INNOVATIONS VI
In Cancer Prevention and Research Conference

CANCER PREVENTION & RESEARCH
INSTITUTE OF TEXAS

Coming up after the break:

- **Epigenome and Cancer: From Biology to Therapy**
  Francis Moody Ballroom

- **Reaching Rural Communities - Discussion**
  Floral Hall A

INNOVATIONS VI
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Epigenome and Cancer: From Biology to Therapy

Epigenome and Cancer: From Biology to Therapy

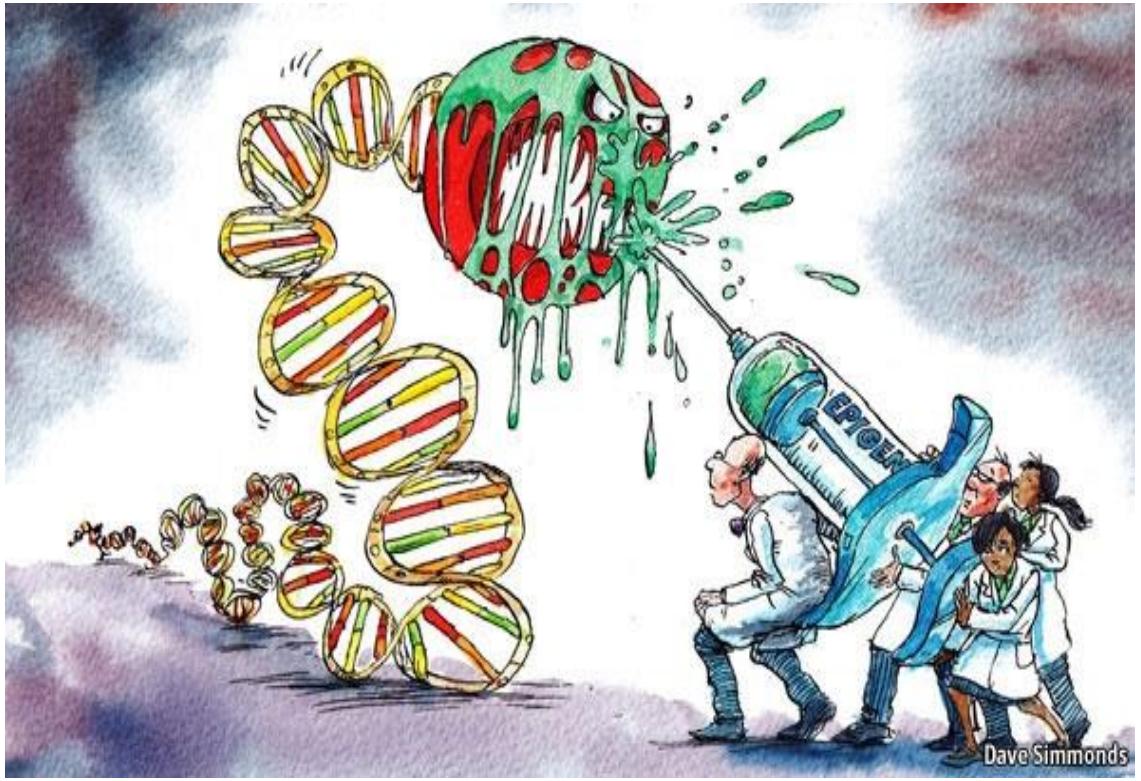
Pre-malignant Tumor Progression, Prevention and Interception

Stephen B. Baylin and colleagues

Components Of The Talk

- **A little bit of history including our group's entry into the field**
- **Molecular mechanisms underlying origins of an epigenetic abnormality we have been studying for over 30 years – very recent insights**
- **An exciting era – cancer evolution from normal cells of tumor origin and the role of their epigenetic "state", dependency of epigenetic changes for a) progression of these cells to point of cancer initiation and b) allowing driver mutations to induce cell transformation**
- **Some basic translational implications including manipulating epigenetic aspects of tumor immunology**

Who Drives Cancer?

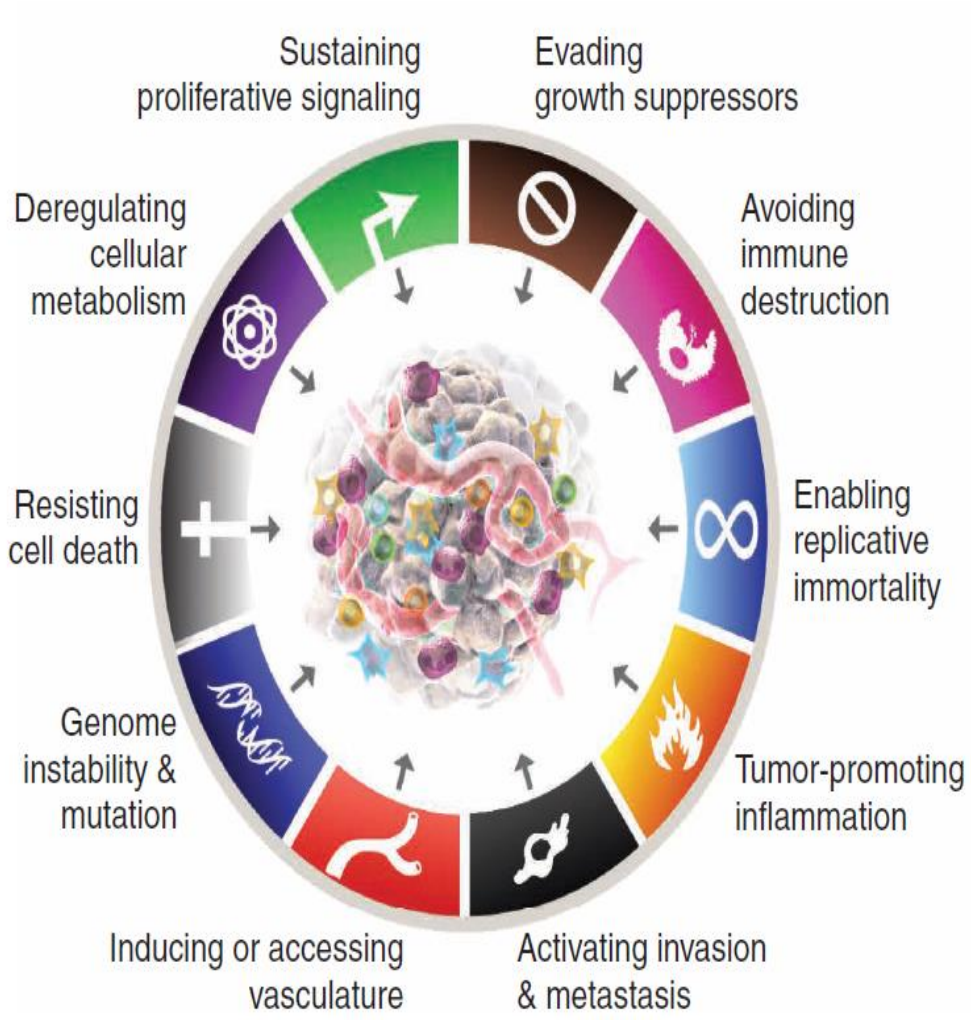


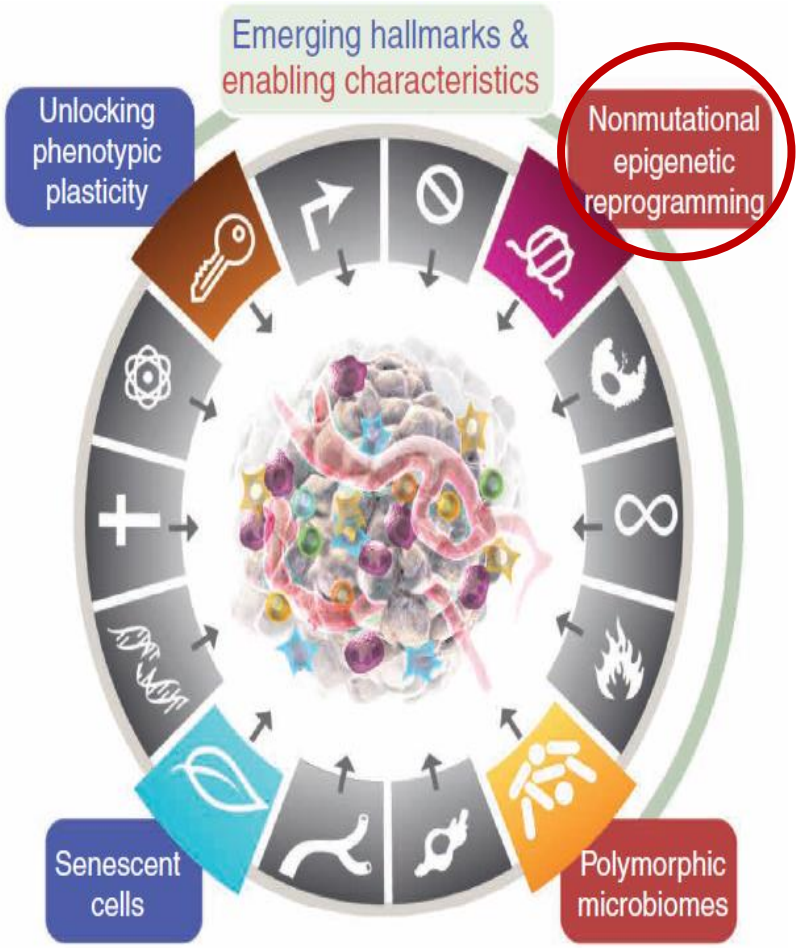
The Economist 2012

When, How?

www.bloomberg.com/news/articles/2019-03-14/

Epigenetic
Genetic
} Abnormalities ?





Hanahan, Cancer Discovery , 2022

Epigenetics = the cell, not the DNA does the work!

Martinez Arias's apparent goal, like Ireland's, is to push aside Occam's razor and free us from the inclination to accept simple answers. Sometimes the truth is the murky old news that's been sitting right in front of us the whole time — undiluted, unsavory and complex.

"Since the discovery of the structure of DNA," Martinez Arias writes, "it's become common to refer to DNA as the 'book of life,' a text made up of a sequence of letters — A's, G's, C's and T's — that serves as an instruction manual for building organisms. But what are the instructions for, and who carries them out?"

Frankenstein Experiment

Martinez Arias builds his argument against the supremacy of DNA around Frankenstein-like experiments that involve borrowing a gene from one organism and dropping it into another. Take, for instance, the fruit fly PAX6 gene. When this gene is mutated, flies develop without eyes. Yet when a human version of PAX6 is swapped in for the fly gene, it makes a fly with fly eyes, not a fly with human eyes = the cell, not the DNA does the work!

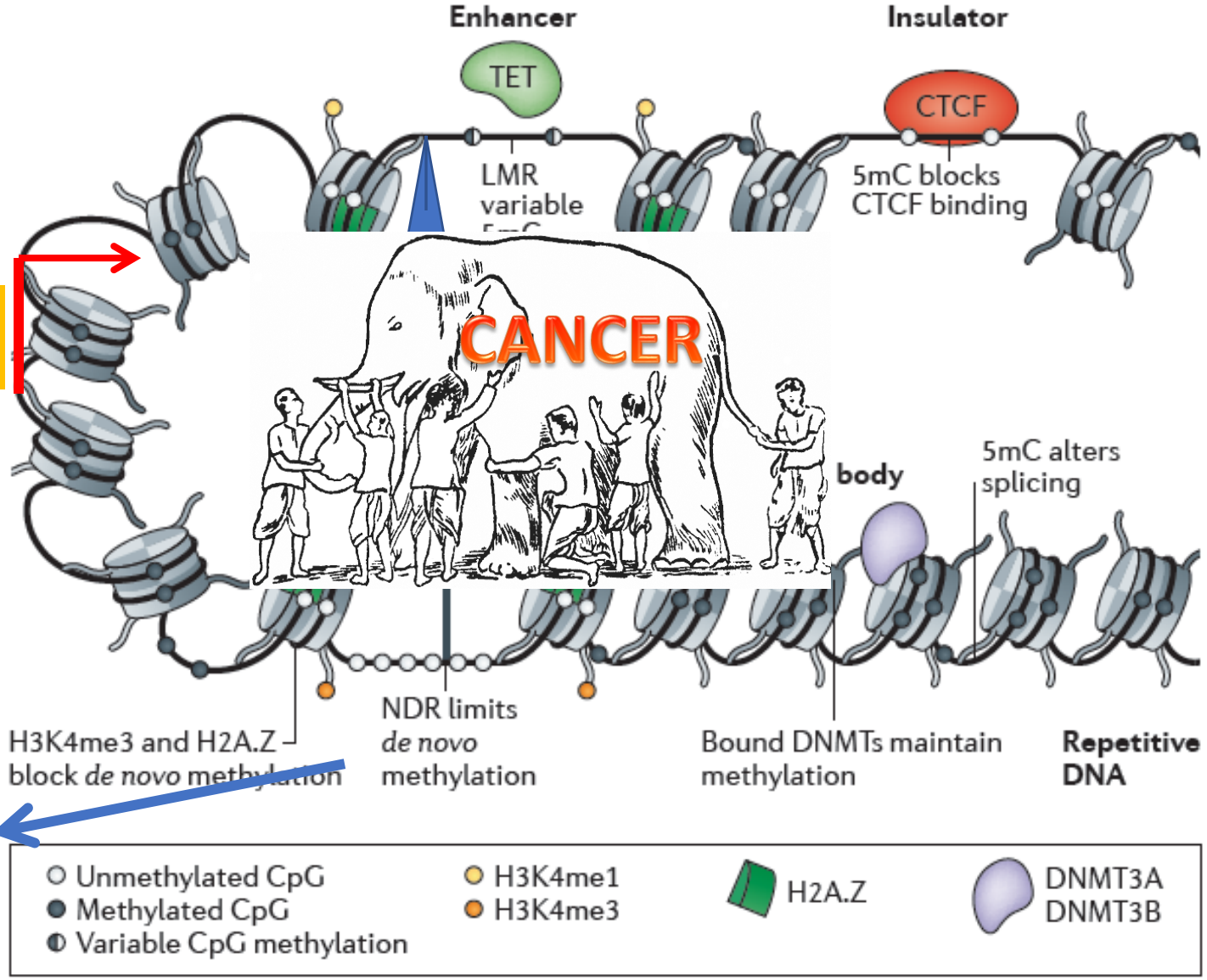
NY Times Book Review – The Master Builder by Alfonso Martinez Arias, developmental biologist for over 40 years

Putative Therapeutic Target -The Epigenome

1) What is the balance – between the regions, and the types, of change ?
2) Who are the passengers vs drivers?

****
MiRNA's
LncRNA's

Key repeat sequences including ERV's



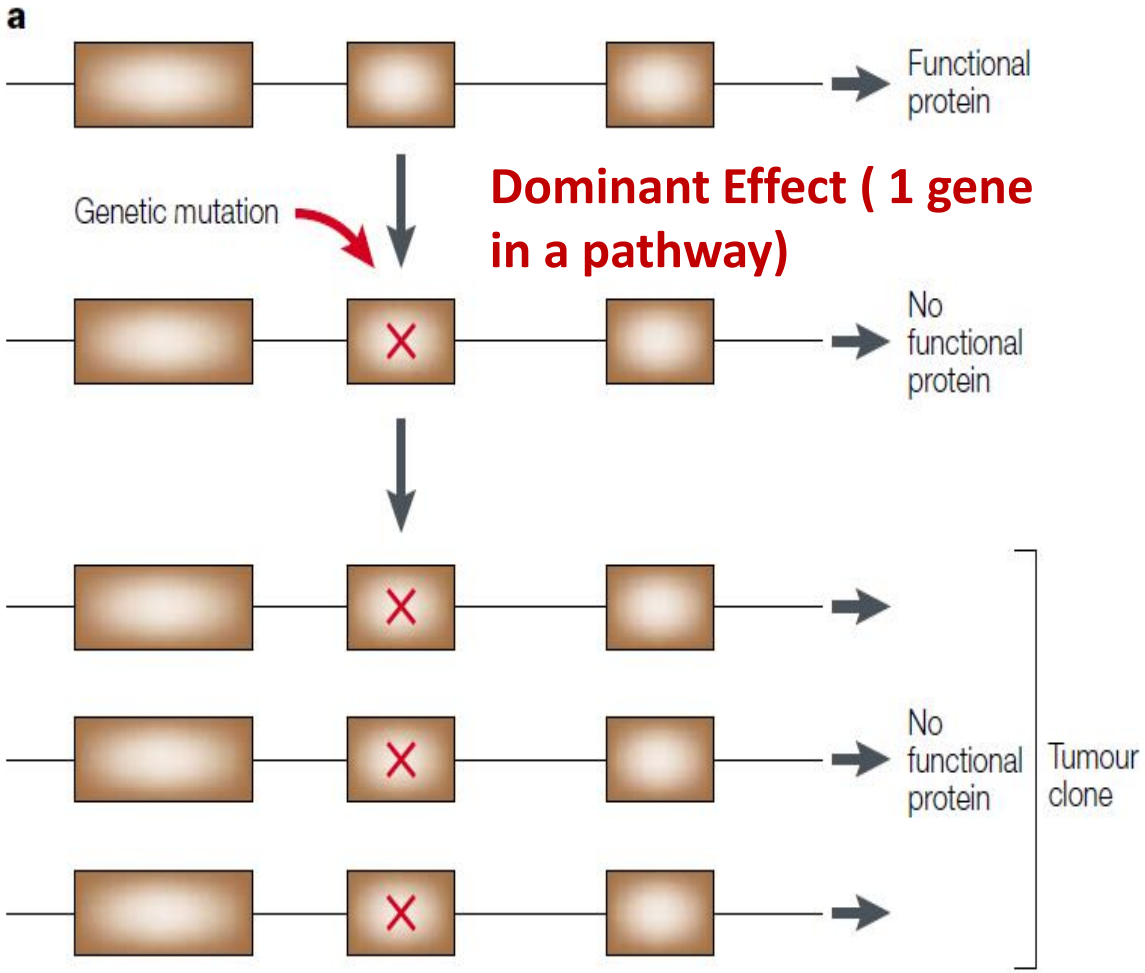
Tumor Suppressors

***CDKN2a (p16)**
***Rb**
***BRCA1**
ECAD
VHL

60 to 80% - PcG, bivalent promoter genes

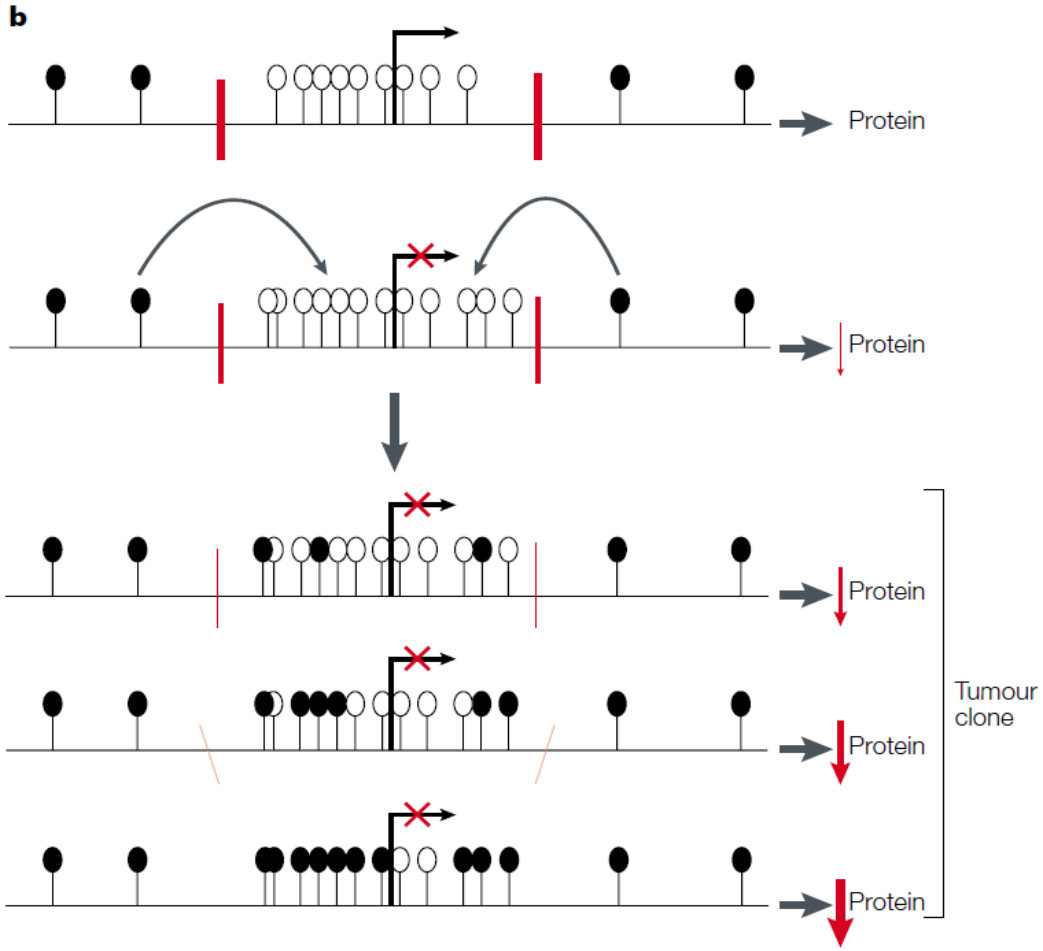
Jones, Nat Rev Genet, 2012

Genetic Alteration vs Promoter Hypermethylation



Dominant Effect (1 gene in a pathway)

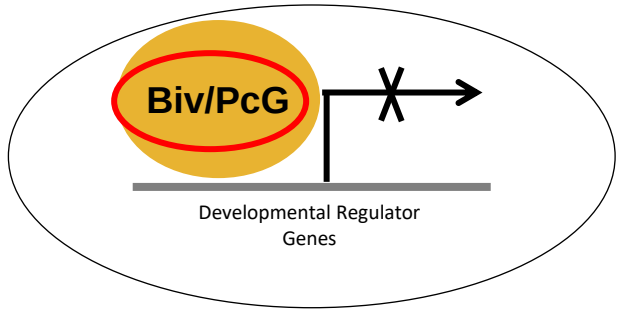
Haploinsufficiency – multiple genes in a pathway



How and when does this evolve in tumorigenesis?

Jones and Baylin, Nat Rev Genet, 2002

Hypotheses for Molecular Progression to DNA Hypermethylation of Many PcG Target Genes in Cancer – Cancer As An Epigenetic and Genetic Disease



Low, poised Expression and **inducible!!**

Embryonic/ Adult Stem Cell

Oncogenic mutations ex. = BRAF, MYC & KRAS

Many, many more "epi" driver genes for this paradigm than we expected

Convert senescence to cell oncogenic addiction?

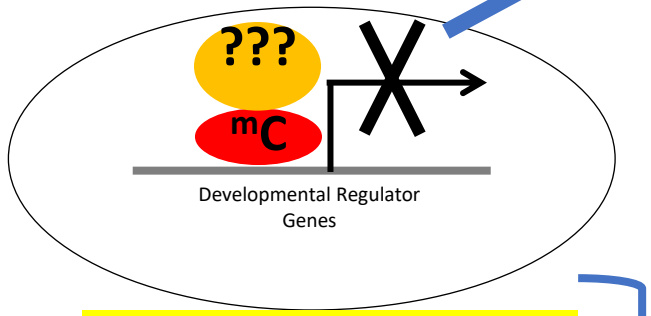
Key link of developmental genes to cancer risk with aging?

Molecular progression

Tumors can be anywhere in here

Epigenetic difference

Locking in the survival of a "relatively primitive" cell population???



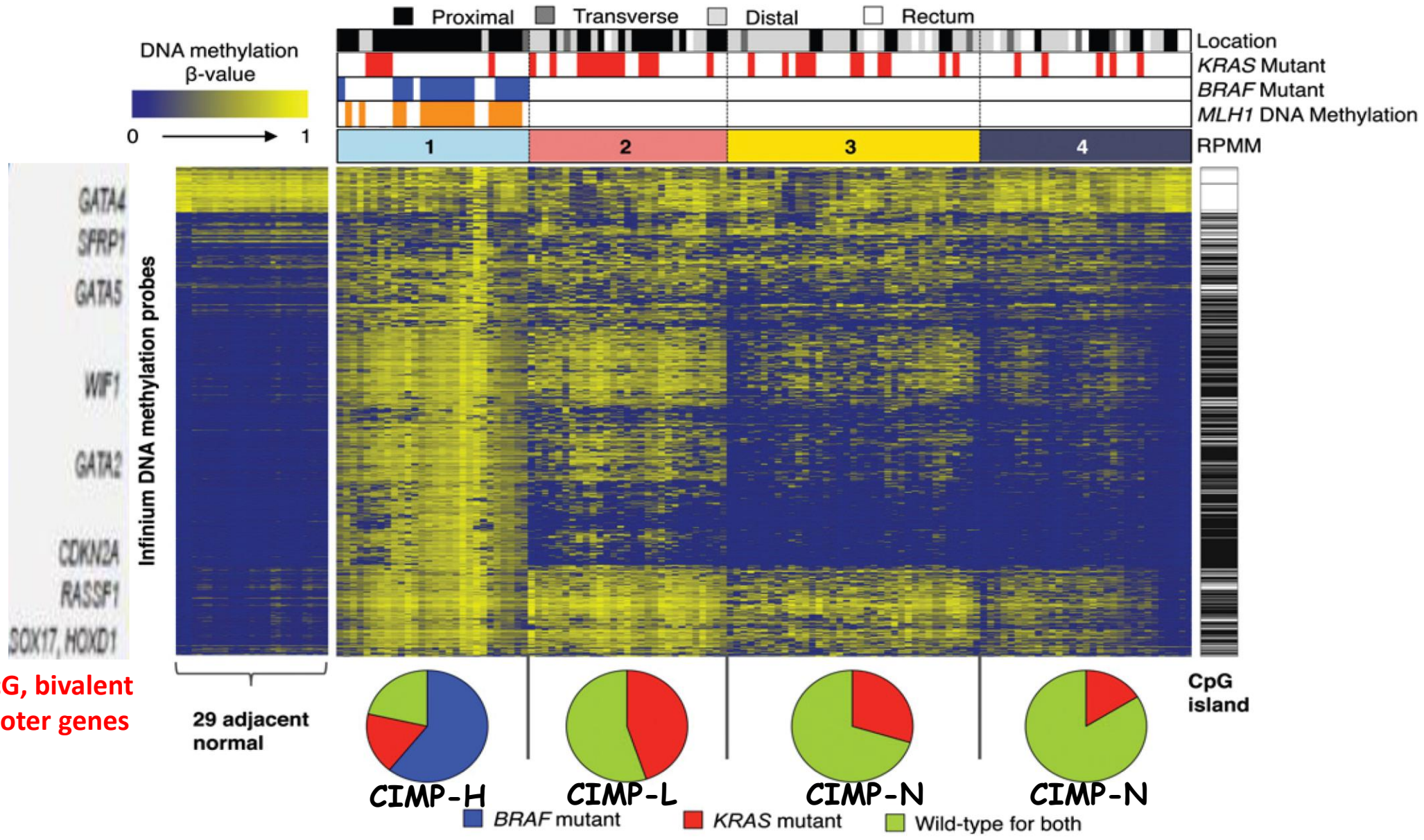
Cancer Cell

Lower Expression and **poorly inducible!!!**

60 to 80%

Easwaran, Johnstone, Collison, Ng et al, 2012

DNA methylation subtypes in colorectal cancers



All PcG, bivalent promoter genes

What Are The Mechanisms Underlying CIMP?

- **Role of DNA damage, especially ROS Exposure**
- **Role Of Altered Transcription Factor Expression (PcG genes dominate)**

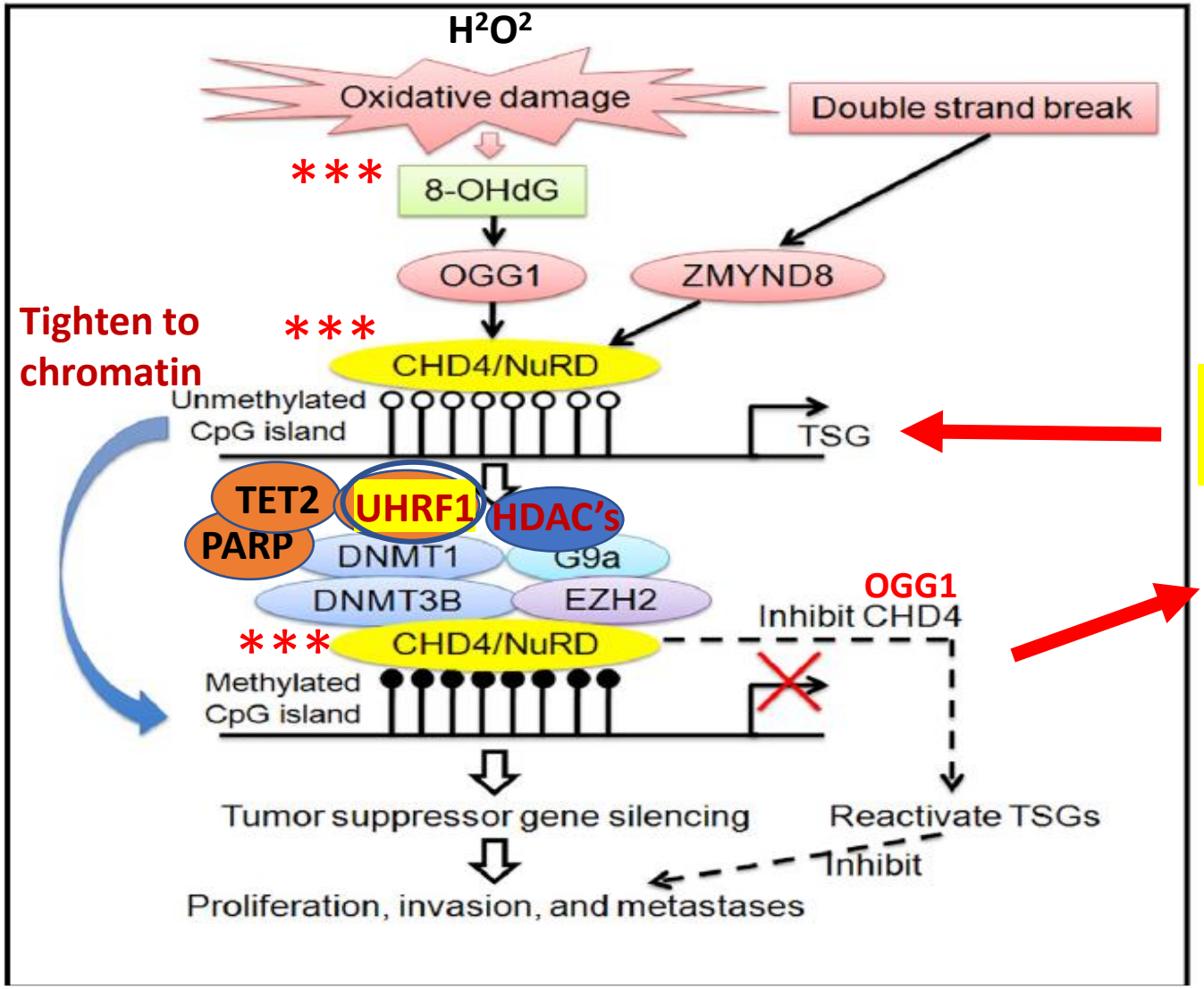
DSB's and Oxidative Damage Inducing A Systemic Signal for Repair in GC/CpG Rich Regions

Heather O'Hagan

Feyruz Rassool

Limin Xia

State Key Laboratory of Cancer Biology, Fourth Military Medical University



Inflammation
Aging
Cancer risk

60 to 80% developmental genes

Genes induced!

CDH1
WIF1
TIMP2
TIMP3
MLH1
CDKN2A
SFRP4
SFRP5

O'Hagan et al Cancer Cell, 2011

Muvarak et al, Cancer Cell, 2016

Cai et al, Oncogene, 2012
Zhang et al, Mol Cell, 2017

Xia et al, Cancer Cell, 2017

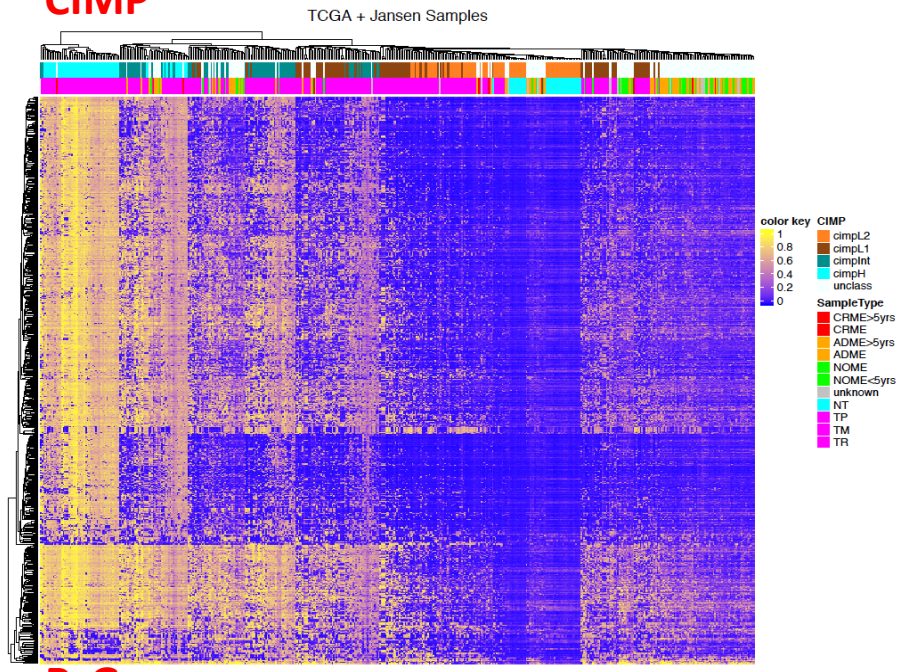
A TF Drive To Sculpting Our Microcosm Of The Cancer Epigenome

Hari Easwaran

Yuba Bhandari

Promoter Methylation (CIMP) versus Enhancer Enhancer Methylation (CEMP)

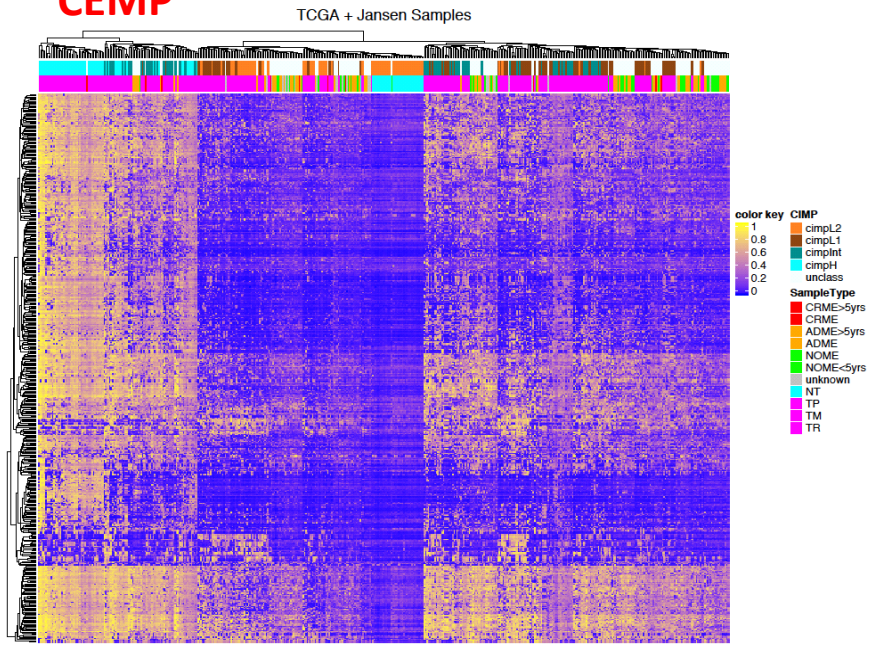
CIMP



PcG

CpG Promoters Probes (739)

CEMP



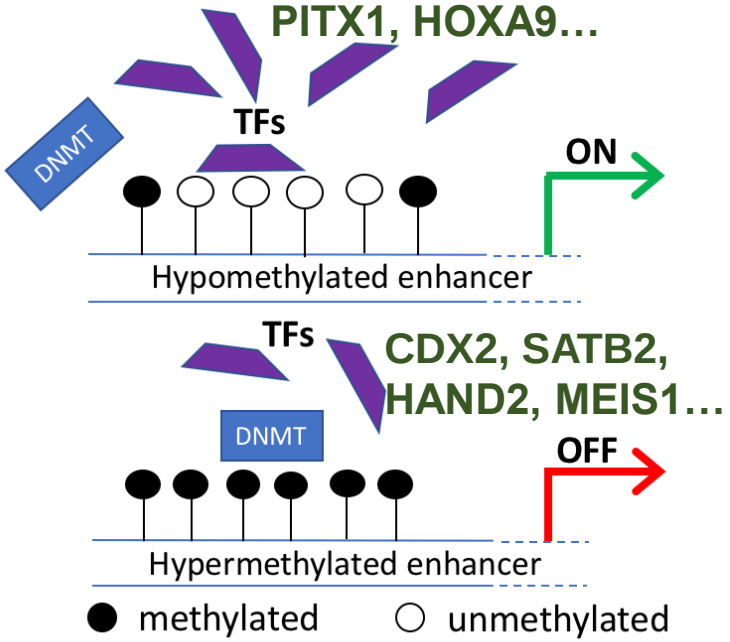
PcG

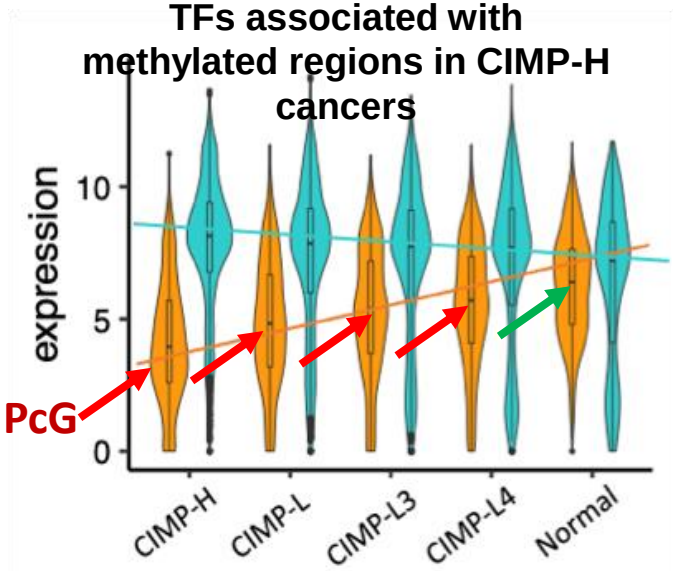
Phantom5 Enhancer Probes (501)

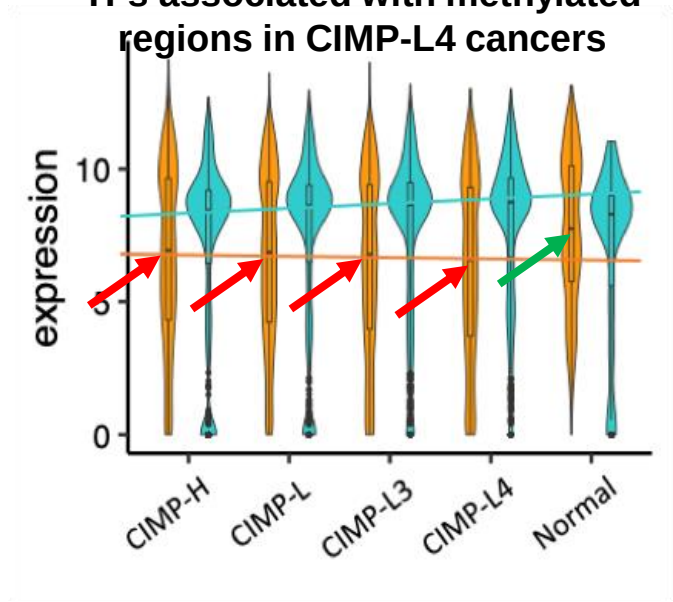
TF's (PcG) and their binding sites are linked for the cancer specific DNA hypermethylation of enhancers and the promoters of their designated target genes and expected gene expression relationships

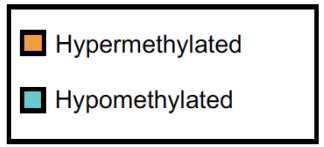
Bhandari et al, PNAS, 2023

TF repertoire forms a basis for setting the DNA methylation landscape









Bhandari et al, PNAS, 2023

Importance Of “Fixing” Cell States And Oncogenesis

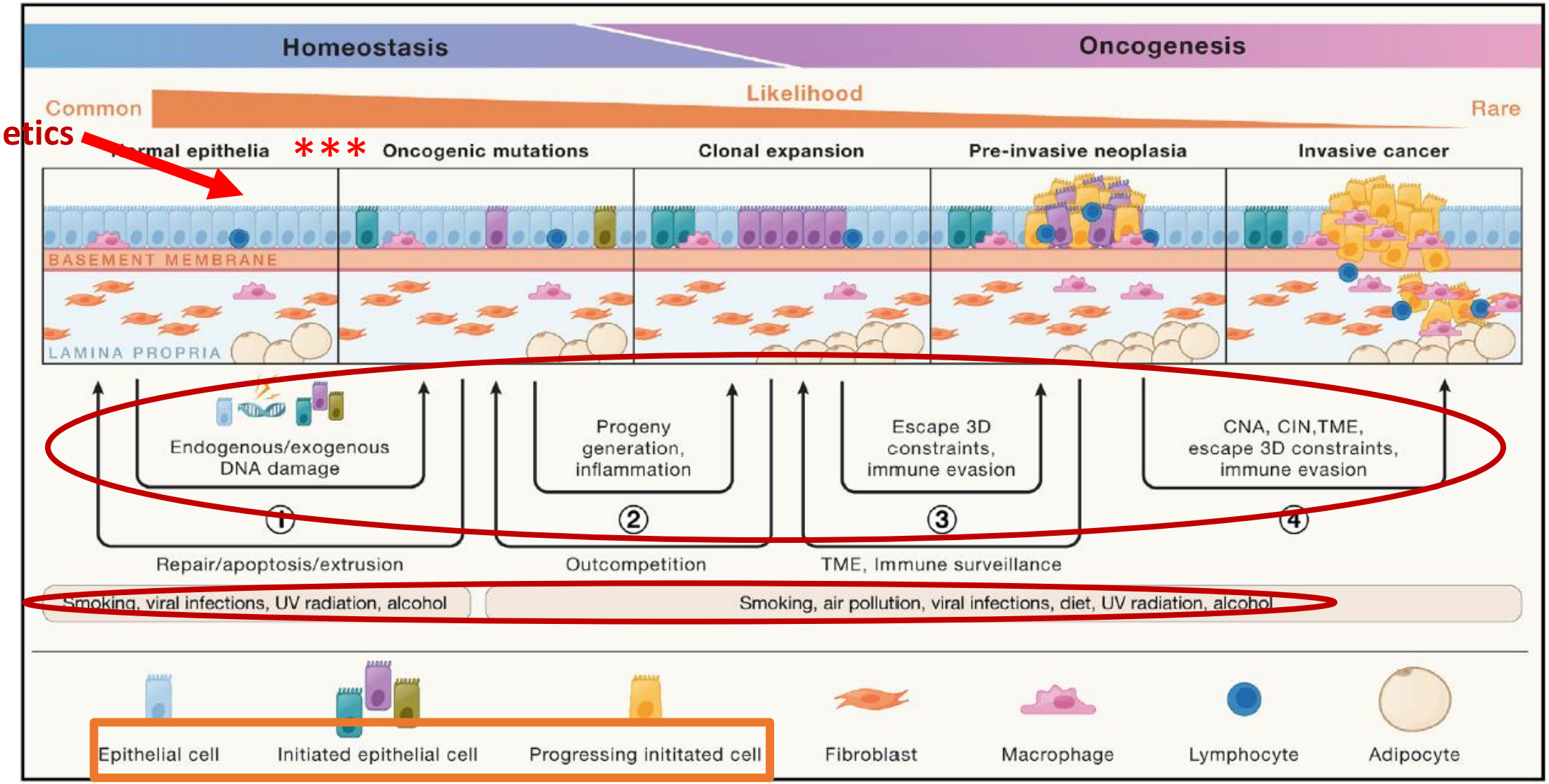
James DeGregori

Our lab seeks to understand how carcinogenic conditions promote cancer evolution and to discover pathway dependencies in cancers that can be exploited therapeutically.

- **Evolutionary based model for cancer development, Adaptive Oncogenesis.**
- **In this model, mutations (including oncogenic mutations) face fitness landscapes (cell states and memory thereof = epigenetics!)**
- **We propose that long-lived multicellular organisms have evolved stem cell populations with high fitness = serving to maintain the status quo, preventing somatic evolution.**
- **But in stem cell pools damaged by aging, irradiation or other insults, the fitness landscape will be dramatically altered = selection for mutations and epigenetic events that improve perverse fitness and fixation of oncogenically initiated cells.**
- **These studies could lead to discovery of adjuvants to current therapies that will more effectively treat or possibly even cure leukemias.**

Importance Of “Fixing” Cell States And Oncogenesis

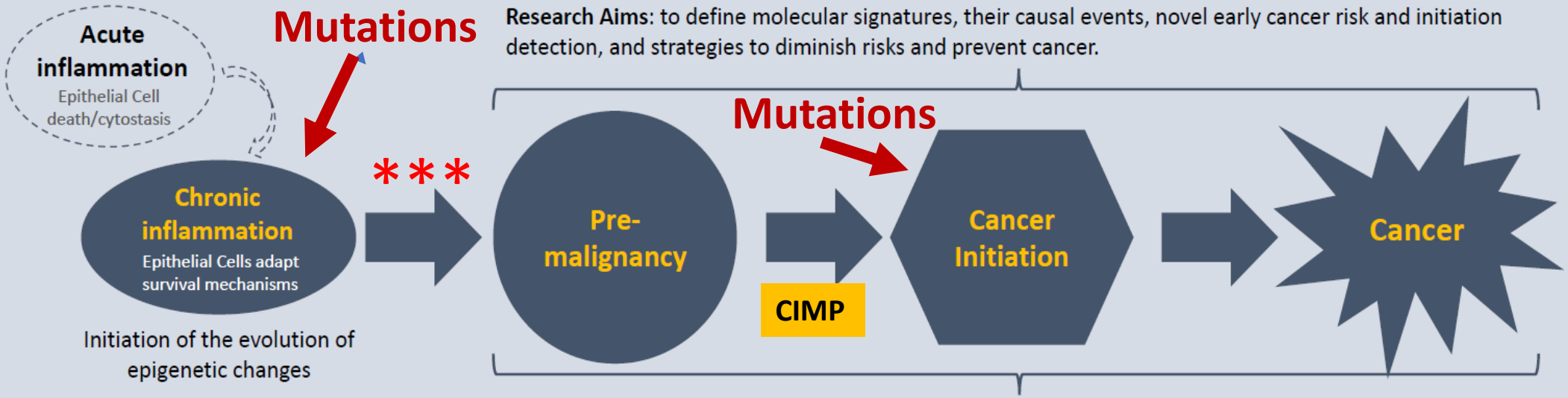
Epigenetics



Parent cell of tumor origin fate!! Determined in development and parent stem cell renewal in adults

Swanton and colleagues, Cell 186, April 13, 2023

Inflammation as a Driving Agent in Tumorigenesis through Epigenetic Remodeling



Research Aims: to define molecular signatures, their causal events, novel early cancer risk and initiation detection, and strategies to diminish risks and prevent cancer.

Epigenetic changes further evolve in *epithelial, microenvironment*, and *immune cells* and help drive immune evasion and permit oncogenic addiction to mutated oncogenes and tumor suppressors.

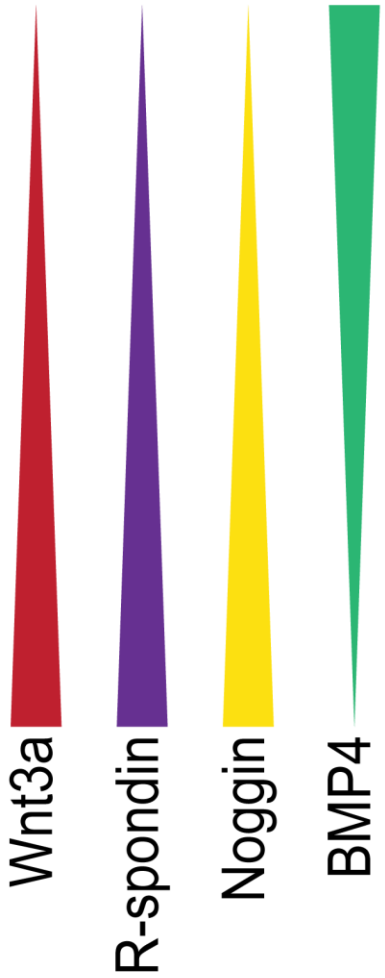
Above Evolution of Events Can Be Causal for Key Cancer Risk Factors:

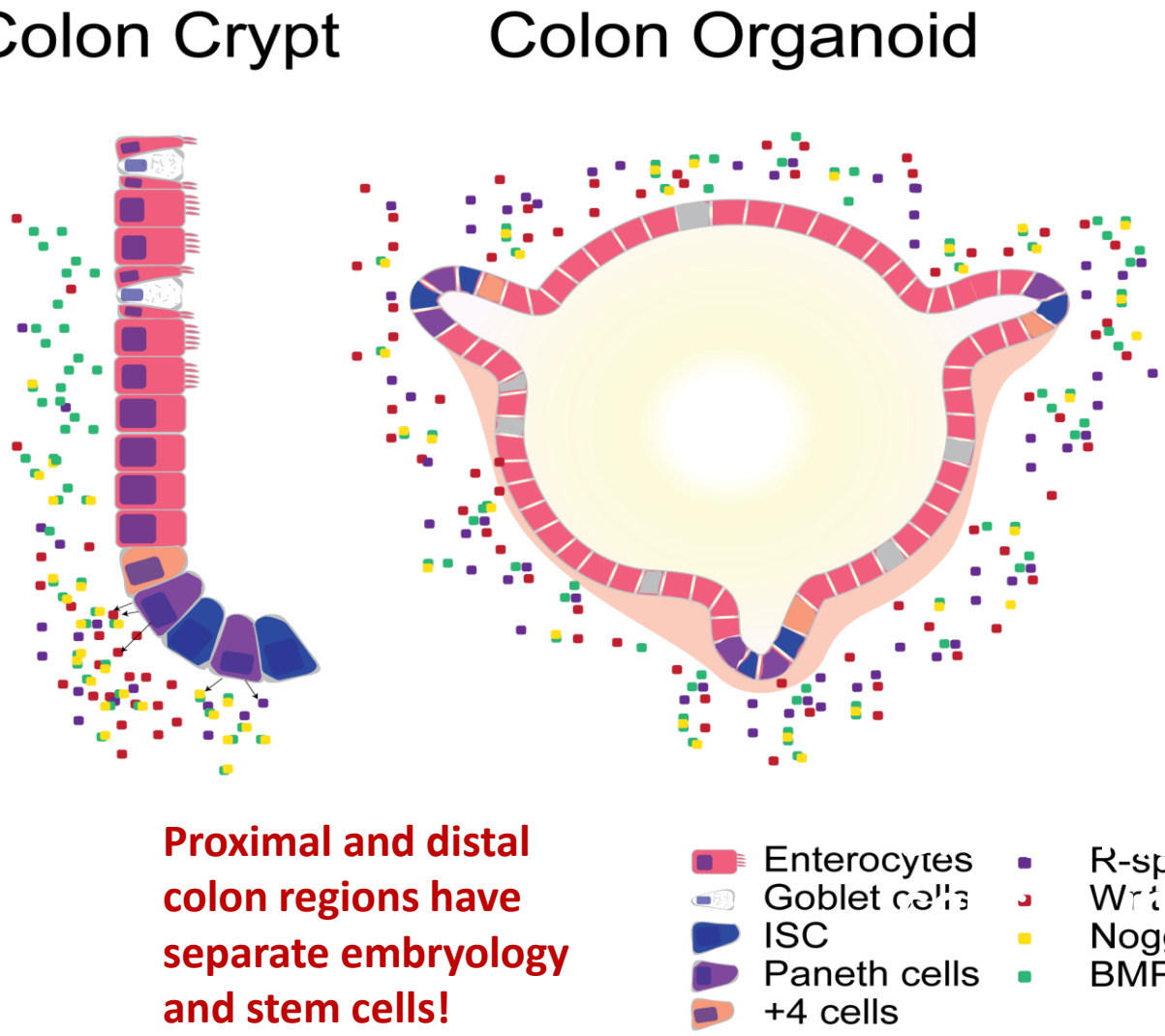
- Aging
- Environmental exposures
- Dietary habits (high fat/carb = metabolic imbalance)
- Obesity
- Exposure to pathogens/infections **VIRUSES Mitochondria**

→ Contributions for evolution of and causal effects for Chronic Inflammation driving cancer risk and initiation

Translational implications: targeting epigenetic reprogramming to derive prevention, interception, early cancer therapy, and biomarker strategies

Ex vivo modeling of early steps in tumorigenesis using colon organoids

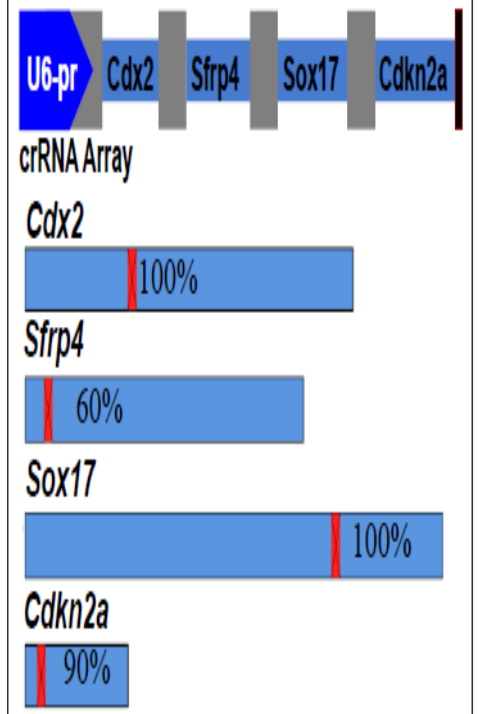




Proximal and distal colon regions have separate embryology and stem cells!

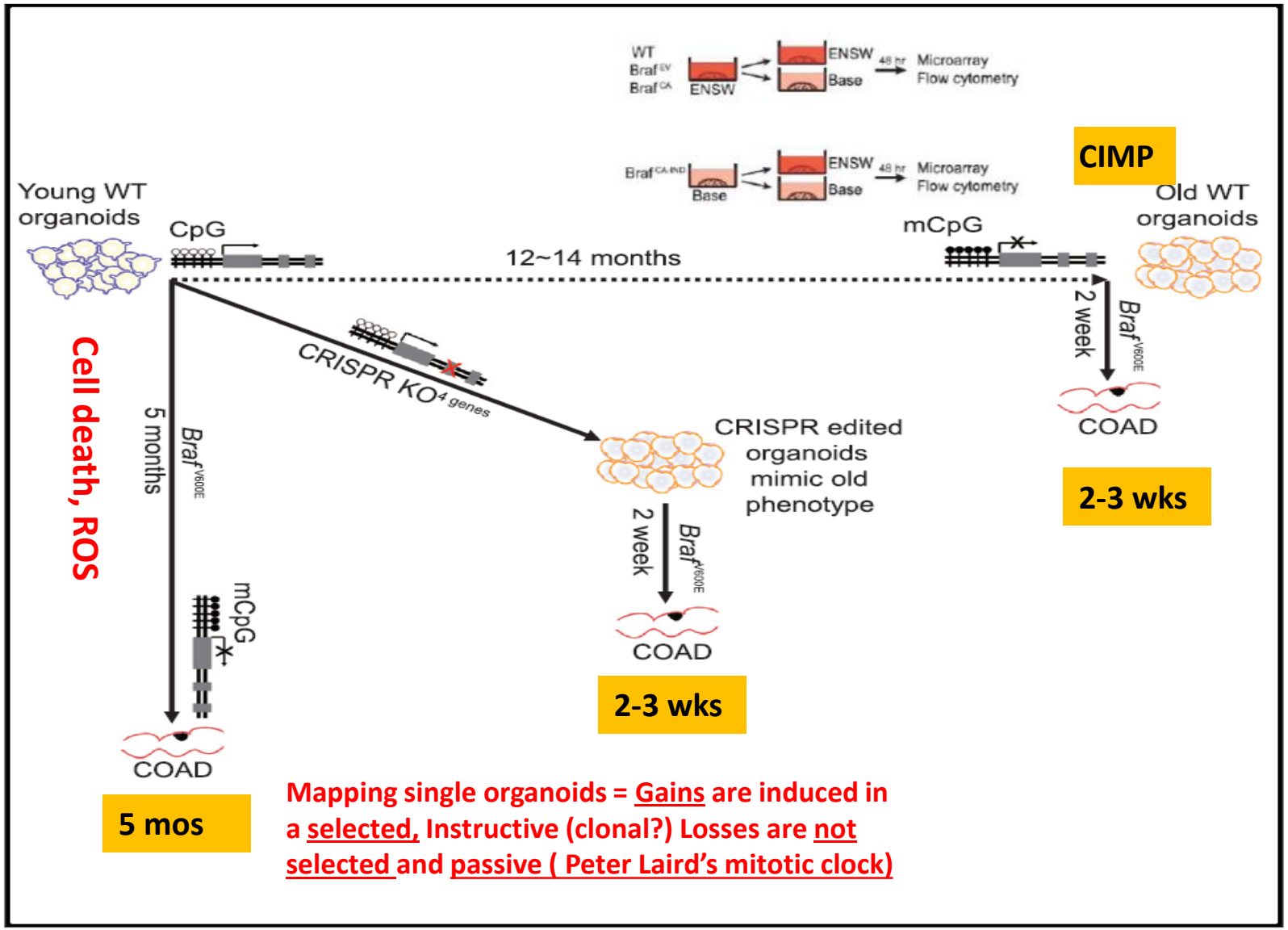
CIMP For Developmental Genes Is Functional For Aging Organoids And Susceptibility to Transformation

CRISPR-Cpf1



Daniel Petkovich

Removal Of Developmental Genes From Young Organoids = Old Organoids



Easwaran

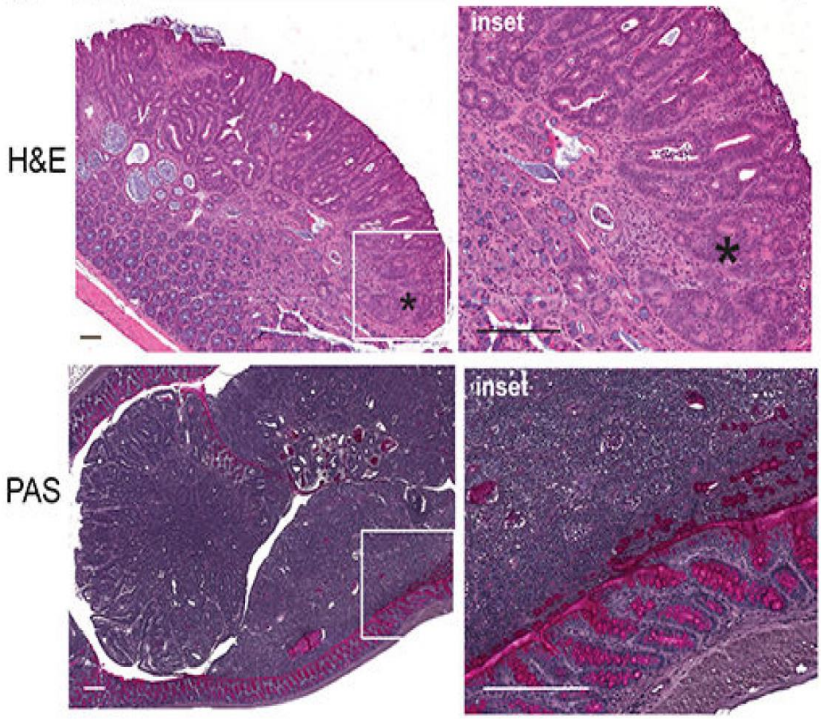
Byunghak KANG

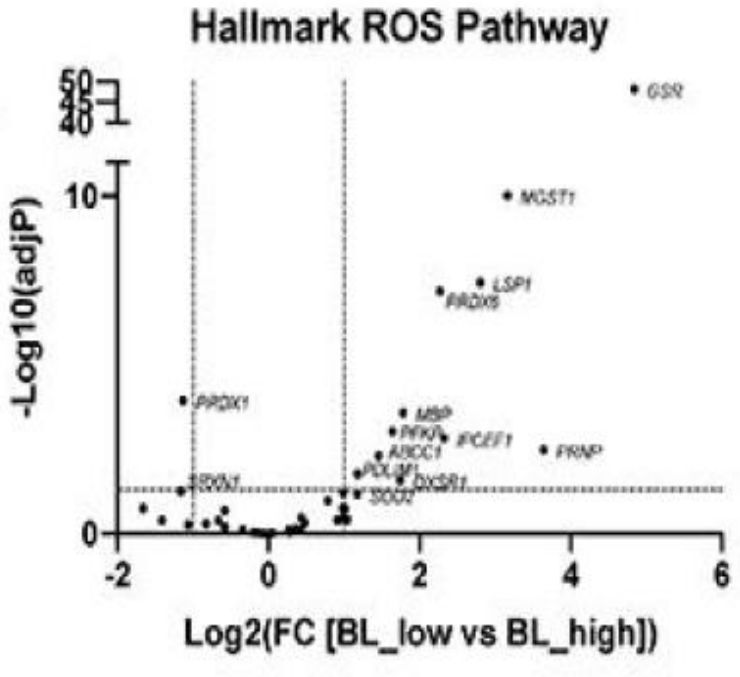
Yong Tao

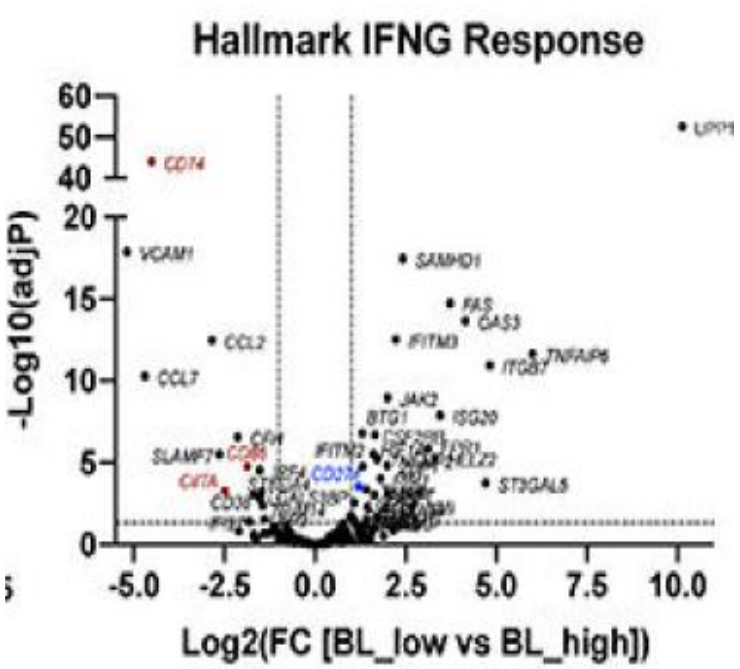
Daniel A. Petkovich

Tao, Khang, Easwaran et al, Cancer Cell, 2019

Inducing *BRAF* Mutation *In-Vivo* In Setting Of ETBF Challenge



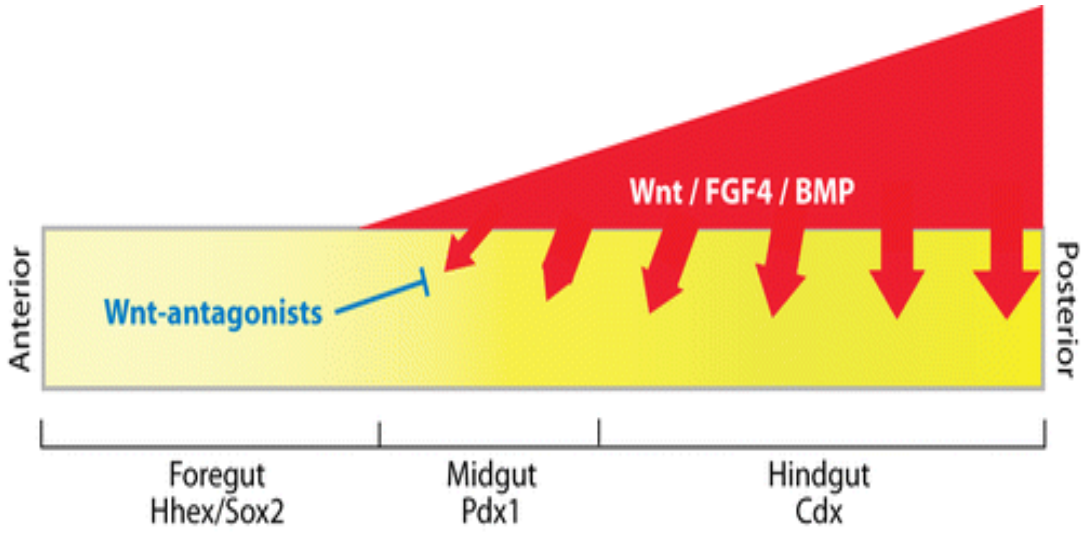




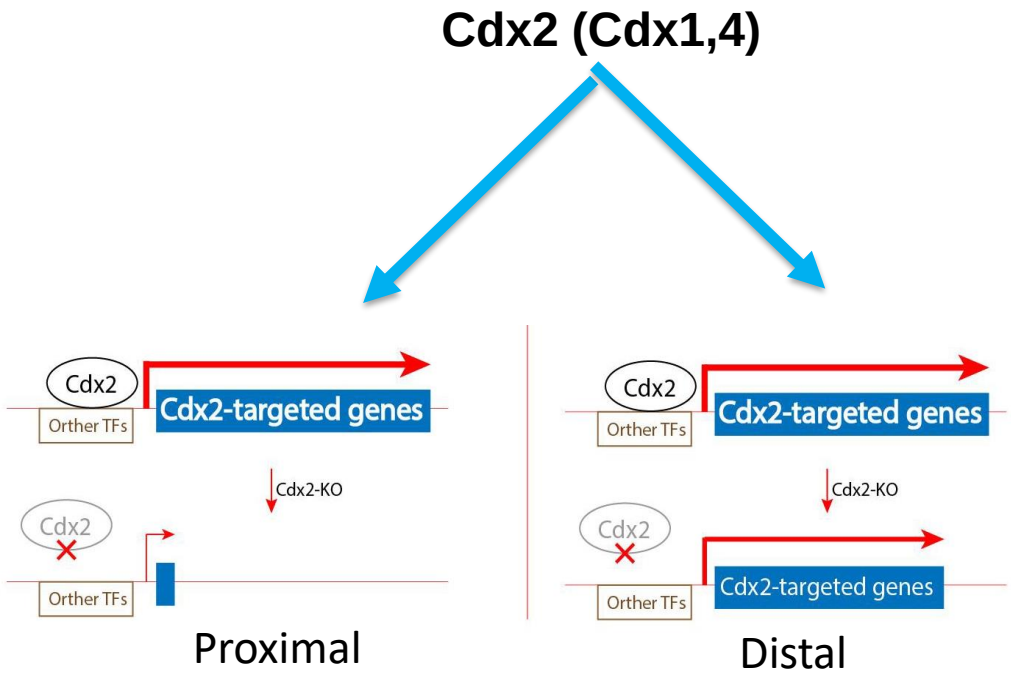
Preceded By Proximal Colon Cell Mucinous Cell Hyperplasia, then serrated polyps and followed by mucinous CRC

DeStefano Shields et al, Cancer Discov, 2021

Different epigenetic and transcriptional landscape in proximal and distal colon define BRAF-driven CRC initiation



Zorn AM, Wells JM. 2009.
Annu. Rev. Cell Dev. Biol. 25:221–51

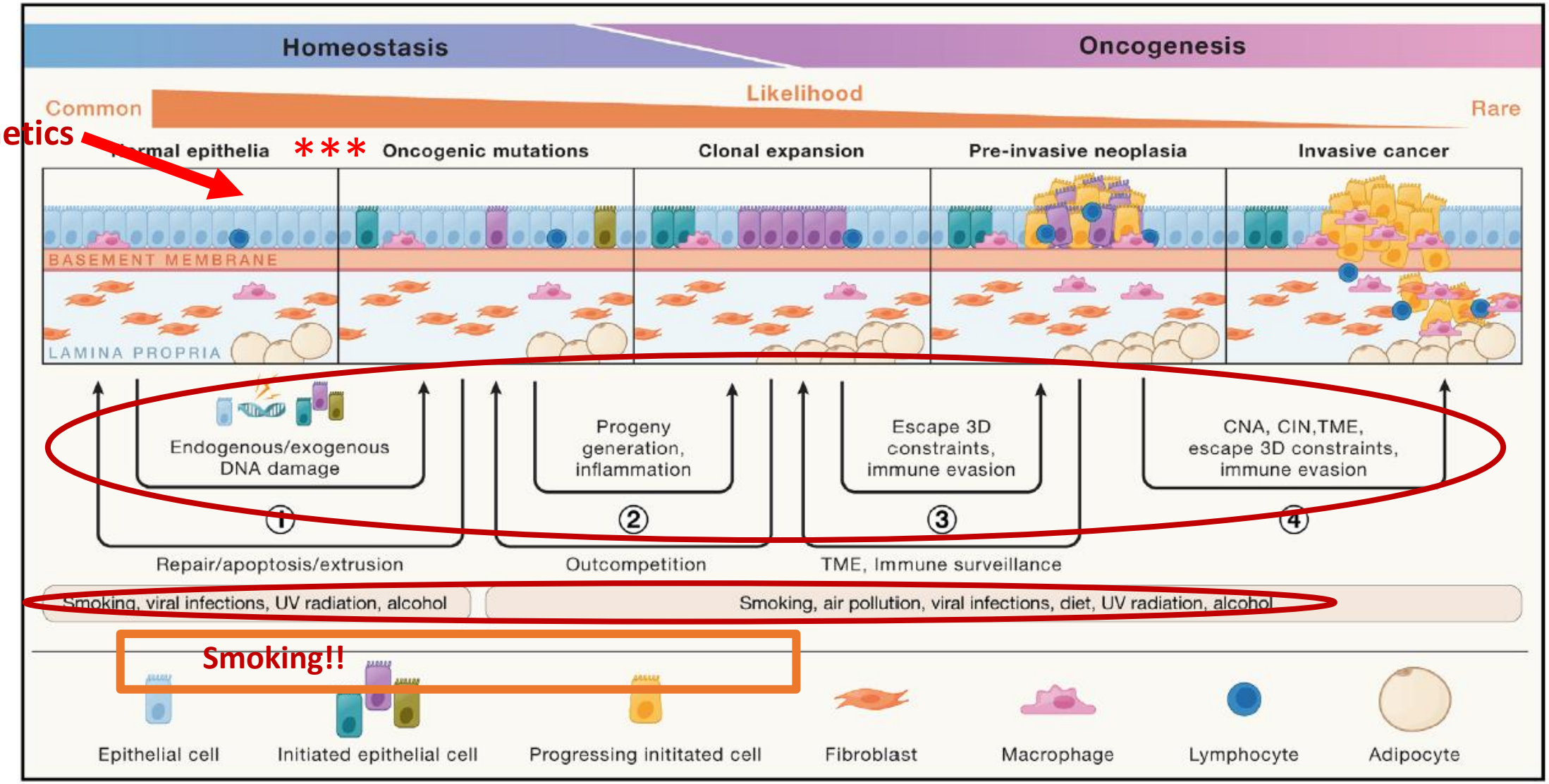


Easwaran and colleagues

In revision, please do not post

Influence of cancer risk factors on carcinogenesis

Epigenetics



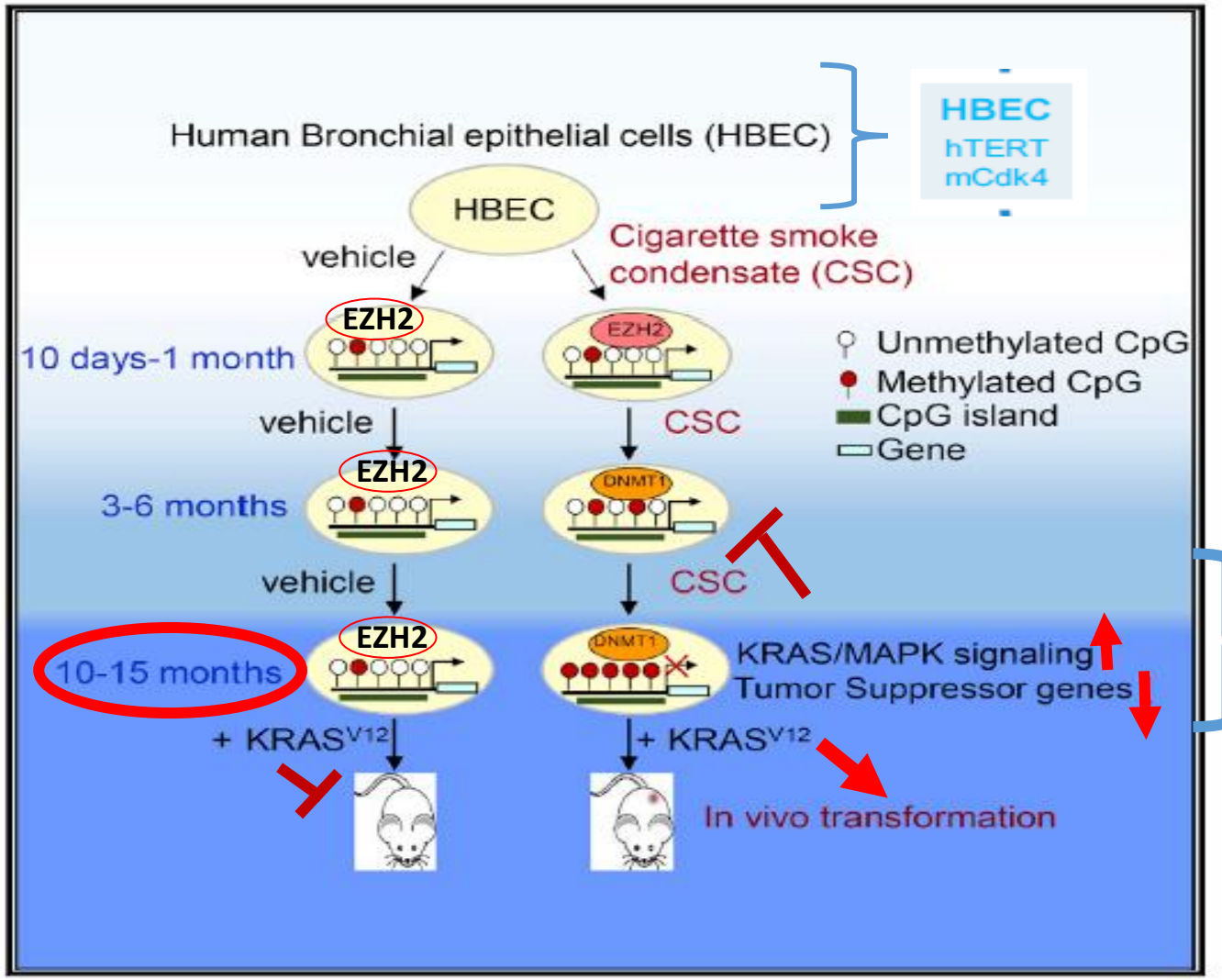
Parent cell of tumor origin fate!! Determined in development and parent stem cell renewal in adults

Swanton and colleagues, Cell 186, April 13, 2023

Smoke-Induced Changes To The Epigenome Provide Fertile Ground For *KRAS* Oncogenic Mutation In NSCLC

Michelle Vaz

Hari Easwaran



Damage complex tightens – cell death

1)No driver mutations;
2)Stemness;
3)Anchorage independence;
4)EMT

Vaz, Easwaran et al, Cancer Cell, 2017

SUMMARY - Airway, Normal Cell Organoids

- Chronic CSC exposure causes key shifts in populations of lung stem cells with an associated decrease in differentiation.

- These changes are accompanied by DNA methylation and gene expression changes of an increased tumorigenic potential.

- CSC treated organoids acquire growth factor independency.

- CSC treated organoids modulate the function of key immune cells associated with lung tumorigenesis from a pro- to an anti-inflammatory phenotype over the course of prolonged exposure.
- Growth capability in factor free media + induced driver mutations = NSCLC

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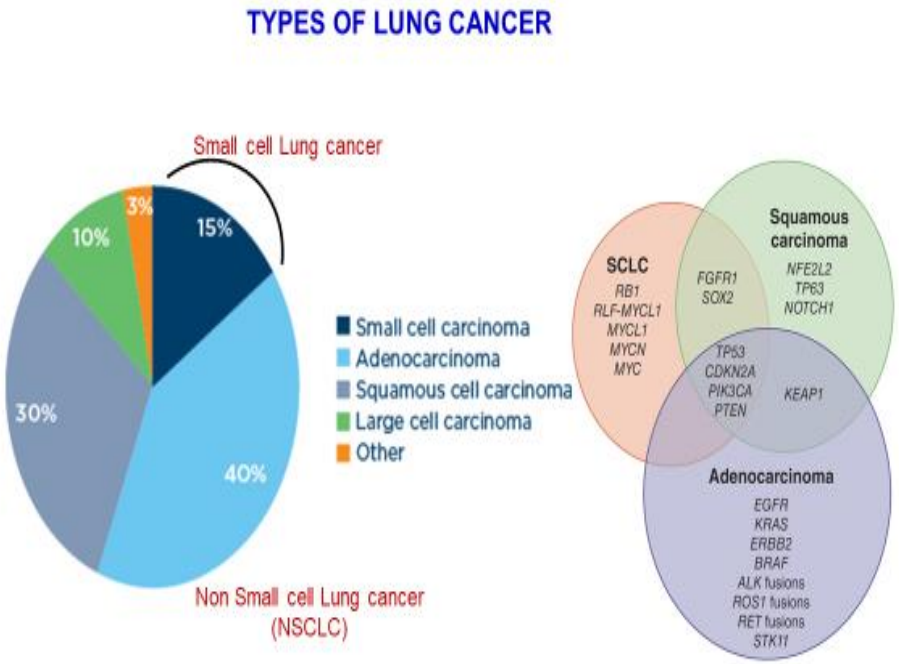
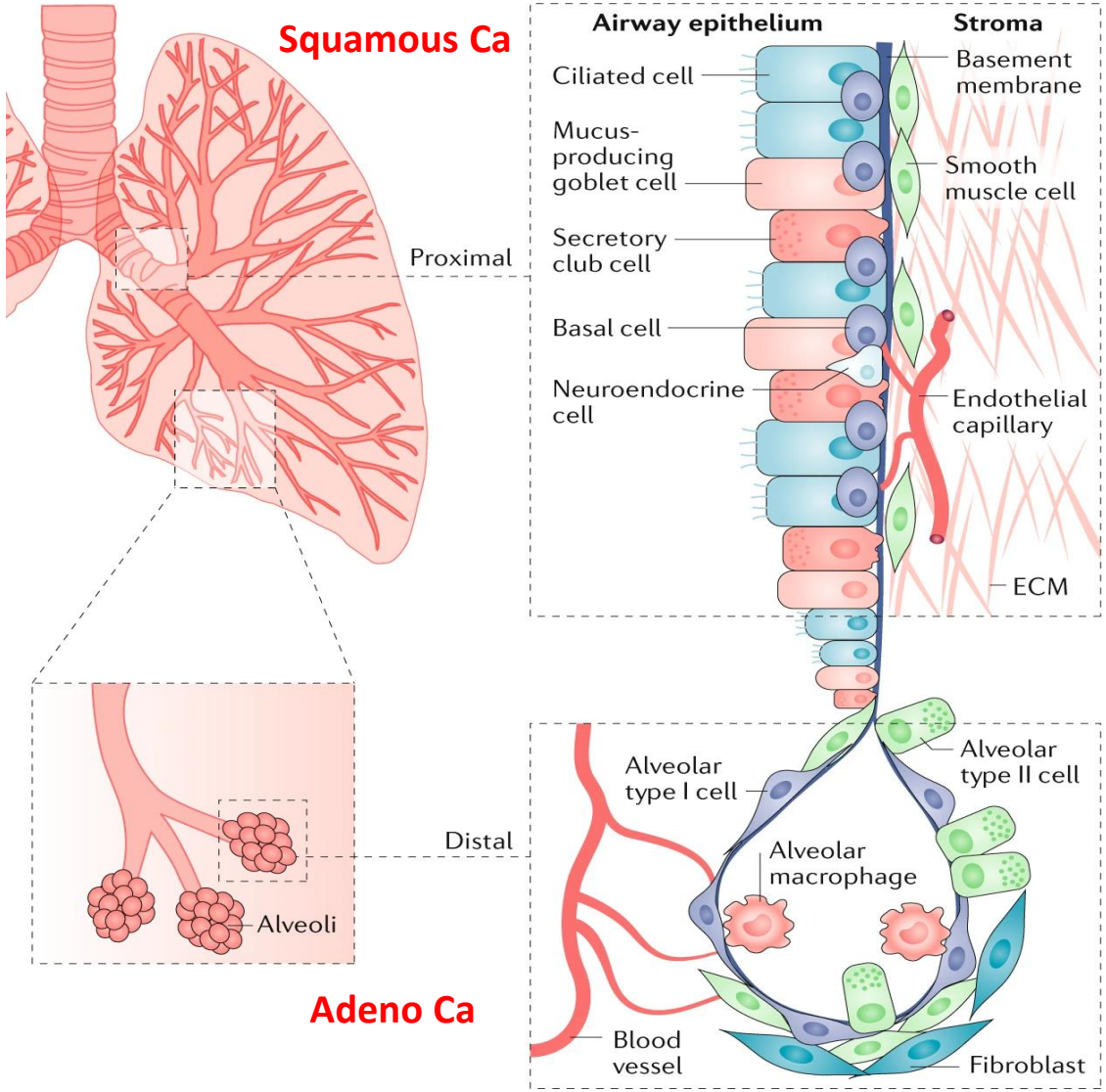
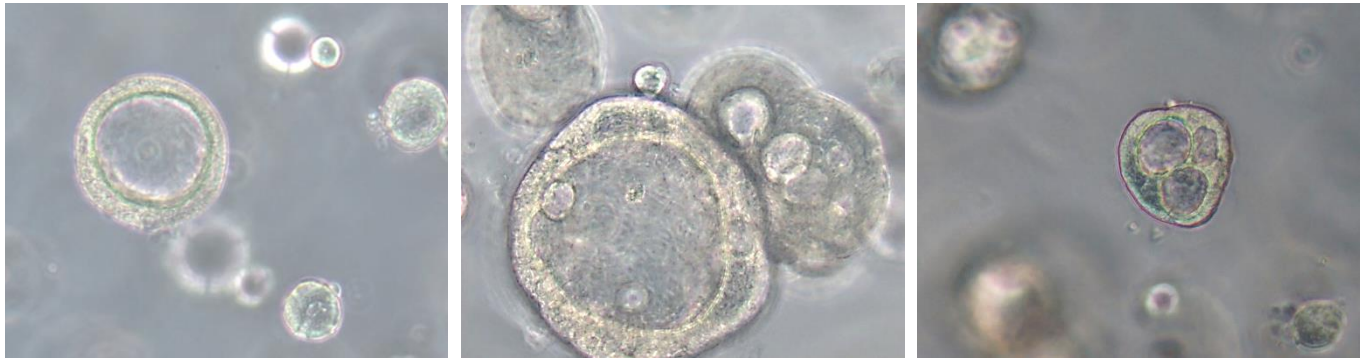
Probing The Evolution of NSCLC With Normal Airway Cell Organoids - Michelle Vaz





Altorki, N.K., *et al. Nat Rev Cancer* 19, 9–31 (2019)

PHASE CONTRAST IMAGES SHOWING MORPHOLOGY OF NORMAL HUMAN LUNG ORGANOIDS (AIRWAY ORGANOIDS)



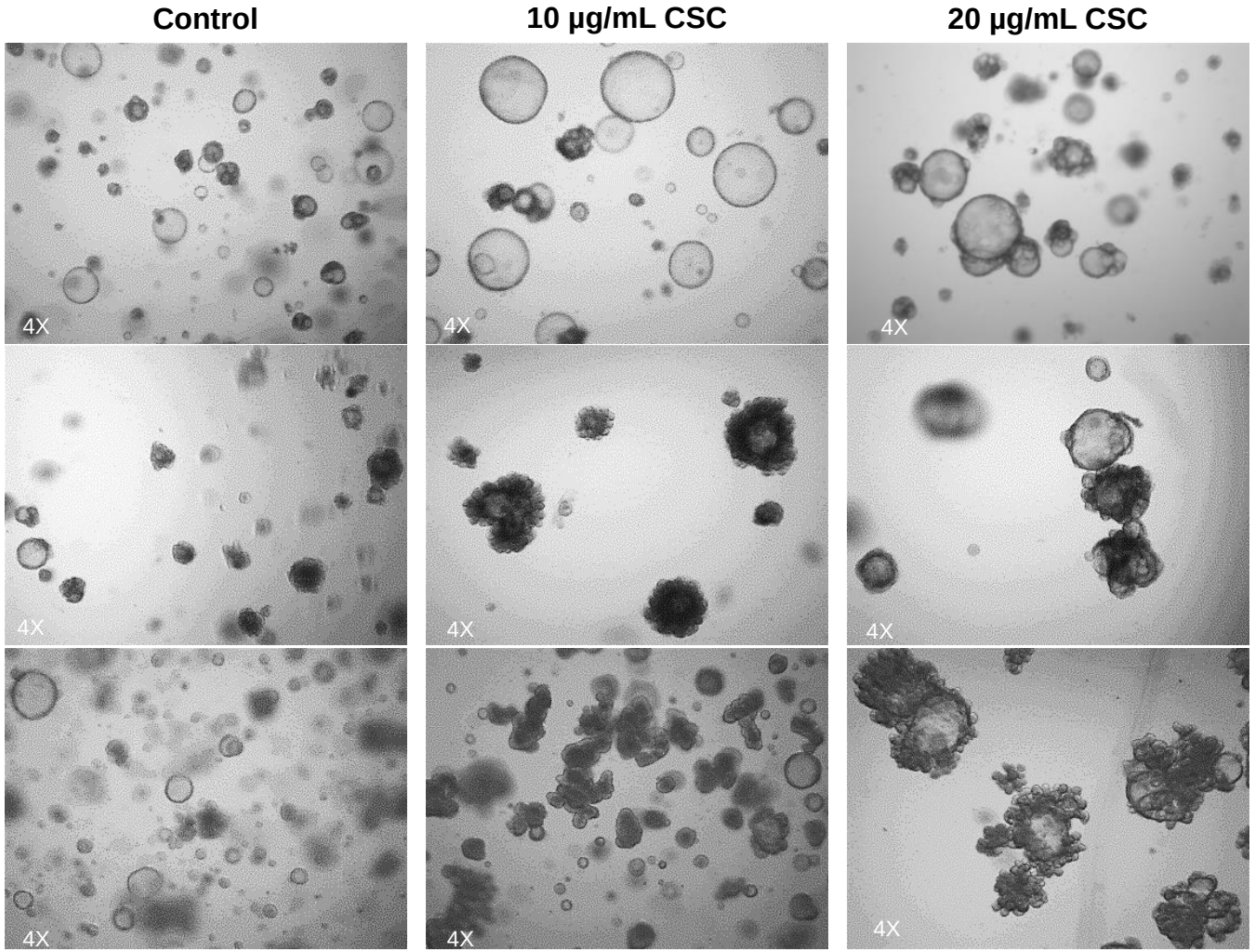
PHASE CONTRAST IMAGES SHOWING MORPHOLOGY OF MURINE LUNG ORGANOIDS

Michelle Vaz

Na Wang

Unpublished, please do not post

CSC-INDUCED MORPHOLOGICAL CHANGES IN MURINE LUNG ORGANOIDS



After CSC exposure:

- **Larger size;**
- **Higher density.**

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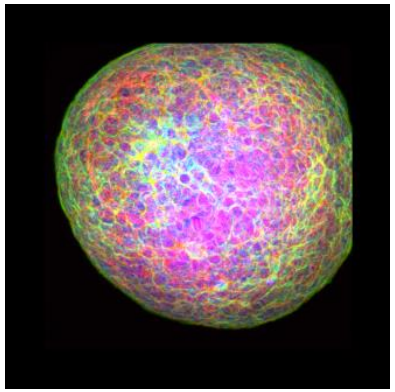
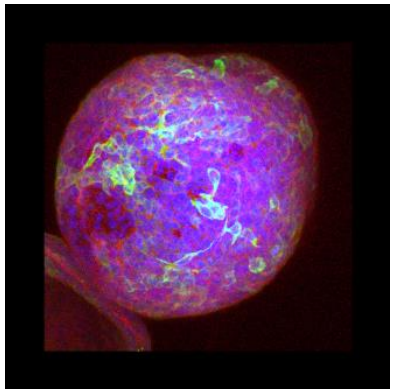
IMMUNOFLUORESCENT STAINING OF CELL TYPE-SPECIFIC MARKERS IN HUMAN LUNG ORGANOIDS

Stem cell markers

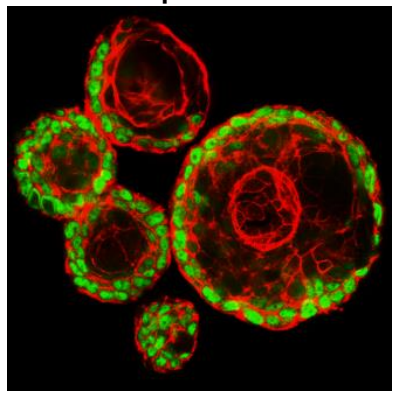
KRT5



KRT14



p63



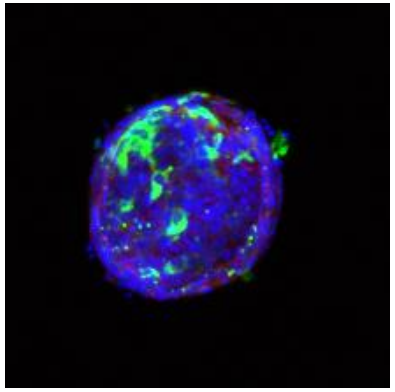
F-actin

Cell type-specific marker

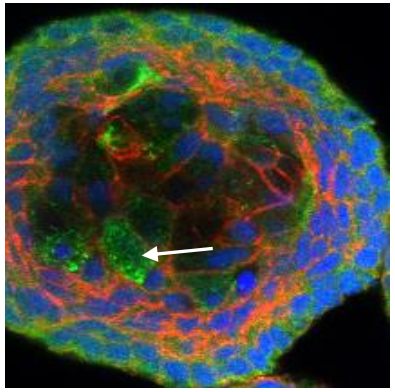
DAPI

Differentiated cell markers

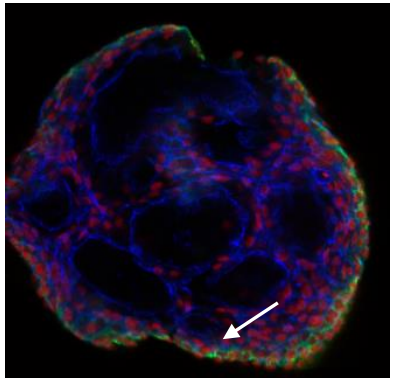
MUC5AC



SCGB1A1



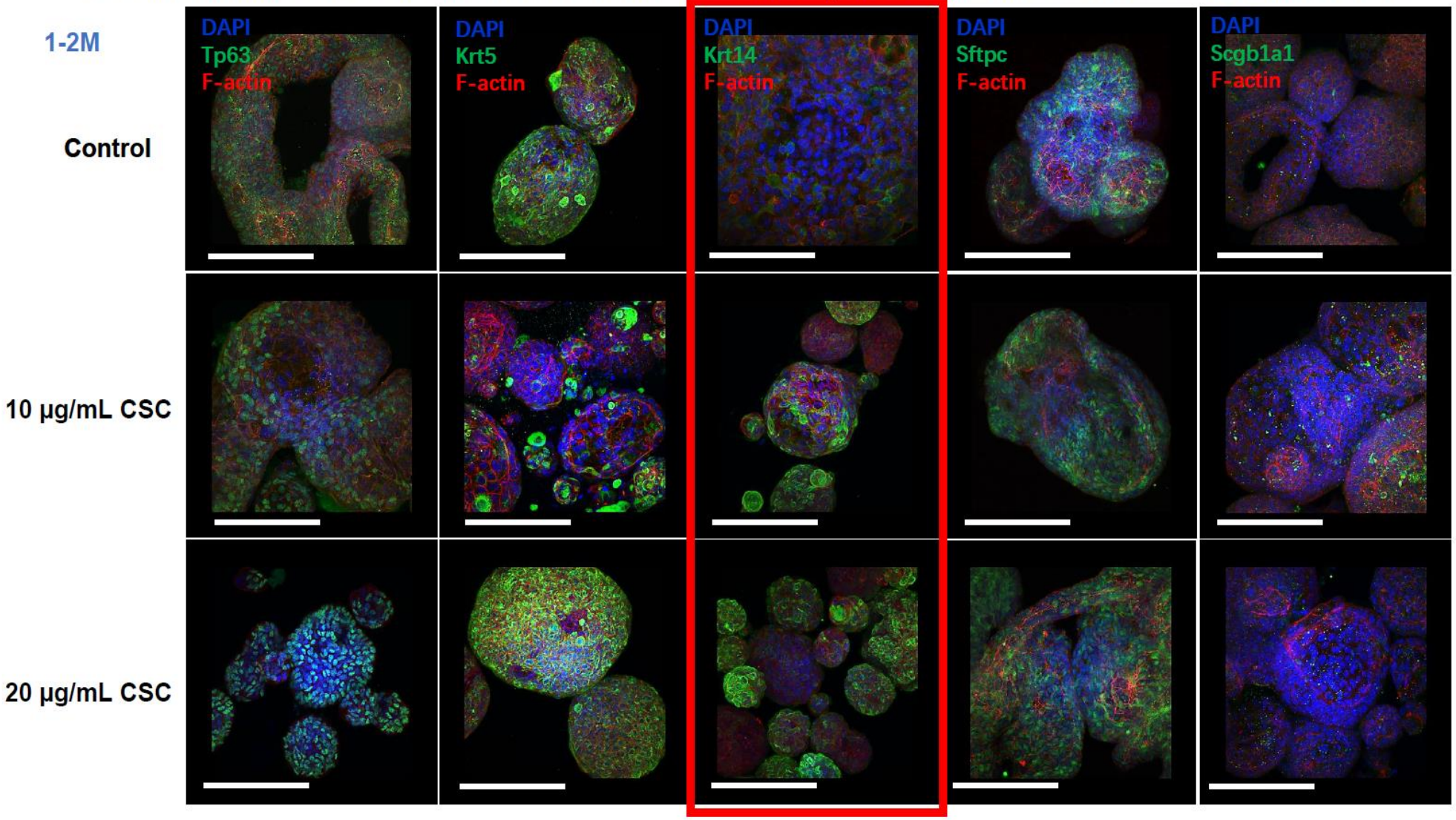
Acetylated Tubulin



H2AXp

Unpublished, please do not post

CSC Treatment Causes A Shift in the Basal Stem Cell Population From P63⁺Krt5⁺ TO P63⁺Krt5⁺Krt14⁺



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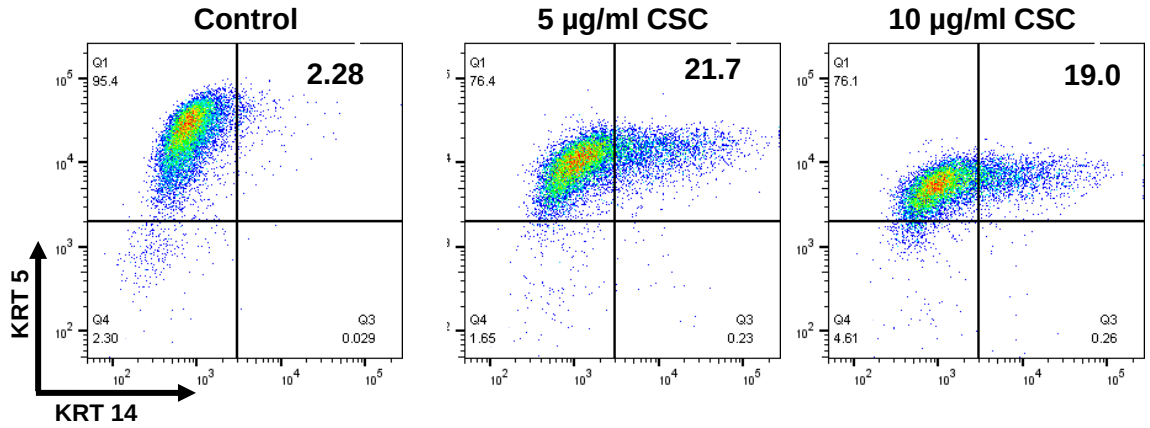
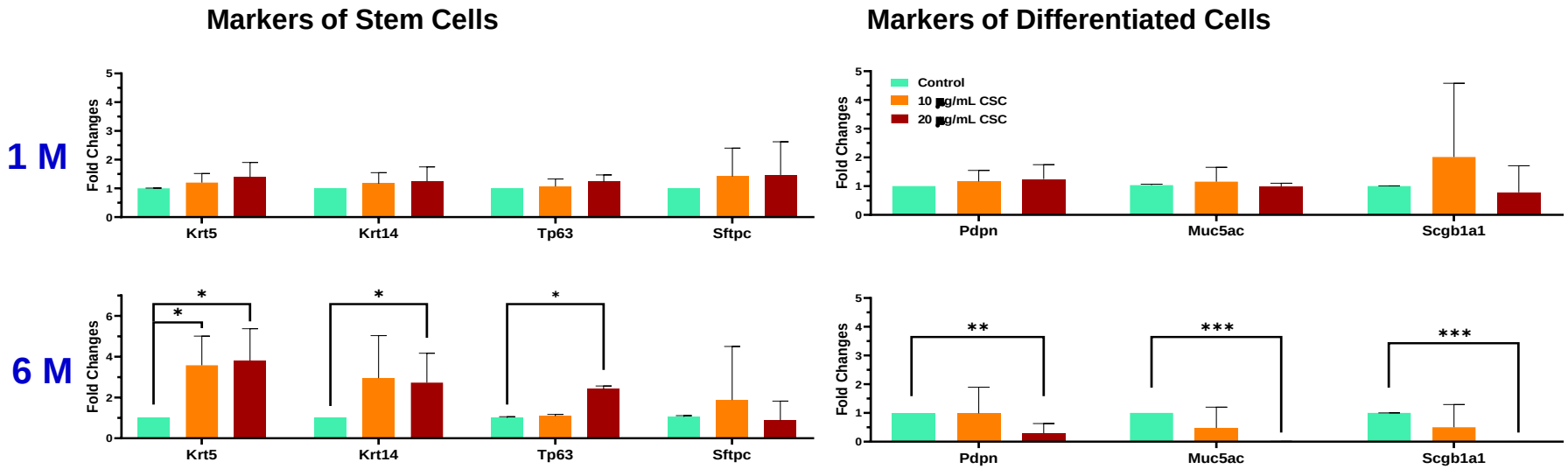
CSC EXPOSURE INDUCES SUBSTANTIAL SHIFTS IN BASAL STEM CELL AND DIFFERENTIATED CELL POPULATIONS

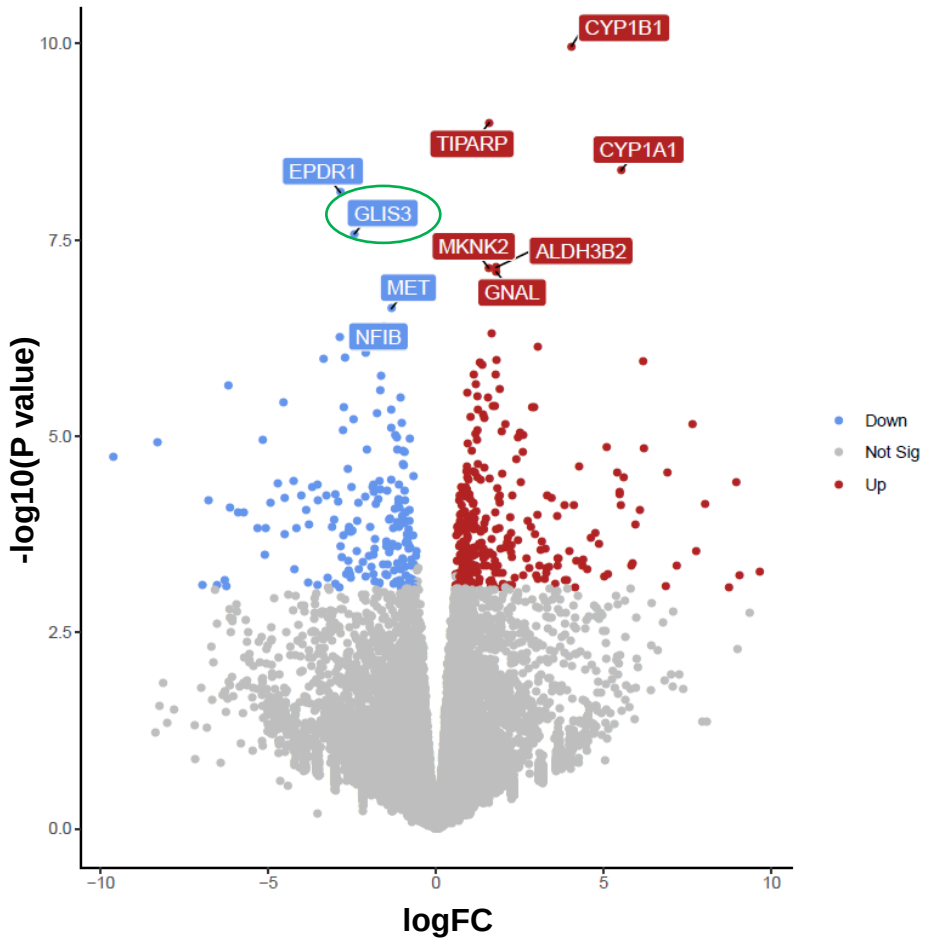




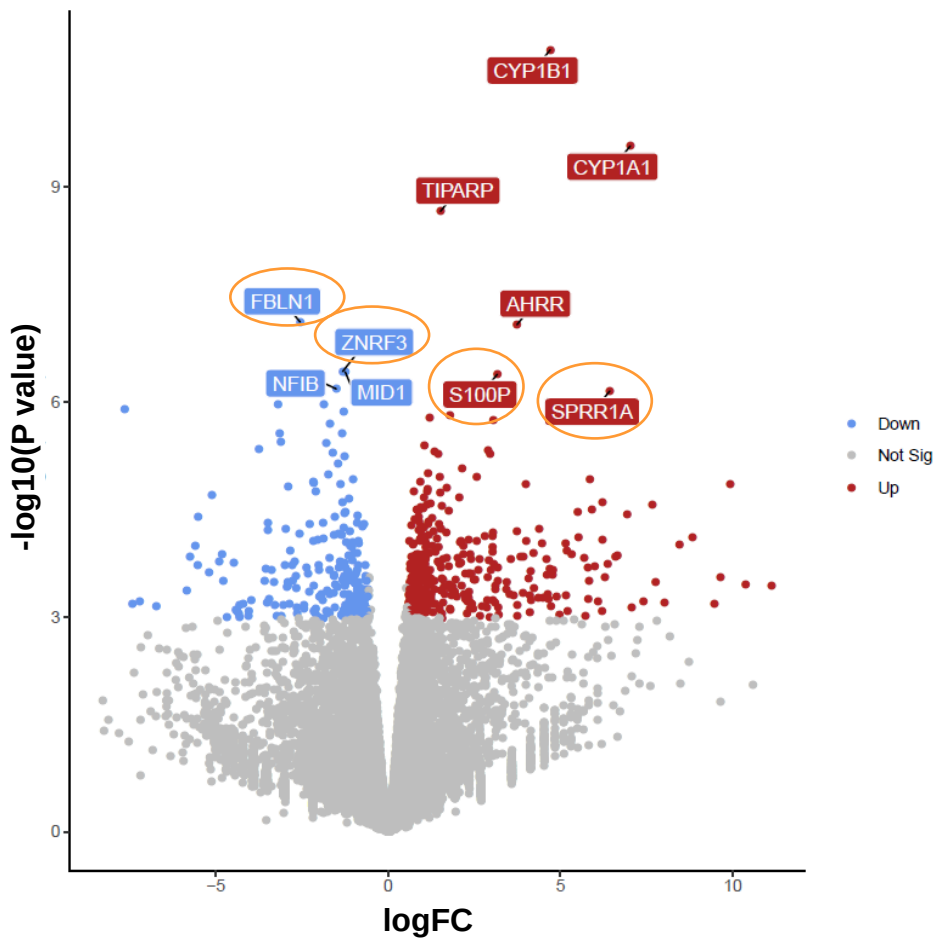
Unpublished, please do not post

CSC-INDUCED DIFFERENTIALLY EXPRESSED GENES AT 3 MONTHS

5µg/ml CSC



10µg/ml CSC

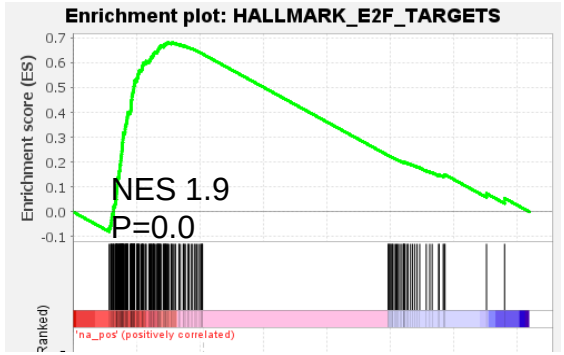


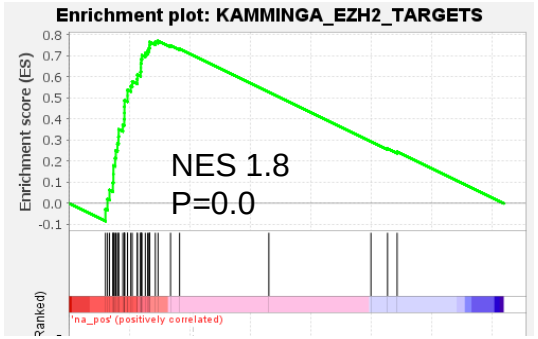
Upregulated (Log2 FC) : 199
Downregulated (Log2 FC) : 133

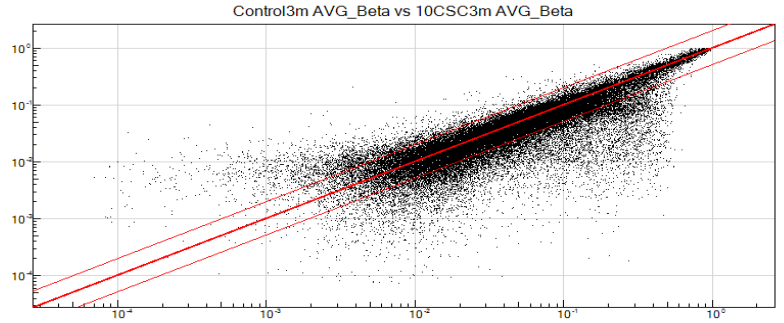
Upregulated (Log2 FC : 247
Downregulated (Log2 FC) : 165

Unpublished, please do not post

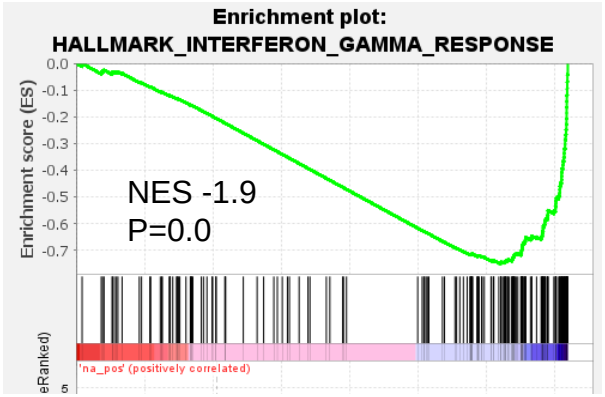
GSEA analysis of CSC-induced differentially expressed genes at 3 months

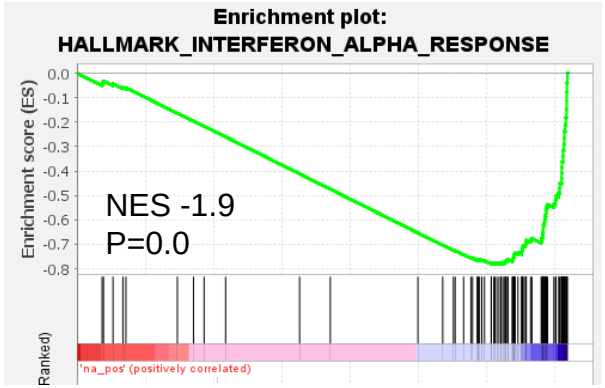


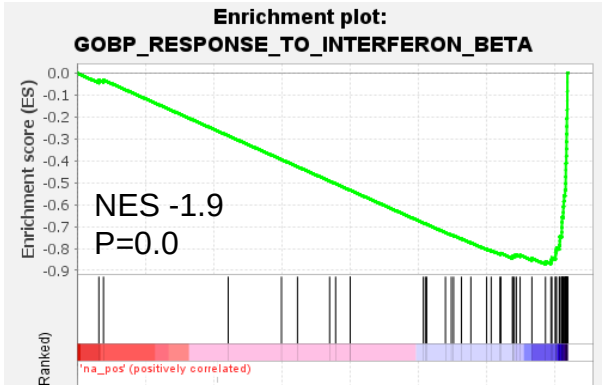




CIMP!

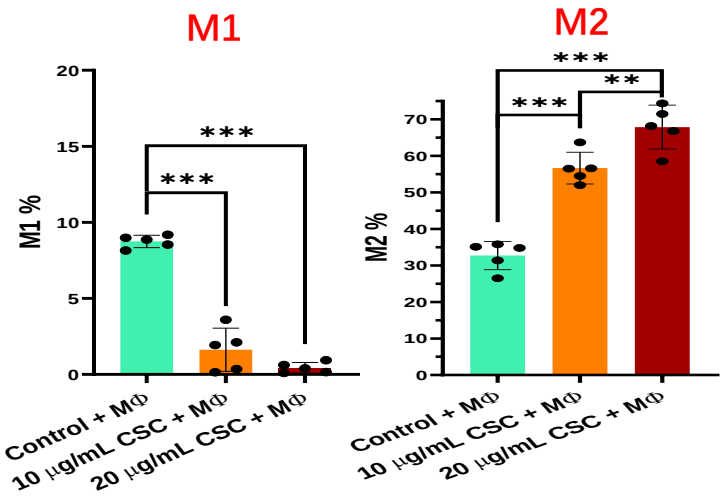




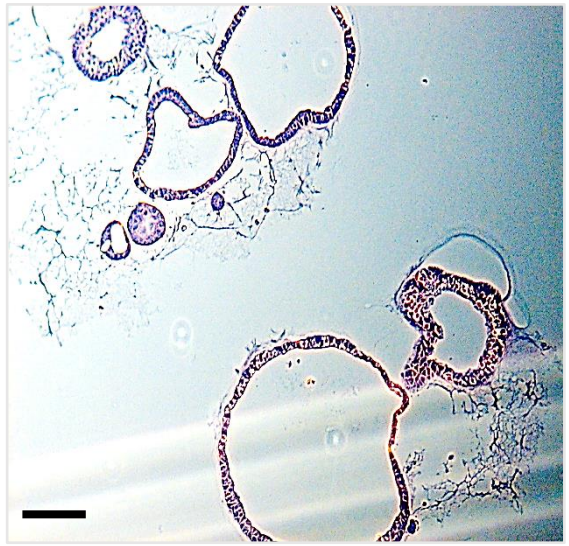
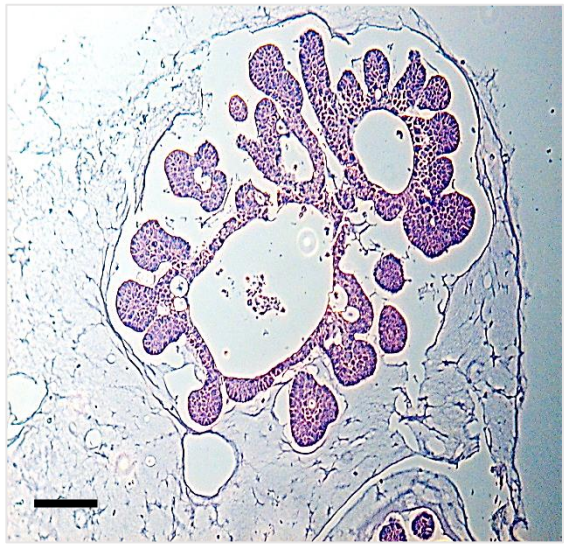


DOWNREGULATION OF IFN SIGNALING PATHWAYS

6M



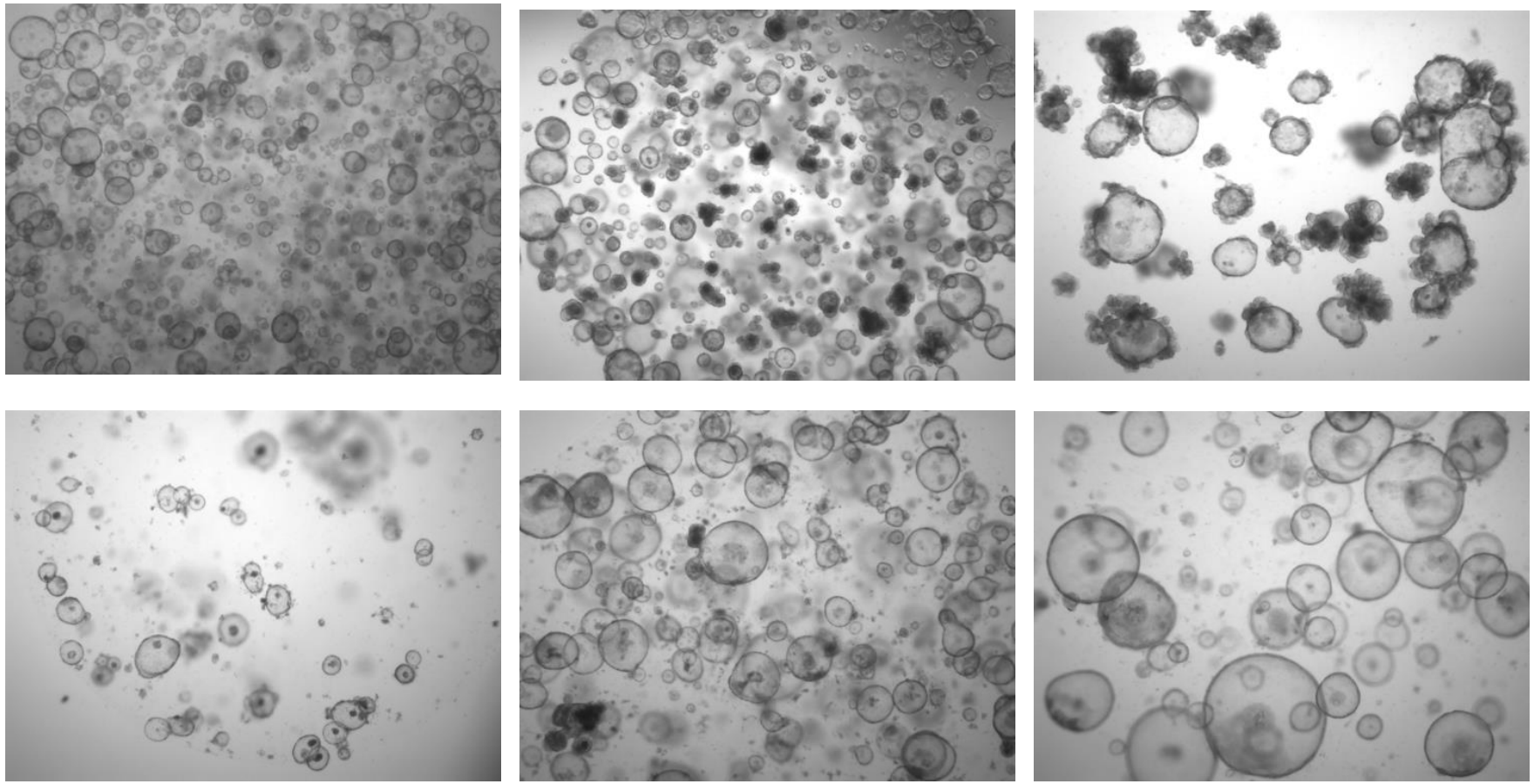
Representative images of H&E-stained sections of control and CSC-treated lung organoids at 6 months.

Control	10 µg/mL CSC	20 µg/mL CSC
		
+	+	+
Kras ^{G12V}	**Kras ^{G12V}**	**Kras ^{G12V}**

In vivo tumor formation
(6-8 weeks post injection)

Unpublished, please do not post

MORPHOLOGICAL CHANGES SUGGESTIVE OF GROWTH FACTOR INDEPENDENCY IN MURINE ORGANOIDS TREATED WITH CSC FOR 6 MONTHS



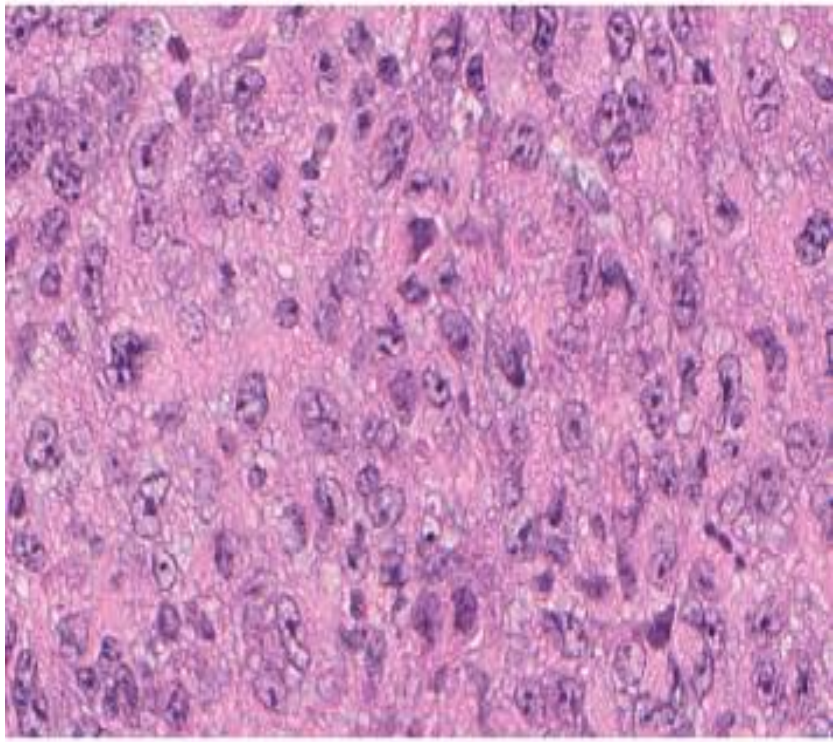
CM : Complete medium
BM: Base medium

Preliminary data suggest that the CSC treated organoids are susceptible to KRAS induced transformation.

Unpublished, please do not post

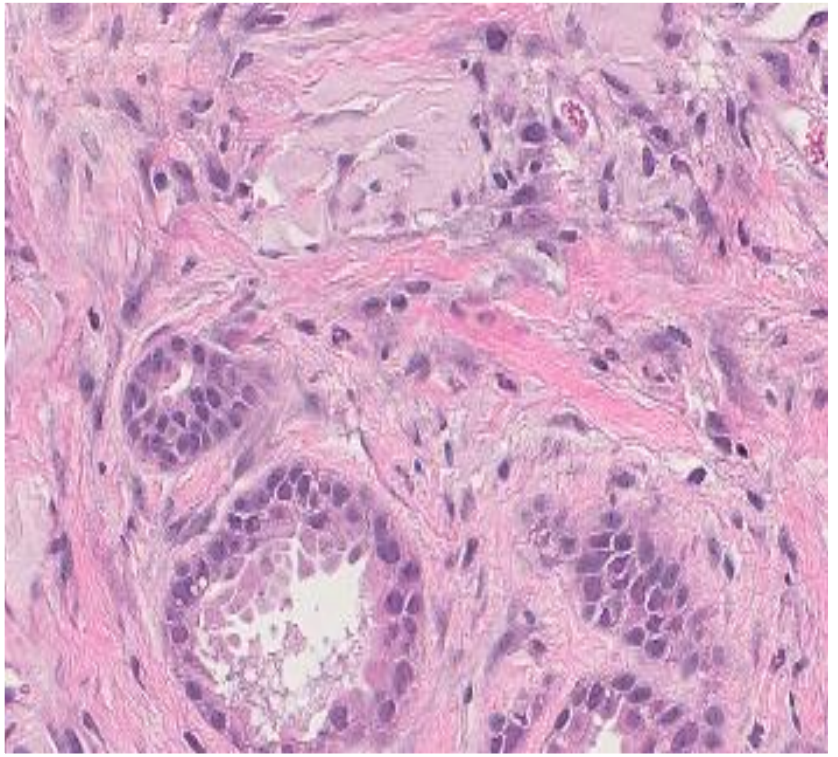
Induction Of A *KRAS* Mutation Or A *P53* Deletion At Time Of Organoid Growth In Basal Media

KRAS^{G12V}



Adenocarcinoma
Highly metastatic to lung

Tp53 KO



Squamous CA

Unpublished, please do not post

SUMMARY

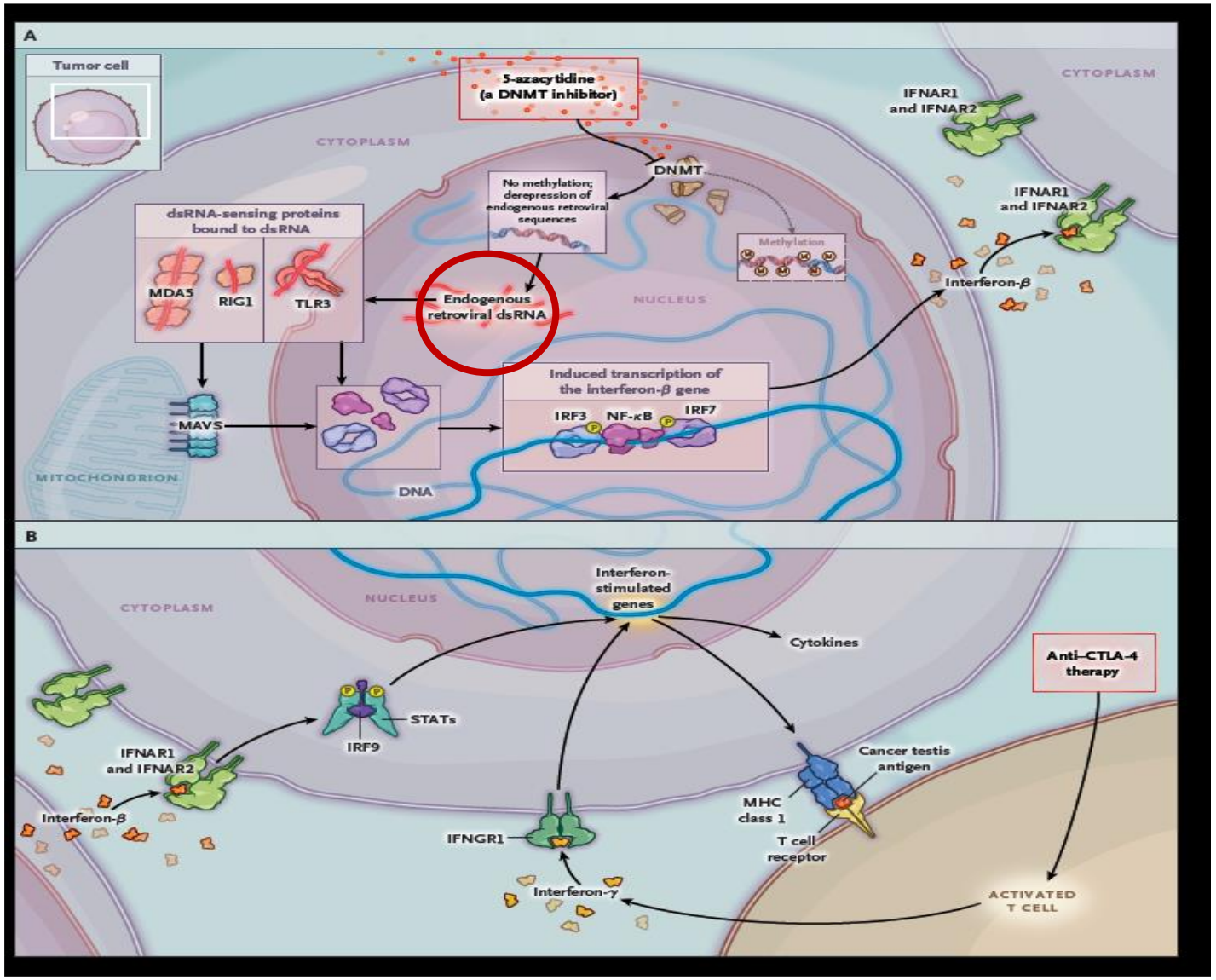
- Chronic CSC exposure causes key shifts in populations of lung stem cells with an associated decrease in differentiation.

- These changes are accompanied by DNA methylation and gene expression changes suggestive of an increased tumorigenic potential.

- CSC treated organoids acquire growth factor independency.

- CSC treated organoids modulate the function of key immune cells associated with lung tumorigenesis from a pro- to an anti-inflammatory phenotype over the course of prolonged exposure.
- Growth capability in factor free media + induced driver mutation = NSCLC

Viral Mimicry Review



Increase efficacy of IO?

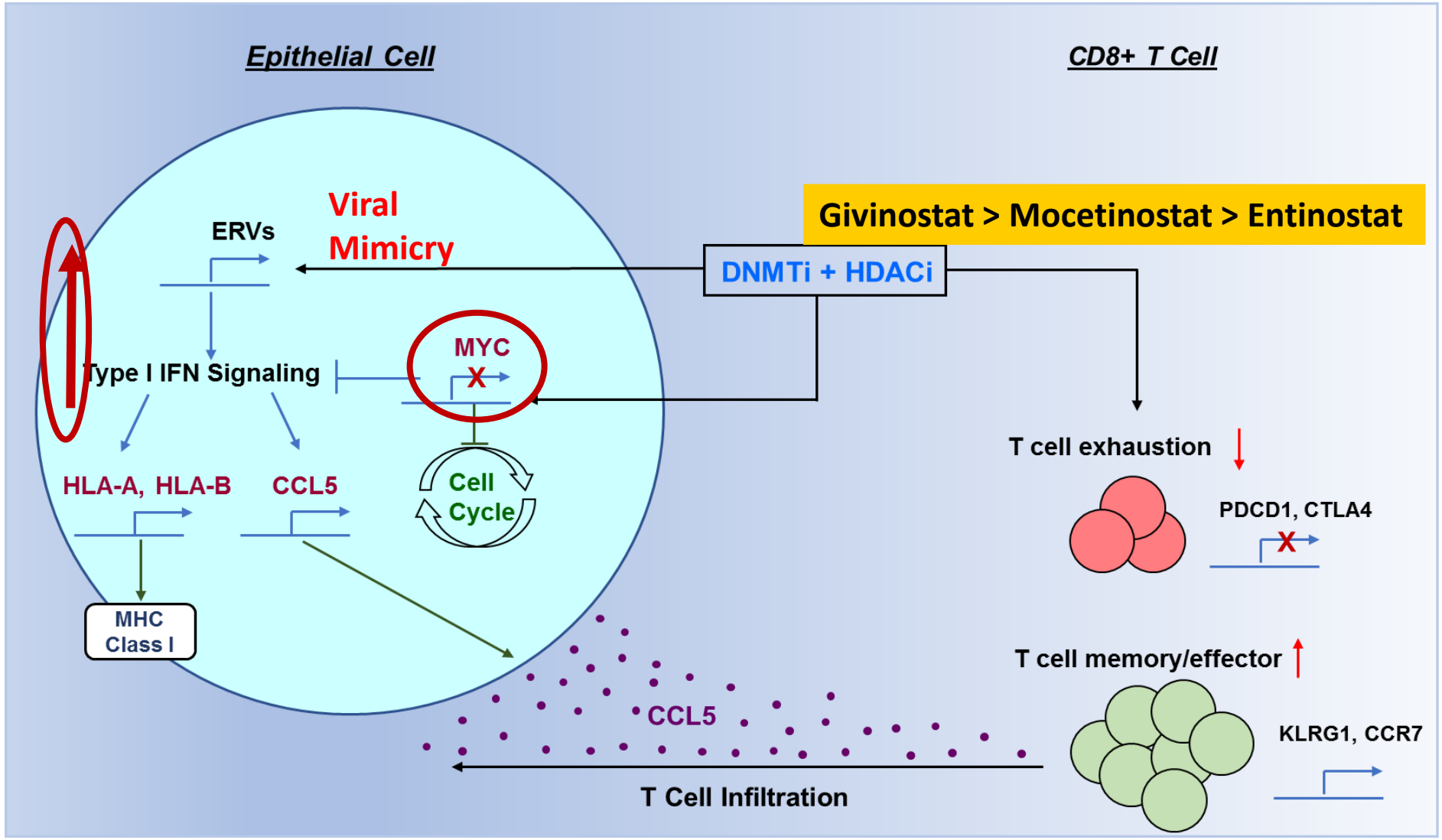
DeCarvalho- Jones; ours-Chiappinelli et al , Cell 2015

Dear and Phimster, NEJM, 2016

Combining DNMTi's And HDACi's To Enhance Immune Checkpoint Therapy

Michael Topper

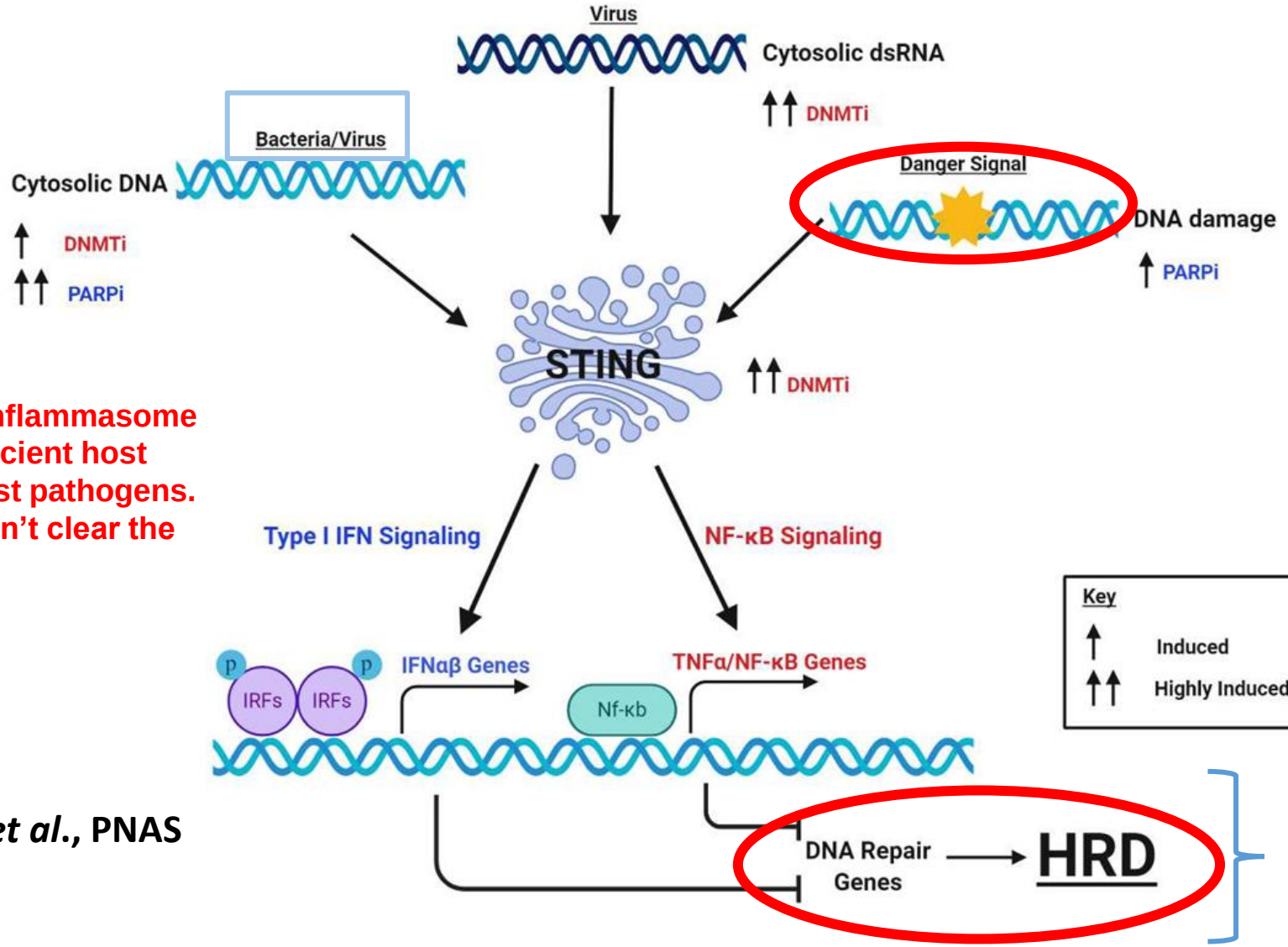
Michelle Vaz



Gerard Evan's findings – Cell, 2017!

Topper, Vaz et al, Cell, 2017

Pathogen Mimicry Response (PMR): DNMTi and PARPi induce STING-dependent interferon/inflammasome signaling leading to HRD in TNBC and OC



This is part of inflammasome signaling, an ancient host response against pathogens. Kill cells that can't clear the pathogen.

Michael Topper
JHSM

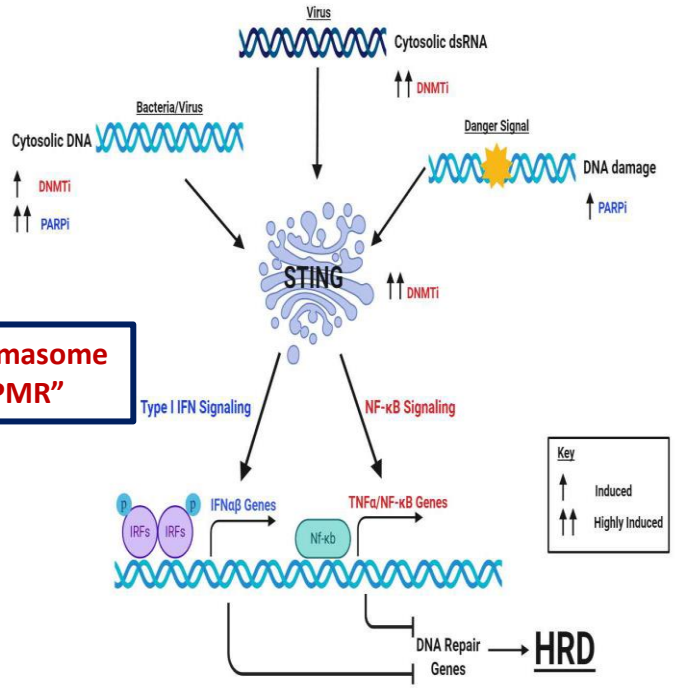
Feyruz Rassool

Rassool lab at UMD

Fey Rassool *et al.*, PNAS 2020, 23

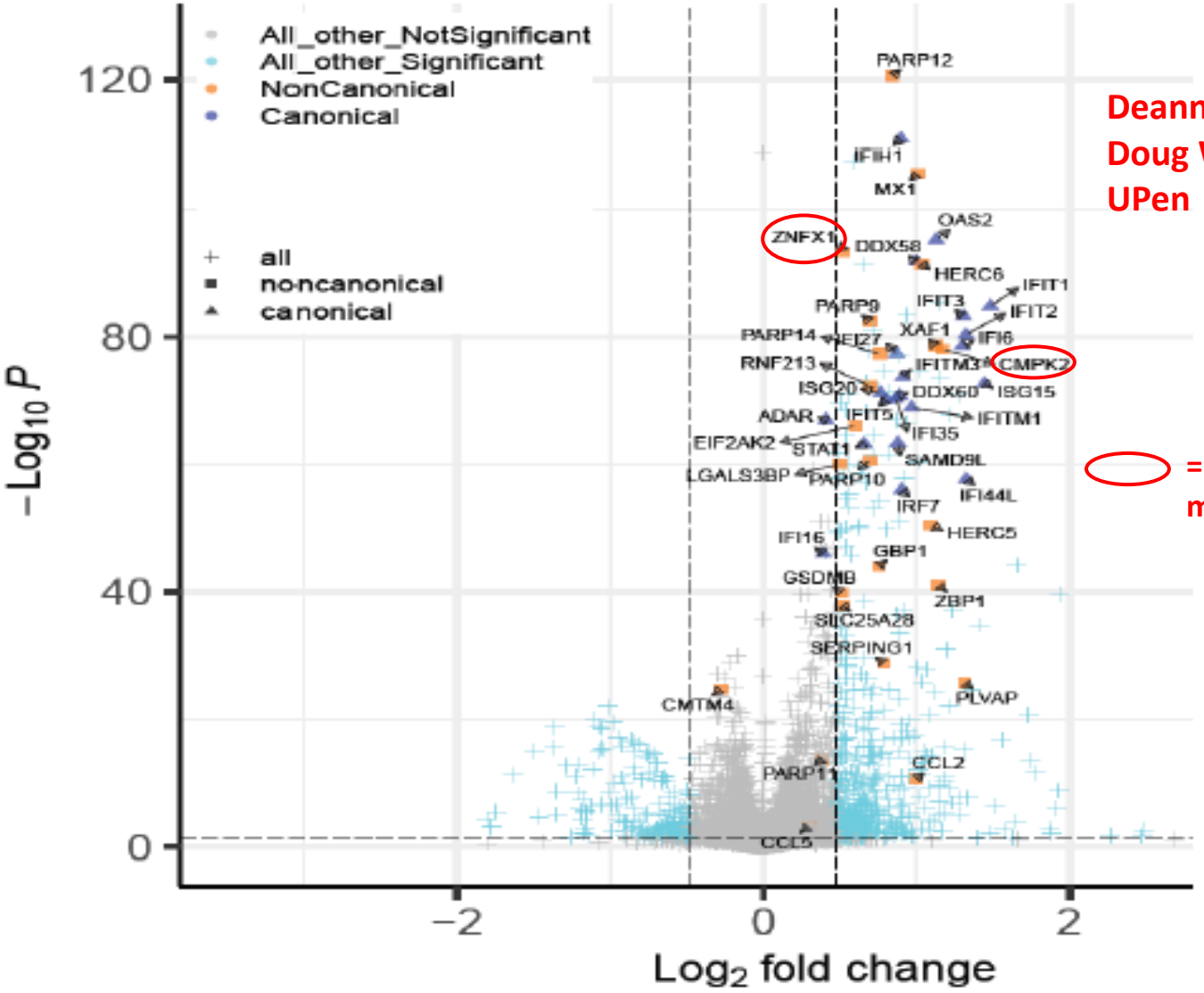
AML, Breast CA

Covid And Epigenetic Rx Viral mimicry



Inflammasome and " PMR"

Fey Rassool *et al.*, PNAS 2020, 23



Deanne Taylor, Doug Wallace UPen

= fct in mitochondria

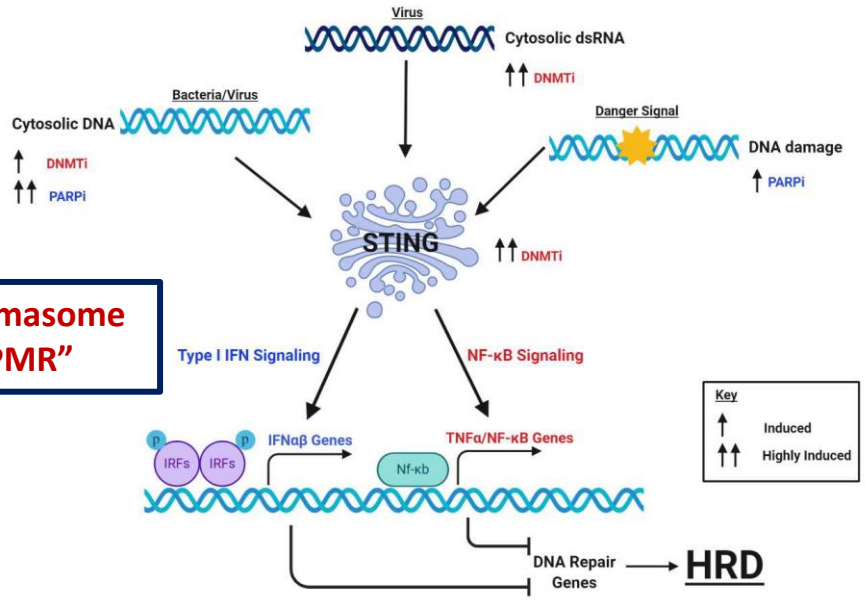
COVIRT Consortium (Beheshti) Baylin, Topper, and Rassool

Unpublished, please do not post

MT ARE THE GATEWAY TO IFN/INFLAMMASOME SIGNALING

Hypothesis

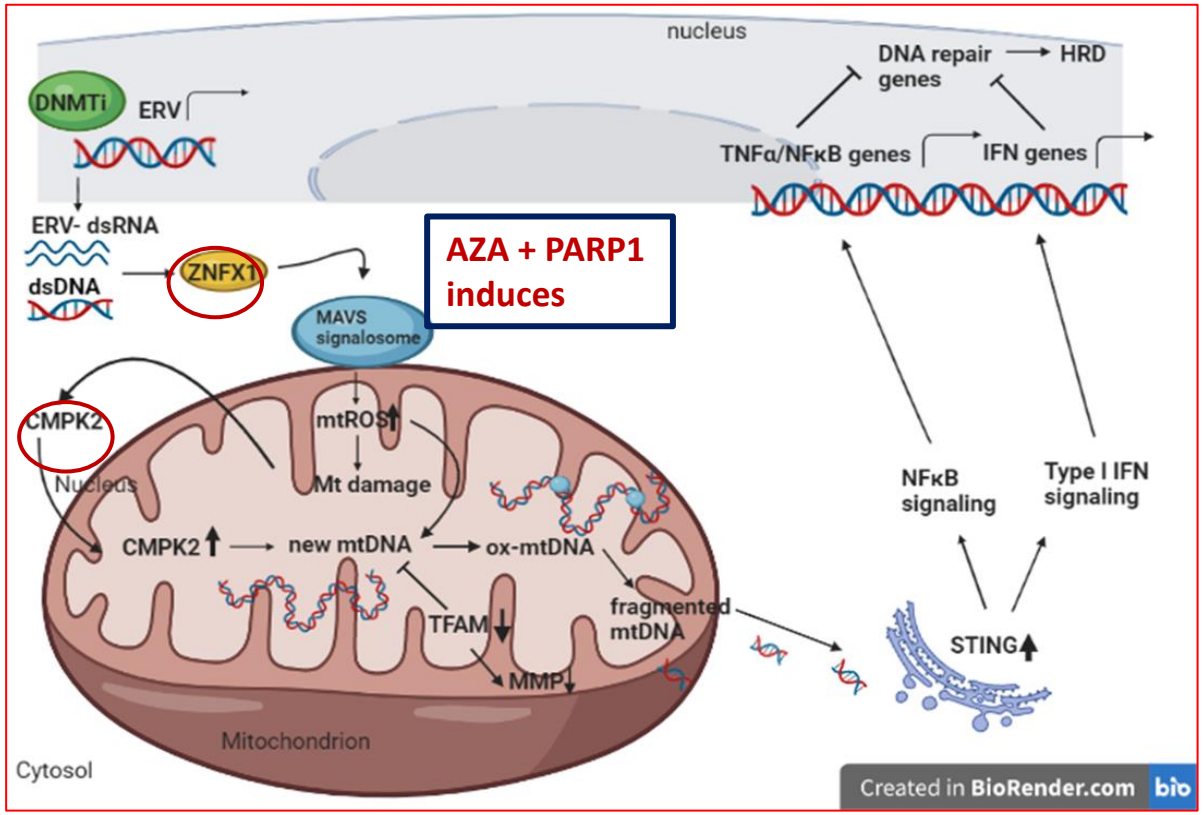
DNMTi and PARPi treatment in BRCA wild-type EOC triggers mt dysfunction and cytoplasmic mtDNA release that activates STING-mediated inflammatory signaling, leading to HRD



Inflammasome and " PMR"

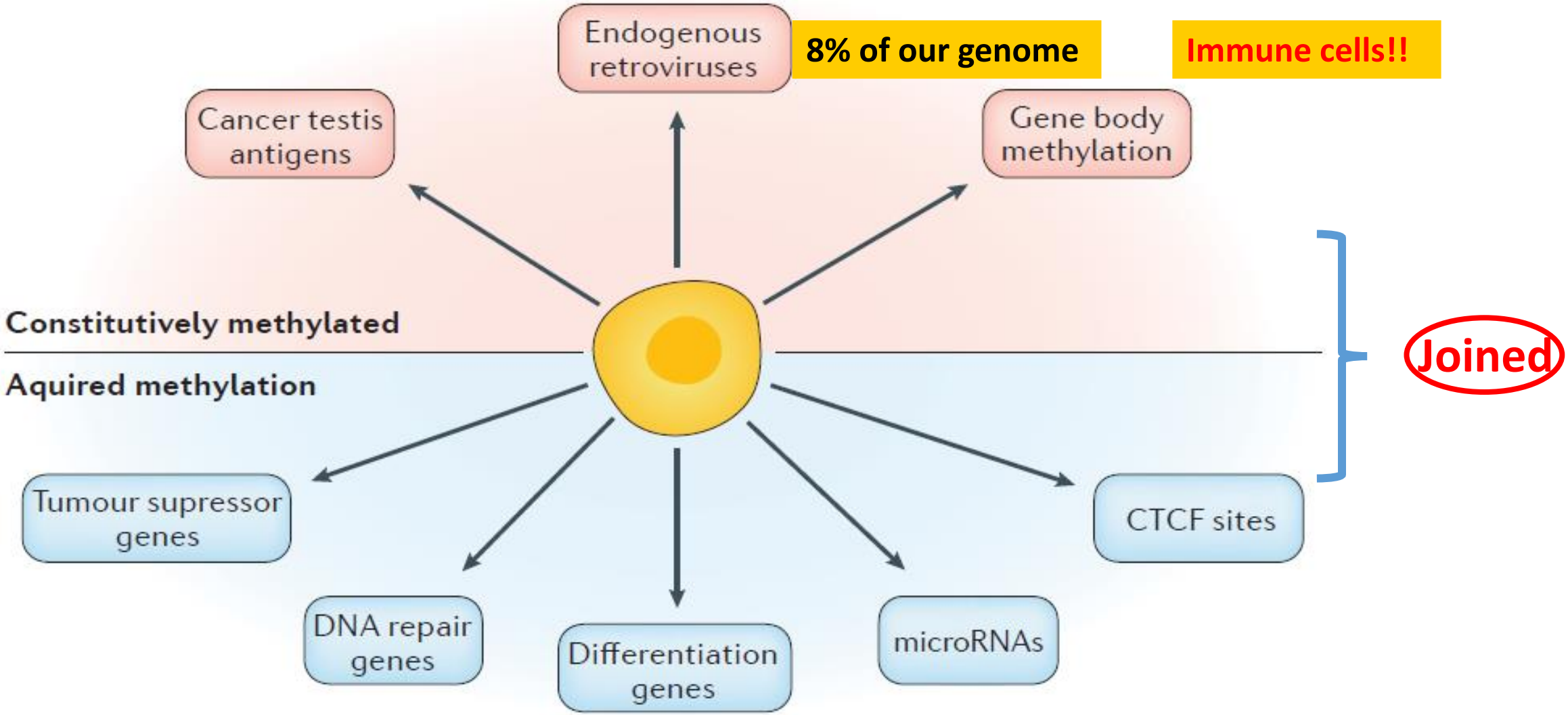
DAC + PARP1 induces

Fey Rassool *et al.*, PNAS 2020, 23



Unpublished – please do not post

The Tumor As A Target Of Epigenetic Therapy -The Triad

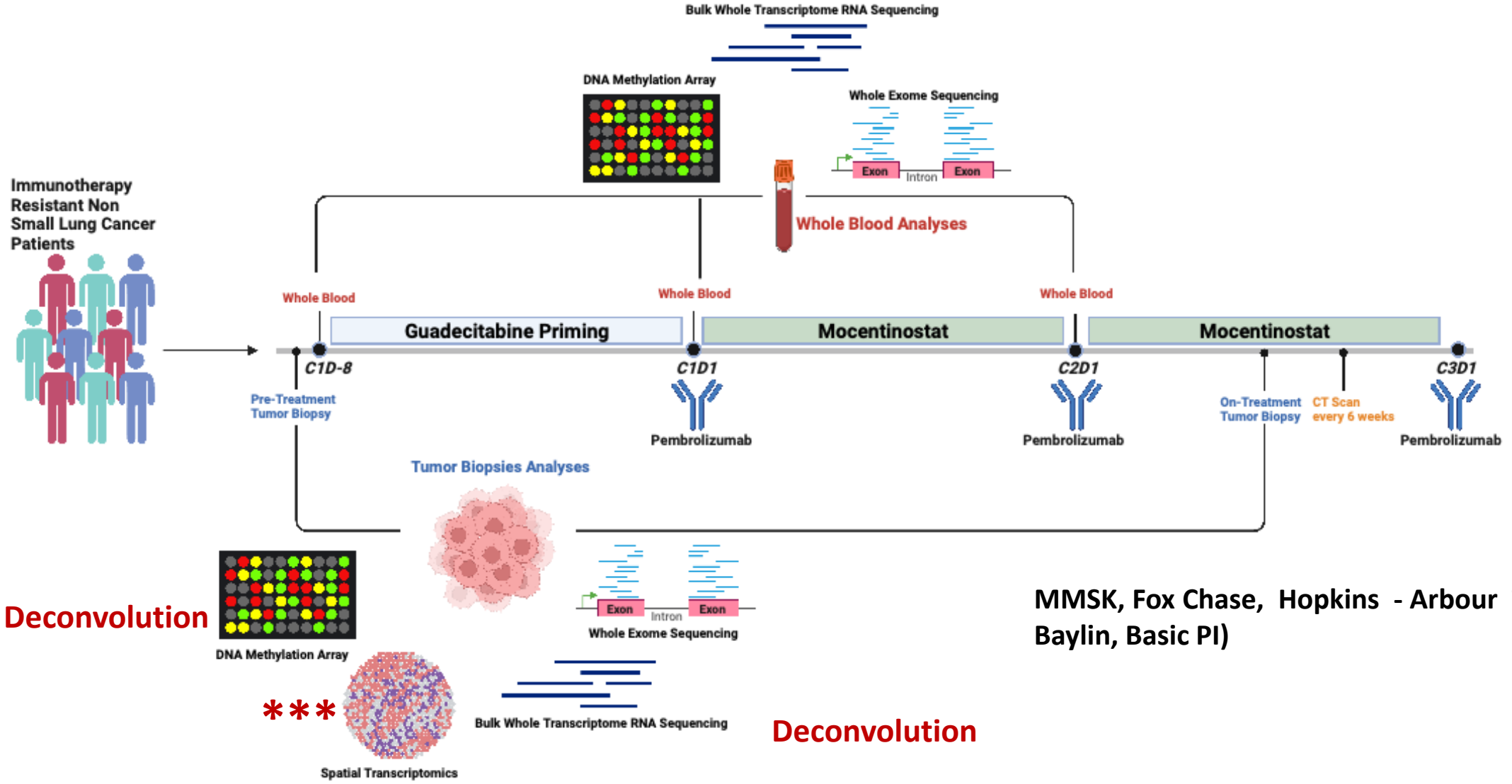


Intermediate CpG island densities
Controlling Genes – many have CpG poor promoters

Nature Reviews | Genetics

Clinical Trial Schema: Reversing IO Resistance –NSCLC

SU2C Merck Catalyst Trial



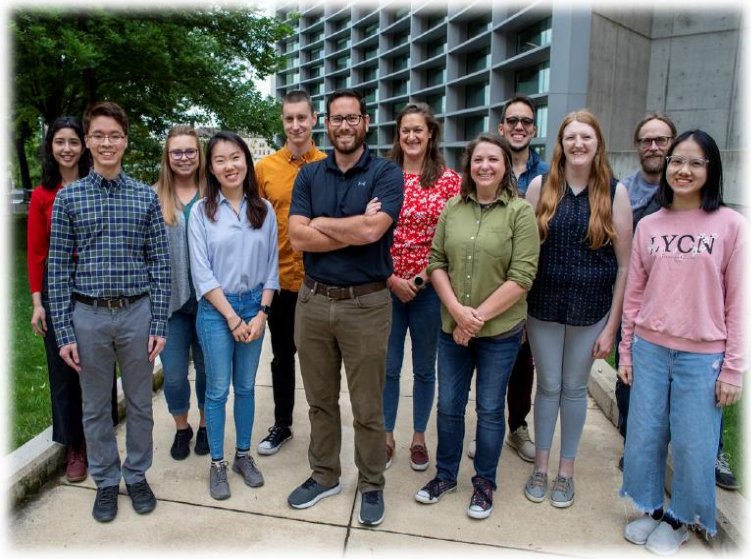
MMSK, Fox Chase, Hopkins - Arbour Trial Clinical PI; Baylin, Basic PI)

Conclusions to date

- Kras, TP53 co-mutations are associated with response.
- Basal responders have high inflammatory signaling.
- Differential expression to therapy is modest, DEGs detected are associated with STAT3, TAM and DC recruitment
- Inflammatory pathways are augmented by therapy, MYC suppressed
- Calcium signaling associated with response in whole blood samples.

Widening A Research Effort Without Walls

Rothbart Lab



Feyruz Rassool

Hari Easwaran

Competitive renewal

Multiple PI NIEHS Grant – Role Of Inflammation And Increased ROS Induced Epigenetic Changes In The Genesis Of CRC

Peter Jones

VAN ANDEL RESEARCH INSTITUTE

STAND UP TO CANCER

EPIGENETICS DREAM TEAM

NIH NATIONAL CANCER INSTITUTE

Discipline based SPORE to develop Cancer Epigenetic based therapies - Issa, Jones, Baylin

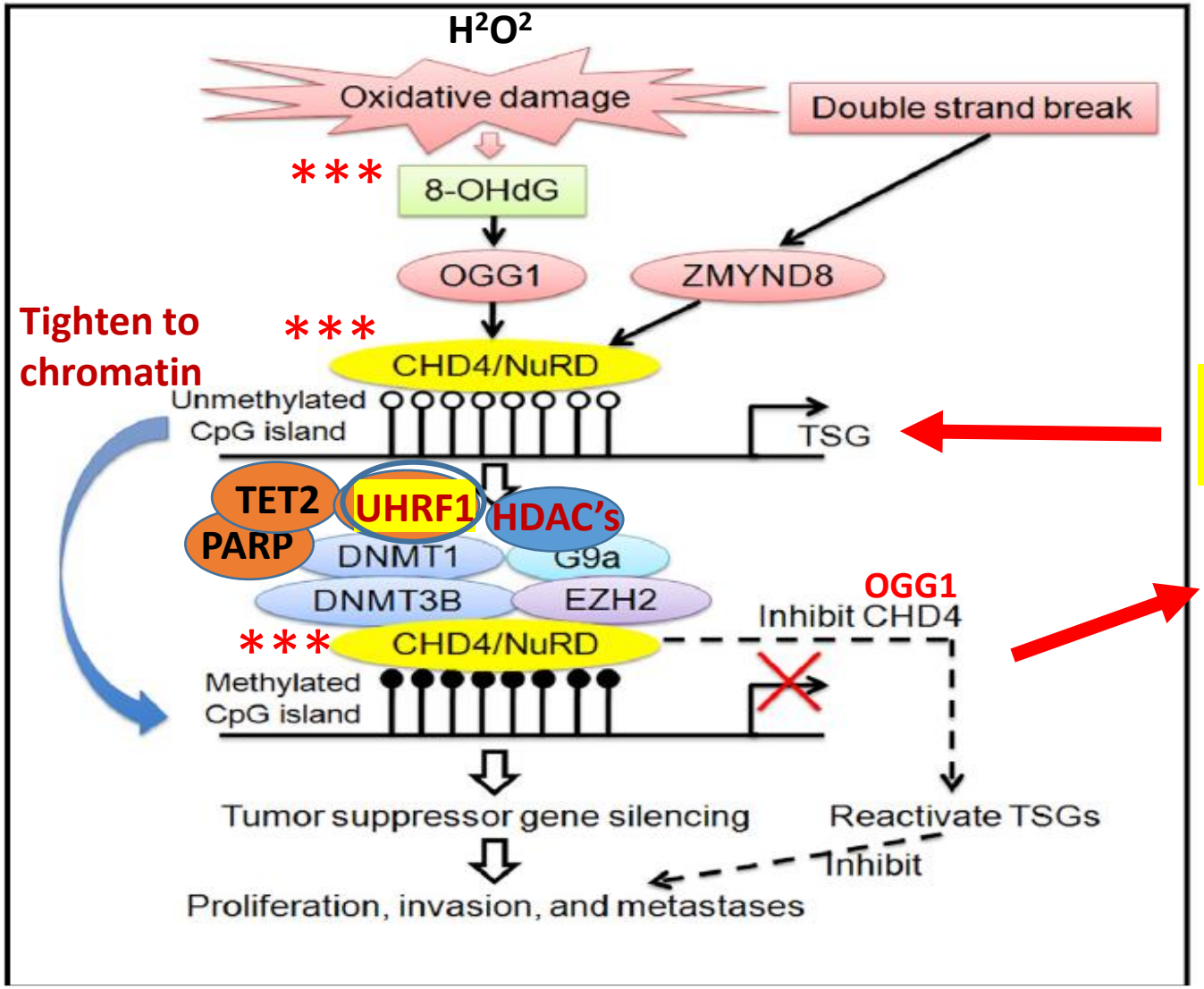
DSB's and Oxidative Damage Inducing A Systemic Signal for Repair in GC/CpG Rich Regions

Heather O'Hagan

Feyruz Rassool

Limin Xia

State Key Laboratory of Cancer Biology, Fourth Military Medical University



Inflammation
Aging
Cancer risk

60 to 80% developmental genes

Genes induced!

CDH1
WIF1
TIMP2
TIMP3
MLH1
CDKN2A
SFRP4
SFRP5

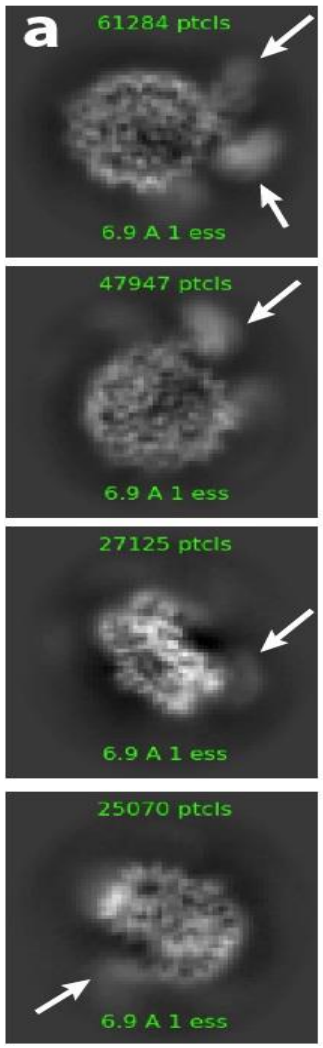
O'Hagan et al Cancer Cell, 2011

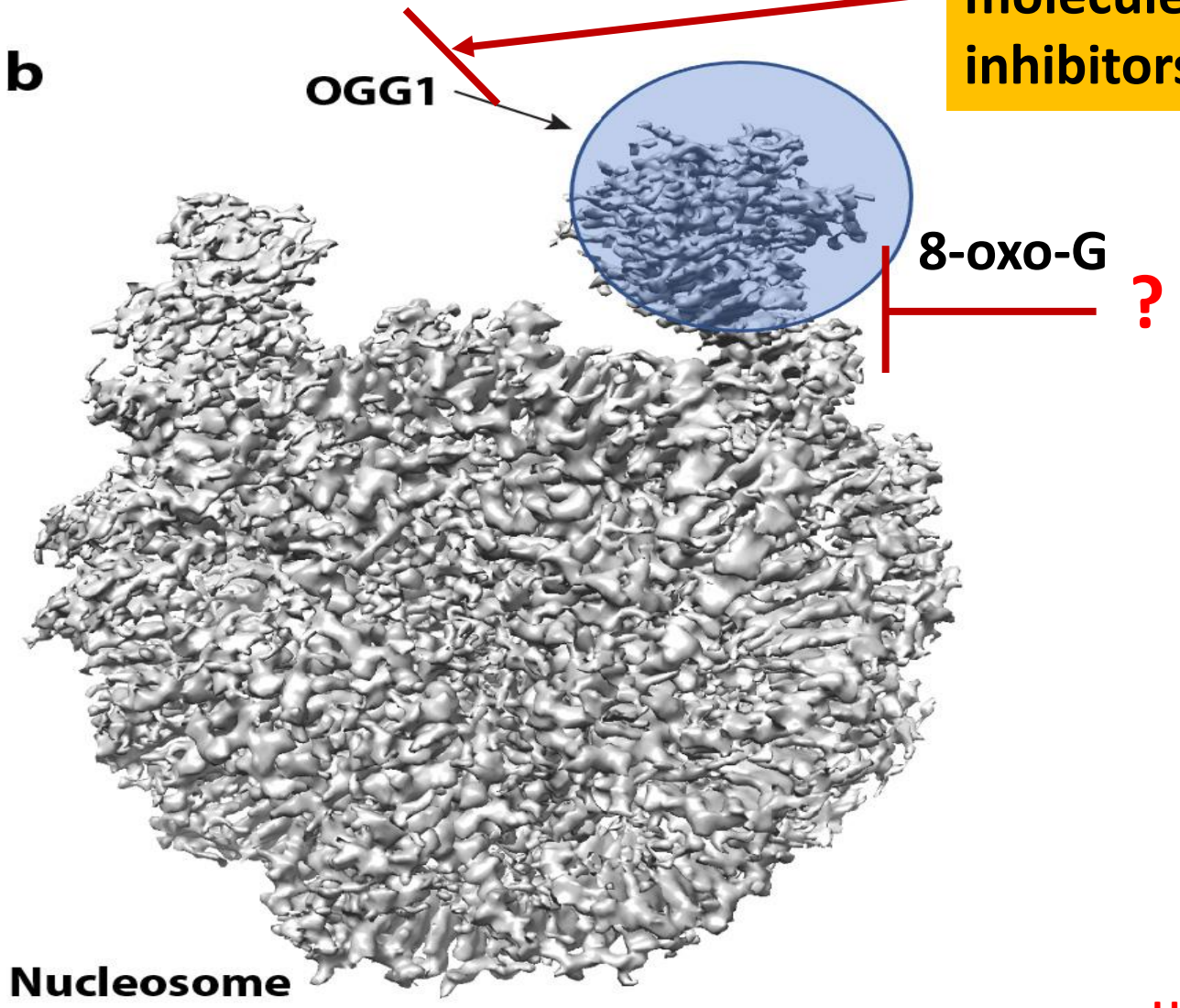
Muvarak et al, Cancer Cell, 2016

Cai et al, Oncogene, 2012
Zhang et al, Mol Cell, 2017

Xia et al, Cancer Cell, 2017

How Does OGG1 Work?

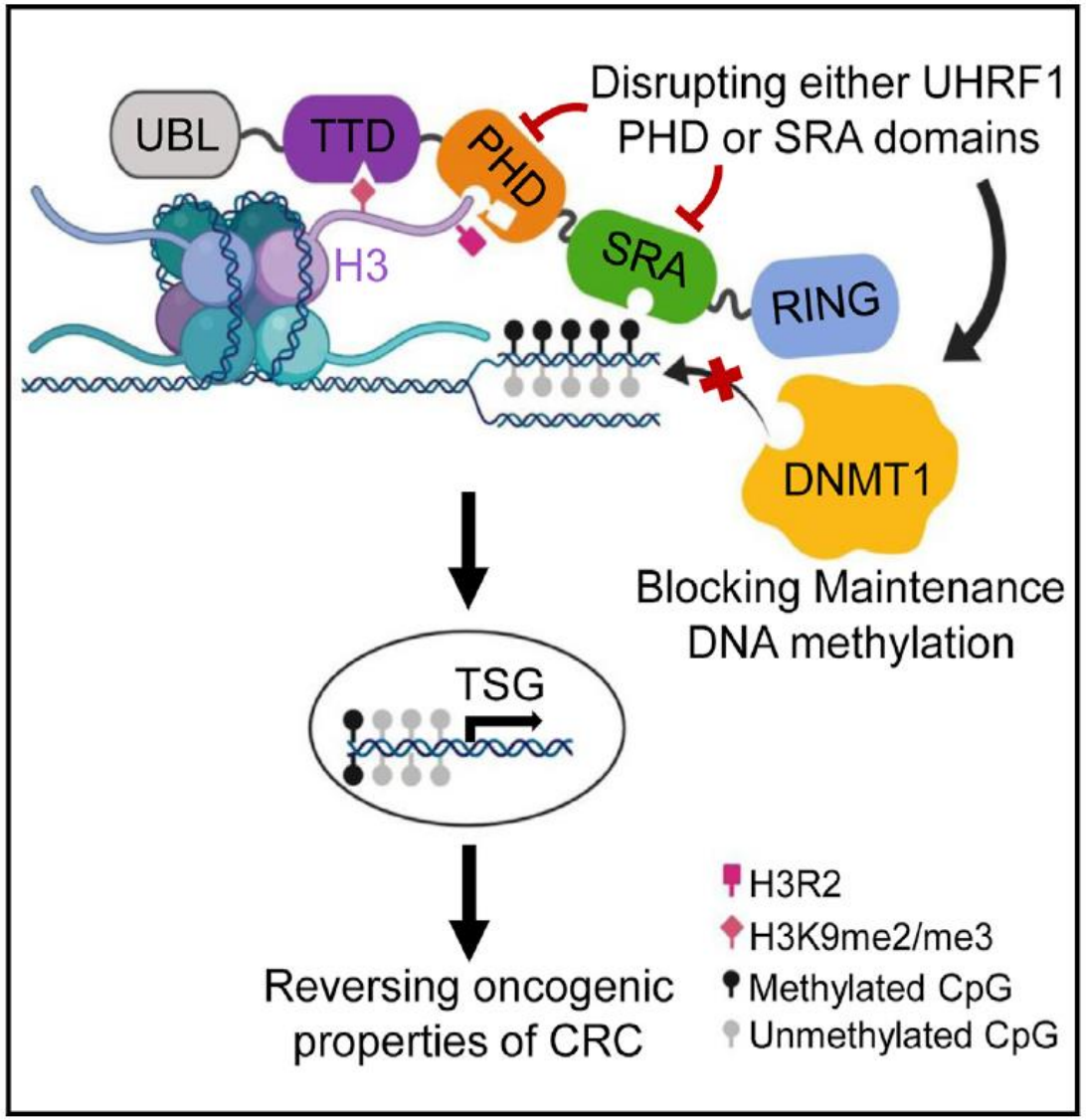


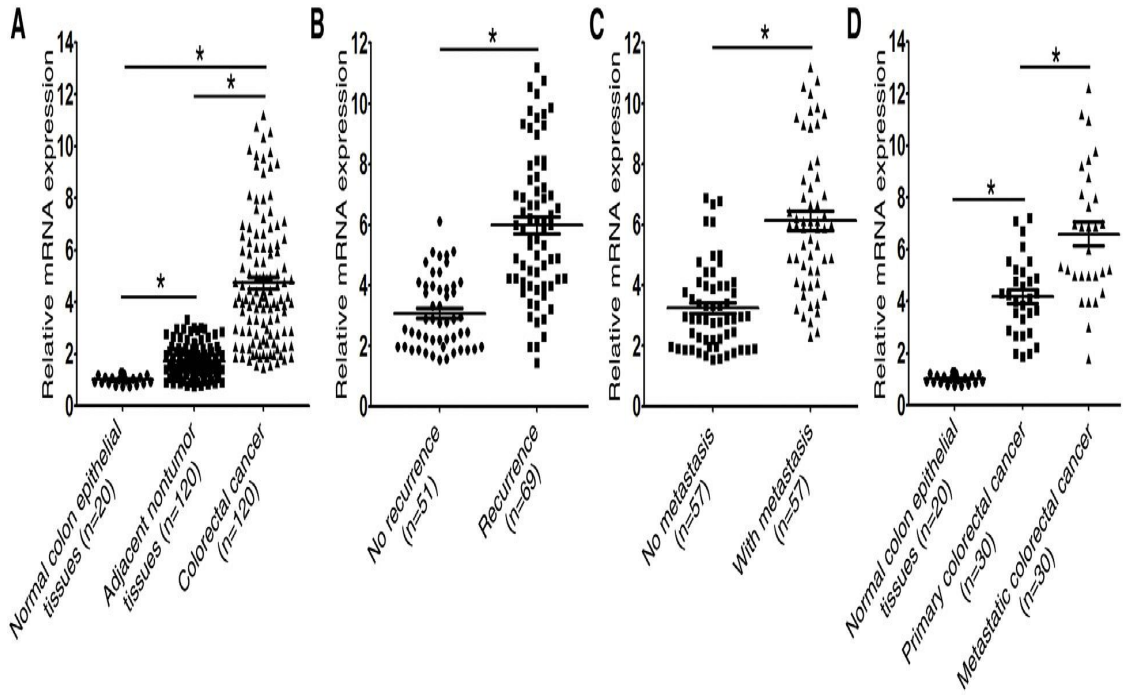


In preparation, You, Qinglong, Yi Cai, S Baylin, Huilin Li

Unpublished–do not post

UHRF1 Mains Abnormal DNA methylation In Cancer – Elevated expression correlates with poor outcomes in human colorectal cancer





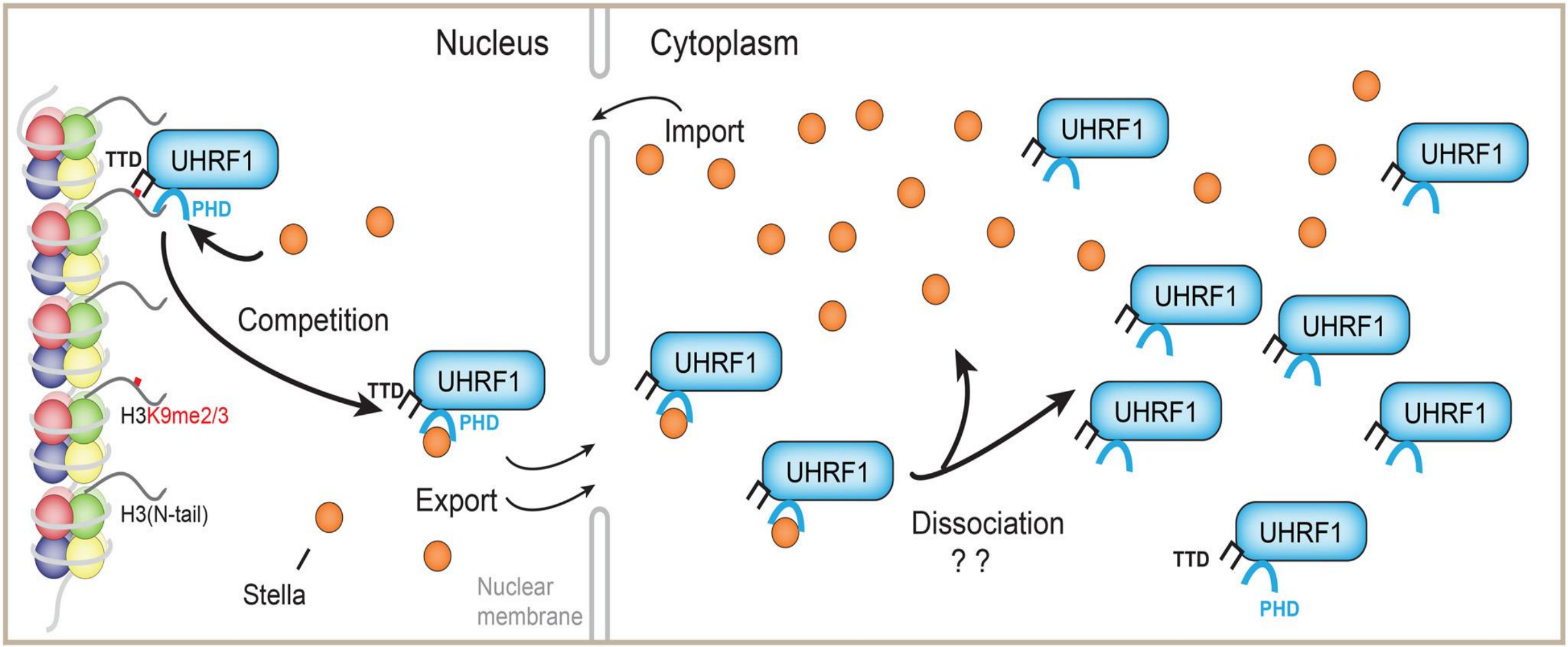
Rothbart

Xiangqian Kong
(Baylin Lab)

Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences

Kong et al., 2019, Cancer Cell 35, 633–648

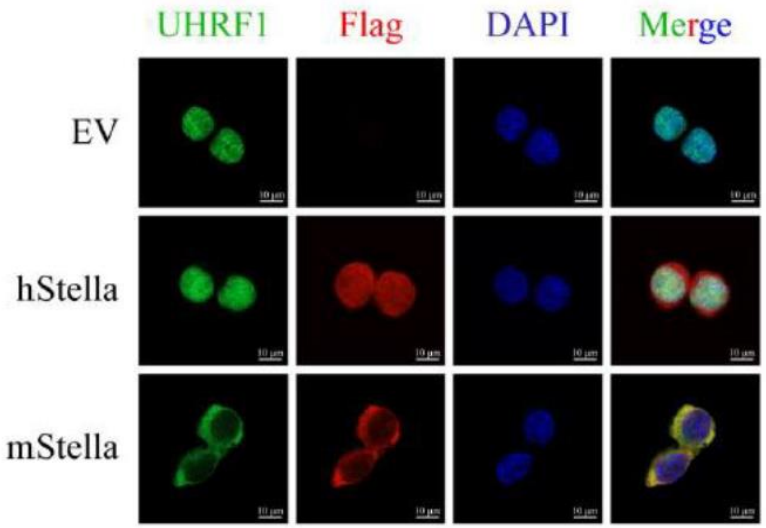
FUNCTION OF STELLA (DPPA1), A NATURAL INHIBITOR OF UHRF1

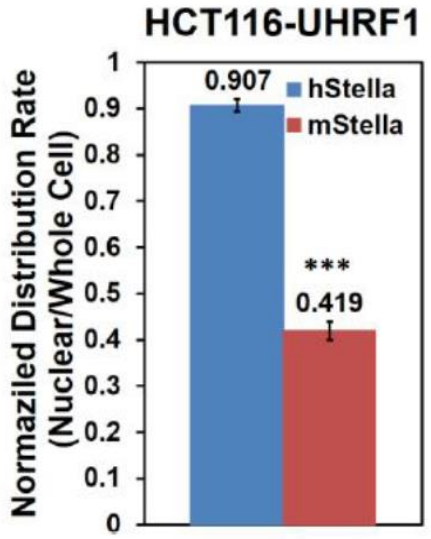


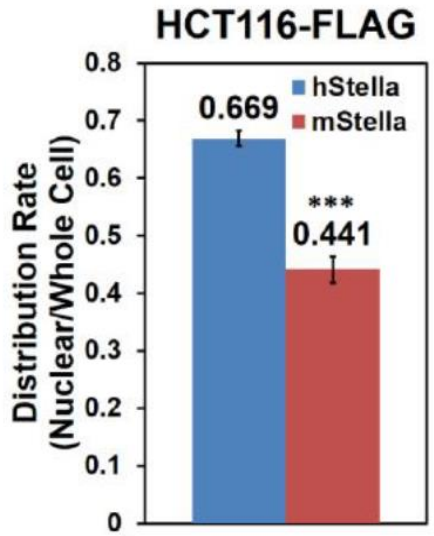
Du et al, J. Biol. Chem. (2019) 294(22) 8907–8917

MOUSE, BUT NOT HUMAN STELLA ACTS AS AN INHIBITOR OF UHRF1 IN HUMAN CANCER CELLS

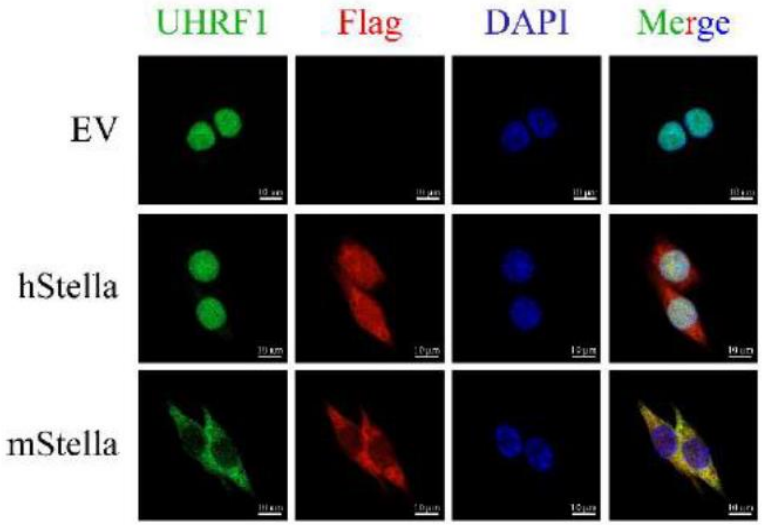
HCT-116

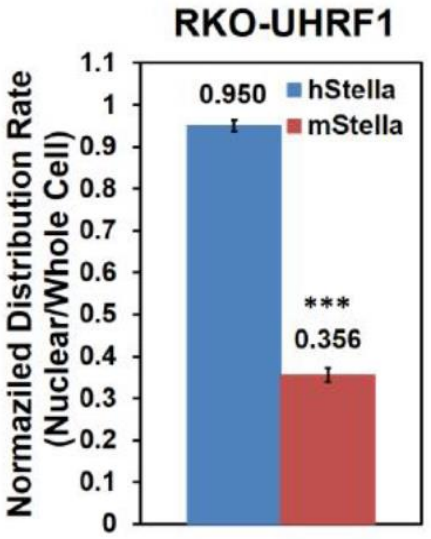


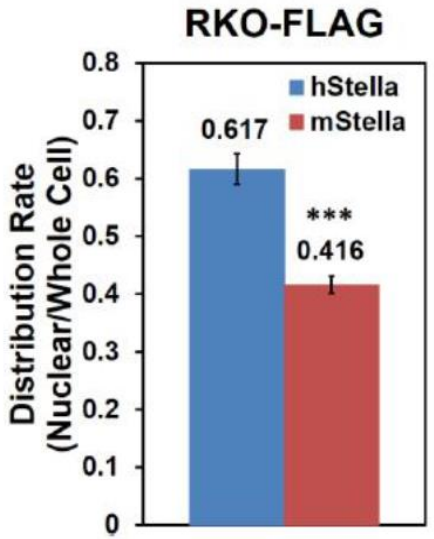




RKO







Xiangqian Kong (Baylin Lab)

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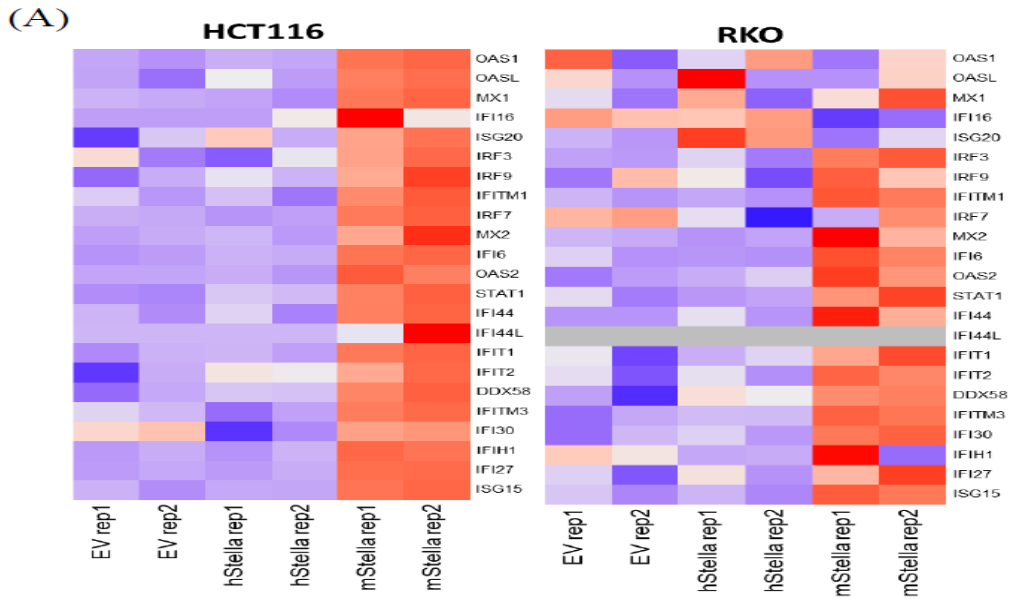
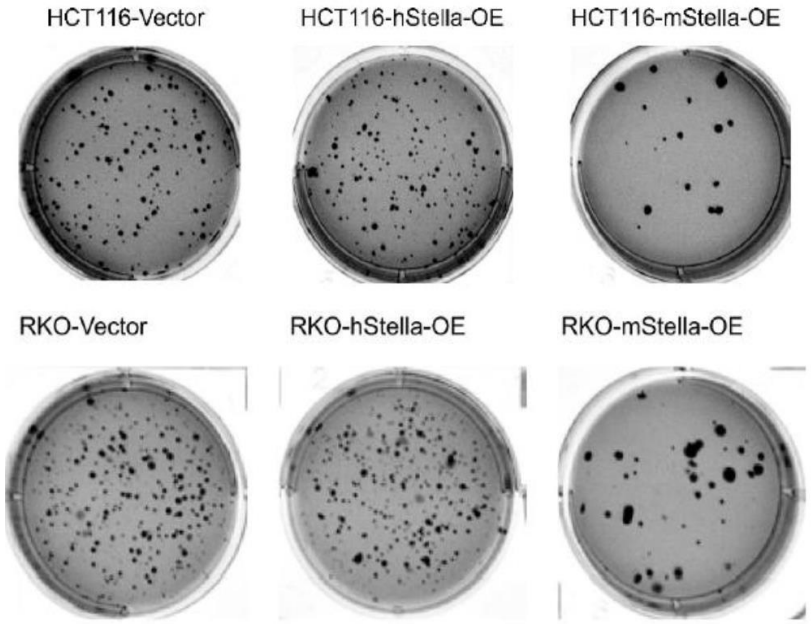
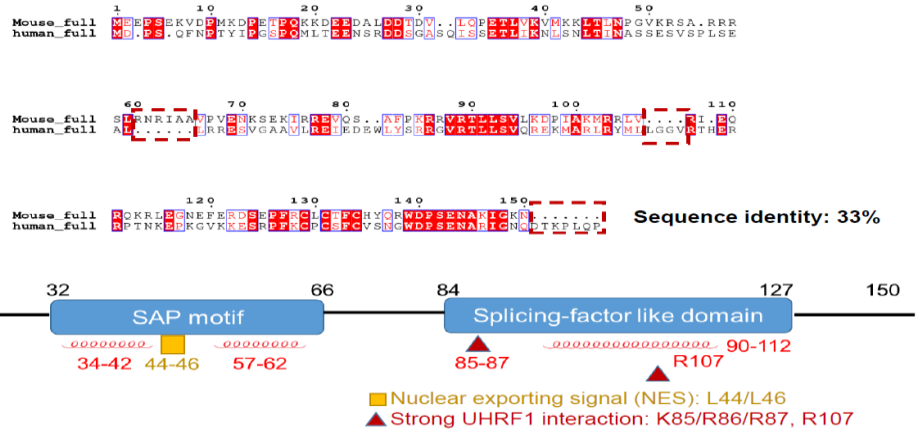
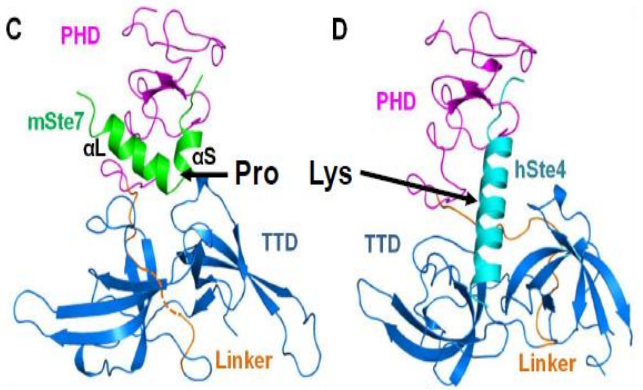
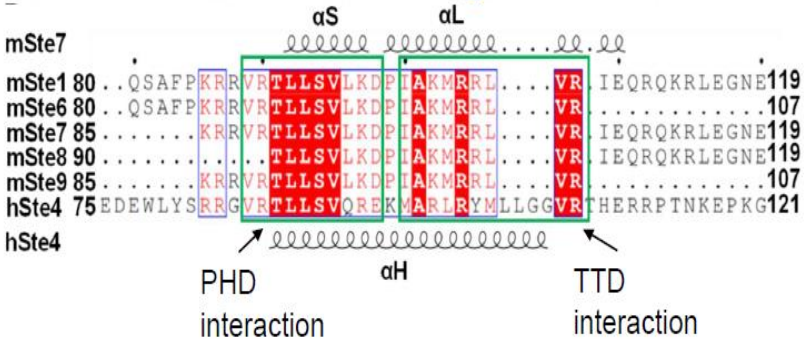










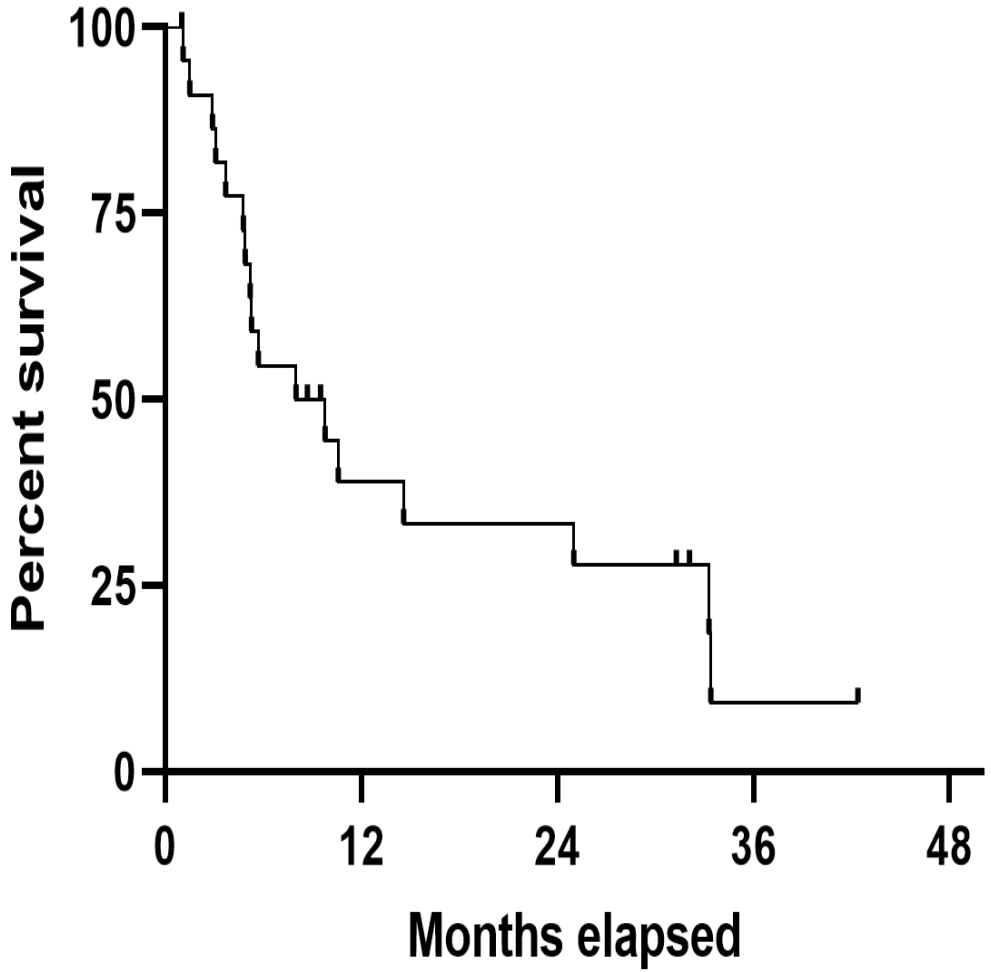
Xiangqian Kong (Baylin Lab)

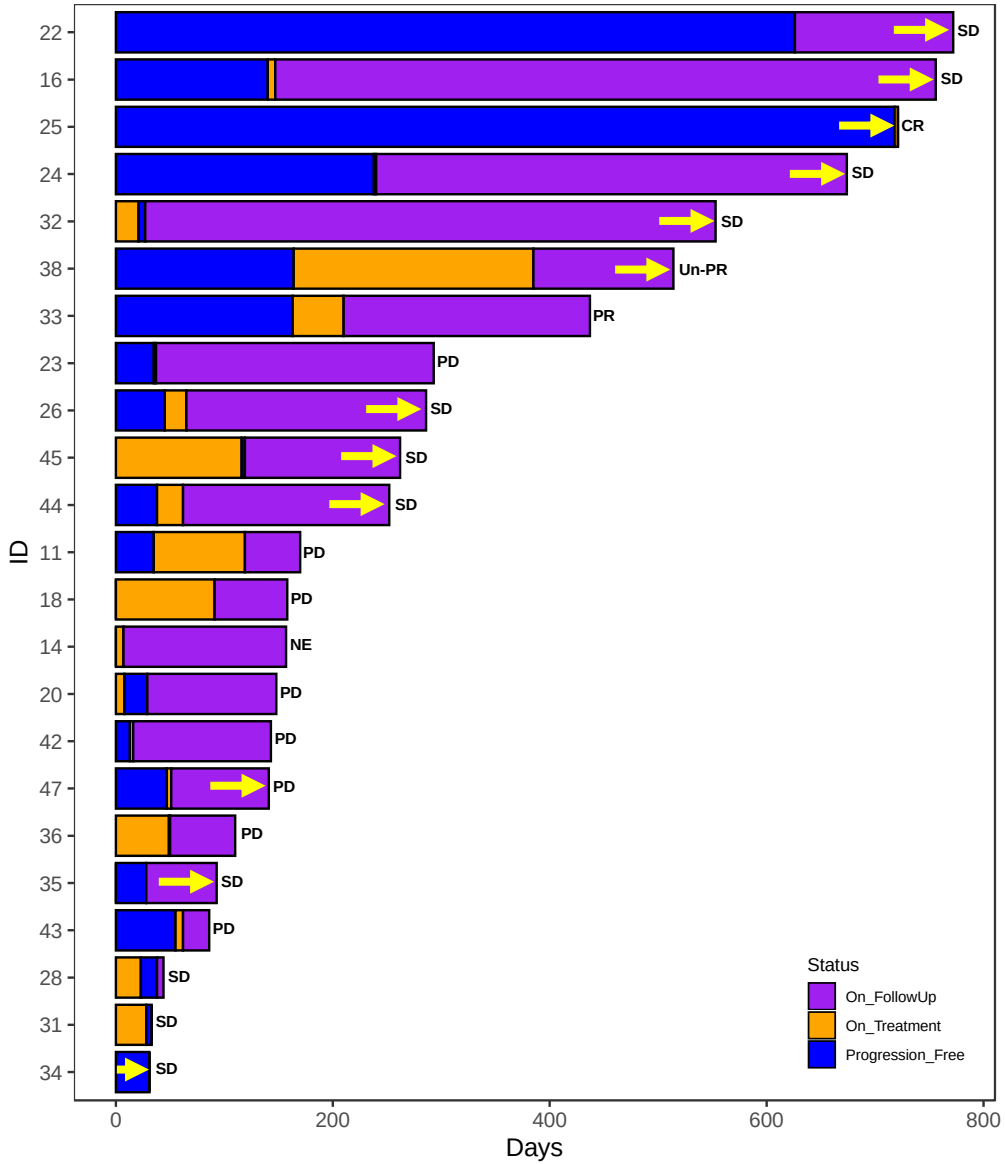
Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences

Components Of The Talk

- **A little bit of history including our group's entry into the field**
- **Molecular mechanisms underlying origins of an epigenetic abnormality we have been studying for over 30 years – very recent insights**
- **An exciting era – cancer evolution from normal cells of tumor origin and the role of their epigenetic "state", dependency of epigenetic changes for a) progression of these cells to point of cancer initiation and b) allowing driver mutations to induce cell transformation**
- **Some basic translational implications including manipulating epigenetic aspects of tumor immunology**

Survival Analysis of Combination Epigenetic and Immunotherapy in αPD-1 Resistant NSCLC

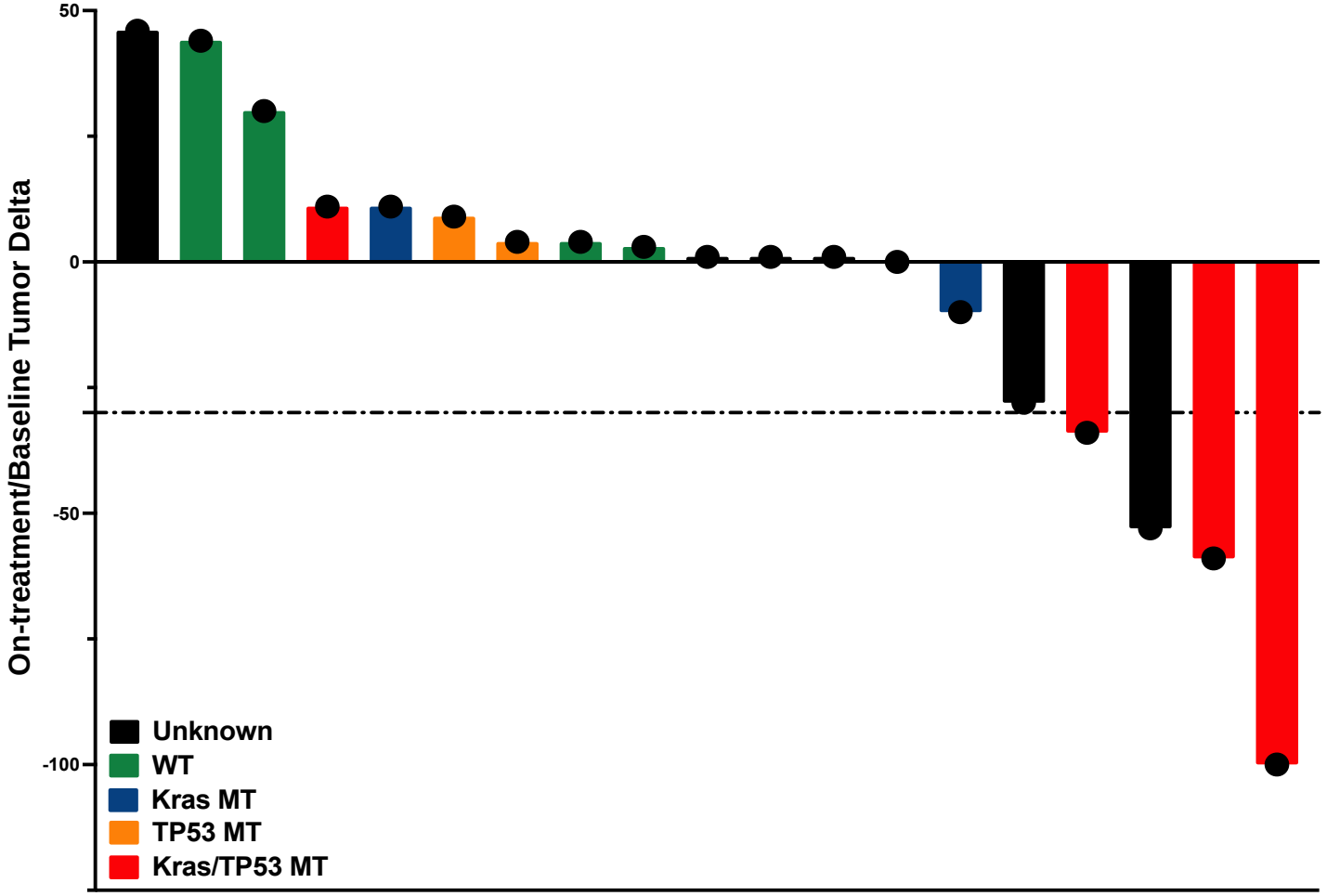




Topper, Arbour, et al

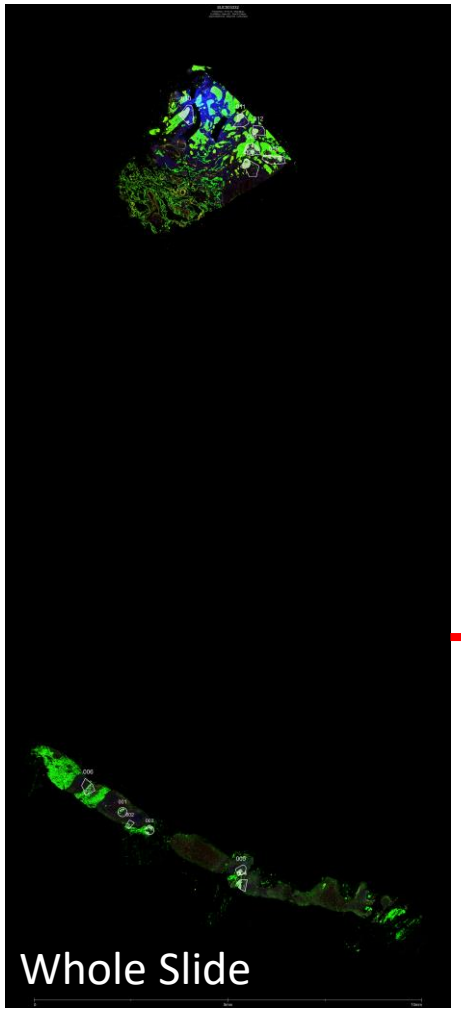
Unpublished– please do not post

Targeted Mutational Profiling (MSK-IMPACT) - Association Between Kras/TP53 Co-mutation and Tumor Regression

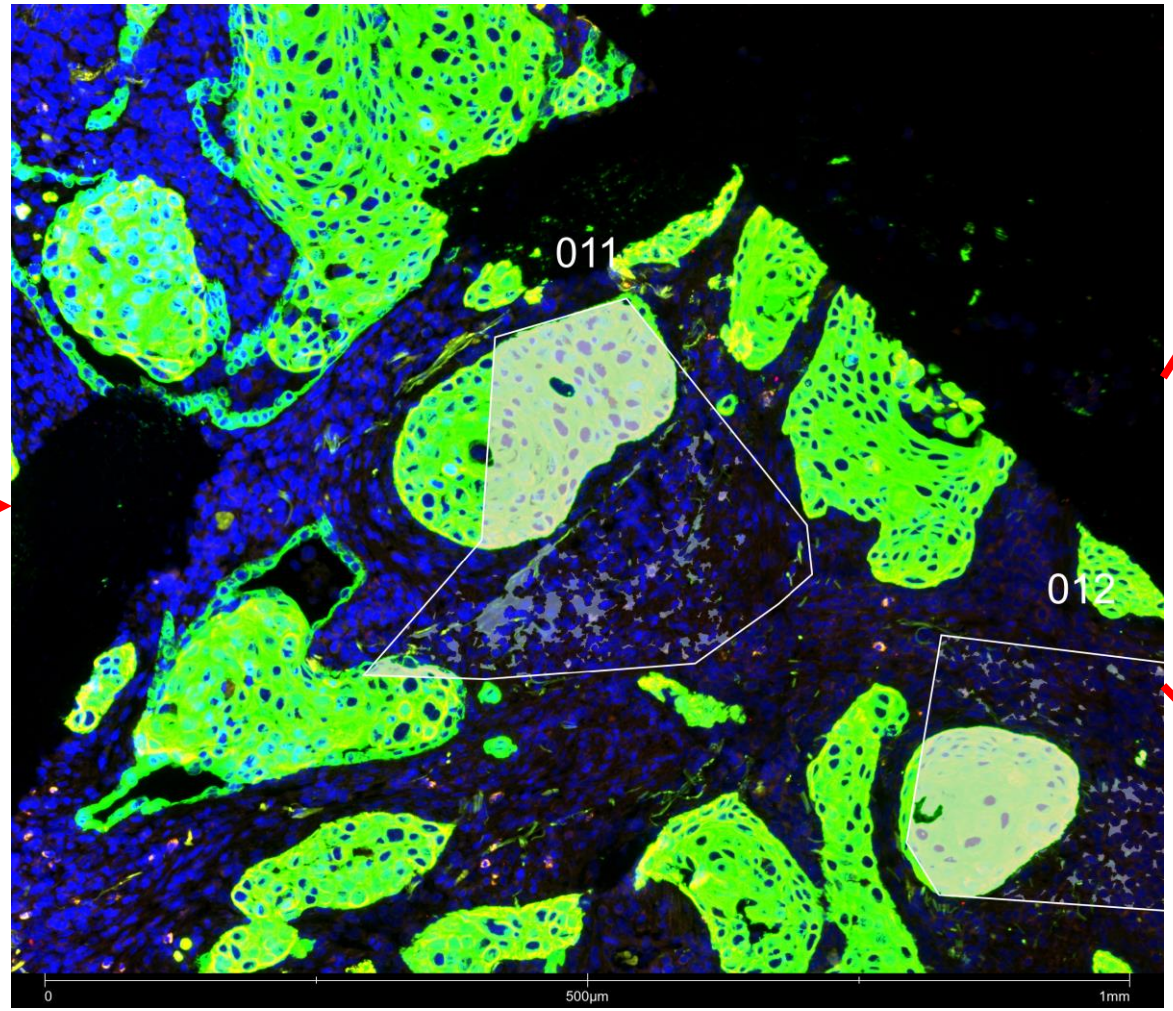


Mutation	w/ Unknown Samples
WT both	NS
Kras MT	NS
TP53 MT	NS
Kras MT, TP53 MT	P-value: 0.0103

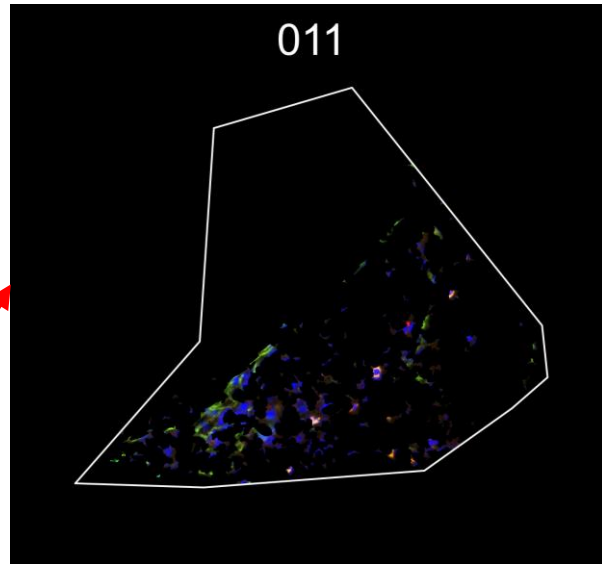
Nanostring GeoMX DSP ROI Selection and Segmentation



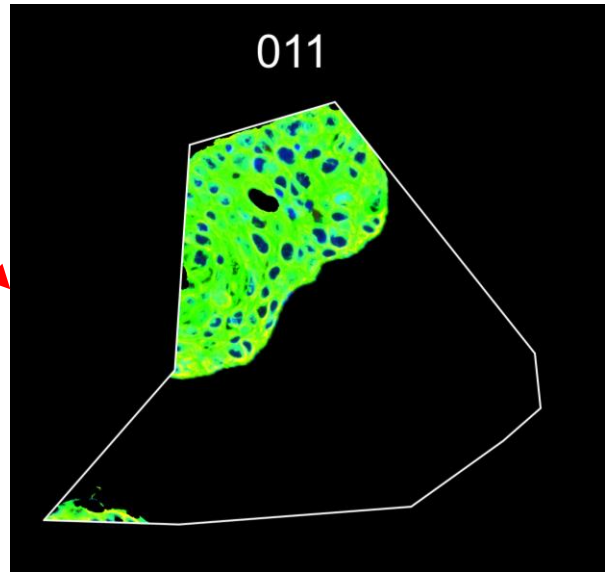
Region of Interest Selection:
Tumor and Immune Cells in Direct Contact (Pathologist Guided)



CD45 Segmentation

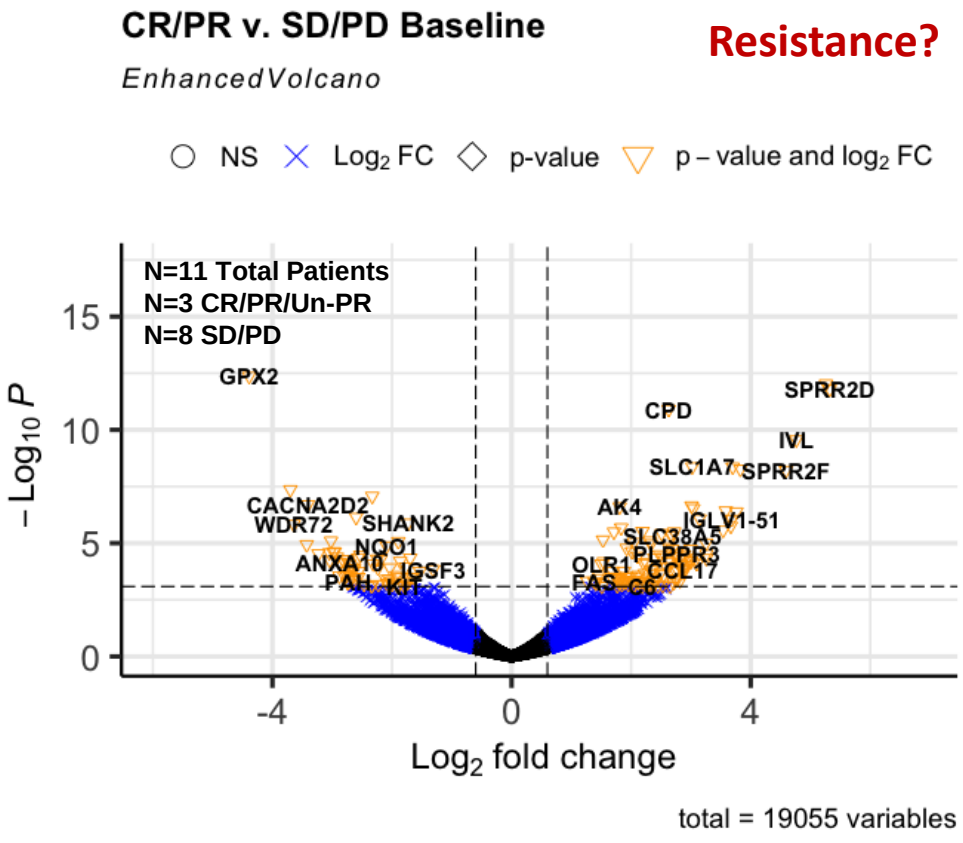


PanCK Segmentation



Channels:
FITC/525nm : SYTO 13 : DNA (Blue)
Cy3/568nm : Alexa 532 : PanCK (Green)
Texas Red/615nm : Alexa 594 : CD45 (Red)

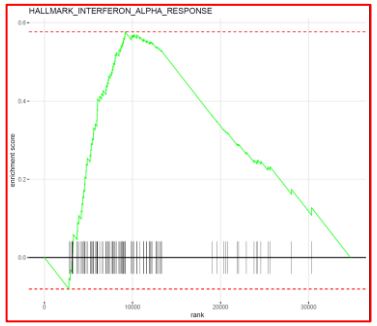
Basal Transcriptome of Responders Display Differential Enrichment of Inflammatory and Kras Pathways Relative to Non-Responders

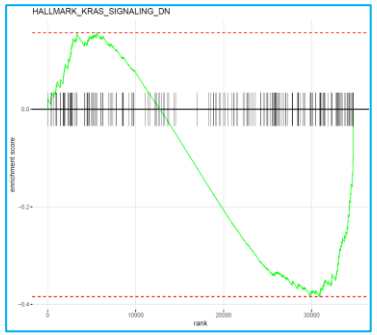


Resistance?

Pathway	Gene ranks	NES	pval	padj
HALLMARK_INTERFERON_ALPHA_RESPONSE		1.99	2.8e−04	2.9e−03
HALLMARK_HEME_METABOLISM		−1.61	2.9e−04	2.9e−03
IALLMARK_INTERFERON_GAMMA_RESPONSE		2.03	3.3e−04	2.9e−03
RK_EPITHELIAL_MESENCHYMAL_TRANSITION		2.24	3.3e−04	2.9e−03
HALLMARK_ALLOGRAFT_REJECTION		1.74	3.3e−04	2.9e−03
HALLMARK_PANCREAS_BETA_CELLS		−1.92	3.4e−04	2.9e−03
HALLMARK_INFLAMMATORY_RESPONSE		1.52	9.8e−04	7.0e−03
HALLMARK_IL6_JAK_STAT3_SIGNALING		1.54	4.8e−03	3.0e−02
HALLMARK_APOPTOSIS		1.40	7.9e−03	4.4e−02
HALLMARK_IL2_STAT5_SIGNALING		1.36	9.5e−03	4.7e−02
HALLMARK_MYOGENESIS		−1.37	1.2e−02	5.5e−02
HALLMARK_OXIDATIVE_PHOSPHORYLATION		−1.35	1.6e−02	6.2e−02
HALLMARK_ANGIOGENESIS		1.54	1.6e−02	6.2e−02
HALLMARK_COMPLEMENT		1.31	2.1e−02	7.3e−02
HALLMARK_KRAS_SIGNALING_DN		−1.33	2.2e−02	7.3e−02

0 10000 20000 30000





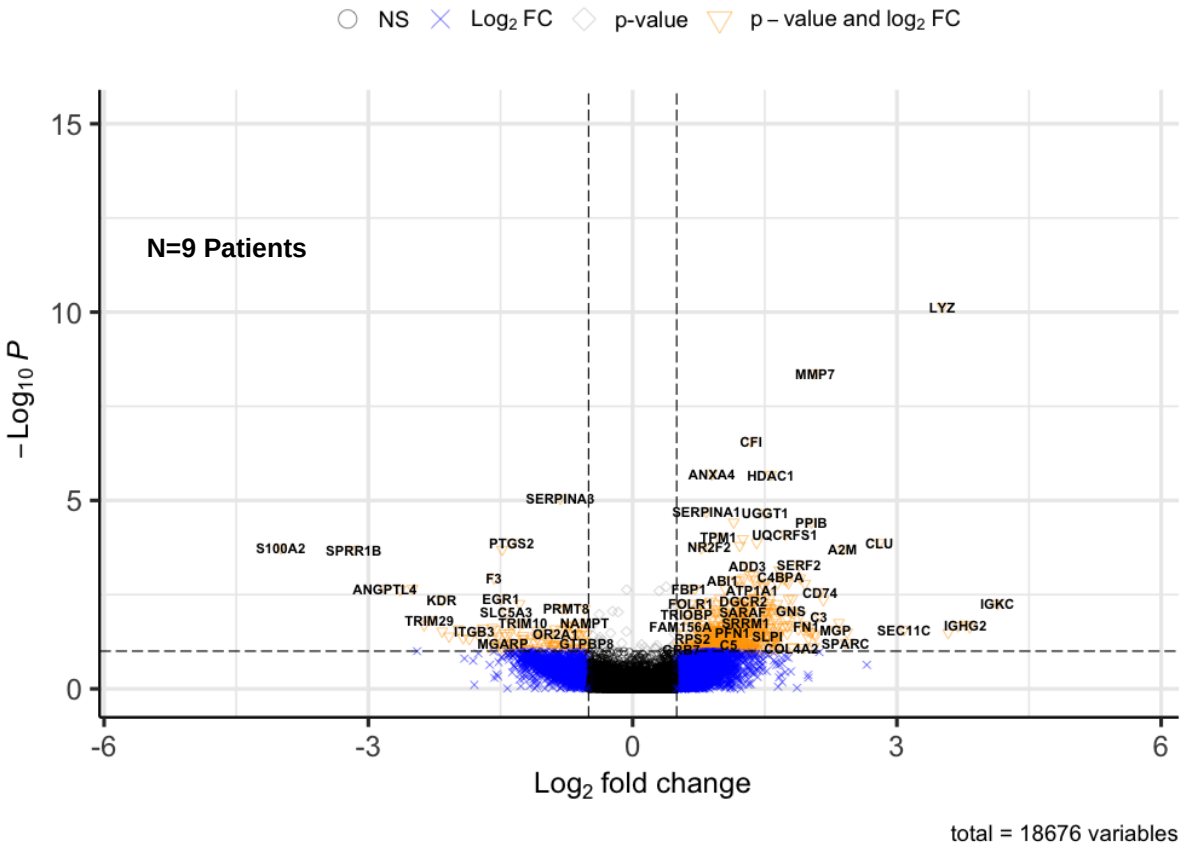
Basal Responder vs Non-Responder based on RECIST Response; all CR/PR patients have achieved DCB (6 Mos. No PD)

DE analysis: High Class II APC, inflammatory genes and immunotherapy target MUC16

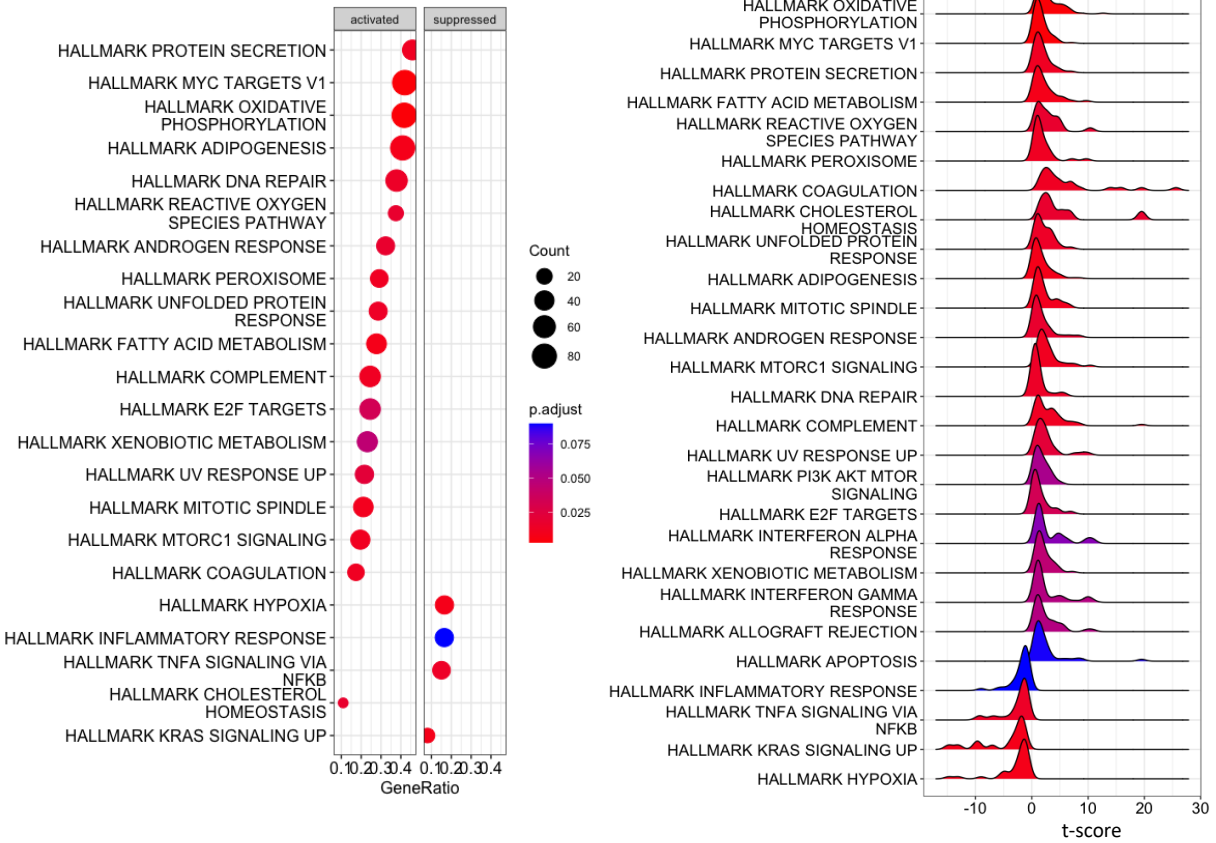
Pathways: Interferon and Allograft pathways (Up)

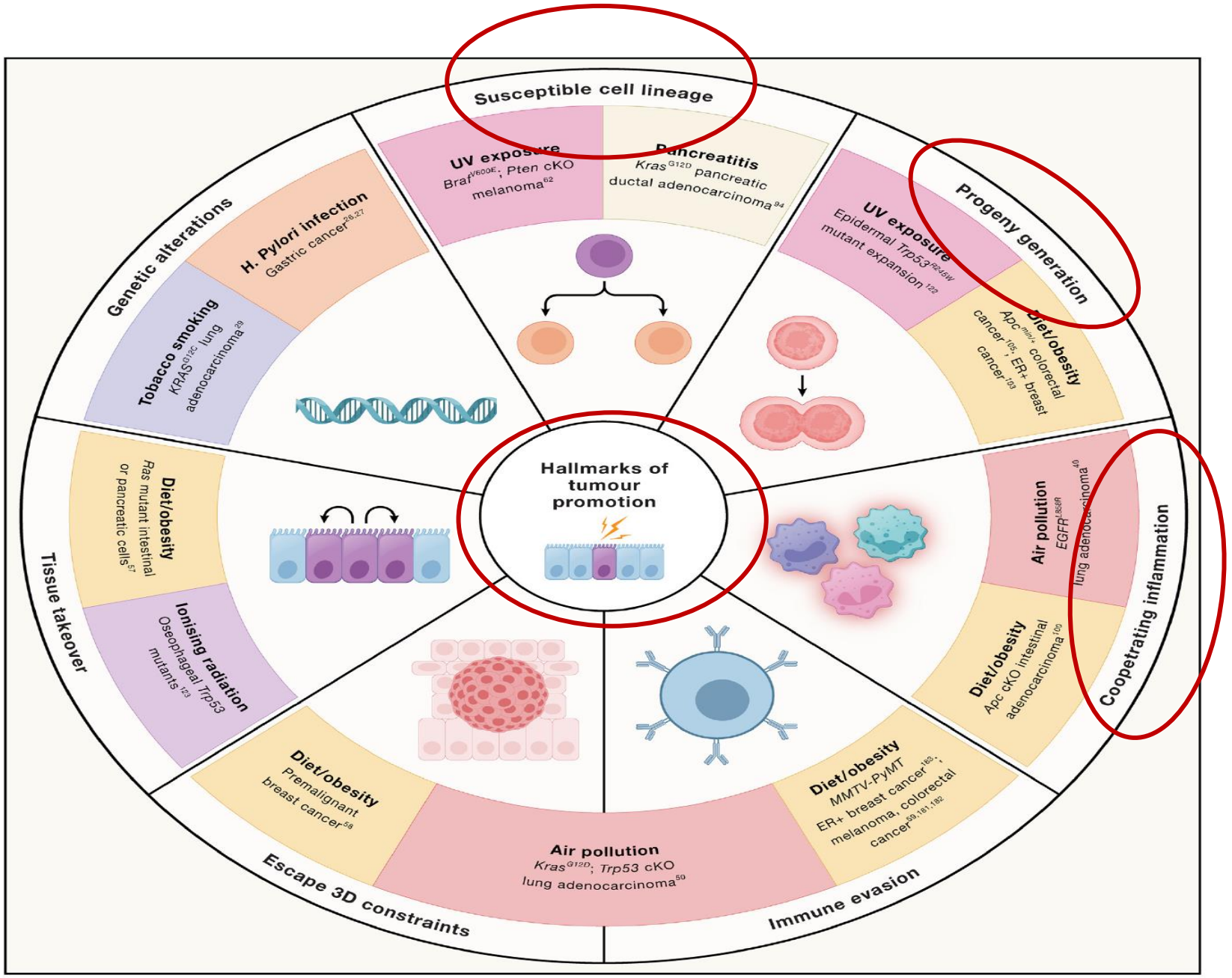
Responders Basally Present with Transcriptional MYC Activation and Interferon Suppression vs. Non-Responders in PanCK+ Tumor Cells

Differential Expression Analysis



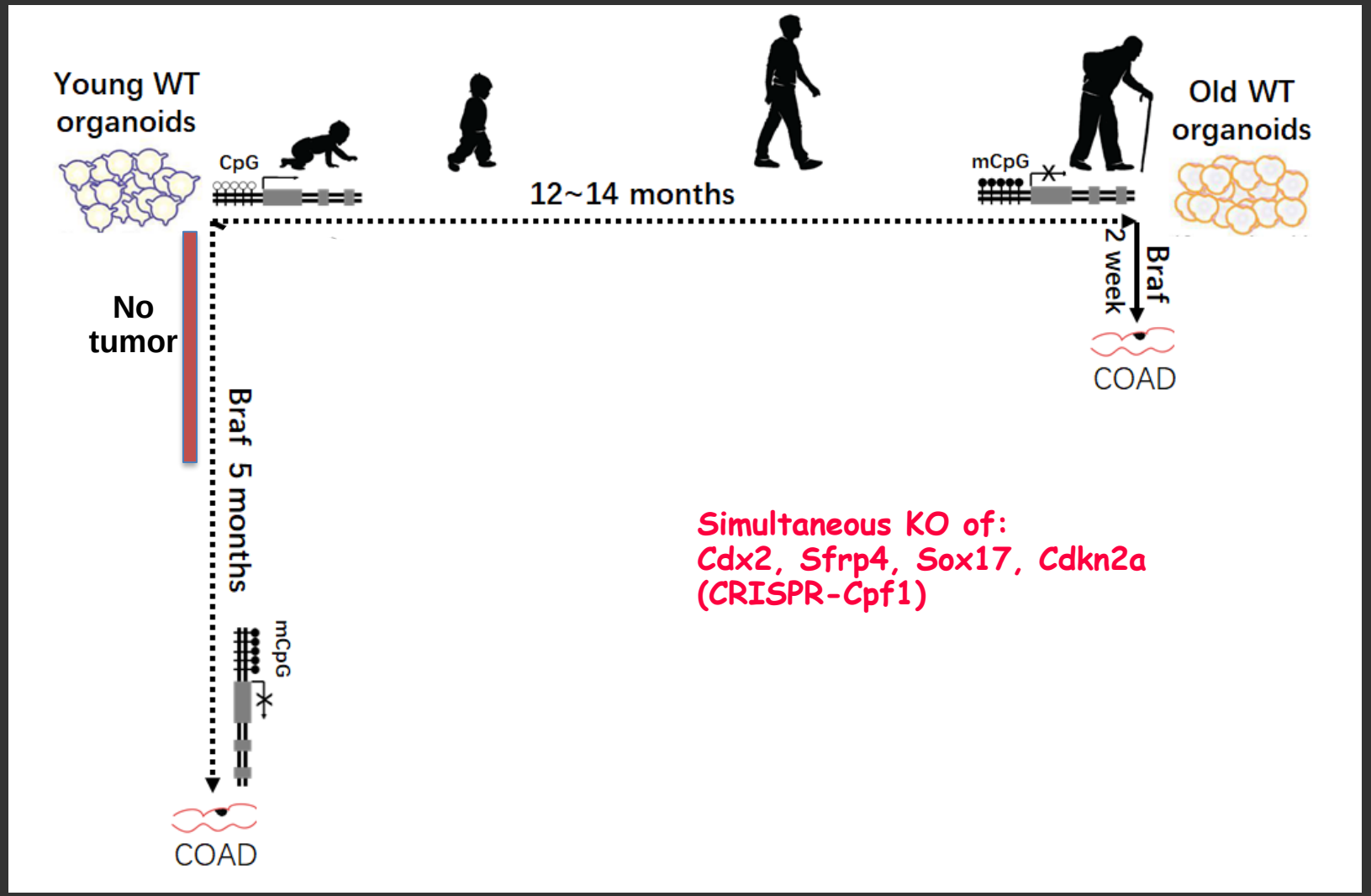
MSigDB: Hallmark



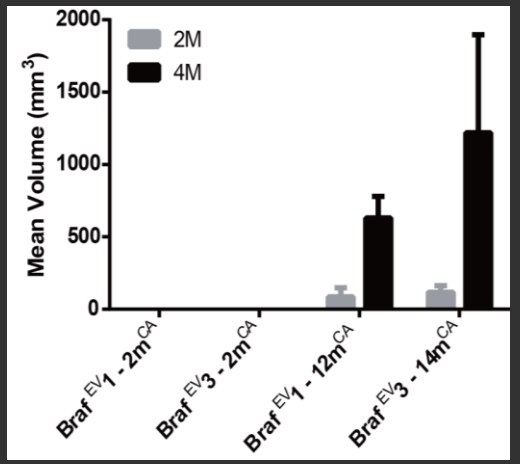


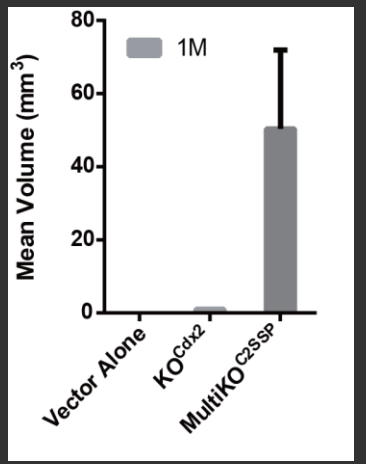
Swanton and colleagues, Cell, 2023

Ageing-associated DNA methylation provides the permissive state for oncogenic mutations



Simultaneous KO of:
Cdx2, Sfrp4, Sox17, Cdkn2a
(CRISPR-Cpf1)

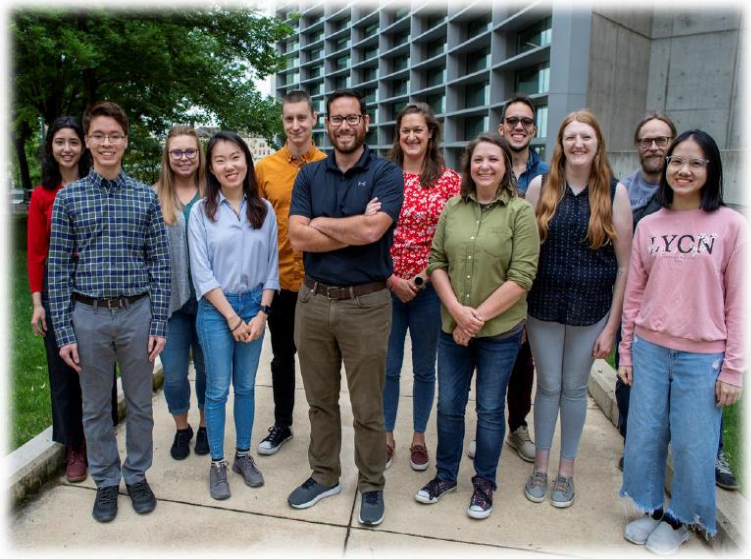




Tao et al., Cancer Cell (2019, PMID:30753828)

Widening A Research Effort Without Walls

Rothbart Lab



Feyruz Rassool

Hari Easwaran

Competitive renewal

Multiple PI NIEHS Grant – Role Of Inflammation And Increased ROS Induced Epigenetic Changes In The Genesis Of CRC

Peter Jones

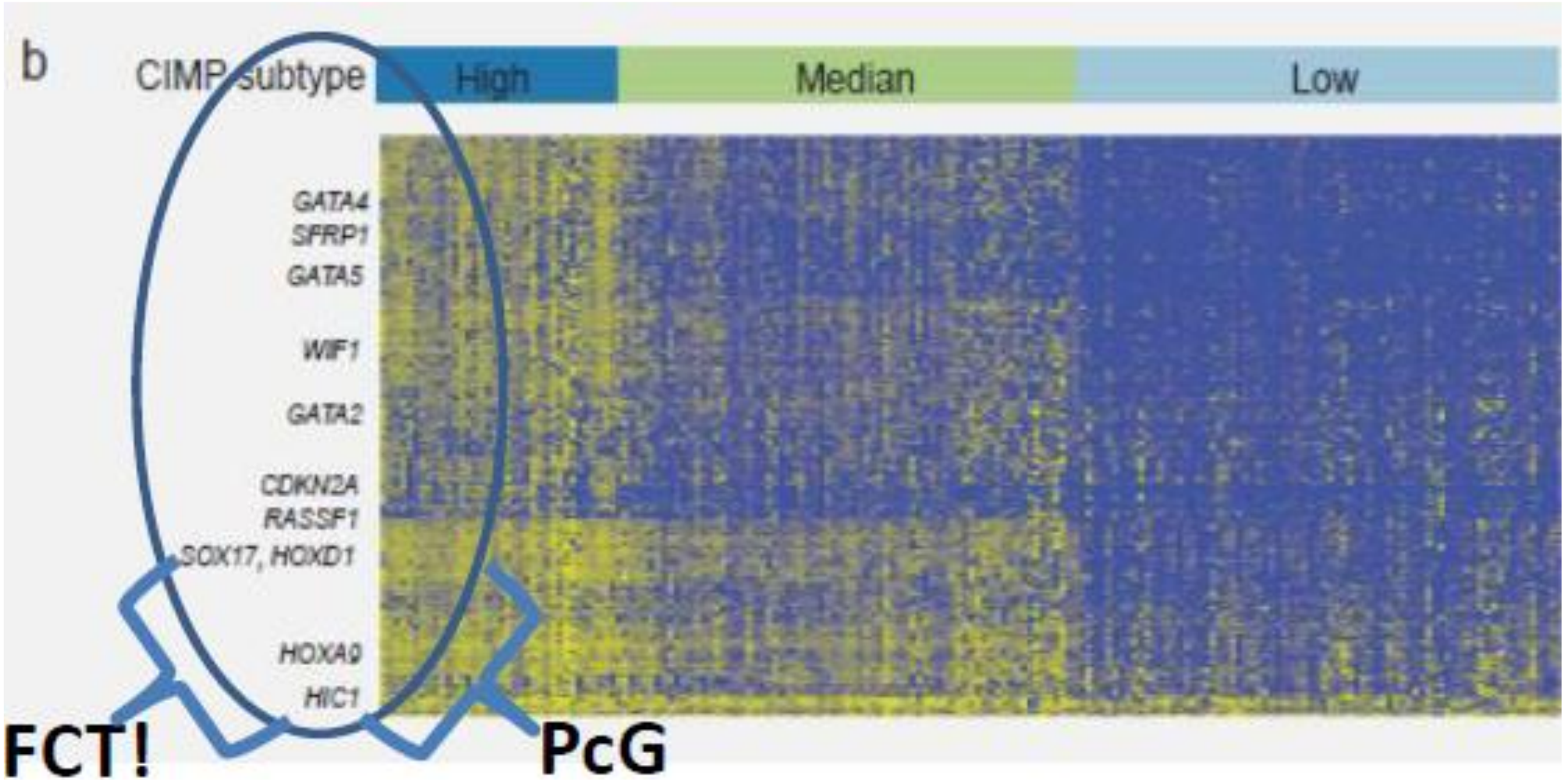
VAN ANDEL RESEARCH INSTITUTE

STAND UP TO CANCER

EPIGENETICS DREAM TEAM

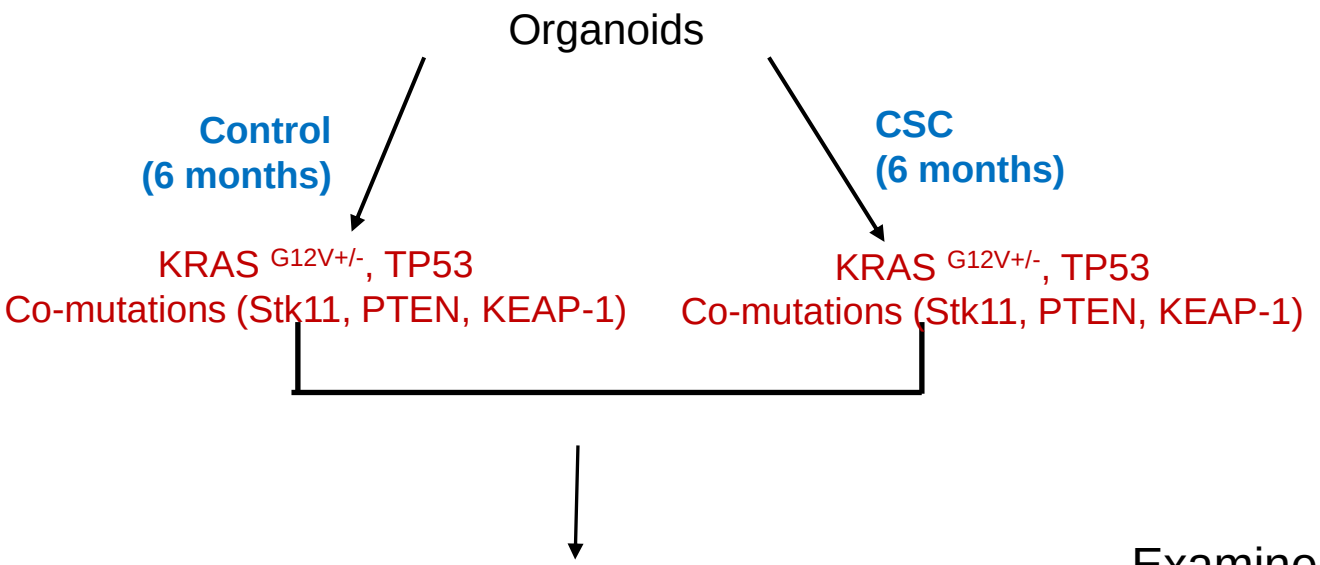
NIH NATIONAL CANCER INSTITUTE

Discipline based SPORE to develop Cancer Epigenetic based therapies - Issa, Jones, Baylin



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

Role of epigenetic alterations in sensitizing to key genetic driver events to drive specific pathological subtypes of NSCLC

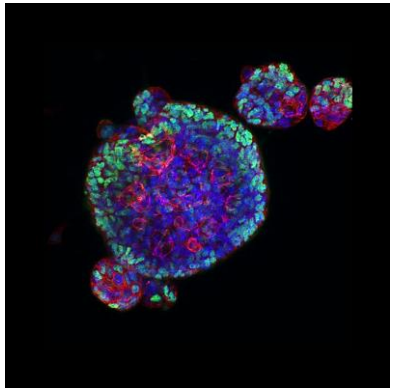


Test their ability to form tumors in vivo and determine the pathological subtype → Examine key differences in molecular pathways driving these phenotypes.

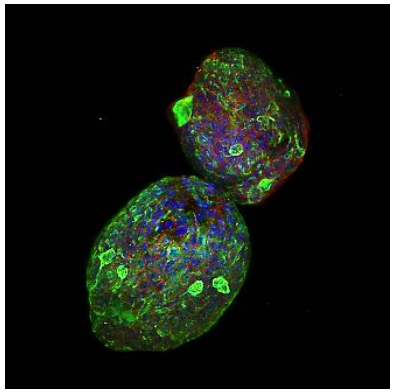
IMMUNOFLUORESCENT STAINING OF CELL TYPE-SPECIFIC MARKERS IN MURINE LUNG ORGANOIDS

Stem cell markers

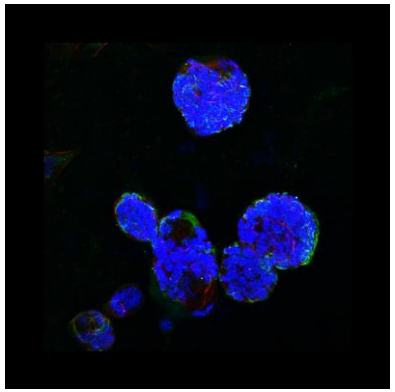
p63



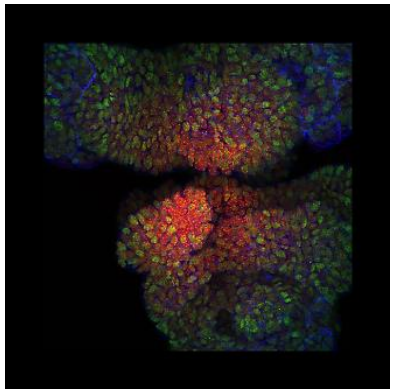
Krt5



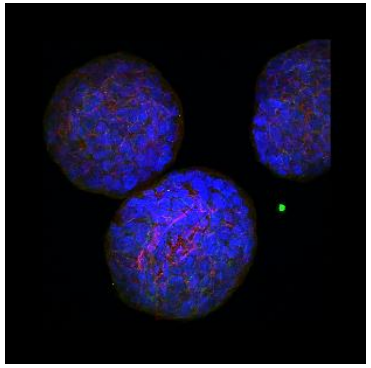
Krt14



Sftpc



SFTPC



Human lung organoids

F-actin

Cell type-specific marker

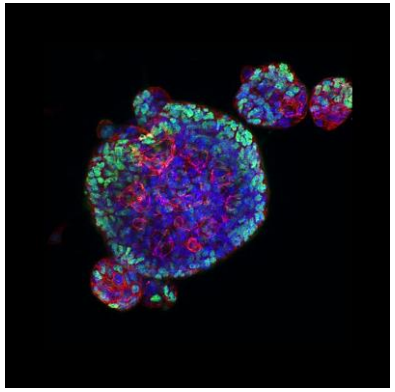
DAPI

Unpublished, please do not post

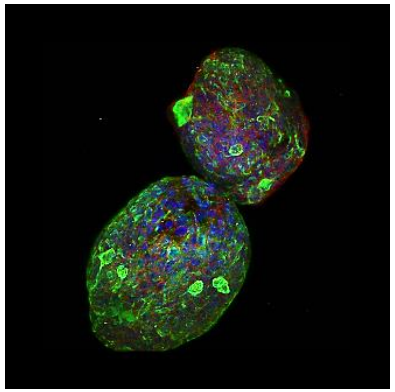
IMMUNOFLUORESCENT STAINING OF CELL TYPE-SPECIFIC MARKERS IN MURINE LUNG ORGANOIDS

Stem cell markers

p63



Krt5



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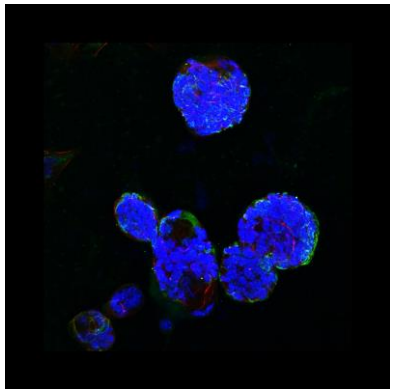

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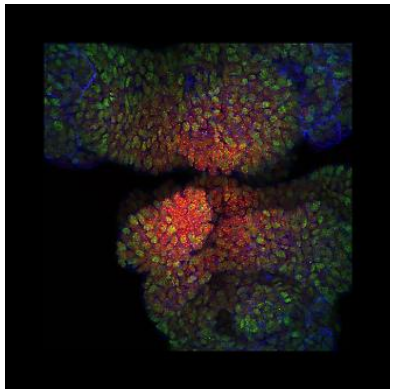

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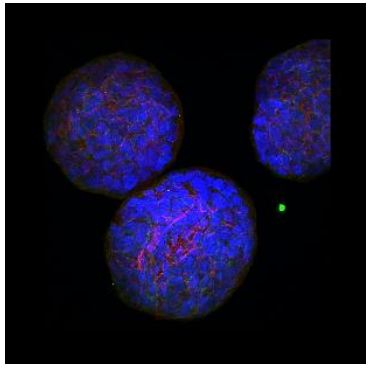

Human lung organoids

F-actin

Cell type-specific marker

DAPI

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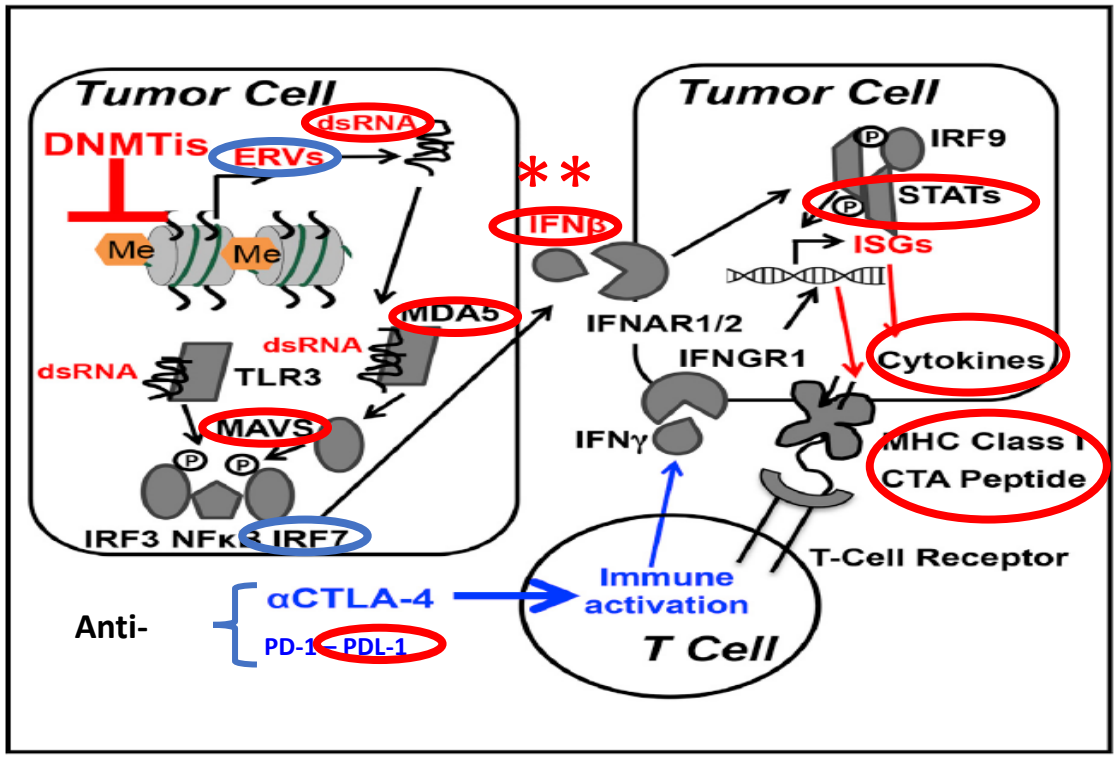
" Viral Mimicry" by DNMTi's – A Key Mechanistic Underpinning of our Hypothesis

Important – occurring within, and collaboratively with, a broader inflammasome and DNA repair response

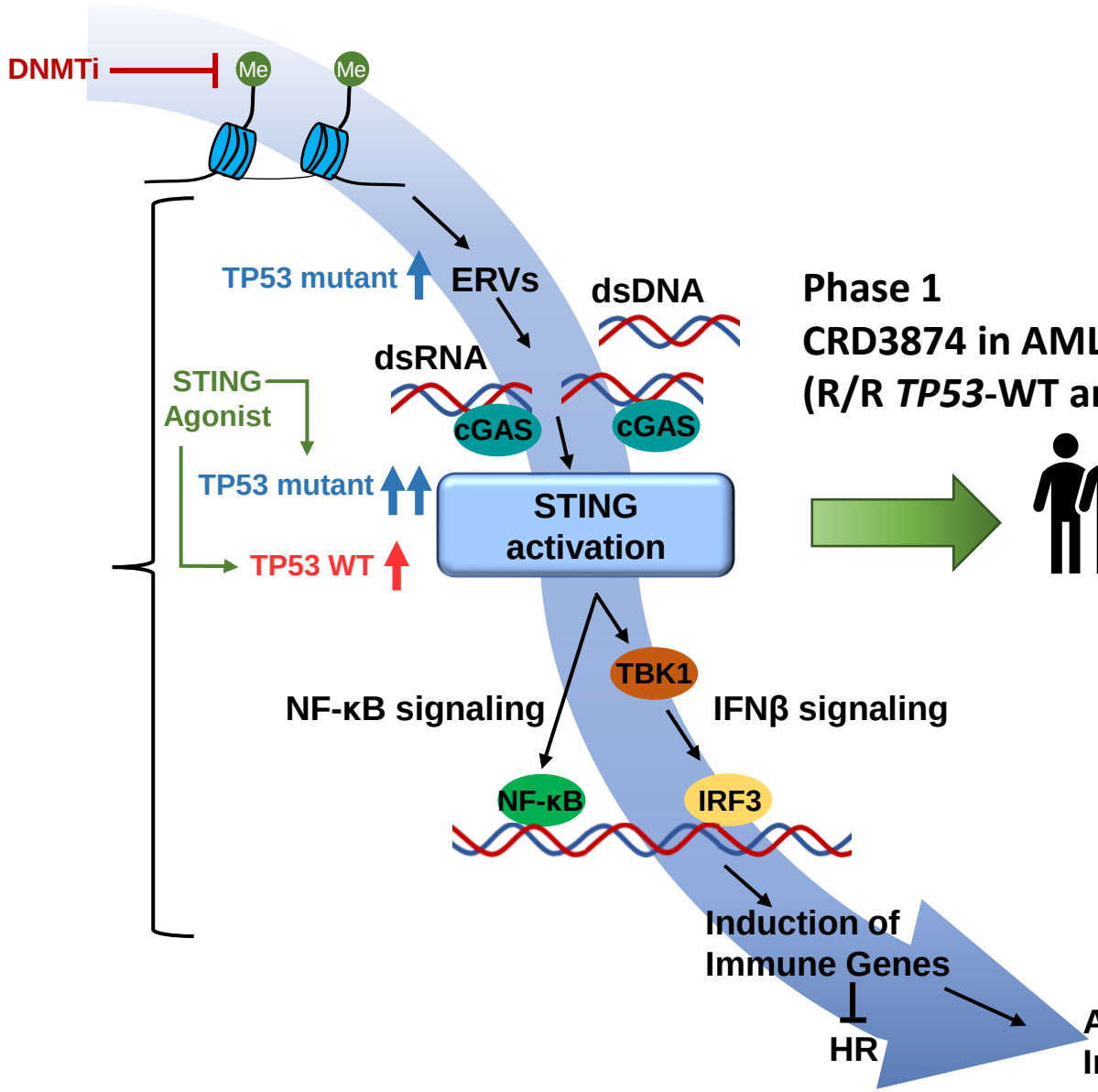


Mechanisms; correlative science; trial parameters

MMSK (Chan) and Erlangen, Germany

Roulois et al, Cell, 2015 **Chiappinelli, et al, Cell, 2015**

Clinical Trial Strategy with STING agonist CRD5500 in AML

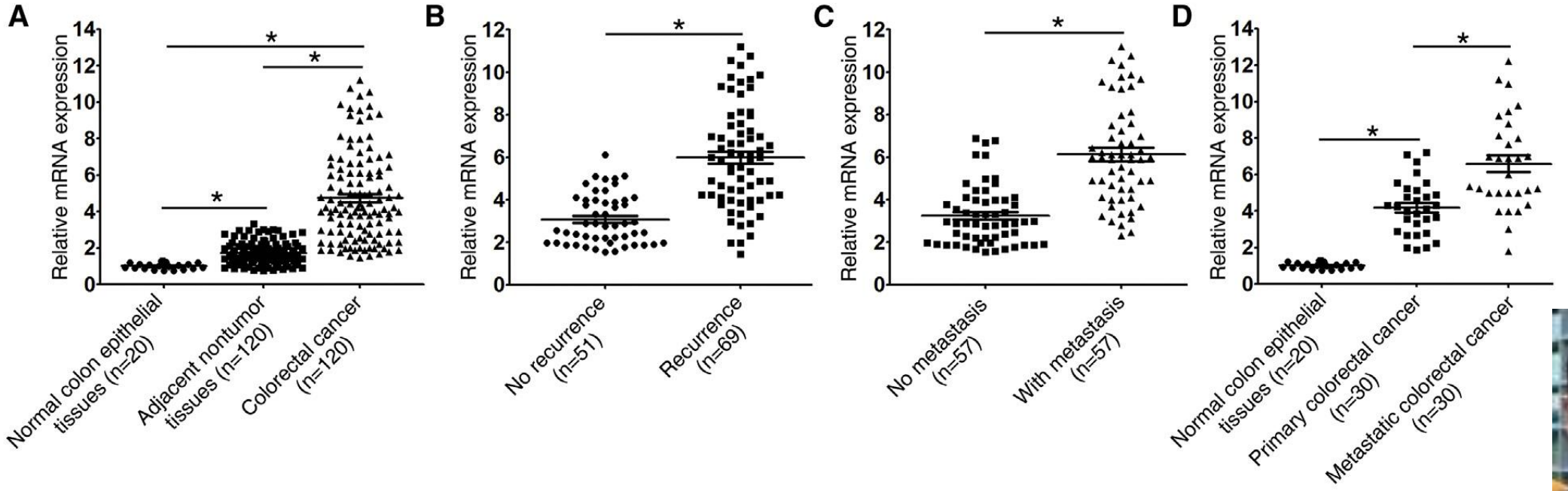


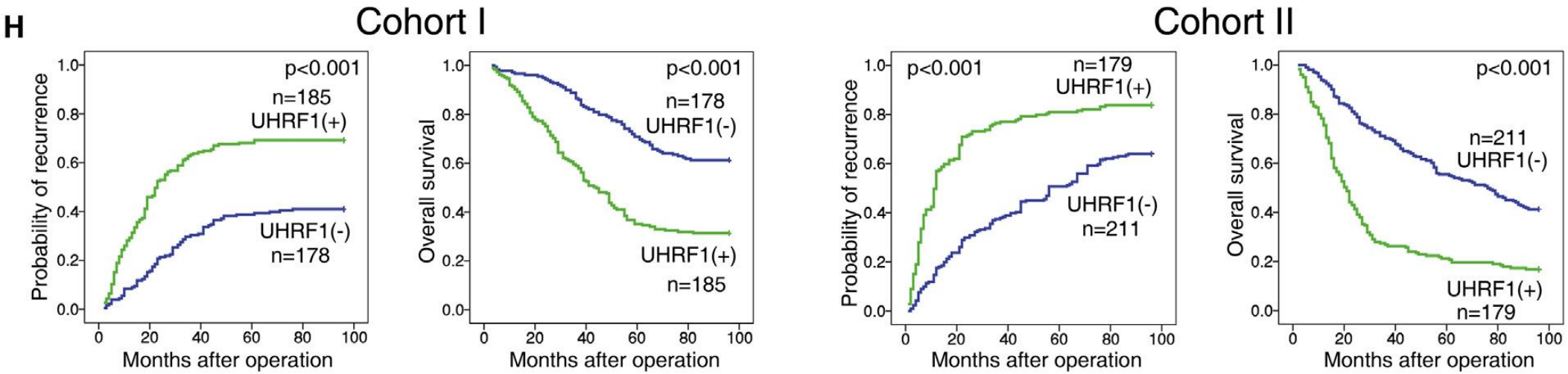
Phase 1
CRD3874 in AML
(R/R *TP53*-WT and -mutated)

Phase 1
CRD3874 plus DAC in AML
(previously untreated *TP53*-mutated)

Fey Rassool *et al.*, PNAS 2020, 23

ELEVATED UHRF1 EXPRESSION CORRELATES WITH POOR OUTCOMES IN HUMAN COLORECTAL CANCER





Rothbart

Xiangqian Kong (Baylin Lab)

Kong *et al.*, 2019 *Cancer Cell*