CHAIRE ÉPIGÉNÉTIQUE ET MÉMOIRE CELLULAIRE

Année 2015-2016 :
"Epigénétique et Cancer"

6 avril, 2016

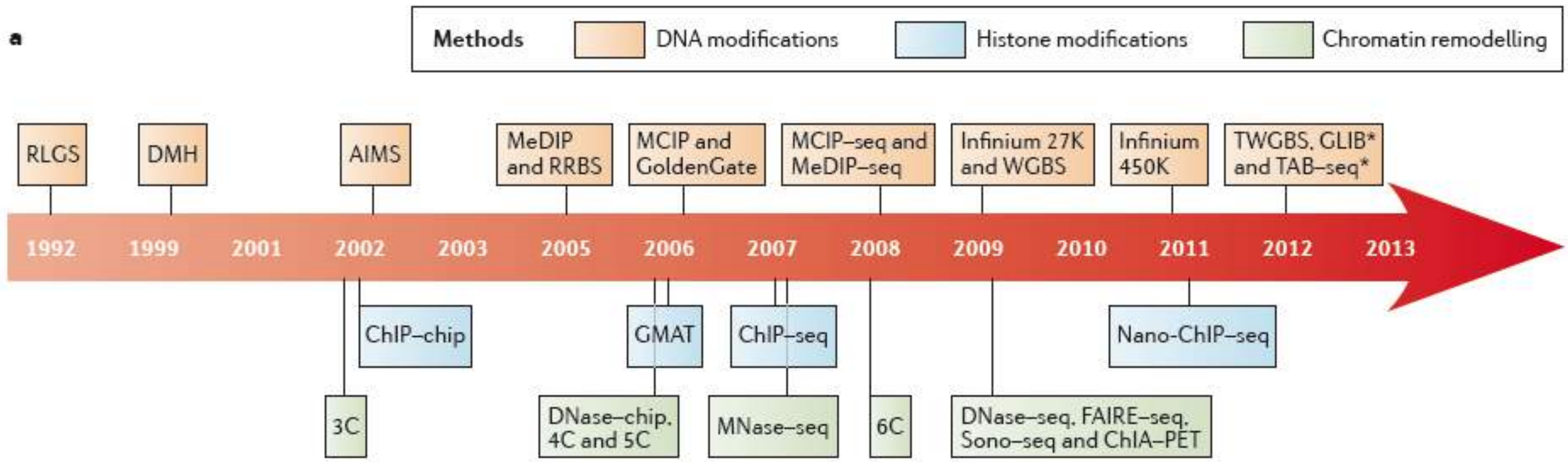
Cours VI
"Perspectives: Marqueurs et thérapies épigénétiques"
"*Perspectives: Epigenetic Biomarkers and Therapies*"

Séminaire par le Professeur Kristian Helin
"Epigenetic Targets in Cancer"
(BRIC, Copenhagen, Denmark)

COLLÈGE DE FRANCE 1530

From Cancer Genomes to Epigenomes

The sequencing of cancer genomes and epigenomes over the last decade or so, has provided unprecedented insights into tumors and their underlying genetic and epigenetic changes:



E. Heard, 2016

Epigenetics Research is flourishing

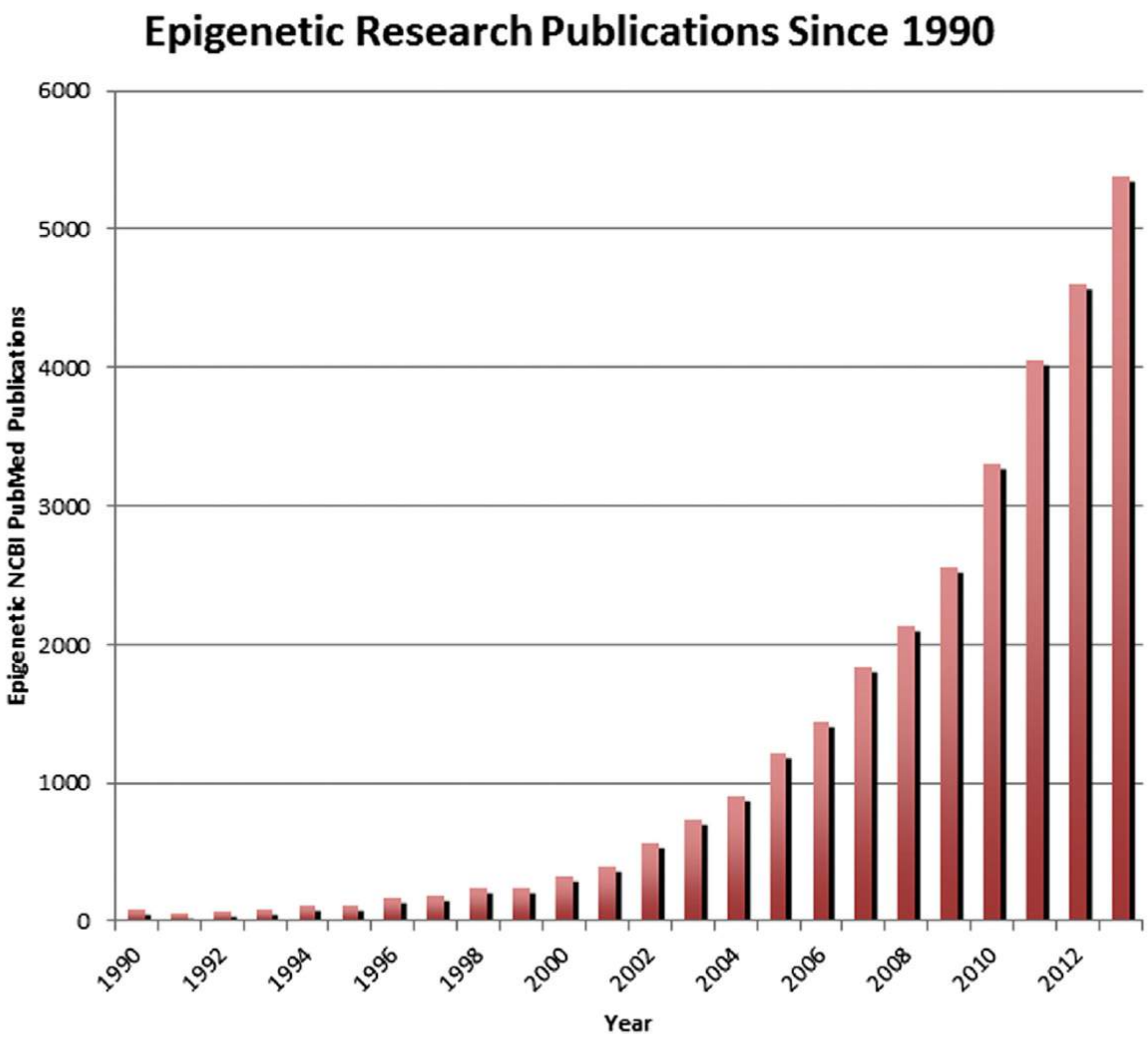


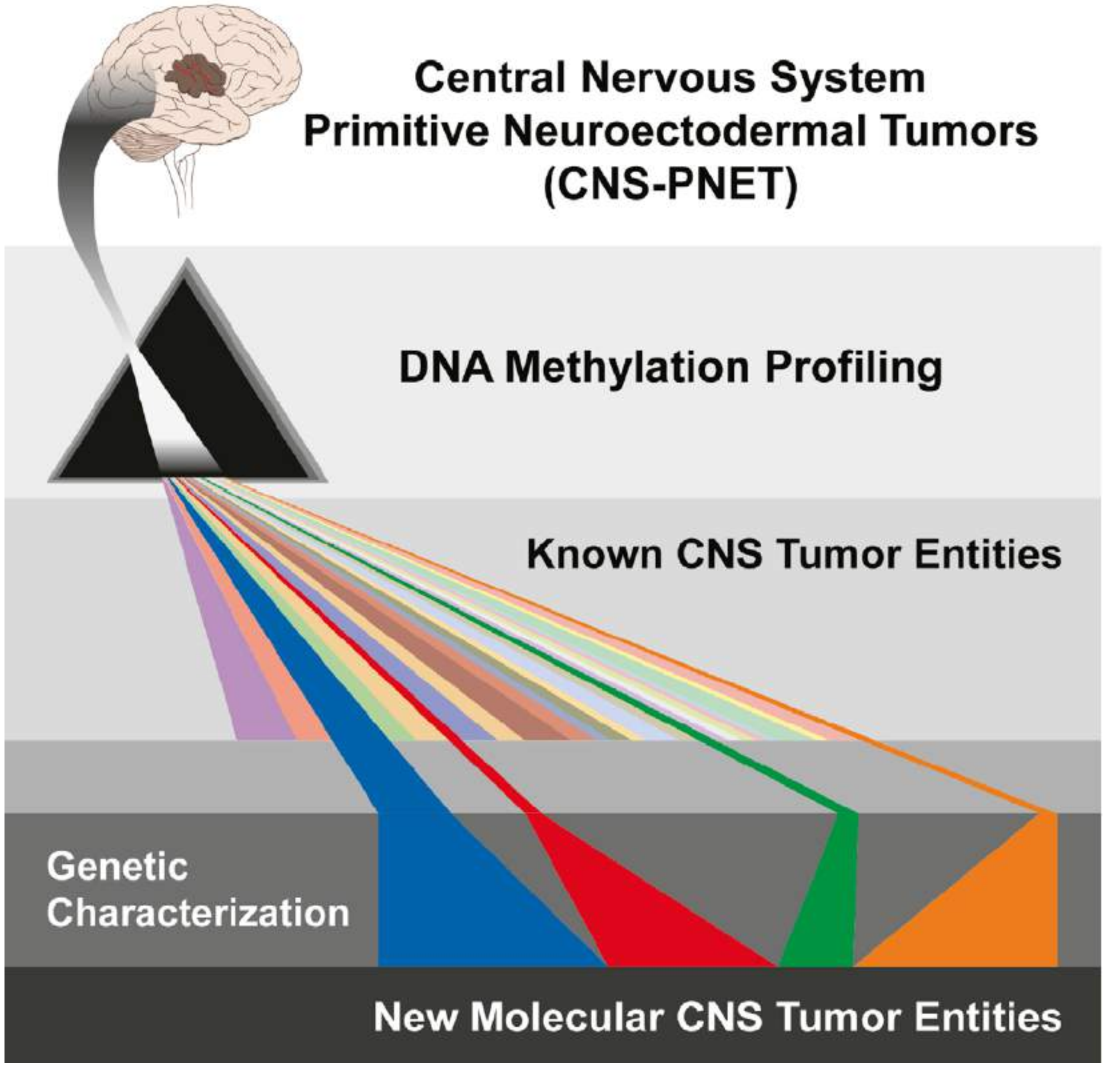
Fig. 1. Growing number of publications in the epigenetics field.

E. Heard, 2016

COLLÈGE DE FRANCE 1530

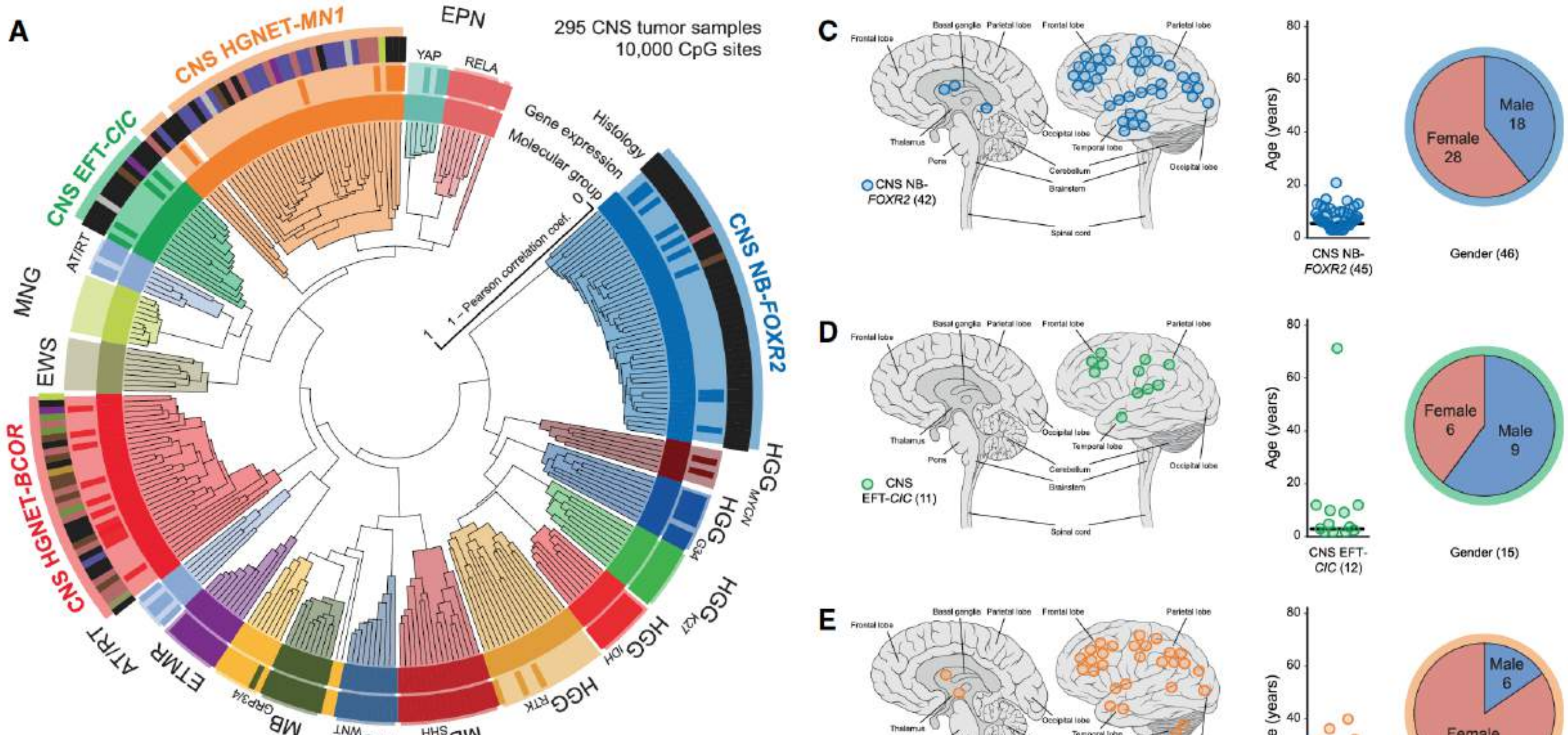
From Cancer Genomes to Epigenomes to Biomarkers

Just one of many recent examples of how epigenomics can help:



Sturm et al., 2016, Cell 164, 1060–1072

From Cancer Genomes to Epigenomes to Biomarkers



Brain tumors can be very challenging to diagnose and distinguish... Molecular profiling means that cancers (eg highly malignant primitive neuroectodermal tumors of the CNS (CNS-PNETs) can be classified.

⇒ **Both known tumor types and several new entities (some linked to epigenetic factors) with distinct histopathological and clinical features, can be identified paving the way for meaningful clinical trials**

Sturm et al., 2016, Cell 164, 1060–1072

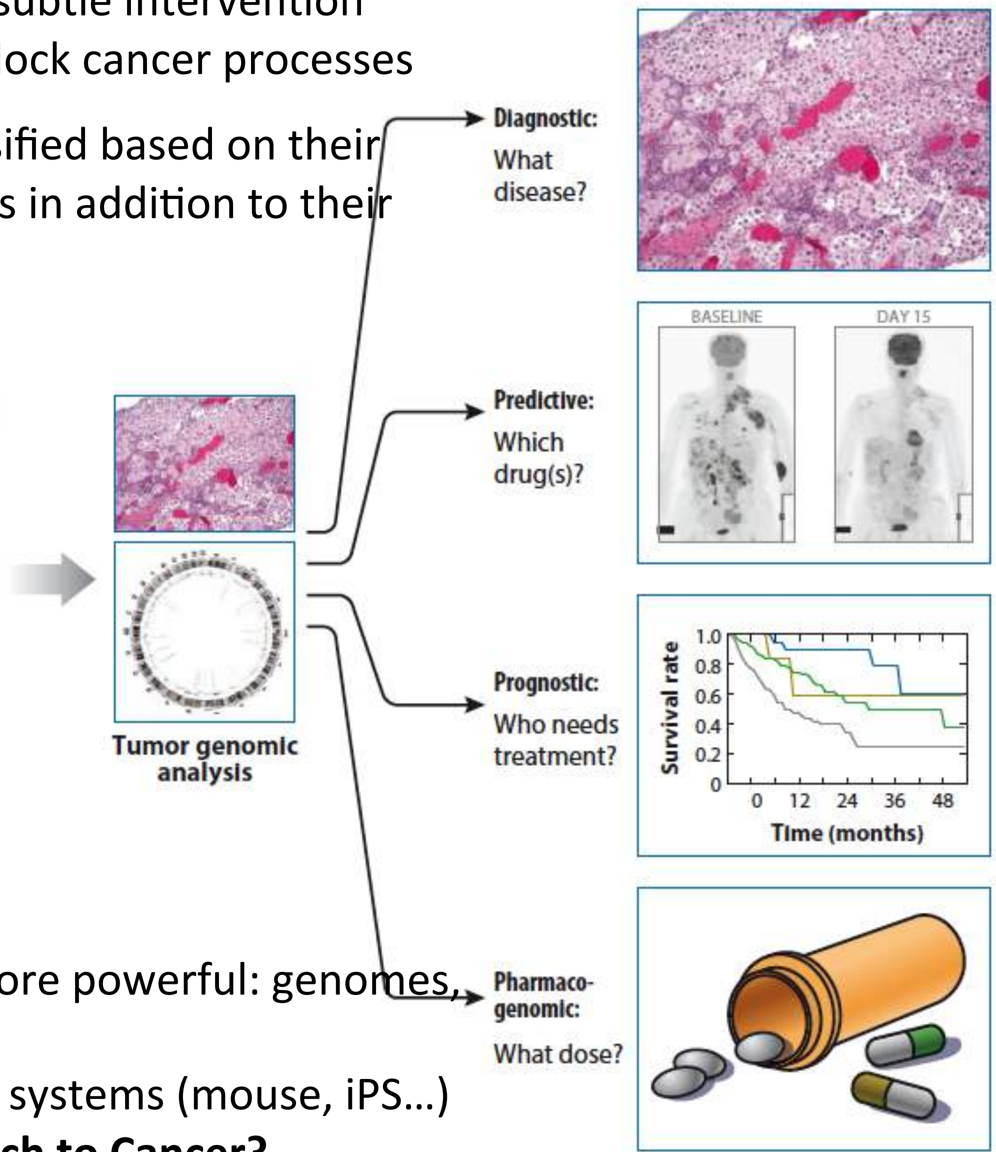
Hopes from Cancer Genomes and Epigenomes

- **Discovery of new pathways / cellular processes in cancer**

- **Therapeutic potential** (targeted therapies) subtle intervention instead of brute force, aiming to disable or block cancer processes

- **Biomarkers:** cancers will eventually be classified based on their molecular (**epigenomic** and **mutation**) profiles in addition to their histologies

TUMOR CLASSIFICATION…
HETEROGENEITY…?
EVOLUTION…?
Important new insights from deep sequencing or single cell sequencing of different regions of tumors and over time



- **Integrated "–omics" information** is even more powerful: genomes, transcriptomes and epigenomes.
- Together with **Functional tests** using model systems (mouse, iPS…)
- **Moving towards a Systems Biology Approach to Cancer?**

Integrating Datasets for Comprehensive Cancer Care

Identify genes and pathways of epigenetic regulators that are putative drivers of tumorigenesis

- Create a patient-specific map for key altered epigenetic components using integrative data analysis
- Combine all patient-specific maps to select the most frequently affected epigenetic regulators

↓

Identify the mechanisms of deregulation of driver epigenetic regulator genes and pathways

Examples of genes inactivated by epigenetics and/or genetics:

Epigenetics: •*DAPK1* •*SFRP1* •*GSTP1*

Epigenetics and Genetics: •*CDKN2A*, •*MLH1* •*BRCA1* •*TCF21*

Genetics: •*ATM* •*TP53*

↓

Identify subgroups or patterns of DNA methylation and/or histone modifications, and the underlying mechanisms

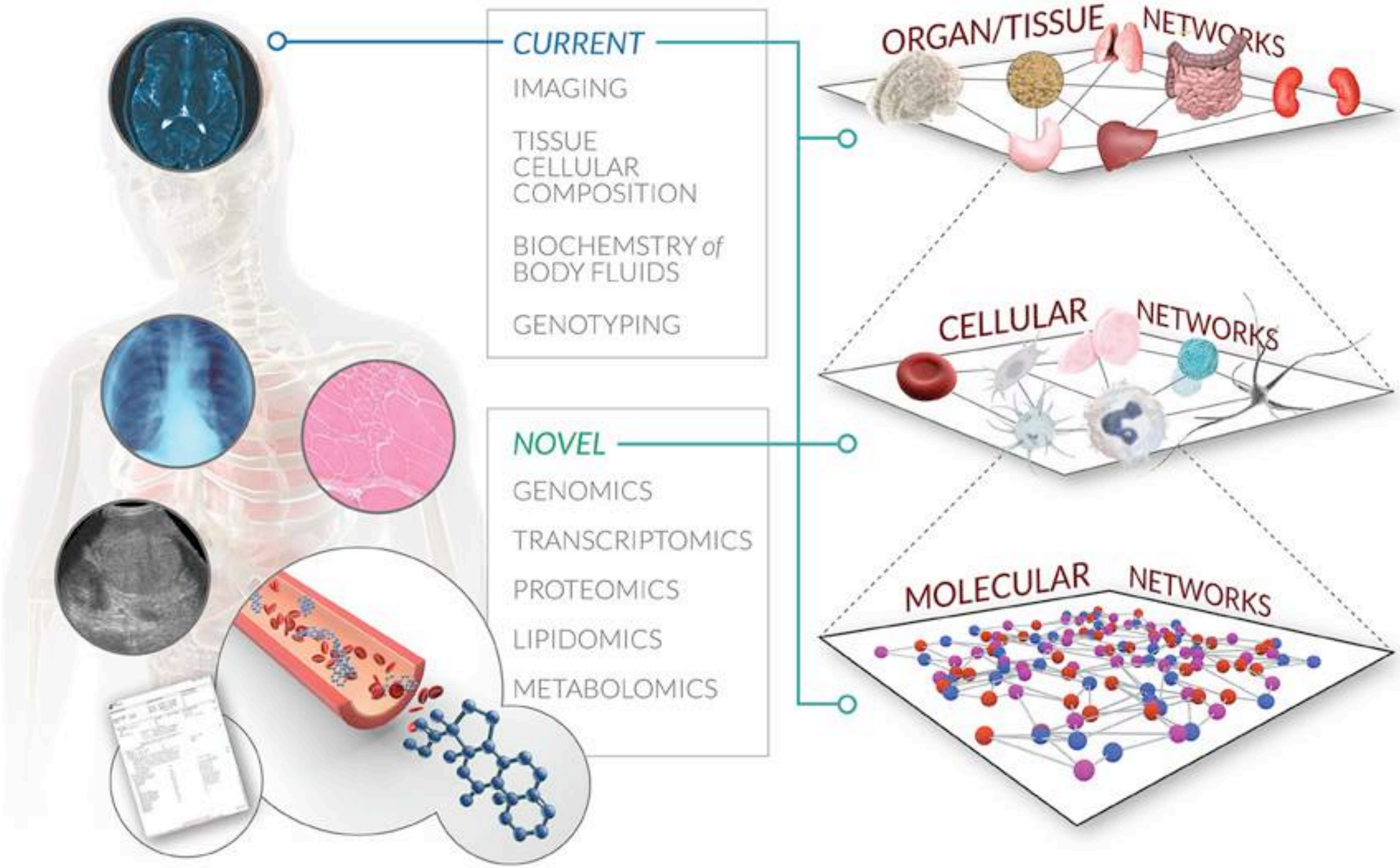
- Cluster analyses of epigenetic data
- Correlation of identified subgroups or patterns with affected driver epigenetic regulator genes and pathways
- Functional studies of epigenetic genes and pathways

↓

- Characterize cancer genes
- Develop molecularly targeted therapies
- Develop biomarkers

Plass et al, Nat. Rev. Genetics, 2013

Systems Biology of Cancer

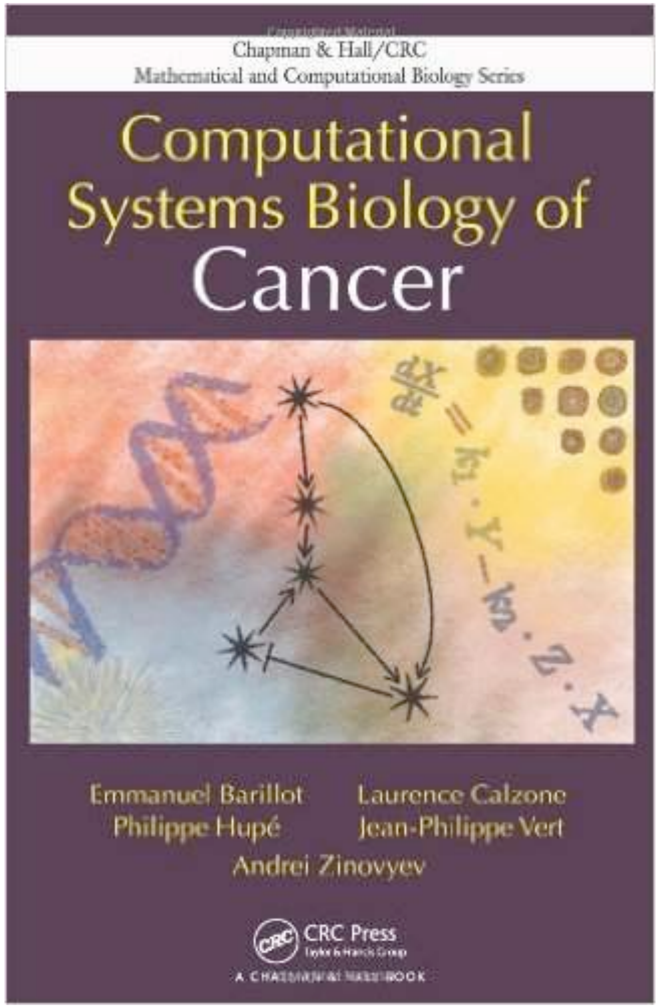


Understanding complex biological systems using computational and mathematical modeling

E. Heard, 2016

COLLÈGE DE FRANCE 1530

Systems Biology of Cancer



Computational Systems Biology of Cancer

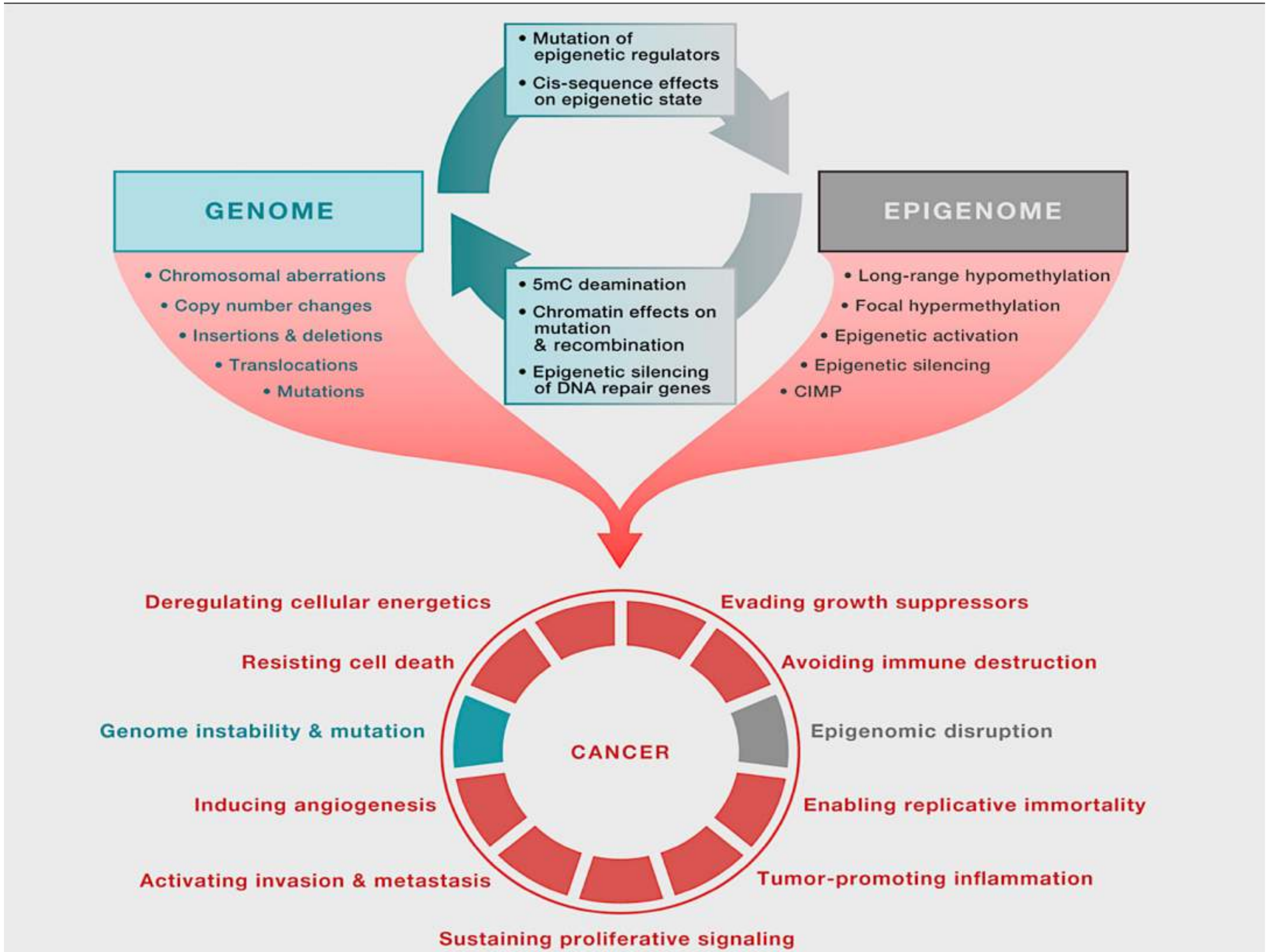
by Emmanuel Barillot, Laurence Calzone, Philippe Hupé, Jean-Philippe Vert and Andrei Zinovyev

An overview of systems biology applied to cancers, from the experimental part over bioinformatics aspects up to dynamical modelling. It covers a large variety of foundations and methods, which are necessary for the understanding of cancer from a computational systems biology angle as cancers are complex and robust dynamical systems.

institutCurie
Together, let's beat cancer.

COLLÈGE DE FRANCE 1530

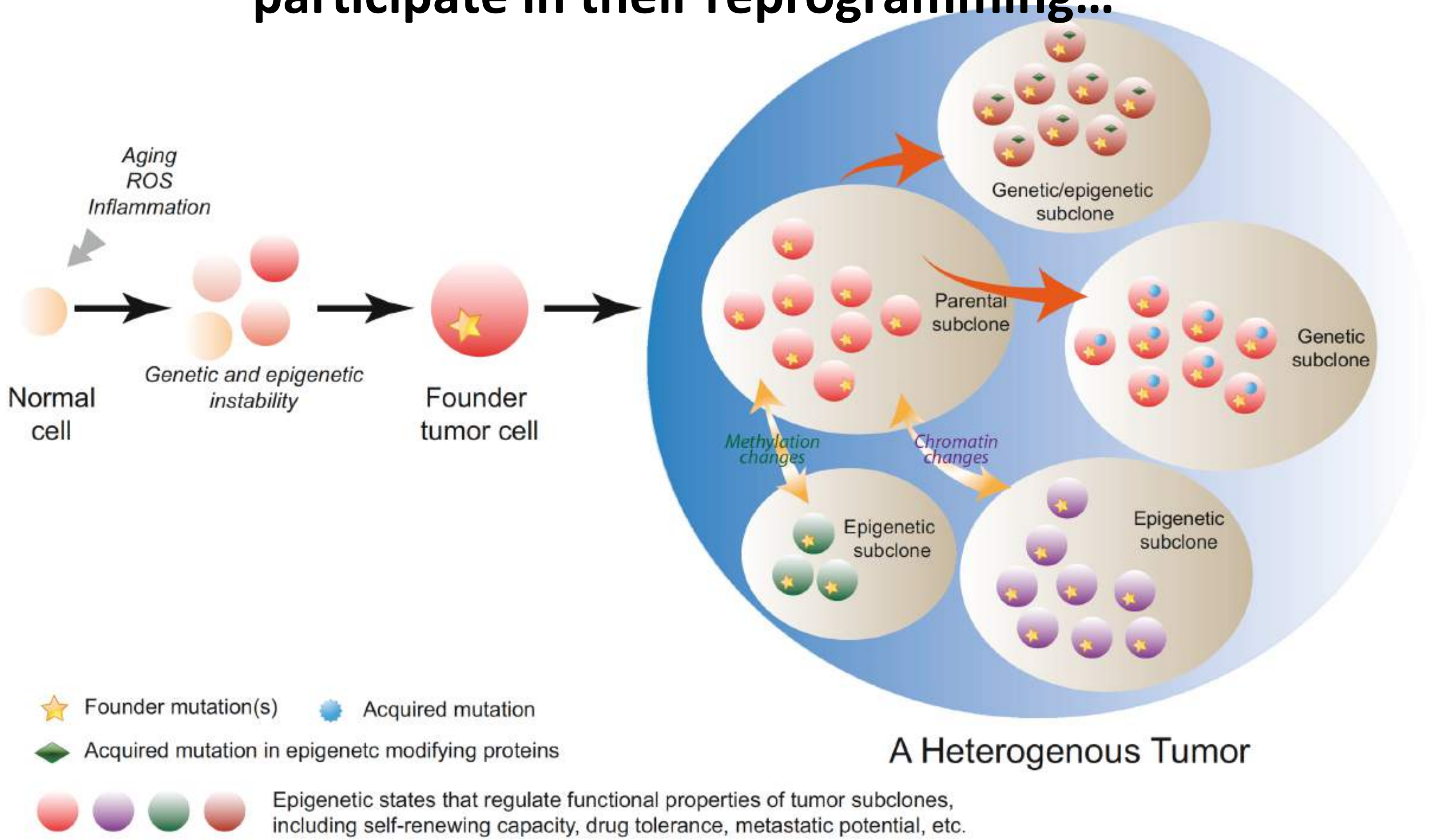
From the Epigenomics to the Epigenetics of Cancer



E. Heard, 2016

Genetic and Epigenetic Changes during Tumor Evolution

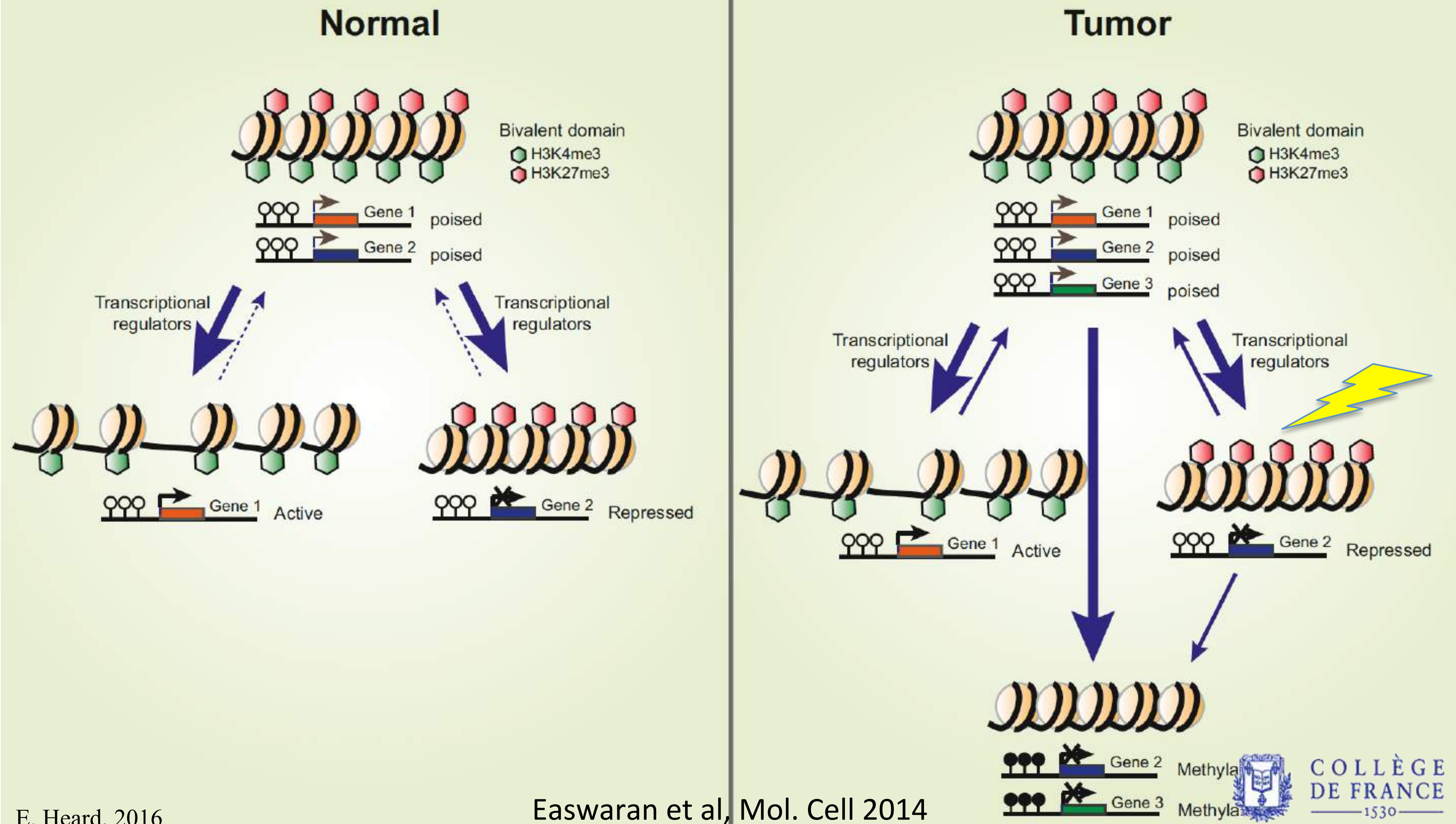
Recurring themes:
epigenetic changes in tumors can impair differentiation,
block cells into a state of self renewal,
participate in their reprogramming…



Easwaran et al, Mol. Cell 2014

Epigenetic Changes in Cancer Cells

Abnormal epigenetic states can help lock in cell states that hinder the ability of cells to exit self renewal and differentiate normally Eg glioblastoma, colon cancer, leukemias – cells retain more primitive stem/ embryonic cell type

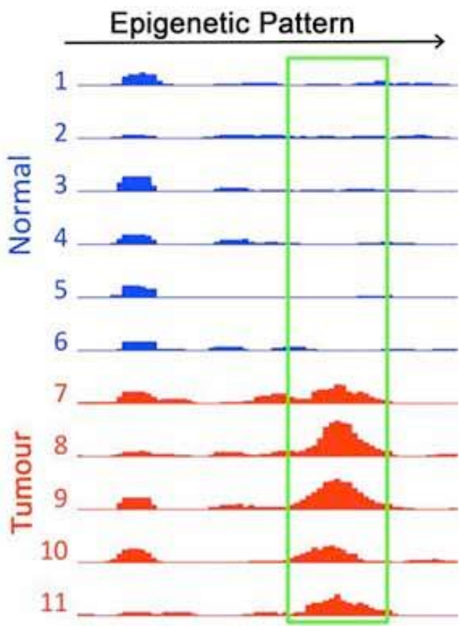


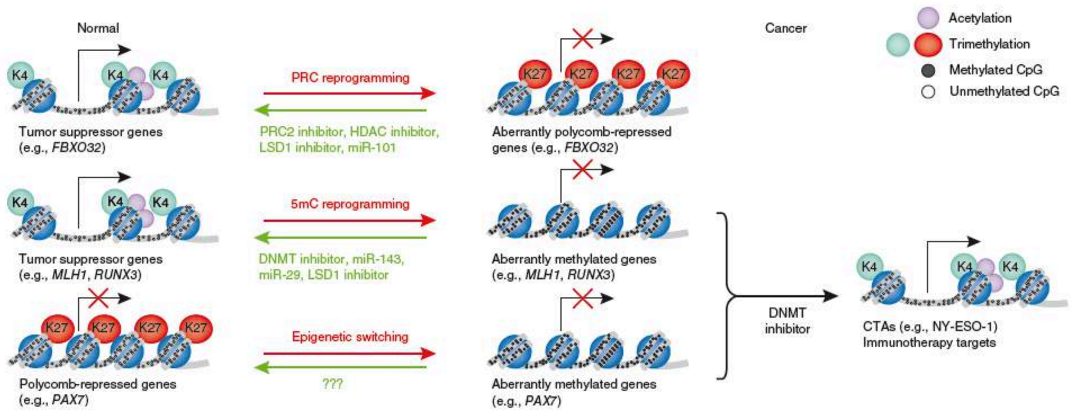
Easwaran et al, Mol. Cell 2014

E. Heard, 2016

Epigenetic therapy: reversal of epigenetic changes

Most new therapies focus on genetic abnormalities.
Cancer genomes has allowed identification of specific driver mutations that can be targeted by simple molecules: this can provide robust initial responses but often has short durability with evolution of resistance





Kelly, Carvalho and Jones, Nat. Biotech. 2010

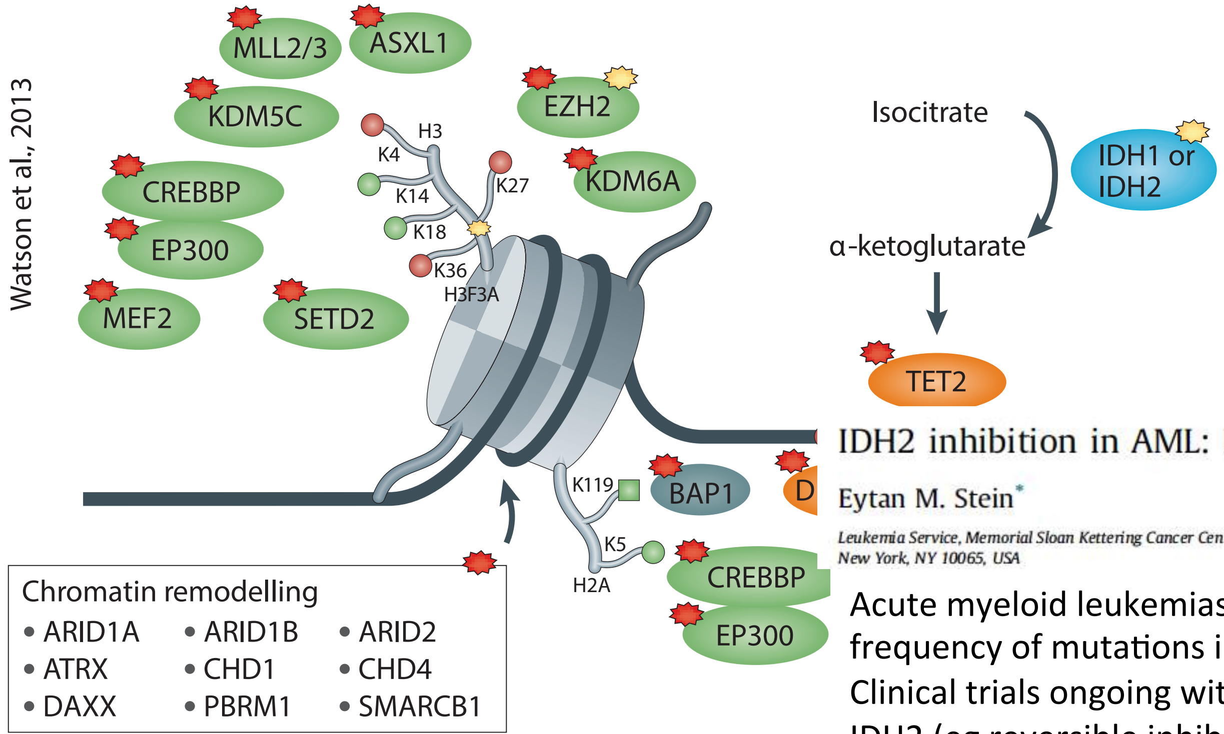
- Epimutations may be induced by stress (replicative stress, inflammation etc)
- Epigenetic states can become aberrantly fixed – blocking tumor cells in self-renewing state
- Epigenetic variation (due to metastable states) within a tumor can generate heterogenity and predispose to cancer progression

E. Heard, 2016

COLLÈGE DE FRANCE 1530

Mutations in Epigenetic Factors

Of the <u>top</u> 58 genes <u>most often mutated</u> in cancers, 16 encode epigenetic factors (writers, readers and erasers…)



IDH2 inhibition in AML: Finally progress?

Eytan M. Stein*

Leukemia Service, Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, 1275 York Avenue, New York, NY 10065, USA

Acute myeloid leukemias (AML) have a high frequency of mutations in R172 and R140. Clinical trials ongoing with inhibitors of mutant IDH2 (eg reversible inhibitor AG-221) and seem promising.

Best Practice & Research Clinical Haematology 28 (2015)

COLLEGE DE FRANCE 1530

E. Heard, 2016

Schapira and colleagues, Epigenetics and Chromatin, 2014.

Epidrugs: reversing/overriding epigenetic states

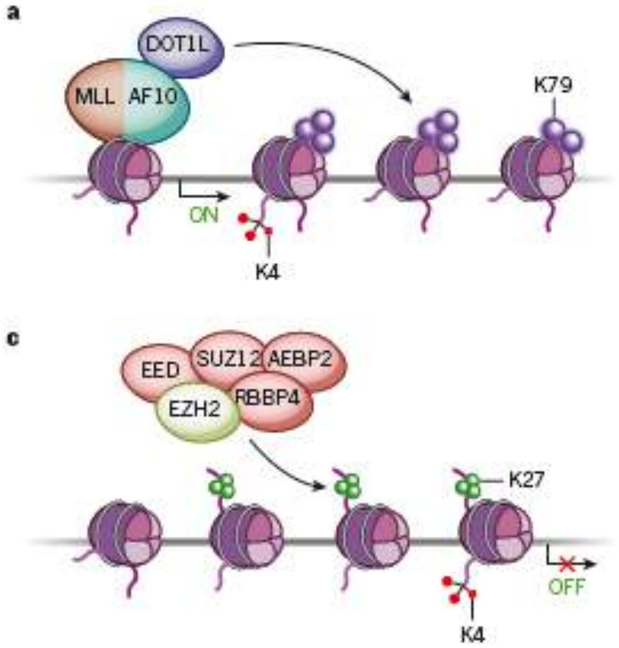


Table 1 | Small molecule inhibitors to chromatin-associated proteins

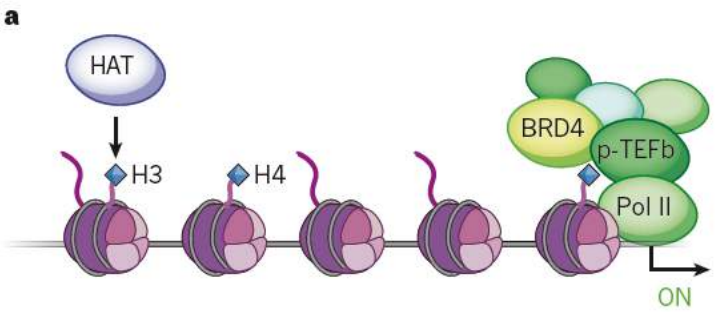
Chromatin-binding protein	Compound
Histone methyltransferases	
DOT1L	EPZ004777 (ref. 21), EPZ-5676 (ref. 24), SGC0946 (ref. 86)
EZH2	GSK126 (ref. 37), GSK343 (refs 87, 88), EPZ005687 (ref. 38), EPZ-6438 (ref. 44), EI1 (ref. 39), UNC1999 (ref. 89)
G9A	BIX01294 (ref. 90), UNC0321 (ref. 91), UNC0638 (ref. 92), NC0642 (ref. 88), BRD4770 (ref. 93)
PRMT3	14u (ref. 94)
PRMT4 (CARM1)	17b (Bristol-Myers Squibb) (refs 95, 96), MethylGene (ref. 97)
Histone demethylases	
LSD1	Tranylcypromine (ref. 62), ORY-1001 (ref. 63)
Bromodomains	
BET	JQ1 (ref. 73), IBET762 (ref. 72), IBET151 (refs 76, 98), PFI-1 (ref. 99)
BAZ2B	GSK2801 (ref. 88)
Chromodomains	
L3MBTL1	UNC669 (ref. 100)
L3MBTL3	UNC1215 (ref. 101)

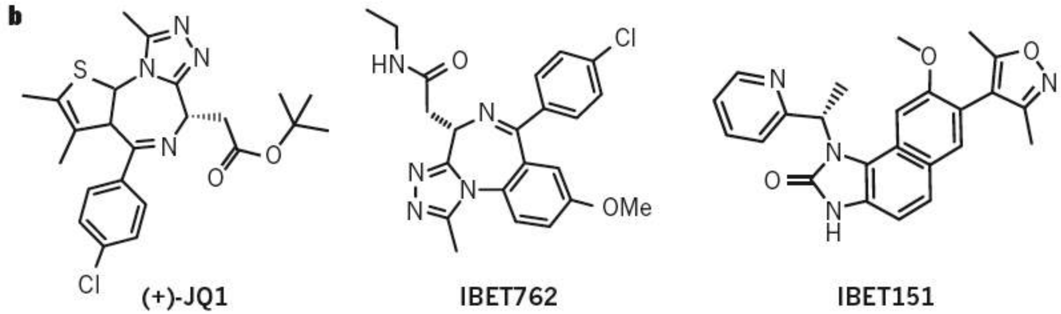
E. Heard, 2016

COLLÈGE DE FRANCE 1530

Epidrugs: reversing/overriding epigenetic states

Bromodomain proteins and their inhibitors.
The bromodomain can bind acetylated lysines, which are associated with actively transcribed promoters.

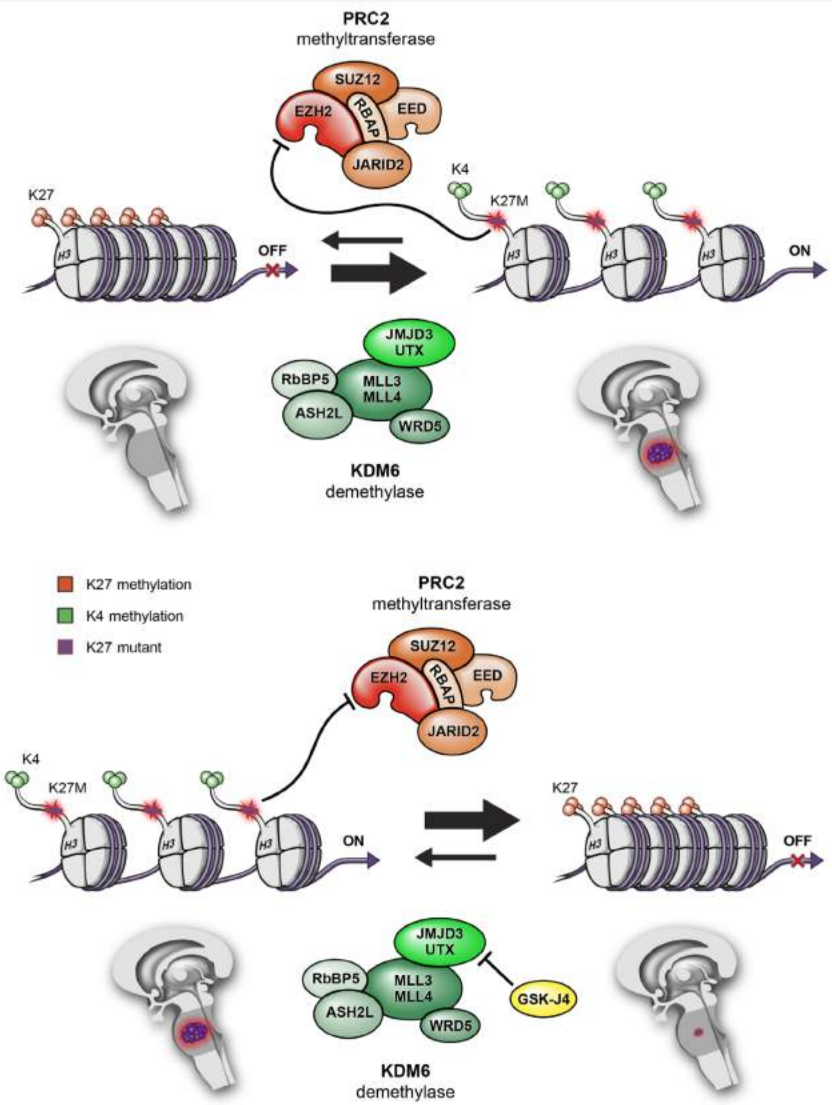




The bromodomain proteins are thought to mediate the initiation and elongation of transcription.

Chemical structures of prototypical bromodomain and extra-terminal (BET) inhibitors. (+)-JQ1, IBET762 and IBET151 bind to all members of the BET sub-family (Brd2, Brd3, Brd4 and BrdT) with similar affinity and regulate the transcription of key oncogenes including the MYC family and BCL2.

Pediatric gliomas with H3.3K27M histone mutations: from mechanisms to therapy?



Pharamcological inhibition of JMJD3 using GSKJ4 in DIPG orthotopic xenografts reduced tumor growth and significantly extended animal survival, and analysis of treated tumors revealed decreased proliferation and increased apoptosis, relative to untreated control tumors.

=> results suggest that GSKJ4 anti- tumor activity is specific to K27M mutant tumors, both in vitro and in vivo, and its antitumor activity occurs in association with increasing K27me2 and K27me3 in tumor cells

Results from high-performance liquid chromatography revealed good penetration of GSKJ4 into the brain, including to the site of brainstem tumor development, following systemic administration of inhibitor, and further support the development of GSKJ4 or other histone demethylase inhibitors as potentially effective targeted therapy for DIPG patients

Application of inhibitor GSKJ4 to T cell acute lymphoblastic leukemia (T-ALL), a hematological malignancy in which H3K27 methylation is reduced by loss-of-function EZH2 mutation, have also shown antitumor activity through use of the JMJD3. As for K27M DIPG, see an accompanying increase in K27M methylation.

=> JMJD3 as an emerging therapeutic epigenetic target for cancer treatment.

Ongoing Clinical Trials: HDAC inhibitors

HDAC inhibitors:

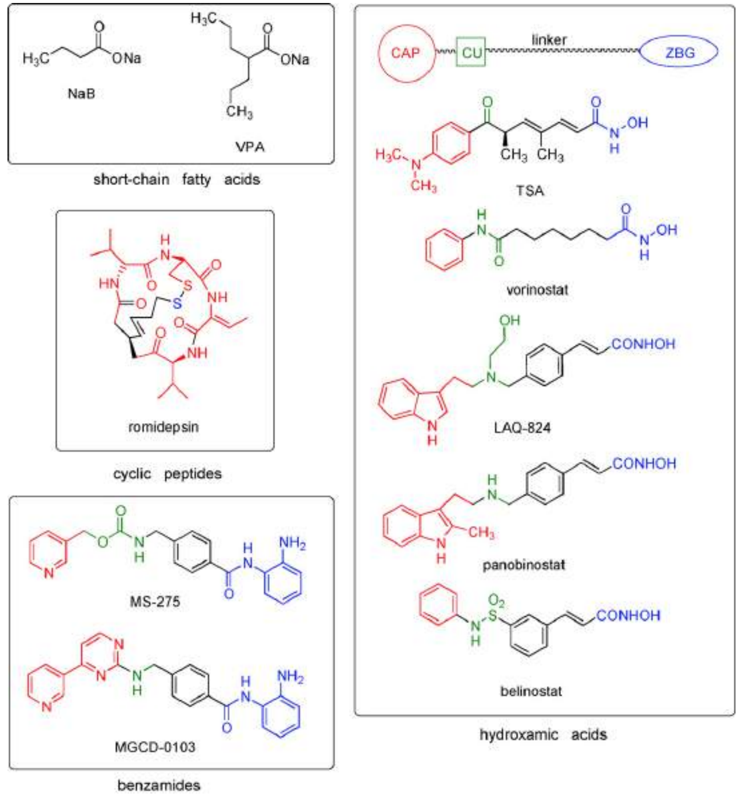
The main biological effects of HDACi are cell cycle arrest, induction of differentiation and promotion of apoptosis (Mai et al., 2005;
Nebbioso et al., 2005).

HDACi can enhance the sensitivity to chemotherapy for cancers and inhibit angiogenesis (Geng et al., 2006;
Qian et al., 2006).

The targets of the HDACs are not always clear – and most HDACs target non-histone proteins

The sources, natures and structures of
known HDACi so far vary greatly, and this has raised the question whether these different HDACi affect tumor occurrence and development through different mechanisms

Despite success on lympomas, one of the major concerns has been toxicity in treatment of solid tumors
- leading to several clinical trials being ended



E. Heard, 2016

Ongoing Clinical Trials HDAC and DNA Me inhibitors

Table 1 Examples of some epigenetic trials in various cancers

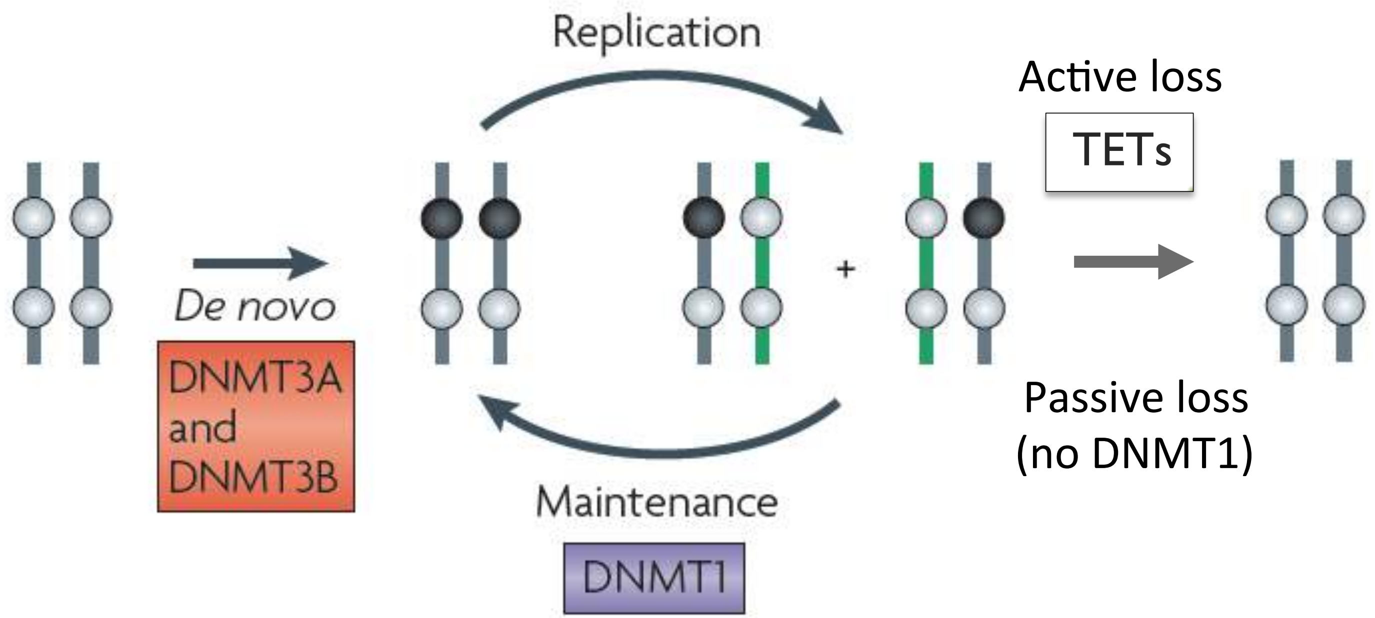
Trial (ClinicalTrials.gov)	Drug	Combination	Target	Study phase	Indication
NCT01034163	Panobinostat (LBH589)	None	Pan-HDAC inhibitor	Phase III	Hodgkin's lymphoma and multiple myeloma
NCT01023308		Bortezomib, dexamethasone	Pan-deacetylase inhibitor	Phase III	Relapsed multiple myeloma
NCT00425555		None		Phase II/III	Cutaneous T cell lymphoma
NCT00866333	Entinostat	None	Class I HDAC	Phase I/II	Hodgkin's lymphoma, kidney cancer
NCT01038778	(SNDX-275)	None	inhibitor	Phase II	Clear cell renal cell carcinoma, metastatic renal cell cancer
NCT01349959		Azacitidine		Phase II	Advanced breast cancer
NCT00357032 (Completed)	Belinostat (PXD101)	None	Pan-HDAC inhibitor	Phase II	Relapsed or refractory acute myeloid leukemia or older patients with newly diagnosed acute myeloid leukemia
NCT01310244		Carboplatin, paclitaxel	HDAC inhibitor	Phase I/II	Non–small cell lung cancer
NCT00274651		None		Phase II	Recurrent or refractory cutaneous and peripheral T cell lymphomas
NCT00301756		None		Phase II	Ovarian cancer
NCT01873703	Pracinostat	Azacitidine	HDAC	Phase II	Myelodysplastic syndrome
NCT01912274	(SB939)	Azacitidine	inhibitor	Phase II	Acute myeloid leukemia
NCT01112384 (Completed)		None		Phase II	Translocation-associated recurrent/metastatic sarcomas
NCT01761968	Givinostat	None	HDAC inhibitor	Phase II	Chronic myeloproliferative neoplasms
NCT01900730	Valproic acid	None	HDAC inhibitor	Phase II	Breast cancer
NCT00477386	Carboplatin	Decitabine	Demethylation	Phase I/II	Platinum-resistant ovarian cancer
NCT00387465	Entinostat	Azacitidine	HDAC inhibitor	Phase I/II	Recurrent advanced non–small cell lung cancer
NCT01105377	Entinostat	Azacitidine	HDAC inhibitor	Phase II	Metastatic colorectal cancer
NCT02115282	Exemestane with or without	Entinostat	HDAC inhibitor	Phase III	Recurrent hormone receptor-positive breast cancer that is locally advanced or metastatic
NCT00091559	Vorinostat	None	HDAC inhibitor	Phase II	Advanced cutaneous T cell lymphoma
NCT00275080	Vorinostat	Decitabine	HDAC inhibitor	Phase I	Advanced solid tumors or relapsed or refractory non-Hodgkin's lymphoma
NCT00071799	Azacitidine	None	Demethylation	Phase III	High-risk myelodysplastic syndromes comparing azacitidine versus conventional care
NCT00007345	Romidepsin	None	HDAC inhibitor	Phase II	Cutaneous T cell lymphoma and peripheral T cell lymphoma

Abbreviation: HDAC, histone deacetylase.

E. Heard, 2016

COLLÈGE DE FRANCE 1530

DNA Methyltransferases: Orchestrators of DNA Methylation

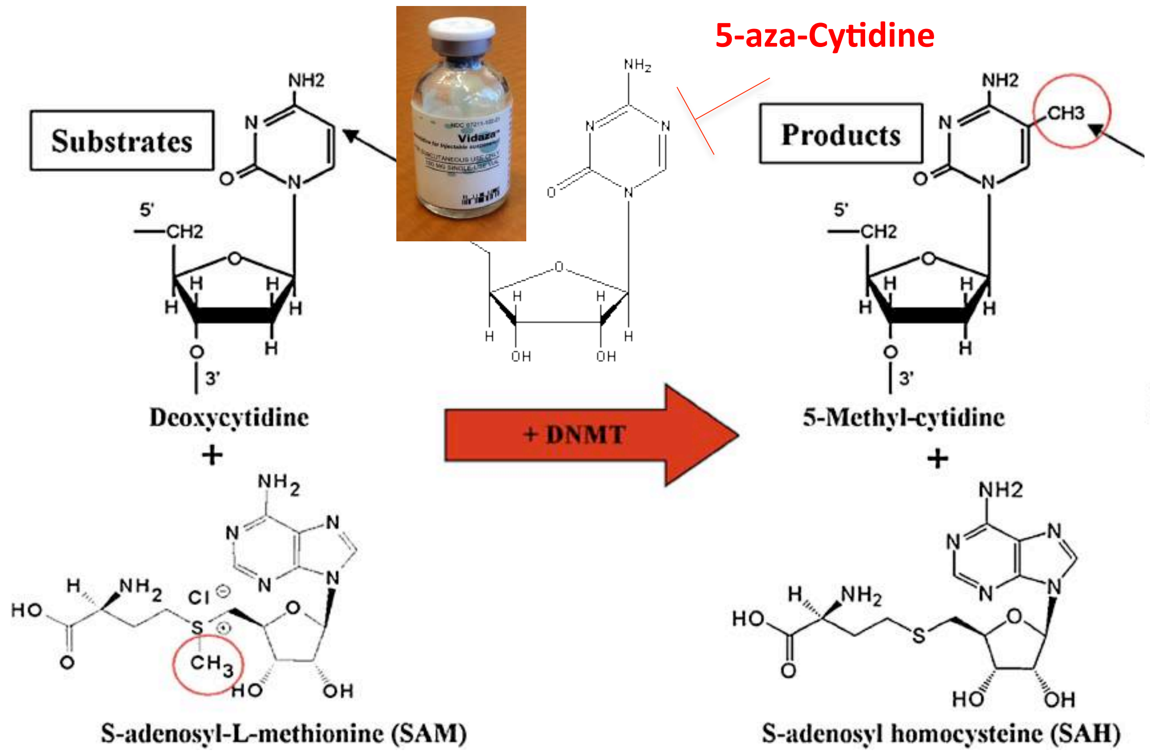


Jones P.A. *et. al.* 2009. *Nat Rev Genet.*

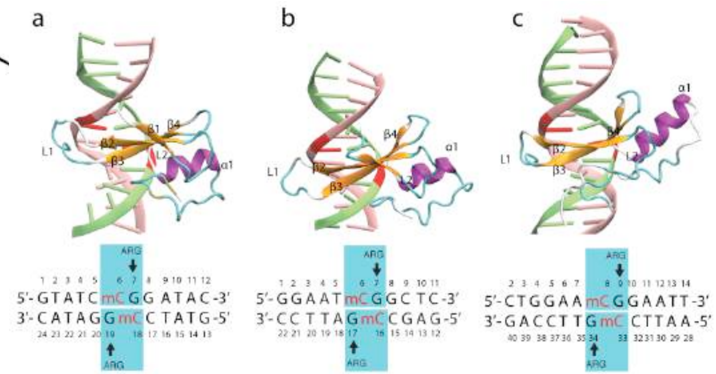
- **DNMT1 preferentially methylates hemimethylated DNA**
- **DNMT3A/3B *de novo* methylate both unmethylated and hemimethylated DNA**
- **DNMT3L stimulates DNMT3A/3B activity in ES cells**
- **TET enzymes result in loss of 5mC through oxidation to 5-hydroxy methylation**
- **DNA methylation can be passively lost in absence of DNMT1 or actively lost via TETs**
- **5-Aza-cytidine can also lead to 'passive' loss of DNA methylation**

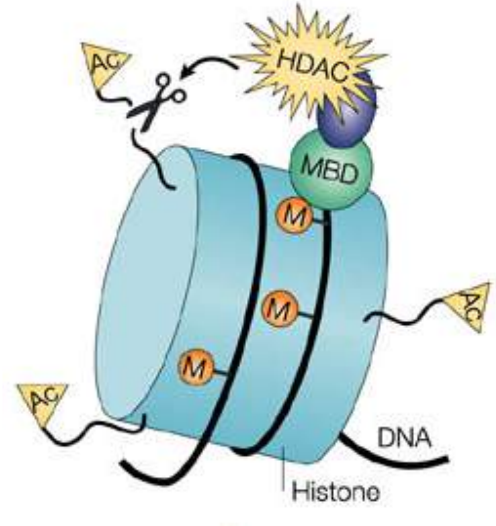
DNA Methyltransferases: Orchestrators of DNA Methylation

Therapy: inhibitors



Methyl Binding Domain (MBD) proteins ("Readers") orchestrate cytosine methylation functions in gene expression, DNA replication, repair…

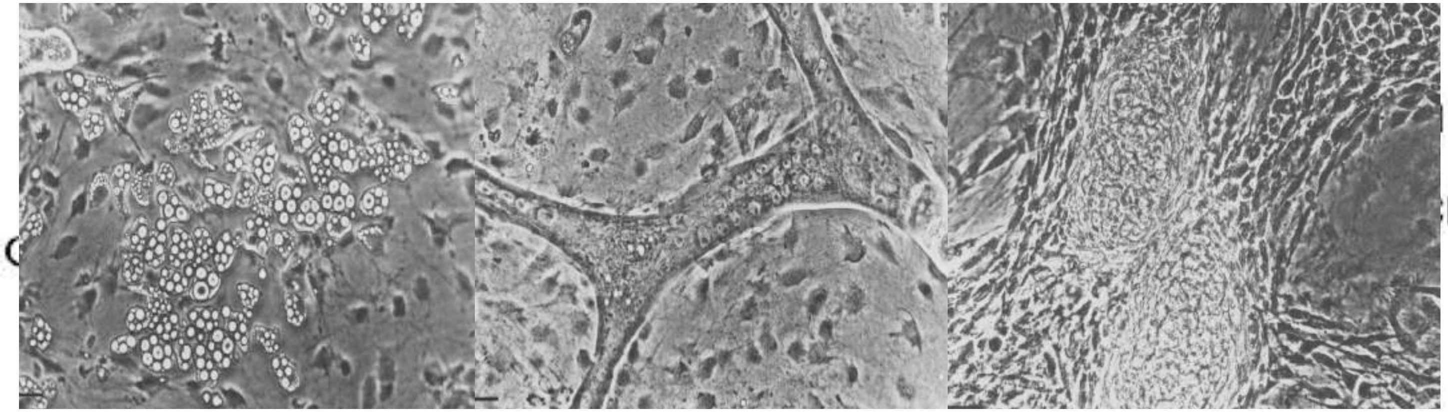




Nutrition can influence the availability of methyl-donors to a cell

E. Heard,

Inhibition of DNA Methylation could affect gene expression



Phenotypes Induced in 1 OT: Cultures after Treatment with 5-aza-CR
(a) Adipocytes (4 weeks after treatment); (b) myotubes (2 weeks after treatment); (c) chondrocytes (5 weeks after treatment). *Taylor and Jones, 1979.*

Advent of the DNA methylation inhibitor 5-azacytidine (Jones, 1984), one of the first drugs to be used to treat cancer

Data on cultured mammalian cells showed that gene expression could be affected by methylation, and loss of DNA methylation could lead to gene reactivation and a change in cell identity

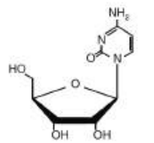
⇒ The inactive expression state of a gene could be stably maintained by DNA methylation (Razin and Riggs,1980; Lock et al., 1987)

⇒ Robin Holliday went on to propose in 1987, that aberrant DNA methylation could sometimes lead to ***epimutations***, or event ***mutations***, for example in cancer…

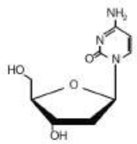
E.

DNA Methylation Inhibitors

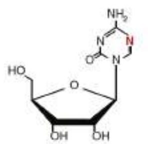
5-AzaC first tested in the 1960's as a chemical to treat cancer but was highly toxic. Its potential for reversing epigenetic alterations was discovered in the 1970's in cultured cells – but clinical application only came later



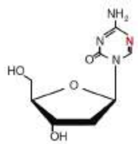
Nucleoside: Cytidine



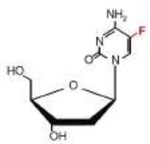
Nucleoside: Deoxcytidine



Cytidine Analog: 5-Azacytidine



Deoxcytidine Analog: Decitabine

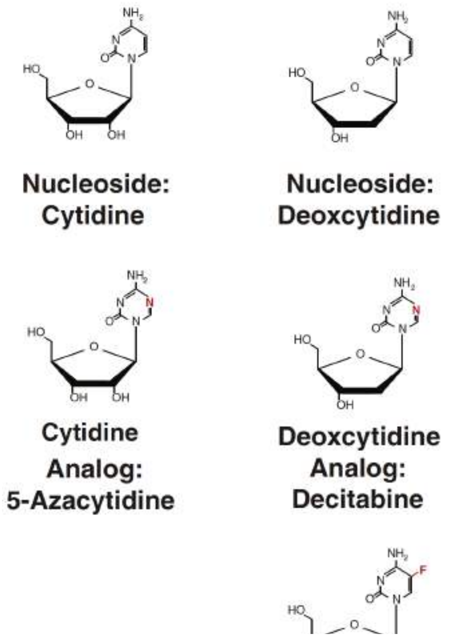


Deoxcytidine Analog: 5–Fluoro–2–Deoxycytidine

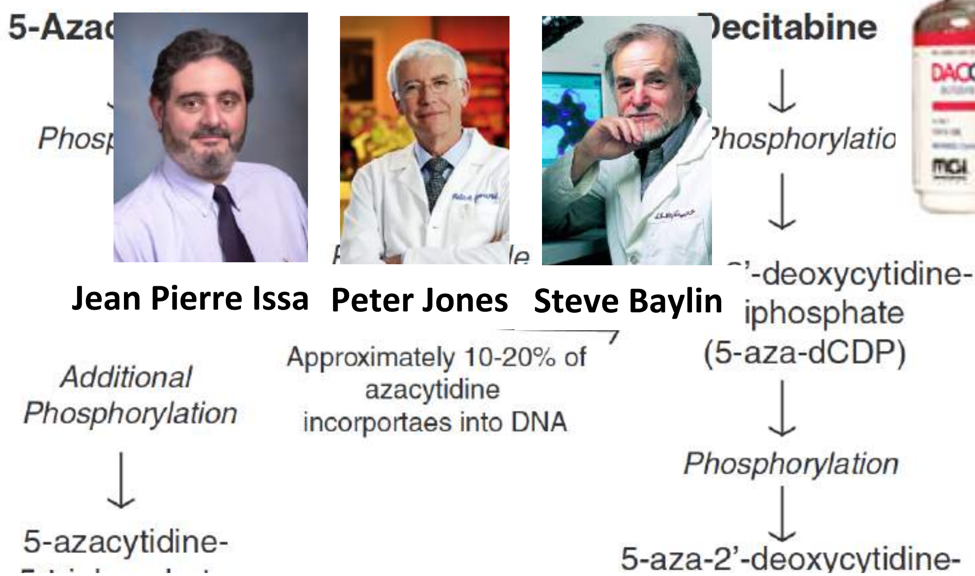
During DNA synthesis, azacytosine can substitute for cytosine – the DNA Methylatransferase enzyme recognizes the nucleotie and initiates the methylation process but remains covalently bound to DNA and its DNA methyltransferase function is blocked.

DNA Methylation Inhibitors

5-AzaC first tested in the 1960's as a chemical to treat cancer but was highly toxic. Its potential for reversing epigenetic alterations was discovered in the 1970's in cultured cells – but clinical application only came later



Some key players:



Azacitidine (trade name **Vidaza**) a chemical analog of cytidine, a nucleoside present in DNA and RNA. Azacitidine and its deoxy derivative, decitabine (5-aza-2'deoxycytidine), are FDA-approved and used in the treatment of myelodysplastic syndrome. Both drugs were first synthesized in Czechoslovakia as potential chemotherapeutic agents for cancer.

Cihák A (1974). "Biological effects of 5-azacytidine in eukaryotes". Oncology **30** (5): 405–422

DNA Methylation Inhibitors

Only in the 1990s were these drugs used in hematologic malignancies, particularly for myelodysplasticsyndrome (MDS) (Decitabine)
Efficiency in the clinic due to lowered dose – improving patient tolerance (& also specificity?)

Randomized Controlled Trial of Azacitidine in Patients With the Myelodysplastic Syndrome: A Study of the Cancer and Leukemia Group B

By Lewis R. Silverman, Erin P. Demakos, Bercedis L. Peterson, Alice B. Kornblith, Jimmie C. Holland, Rosalie Odchimar-Reissig, Richard M. Stone, Douglas Nelson, Bayard L. Powell, Carlos M. DeCastro, John Ellerton, Richard A. Larson, Charles A. Schiffer, and James F. Holland

Purpose: Patients with high-risk myelodysplastic syndrome (MDS) have high mortality from bone marrow failure or transformation to acute leukemia. Supportive care is standard therapy. We previously reported that azacitidine (Aza C) was active in patients with high-risk MDS.

Patients and Methods: A randomized controlled trial was undertaken in 191 patients with MDS to compare Aza C (75 mg/m²/d subcutaneously for 7 days every 28 days) with supportive care. MDS was defined by French-American-British criteria. New rigorous response criteria were applied. Both arms received transfusions and antibiotics as required. Patients in the supportive care arm whose disease worsened were permitted to cross over to Aza C.

Results: Responses occurred in 60% of patients on the Aza C arm (7% complete response, 16% partial response, 37% improved) compared with 5% (improved) receiving supportive care ($P < .001$). Median time to leukemic transformation or death was 21 months for Aza C versus 13 months for supportive care ($P = .007$). Transformation to acute myelogenous leukemia occurred as the first event in 15% of patients on the Aza C arm and in 38% receiving supportive care ($P = .001$). Eliminating the confounding effect of early cross-over to Aza C, a landmark analysis after 6 months showed median survival of an additional 18 months for Aza C and 11 months for supportive care ($P = .03$). Quality-of-life assessment found significant major advantages in physical function, symptoms, and psychological state for patients initially randomized to Aza C.

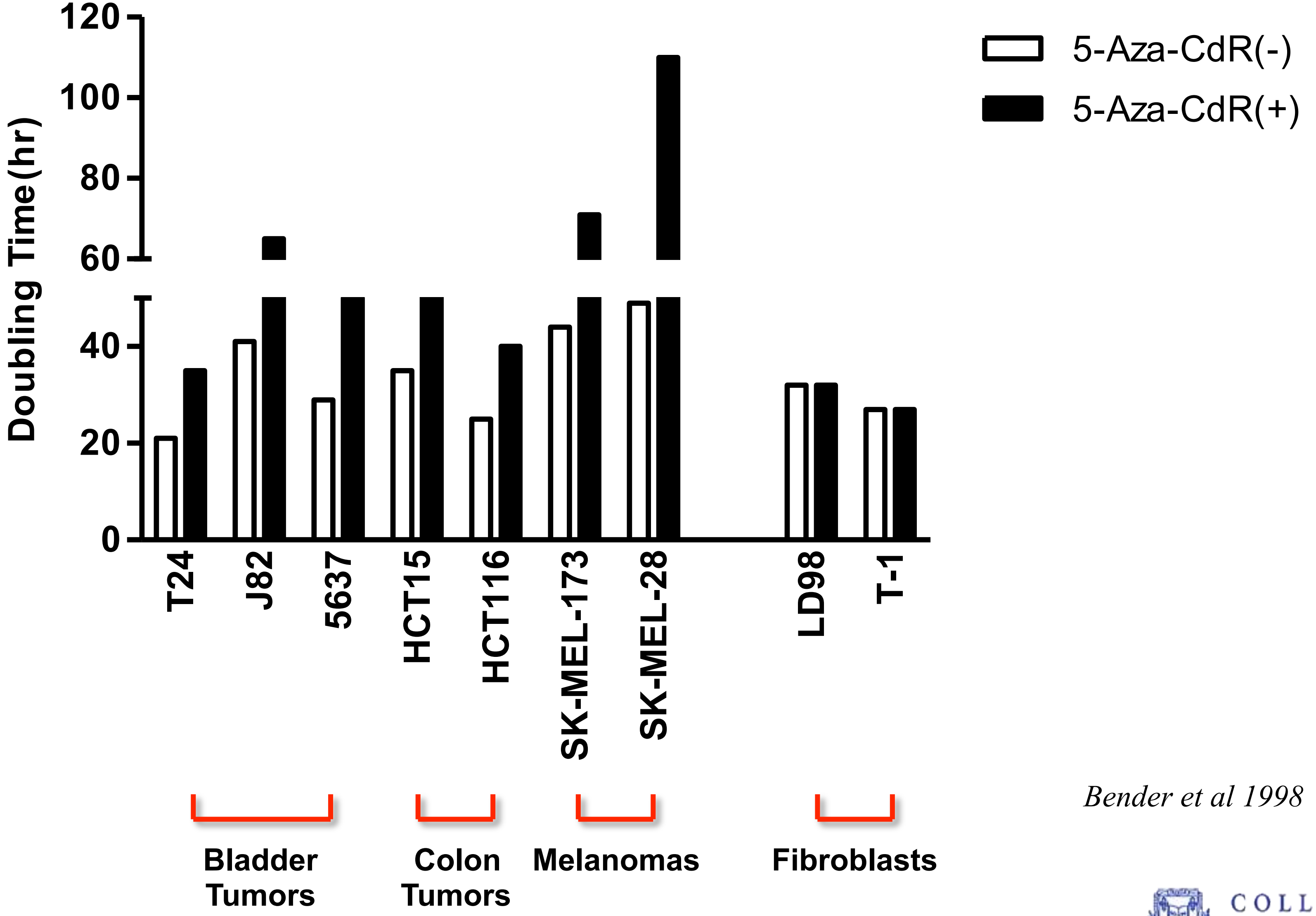
Conclusion: Aza C treatment results in significantly higher response rates, improved quality of life, reduced risk of leukemic transformation, and improved survival compared with supportive care. Aza C provides a new treatment option that is superior to supportive care for patients with the MDS subtypes and specific entry criteria treated in this study.

J Clin Oncol 20:2429-2440.

E. Heard, 2016

COLLÈGE DE FRANCE 1530

Selectivity of 5-Aza-CdR (50 nM) Ten Days After treatment



Bender et al 1998

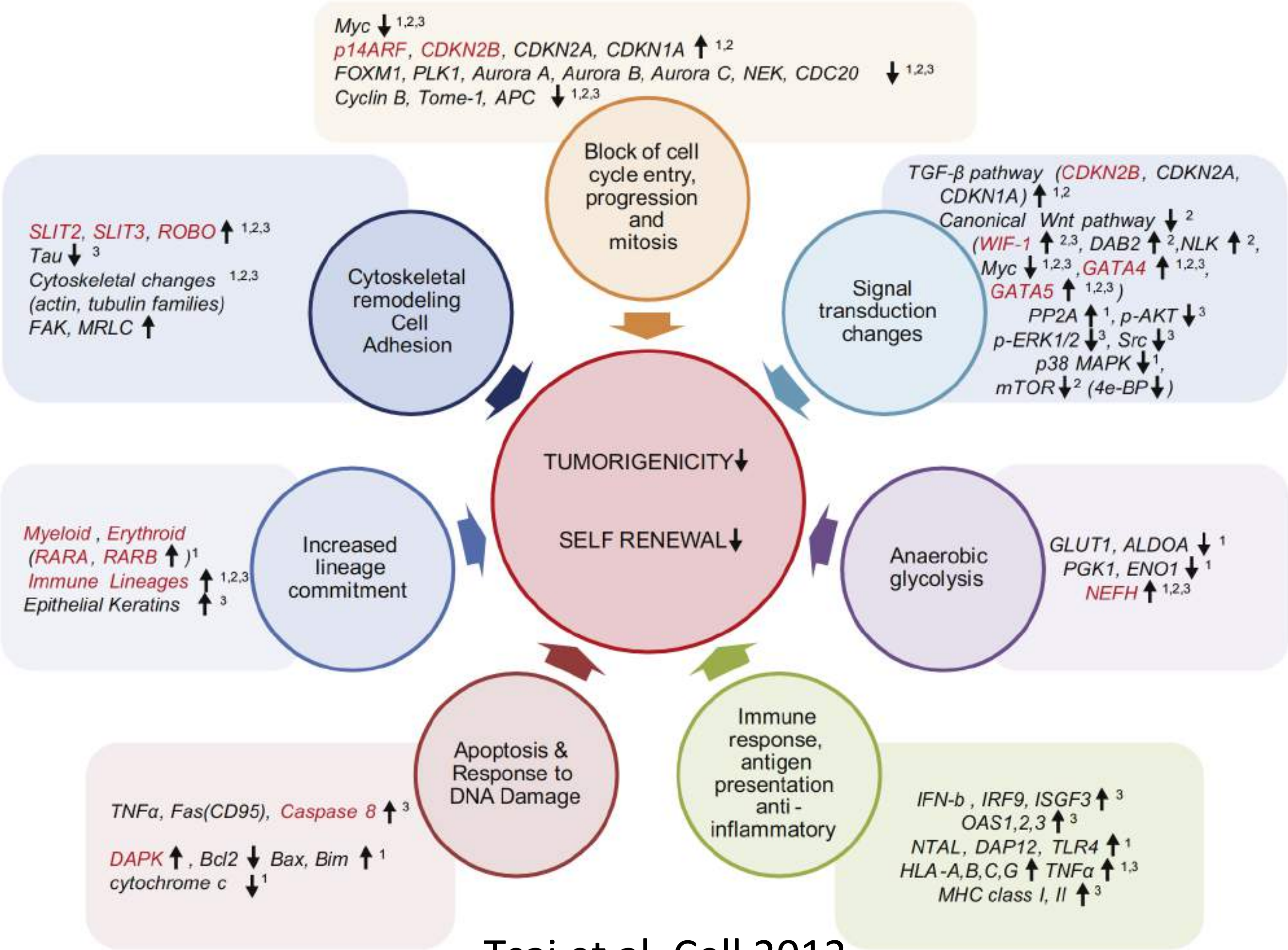
Courtesy of Peter Jones

E. Heard, 2016

COLLÈGE DE FRANCE 1530

Transient, low-dose DAC decreases Tumorigenicity of Leukemia cells with minimal Acute DNA Damage, Cell Cycle changes or Apoptosis

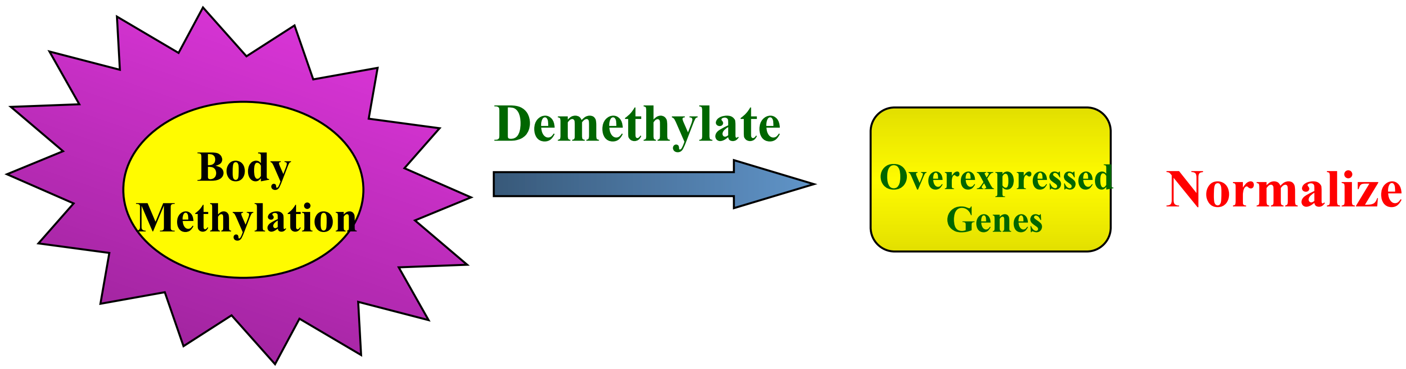
Demethylating agents are potent anti-cancer drug for leukemias
Less successful (used alone) in solid tumors
Their method of action remained mysterious until recently…



Tsai et al, Cell 2012

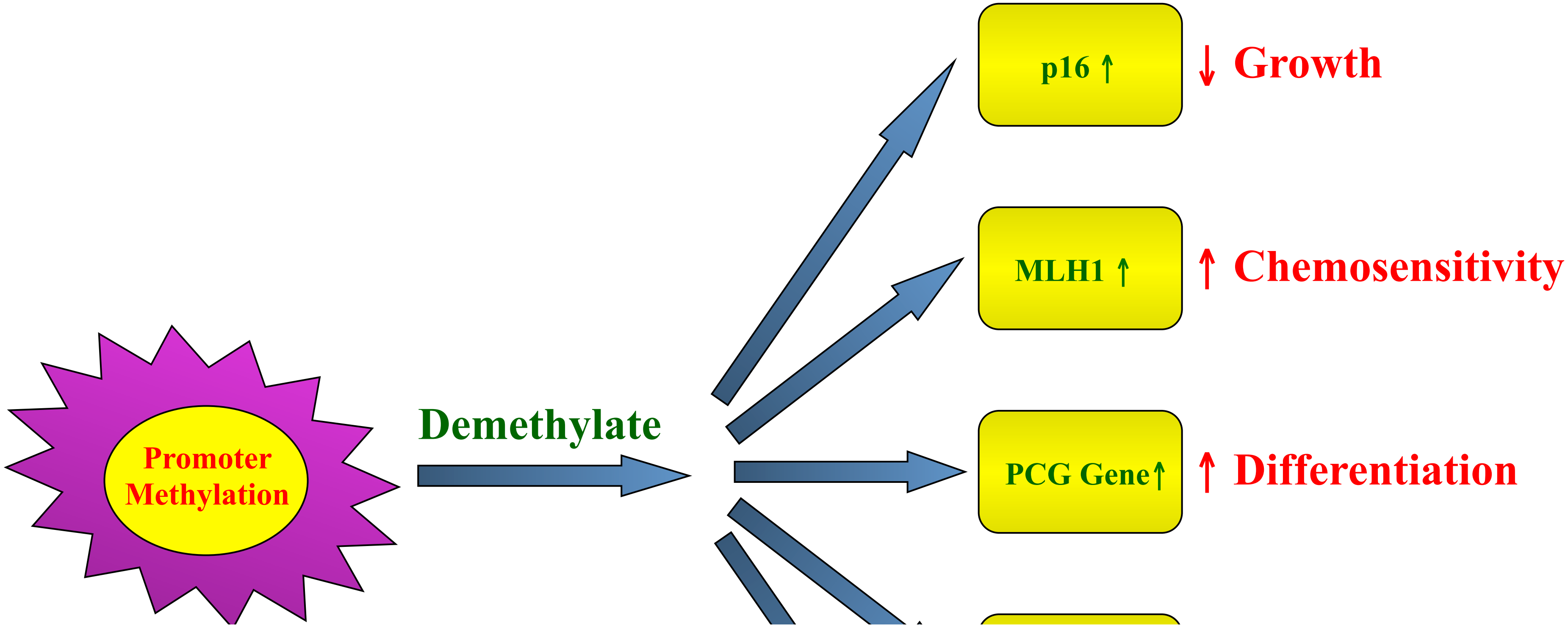
E. Heard, 2016

Multiple Pathways are Misregulated by Epigenetic Therapy



Courtesy of Peter Jones

Multiple Pathways are Misregulated by Epigenetic Therapy



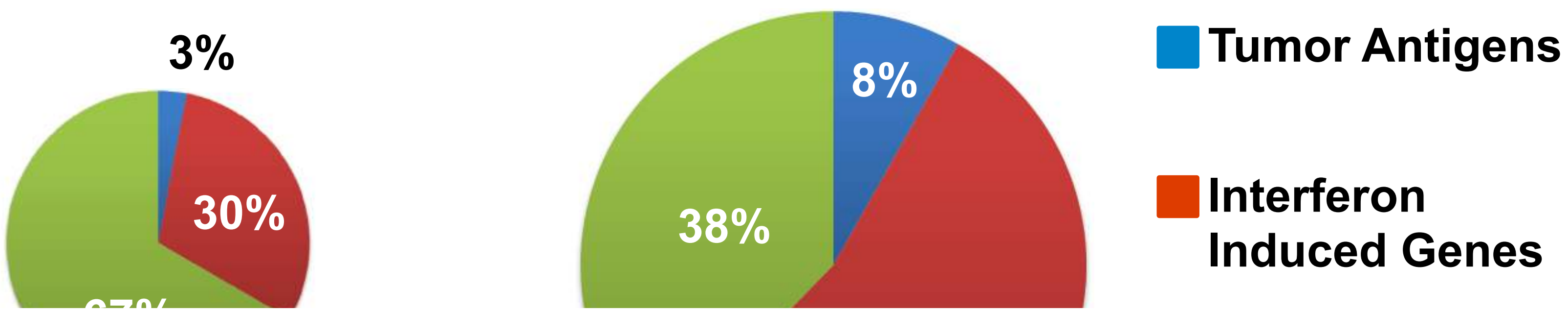
Low dose AZA or DEC treatment show slow onset, and induce long lasting decrease in self renewal and tumorigenicity *without* cytotoxicity or changes in cell cycle, as would have been predicted by reactivation of tumor suppressors.

⇒ What <u>are</u> the key genes that are reactivated, that predict or mediate the response???

E. H

Genes Induced (> 4 fold) by 5-Aza-CdR after 8 days

- **AZA can demethylate and activate genes encoding MHC class I genes and tumor antigen genes (Karpf et al., 1999, 2004).**
- **Interferon pathway genes are also upregulated by AZA, and this correlates with increased expression of endogenous retroviral transcripts rather than de-repression of interferon pathway transcription factors**
- **The most common set of genes induced by AZA in solid tumor cell lines are those involved in antigen presentation and interferon response (Li et al., 2014).**



- **Patients who had previously received AZA for lung cancer subsequently had a highly efficient response to <u>immune checkpoint inhibitors</u> (Wrangle et al., 2013).**

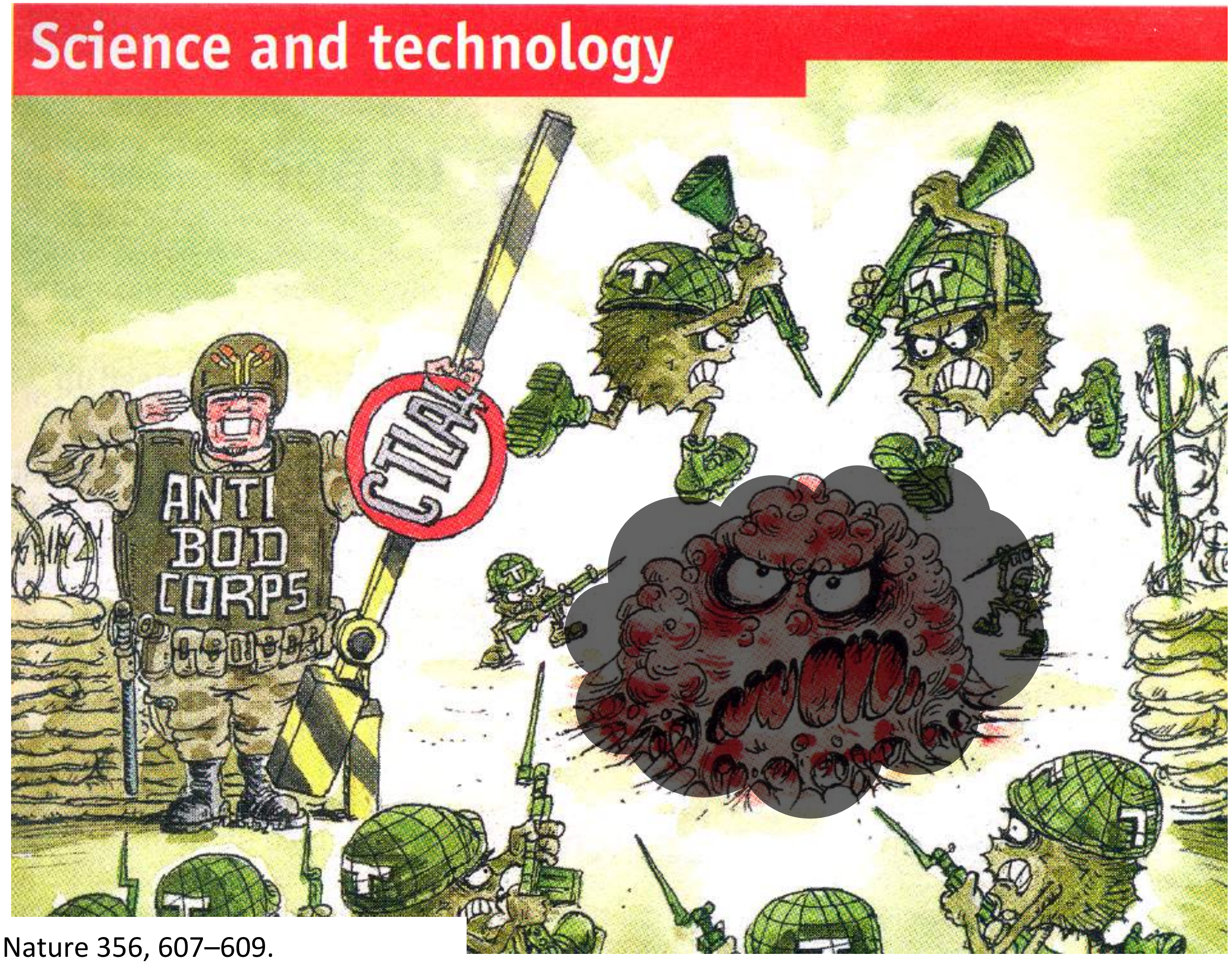
N= 61

Liang et al, Cancer Res. 2002

Courtesy of Peter Jones

Immunotherapy and immune checkpoint inhibitors

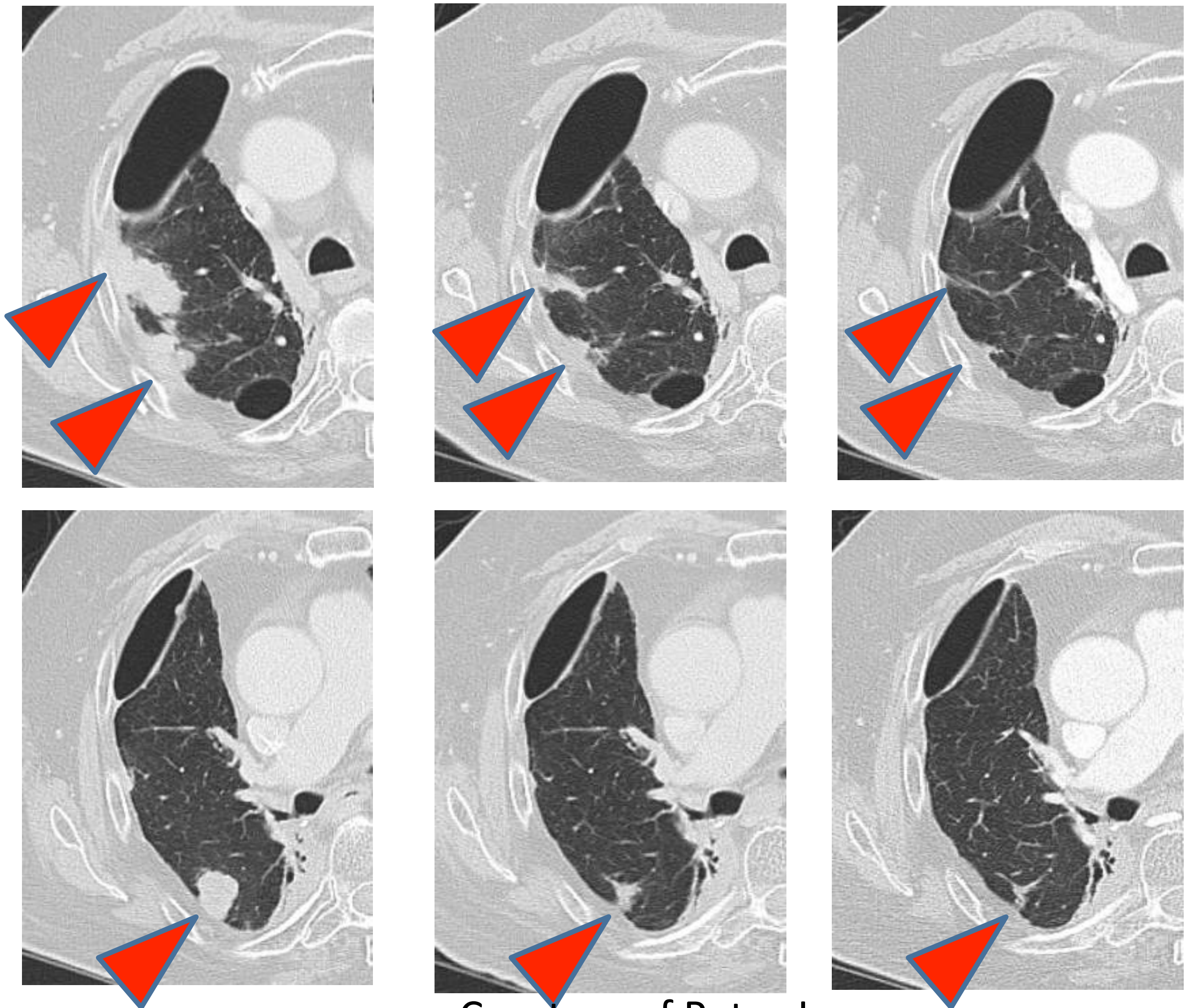
Switching off CTLA-4 T-cell receptors on tumor cells helps to shut off the immune checkpoint, exposing tumors antigens to immune system!



The Economist June 8th, 2013

Harding et al (1992). Nature 356, 607–609.
Hodi et al. (2010). N. Engl. J. Med. 363, 711–723.
Topalian (2012). N. Engl. J. Med. 366, 2443–2454.

Response of a "non-immunogenic" tumor to anti-PD-1: Stage IV Non-Small Cell Lung Cancer with prior epigenetic therapy

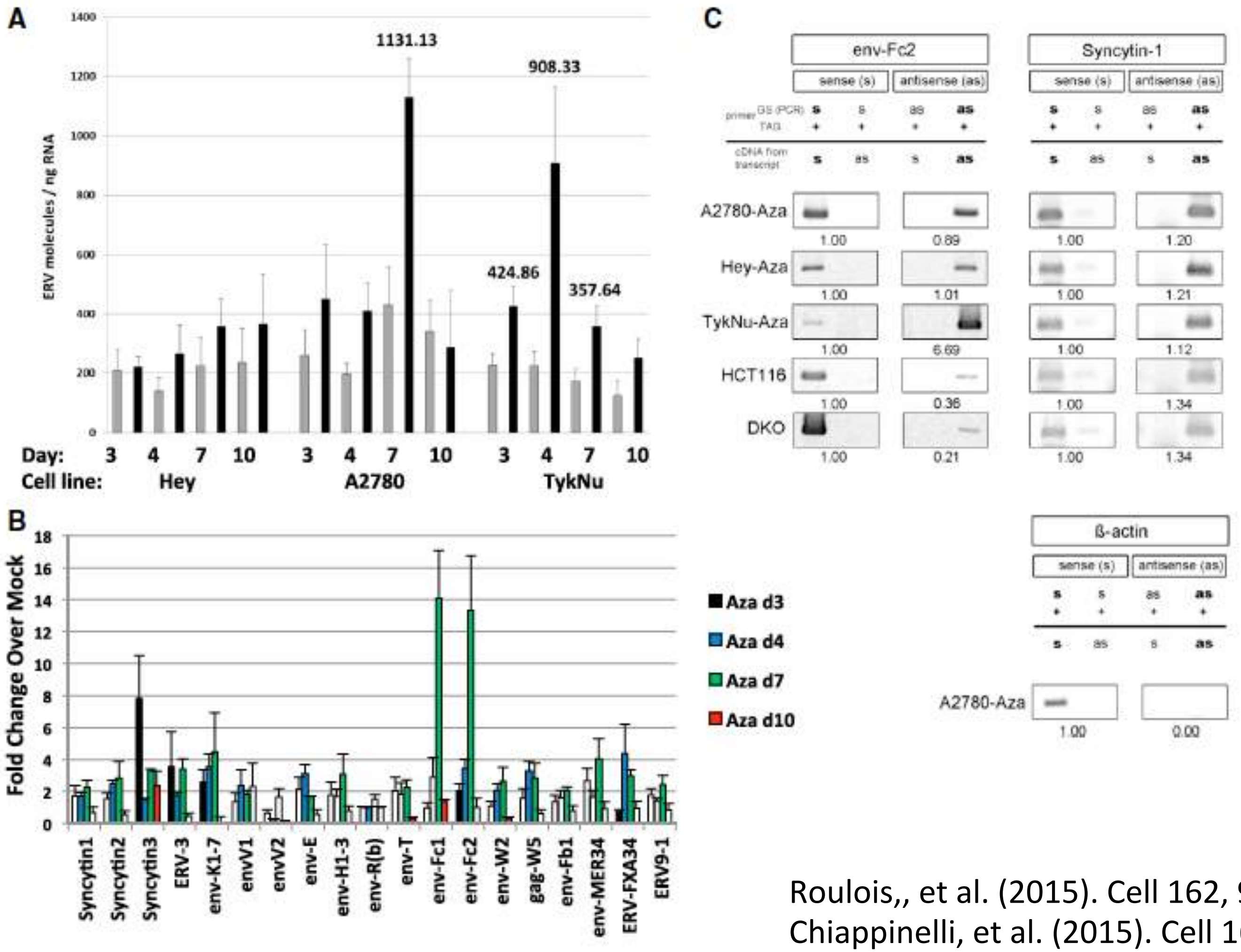


Pt. 001-0605
History: 61 y.o. male with stage IV NSCLC refractory to multiple surgeries, RT, two multidrug chemotherapy regimens, 5-AZA and entinostat (HDACi).

Courtesy of Peter Jones

DNA Methylation inhibitors: Activation of endogenous retroviral expression

DNMT inhibitors induce ERV demethylation and expression (sense and antisense), which triggers a dsRNA response



E. Heard, 2016

Roulois,, et al. (2015). Cell 162, 961–973.
Chiappinelli, et al. (2015). Cell 162, 974–986.

DNA Methylation inhibitors:
Activation of endogenous retroviral expression

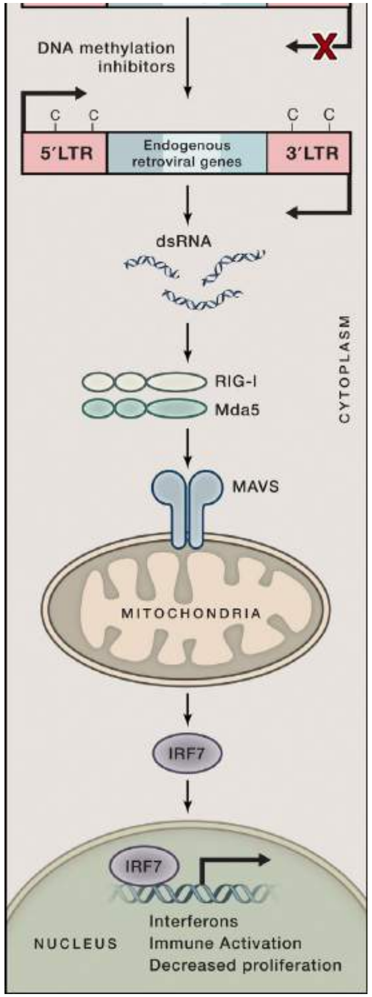
- Gene expression profiling of colorectal and ovarian carcinoma cells treated with low-dose AZA identified genes significantly upregulated with delayed kinetics whose expression was **NOT** correlated with changes in **DNA methylation**
- Many of these were targets of **the IRF7 protein -** a known antiviral mediator!
- AZA induces nuclear localization of IRF7 by stimulation of the MDA5 and RIG-I proteins that recognize double stranded viral RNA
- Colon cancer cells treated with AZA actually began to secrete interferon, but again, not linked to demethylation of interferon pathway genes.
- Transfection with dsRNA of a fresh culture of cells derived from AZA-treated cells, but not control cells, induced an antiviral response in recipient cells.
- Activation of endogenous retroviral sequences by AZA induced interferon response
- Inhibition of DNA methylation sensitizes a murine melanoma model to anti-CTLA4 immune checkpoint therapy
- **Clinical trials on combined ASA or DEC treatment with immunotherapy look very promising - on solid tumors - not just on hematological tumors!**

Roulois,, et al. (2015). Cell 162, 961–973.
Chiappinelli, et al. (2015). Cell 162, 974–986.

DNA Methylation inhibitors: Activation of endogenous retroviral expression

DNMT inhibitors probably sensitise cells by inducing an antiviral, anti-proliferative state, reactivating tumor antigen expression and altering cell signaling pathways

DNMT inhibitors induce a "viral mimicry" response in cells by activating endogenous retroviral repeats and upregulating immune signaling through secreted interferon In addition to activating tumor antigen genes



Roulois et al. (2015). Cell 162, 961–973.
Chiappinelli, et al. (2015). Cell 162, 974–986.

E. Heard, 2016

COLLÈGE DE FRANCE 1530

Enhancing Cancer Immune checkpoint therapy with DNMT inhibitors

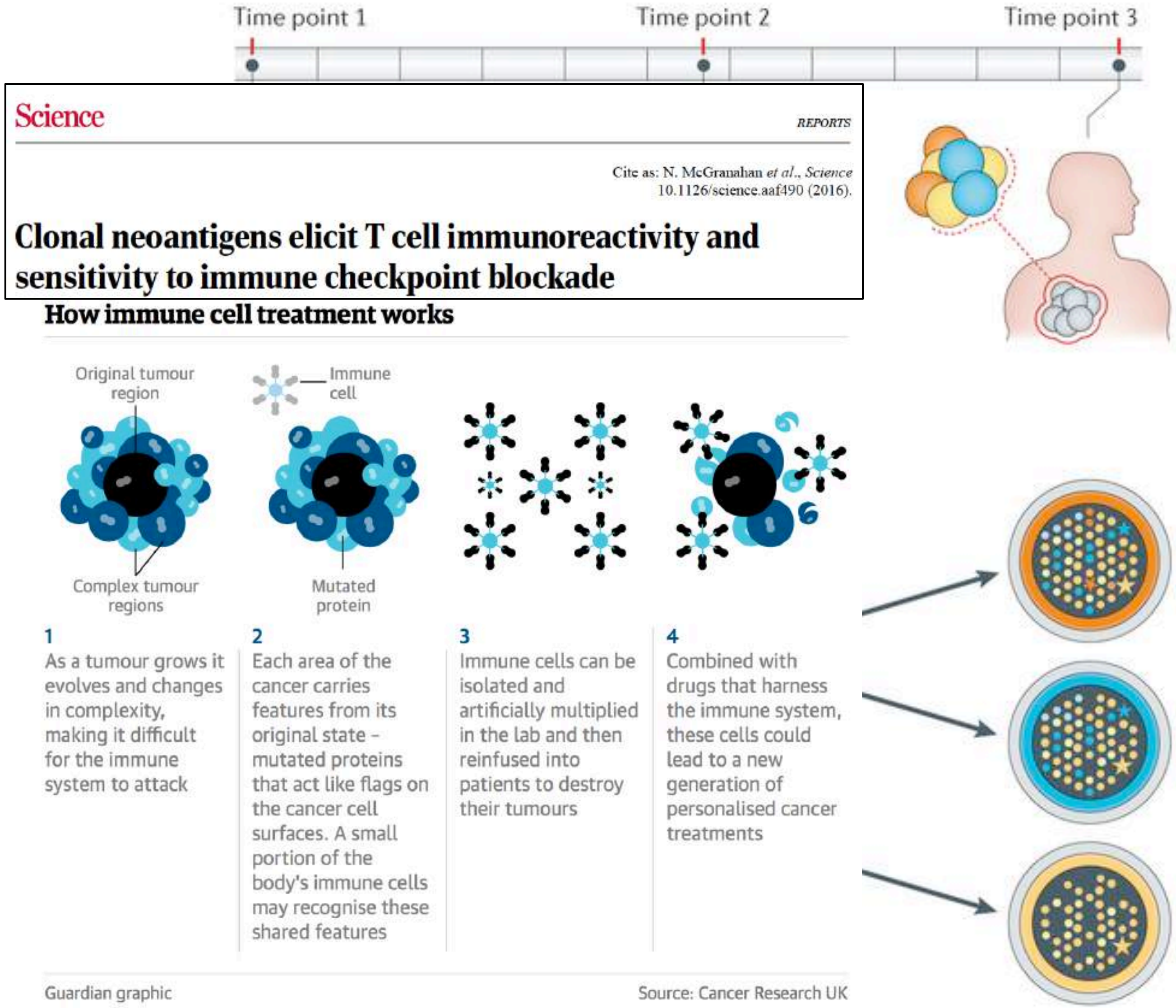
Epigenetic effects of DNMT inhibition by azacitidine (AZA) or decitabine (DAC).

5-azacitidine and entinostat, which alter the epigenome, may prime patients' immune systems to respond to the checkpoint inhibitor.

Pairing these drugs may radically improve patient outcomes.
Large clinical trials ongoing

Neoantigens generated during clonal evolution within Tumors and/ or by Demethylating agents - are key to successful Immunotherapy

Clonal Evolution: Sequencing of Tumor samples through disease progression



E. Heard, 2016 Ding et al, NRG (2014) Expanding the computational toolbox for mining cancer genomes

COLLÈGE DE FRANCE 1530

Epigenetic Therapy Plus Chemotherapy

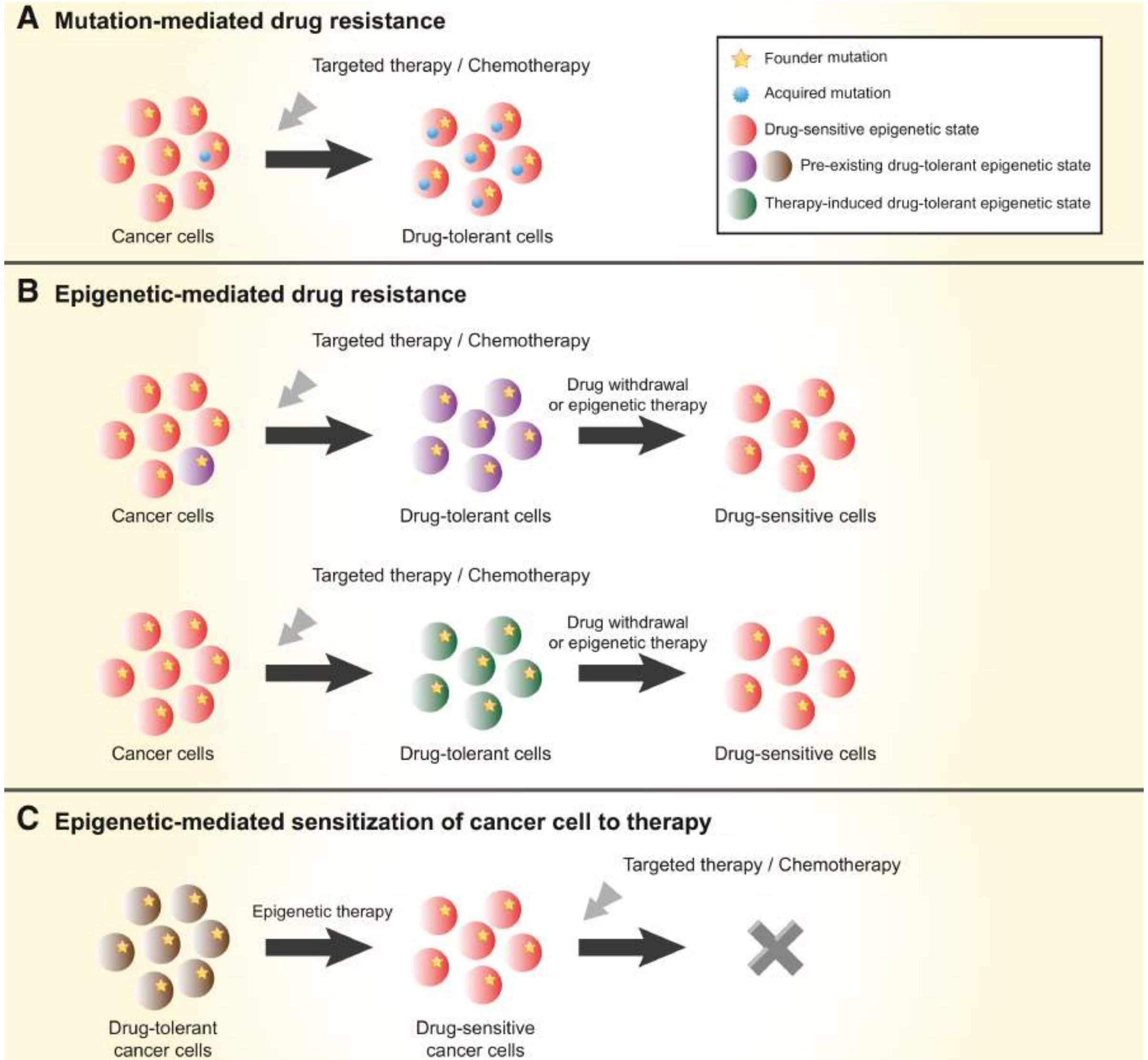
Clinical Studies

Cancer Research

Epigenetic Resensitization to Platinum in Ovarian Cancer

Daniela Matei[1,2,3,4], Fang Fang[8], Changyu Shen[5], Jeanne Schilder[1,2], Alesha Arnold[1], Yan Zeng[5], William A. Berry[6], Tim Huang[9], and Kenneth P. Nephew[1,2,7,8]

Genetic and Epigenetic basis of Drug Resistance - Sensitisation



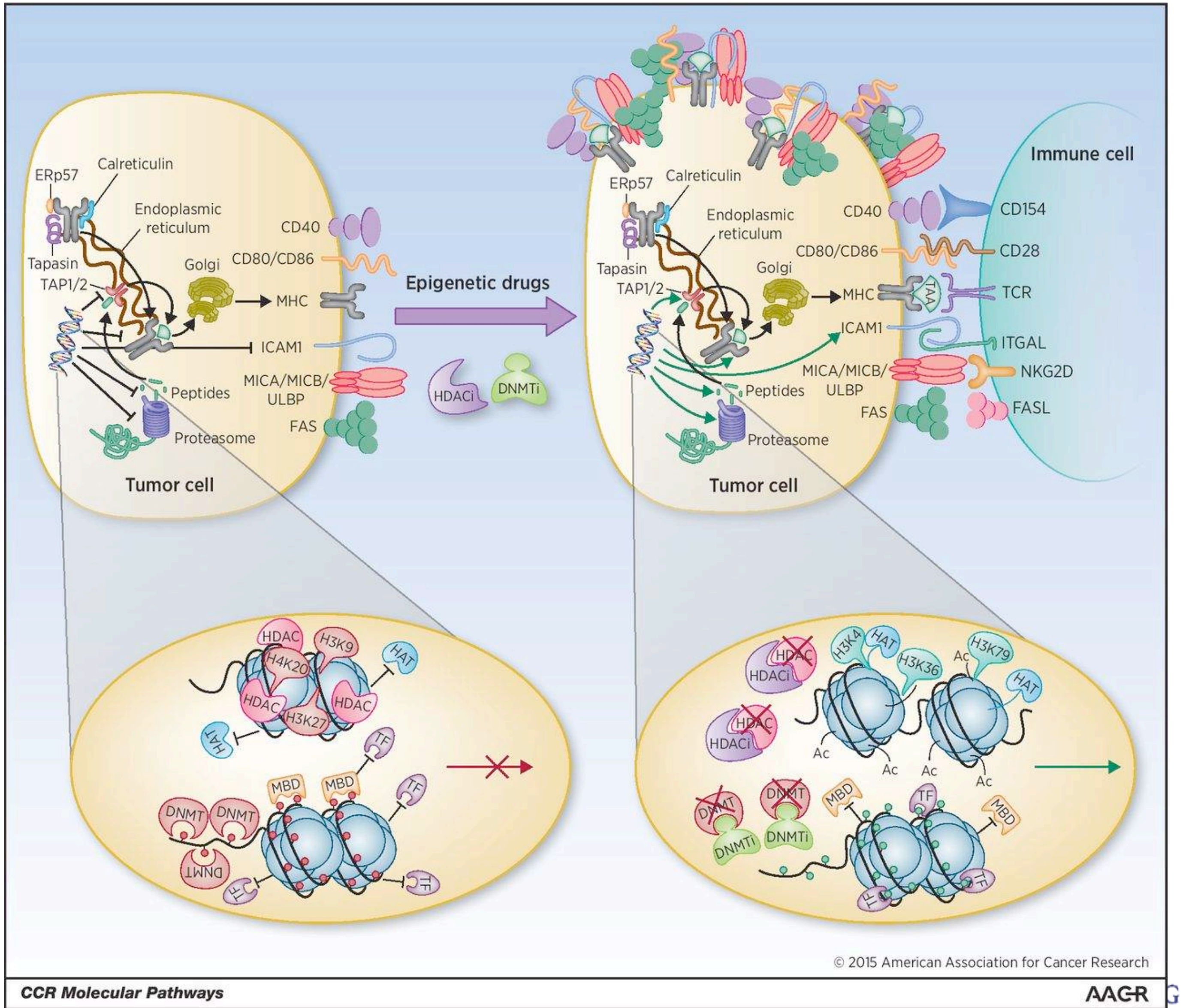
Easwaran et al, Mol. Cell 2014

E. Heard, 2016

COLLÈGE DE FRANCE 1530

Drug Resistant Cancer Cells: Low Dose Epigenetic Drugs in combination with other therapies may be effective

Contrary to high-dose cytotoxic chemotherapy, where they proliferate unopposed, drug-resistant cancer cells may be at an evolutionary disadvantage in presence of low-dose chemotherapy owing to the high metabolic cost of their resistance mechanisms



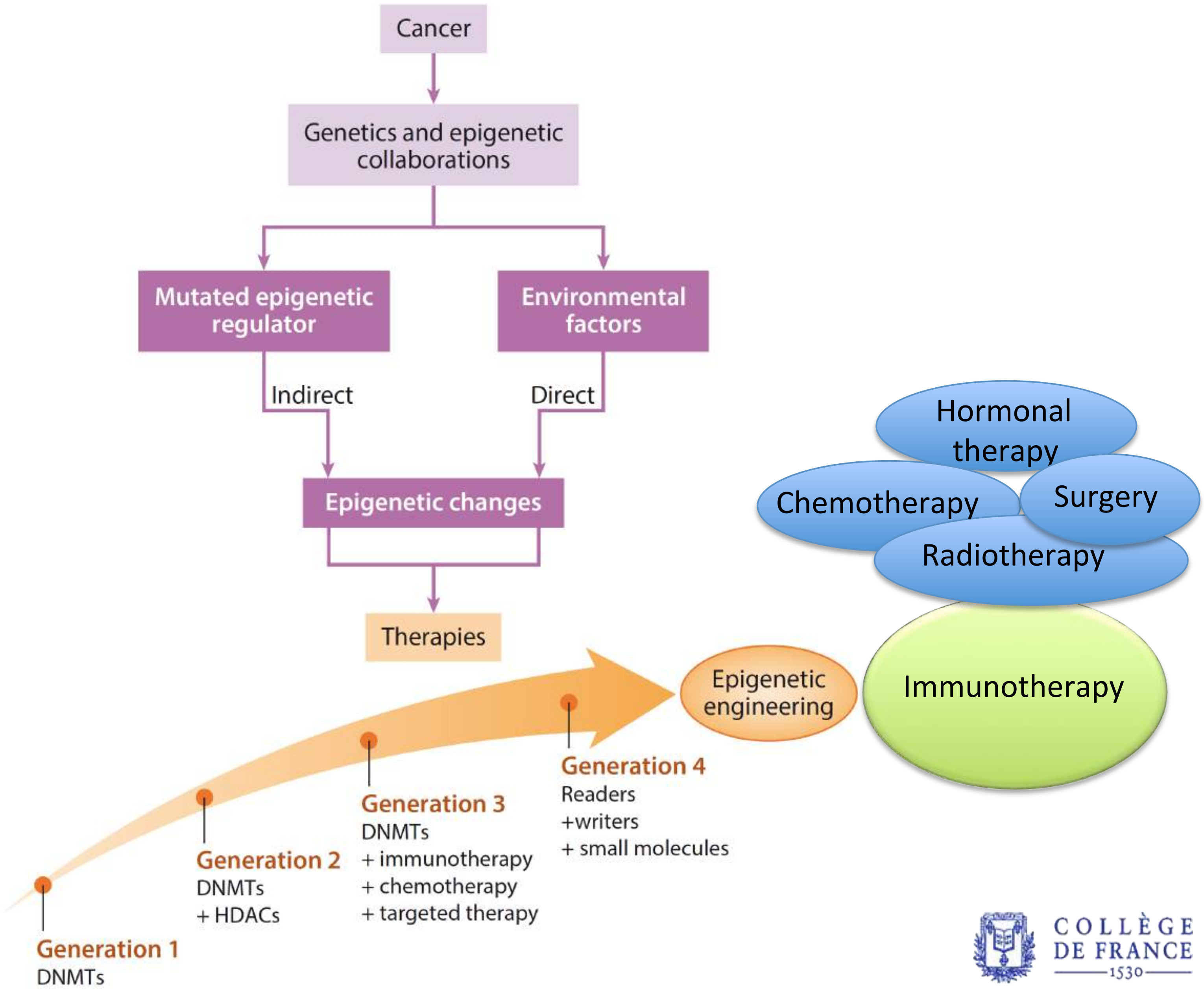
Eco-evolution of cancer resistance

Giannoula L. Klement

E. Heard, 2016

GE
DE FRANCE
1530

Cancer Therapies based on Mutational and Epigenetic Alterations

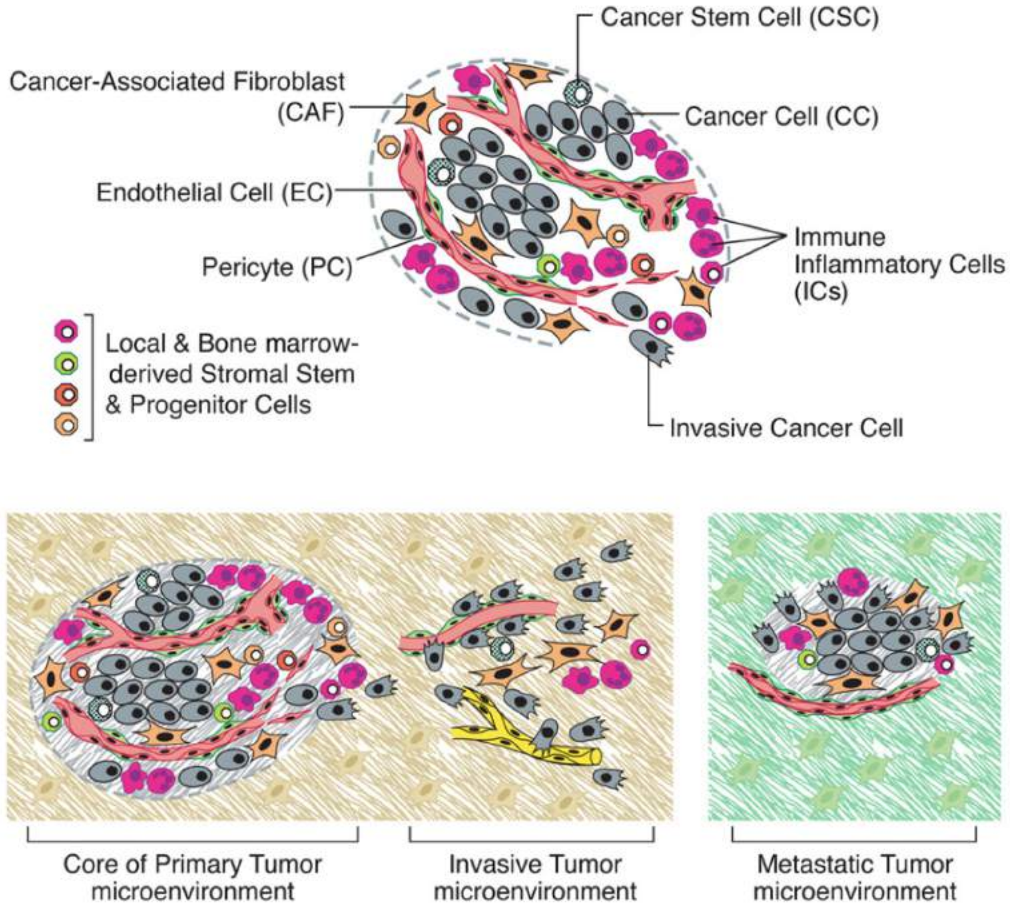


E. Heard, 2016

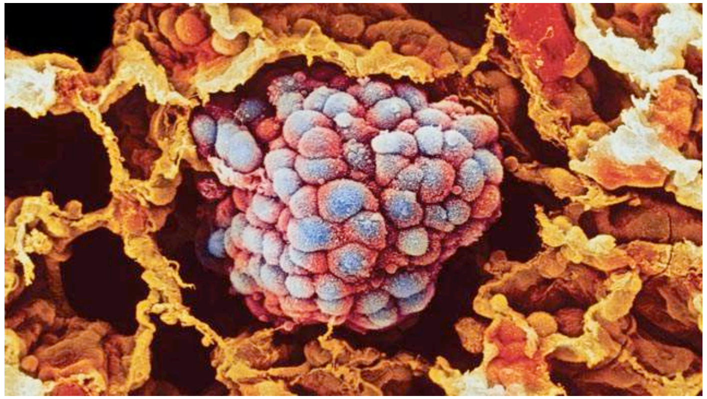
COLLÈGE DE FRANCE 1530

Cancer Epigenetics: From Mechanisms to Therapy

Single cell cancer monitoring: Biopsies, Circulating Tumor Cells



Hanahan and Weinberg "The Hallmarks of Cancer" 2011



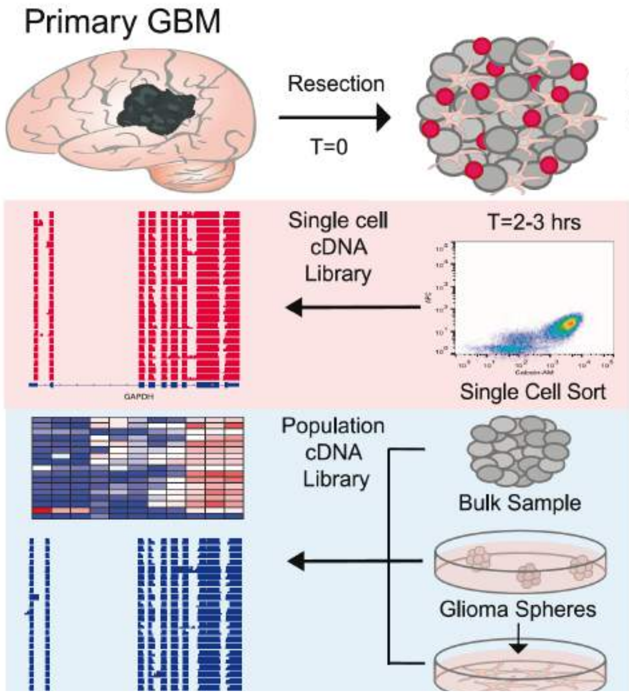
Lung carcinoma (blue) filling an alveolus of the human lung

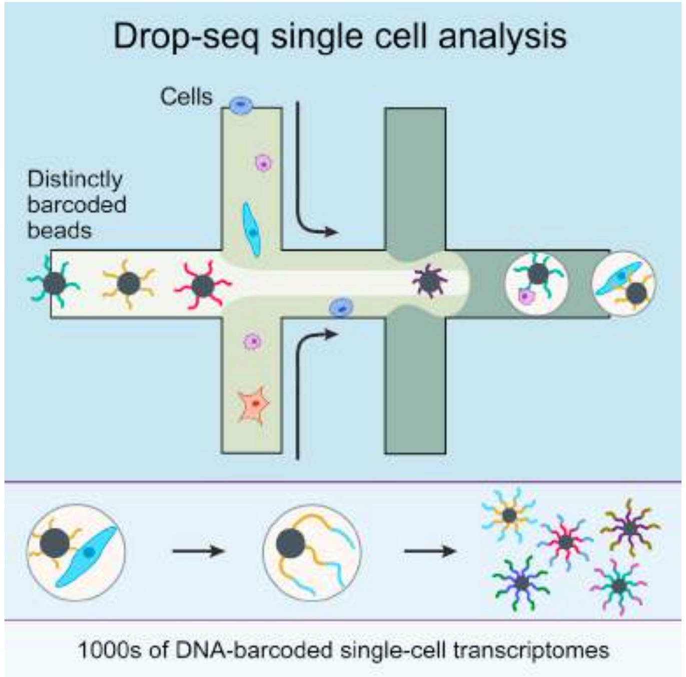
E. Heard, 2016

COLLÈGE DE FRANCE 1530

Cancer Epigenetics: From Mechanisms to Therapy

Single cell cancer monitoring: Biopsies, Circulating Tumor Cells



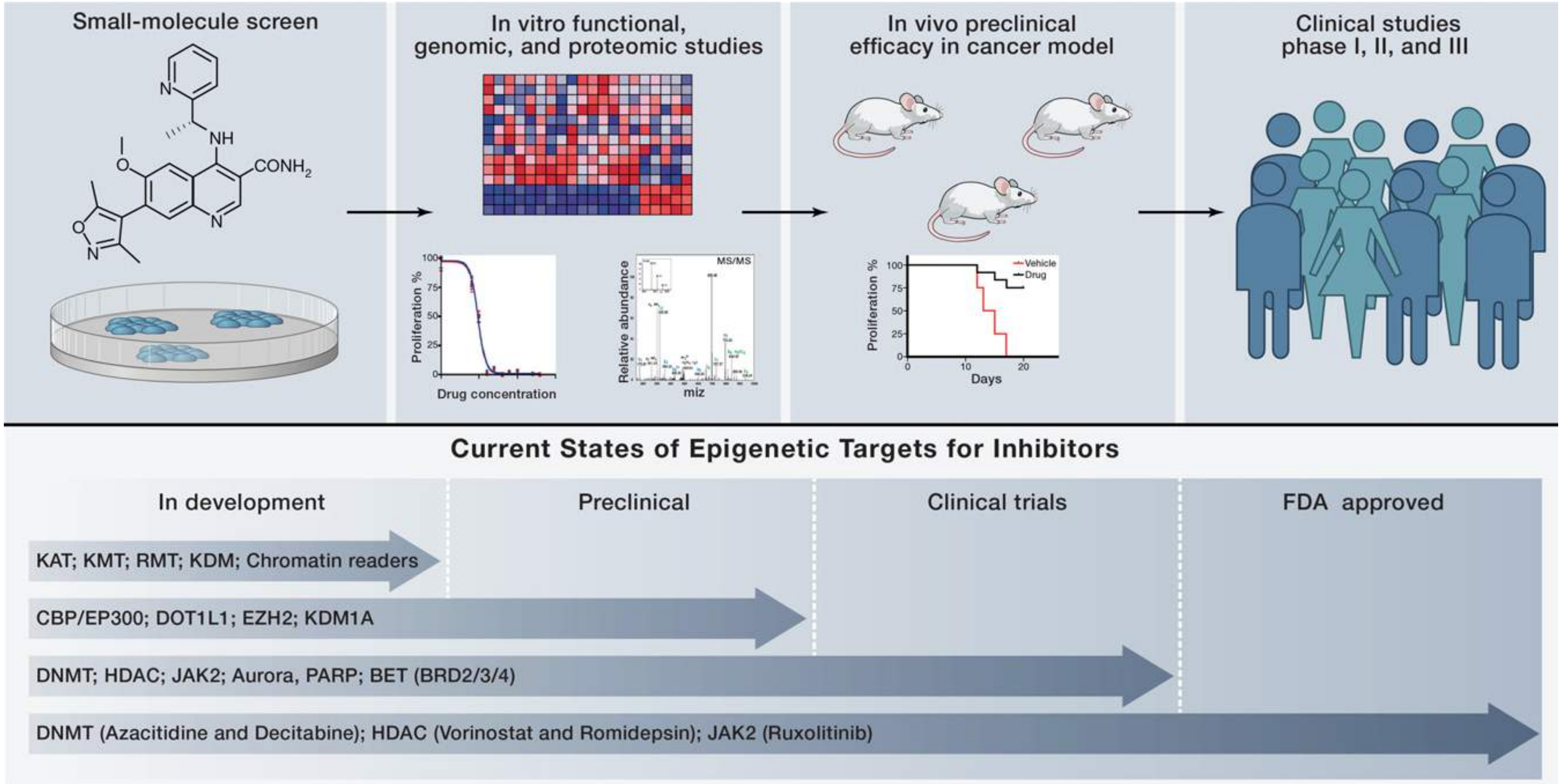


- Single cell "omics" approaches are providing revolutionary insights into Biology – especially cancer
- Connecting genotypes, epigenotypes to the phenotypes
- Allow identification of heterogeniety ("diversity index") => valuable prognostic marker
- Allows estimation of mutation rates (not just frequencies!)
- Enables detection of early and late events – and of slow versus sudden events (eg chromothripsis…)
- Addresses the question of Cancer Stem Cells (CSCs - now renamed Tumor Initiating Cells (TICs)
- Phylogenetic trees and insights into tumor evolution (Darwinian or macroevolution)
- Sequencing of circulating tumor cells (CTCs) and tumor biopsies monitors disease progression and responses to therapy….

E. See *Navin Genome Research, 2015; Patel et al Science, 2014 and Macosko et al, Cell 2015*

Cancer Epigenetics: From Mechanisms to Therapy

Targeted molecules against mutated epigenetic factors (eg IDH, BETs) or general inhibitors of epigenomic modifiers (eg DNMTs, HDACs):



From Dawson and Kouzarides, 2012

Année 2015-2016 :
"Epigénétique et Cancer"

6 avril, 2016

Séminaire par le Professeur Kristian Helin
Epigenetic Targets in Cancer
(BRIC, Copenhagen, Denmark)

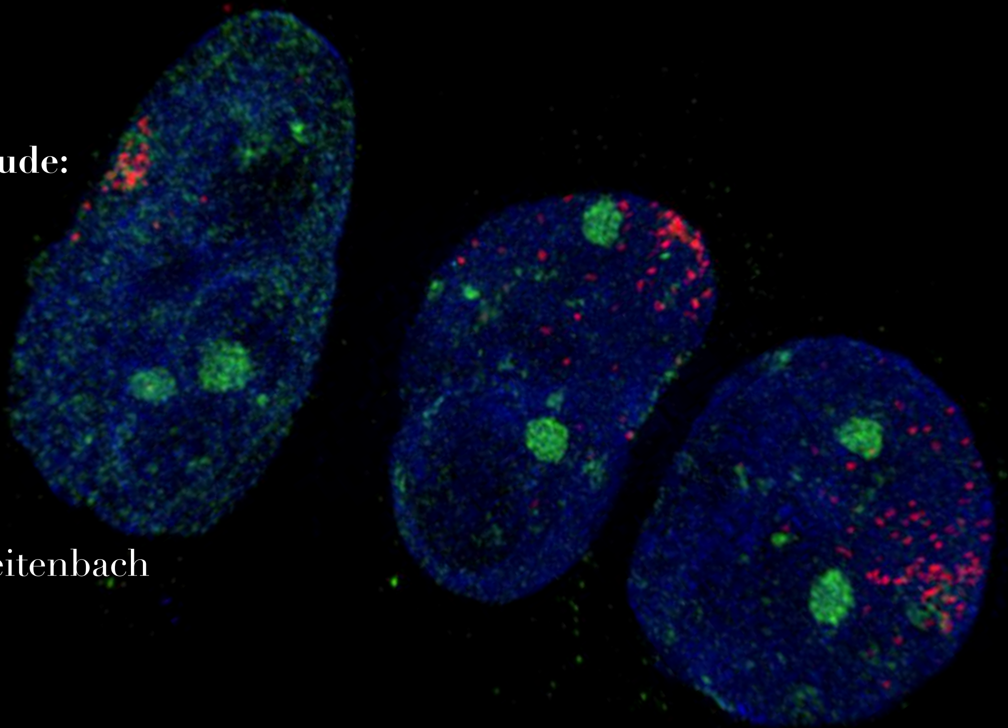
COLLÈGE DE FRANCE 1530

“Epigenetics and Cancer”

Organized by **Edith Heard & Hugues de Thé**

May 9th - 10th, 2016

(from 9am May 9th, to 1pm May 10th)



Speakers / chairs include:

Genevieve Almouzni
Steve Baylin
Stephan Beck
Manuel Estellar
Andy Feinberg
Jean Pierre Issa
Nada Jabado
Cigall Kadoch
Valérie Lallemand-Breitenbach
Raphael Margueron
Thomas Mercher
Paolo Salomoni
Eric Solary
Henk Stunnenberg
Anne Vincent-Salomon

Colloquium in English
Free entry, no registration required