Clínica Universidad de Navarra

cima
CENTER FOR APPLIED MEDICAL RESEARCH
UNIVERSITY OF NAVARRA

Targeting Epigenetics in Hematological Malignancies

GOBIERNO DE ESPAÑA
MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD

SOCIEDAD ESPAÑOLA DE HEMATOLOGÍA Y HEMOTERAPIA

ACTIVIDADES DE FORMACIÓN

FEHH
FUNDACIÓN ESPAÑOLA DE HEMATOLOGÍA Y HEMOTERAPIA

Epigenetics

Heritable change in pattern of gene expression mediated by mechanisms other than alterations in primary nucleotide sequence

"The difference between genetics and epigenetics can probably be compared to the difference between writing and reading a book. Once a book is written, the text (the genes or DNA: stored information) will be the same. However, each individual reader of a given book may interpret the story slightly differently. In a very similar manner, epigenetics would allow different interpretations of a fixed template (the book or genetic code) and result in different read-outs, dependent upon the variable conditions under which this template is interrogated."

Thomas Jenuwein (Vienna, Austria)

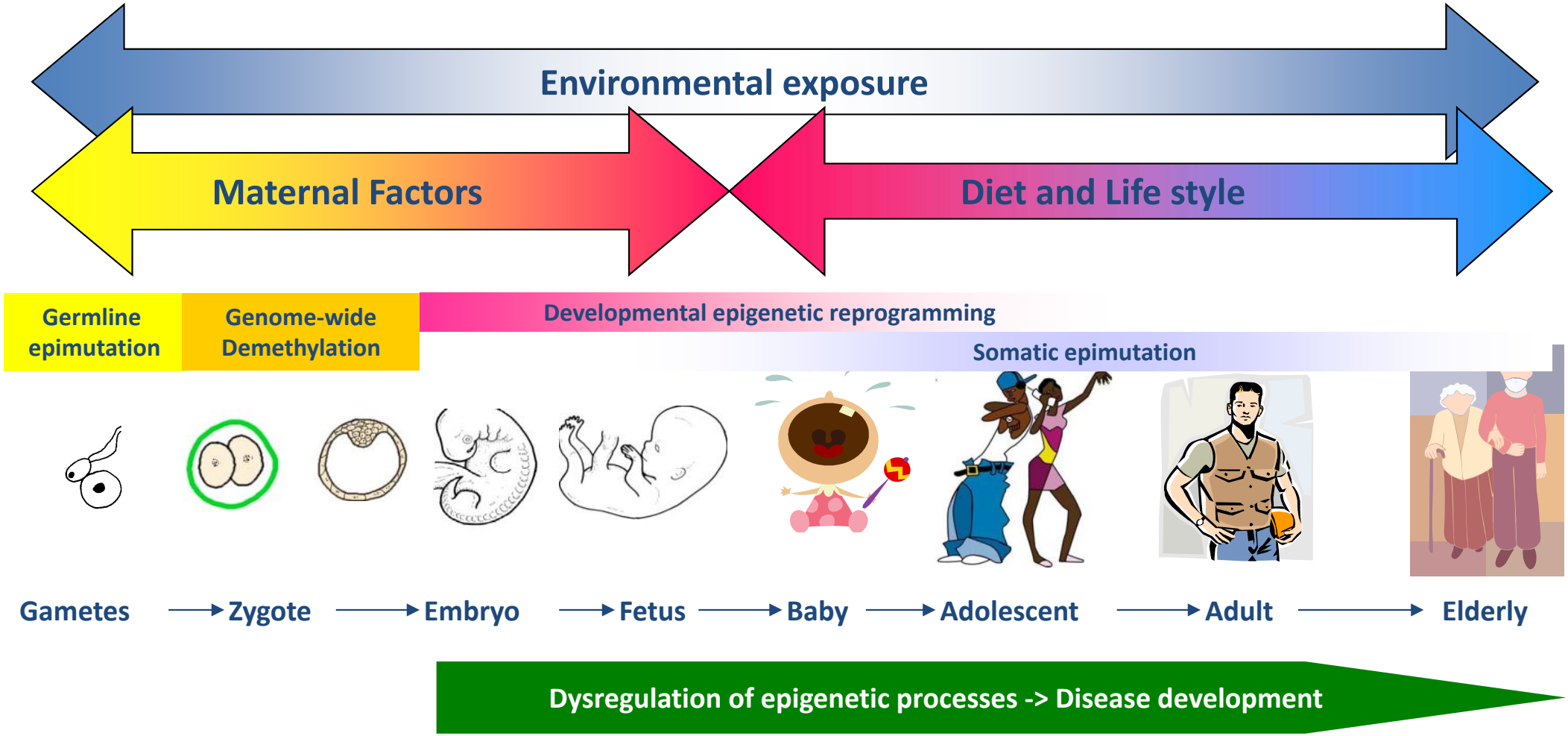
Epigenetics

PNAS

Epigenetic differences arise during the lifetime of monozygotic twins

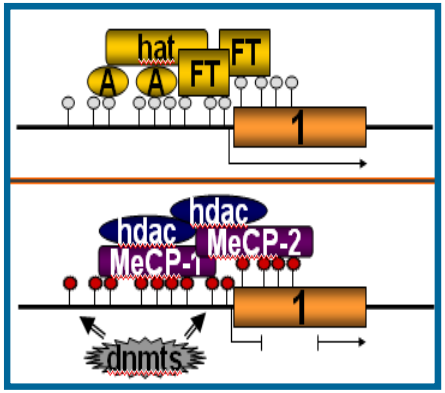
Mario F. Fraga*, Esteban Ballestar*, Maria F. Paz*, Santiago Ropero*, Fernando Setien*, Maria L. Ballestar†, Damia Heine-Suñer‡, Juan C. Cigudosa§, Miguel Urioste¶, Javier Benitez¶, Manuel Boix-Chornet†, Abel Sanchez-Aguilera†, Charlotte Lingl, Emma Carlsson||, Pernille Poulsen**, Allan Vaag**, Zarko Stephan††, Tim D. Spector††, Yue-Zhong Wu‡‡, Christoph Plass‡‡, and Manel Esteller*§§

Epigenetics, microenvironment and development

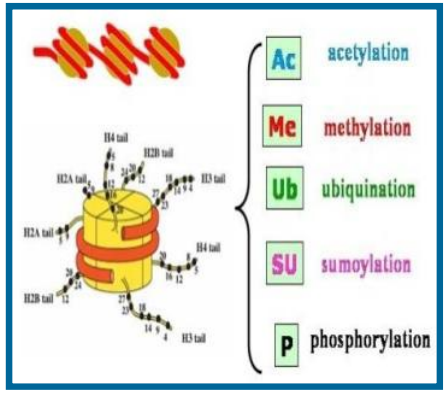


Epigenome and Epigenetic Mechanisms

The epigenome regulates gene expression patterns, in other words, what genes need to be silenced or expressed in a cell



DNA Methylation

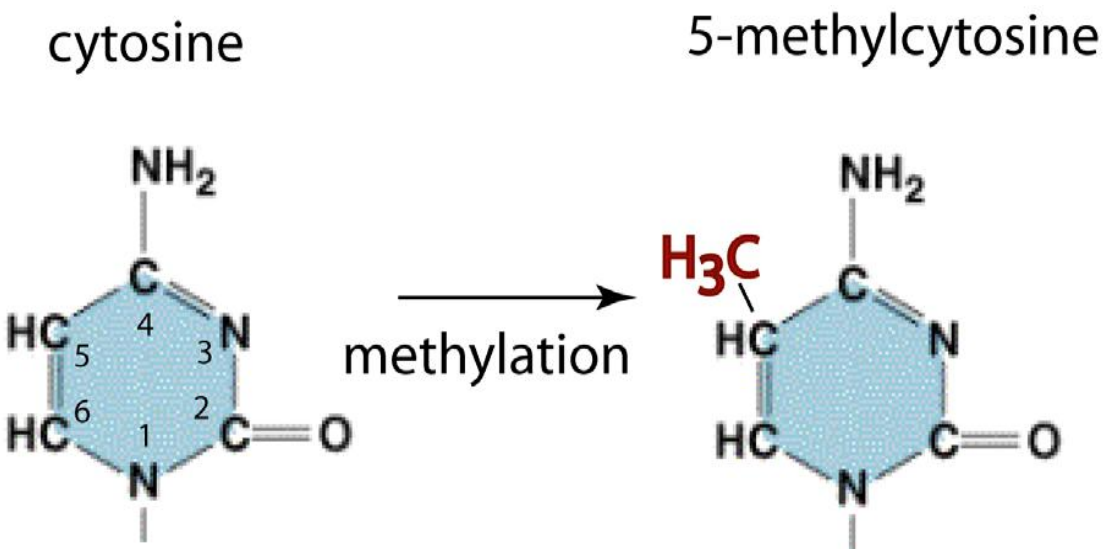


Histone Modifications

Nucleosome remodelling

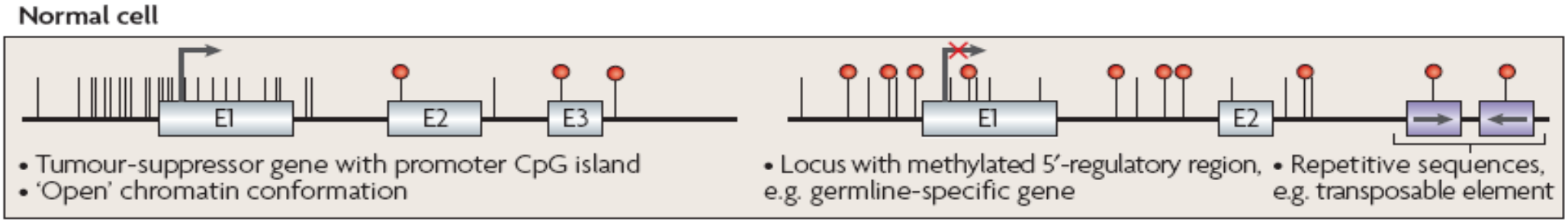
Non coding RNAs

DNA Methylation



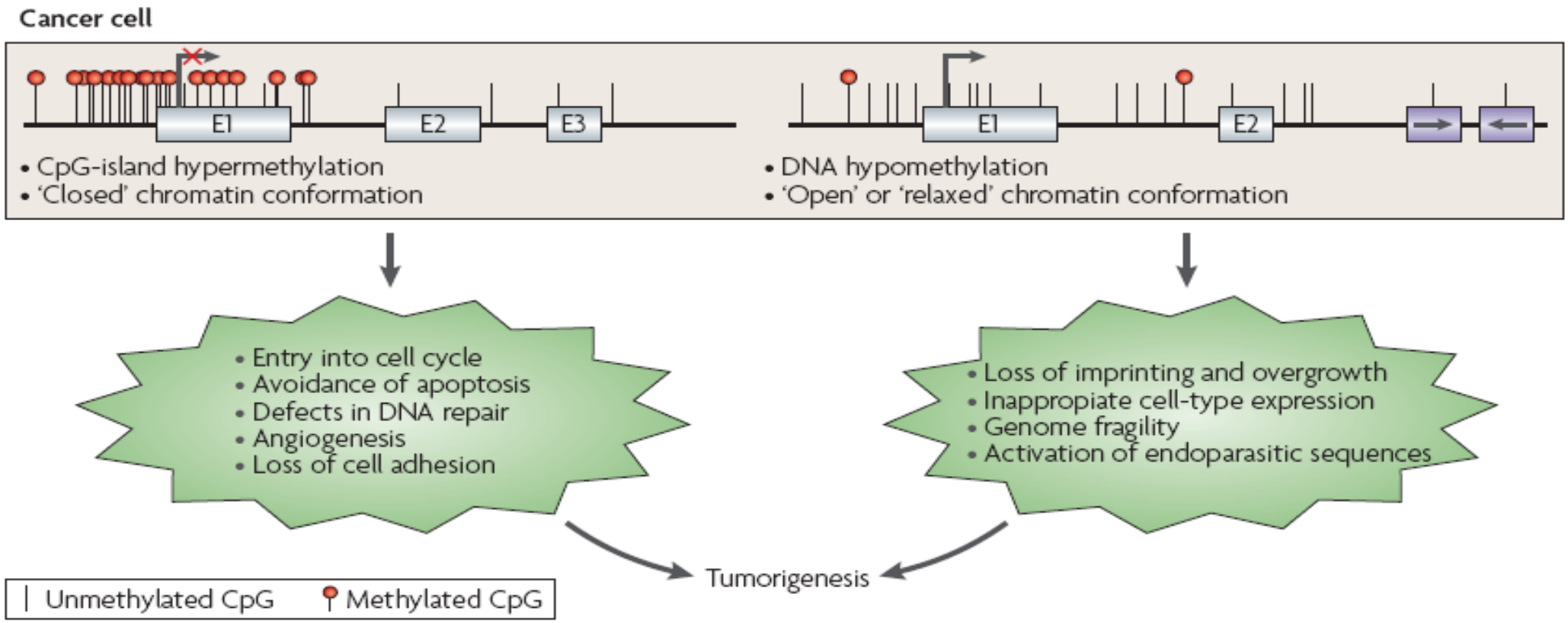
- **Best characterized epigenetic event**
- **Methylation occurs in a cytosine-containing nucleotides that are immediately followed by guanine-containing nucleotides (CpG regions)**
- **CpG regions in 60% of promoters**
- **Usually associated to gene silencing**
- **More frequent that tumor suppresor gene mutations**

DNA Methylation and Normal Cell



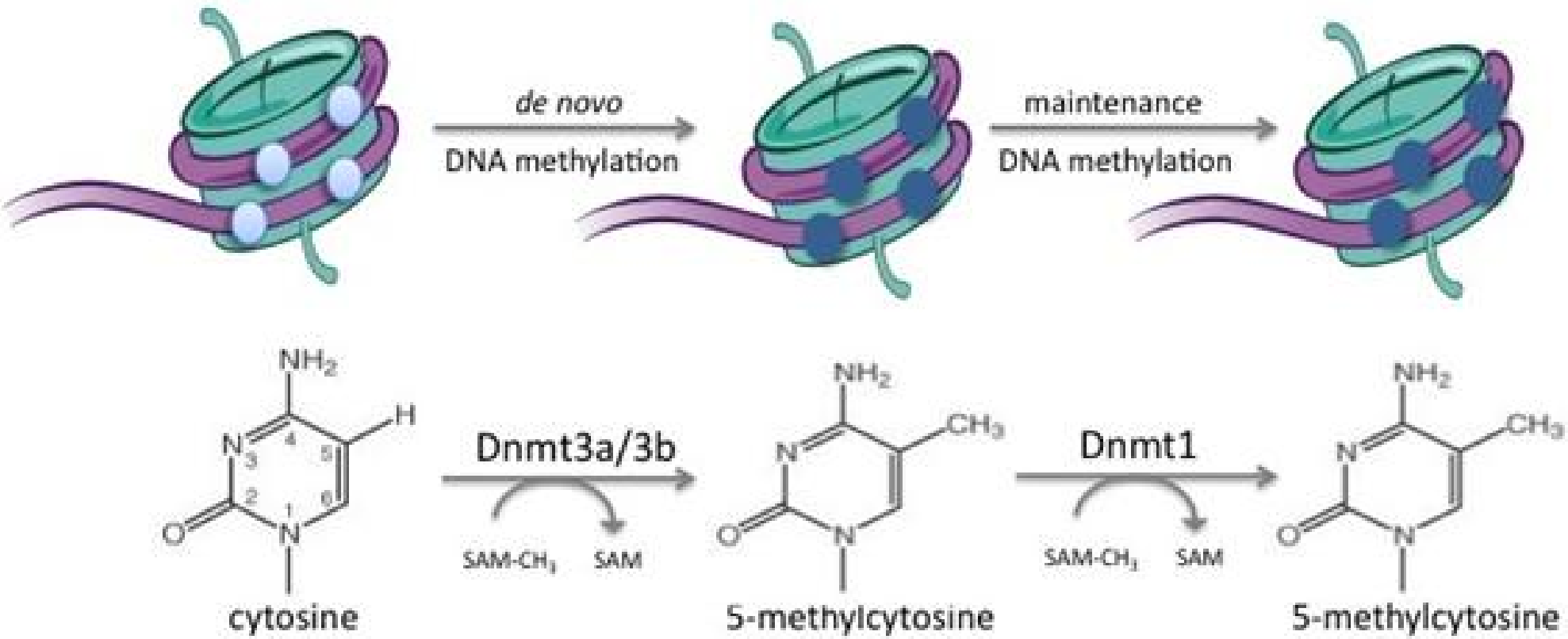
- X chromosome inactivation
- Silencing of repetitive sequences
- Chromatin organization
- Tissue specific methylation
- Imprinting

DNA Methylation and Cancer



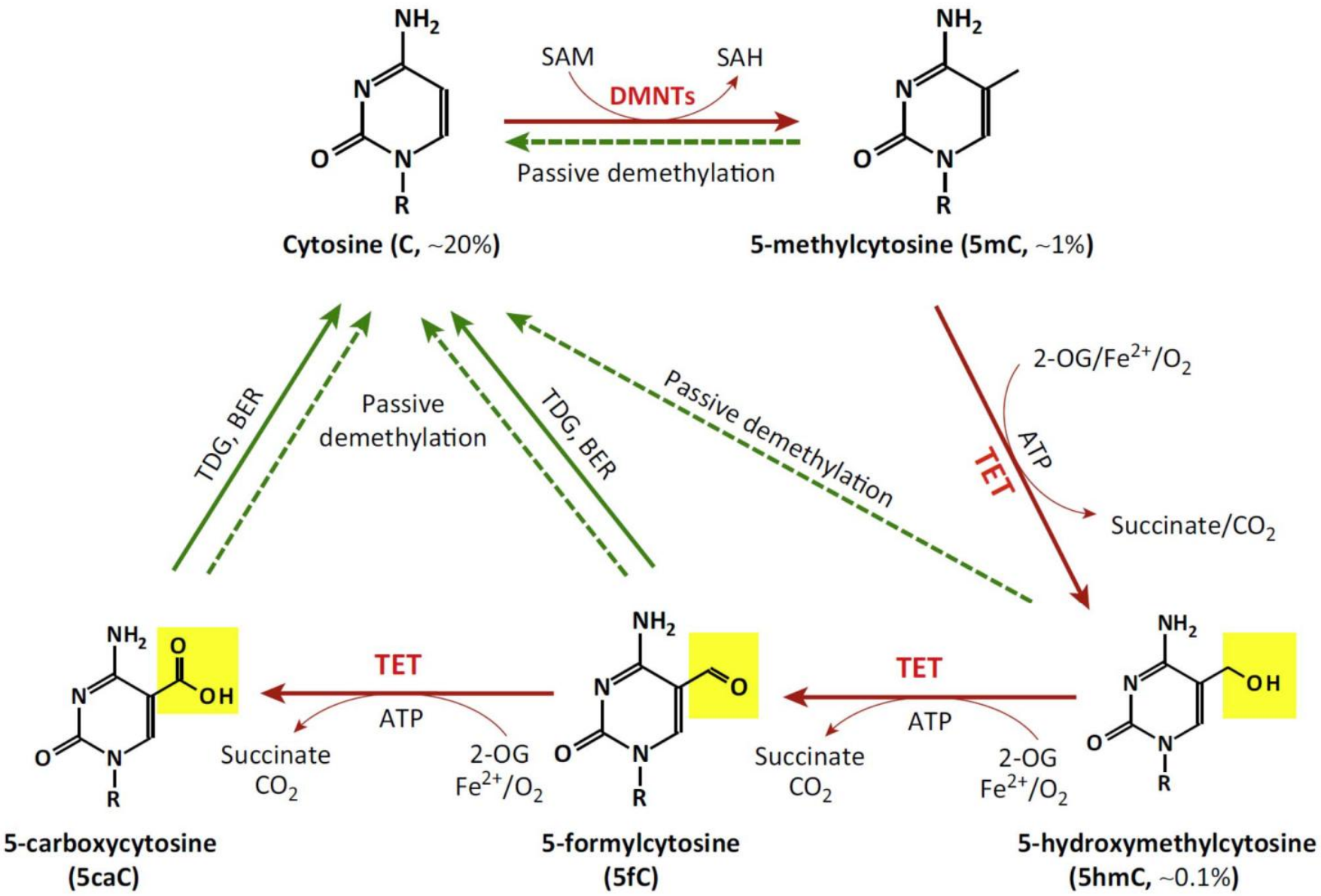
Esteller M, *Nature Reviews Genetics* 8, 286-98 (2007)

Regulation of DNA Methylation



DNMT3L and DNMT2

Enzymes involved in DNA modification



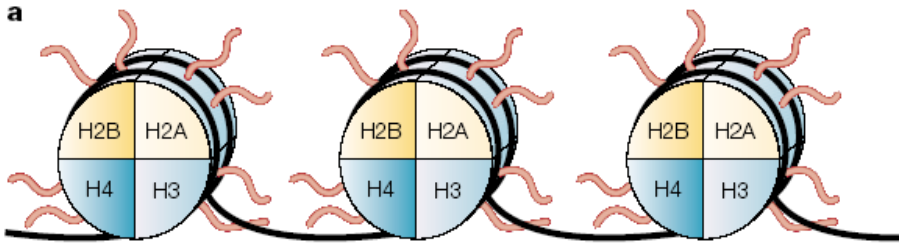
Trends in Genetics 2014; 30:464-474

Mutations in enzymes involved in DNA modification

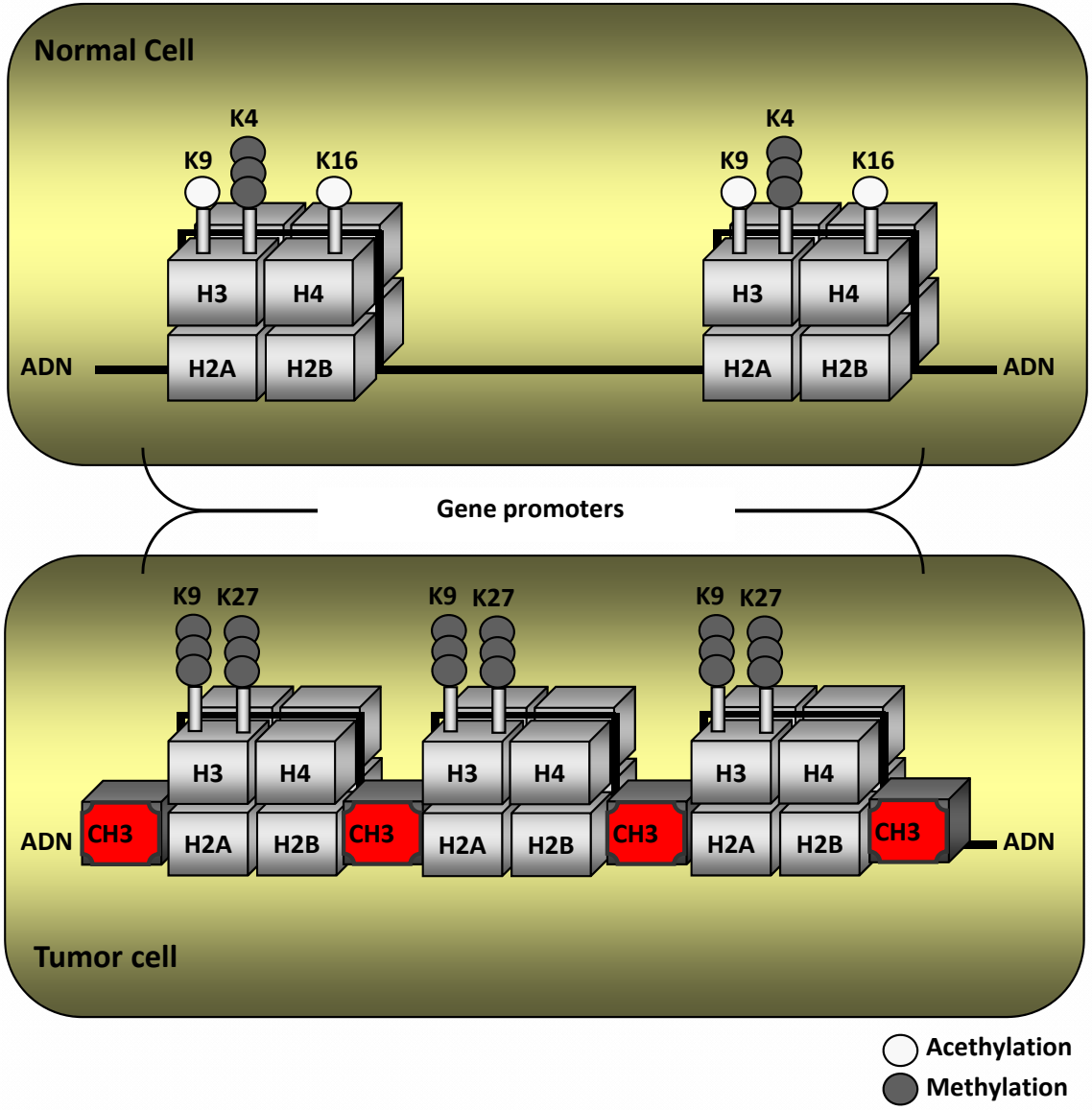
Gene	Cancer	Frequency or stage of cancer	Frequency of mutation (*N*)	Effect	Refs
DNA methyltransferases					
DNMT1	Colorectal cancer		2% (29)	Mutation	151
DNMT3A	AML	Stage M4	13.6% (66)		87
		Stage M5	20.5% (112)		87
	AML	Common	22.1% (281)		88
DNA demethylases					
TET2	BCR-ABL-negative myeloproliferative neoplasms	Rare form	13% (239)		152
	CMML	Common form	50% (88)		90
	MDS	Rare	26% (102)		153
IDH1	Anaplastic astrocytoma	Rare	73% (52)		154
	Diffuse astrocytoma	Rare	90% (30)		154
	AML	Common	6.2% (385)		89
IDH2	AML	Common	8.6% (385)		89

Timp et al. Nat Rev Cancer. 2013;13:497-510

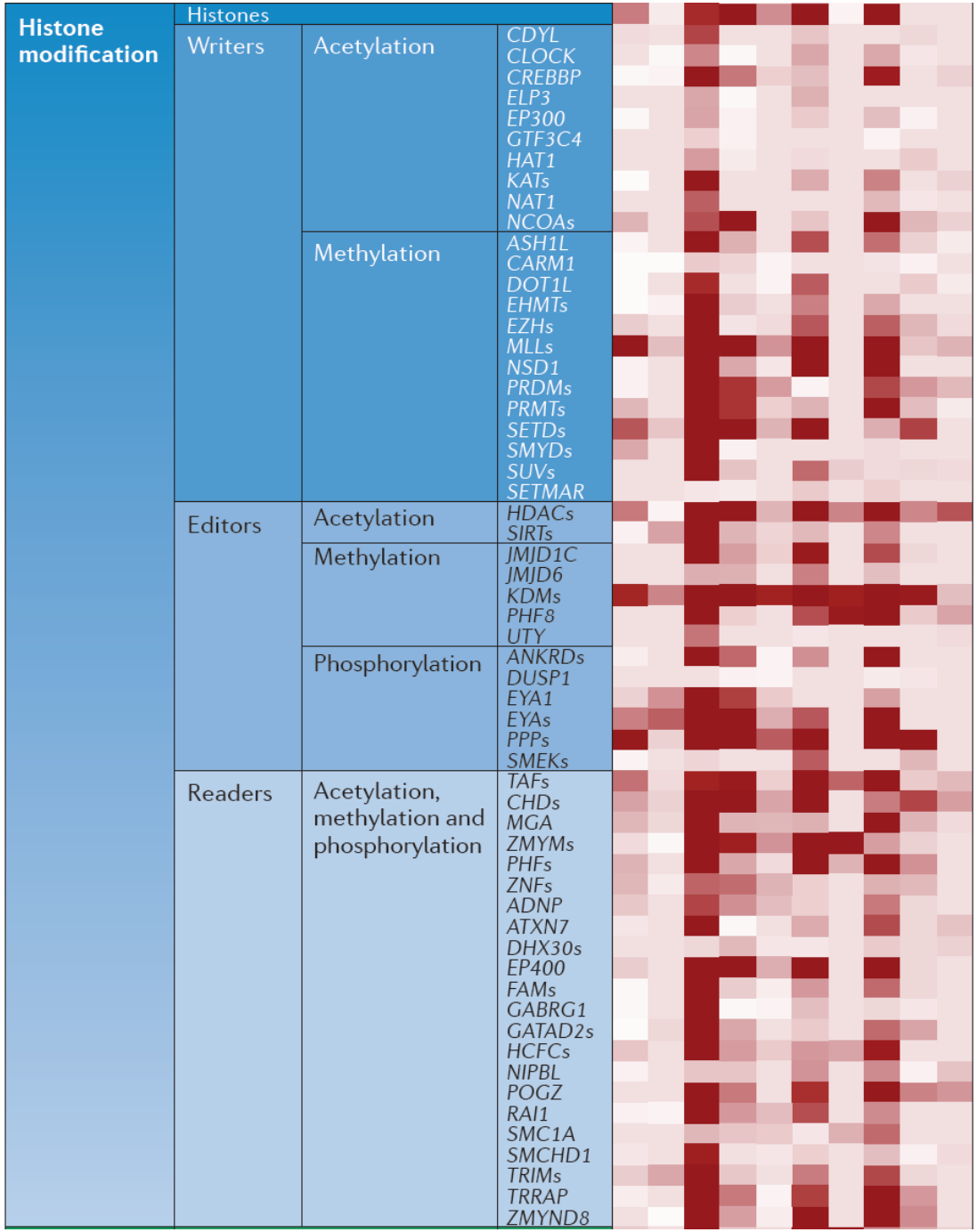
Histone Modifications



- Des/Acethylation
- Methylation
- Phosphorylation
- Ubiquitination
- ADP-Ribosilation
- Isomerization



Mutations in regulators of the epigenome identified in cancer



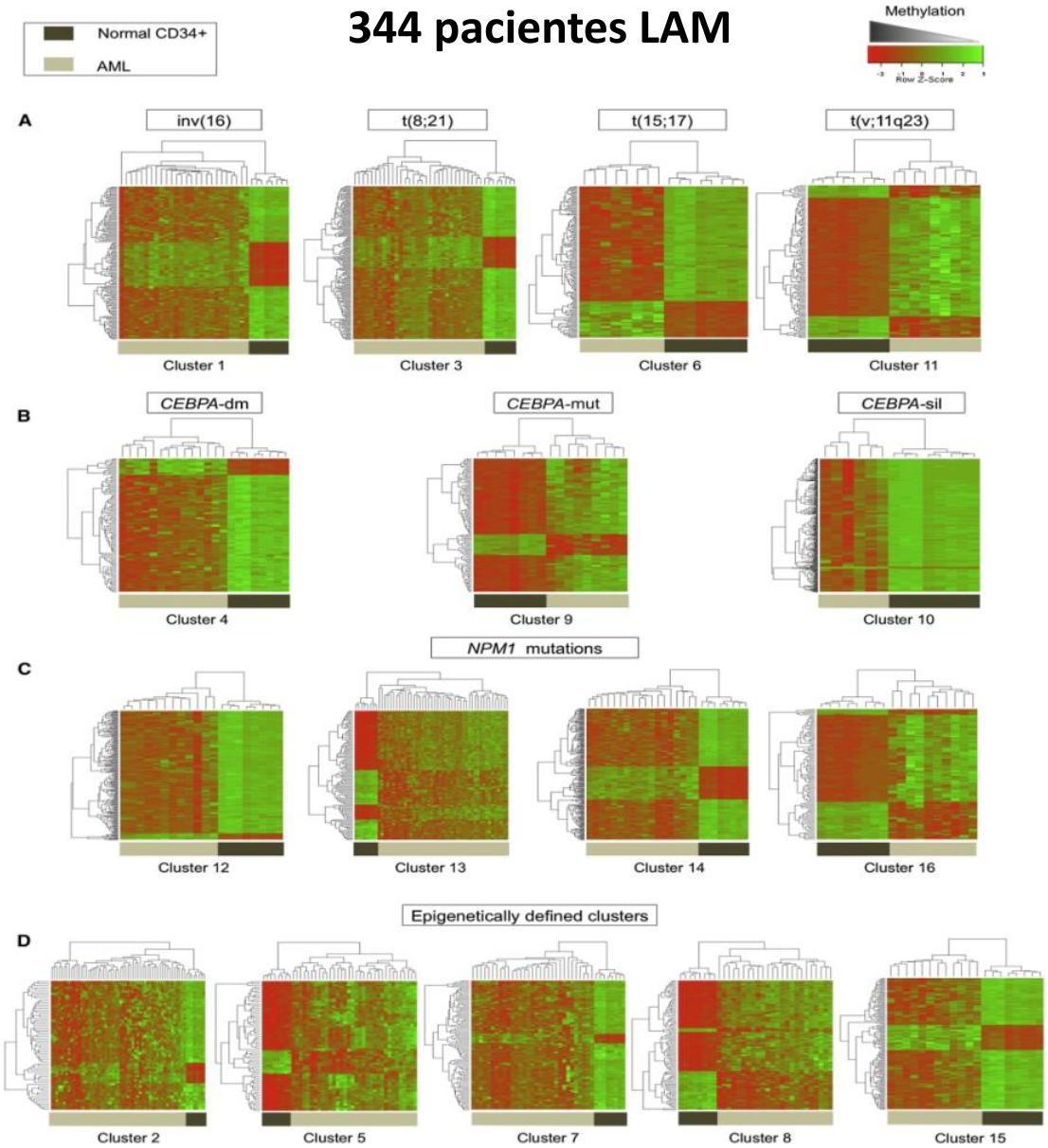
Plass et al. Nat Rev Genet. 2013; 14:765-80

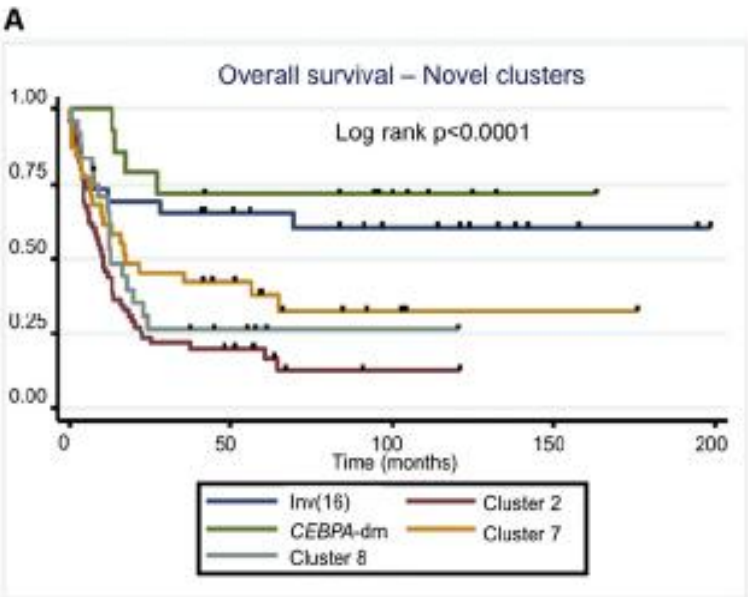
Role of epigenetics

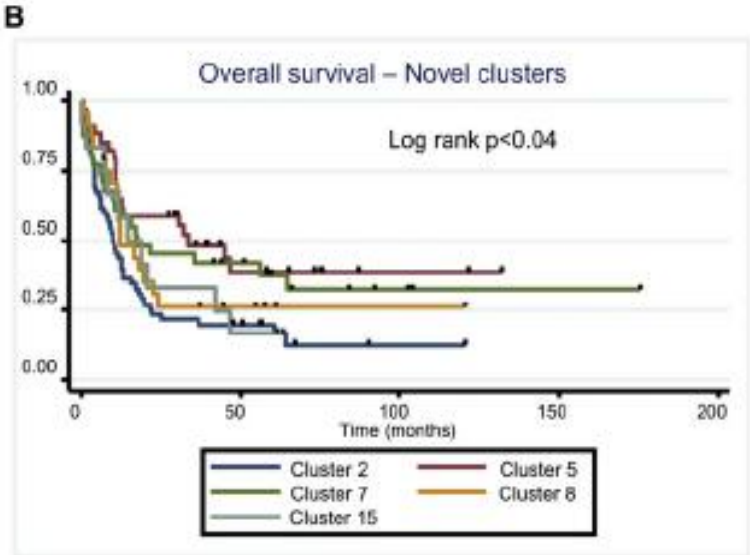
- Epigenetic changes as prognostic factors and biomarkers
- Development of therapeutic approaches

DNA methylation as epigenetic marker: AML

DNA Methylation Captures Clinically Significant Differences among AML Patients

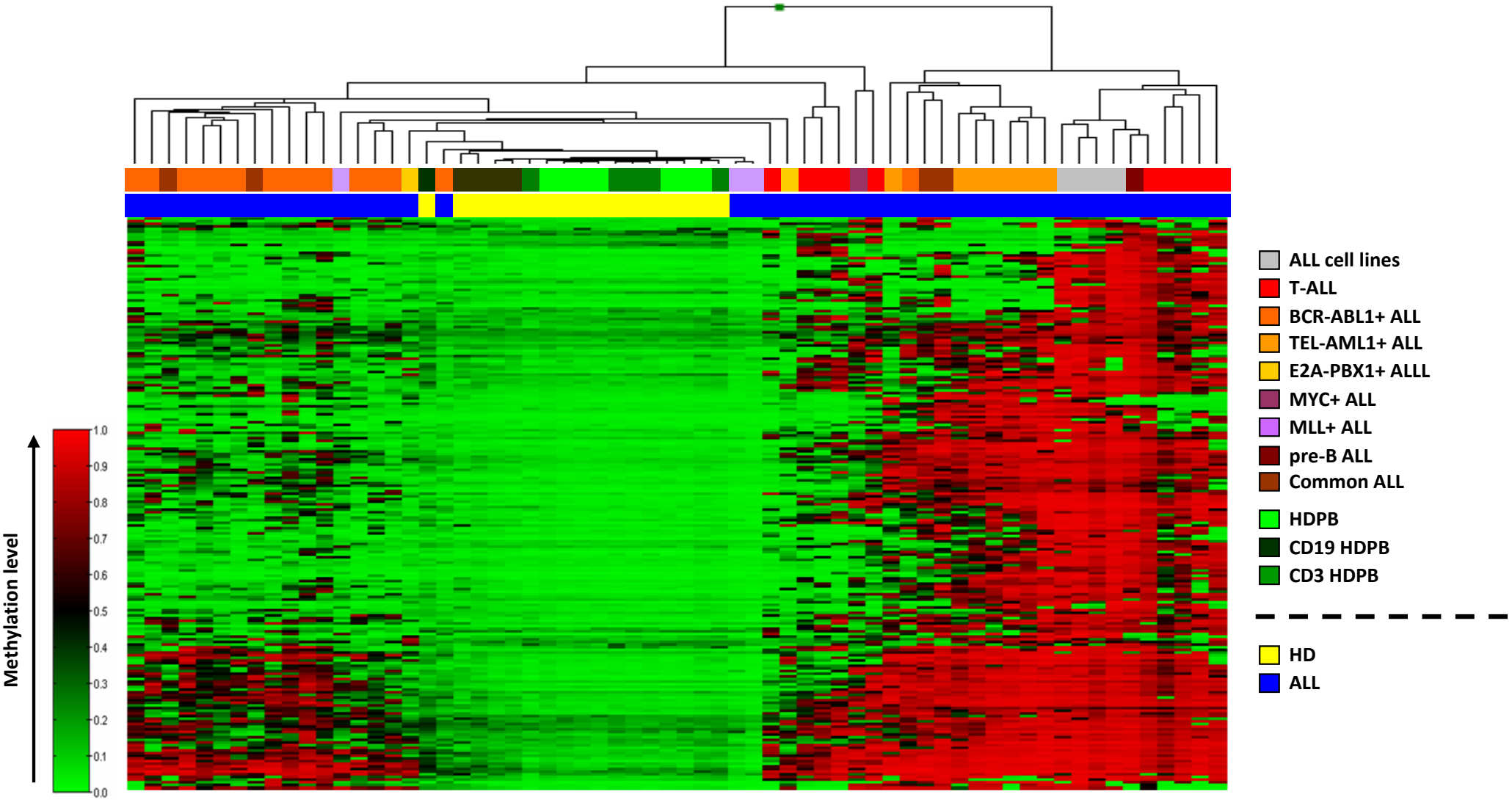






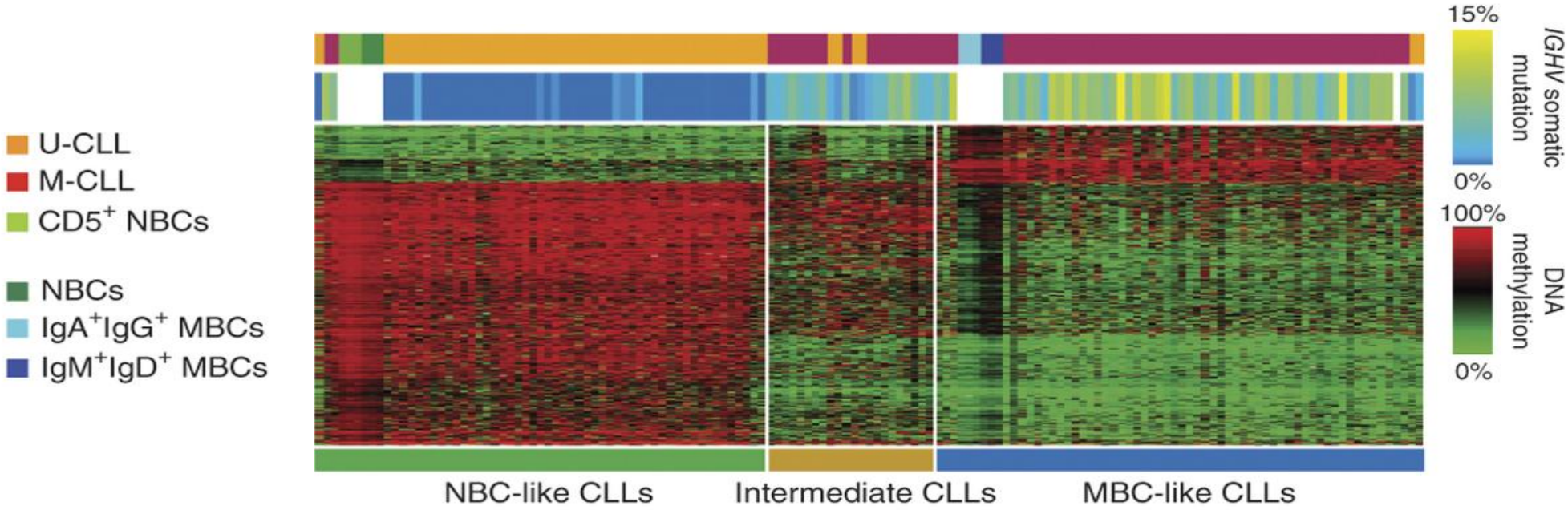
Cancer Cell. 2010; 17:13-27

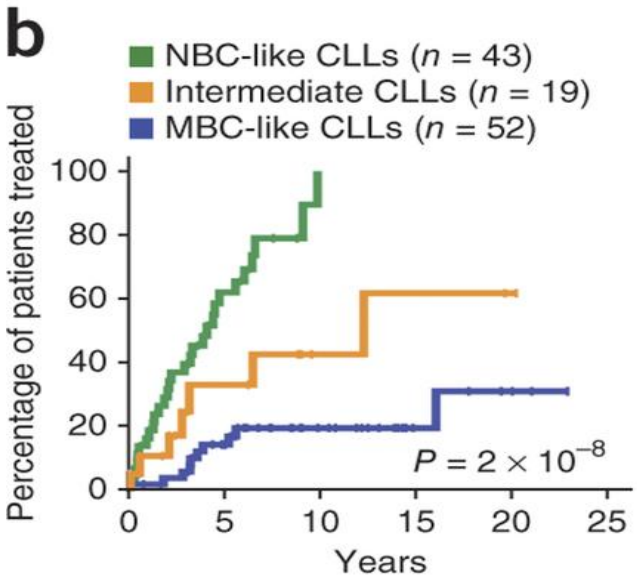
DNA methylation as epigenetic marker: ALL

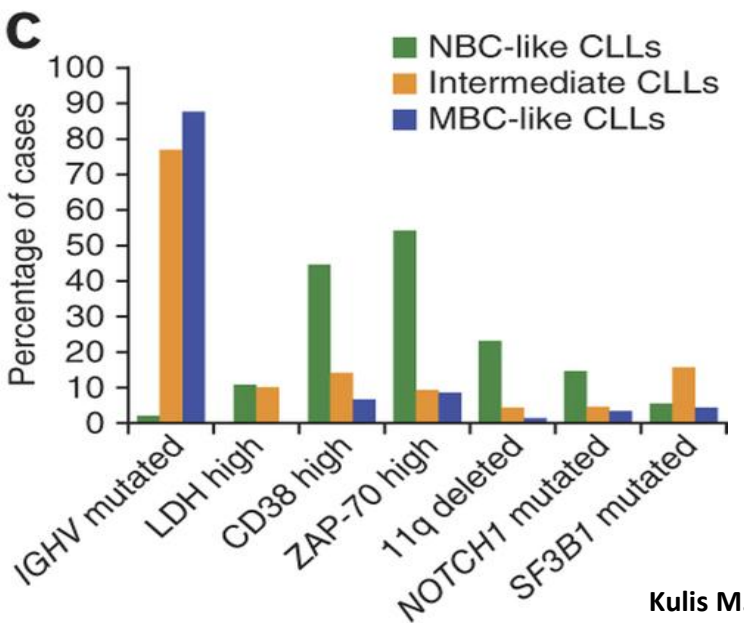


Vilas-Zornoza et al. PLoS One. 2011; 6:e17012

DNA methylation as epigenetic marker: CLL

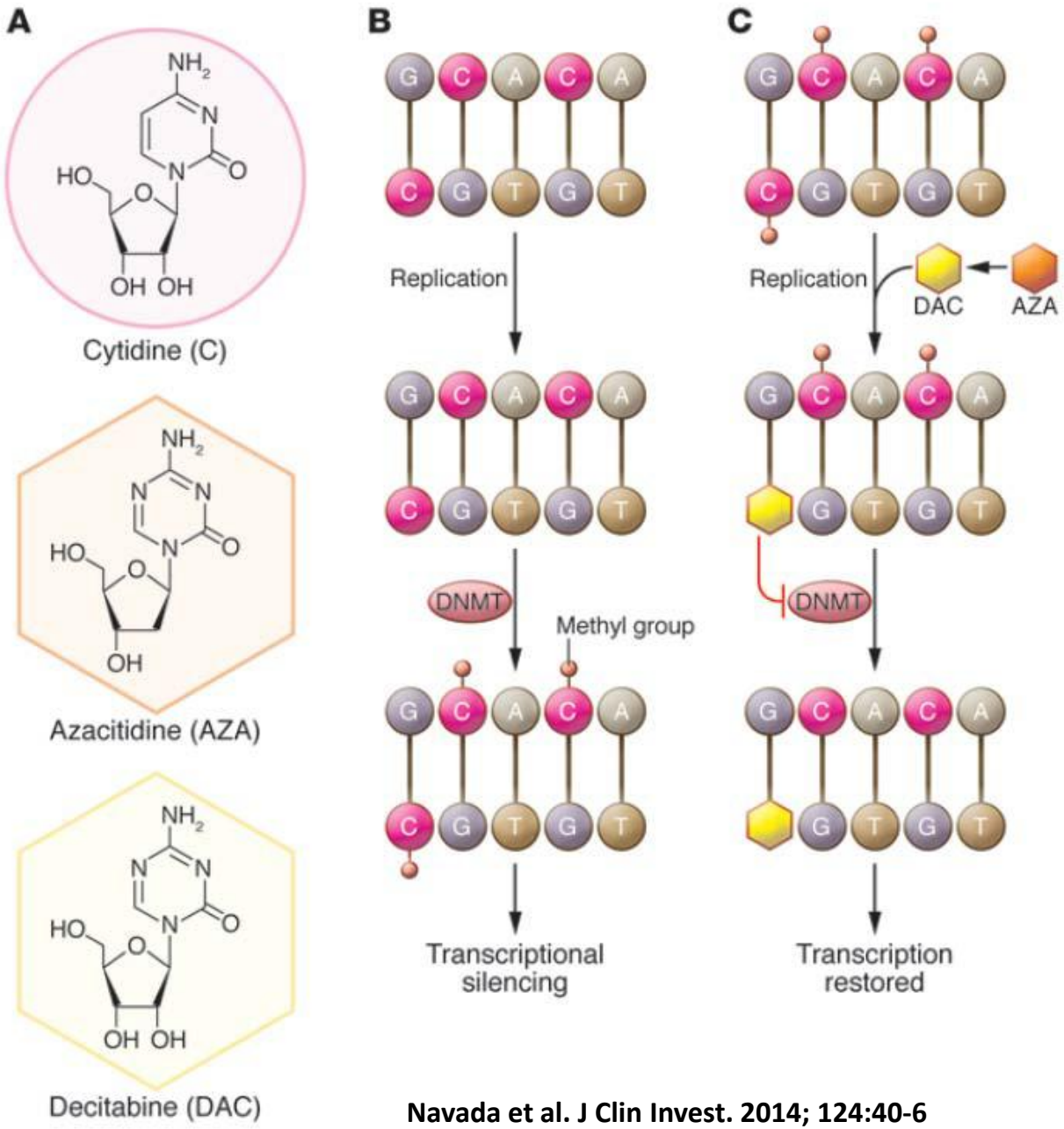






Kulis M. Nature Genetics 2012

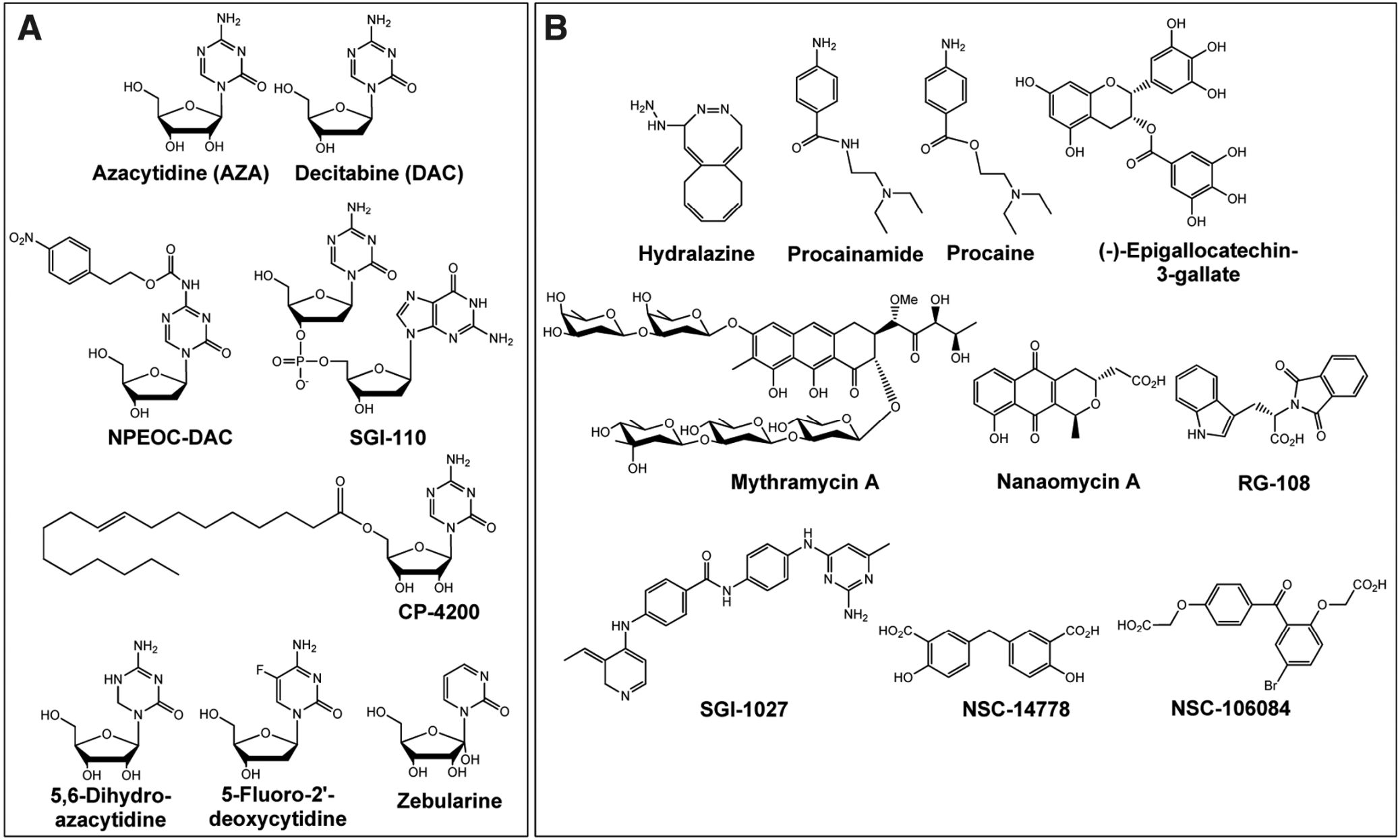
Hypomethylating Agents: Mechanism of Action (MoA)



Navada et al. J Clin Invest. 2014; 124:40-6

- Decitabine and 5-Azacytidine are S-phase specific
- Higher potency of Decitabine versus 5-Azacytidine (Decitabine only binds to DNA)
- The majority (80–90%) of 5-azacitidine is incorporated into RNA
- High-dose causes DNA damage and DNA synthesis arrest, leading to cytotoxicity
- Low-dose induces DNMT inhibition with minimal cytotoxicity

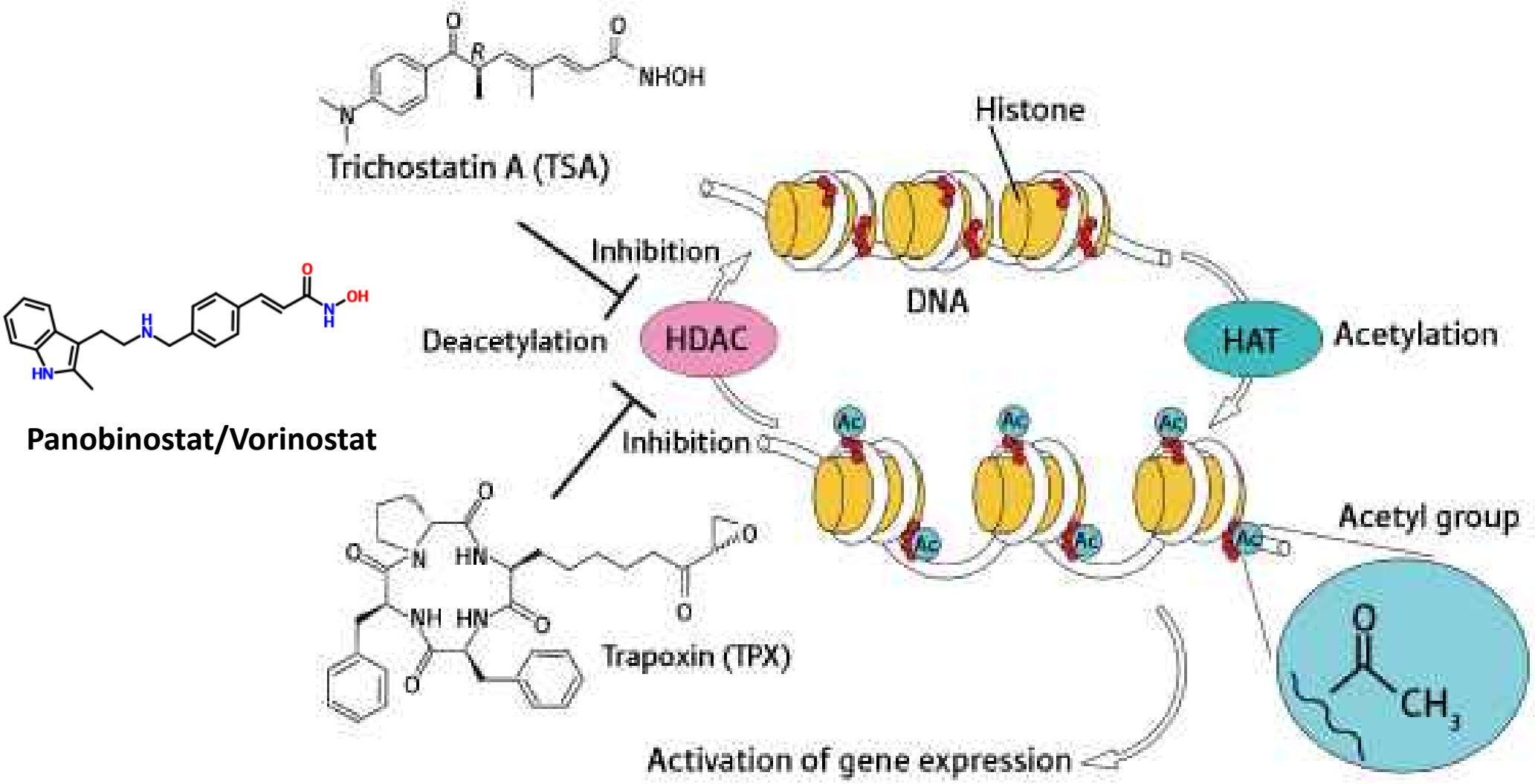
New Hypomethylating Agents



Hypomethylating Agents (Caveats)

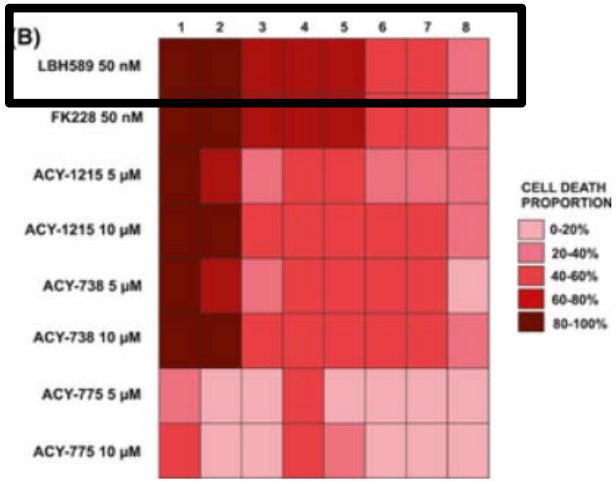
- MoA: evidence for hypomethylation of specific genes is limited
- Biomarkers to predict response
- Combinations with other chemotherapy

HAT and HDACs



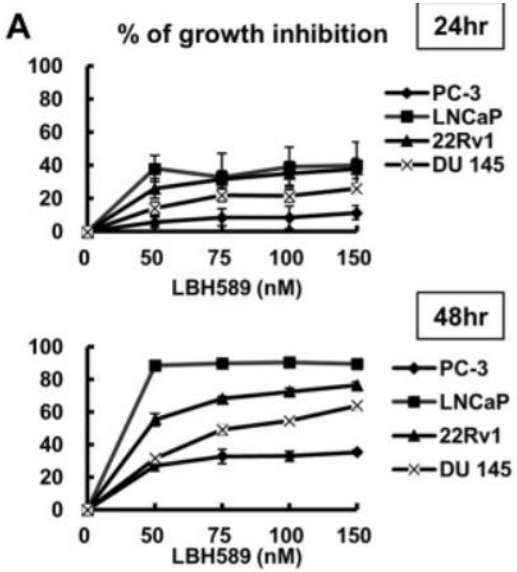
HDAC inhibitors (Panobinostat) in Cancer

Multiple myeloma



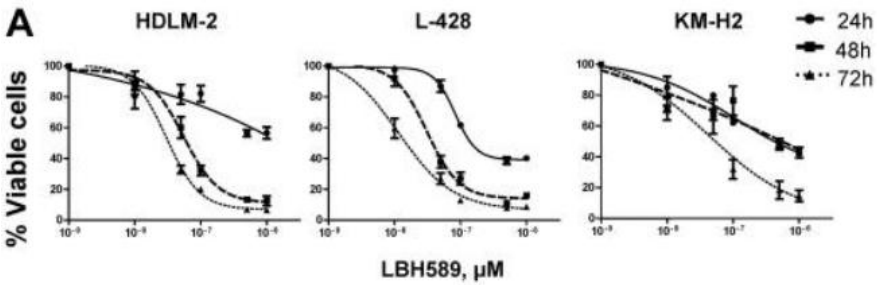
Mithraprabhu S, Br J Haematol, 2013

Prostate cancer



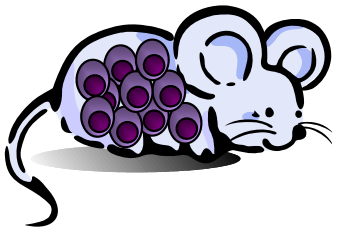
Chuang MJ, Plos One, 2013

Lymphoma

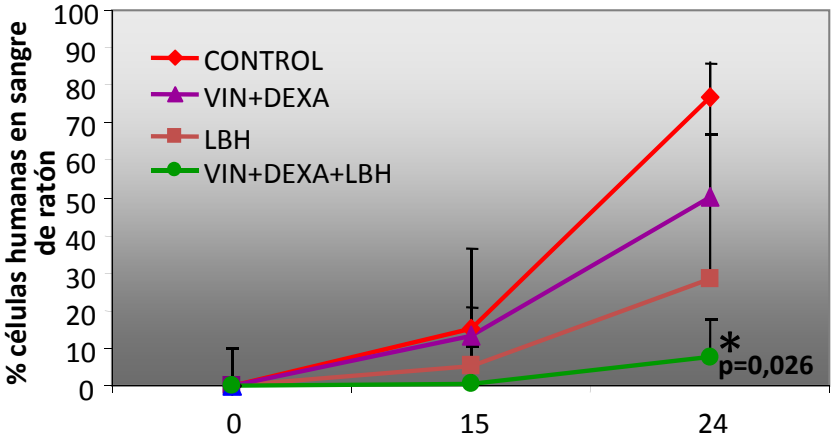


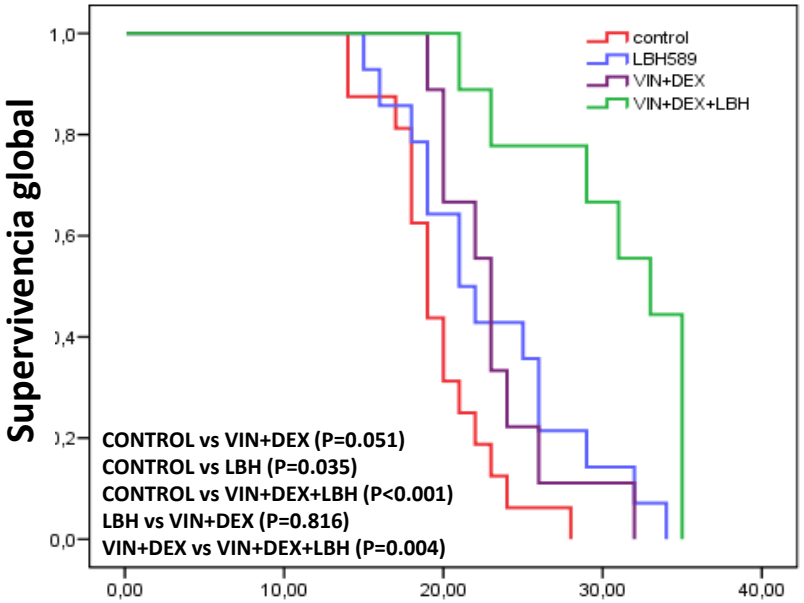
Lemoine M, Blood, 2012

ALL



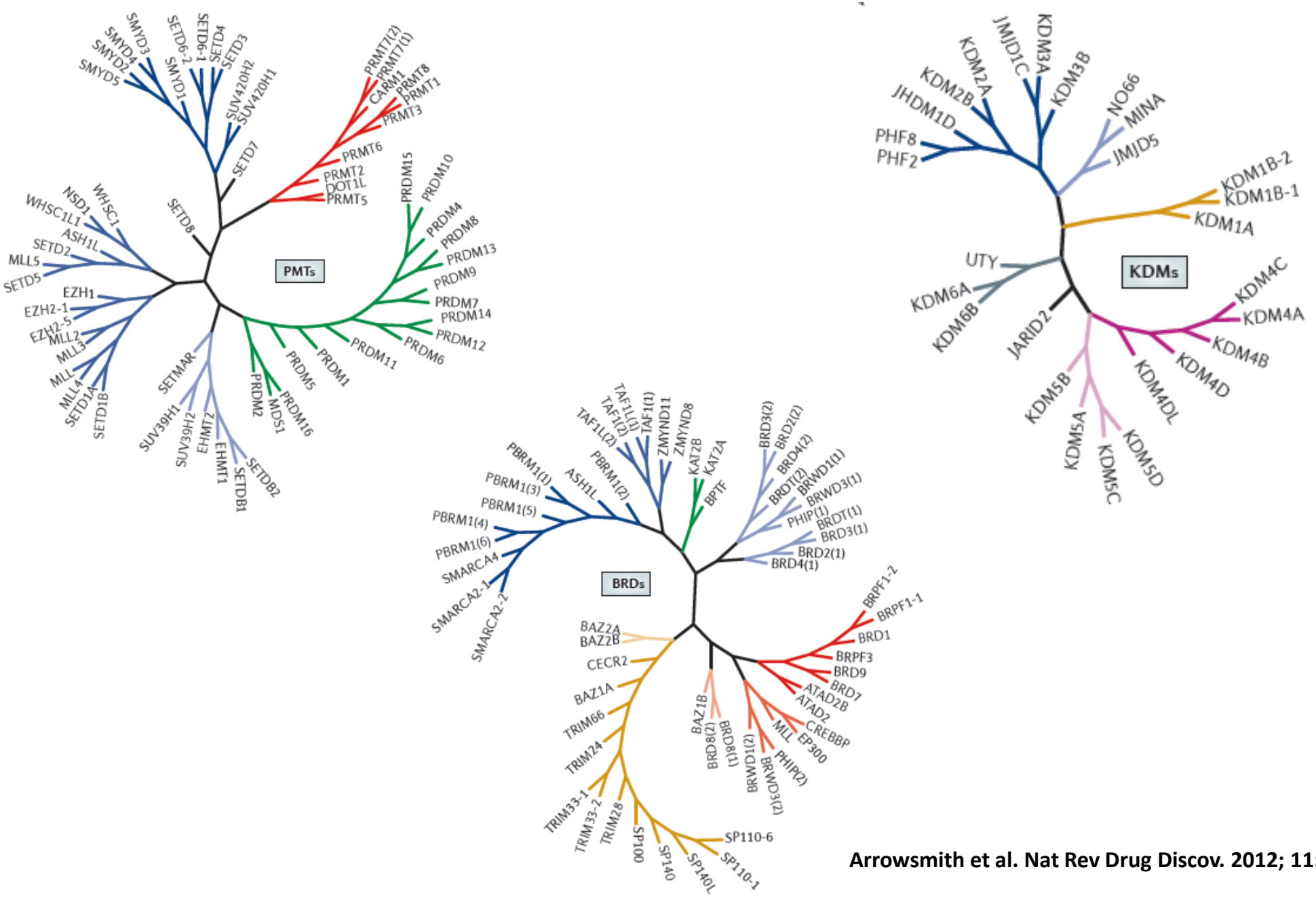
Rag2 + LAL humana





Agirre X, Vilas-Zornoza A. Leukemia 2012

Protein Methyltransferase and Demethlyase Inhibitors



Arrowsmith et al. Nat Rev Drug Discov. 2012; 11:384-400

Selected novel drugs in preclinical or clinical development targeting components of the epigenetic machinery

Substance	Target structure	Clinical trial	Disease
SGI110	DNMT	Phase I/II	MDS, AML, ovarian and hepatocellular cancer
AGI-5198	Mutant IDH	Preclinical	Glioma
Pivanex (also known as AN-9)	HDAC	Phase I/II	CLL, small lymphocytic lymphoma, malignant melanoma and NSCLC
ACY-1215	HDAC6	Phase I/II	Multiple myeloma
Resveratrol (SRT501)	SIRT1 and SIRT5 activation	Phase I/II	Colorectal cancer, melanoma, multiple myeloma
	SIRT3 inhibition	Phases I–III	Metabolic and cardiovascular diseases
Curcumin	HAT	Phase I/II	Breast cancer, colorectal cancer and multiple myeloma
Tranylcypromine	KDM1A	Phase II	AML
EPZ-5676	DOT1L	Phase I	Advanced haematological malignancies and acute leukaemia with 11q23 or *MLL* abnormalities
EPZ-6438	EZH2	Phase I	NHL and breast cancer
GSK126	EZH2	Preclinical	Haematological malignancies, including NHL
GSK525762	BET bromodomain	Phase I	NMC
RVX-208	BET bromodomain	Phase II	Atherosclerosis
		Preclinical	Haematological malignancies
JQ1	BET bromodomain	Preclinical	NMC, AML and multiple myeloma
PFI-1	BET bromodomain	Preclinical	B cell acute lymphoblastic leukaemia

Plass et al. Nat Rev Genet. 2013; 14:765-80

Programa de Onologia (CIMA)

Xabier Agirre
Edurne San José
Marien Pascual
Andoni Garitano
Leire Garate
Amaia Vilas
Estíbaliz Miranda
Raquel Ordoñez

Iñaki Martin-Subero

Ari Melnick

Universidad de Navarra CIMA-Lab

María José Calasanz
María José Larráyoz
Bruno Paiva

Plataforma de moléculas pequeñas

Julen Oyarzabal
Obdulia Rabal

GOBIERNO DE ESPAÑA
MINISTERIO DE CIENCIA E INNOVACIÓN

RTICC Red Temática de Investigación Cooperativa en Cáncer

COOPERAT