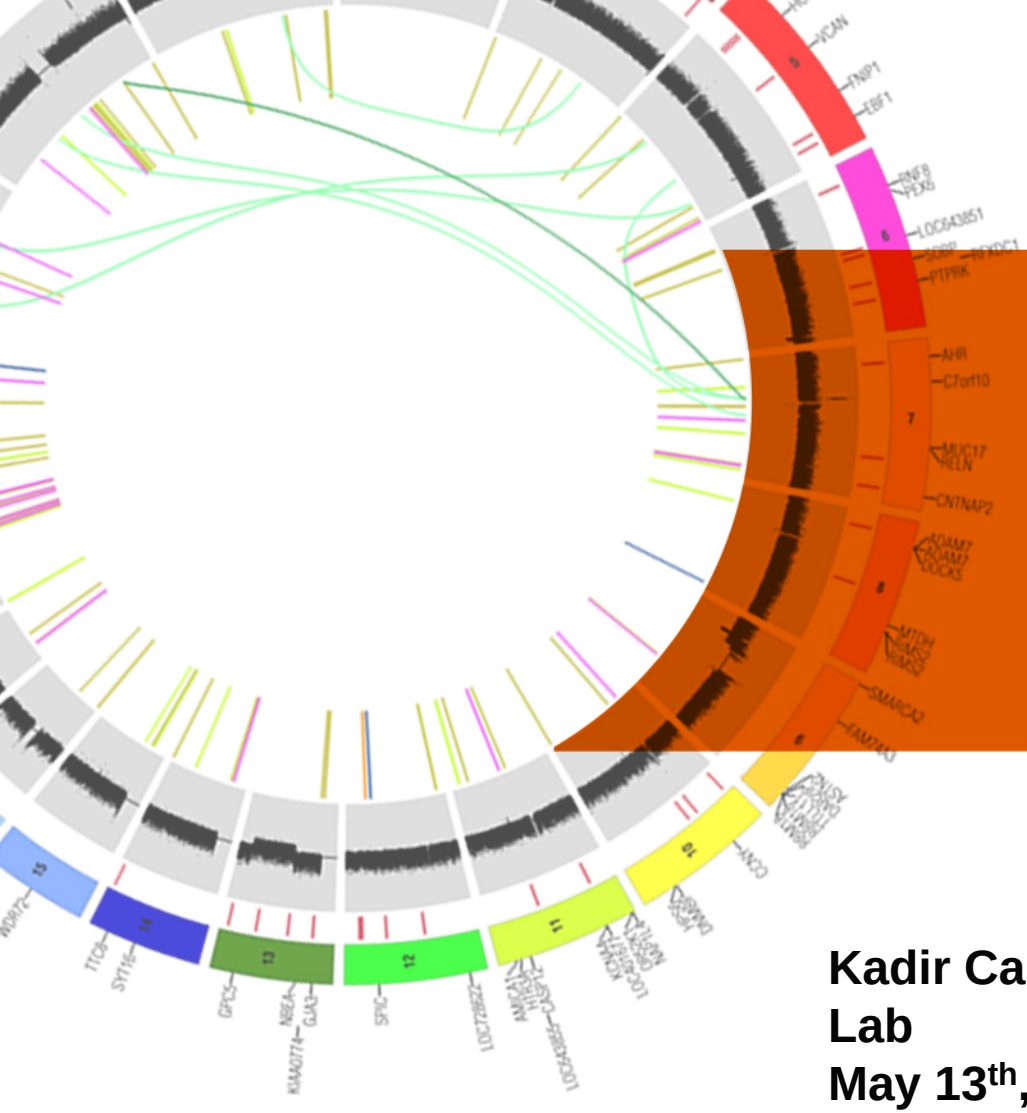


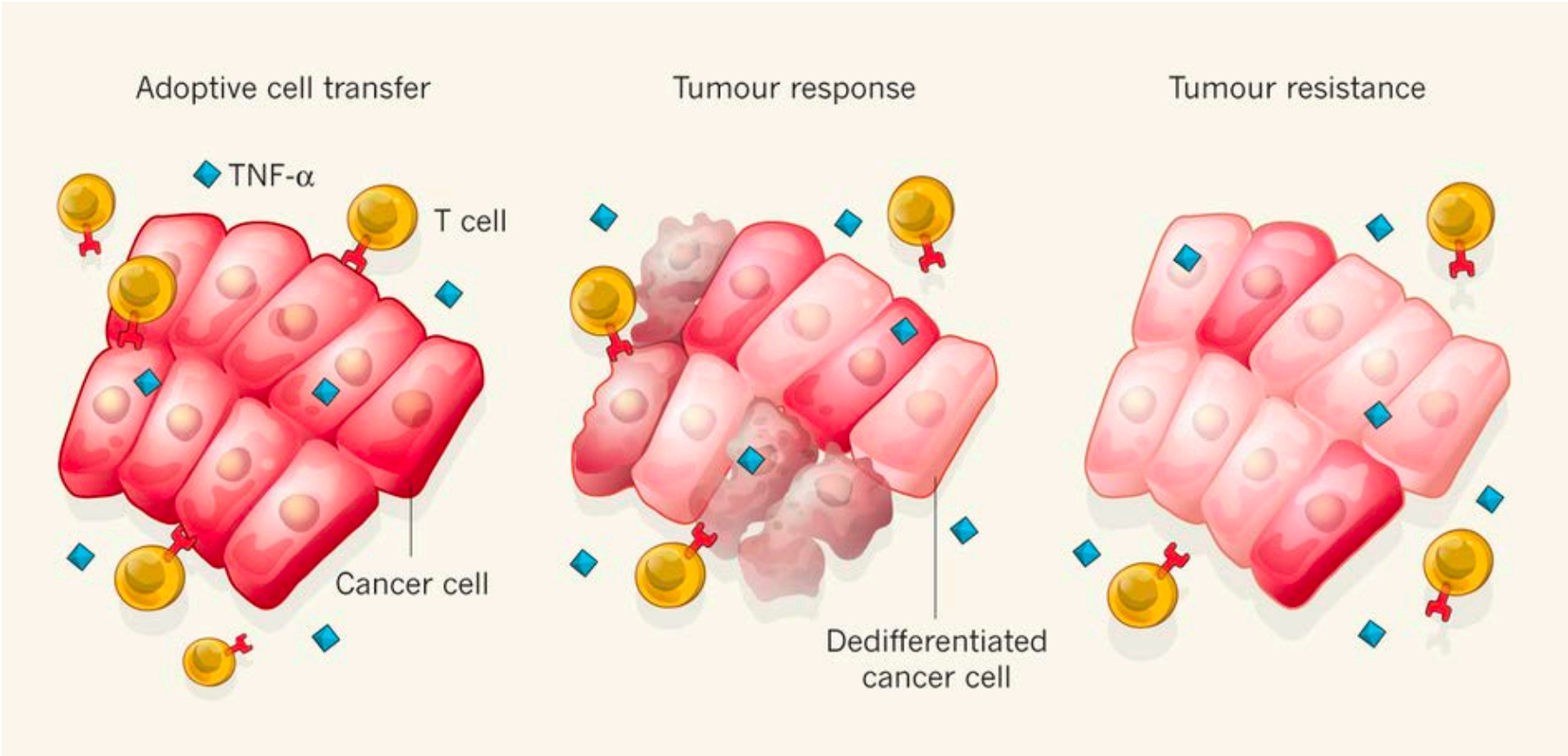
The Cancer Genome Atlas

Understanding the evolution of melanoma epigenome

Kadir Caner Akdemir, PhD – Chin Lab

May 13th, 2014

Melanomas Resist Therapy Through Dedifferentiation



Ribas A. et al, Nature 2012

Epigenetic Signatures in Human Cancers

Cell

Loss of 5-Hydroxymethylcytosine Is an Epigenetic Hallmark of Melanoma

Christine Guo Lian,[1,2,13] Yufei Xu,[1,13] Craig Ceol,[3,6] Feizhen Wu,[9] Allison Larson,[5] Karen Dresser,[7] Wenqi Xu,[9] Li Tan,[9] Yeguang Hu,[1] Qian Zhan,[2] Chung-wei Lee,[2] Di Hu,[1] Bill Q. Lian,[1,8] Sonja Kleffel,[5] Yijun Yang,[10] James Neiswender,[6] Abraham J. Khorasani,[1] Rui Fang,[1] Cecilia Lezcano,[2] Lyn M. Duncan,[4] Richard A. Scolyer,[11] John F. Thompson,[11] Hojabr Kakavand,[11] Yariv Houvras,[3,12] Leonard I. Zon,[3] Martin C. Mihm Jr.,[5] Ursula B. Kaiser,[1] Tobias Schatton,[5] Bruce A. Woda,[7] George F. Murphy,[2,*] and Yujiang G. Shi[1,9,*]

Science AAAS

Epigenomic Enhancer Profiling Defines a Signature of Colon Cancer
Batool Akhtar-Zaidi *et al.*
Science **336**, 736 (2012);
DOI: 10.1126/science.1217277

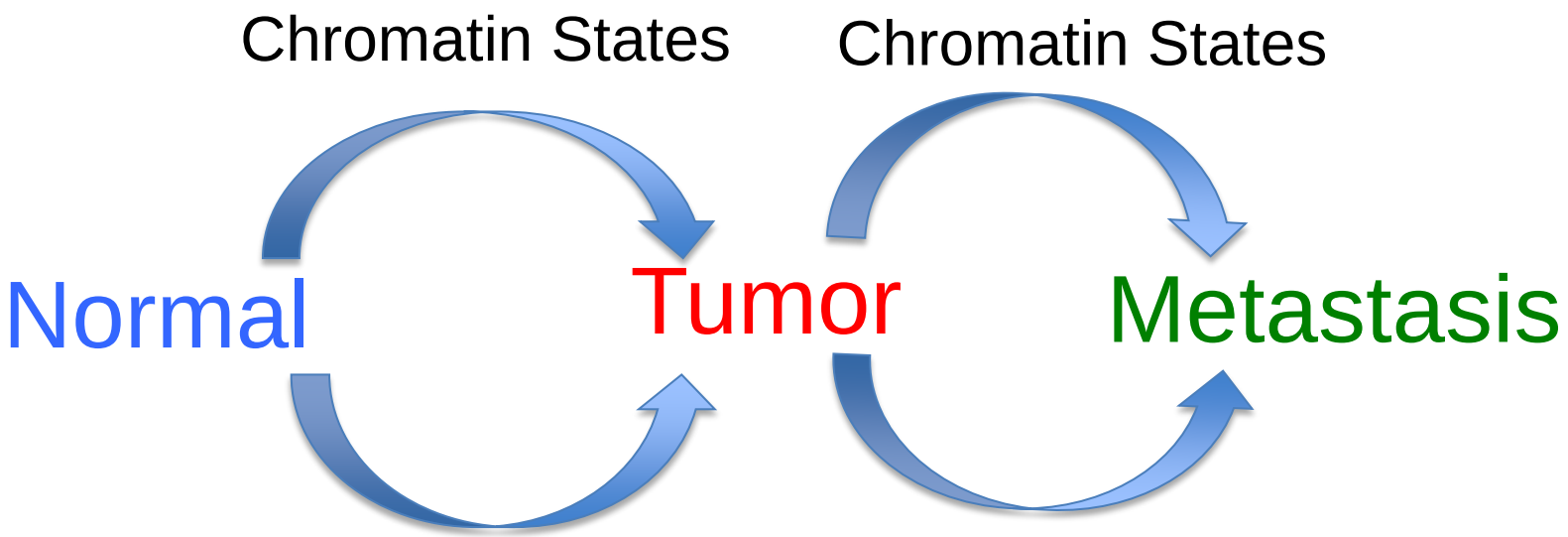
Cancer Research

AACR American Association for Cancer Research

A Blueprint for an International Cancer Epigenome Consortium. A Report from the AACR Cancer Epigenome Task Force

Stephan Beck[1], Bradley E. Bernstein[2], Robert M. Campbell[4], Joseph F. Costello[5], Dashyant Dhanak[9], Joseph R. Ecker[6], John M. Greally[11], Jean-Pierre Issa[10], Peter W. Laird[7], Kornelia Polyak[3], Benjamin Tycko[12], and Peter A. Jones[8], for the AACR Cancer Epigenome Task Force

How Does Epigenome Contribute to Melanoma Progressi

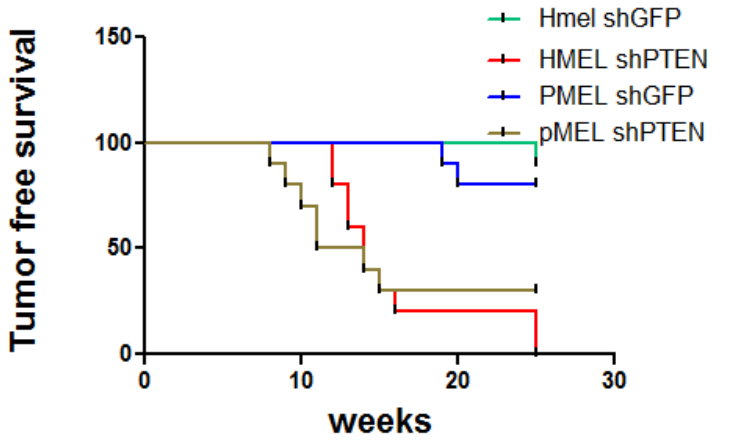


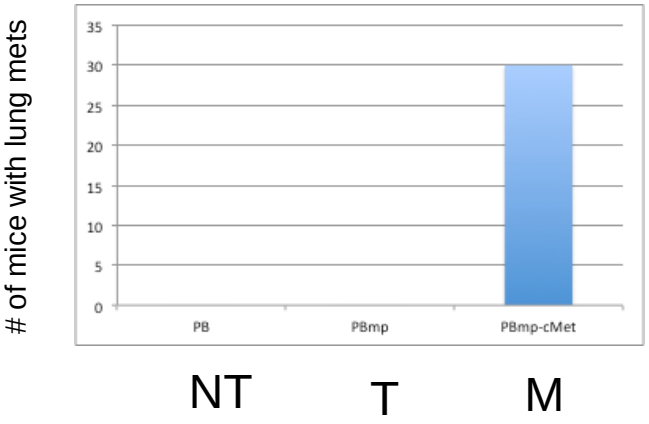
Chromatin State = Combinatorial Patterns of Epigenetic Modifications

Cell System to Identify Epigenetic Changes

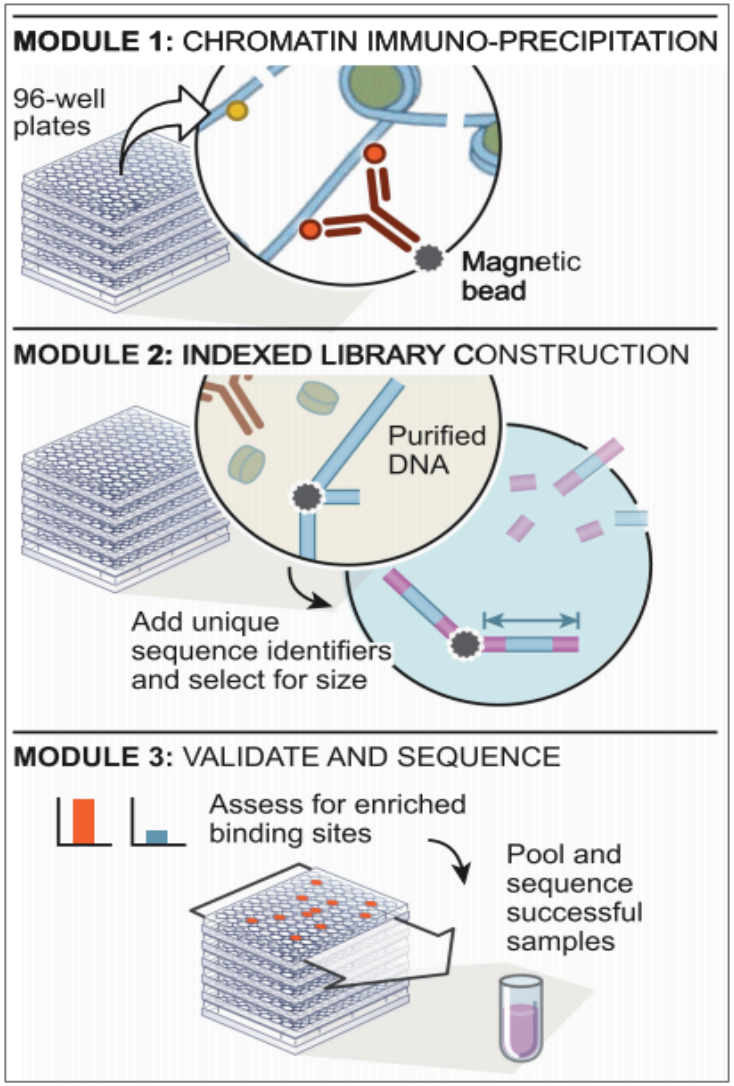
HMEL-BRAF
PMEL-BRAF
} Primary Human Melanocytes Immortalized with TERT& Expressing p53DD, $CDK4^{R24C}$, $BRAF^{V600E}$

Non/less Tumorigenic NT	Tumorigenic but not metastatic T	Metastatic M
HMEL-BRAF-shGFP (H)	HMEL-BRAF-shPTEN (Hmp)	HMEL-BRAF-shPTEN-cMET (Hmp-M)
PMEL-BRAF-shGFP (PB)	PMEL-BRAF-shPTEN (PBmp)	PMEL-BRAF-shPTEN-cMET (PBmp–M)





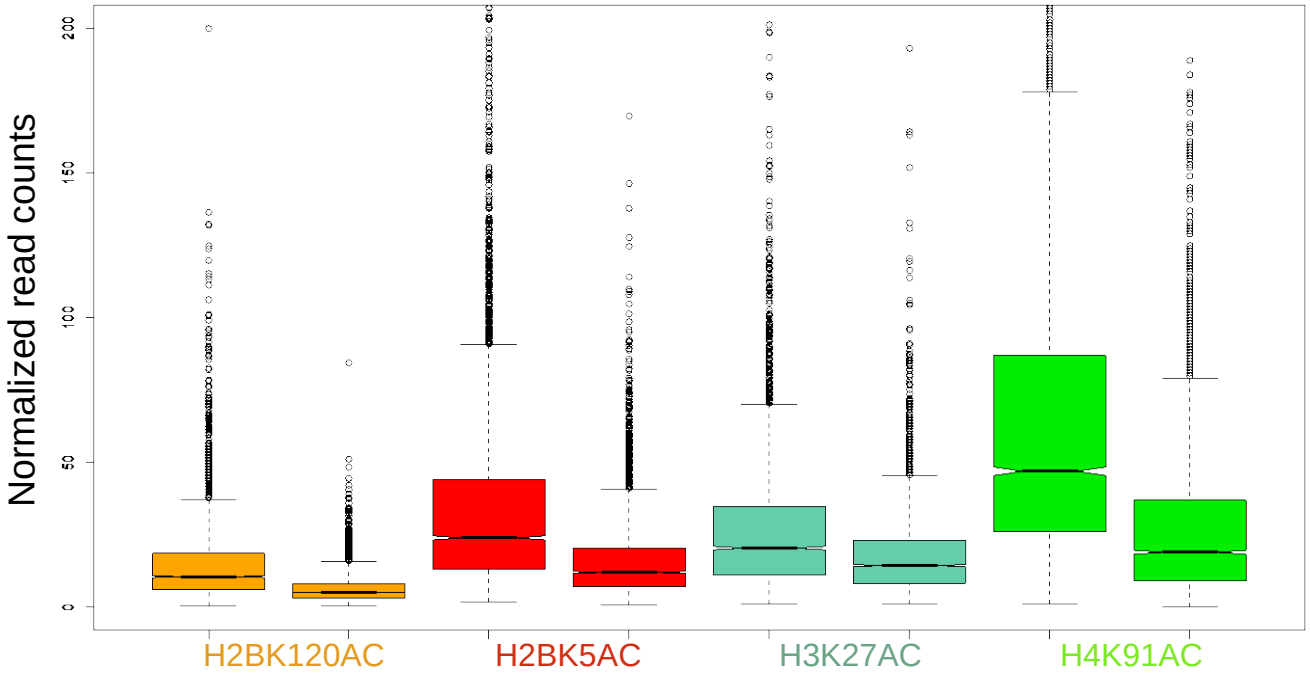
High-Throughput ChIP-Sequencing to Profile Chromatin Marks



H2AK5ac	H3K4me1	H3
H2BK5ac	H3K4me2	H4
H2BK15ac	H3K4me3	IgG
H2BK120ac	H3K9me1	
H3K4ac	H3K9me3	
H3K9ac	H3K27me1	
H3K14ac	H3K27me3	
H3K18ac	H3K36me1	
H3K23ac	H3K36me2	
H3K27ac	H3K36me3	
H3K36ac	H3K79me1	
H4K12ac	H3K79me2	
H4K16ac	H3K79me3	
H4K5ac	H4K20me1	
H4K8ac	H4K20me2	
H4K91ac	H4K20me3	
H4TETRAac		

Garber et al. Molecular Cell, 2012

Loss of Histone Acetylations at Observed in Pro-tumorgenic Melanocytes



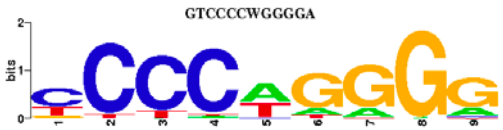
# Term Name	Binom FDR Q-Val
Apoptosis signaling pathway	1.63E-50
Integrin signalling pathway	5.48E-47
DNA replication	7.54E-29
Toll receptor signaling pathway	8.95E-16
Cell cycle	9.06E-11

De-acetylated Enhancers Contains Putative Tumor-suppressors Motifs

FOXO3
(8.4e-10)

RUNX1
(5.69e-08)

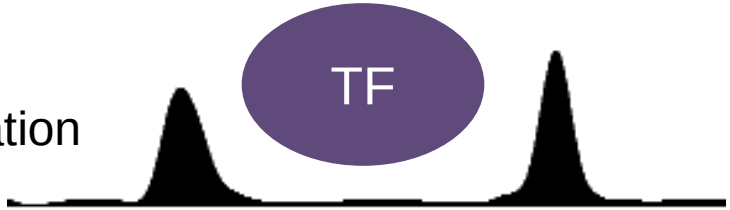
EBF1
(5.83e-08)



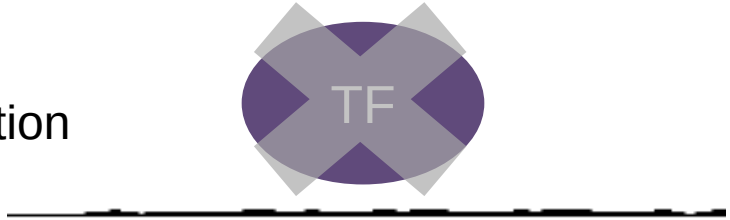
NFI
(4.36e-06)

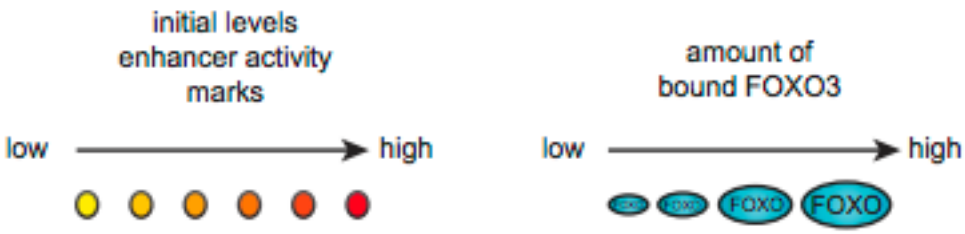
Pre-existing chromatin landscape could determine tumor suppressor-based regulations

High-acetylation



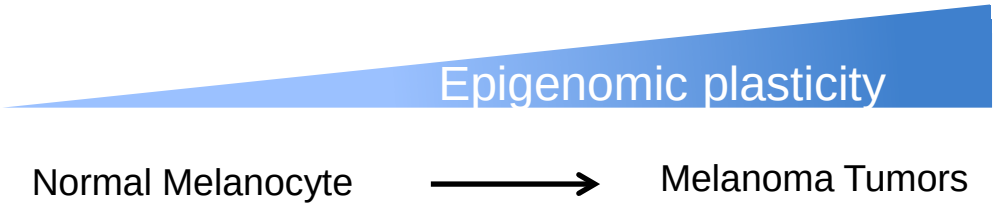
Low-acetylation





Eijkelenboom A. et al. Cell Reports 2013

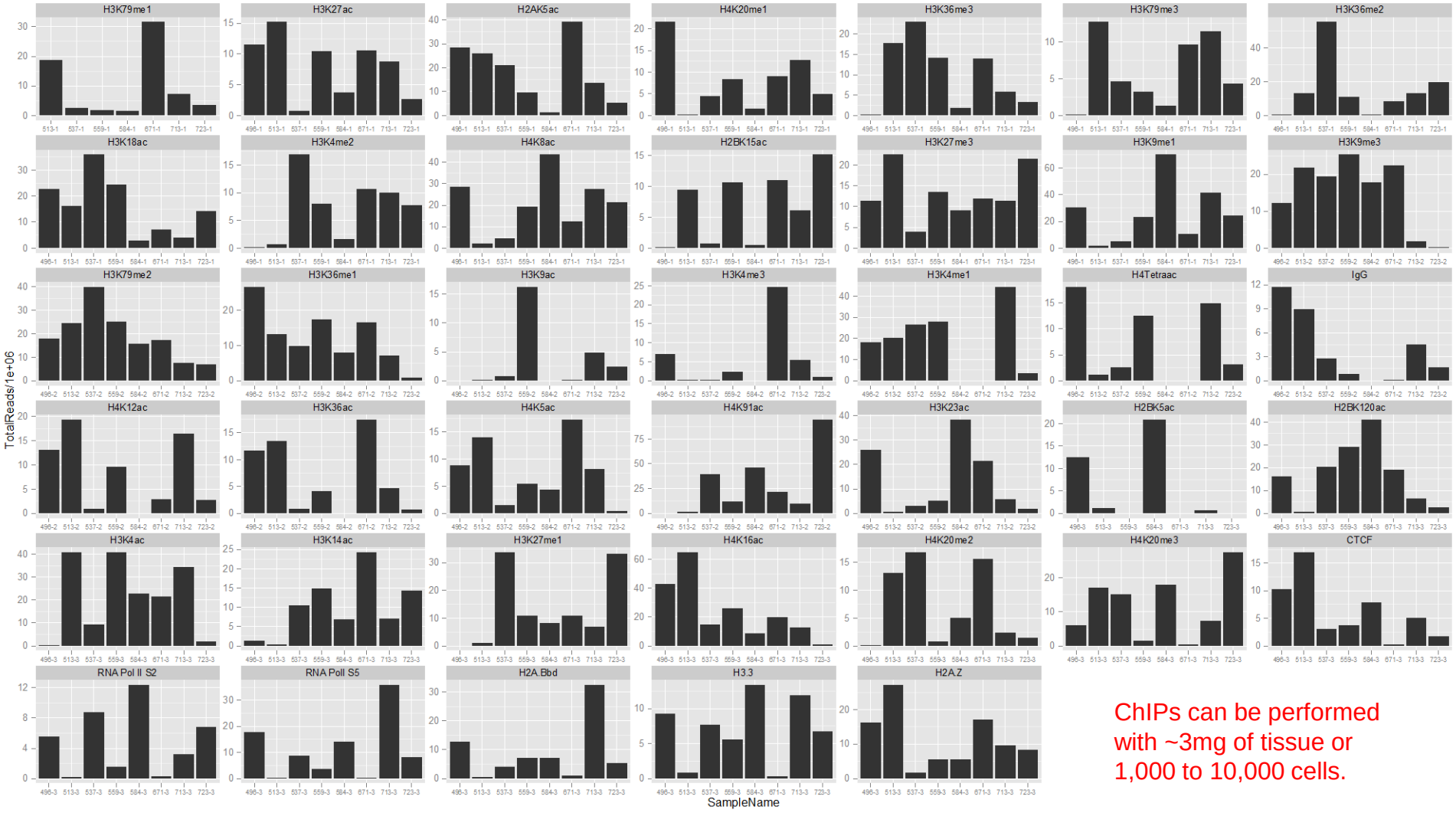
Characterizing Evolution of the Epigenome During Human Melanoma Development



Changes in chromatin states

10 melanoma tumor samples (from primary and metastatic lesions) that have been comprehensively profiled by TCGA.

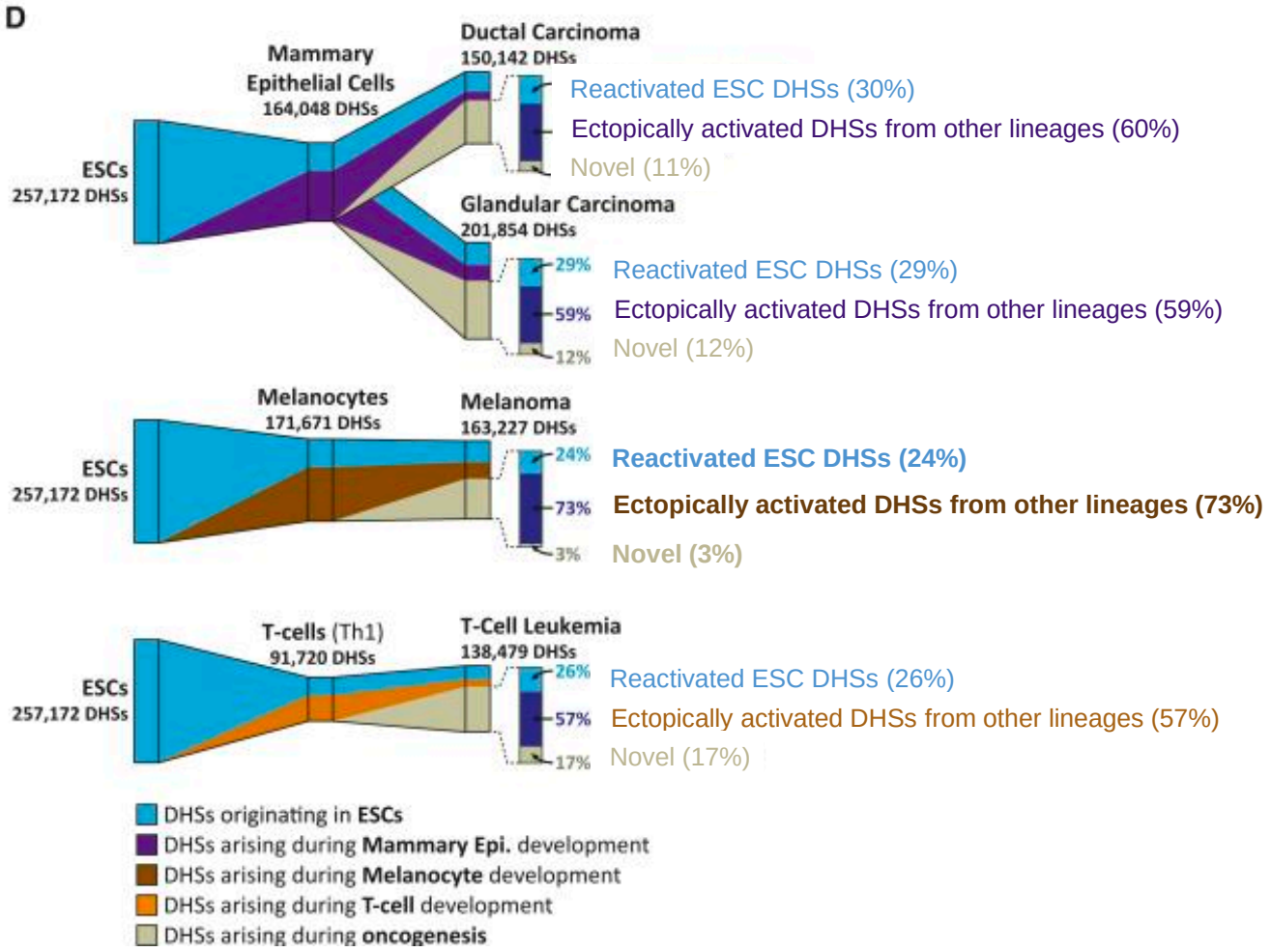
Epigenome Profiling of Genomically Characterized Human Melanoma Tumors



ChIPs can be performed with ~3mg of tissue or 1,000 to 10,000 cells.

36 histone marks, 2 forms of RNA Polymerase and 3 histone variants and CTCF (so far total of 6 billion reads)

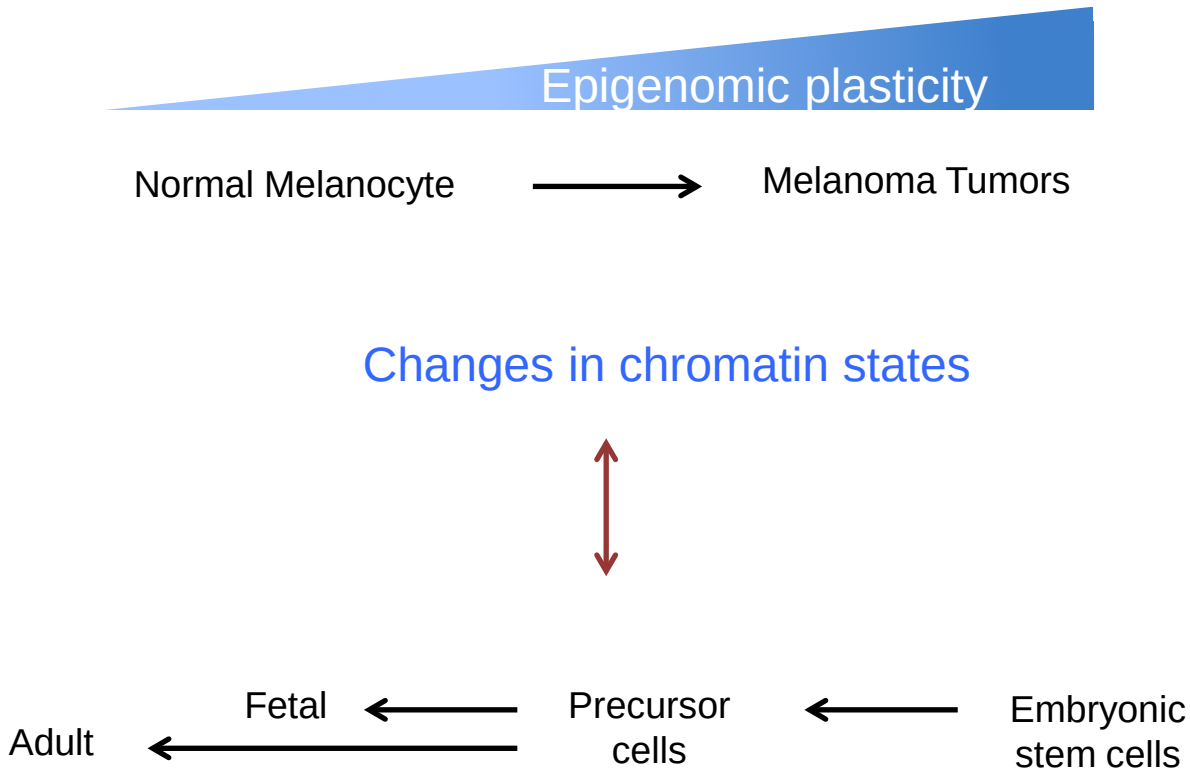
Cancers Show Retrograde Remodeling of Their Regulatory Landscape

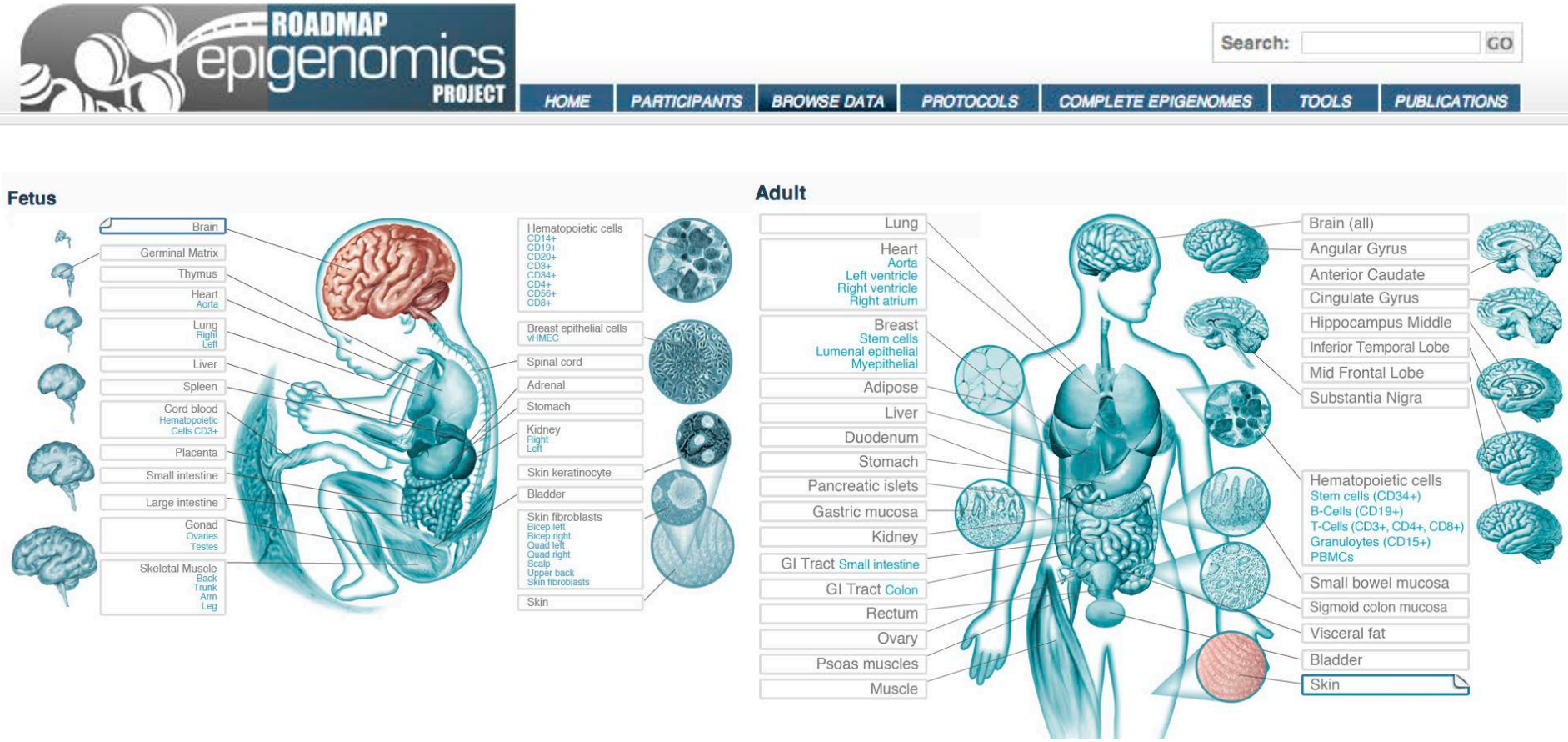


New "oncogenic" sites that are actually older developmental pathways

Stargechis A. et al, Cell 2013

Characterizing Evolution of the Epigenome During Human Melanoma Development

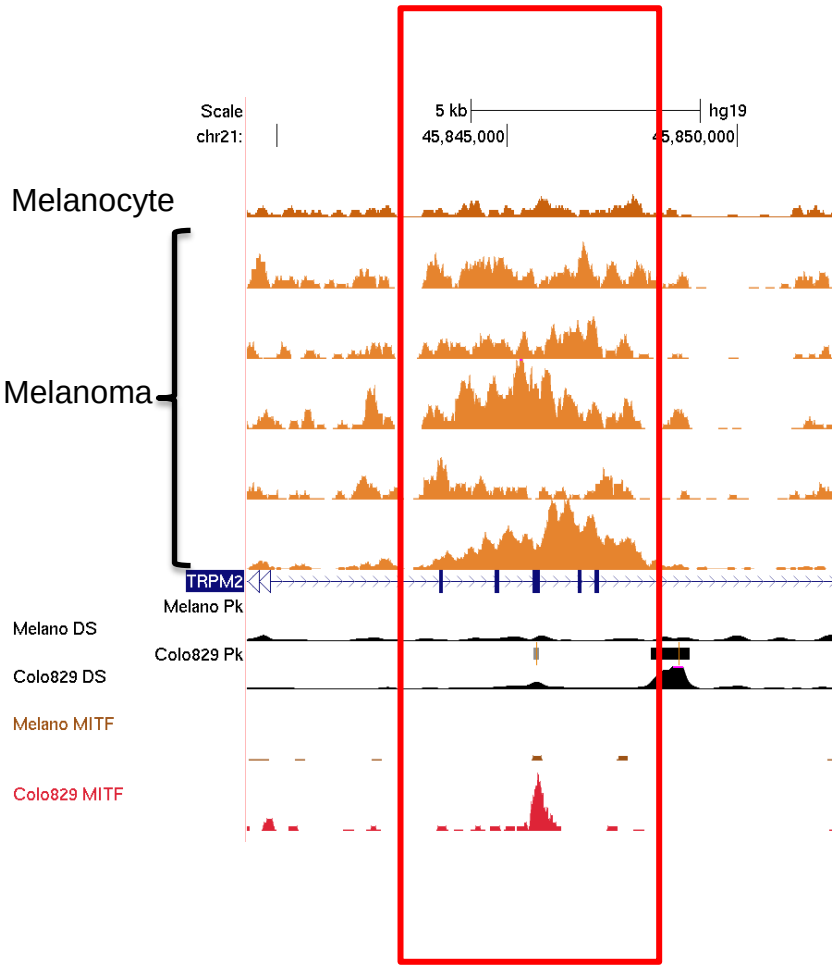




Epigenomic profiles of 127 different human-body cell types

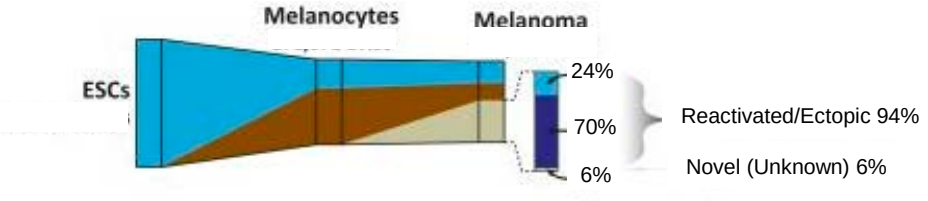
Bernstein B. et al. Nat. Biotech (2010)

Potential Reorganization in the Regulatory Landscape During Melanoma Formation

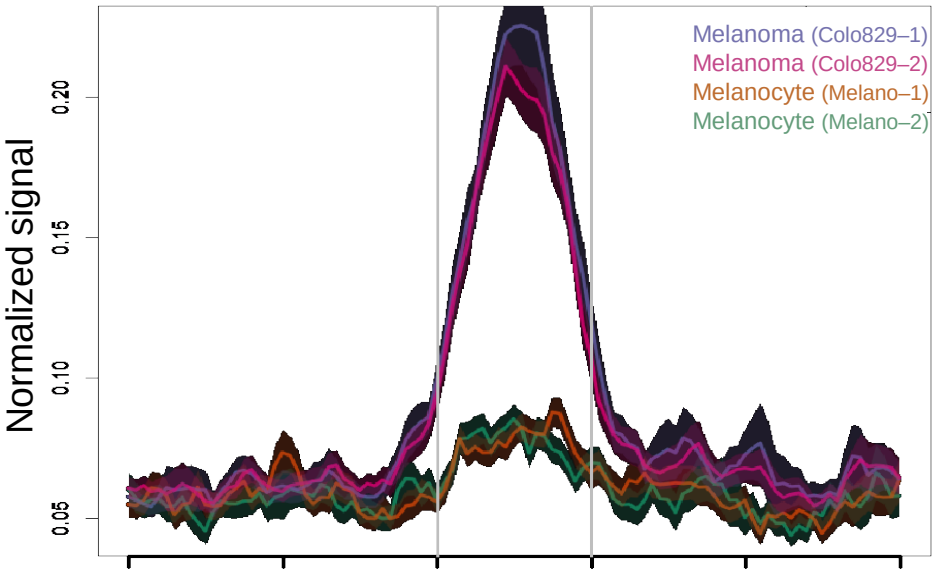


MITF: lineage-specific master regulator

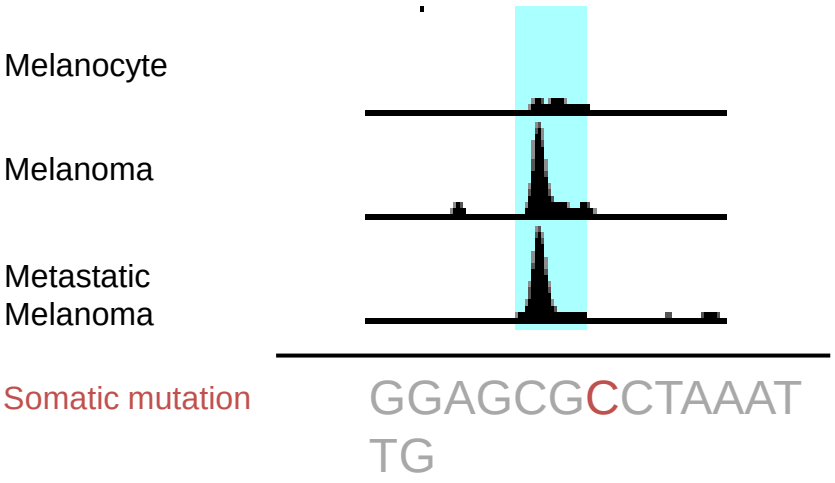
H3K4me1 site evolution

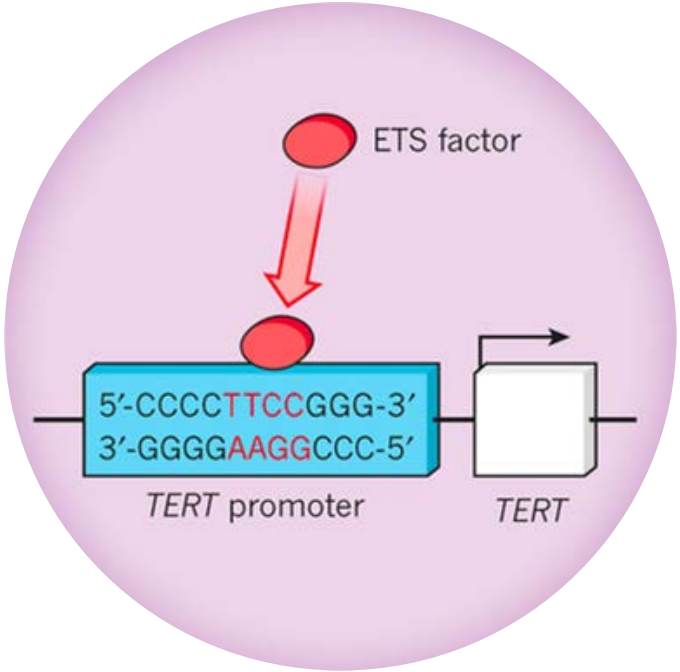


DNaseI hypersensitivity at tumor H3K4me1 sites



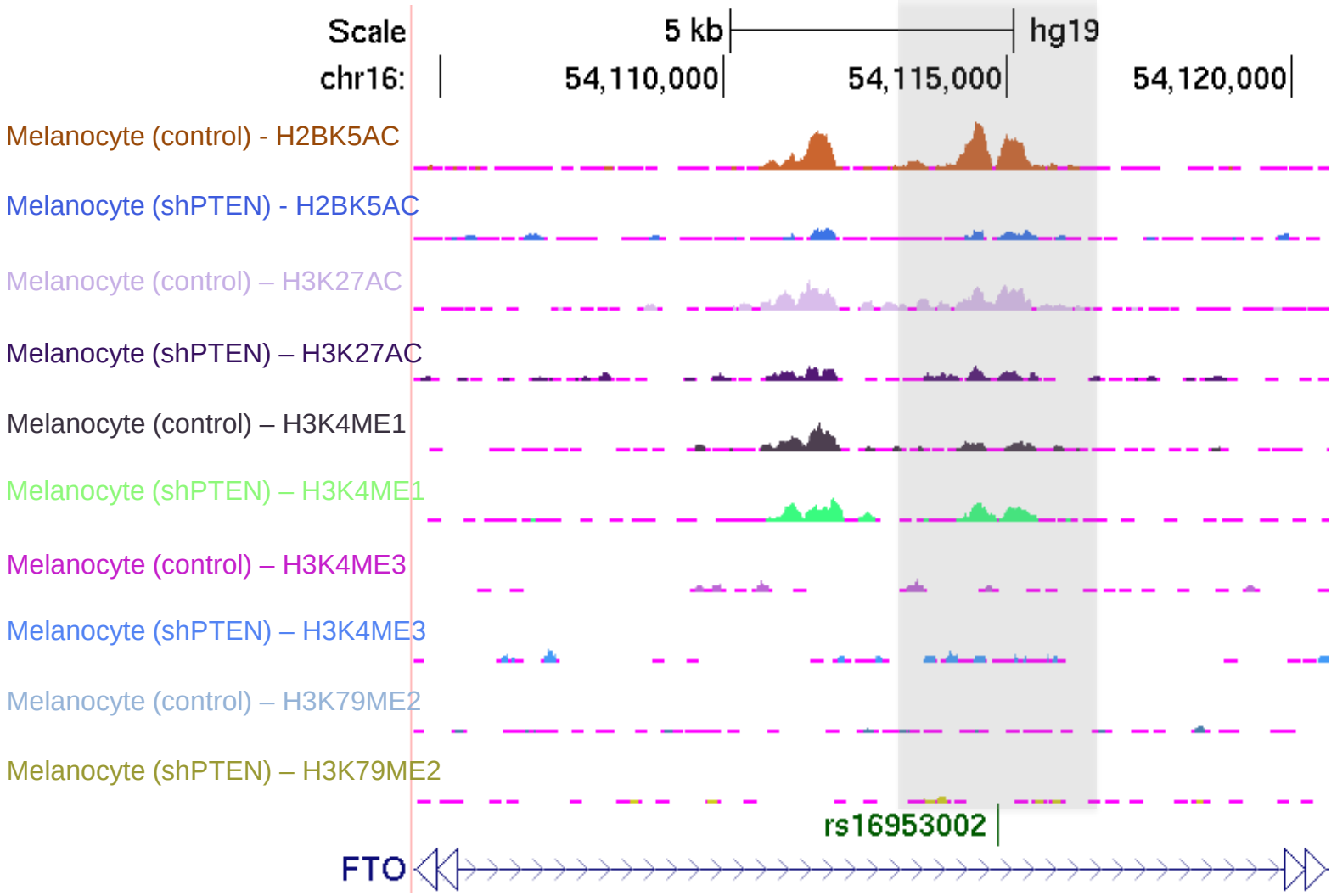
Determining the Functionality of Non-coding Variants with Epigenome Integration





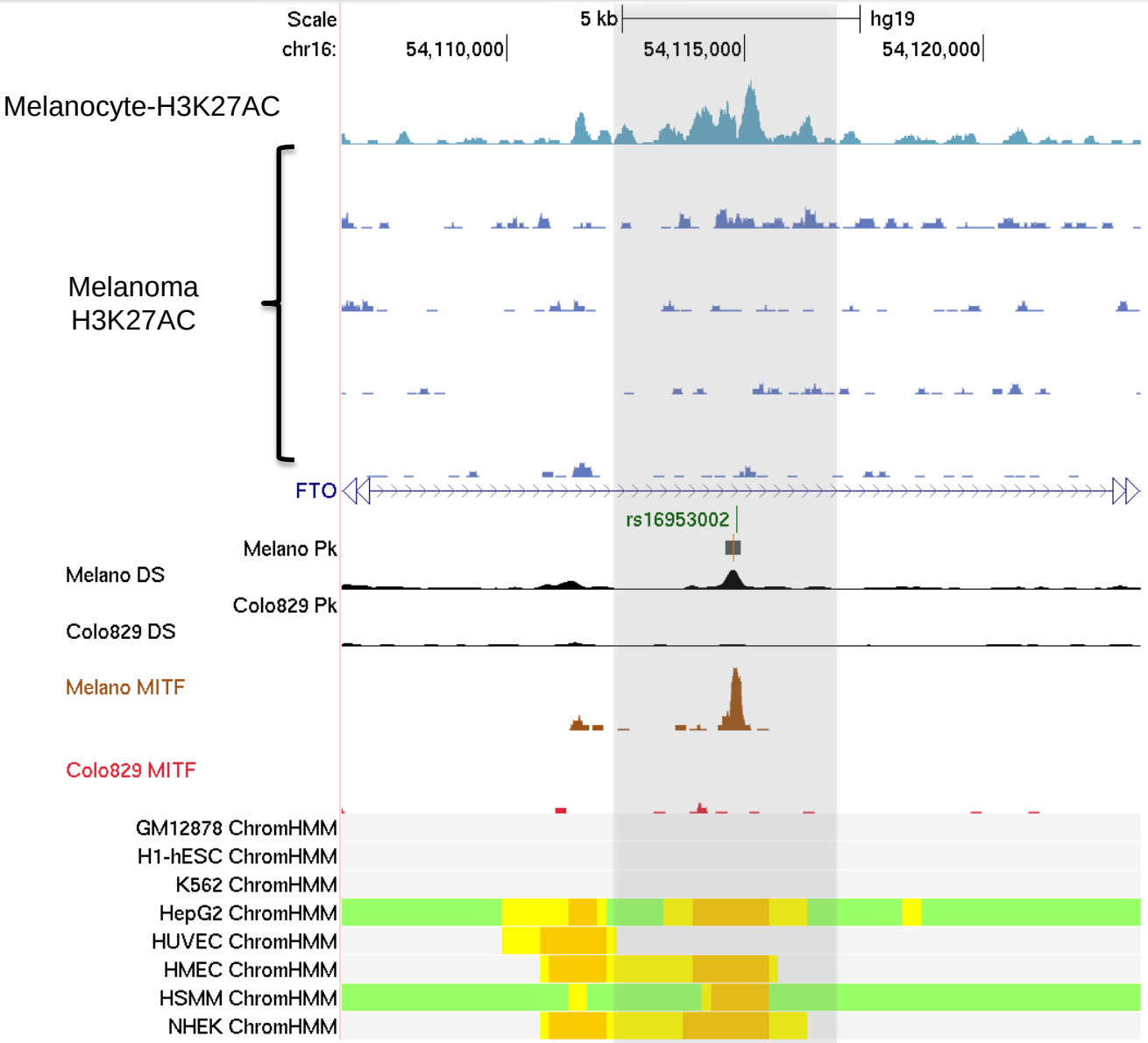
Huang, F. W. et al. - Horn, S. et al. Science (2013)

Melanoma GWAS Site Loses Active Histone Marks in Pro-tumorgenic Melanocytes



FTO GWAS in 12,313 melanoma patients vs 55,667 controls. Nature Genetics 2013

Melanoma GWAS Site Loses Active Histone Marks In Human Melanoma



FTO GWAS in 12,313 melanoma patients vs 55,667 controls. Nature Genetics 2013

Summary

Comprehensive epigenomic characterization in primary melanocyte-based melanoma progression model revealed:

- **Loss of histone acetylation around genes involved in carcinogenesis.**
- **De-acetylated enhancers could hinder binding of key transcription factors to DNA.**

Preliminary epigenome profiling human melanoma tumors suggests epigenomic re-orientation during melanomagenesis.

Epigenomic profiles are useful to annotate non-coding variants in cancer.

Acknowledgements

Chin Lab

Lynda Chin, MD

Kunal Rai
Emily Keung

Giannicola Genovese
Tony Gutschner
Lawrence Kwong
Yonathan Lissanu
John Miller
Sharmistha Sarkar
Koichi Takahashi
Peiling Tsou
Ian Watson

Genomic Medicine Computational Group, MDACC

Samir Amin
Terrence Wu
Per Wu
Christopher Bristow
Verhaak Lab
Jannik Andersen

UCLA

Jason Ernst
Petko Fiziev

Weizmann Institute

Ido Amit

Poznan University

Maciej Wiznerowicz

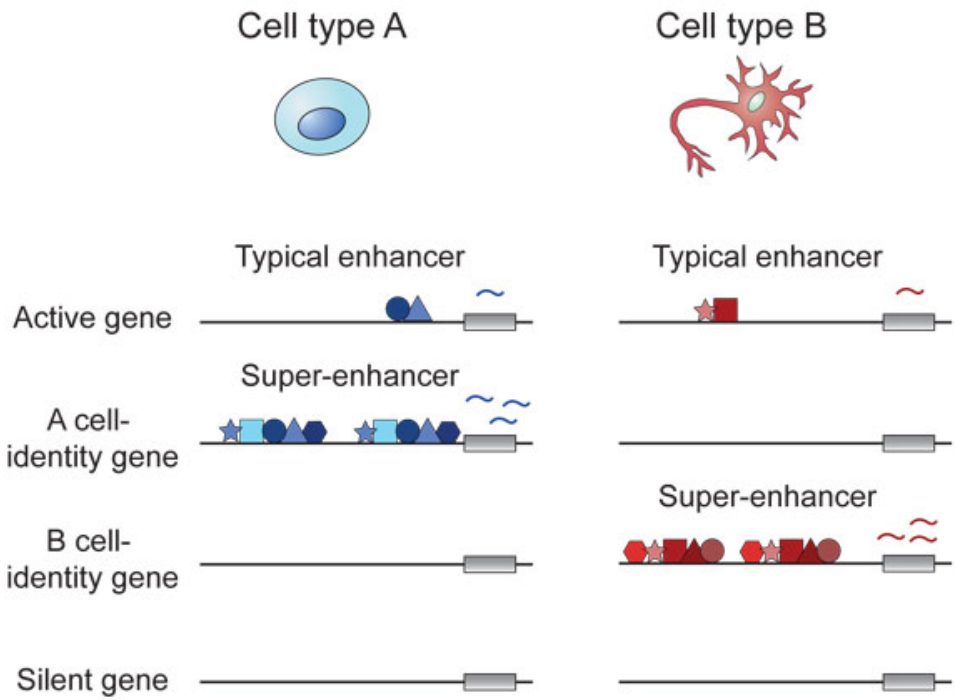
Broad Institute

Aviv Regev

…And the rest of the TCGA Community

The Cancer Genome Atlas

Identification of Melanoma Super-enhancers



Warren A. Whyte et. al, Cell 2013