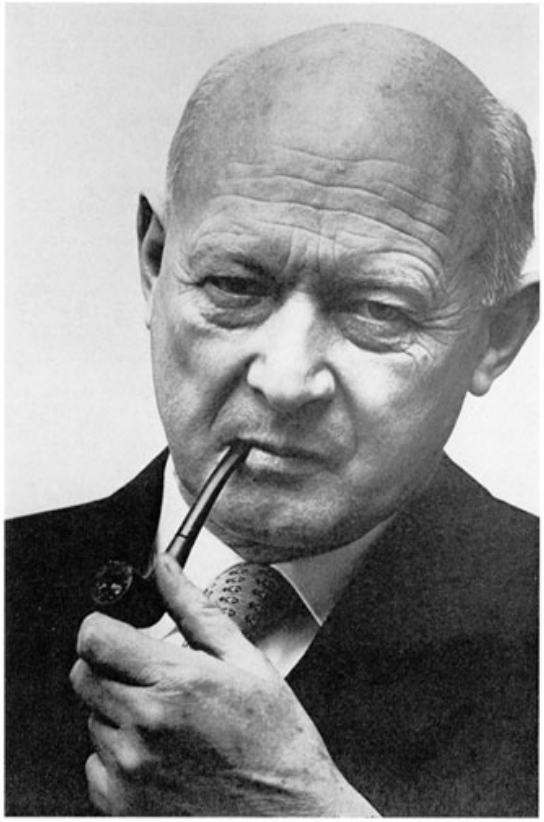
Mining the Genome to Understand Epigenetic Abnormalities in Cancer and Enhance Development of New Therapeutic Approaches

Stephen B. Baylin

Epigenetics



Nature Reviews | Genetics

Classic Definition

The branch of biology which studies the causal interactions between genes and their products, which bring the phenotype into being.

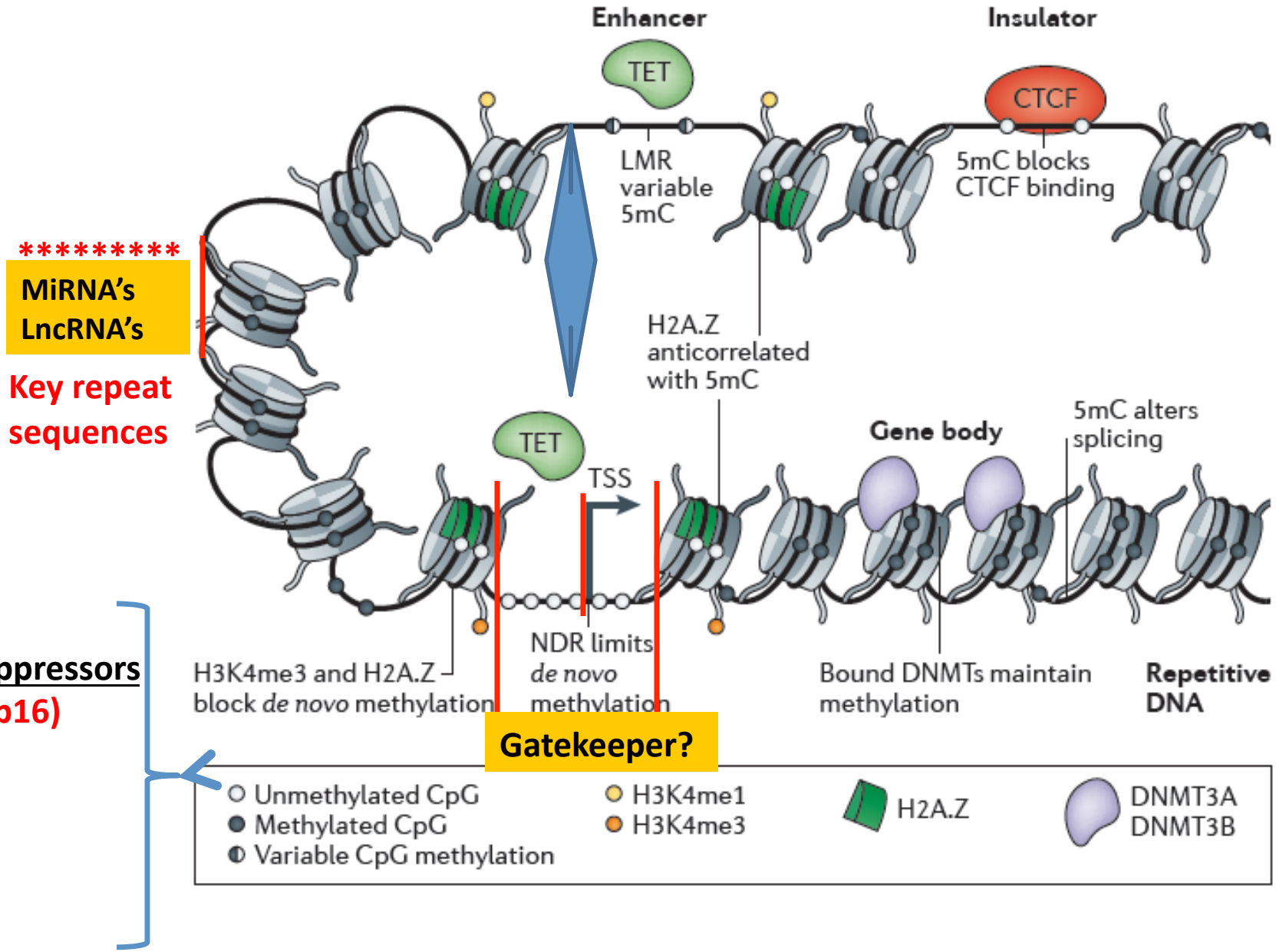
Modern Definition

The study of heritable changes (mitotic or meiotic) in gene function which create a new phenotype without a corresponding change in DNA sequence.

"Above" , but integral to, and informed by, the genome –software for the hard drive of DNA

Cancer translation – the potential to reverse abnormalities and reprogram tumor cells - think of induced pluripotent stem cells (iPS)!

Putative Therapeutic Target -The Epigenome



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MiRNA's
LncRNA's

Key repeat sequences

Gatekeeper?

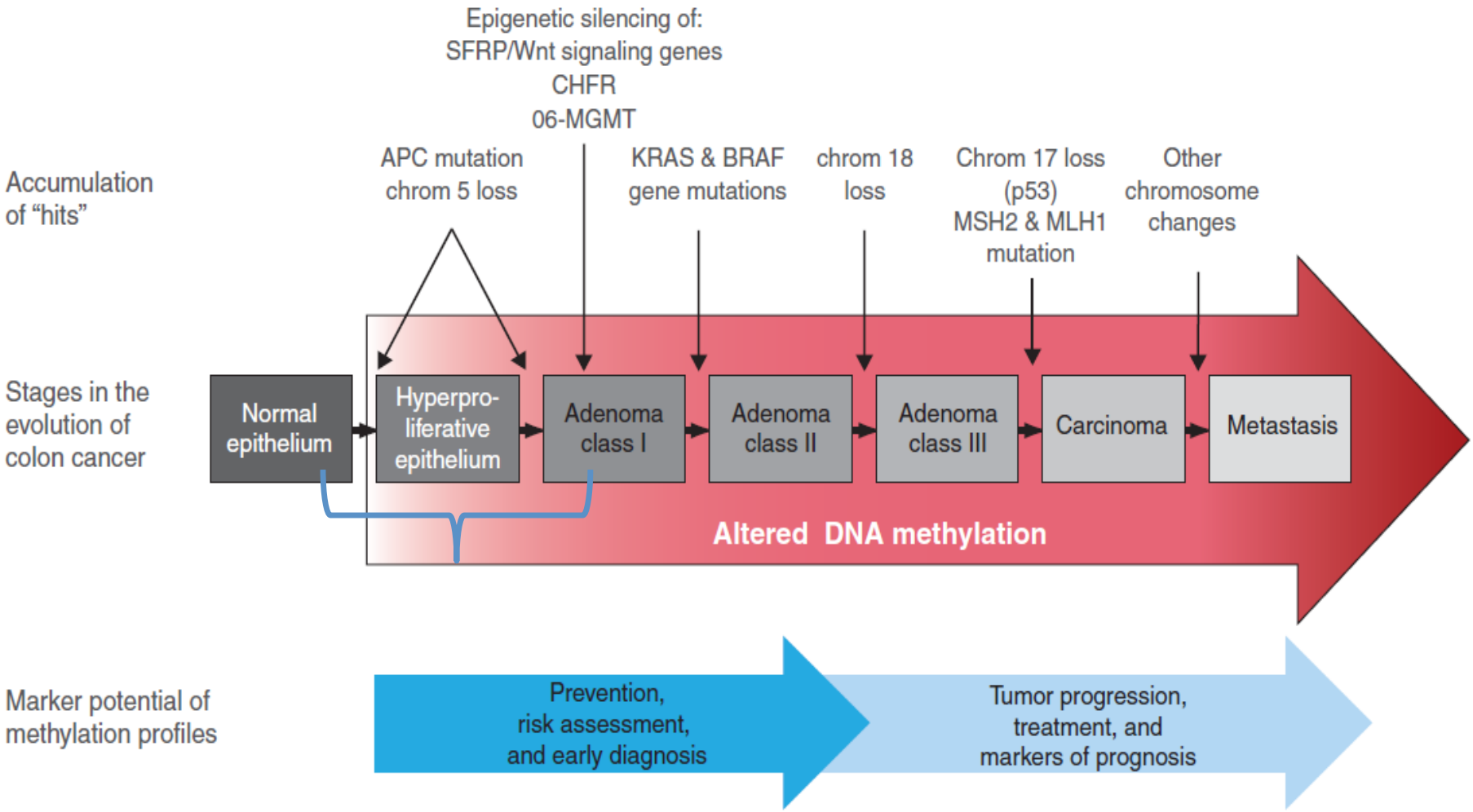
Tumor Suppressors

CDKN2a (p16)
Rb
BRCA1
ECAD
VHL

Jones, Nat Rev Genet, 2012

The position of mutations and the abnormal epigenome in tumor progression

Cancer = disease of abnormal retention of self-renewal and defective lineage commitment



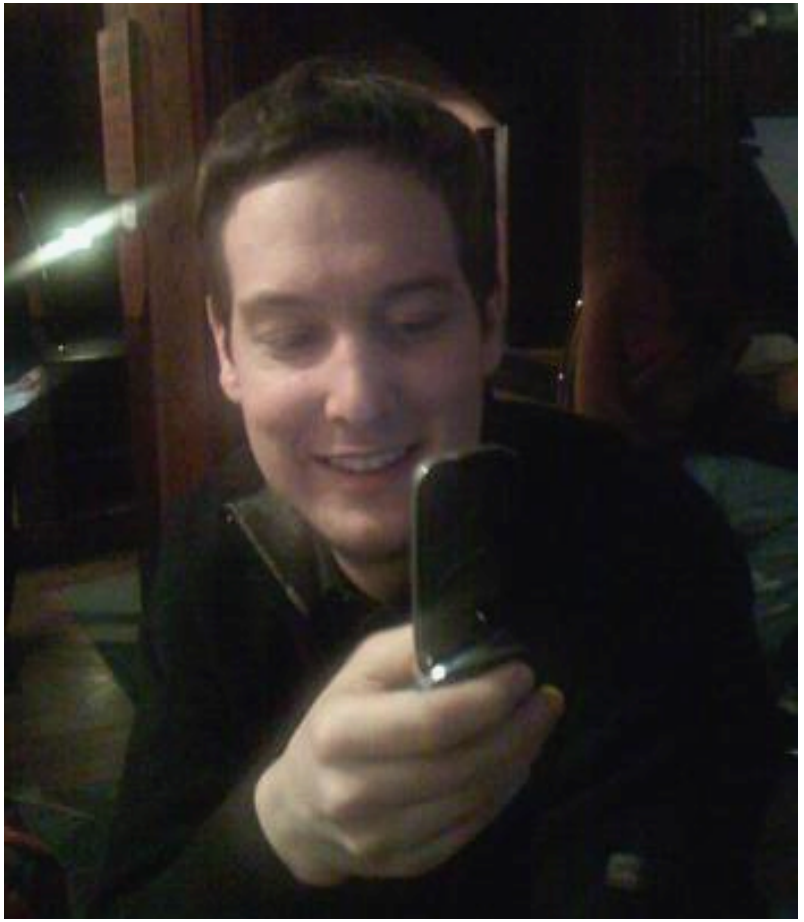
Baylin & Jones, Cold Spring Harb Perspect Biol 2014

Some Things We Need To Know

- **Relationships and balance, during cancer initiation and progression between DNA methylation and chromatin changes in key genomic regions – enhancers, promoters, gene bodies, and non-coding**

Genome-Wide Studies of DNA Methylation and Chromatin

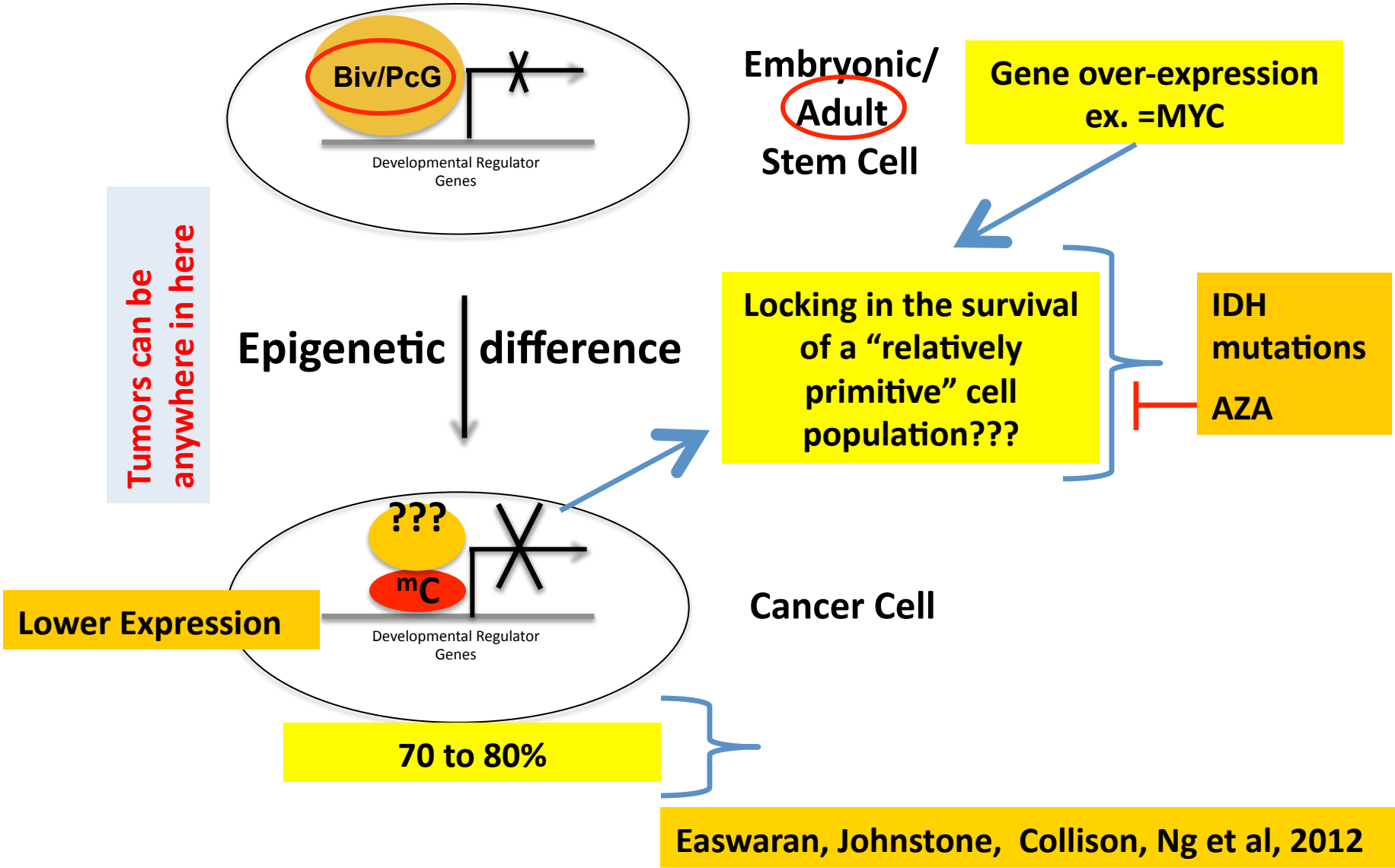
Hariharan Easwaran



Leander Van Neste

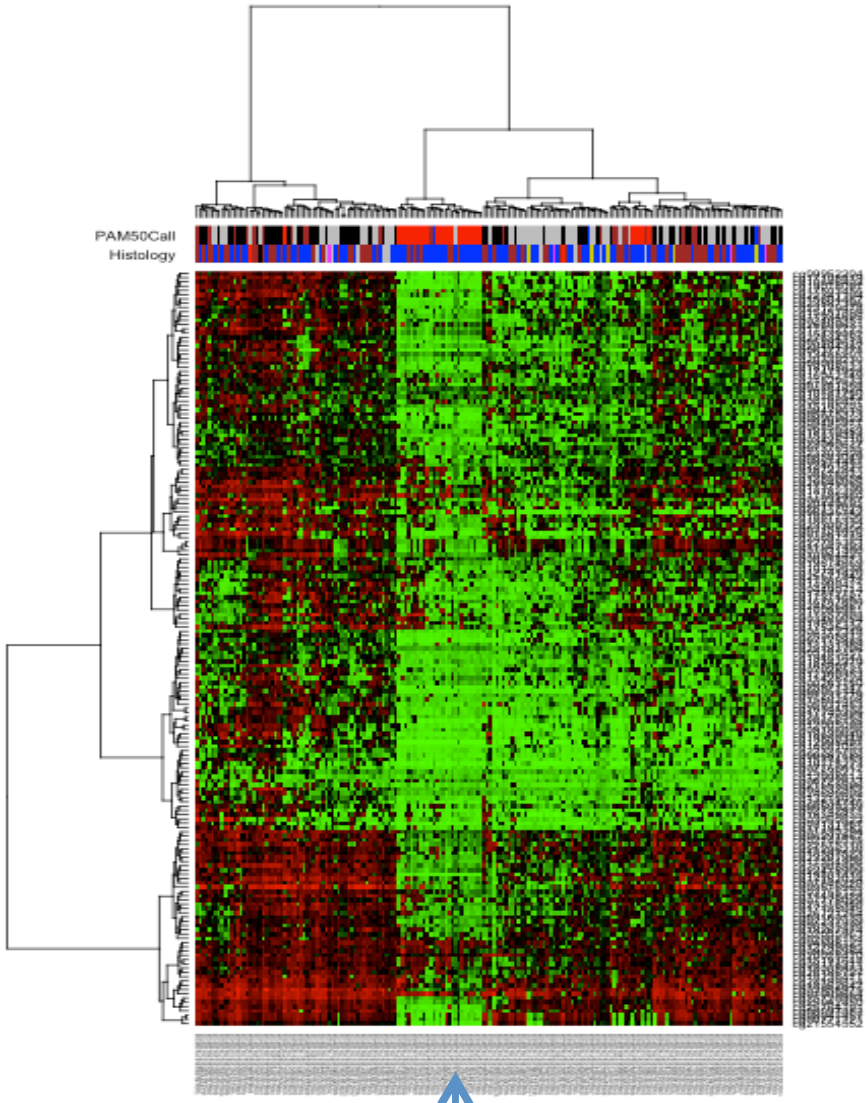
Sarah Johnstone

Model for Molecular Progression to DNA Hypermethylation of Many Genes in Cancer



TCGA Data

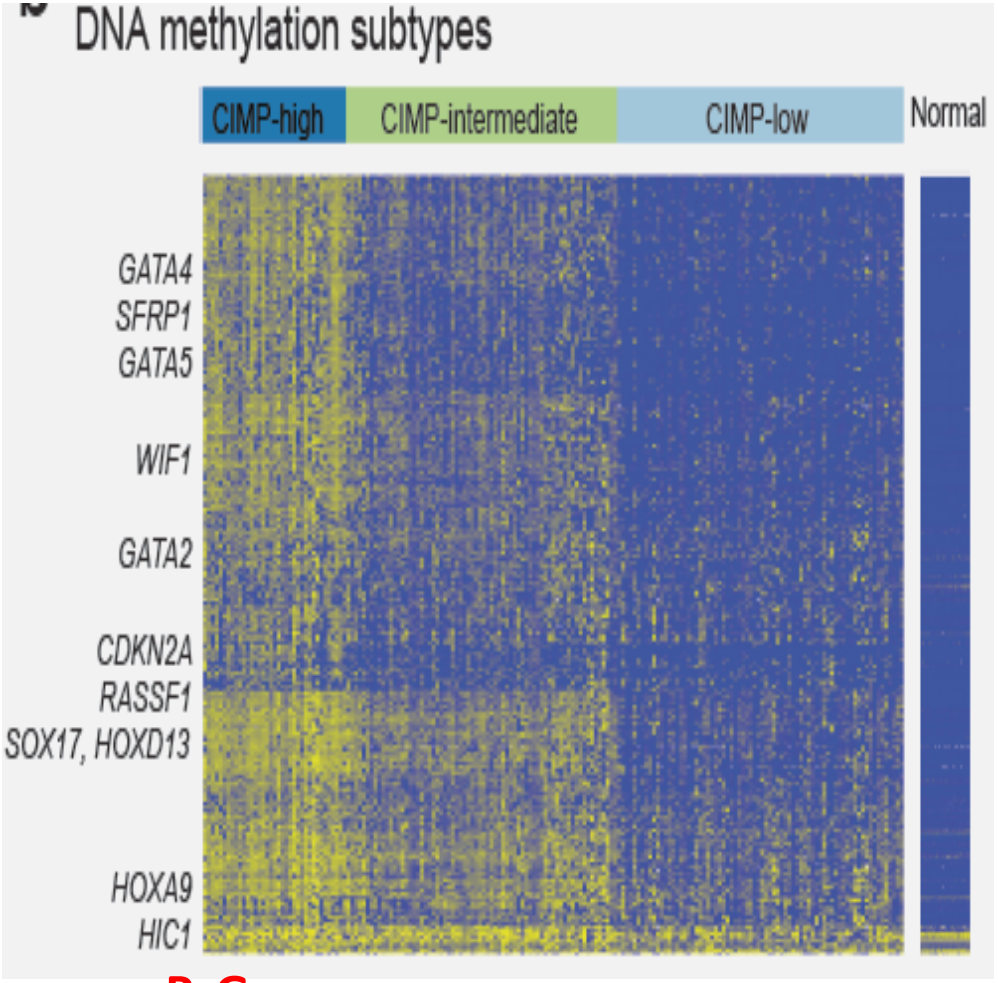
Breast Carcinoma



PcG Driven?

Easwaran, Johnstone, Collison et al, 2012

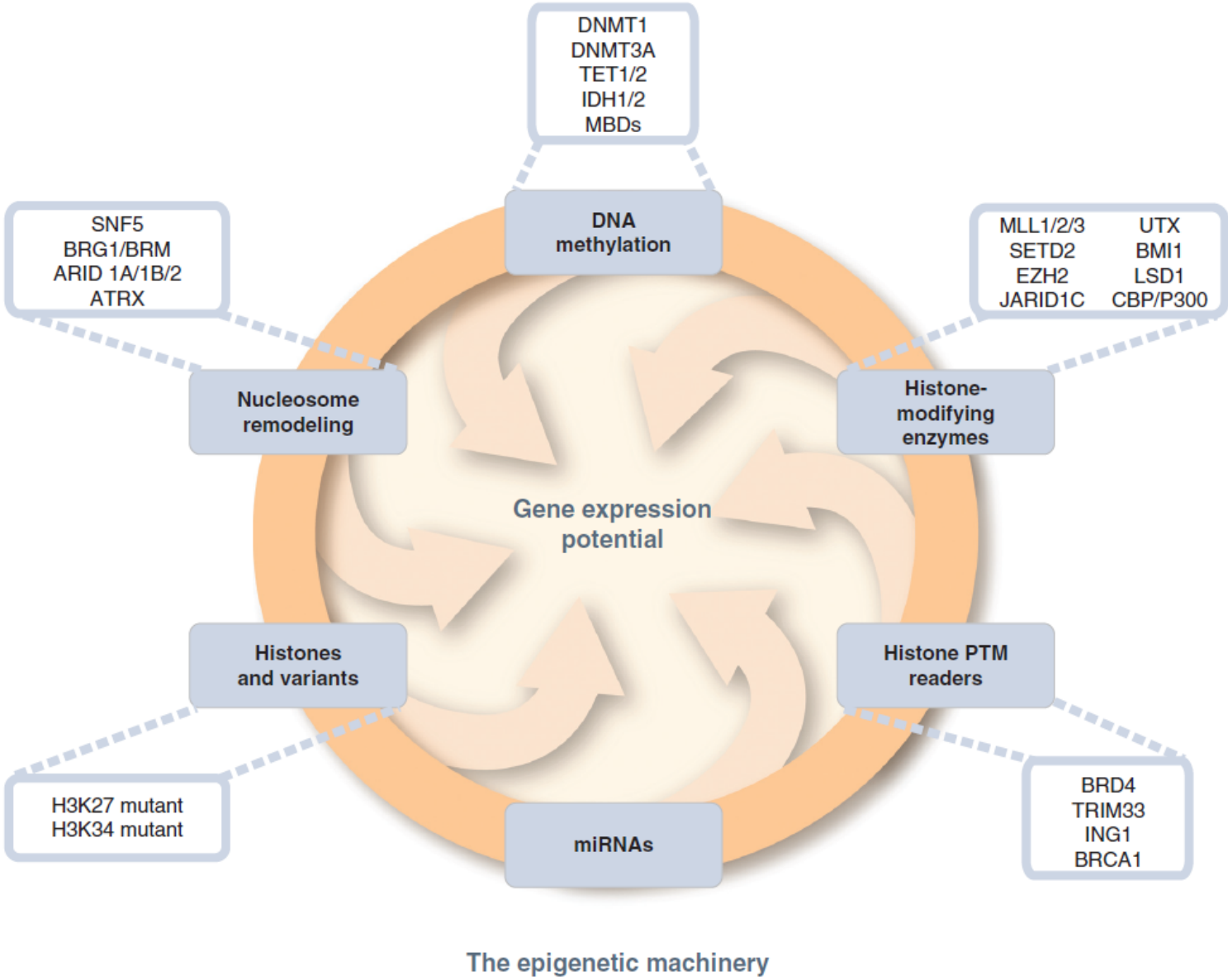
Lung Adenocarcinoma



PcG

Danilova, Cope, Weisenberger, Laird, and TCGA Consortium , Nature, 2014

Mutations in Genes Encoding Chromatin Regulatory Proteins



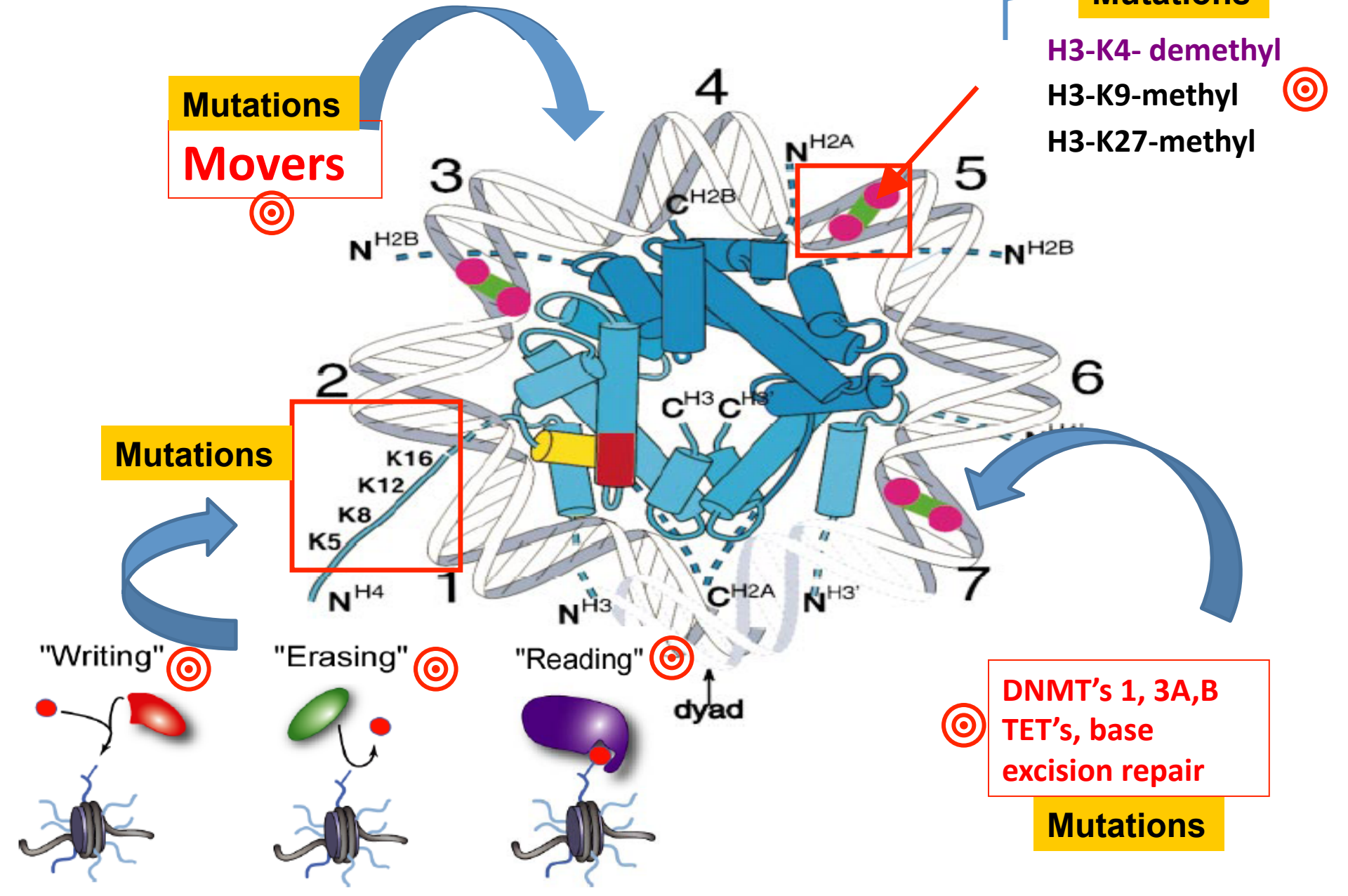
Baylin & Jones, Cold Spring Harb Perspect Biol 2015

Some Things We Need To Know

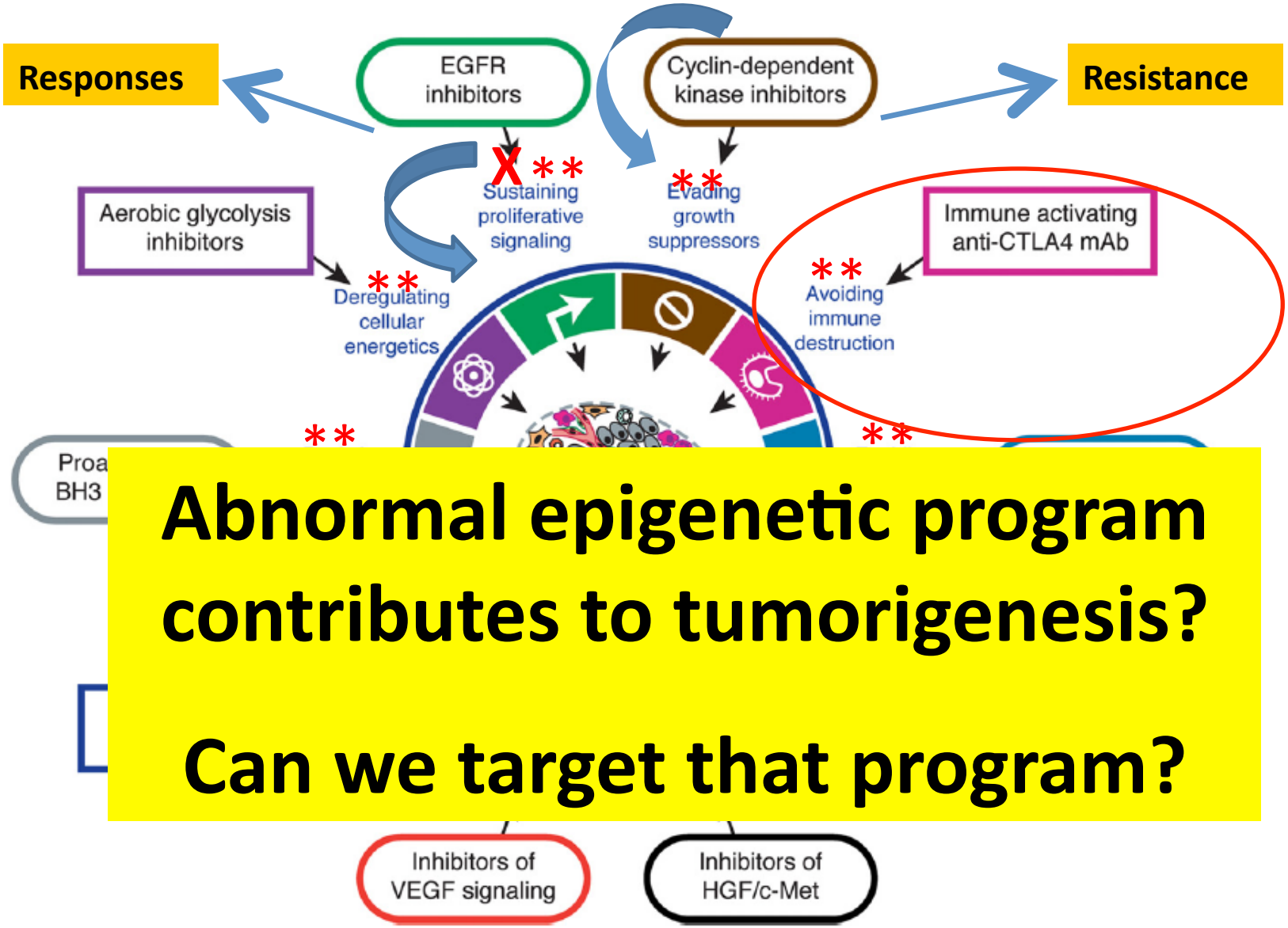
- **Relationships and balance, during cancer initiation and progression between DNA methylation and chromatin changes in key genomic regions – enhancers, promoters, gene bodies, and non-coding**

- **Above as these parameters relate to the DNA methylation and chromatin events either created by and/or "inherited " by the mutations in genes encoding for proteins regulating the epigenome**

The Nucleosome



The Hallmarks of Cancer and Therapy Targets



Abnormal epigenetic program contributes to tumorigenesis?

Can we target that program?

Hanahan and Weinberg, Cell 2011

Some Things We Need To Know

- **Relationships and balance, during cancer initiation and progression between DNA methylation and chromatin changes in key genomic regions – enhancers, promoters, gene bodies, and non-coding**

- **Above as these parameters relate to the DNA methylation and chromatin events either created by and/or "inherited " by the mutations in genes encoding for proteins regulating the epigenome**

- **Above during effects of agents which are targeting the epigenome for possibilities in cancer therapy**

Dream Team for Epigenetic Therapy

Peter Jones

USC NORRIS

Van Andel Institute

STAND UP TO CANCER

TEMPLE UNIVERSITY

Jean-Pierre Issa

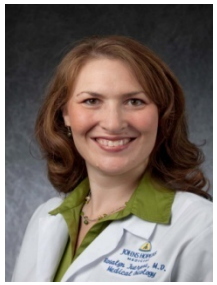
USC NORRIS

Anthony El-Khoueiry,
Casey O'Connell
Barbara Gitlitz
Debu Tripathy

Leukemia
Breast,
Lung, &
Colon
Ovarian Cancer

JOHNS HOPKINS MEDICINE
THE SIDNEY KIMMEL COMPREHENSIVE CANCER CENTER

Charles Rudin



Ros Juergens

Malcolm Brock

Nita Ahuja

Nilo Azad

Vered Stearns
Roisin Connolly, M.B.

John Wrangle

Suzanne Topalian,
Drew Pardoll
Immunotherapy Team

Julie Brahmer

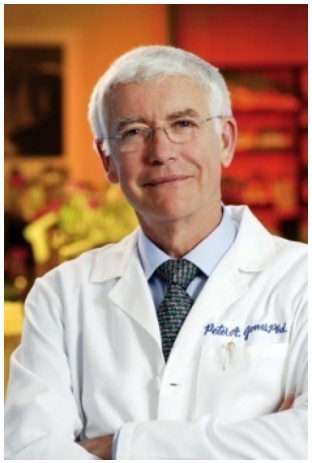
UPMC

Nancy Davidson

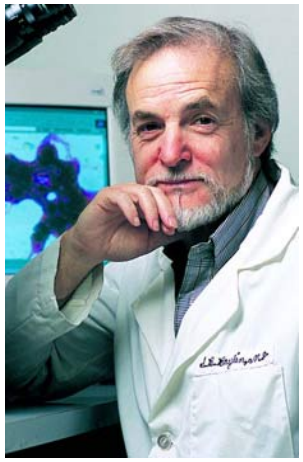
Rachel Jankowitz, M.D.

NCI, TCGA,CTEP, Celgene, BMS,Syndax

Correlative Science and Biomarker Development Derivation



Peter Jones



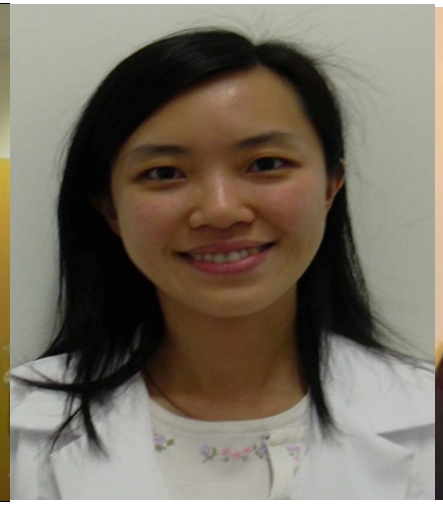
Steve Baylin

Cindy Zahnow

Kate Chiappinelli

John Wrangle

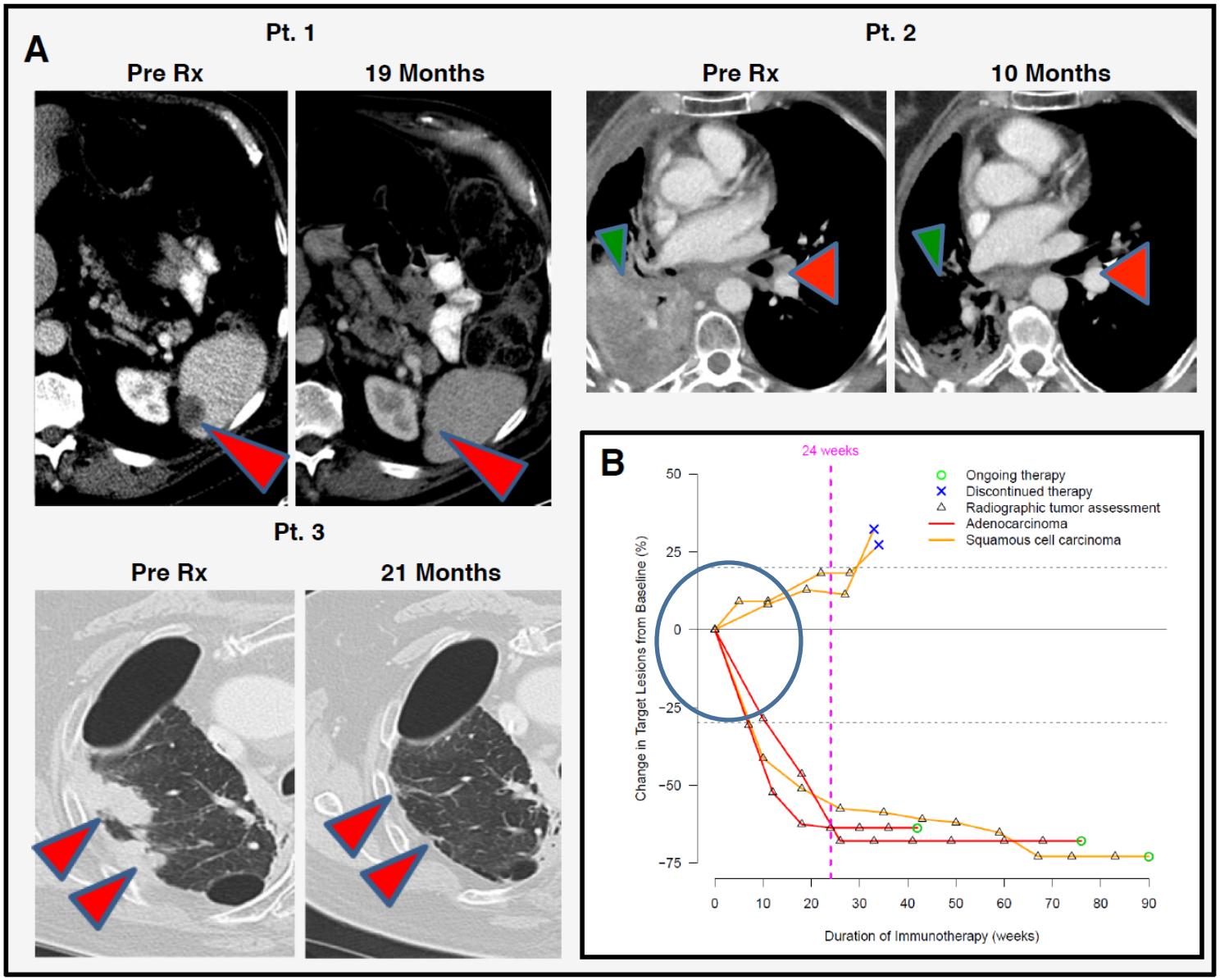
Huili Li



Hsing Tsai

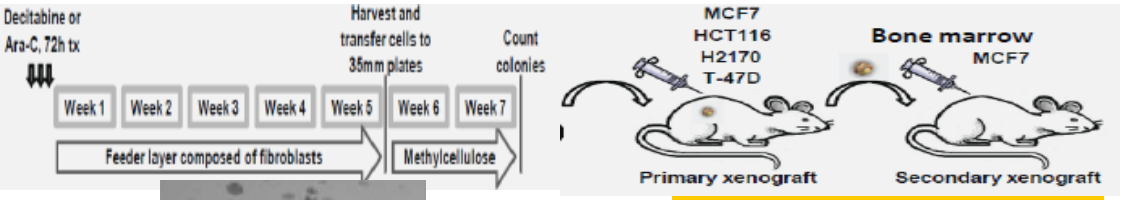
Nita Ahuja

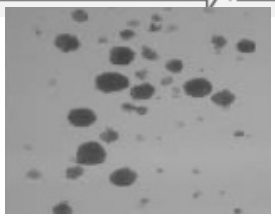
Potential for Epigenetic Rx Priming to Immune Tolerance Therapy



Wrangle, Wang, Easwaran et al, 2013

Study Design Figure





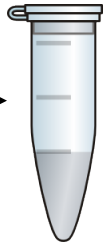
Self renewing cells!

Tumor Cell Line

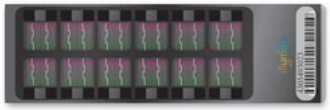
500 nM
5-AZA
for 72 hr

Rest Cells
for 3-21
Days

Harvest
Cells

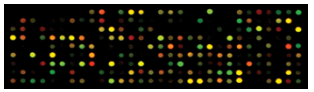


DNA



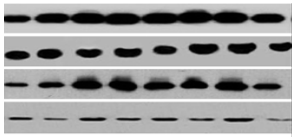
Illumina Infinium Human
450K Methylation Array

RNA

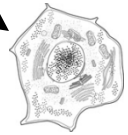


Agilent Human 44K
Expression Array

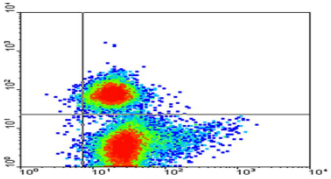
Protein



Western Blots

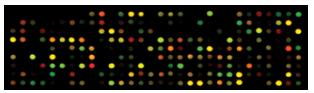


Whole
Cells



Flow Cytometry

Protein



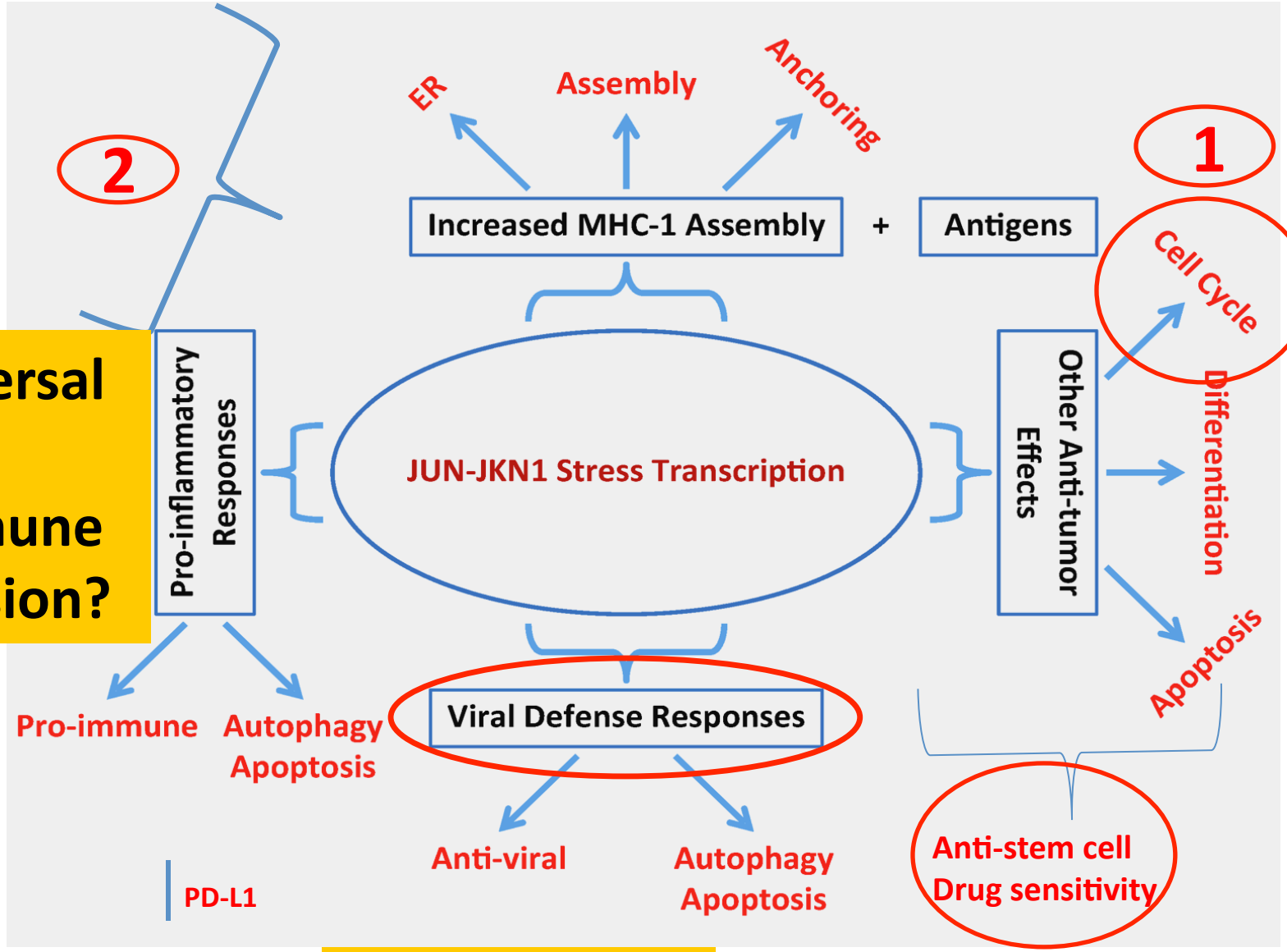
Proteomics

RNA seq and DNA Methylation in
TCGA and other cohort primary
samples

Over 70 cell lines, primary samples – breast,
colon, leukemia, lung, and ovarian cancers

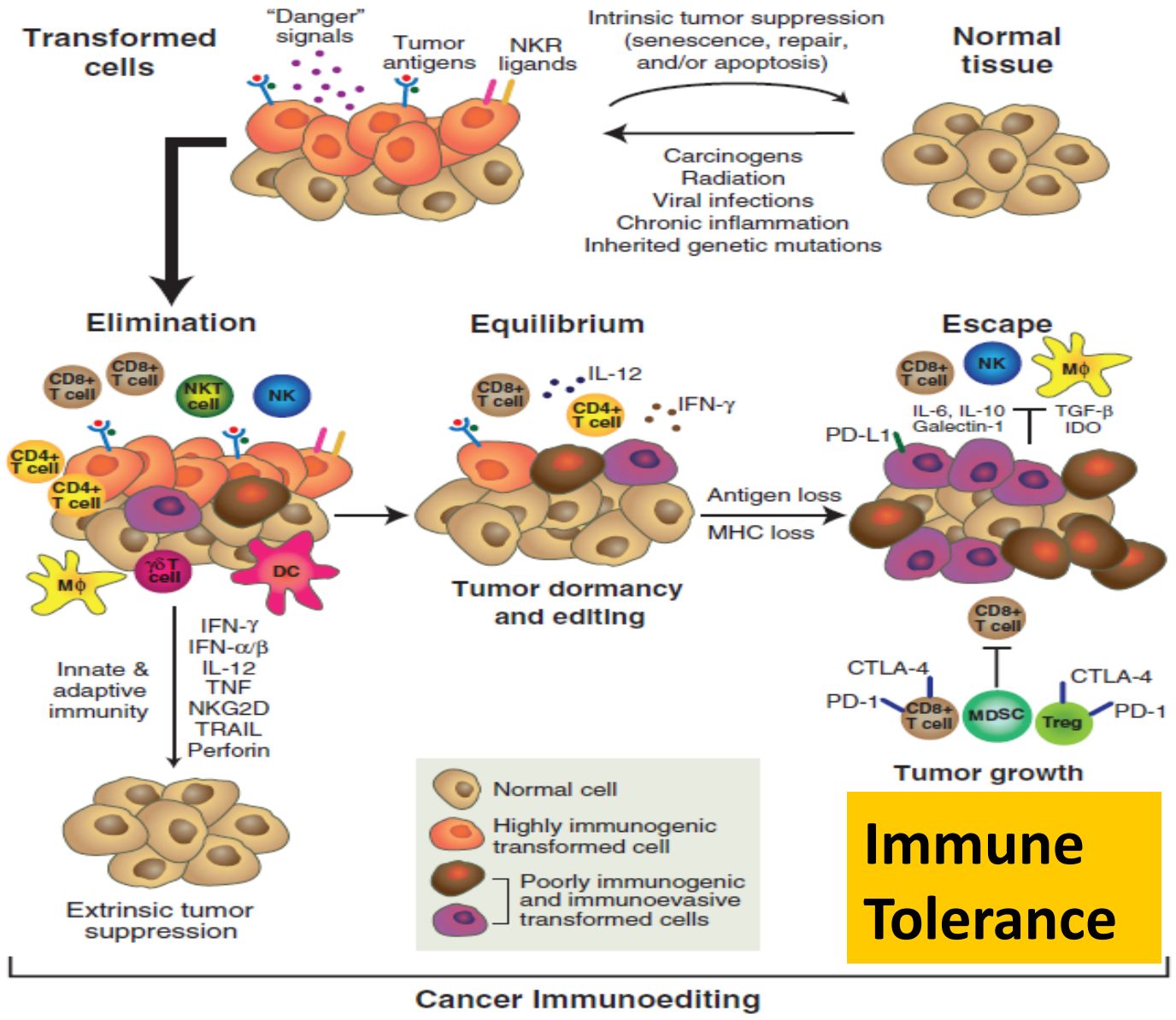
Tsai, Li et al, Cancer Cell , 2012

Summary of Molecular Responses of NSCLC Lines to Low Dose 5AZA



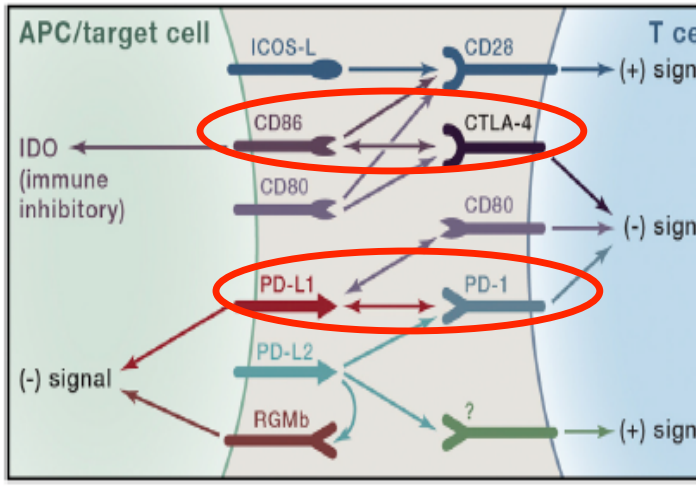
Wrangle, Wang, Easwaran, et al, 2013

Concept of Tumor Immune Evasion



Schreiber et al, Science, 2011

Breaking Immune Tolerance



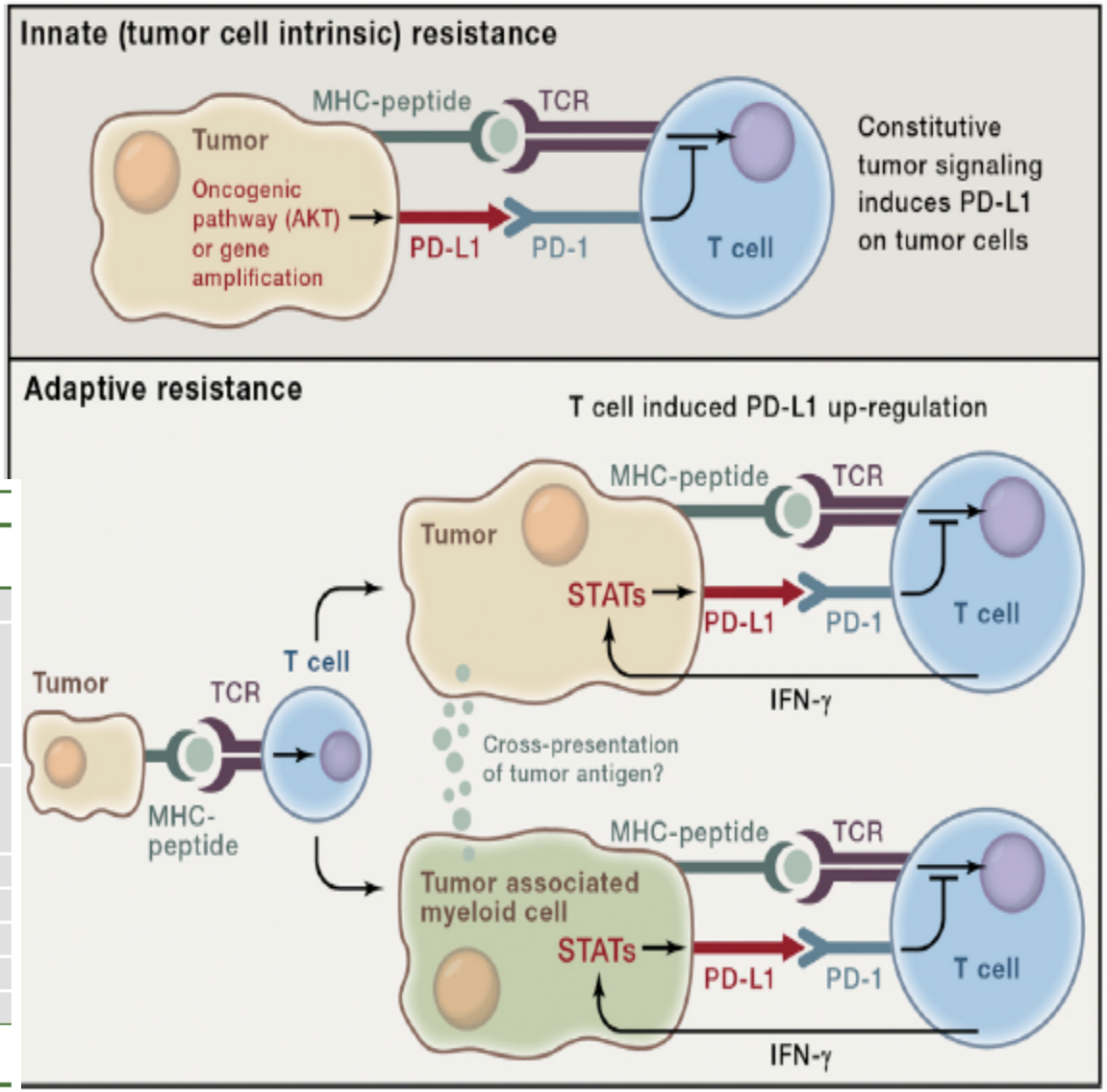
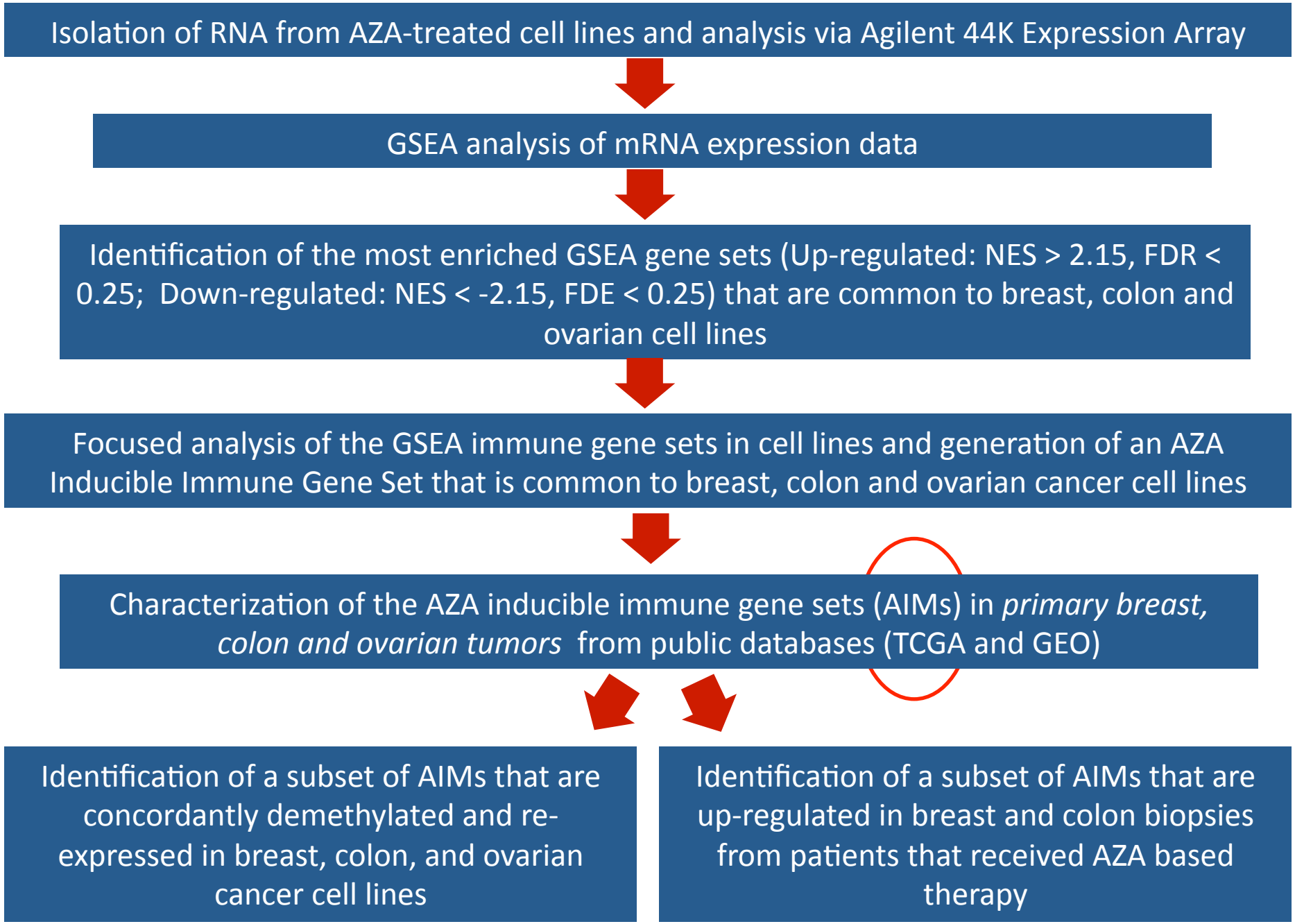


Table 1. Drugs in Clinical Development that Block PD-1 or PD-L1

Target	Drug Name	Other Names	Source	Isotype and Characteristics	Clinical Testing Phase
PD-1	MEDI0680	AMP-514	MedImmune/ AstraZeneca	information not available	phase I
	nivolumab	Opdivo, BMS-936558, MDX-1106, ONO-4538	Bristol-Myers Squibb, Ono Pharmaceuticals	fully human IgG4[a]	approved, treatment-refractory unresectable melanoma (Japan, United States) and squamous NSCLC (United States)
	pembrolizumab	Keytruda, MK-3475, lambrolizumab	Merck	humanized IgG4	approved, treatment-refractory unresectable melanoma (United States)
	pidilizumab	CT-011	CureTech	humanized IgG1	phase I-II
PD-L1	BMS-936559	MDX-1105	Bristol-Myers Squibb	fully human IgG4[a]	phase I
	MEDI4736	none	MedImmune/ AstraZeneca	Fc-modified human IgG1[b]	phase I-III
	MPDL3280A	RG7446	Genentech/ Roche	Fc-modified human IgG1[b]	phase I-III
	MSB0010718C	none	EMD Serono	fully human IgG1[a]	phase I-II

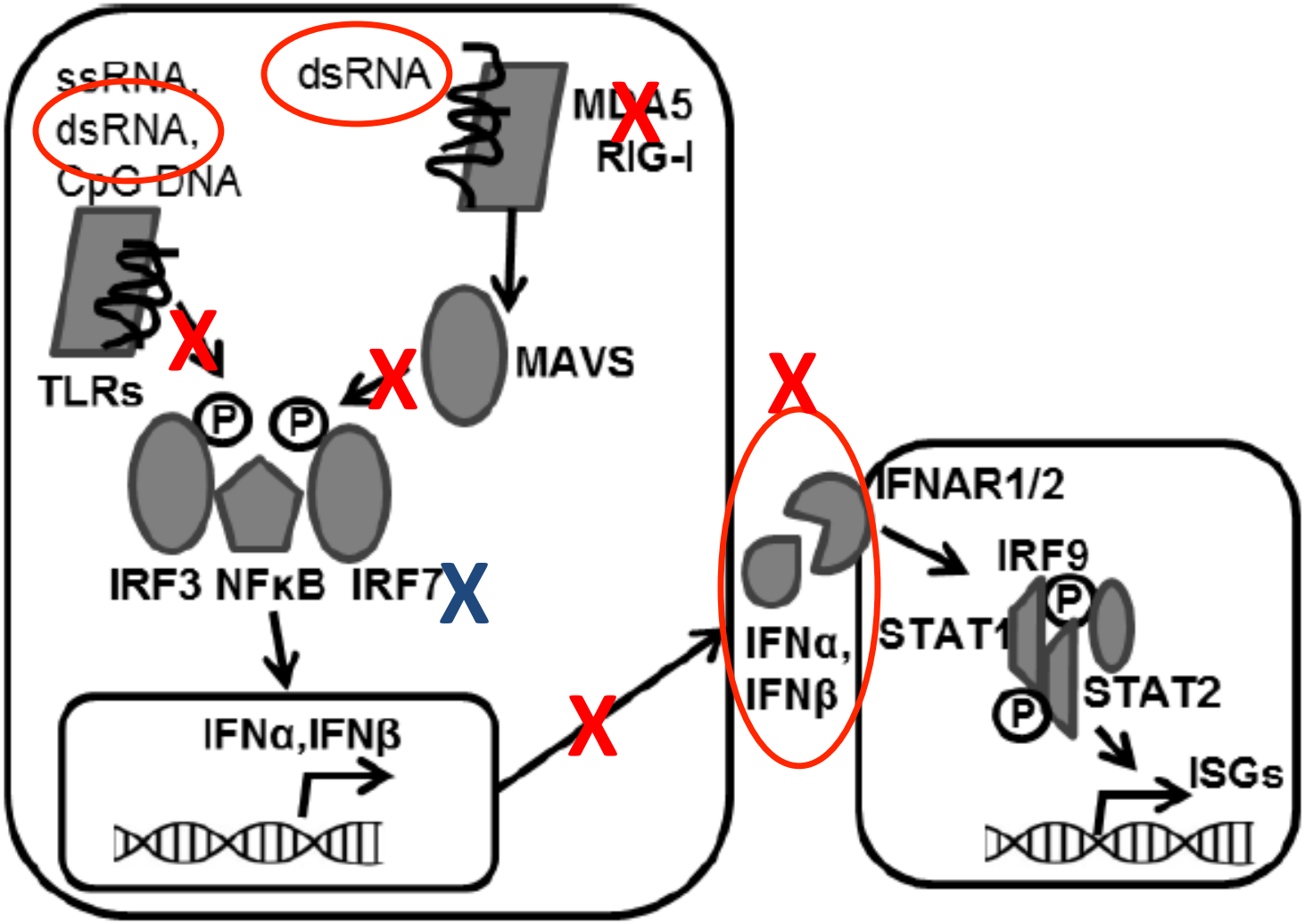
[a]Fully human mAbs were produced in genetically engineered mice.
[b]Fc-modified mAbs were engineered to abrogate ADCC and complement-dependent cytotoxicity (CDC).

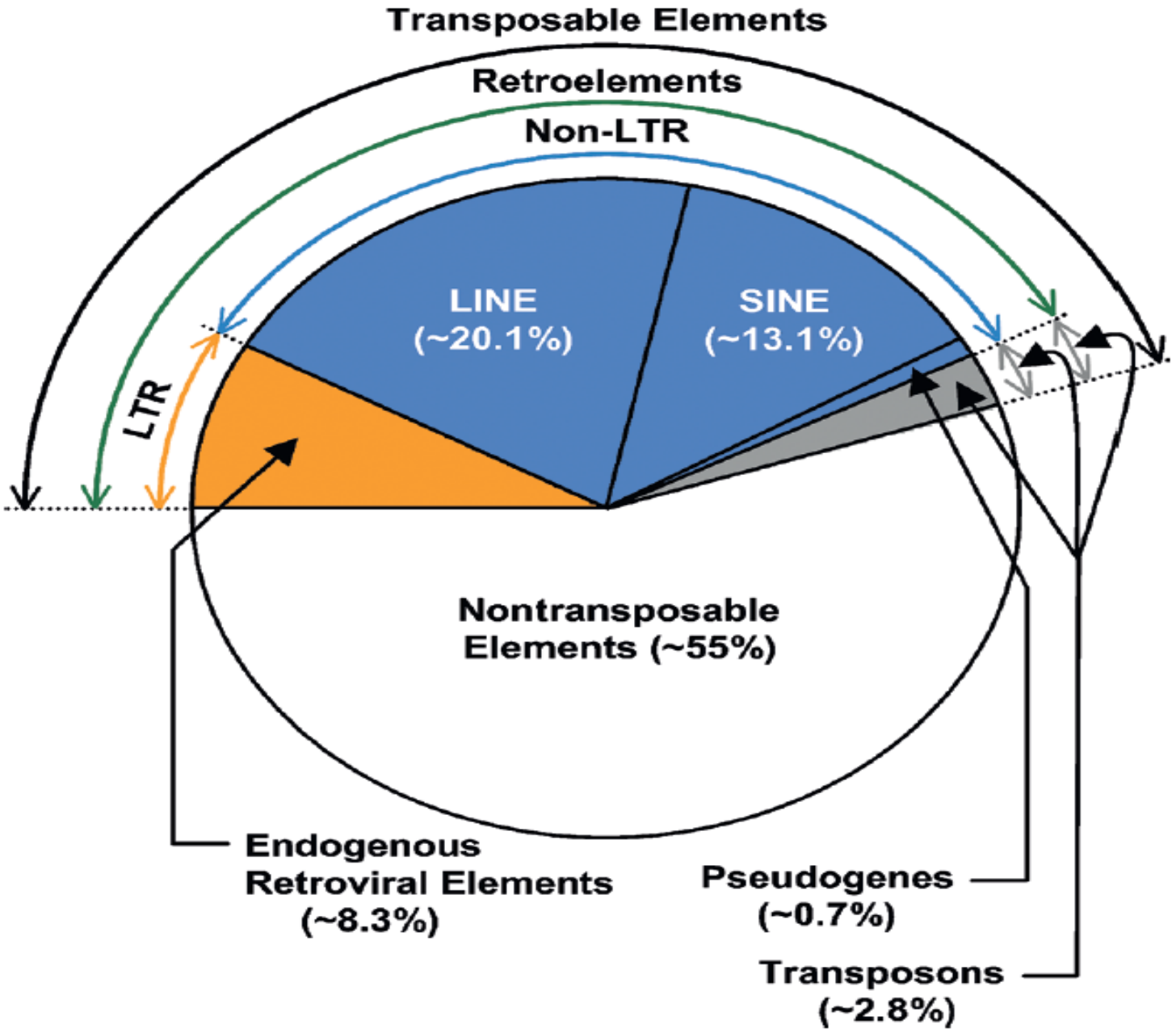
Topalian et al, Cancer Cell, 2015



Li, Chiapinelli, et al, 2014

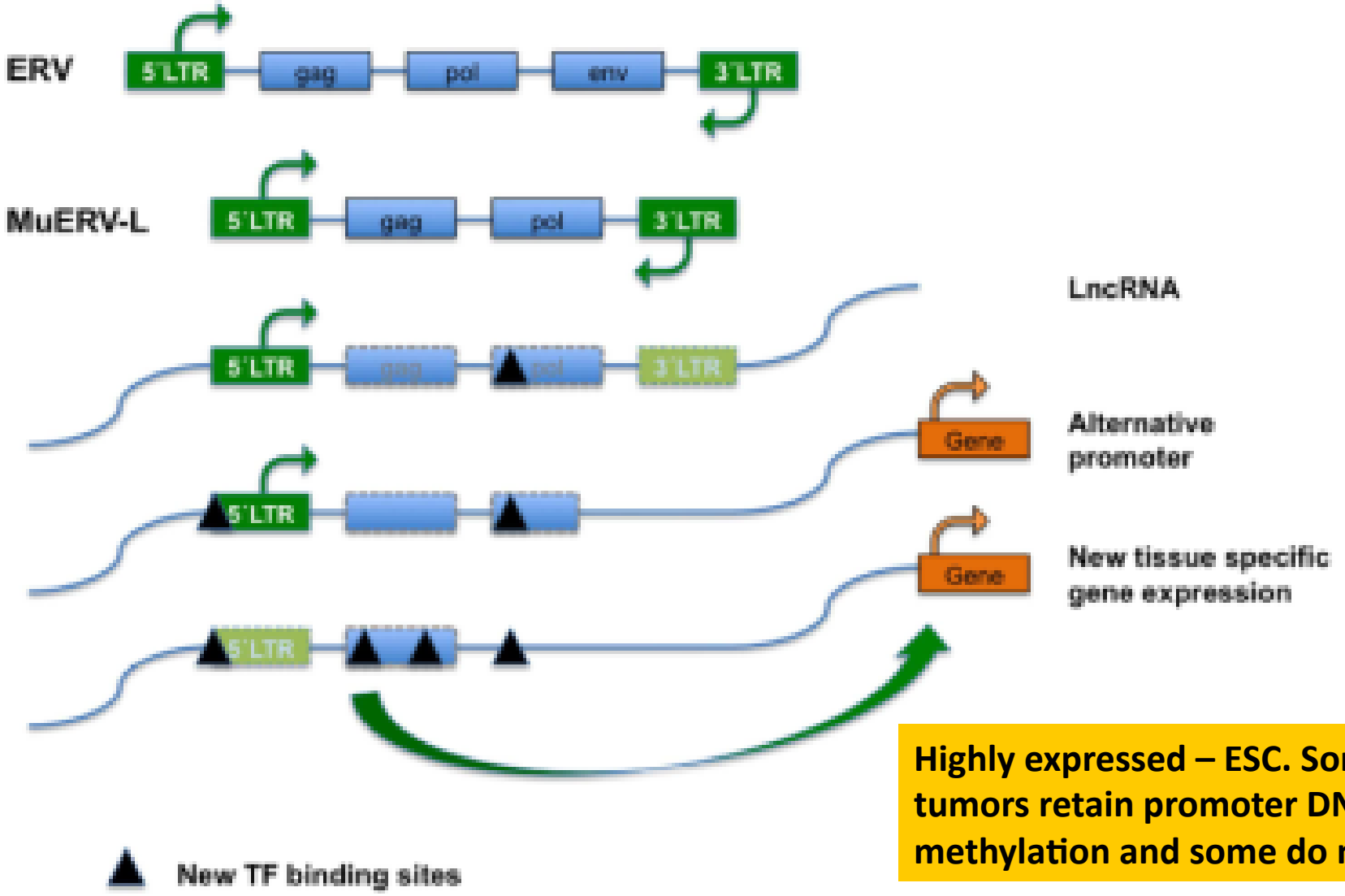
Viral Defense - Nucleotide Sensing





Cho K et al, Shock, 2008

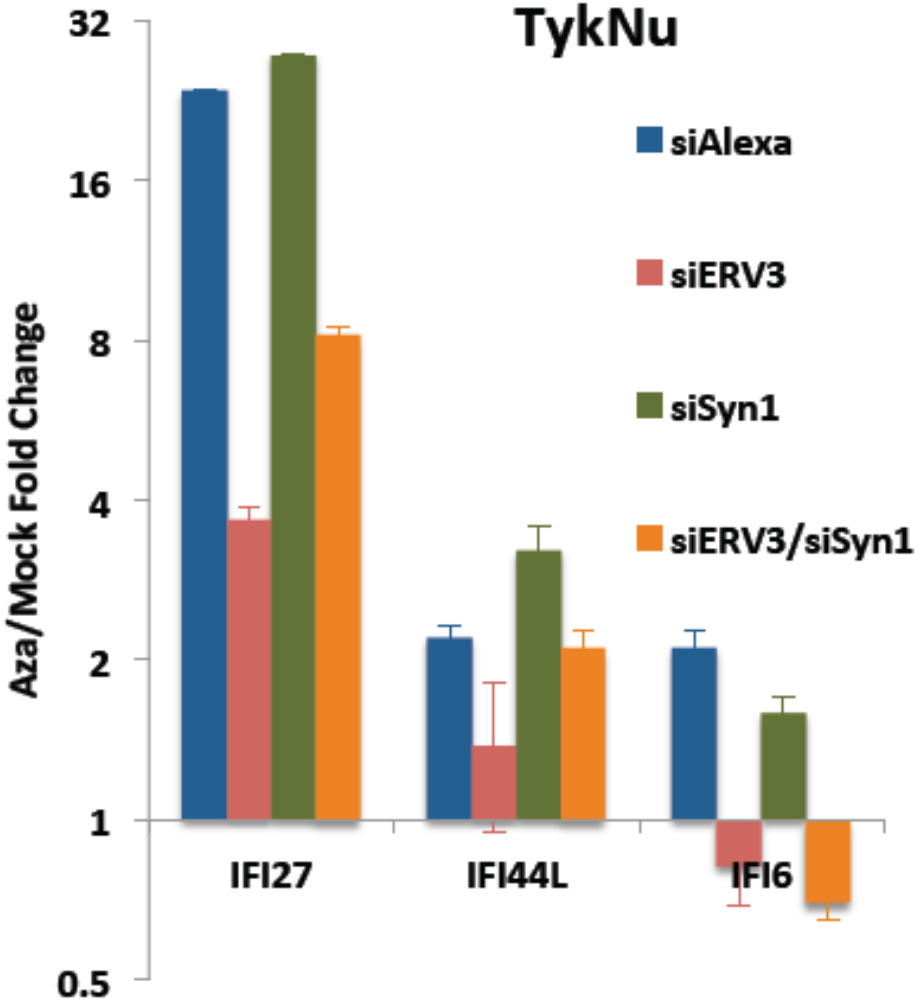
Structure of Endogenous Retroviruses (ERV's)

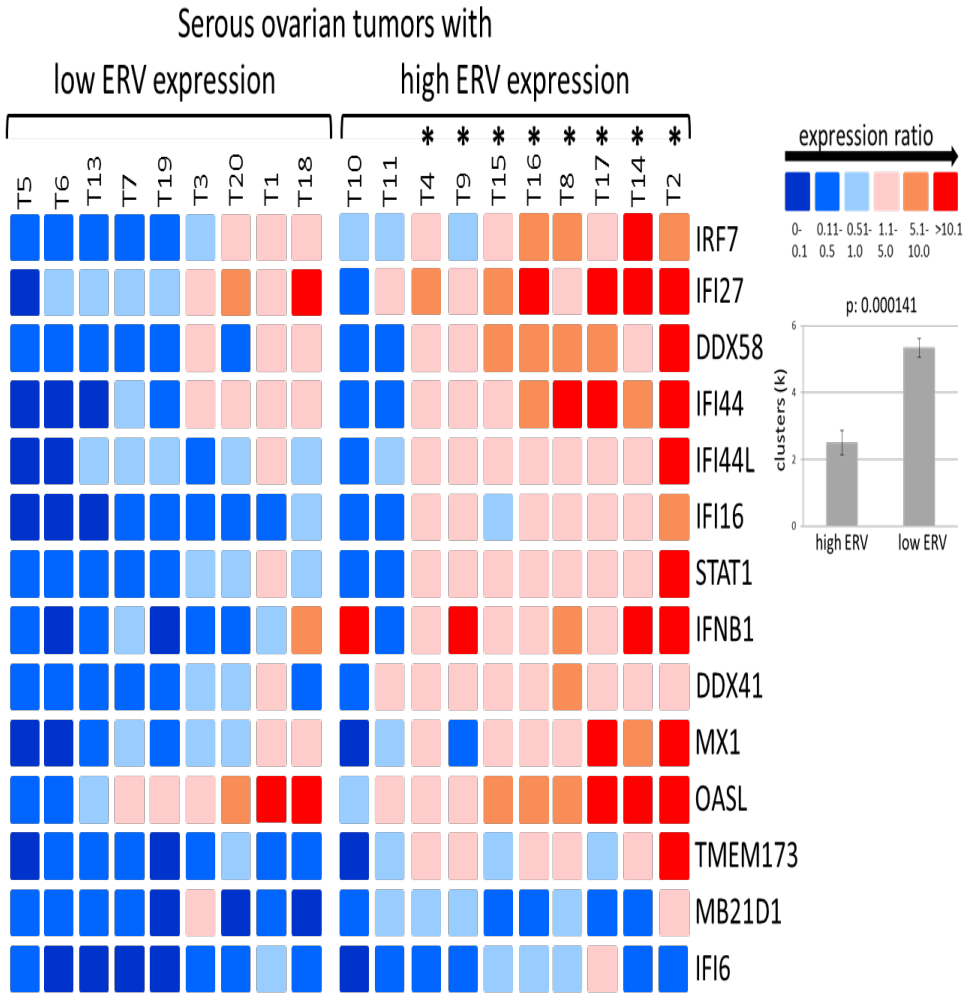


Highly expressed – ESC. Some tumors retain promoter DNA methylation and some do not

Schoorlemmer et al, Front Oncol, 2014

Effects of ERV's KD on AZA Induction of ISG's in TYKNU Cells

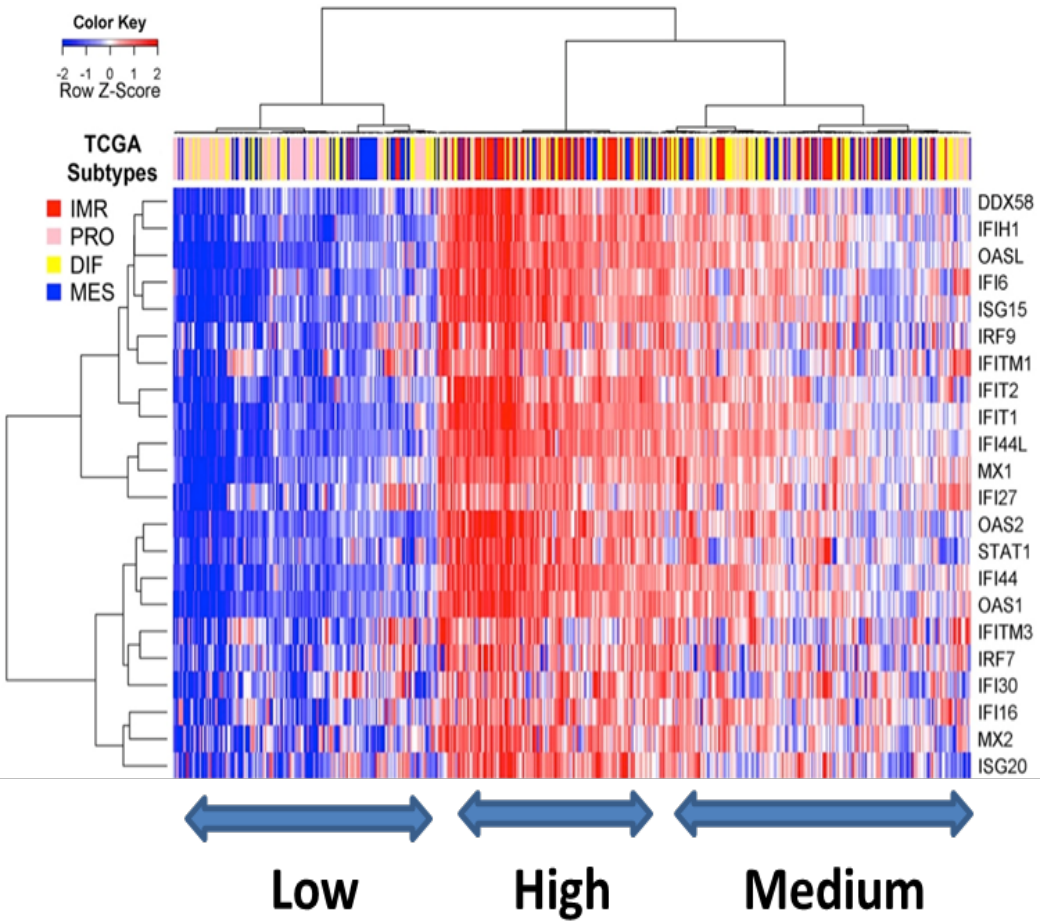




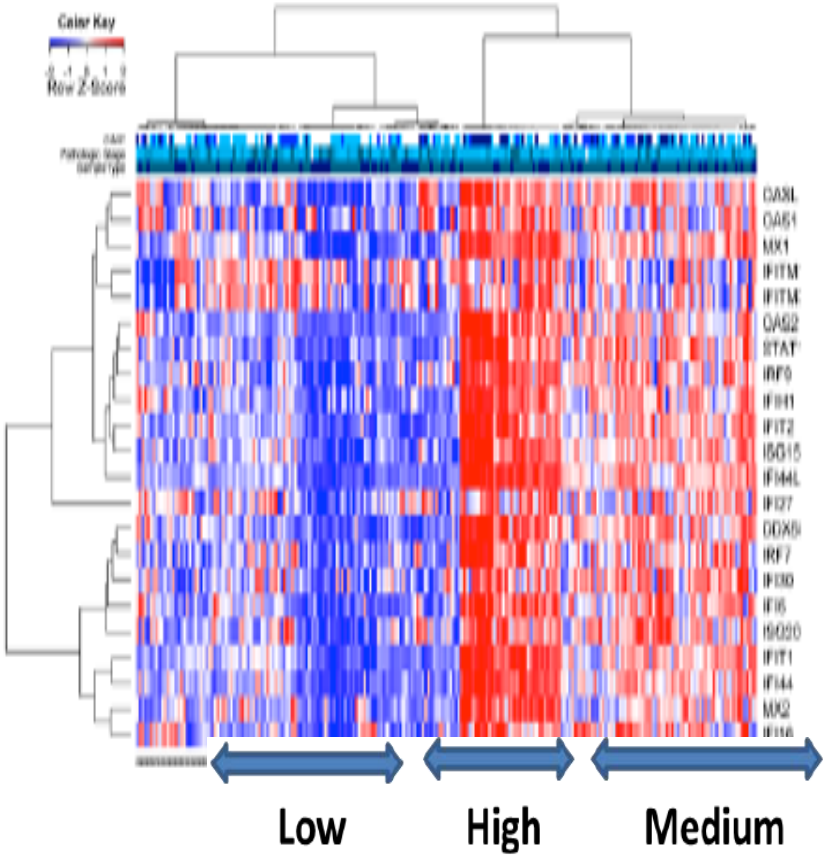
Chiapinelli, et al, Cell, in press

TCGA RNA-seq

Ovarian Cancer K=3

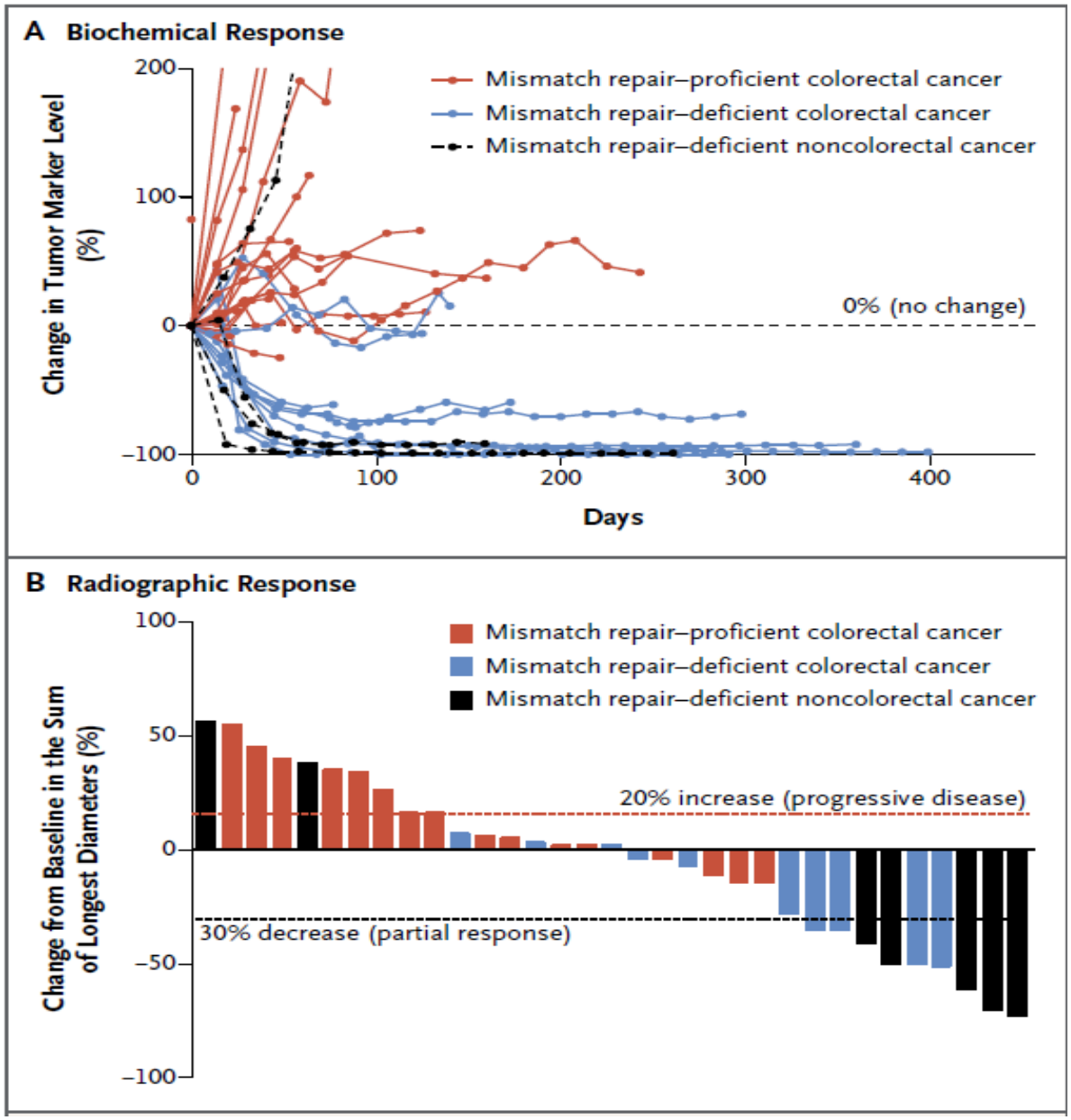


Colorectal Cancer k=4



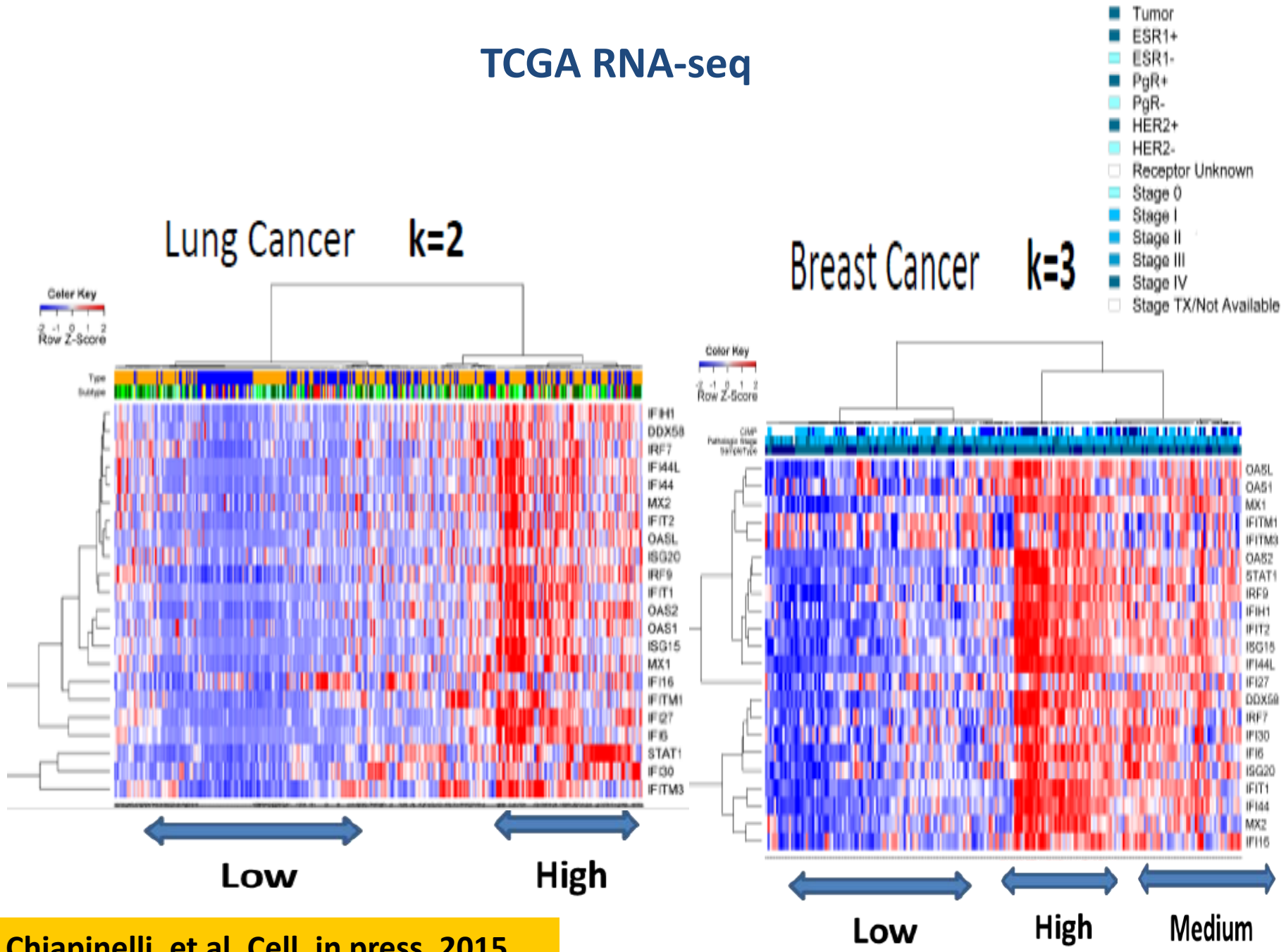
Chiapinelli, et al, Cell, in press, 2015

Mutational Burden And Resonse To Immune Checkpoint Therapy



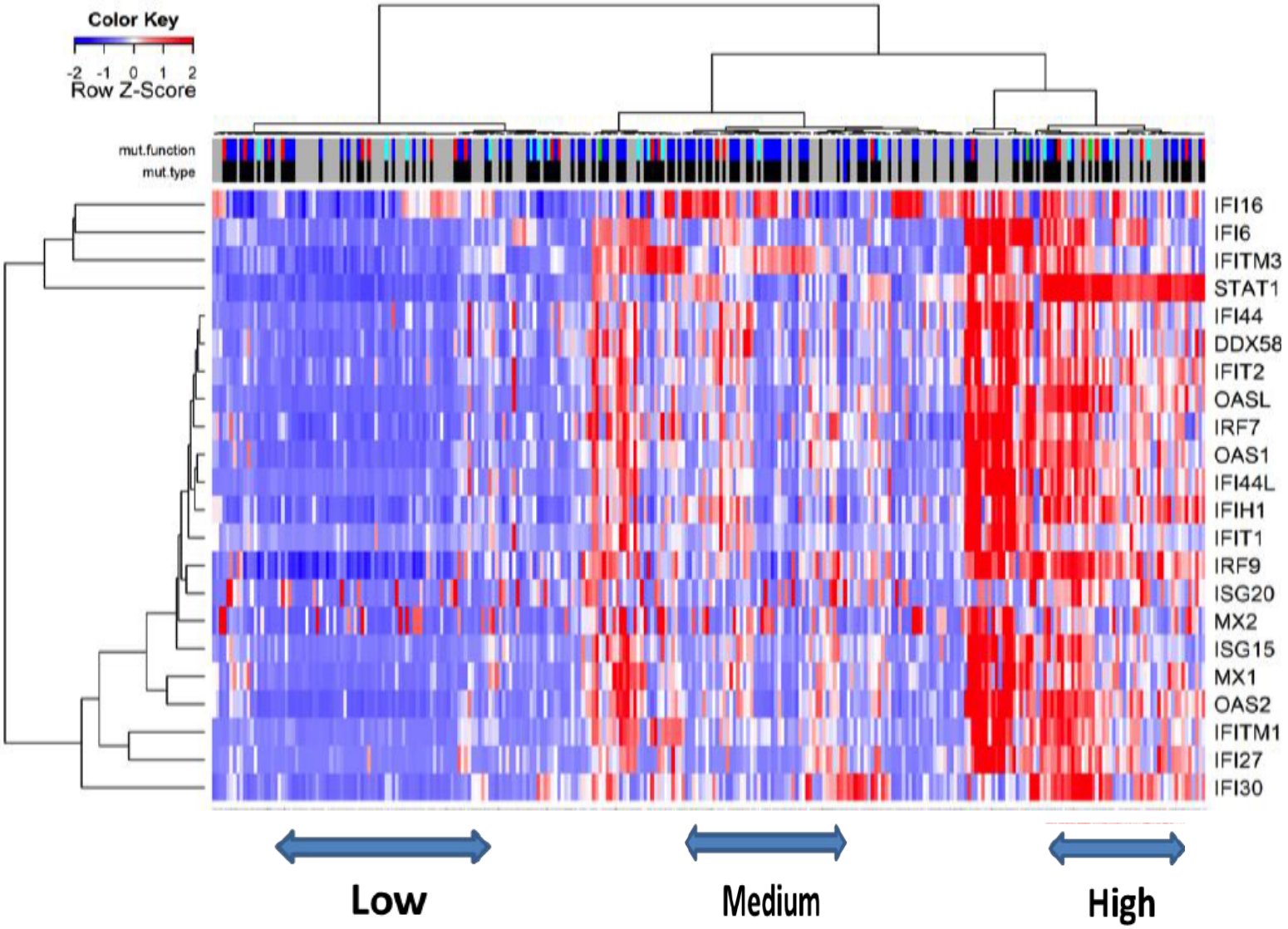
Le et al, NEJM, 2015

TCGA RNA-seq



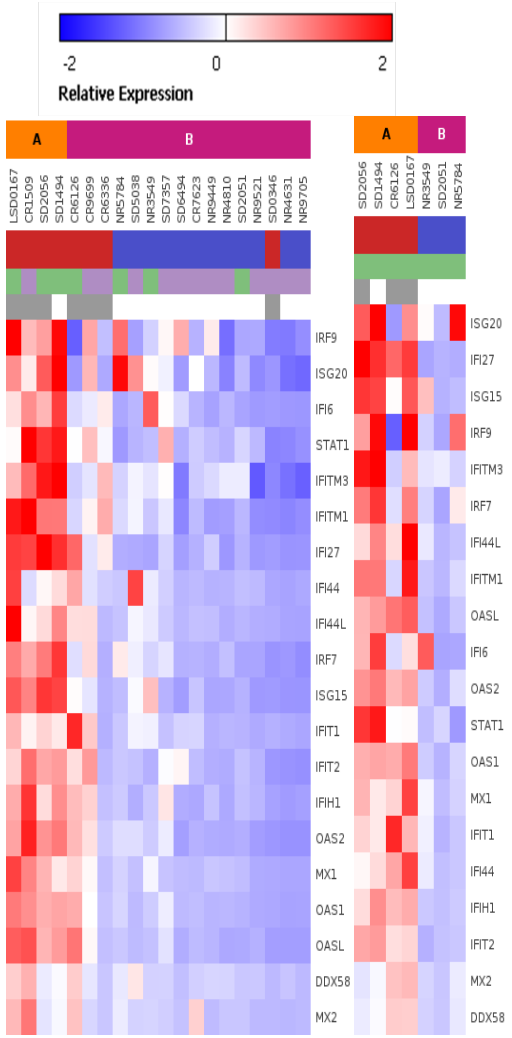
Chiapinelli, et al, Cell, in press, 2015

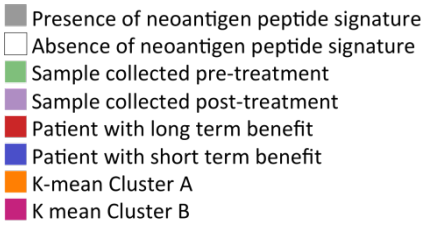
TCGA Melanoma

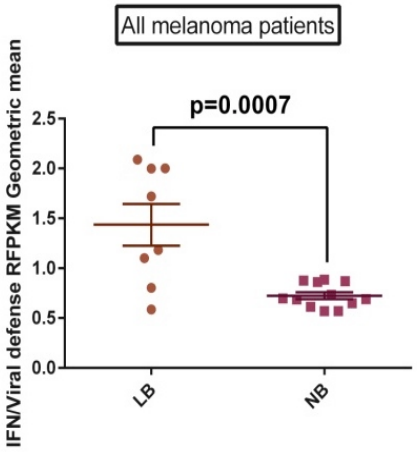


Chiapinelli, et al, Cell, in press, 2015

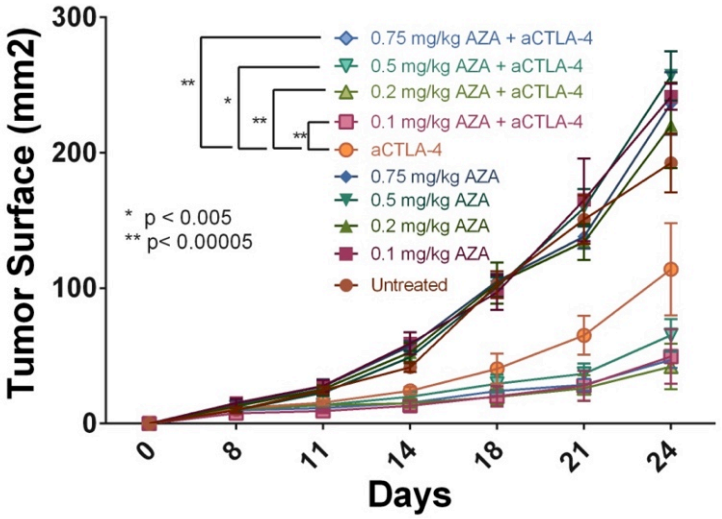
Melanoma Trial –Anti-CTLA4 (MMSK)

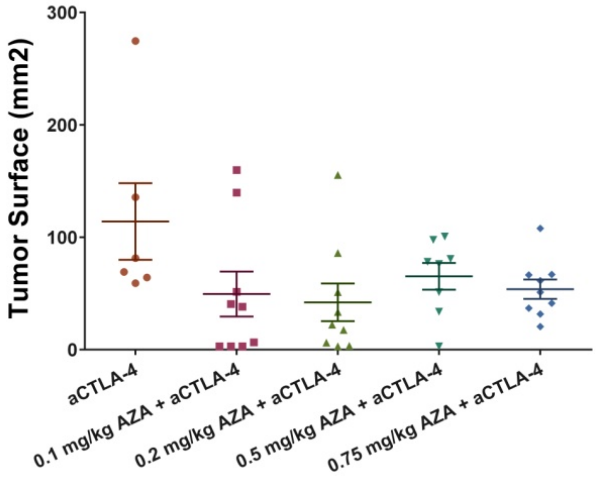






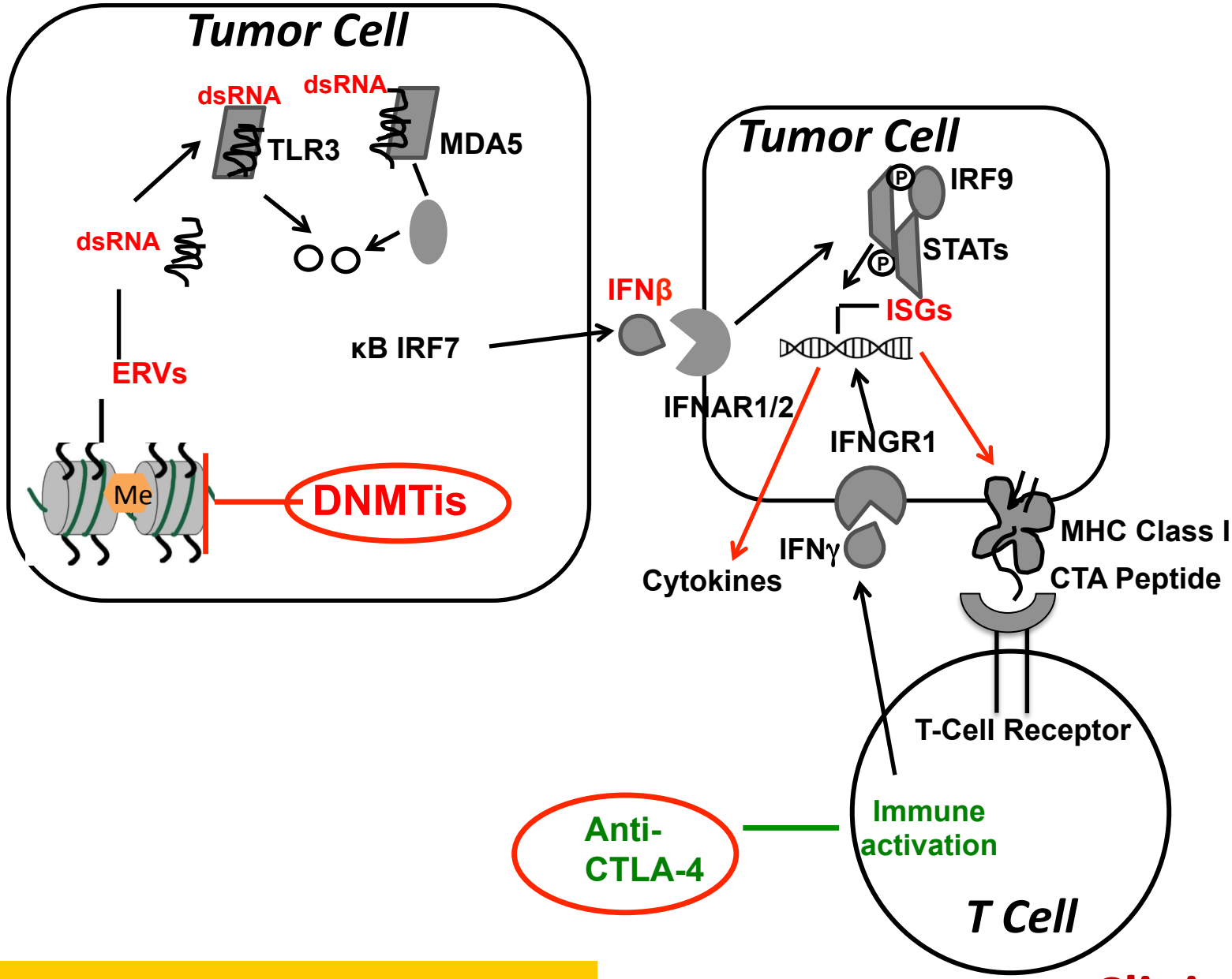
Mouse B16 model





Chiapinelli, et al, Cell, in press, 2015

Model for the Hypothesis



Chiapinelli, et al, Cell, in press, 2015

Clinical Trials!

COMBINATION BIOMARKER HYPOTHESIS

1. Mutation burden (RNA?)
2. Viral defense gene panel
3. ERV transcripts