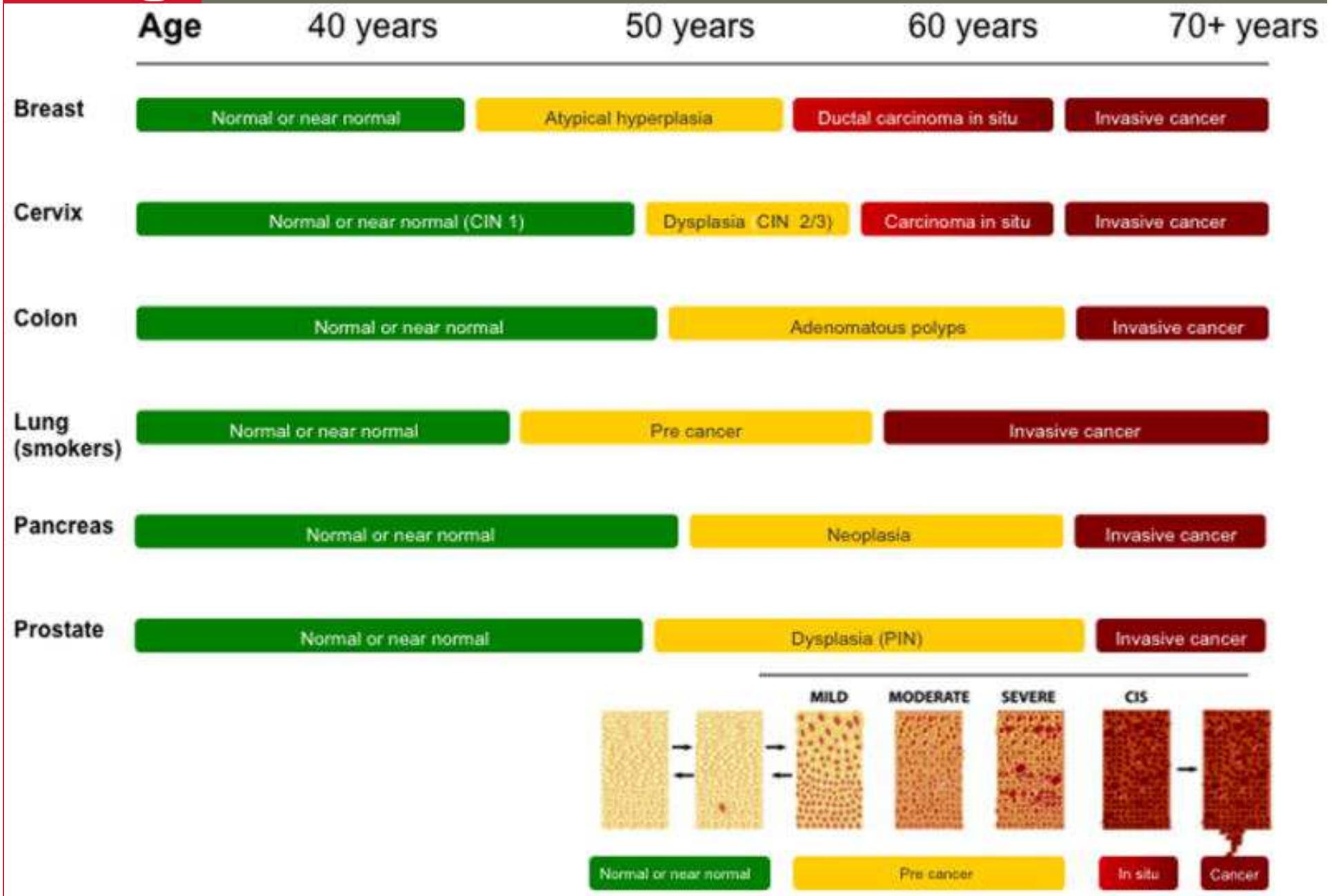
Cancer Development is a Multi-step Process

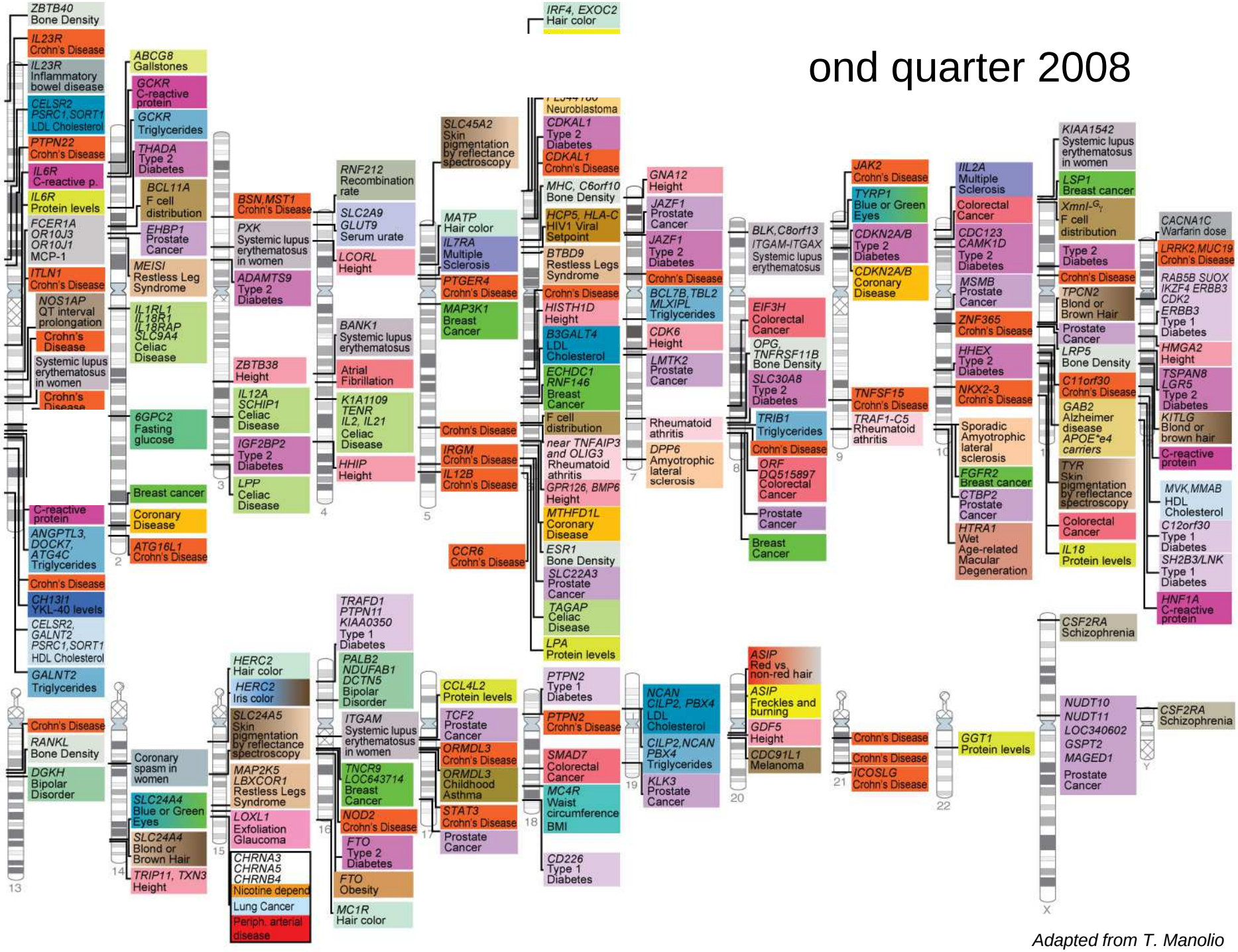


Genetic alterations and the progression of colorectal cancer

The major signaling pathways that drive tumorigenesis are shown at the transitions between each tumor stage. One of several driver genes that encode components of these pathways can be altered in any individual tumor. Patient age indicates the time intervals during which the driver genes are usually mutated. Note that this model may not apply to all tumor types. TGF-β, transforming growth factor–β.

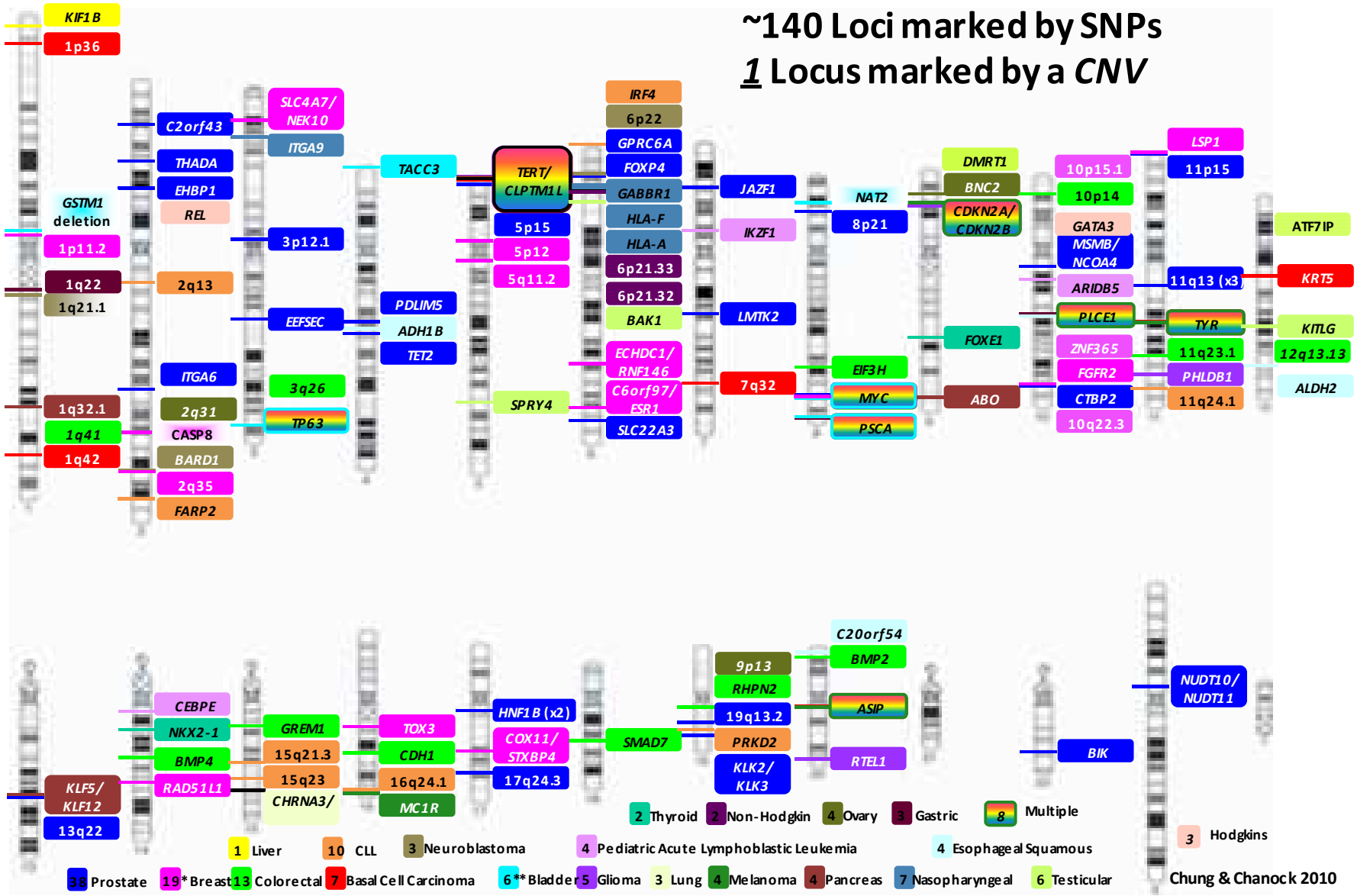
dapted from Vogelstein et al 2013


Age
40 years
50 years
60 years
70+ years
Breast
Normal or near normal
Atypical hyperplasia
Ductal carcinoma in situ
Invasive cancer
Cervix
Normal or near normal (CIN 1)
Dysplasia CIN 2/3)
Carcinoma in situ
Invasive cancer
Colon
Normal or near normal
Adenomatous polyps
Invasive cancer
Lung (smokers)
Normal or near normal
Pre cancer
Invasive cancer
Pancreas
Normal or near normal
Neoplasia
Invasive cancer
Prostate
Normal or near normal
Dysplasia (PIN)
Invasive cancer
MILD
MODERATE
SEVERE
CIS
Normal or near normal
Pre cancer
In situ
Cancer



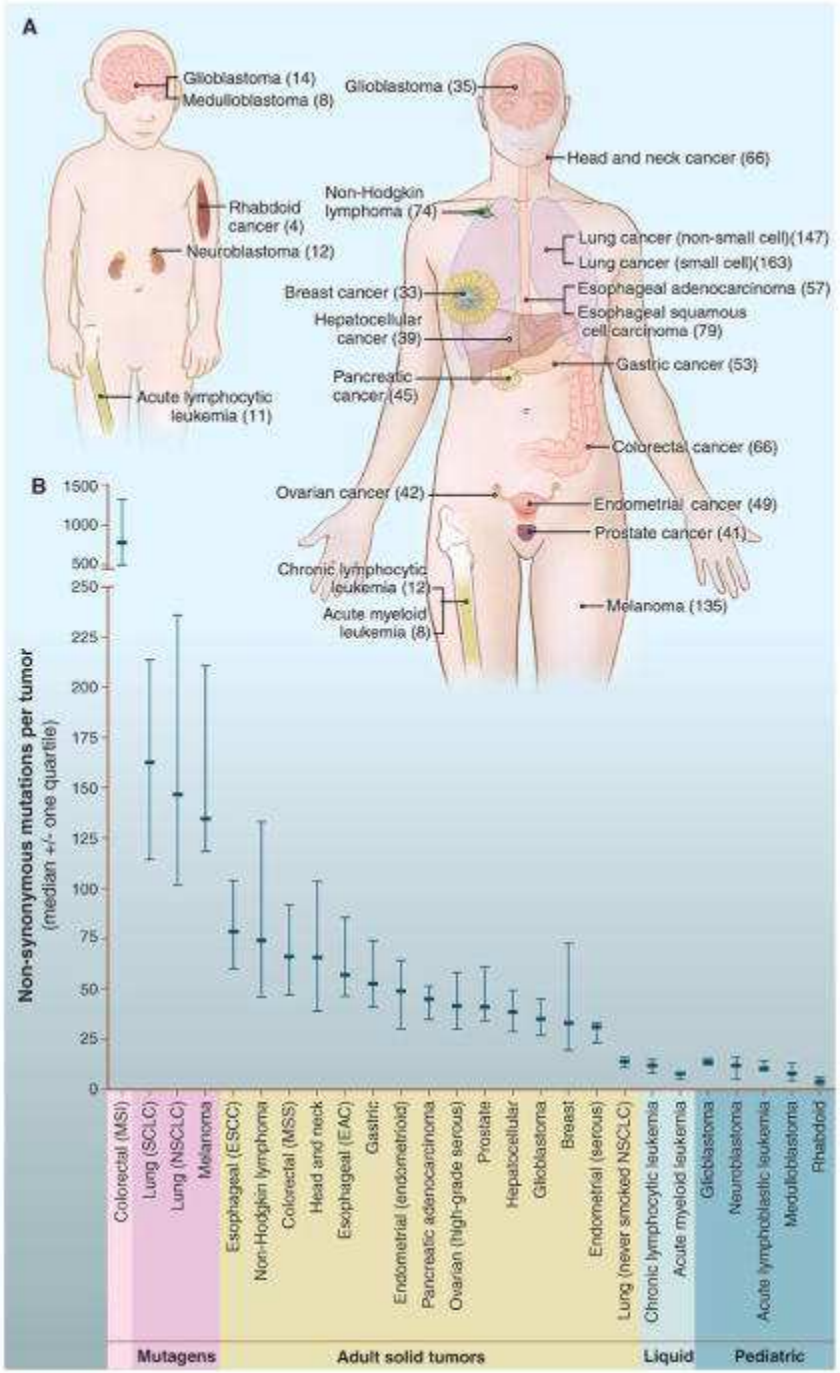
Adapted from T. Manolio

Published GWAS Etiology Hits



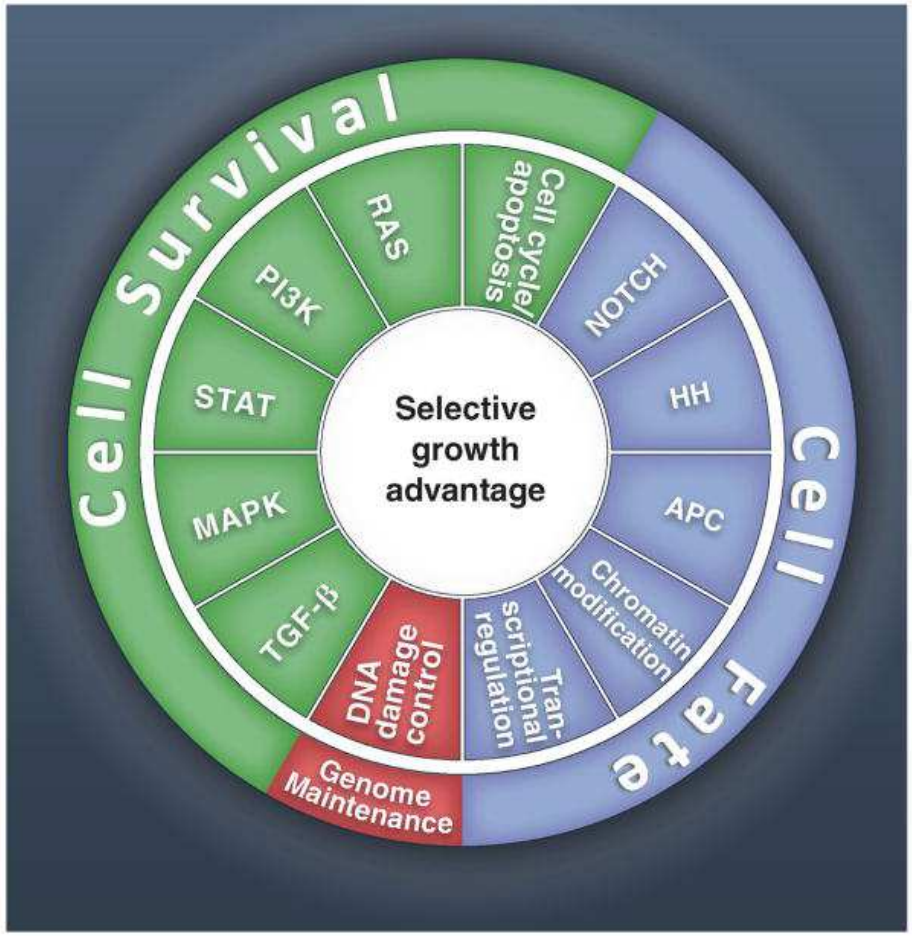
Hindorff L, Gillanders EM, Manolio T.

Adapted from T. Manolio



CANCER GENOME LANDSCAPE

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

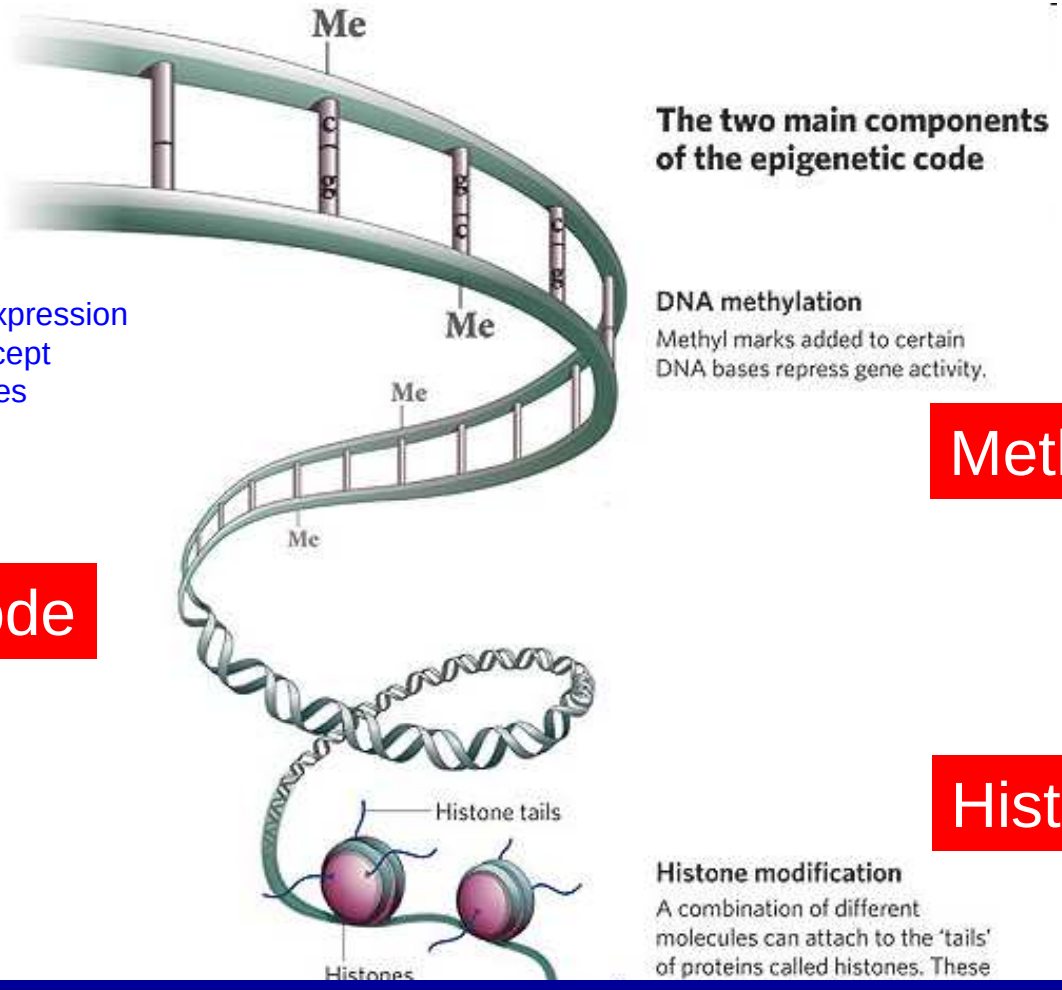


Adapted from Vogelstein and Kinzler (Science 2013)



Happiness Genes: Unlock the Positive Potential Hidden in Your DNA by James D. Baird and Laurie Nadel, in which we are told**, "Happiness is at your fingertips, or rather sitting in your DNA, right now! The new science of epigenetics reveals there are reserves of natural happiness within your DNA that can be controlled by you, by your emotions, beliefs and behavioral choices."**

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

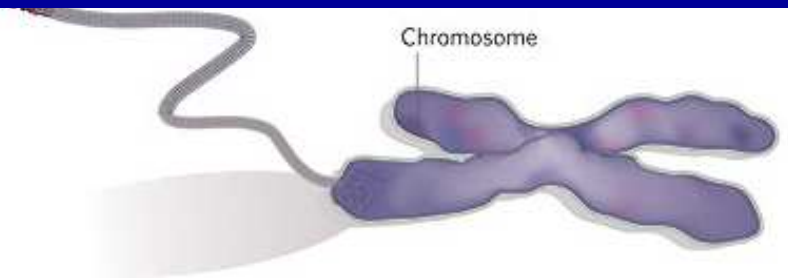


Genetic Code

Methylation Code

Histone Code

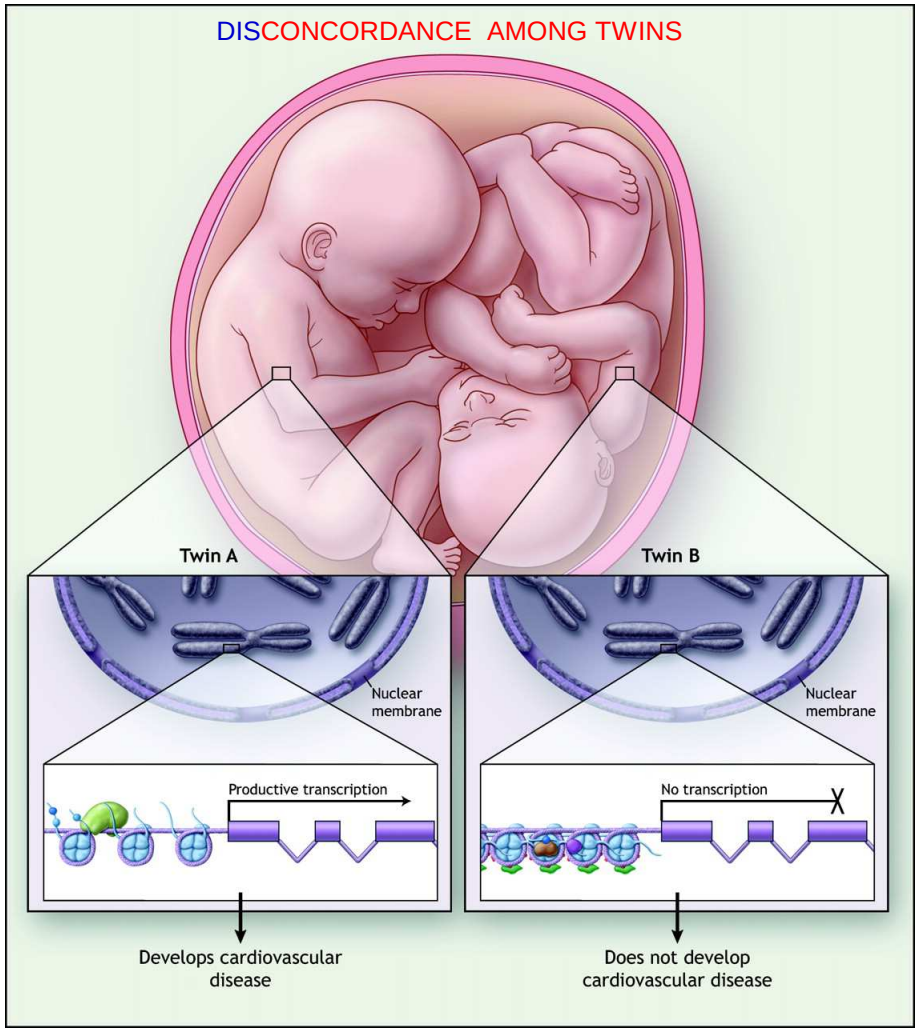
The genetic information provides the blue print for the manufacture of all the proteins necessary to create a living organism, whereas the epigenetic information provides the instructions on how, where and when the genetic information will be used.



Qiu NATURE 441: 143



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



Epigenetic predisposition to angiogenesneis? Individual? Populations?

Pharmacogenomics and pharmacoepigenomics (personalized medicine)

Microenvironment, microbiome, and gene expression

GWAS and EWAS

Adapted from Matouk and Marsden Cir Res 102:873

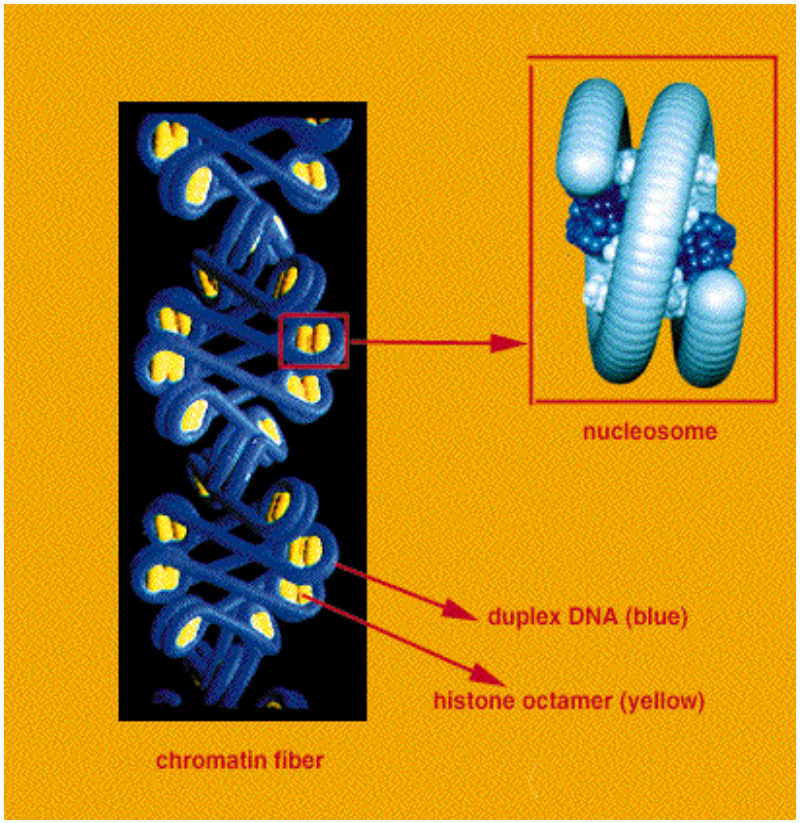
Nucleosomes (Units of Chromatin)

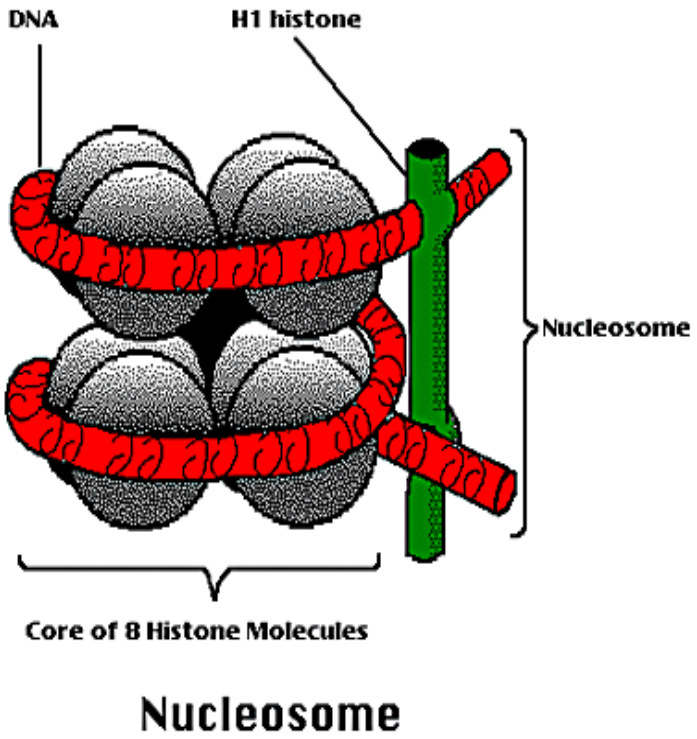
DNA
Histones H2a, H2b, H3, H4

} To neutralize charge and provide stability

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

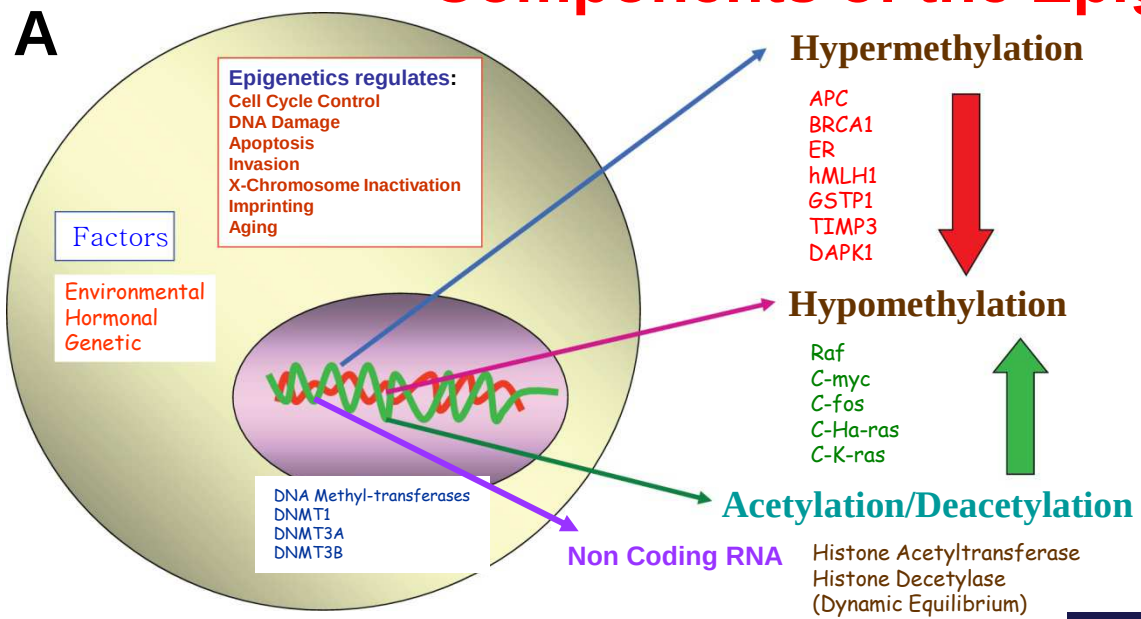
Nucleosome: two turns of DNA (146 base pairs) wrapped around an octomeric complex of two of each of histone types

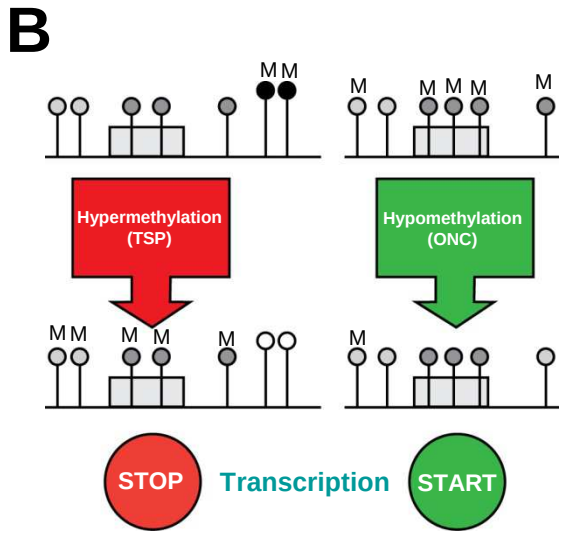




Shores are 0-2kb from islands
Shelves are 2-4 kb and enhancers are beyond shelves

Components of the Epigenome

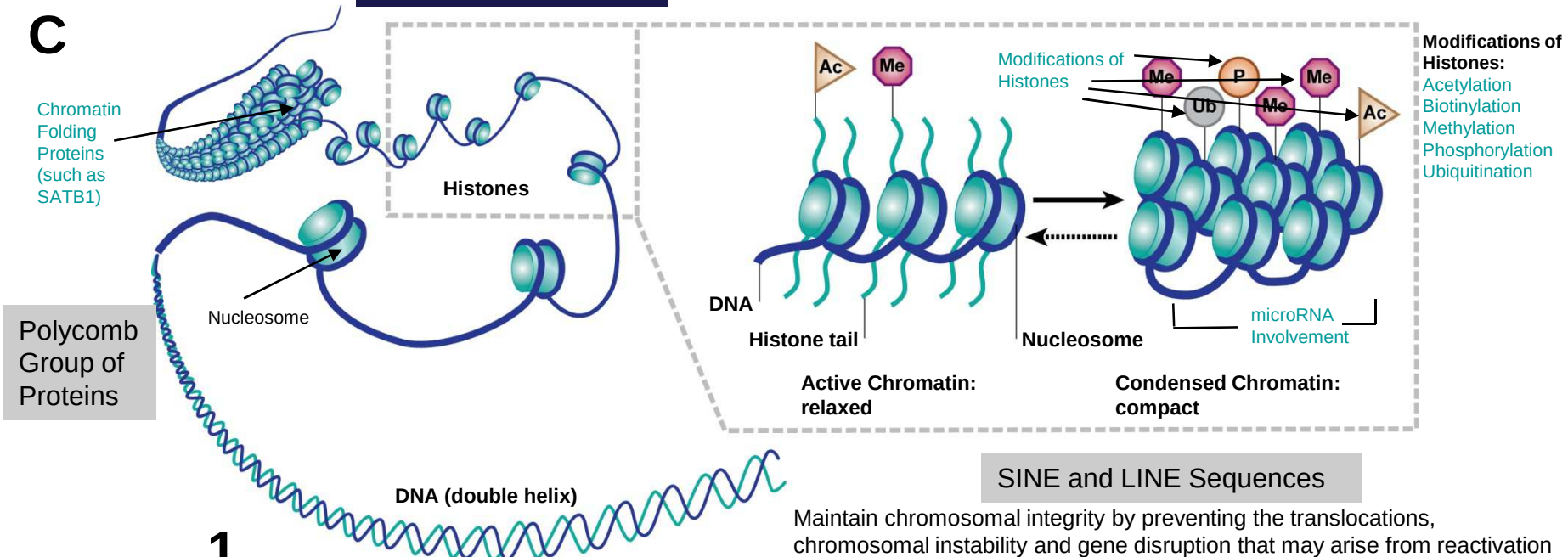




Chromatin Remodeling

Methylation Code

Histone Code



SINE and LINE Sequences

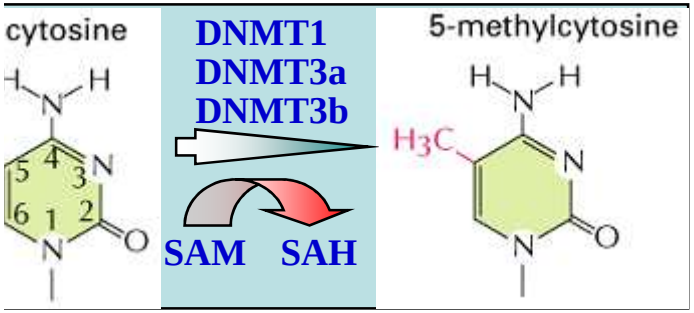
Maintain chromosomal integrity by preventing the translocations, chromosomal instability and gene disruption that may arise from reactivation of endoparasitic sequences

Verma (2009) In: Hum Genome Epidemiology, pp. 551-578

EPIGENETICS

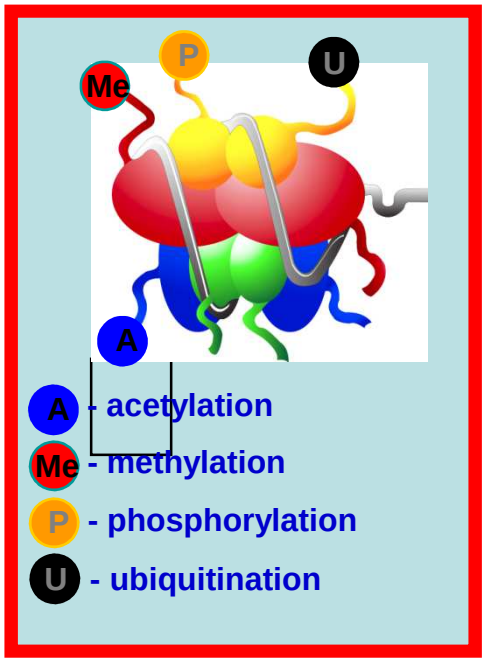
Epigenetic alterations – changes induced in cells that alter expression of the information on transcriptional, translational, or post-translational levels without change in DNA sequence

Methylation of DNA



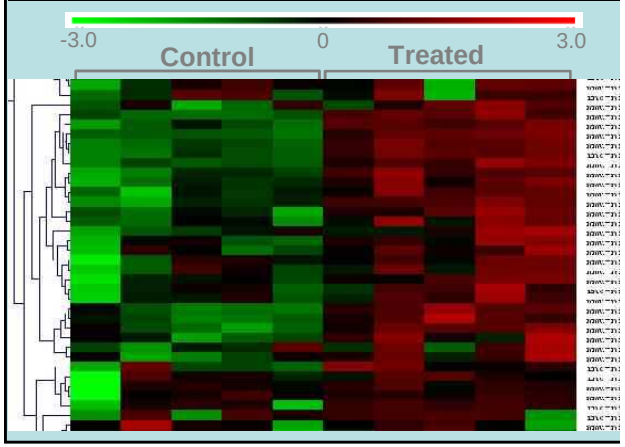
Genomic Imprinting

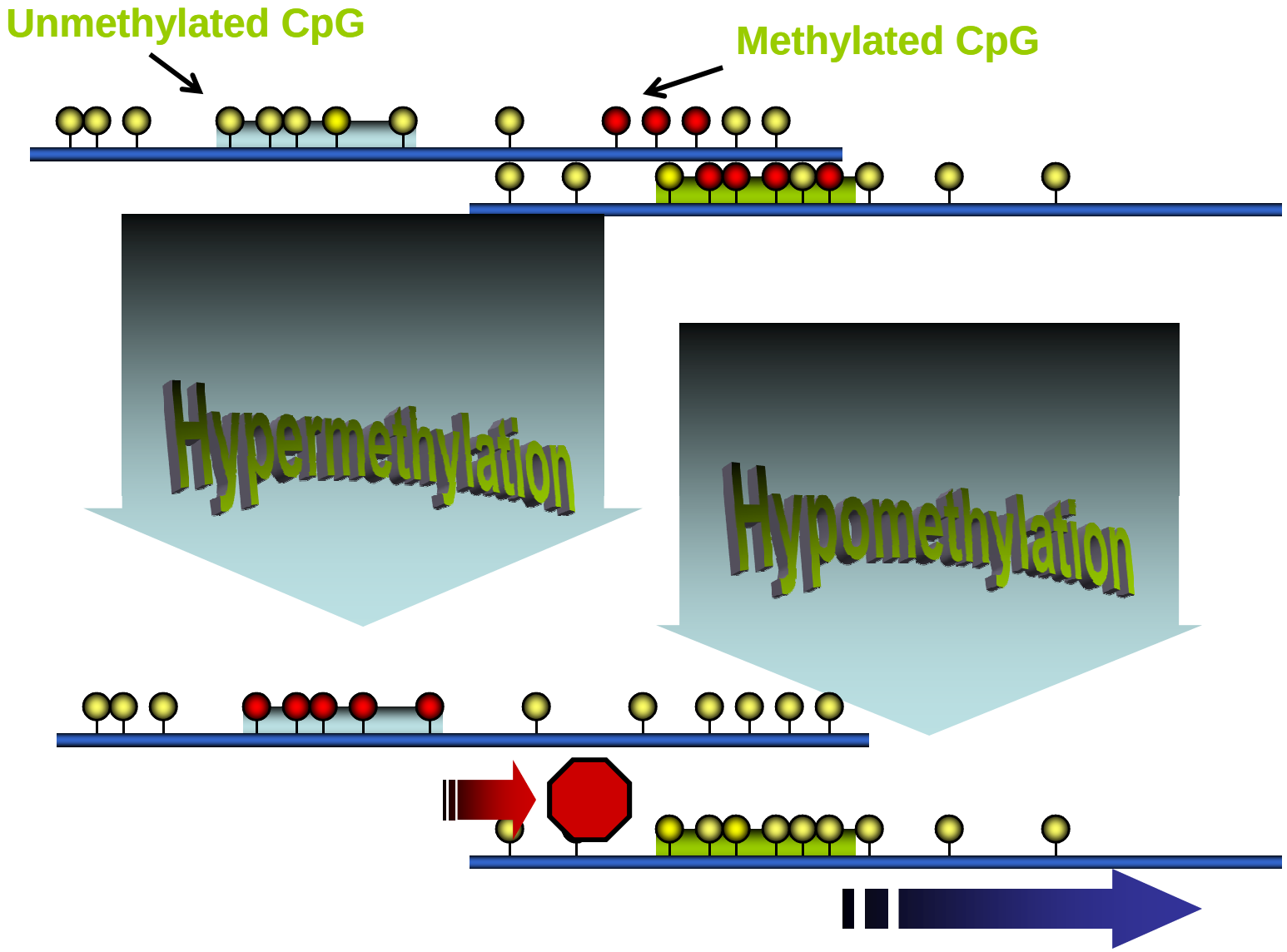
Modifications of histones

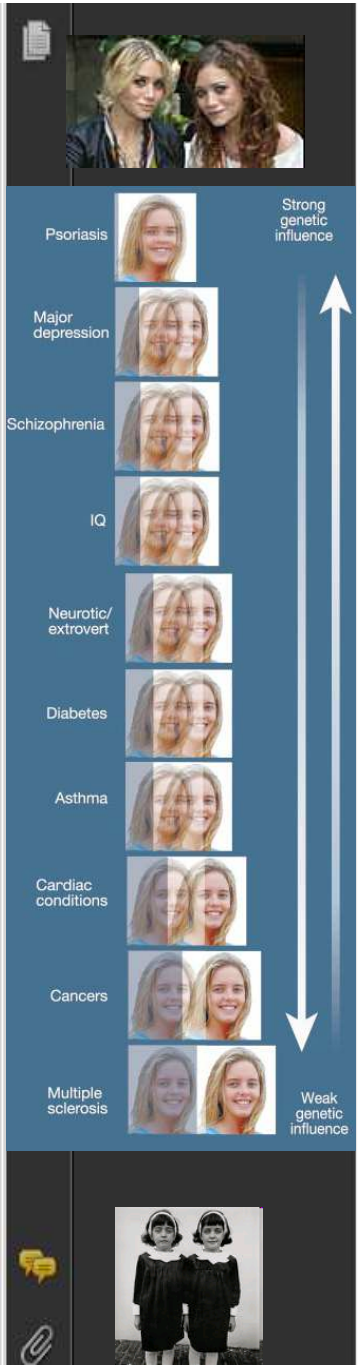


RNA-mediated modifications

- RNA-directed DNA methylation
- RNA-interference mediated chromatin remodeling
- RNAi, siRNA, miRNA …



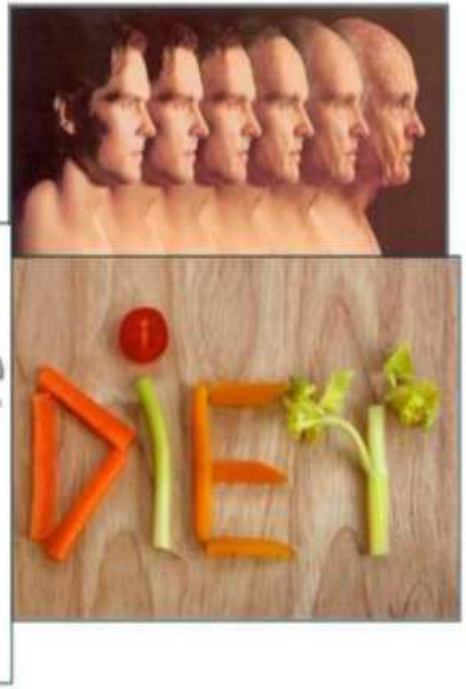

Unmethylated CpG
Methylated CpG
Hypermethylation
Hypomethylation
Inactivated Tumor Suppressors
Activated Oncogenes



Genome vs. epigenome – why is it important?

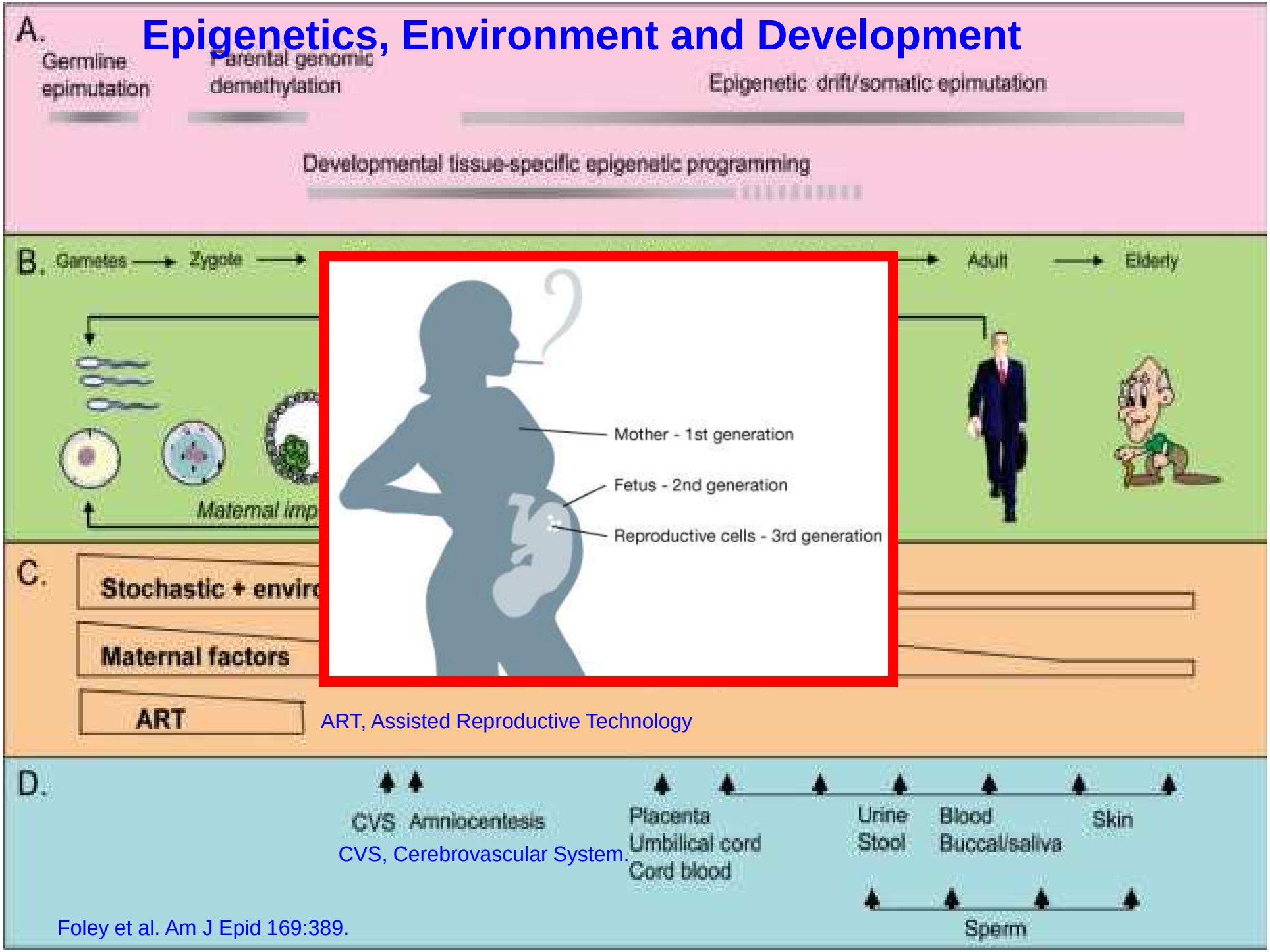


- **Genome is generally constant; epigenome changes**
  - Age
  - Diet
  - Disease
  - Lifestyle
  - Environment
- **Areas of interest:**
  - Molecular basis of disease
  - Biomarker identification
  - Diagnostics development
  - Drug targeting



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

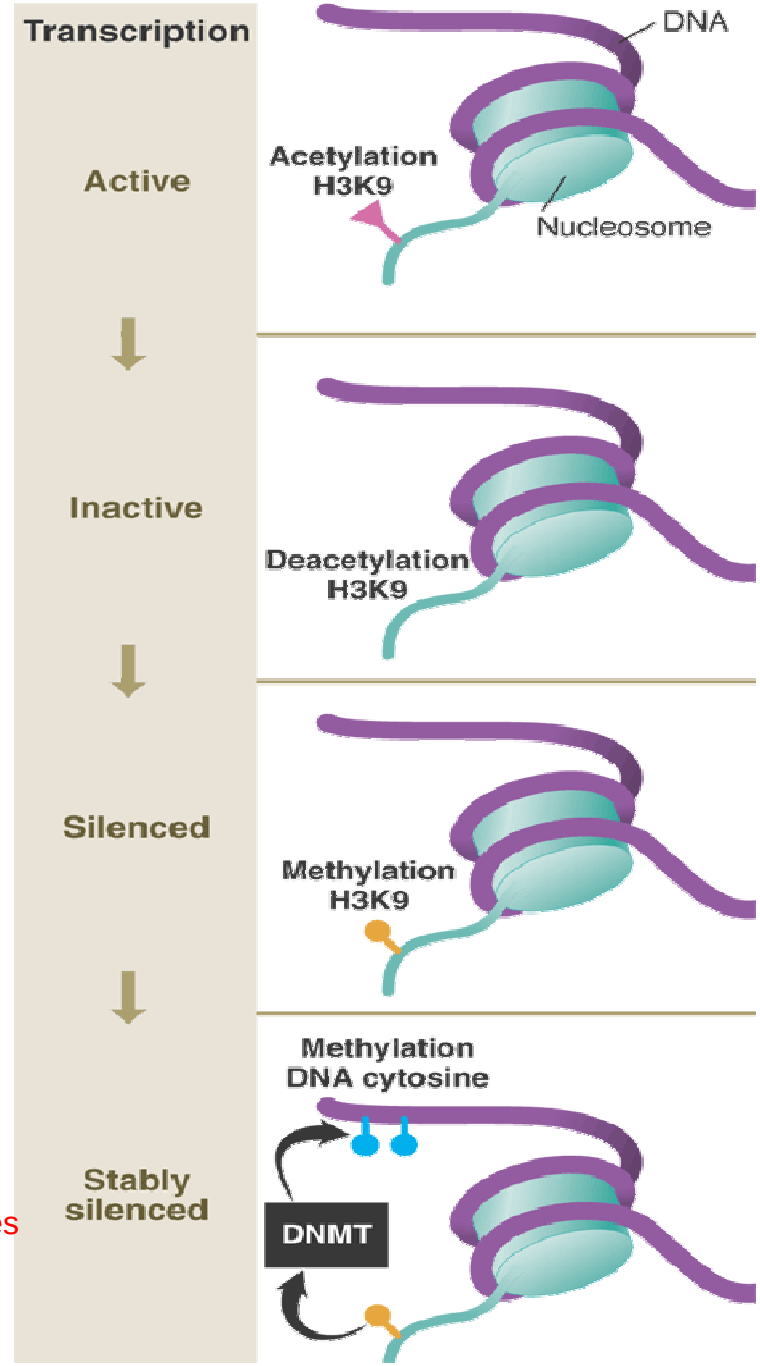
Epigenetics, Environment and Development



ART, Assisted Reproductive Technology

CVS, Cerebrovascular System.

Foley et al. Am J Epid 169:389.

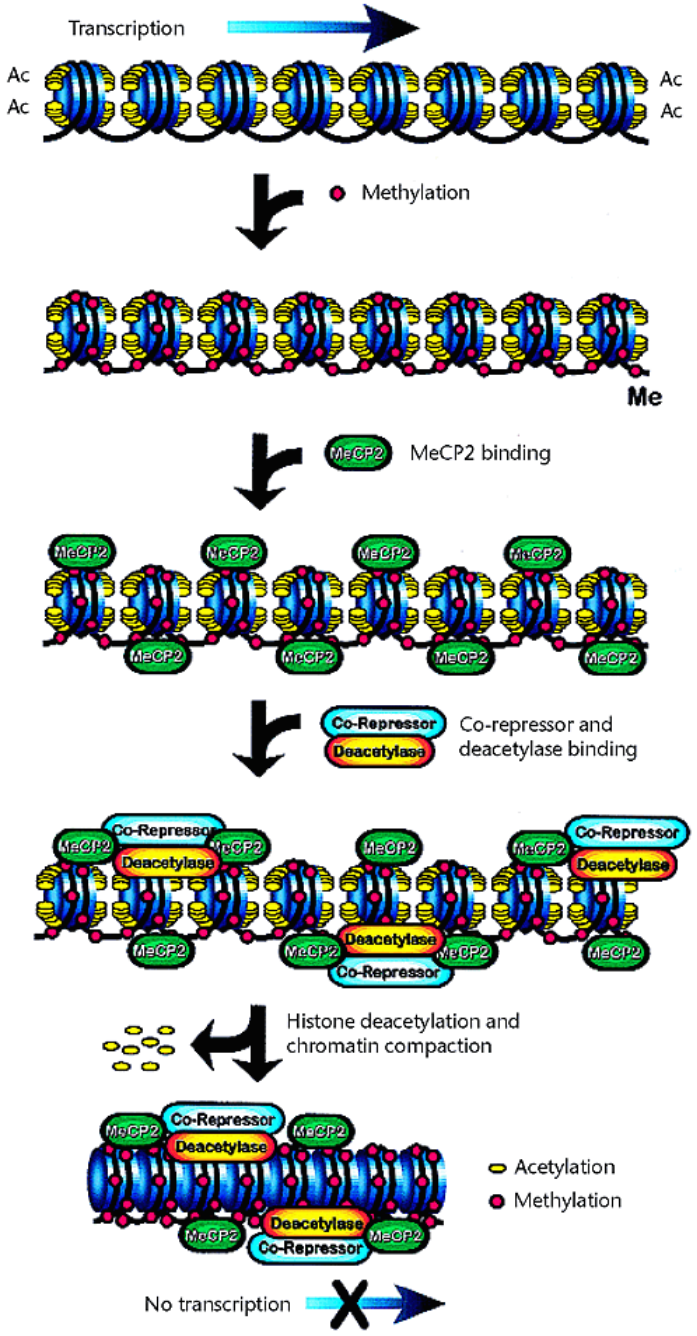




Peter Jones

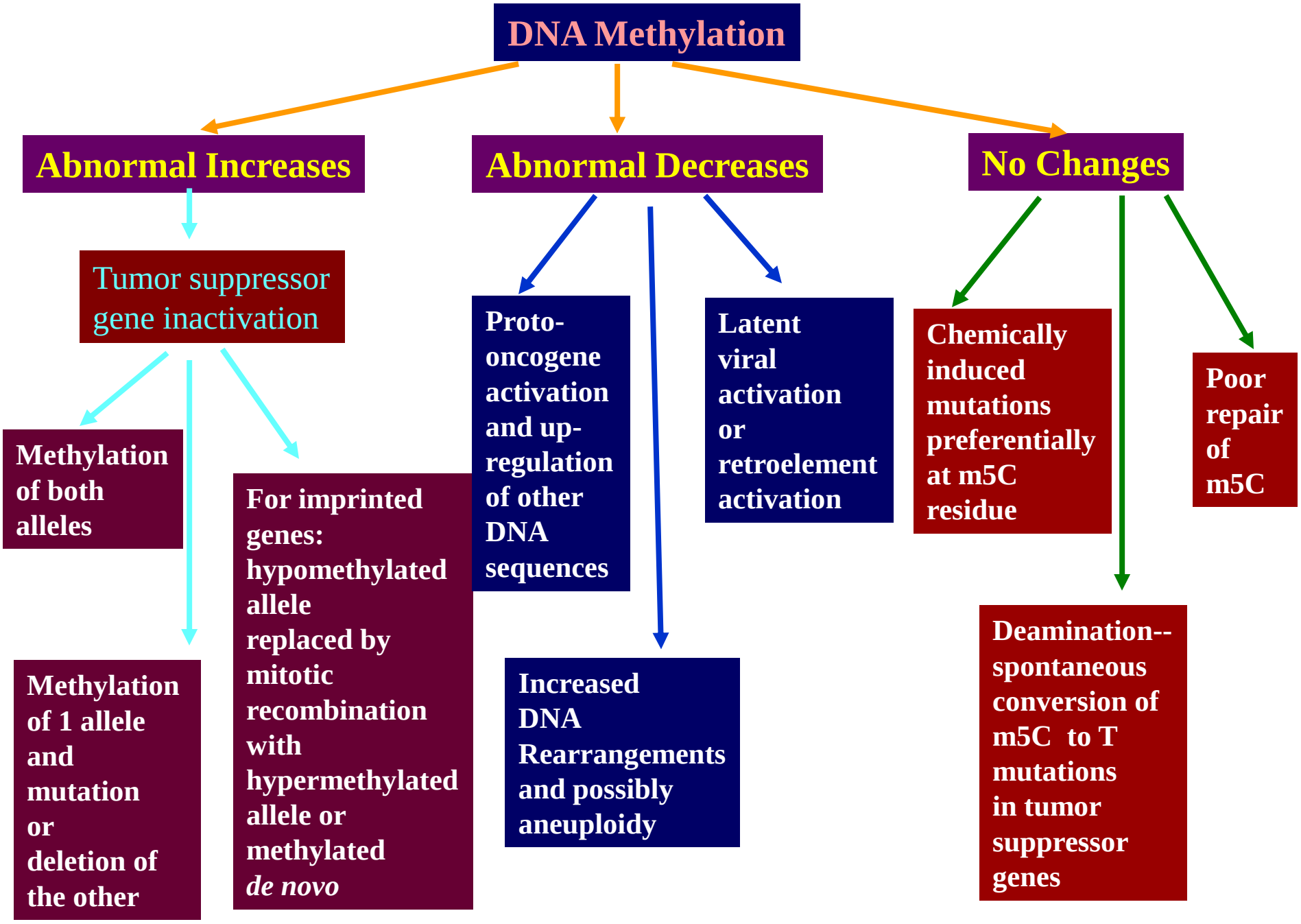


Andrew Feinberg

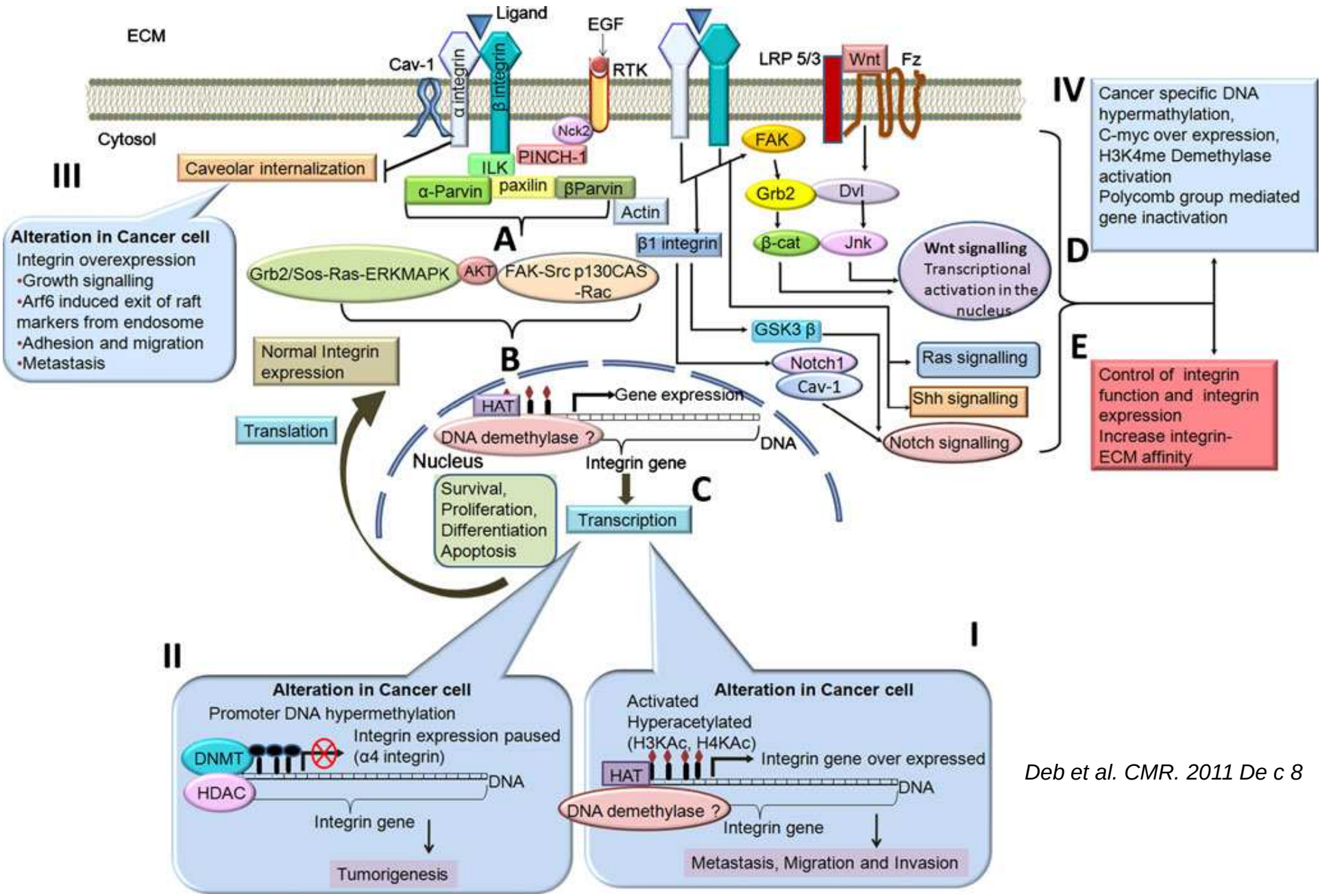


Jones and Laird. *Nat Rev Gen* 21: 163

DNA Methylation and Carcinogenesis



Integrin Signaling Network and Epigenetic Regulation



Deb et al. CMR. 2011 De c 8

Mirco RNA Signatures in Human Cancers

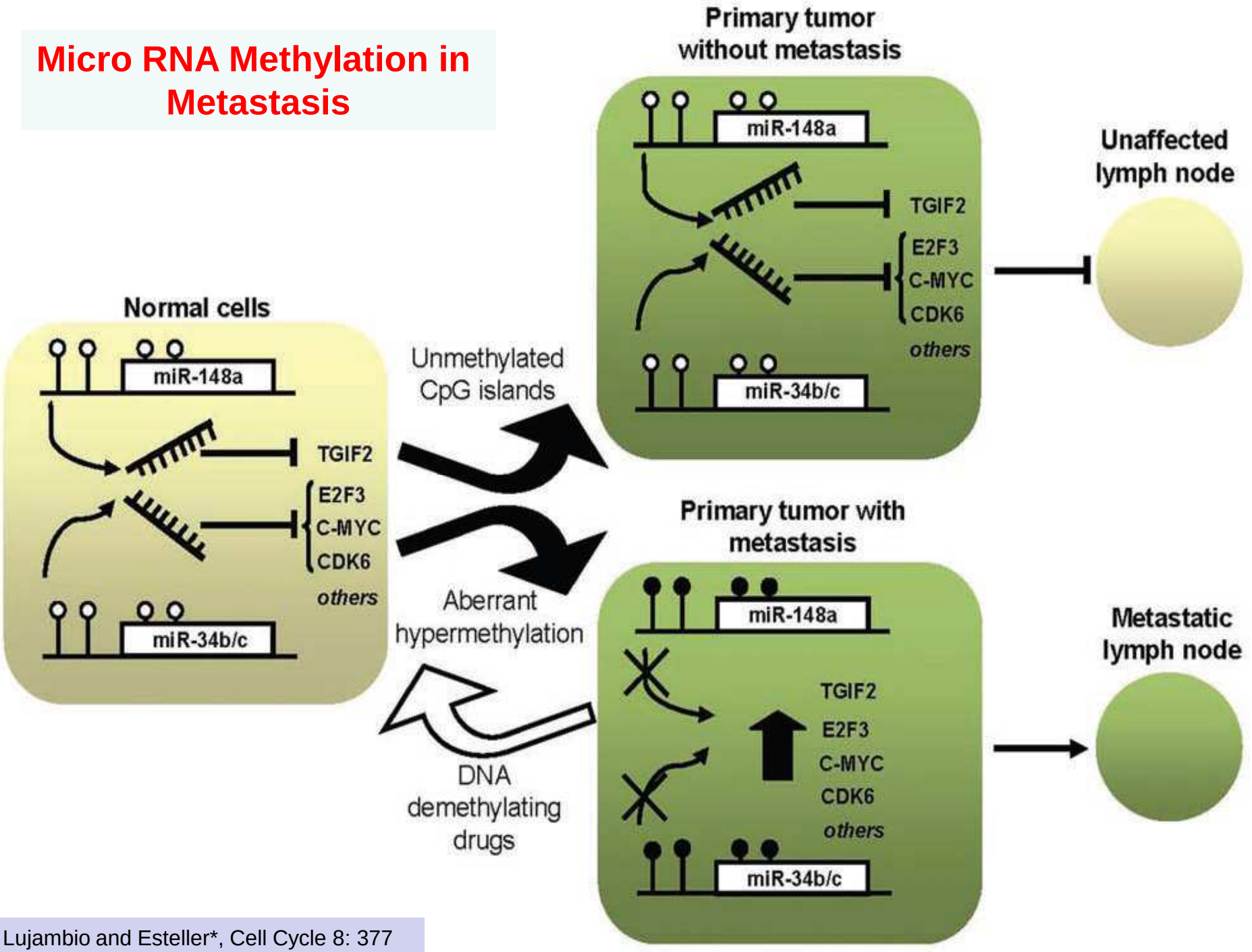


Micro RNA Polymorphism to Identify High Risk Populations

Mir-31 inhibits metastasis in breast cancer

nature REVIEWS CANCER

Micro RNA Methylation in Metastasis



Lujambio and Esteller*, Cell Cycle 8: 377

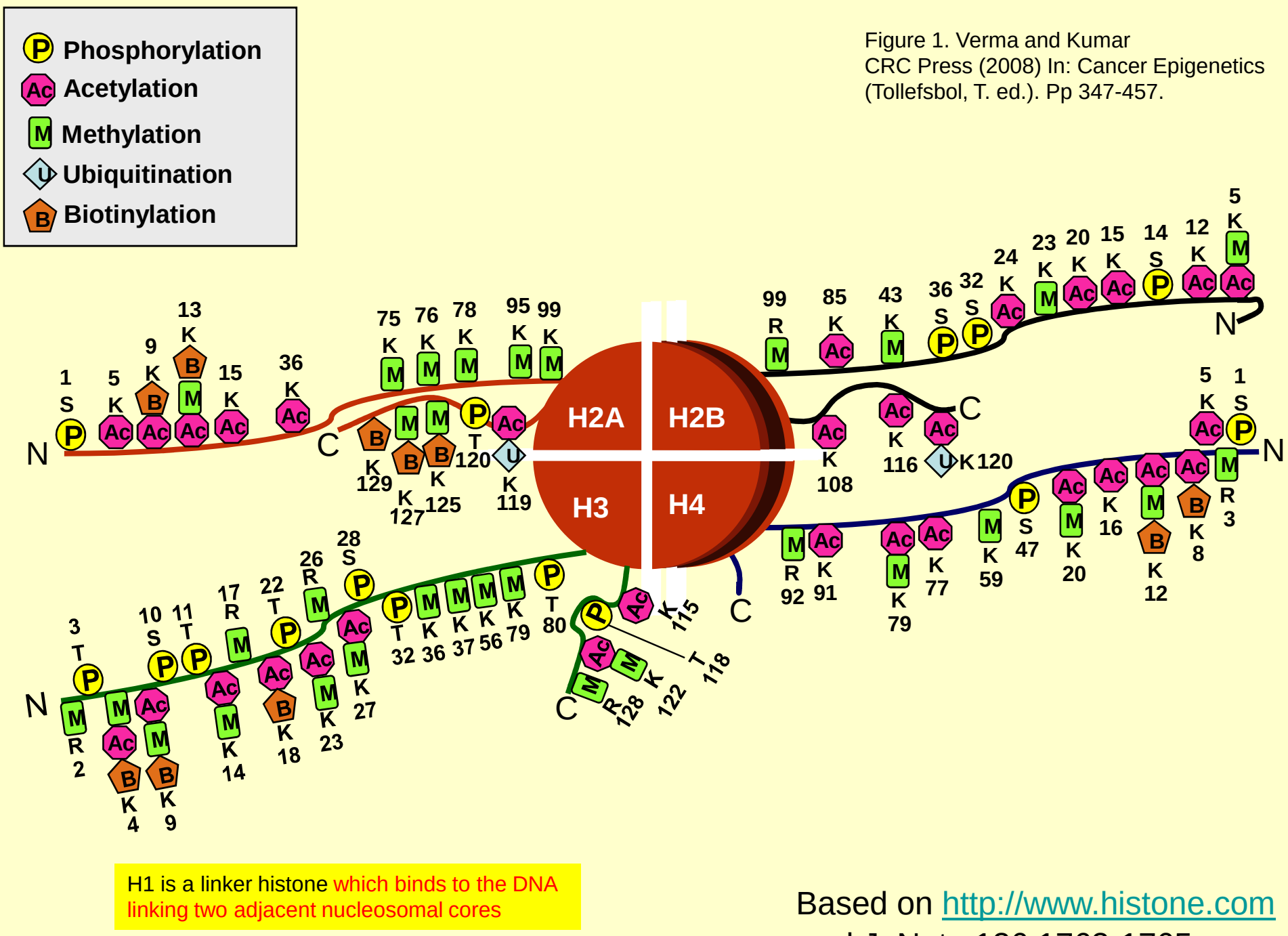
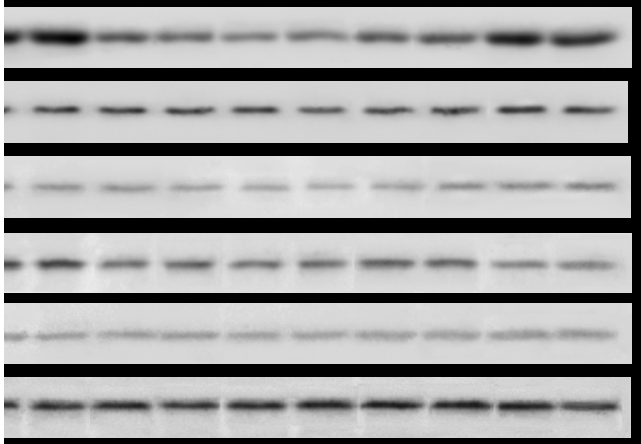


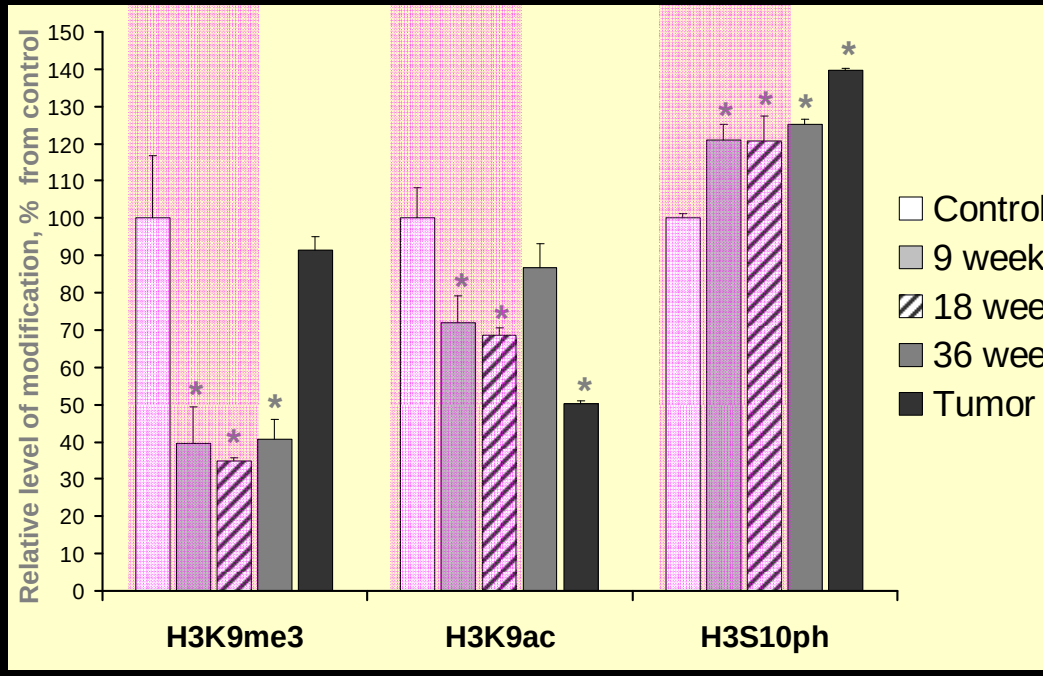
Figure 1. Verma and Kumar
CRC Press (2008) In: Cancer Epigenetics
(Tollefsbol, T. ed.). Pp 347-457.

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

Based on http://www.histone.com
and J. Nutr. 136:1763-1765

ALTERATIONS OF HISTONE H3 MODIFICATIOINS IN LIVER DURING METHYL DEFICIENCY

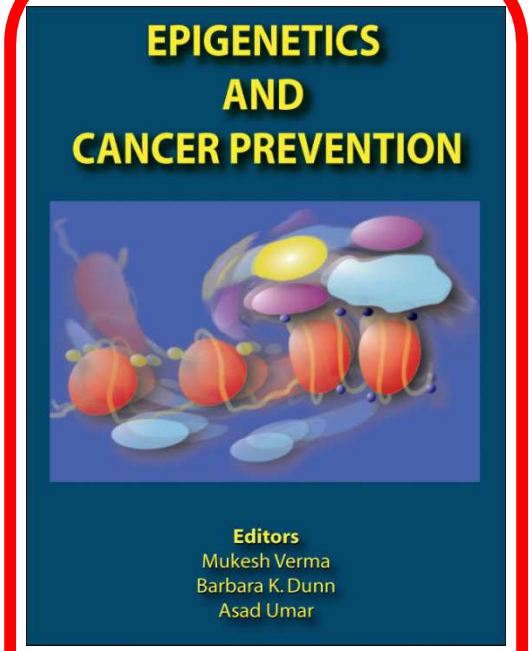




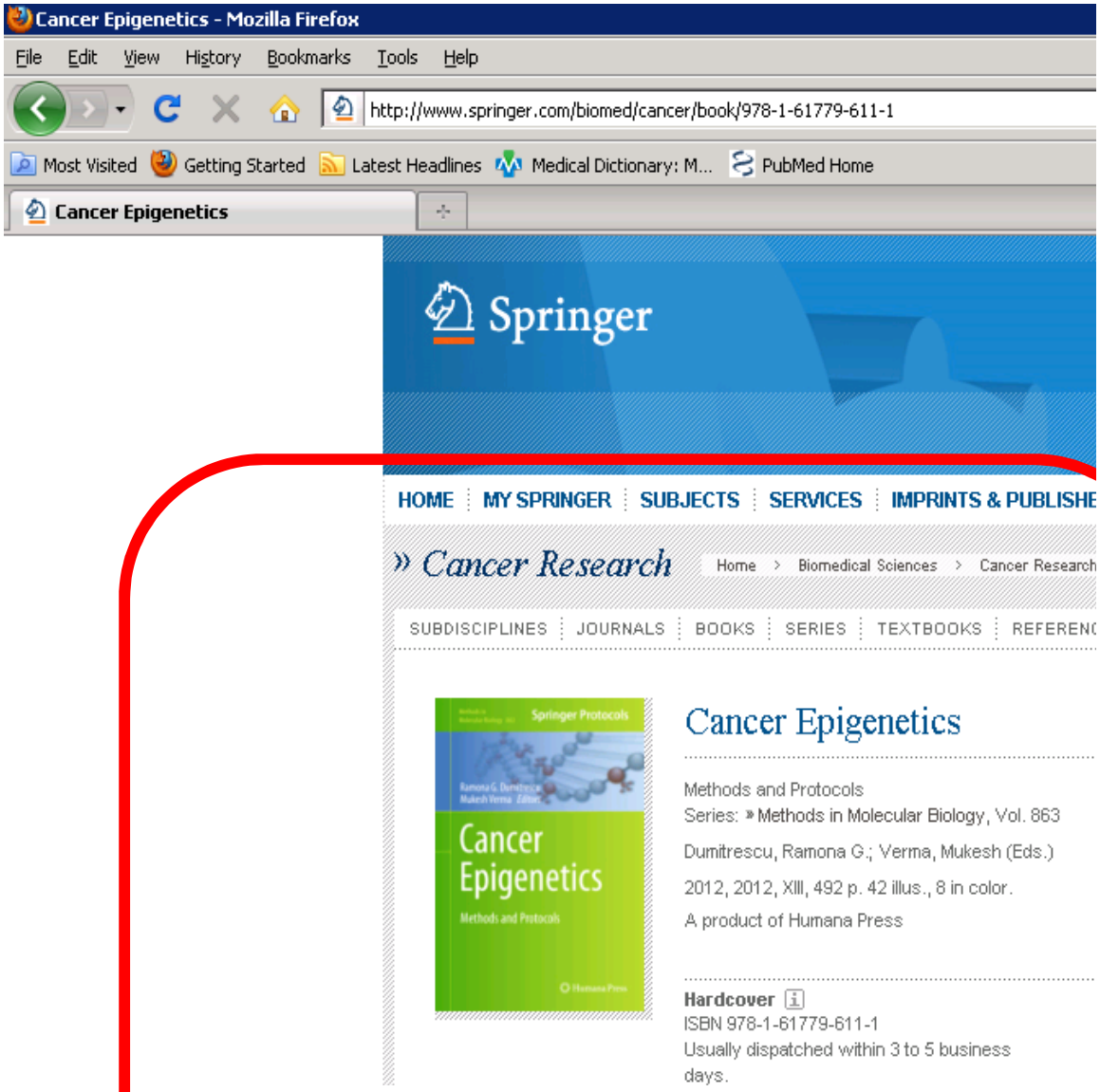


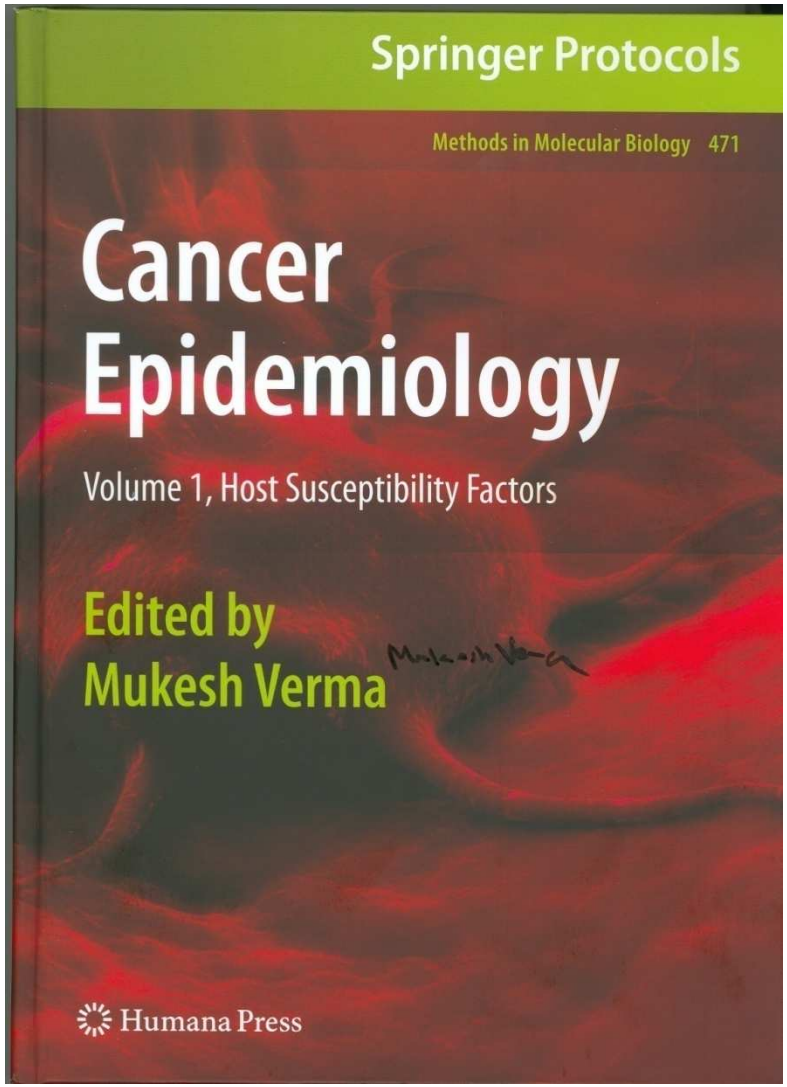
N-ARTKQTARKSTGGKAPRKQLATKAARKSAPATGGVKKP-…-C

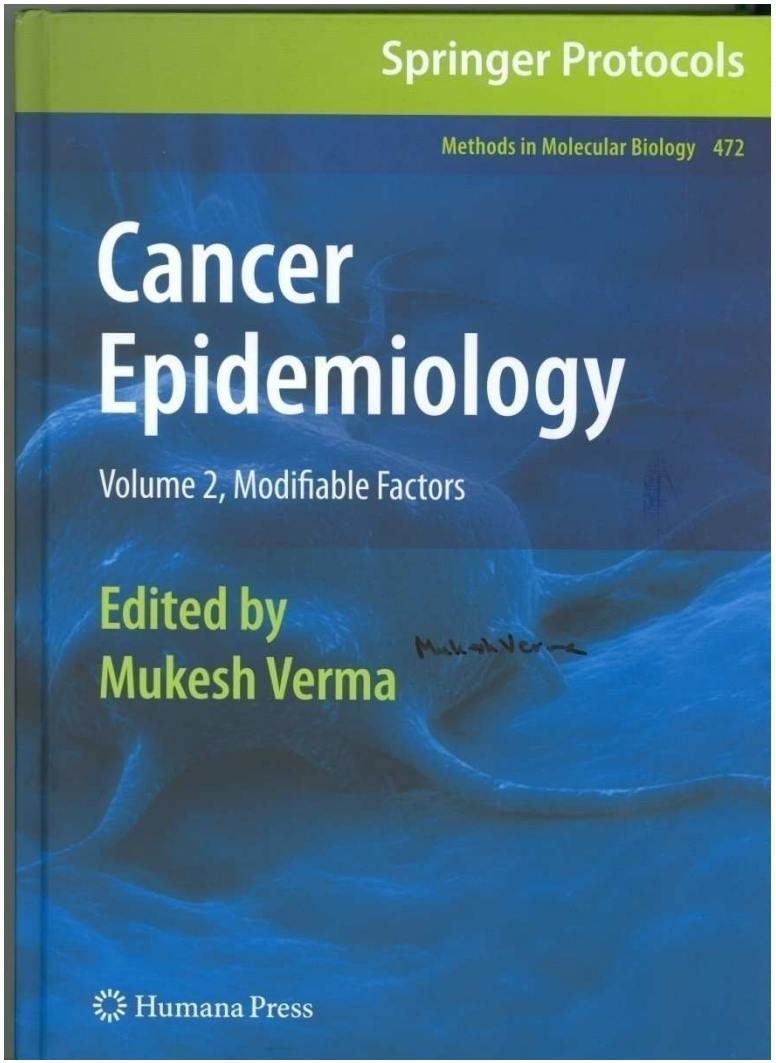
Interplay between H3K9me3, H3K9Ac, and H3S10ph



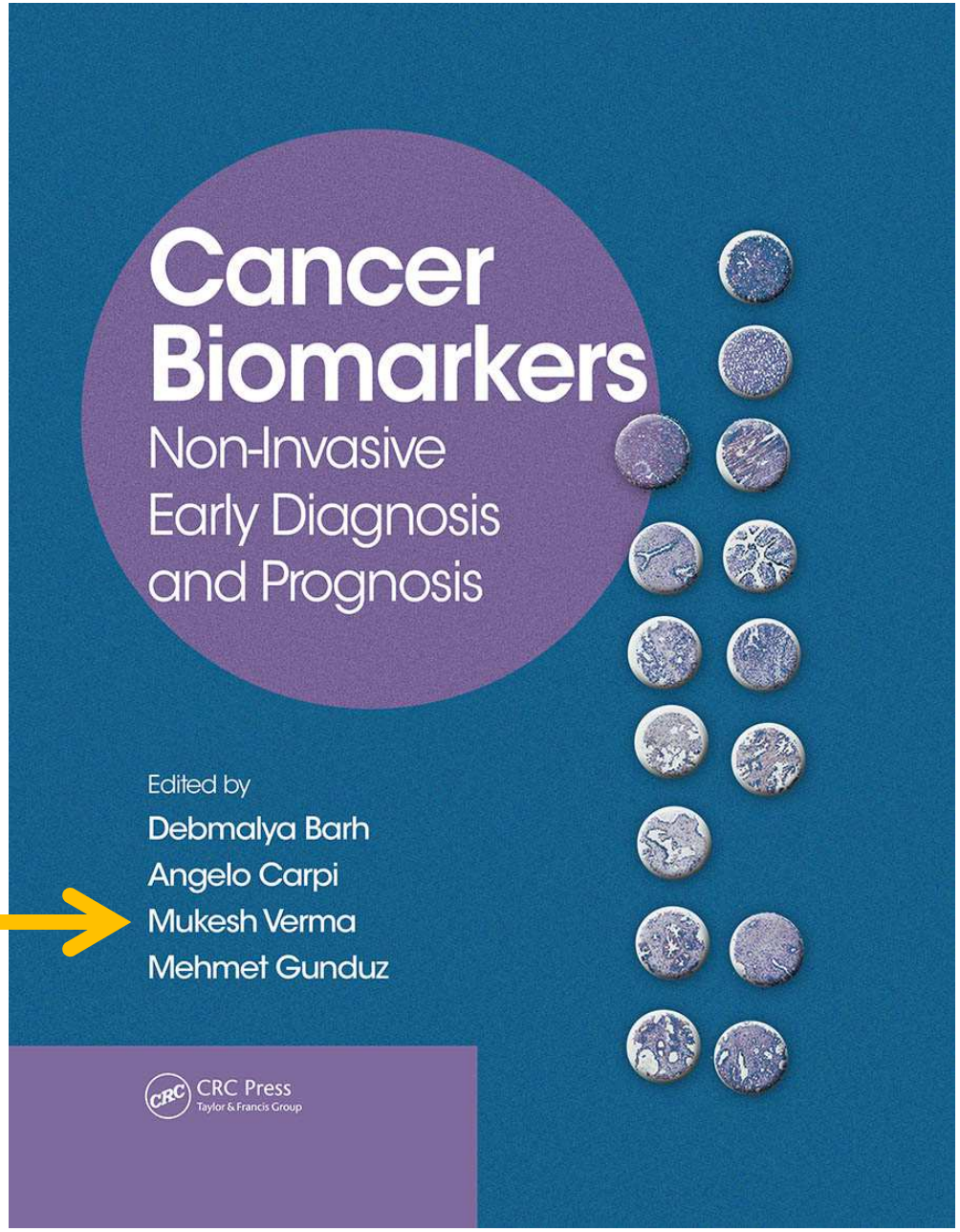
Book Published by:
New York Academy of Sciences
2003

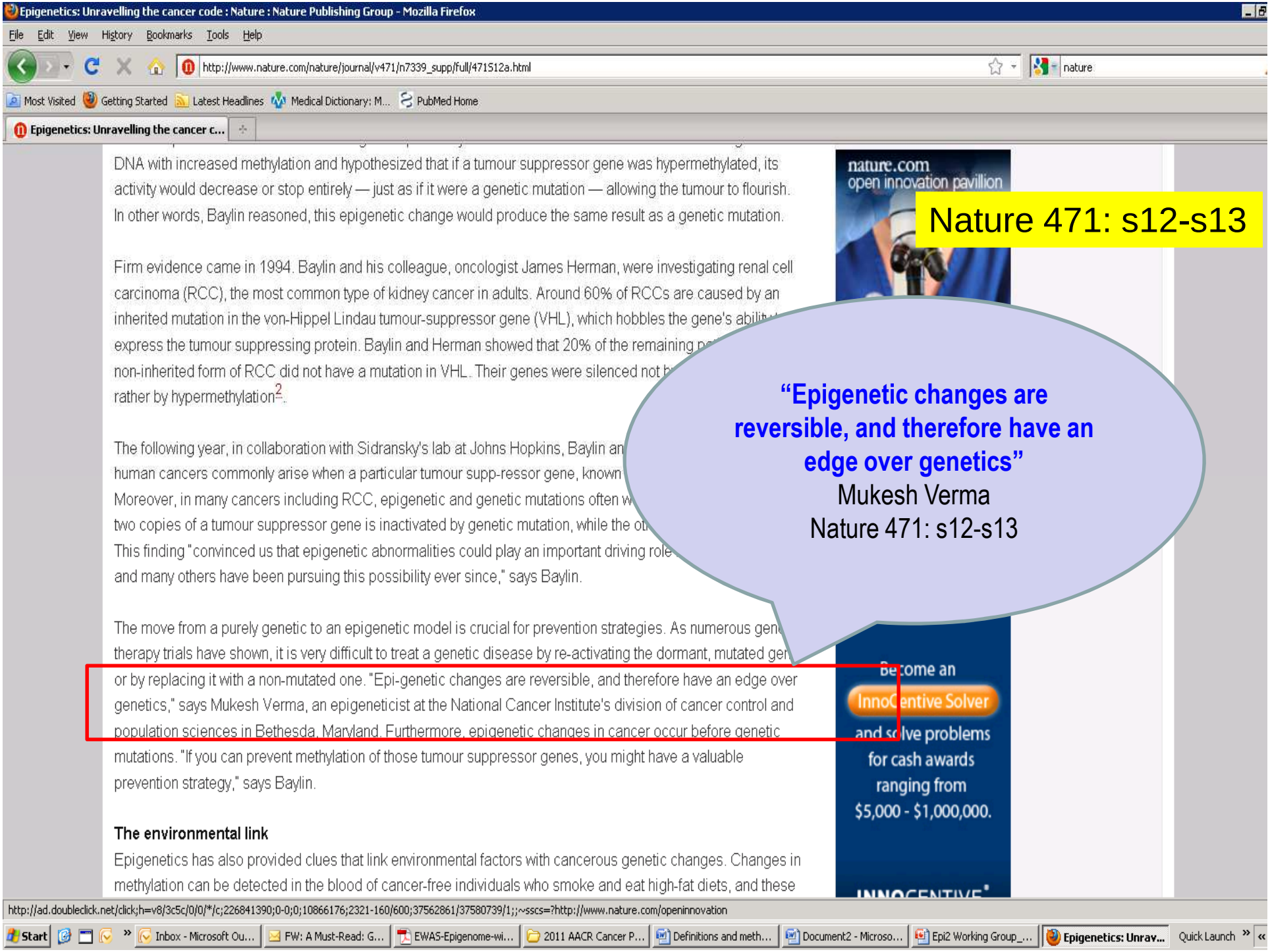






Methods in Molecular Biology. Vol 471 and 472


Cancer
Biomarkers
Non-Invasive
Early Diagnosis
and Prognosis
Edited by
Debmalya Barh
Angelo Carpi
Mukesh Verma
Mehmet Gunduz
CRC Press
Taylor & Francis Group


Epigenetics: Unravelling the cancer code : Nature : Nature Publishing Group - Mozilla Firefox
File Edit View History Bookmarks Tools Help
http://www.nature.com/nature/journal/v471/n7339_supp/full/471512a.html
Most Visited Getting Started Latest Headlines Medical Dictionary: M... PubMed Home
Epigenetics: Unravelling the cancer c...
DNA with increased methylation and hypothesized that if a tumour suppressor gene was hypermethylated, its activity would decrease or stop entirely — just as if it were a genetic mutation — allowing the tumour to flourish. In other words, Baylin reasoned, this epigenetic change would produce the same result as a genetic mutation.
Firm evidence came in 1994. Baylin and his colleague, oncologist James Herman, were investigating renal cell carcinoma (RCC), the most common type of kidney cancer in adults. Around 60% of RCCs are caused by an inherited mutation in the von-Hippel Lindau tumour-suppressor gene (VHL), which hobbles the gene's ability to express the tumour suppressing protein. Baylin and Herman showed that 20% of the remaining
non-inherited form of RCC did not have a mutation in VHL. Their genes were silenced not
rather by hypermethylation[2].
The following year, in collaboration with Sidransky's lab at Johns Hopkins, Baylin an
human cancers commonly arise when a particular tumour supp-ressor gene, known
Moreover, in many cancers including RCC, epigenetic and genetic mutations often w
two copies of a tumour suppressor gene is inactivated by genetic mutation, while the ot
This finding "convinced us that epigenetic abnormalities could play an important driving role
and many others have been pursuing this possibility ever since," says Baylin.
The move from a purely genetic to an epigenetic model is crucial for prevention strategies. As numerous gen
therapy trials have shown, it is very difficult to treat a genetic disease by re-activating the dormant, mutated ge
or by replacing it with a non-mutated one. "Epi-genetic changes are reversible, and therefore have an edge over genetics," says Mukesh Verma, an epigeneticist at the National Cancer Institute's division of cancer control and population sciences in Bethesda, Maryland. Furthermore, epigenetic changes in cancer occur before genetic mutations. "If you can prevent methylation of those tumour suppressor genes, you might have a valuable prevention strategy," says Baylin.
The environmental link
Epigenetics has also provided clues that link environmental factors with cancerous genetic changes. Changes in methylation can be detected in the blood of cancer-free individuals who smoke and eat high-fat diets, and these
nature.com
open innovation pavilion
Nature 471: s12-s13
"Epigenetic changes are reversible, and therefore have an edge over genetics"
Mukesh Verma
Nature 471: s12-s13
Become an
InnoCentive Solver
and solve problems
for cash awards
ranging from
$5,000 - $1,000,000.
INNOCENTIVE
http://ad.doubleclick.net/click;h=v8/3c5c/0/0/*/c;226841390;0-0;0;10866176;2321-160/600;37562861/37580739/1;;~sscs=?http://www.nature.com/openinnovation
Start
Inbox - Microsoft Ou...
FW: A Must-Read: G...
EWAS-Epigenome-wi...
2011 AACR Cancer P...
Definitions and meth...
Document2 - Microso...
Epi2 Working Group_...
Epigenetics: Unrav...
Quick Launch

Epigenetics: Marked for success : Naturejobs - Mozilla Firefox

File Edit View History Bookmarks Tools Help

http://www.nature.com/naturejobs/science/articles/10.1038/nj7391-637a

Most Visited Getting Started Latest Headlines Medical Dictionary: M... PubMed Home

Epigenetics: Marked for success : Nat...

programme has funded around 200 jobs. The bulk of the funding for these large-scale programmes is 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 c... wealth of new drug targets. The finding that mutations in epigenetics-related genes may be drivi... offers the tantalizing possibility of taking a personalized approach to cancer treatment, a tack that is rapi... 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 $630 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."

"Successful approval of first generation of drugs intended to target epigenetic pathways, has convinced almost every major drug company to invest in cancer epigenetics."
Mukesh Verma

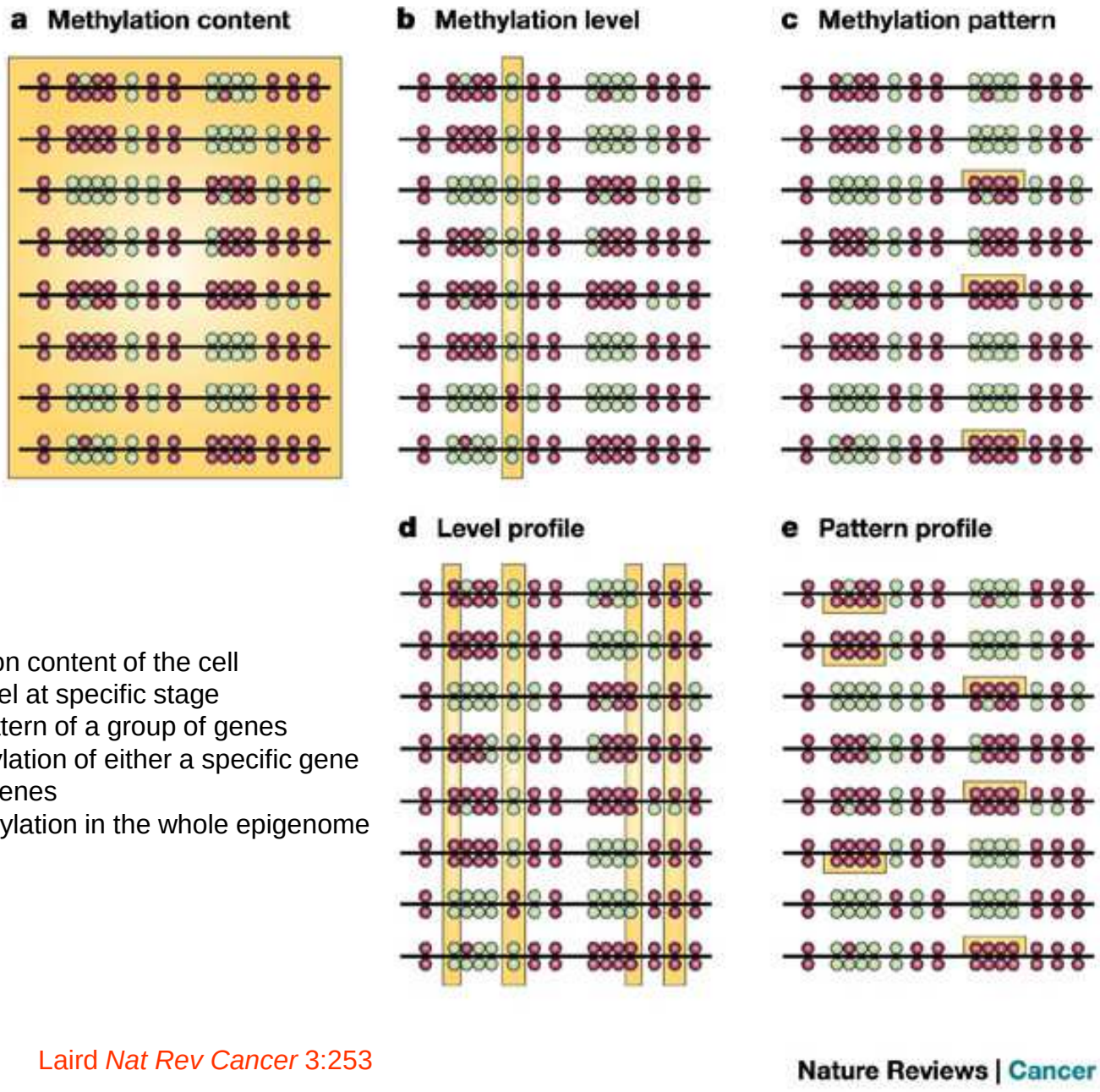
Nature 483:637-639

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 Brd4 — a 'reader' protein that binds to certain modified histones and modulates gene expression — in acute myeloid leukaemia (J. Zuber *et al.* *Nature* **478**, 524–528; 2011). After his team's paper was published, Vakoc heard rumours that ten companies were racing to capitalize on the results.

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

Done

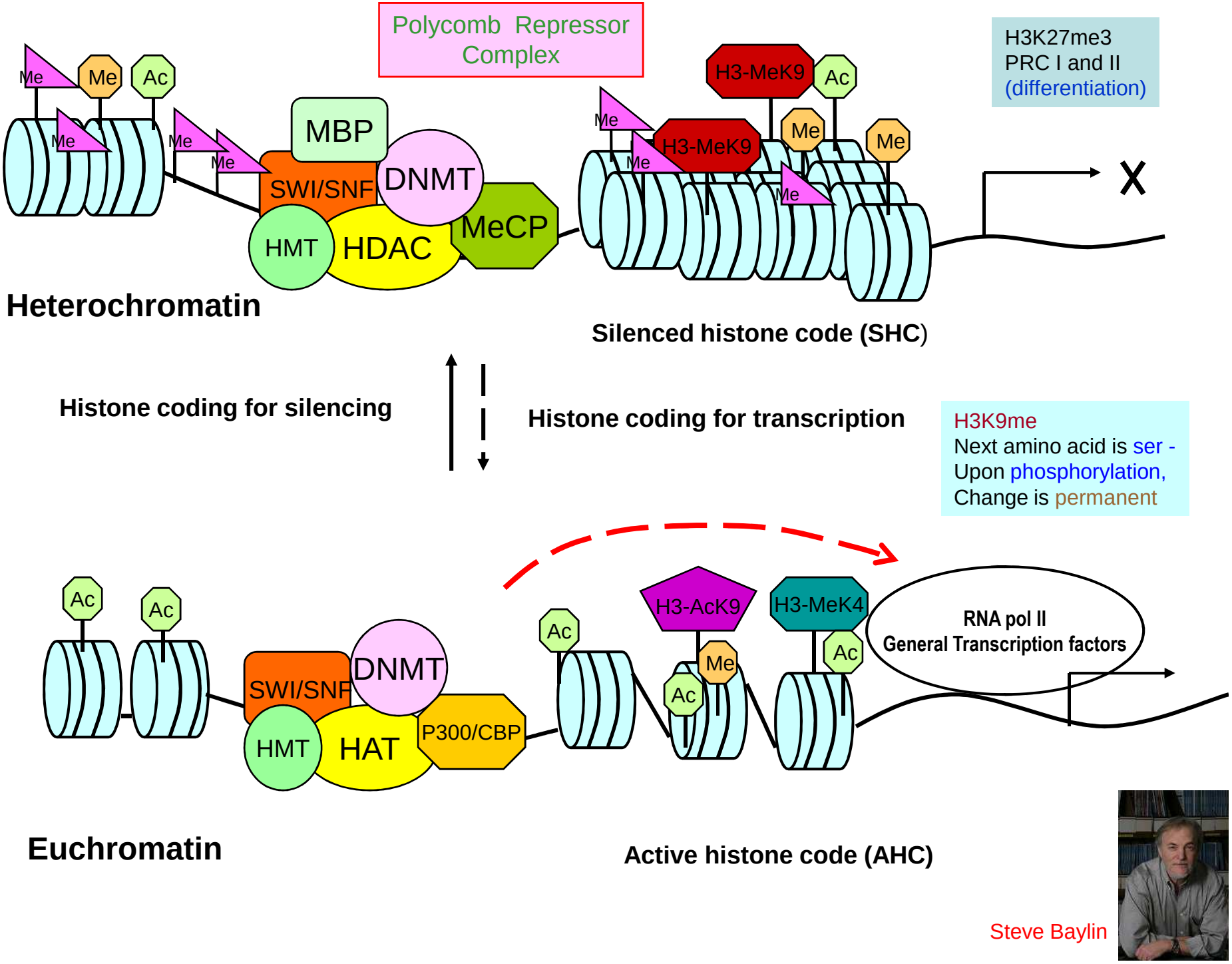
Start Inbox - Microsoft Outlook FW: A Must-Read: Geno... EWAS-Epigenome-wide a... 2011 AACR Cancer Prev... Definitions and methodol... Epi2 Working Group_upd... Epigenetics: Marked f... Quick Launch



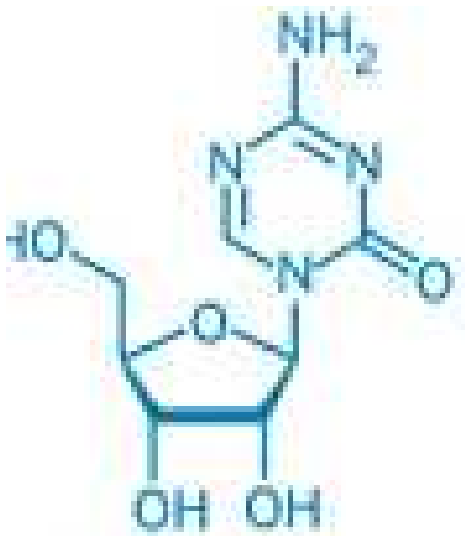
- Total methylation content of the cell
- methylation level at specific stage
- methylation pattern of a group of genes
- profile of methylation of either a specific gene or a number of genes
- pattern of methylation in the whole epigenome

To reduce
- false negative
- false positives

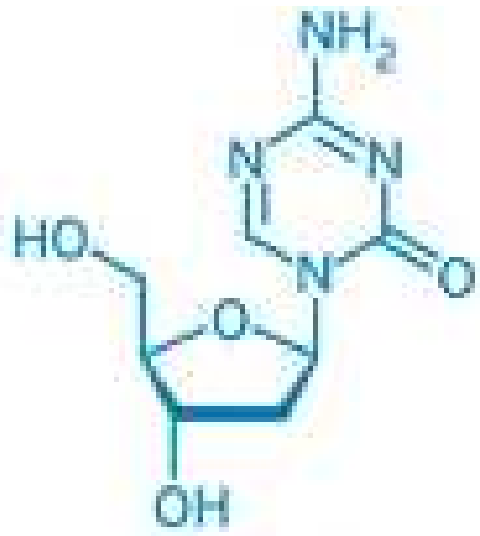
Laird *Nat Rev Cancer* 3:253


Polycomb Repressor Complex
H3K27me3
PRC I and II
(differentiation)
Me
Me
Ac
Me
Me
Me
MBP
SWI/SNF
DNMT
HMT
HDAC
MeCP
H3-MeK9
Ac
Me
H3-MeK9
Me
Me
Me
Me
X
Heterochromatin
Silenced histone code (SHC)
Histone coding for silencing
Histone coding for transcription
H3K9me
Next amino acid is ser -
Upon phosphorylation,
Change is permanent
Ac
Ac
SWI/SNF
DNMT
HMT
HAT
P300/CBP
Ac
H3-AcK9
Me
Ac
H3-MeK4
Ac
RNA pol II
General Transcription factors
Euchromatin
Active histone code (AHC)
Steve Baylin

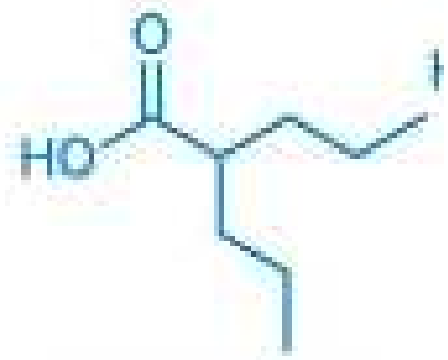
FDA Approved Epigenetic Inhibitors



5-Azacitidine



Decitabine

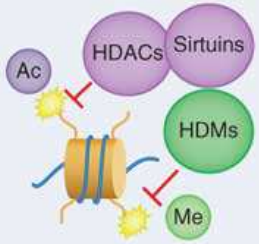


Valproic acid

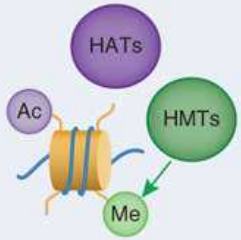


SAHA

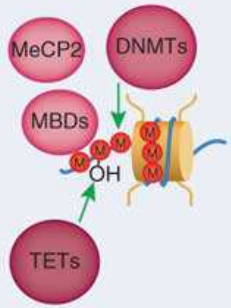
Category	Gene
HDACs	*HDAC1*
	HDAC2
	HDAC6
Sirtuins	*SIRT1*
	SIRT2
	SIRT3
	SIRT7
HDMs	*KDM1A*
	KDM2B
	KDM4C
	KDM5A
	KDM5B
	KDM5C
	KDM6A
	KDM6B



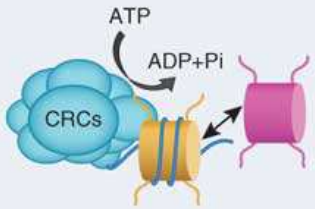
Category	Gene
HATs	*CREBBP*
	EP300
	MYST3
	MYST4
	KAT5
HMTs	*MLL*
	EZH2
	NSD1
	PRDM2
	SMYD3
	WHSC1



Category	Gene
DNMTs	*DNMT1*
	DNMT3A
	DNMT3B
(2OG)-Fe(II)–dependent oxygenases	*TET1*
	TET2
Methyl-CpG binding proteins	*MBD1*
	MBD2
	MBD3
	MBD4
	MECP2



Category	Gene
Histone variants	*H2AFZ*
Chromatin remodeling factors	*ARID1A*
	CHD5
	CHD7
	MTA1
	MTA2
	MTA3
	SMARCA2
	SMARCA4
	SNF5

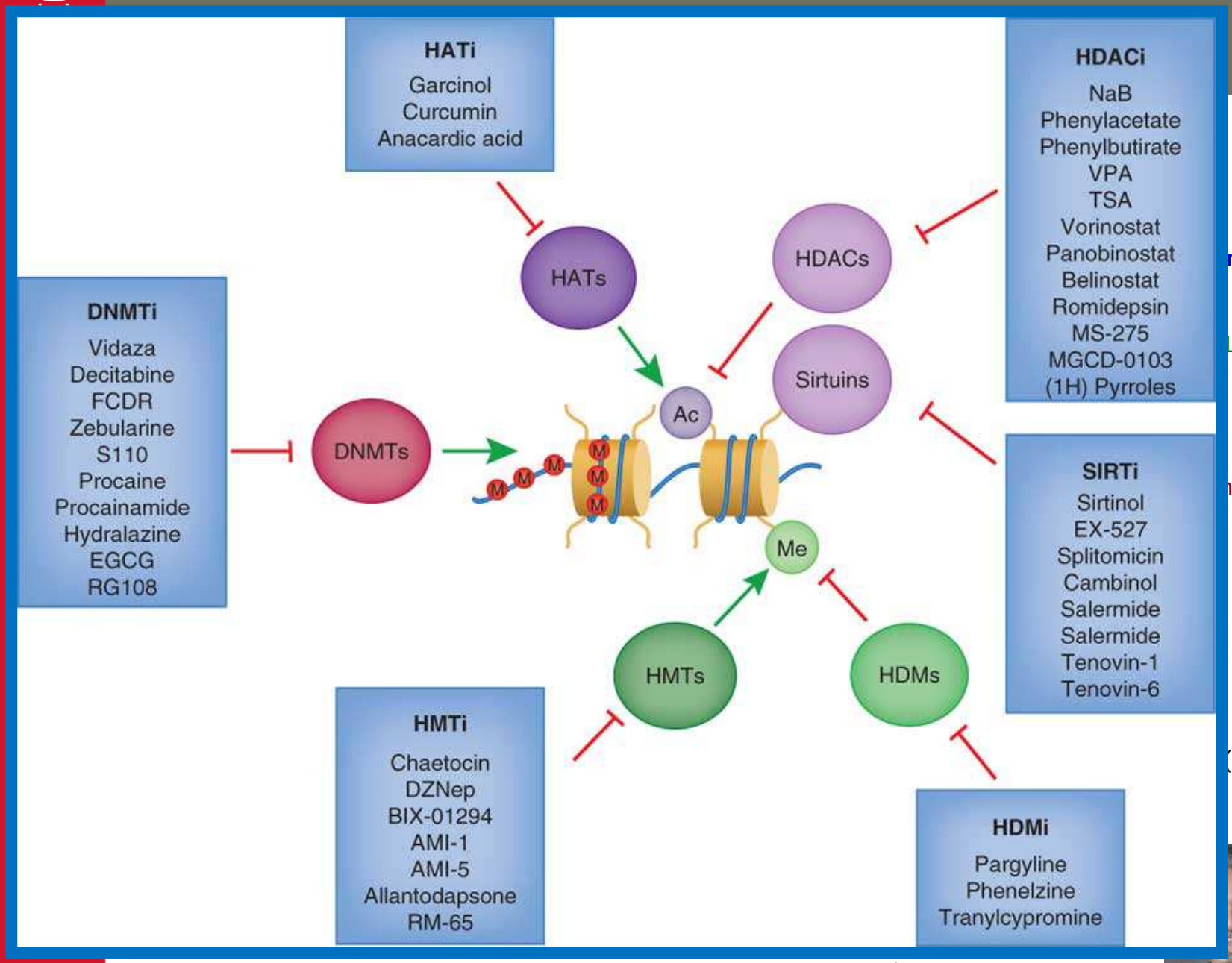


3CACC6

Category	Gene
Histone modification readers	*ING1*
	ING2
	ING3
	ING4
	ING5



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.



Eggr et al Nature. 429:457.

Valproic Acid

Phase I/II

Jean-Pierre Issa



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. 2008 Oct 1;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.

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. 2007. 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 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

Combination epigenetic therapy has efficacy in... [Cancer Discov. 2011] - PubMed - NCBI - Mozilla Firefox
File Edit View History Bookmarks Tools Help
http://www.ncbi.nlm.nih.gov/pubmed/22586682
Most Visited Getting Started cricinfo records Latest Headlines file:///O:/Documents... pagehasmoved.html
NCBI Resources How To
PubMed.gov
US National Library of Medicine
National Institutes of Health
PubMed
Advanced
Display Settings: Abstract
Send to:

Cancer Discov. 2011 Dec;1(7):598-607. doi: 10.1158/2159-8290.CD-11-0214. Epub 2011 Nov 9.

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

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

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

Abstract

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

Comment in

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

PMID: 22586682 [PubMed - indexed for MEDLINE] PMCID: PMC3353724 [Available on 2012/12/1]

Publication Types, MeSH Terms, Substances, Grant Support

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Article

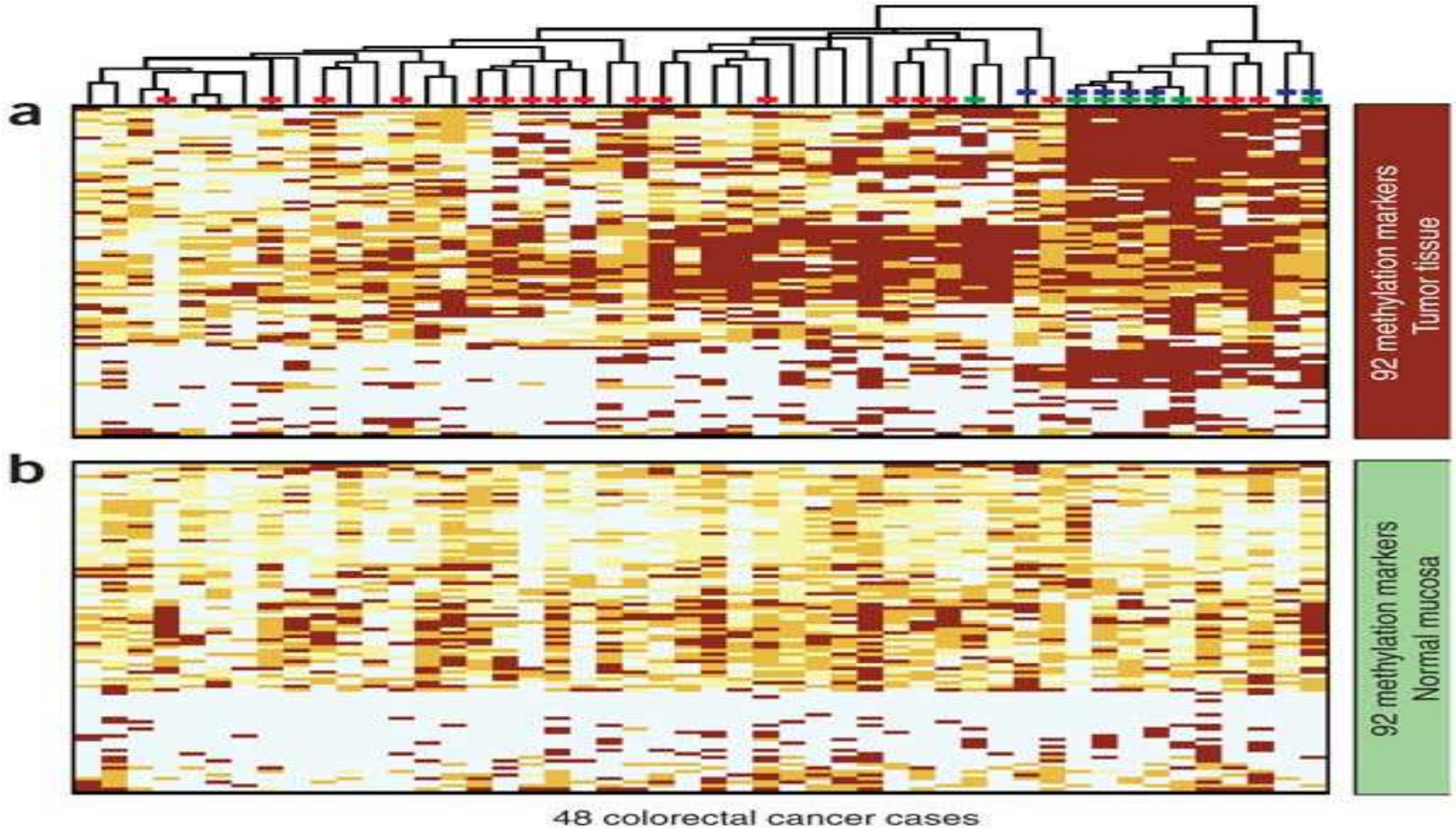
Transient Low Doses of DNA-Demethylating Agents Exert Durable Antitumor Effects on Hematological and Epithelial Tumor Cells

Hsing-Chen Tsai,[1,2,10] Huili Li,[2,10] Leander Van Neste,[3,10] Yi Cai,[2] Carine Robert,[4] Feyruz V. Rassool,[4] James J. Shin,[2,5] Kirsten M. Harbom,[2] Robert Beaty,[2] Emmanouil Pappou,[2,5] James Harris,[2,5] Ray-Whay Chiu Yen,[2] Nita Ahuja,[2,5] Malcolm V. Brock,[2,5] Vered Stearns,[2,6] David Feller-Kopman,[7] Lonny B. Yarmus,[7] Yi-Chun Lin,[8] Alana L. Welm,[8] Jean-Pierre Issa,[9] Il Minn,[2] William Matsui,[1,2] Yoon-Young Jang,[2] Saul J. Sharkis,[1,2] Stephen B. Baylin,[1,2,*] and Cynthia A. Zahnow[2,6,*]

[1]The Graduate Program in Cellular and Molecular Medicine, Johns Hopkins University School of Medicine, Baltimore, MD 21231, USA
[2]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD 21231, USA
[3]MDxHealth PharmacoDx BVBA, Technologiepark 4, 9052 Ghent, Belgium
[4]Department of Radiation Oncology, Greenebaum Cancer Center, University of Maryland School of Medicine, Baltimore, MD 21201, USA
[5]Department of Surgery, School of Medicine, Johns Hopkins University, Baltimore, MD 21231, USA
[6]Breast Cancer Program, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD 21231, USA
[7]Bronchoscopy and Interventional Pulmonology, Johns Hopkins Hospital, Baltimore, MD 21205, USA
[8]Department of Oncological Sciences, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT 84112, USA
[9]Department of Leukemia, The University of Texas M.D. Anderson Cancer Center, Houston, TX, 77030 USA
[10]These authors contributed equally to this work
*Correspondence: sbaylin@jhmi.edu (S.B.B.), zahnoci@jhmi.edu (C.A.Z.)
DOI 10.1016/j.ccr.2011.12.029

Inbox - Micr... 2012 TRACO... Combination ... Mozilla Firefox Transient lo... ScienceDirec... Mozilla Firefox Downloads 2012 Khan e... Tsai et al 2... 2 Microsoft... Quick Launch

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.

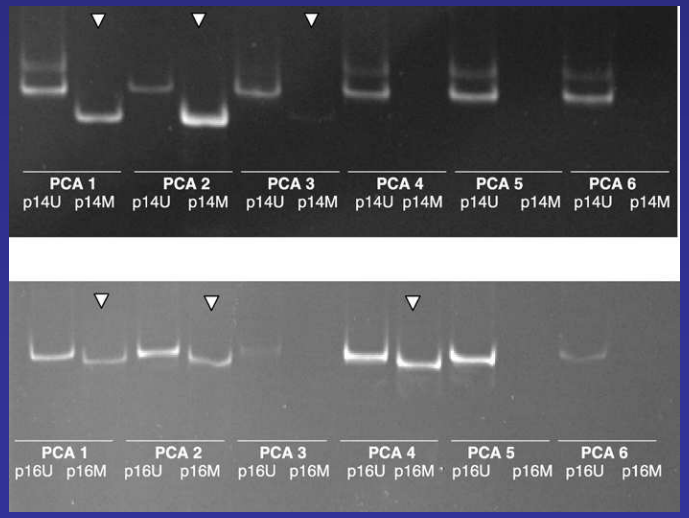
48 Colorectal tumors

Nature Genetics ***38****, 787 - 793*

Pancreatic Cancer: Methylation of p14ARF and p16INK4a

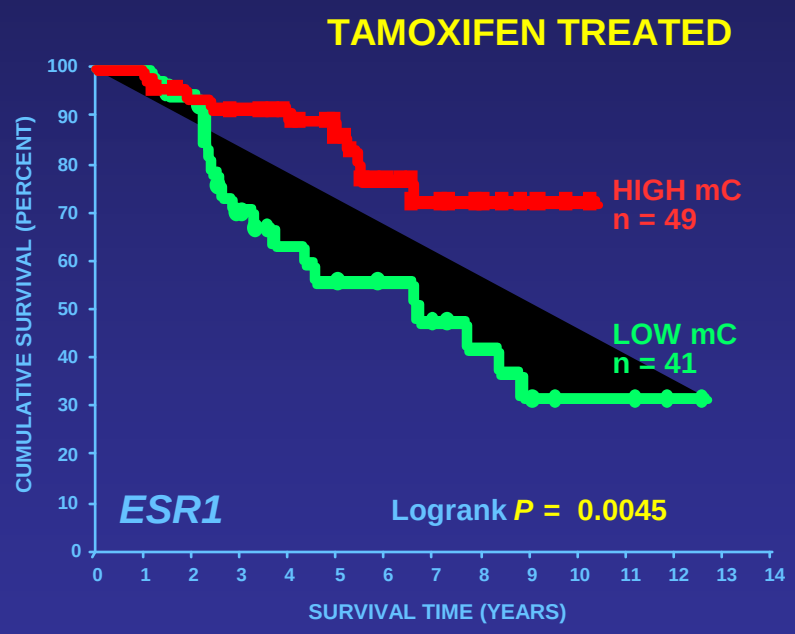
Pancreatic Carcinoma (PCA) : 39	**19/39**	**p16INK4a**
Chronic Pancreatitis (CP) : 16	**0/16**	**p16INK4a**
Normal Pancreatogram (NAD) : 6	**0/6**	**p16INK4a**

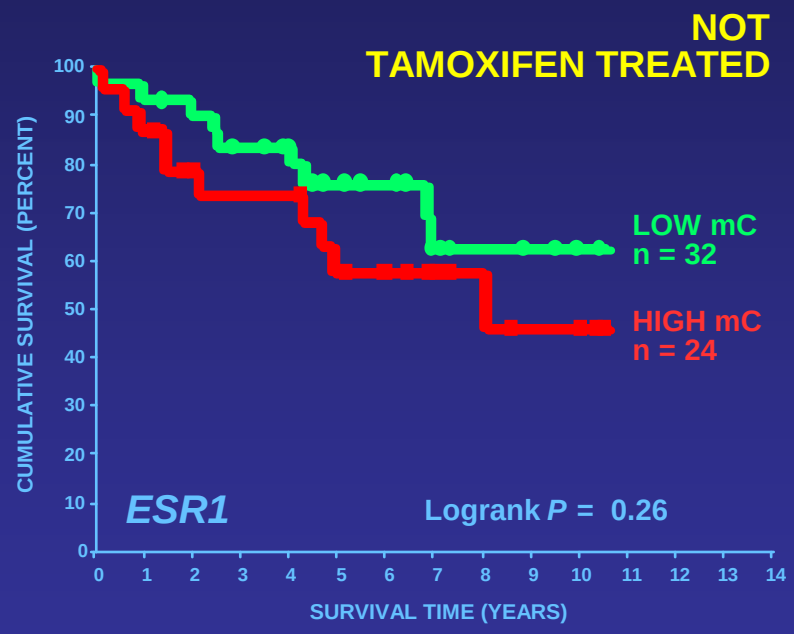
Sample: Pancreatic Fluid



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

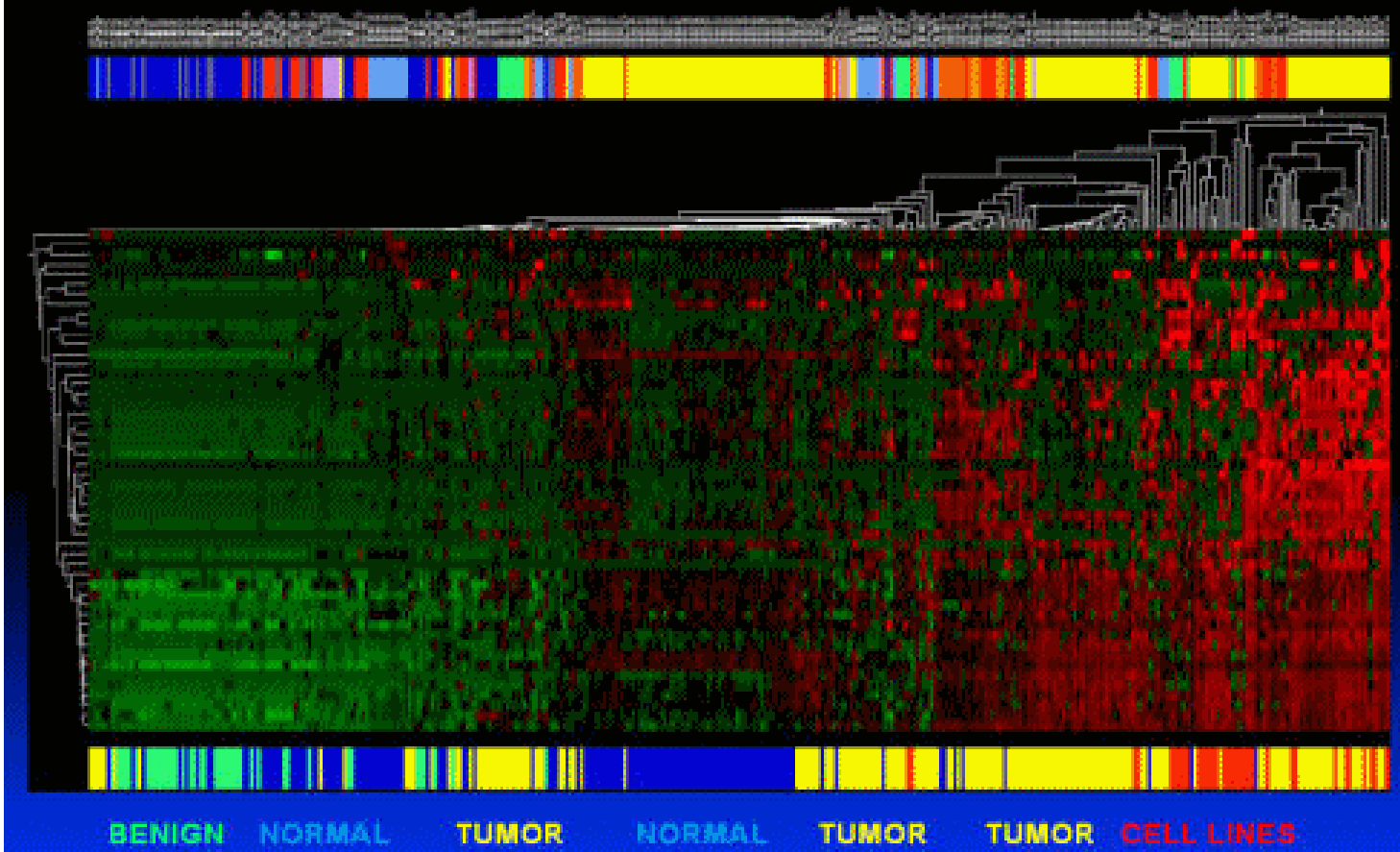
Breast Cancer Response to Tamoxifen Treatment by ESR1 Methylation





Widschwendter et al. *Cancer Research* 4, 3807

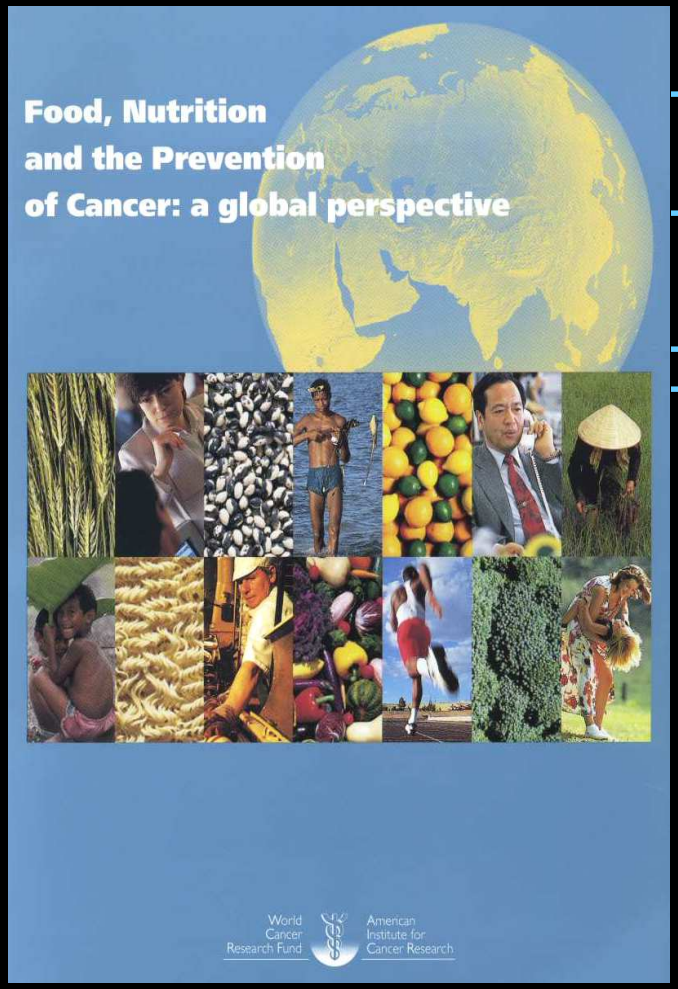
Clustering of Sample Type by CpG Island Hypermethylation



Cluster Analysis of 365 Human Samples with 50 DNA Methylation Markers



DIET AND CANCER: FOCUS ON PREVENTION



Igor Pogribny

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

Reader
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Zoom in (Ctrl+Plus)

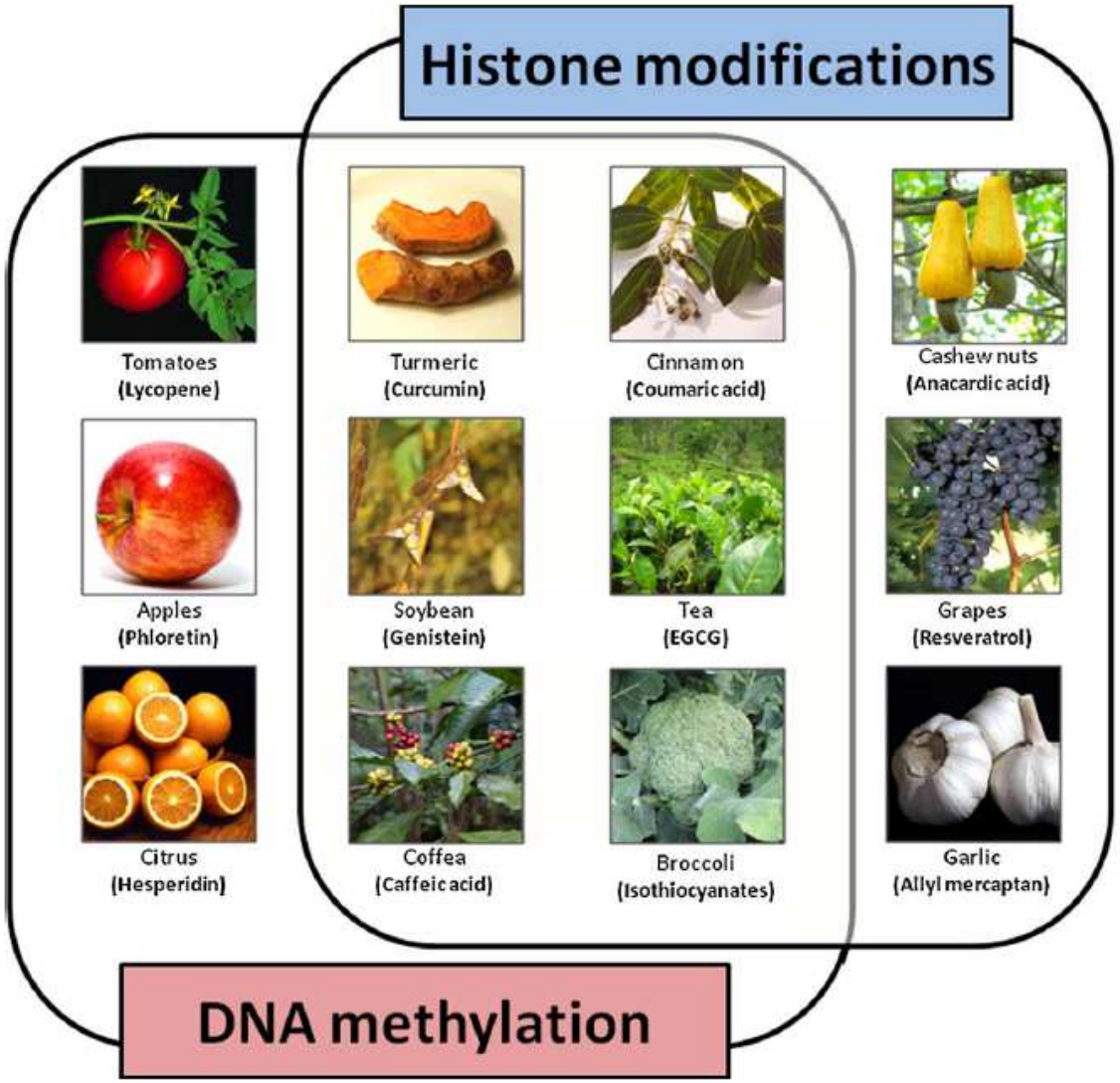


Fig. 2. Illustration depicting major plants with evidence for epigenetic modifications. The figure illustrates photographs from major plants with demonstrated evidence for epigenetic alterations in cancer cells. The 'active principles' for each of the plants are shown within parenthesis. These images were borrowed from various websites for illustration purposes only, and these websites are listed in Supplementary Table 1.

Epigenomics Program Budget

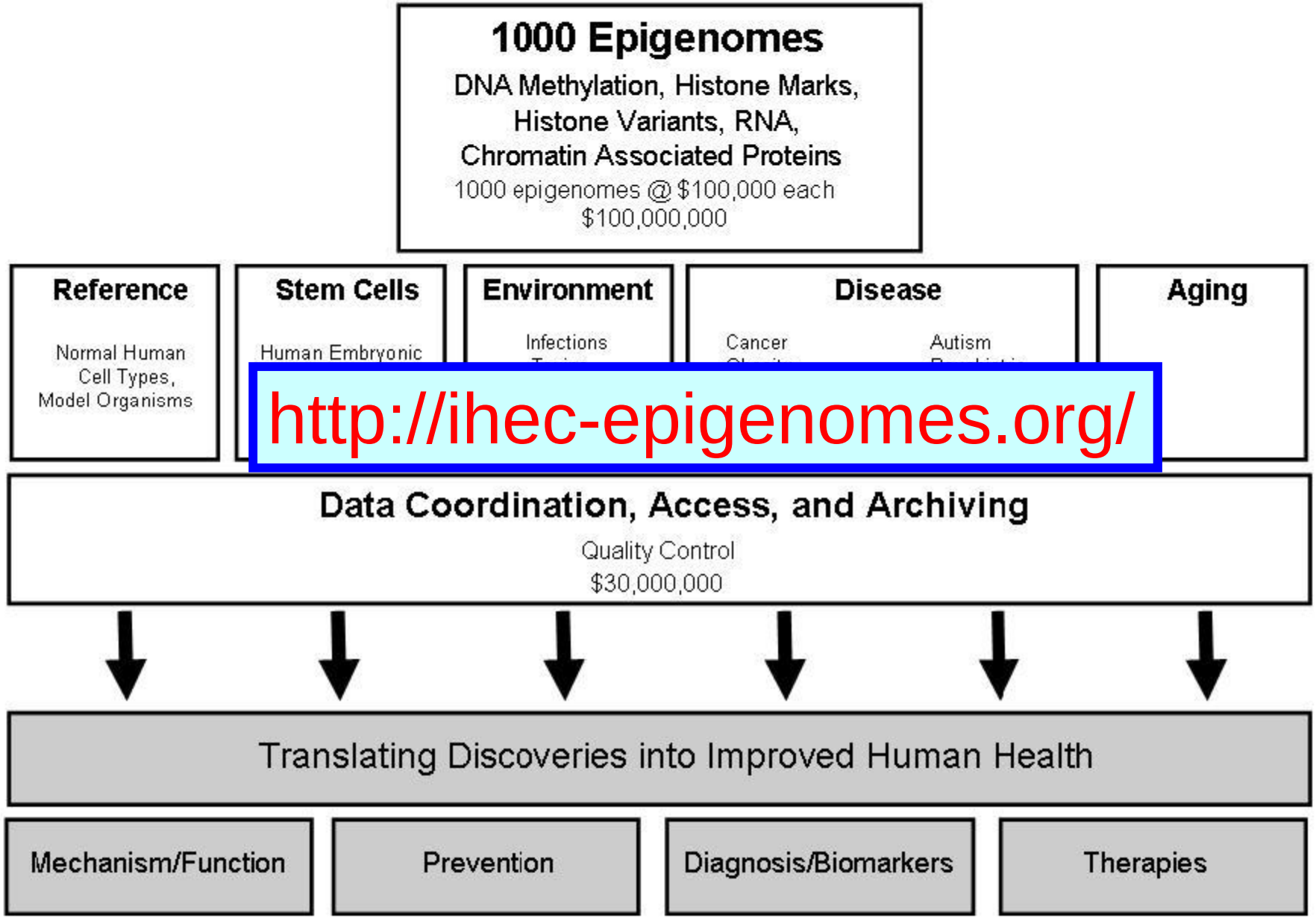
(RM funds in millions)

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)

INTERNATIONAL HUMAN EPIGENOME CONSORTIUM



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IHEC
International Human Epigenome Consortium

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The International Human Epigenome Consortium (IHEC) unites scientists from all over the world working together to achieve one common goal: deciphering 1000 epigenomes.

Welcome to IHEC | Annual Meeting | IHEC Datasets | Lectures

Research



By setting quality standards and providing

Why Epigenomics?



Epigenomics research and human health are

News+Events



Be it international conferences, workshops,

Inbox - Microsoft Outlook | 2014 Biomarker Meeting ... | Cancer epigenetic and it... | Microsoft PowerPoint - [... | Welcome to IHEC · IH...

National Cancer Institute

Research Opportunities

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?

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

EWAS (Epigenome-wide Association Studies)



Christopher Plass (Heidelberg)



Nancy Kiviat (Seattle)

Christine Ambersone
(Rosewell Park, Buffellow)



National Cancer Institute

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Scott Rogers
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David Sidransky
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Debbie Winn