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Identifying Novel Targets for Melanoma Treatment

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Tackett Laboratory at UAMS

- Project 1: We develop new tools and assays for determining how proteins interact with each other to drive cancer phenotypes

- Project 2: We take a translational research approach for using patient skin biopsies archived at UAMS for the identification of new targets for melanoma prevention and therapy

Melanoma

•Melanoma: a cancer that develops in melanocytes and is the most deadly of all skin cancers

•1 person diagnosed every 8 min with melanoma

•Melanoma claims the life of one American every 62 minutes

•The mean age for diagnosis of melanoma is 50
    •Many other cancers it is 65 to 70 years old

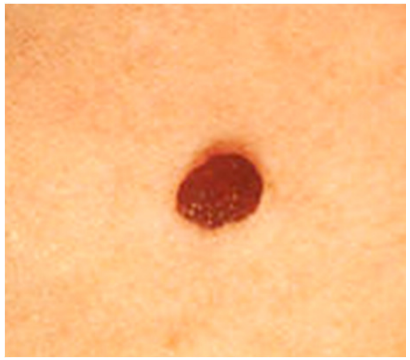
•Most common form of cancer for young adults 25- to 29-years-old

•65% cases attributed to UV exposure

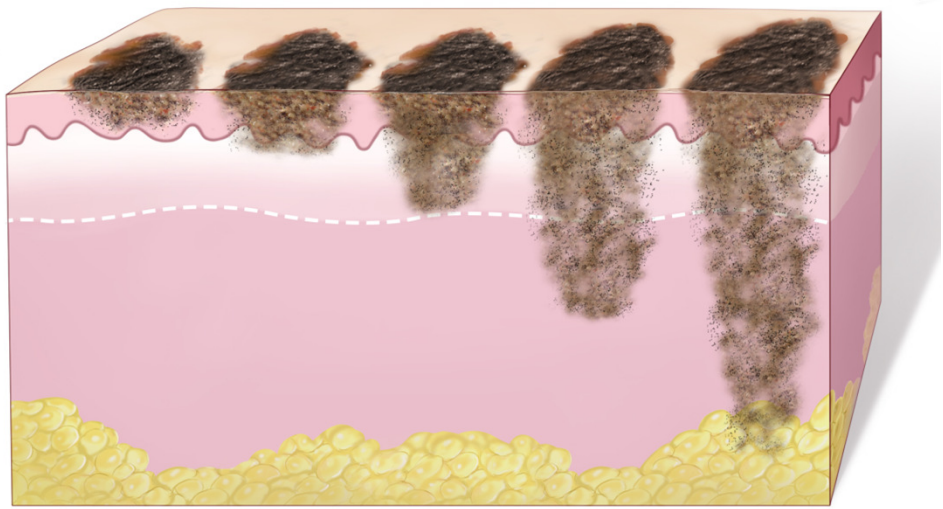
Risk Factors for Melanoma
Fair skin
Light hair and eye color
Moles
Dysplastic nevi
Personal and/or family history
Non-melanoma skin cancer
Weakened immune system
Severe sunburns
Exposure to UV
Age

Melanoma

Mole



Melanoma



Melanoma

-123,590 cases in 2011

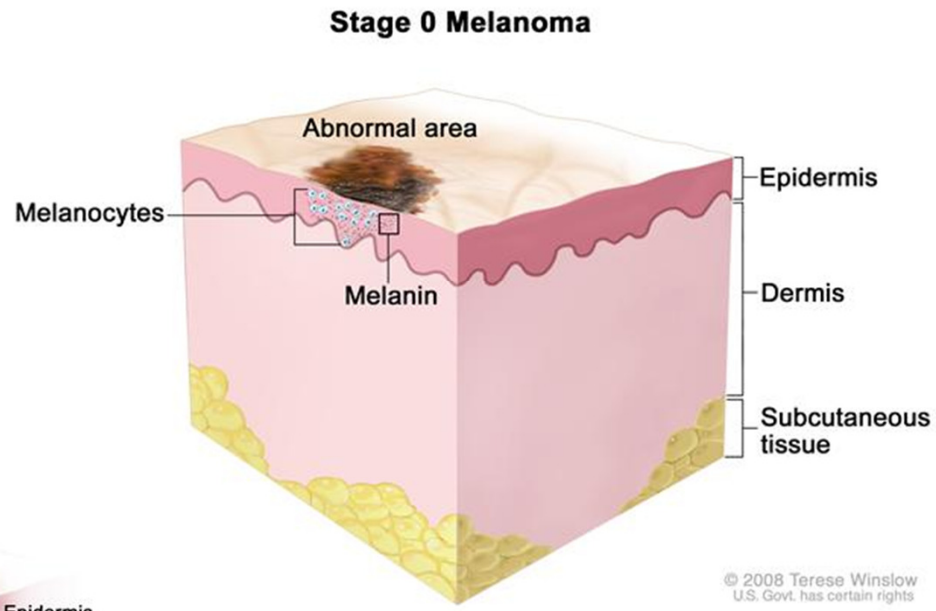
-8,790 deaths in 2011

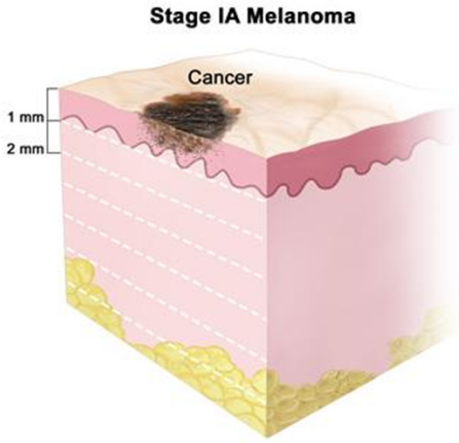
-Accounts for 75% of skin cancer deaths

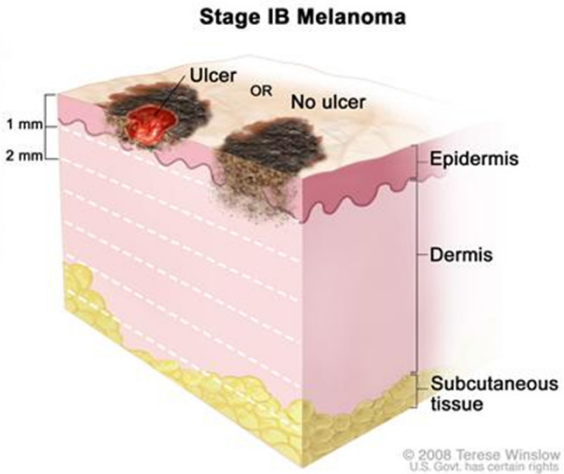
Stages of Melanoma: Stage 1

Stage	Description
0	Superficial, little danger of spreading if surgically removed
1a	Tumor ≤1mm, no ulcer
1b	Either ≤1mm w/ ulcer OR ≤2mm w/o ulcer

Melanoma *in situ*



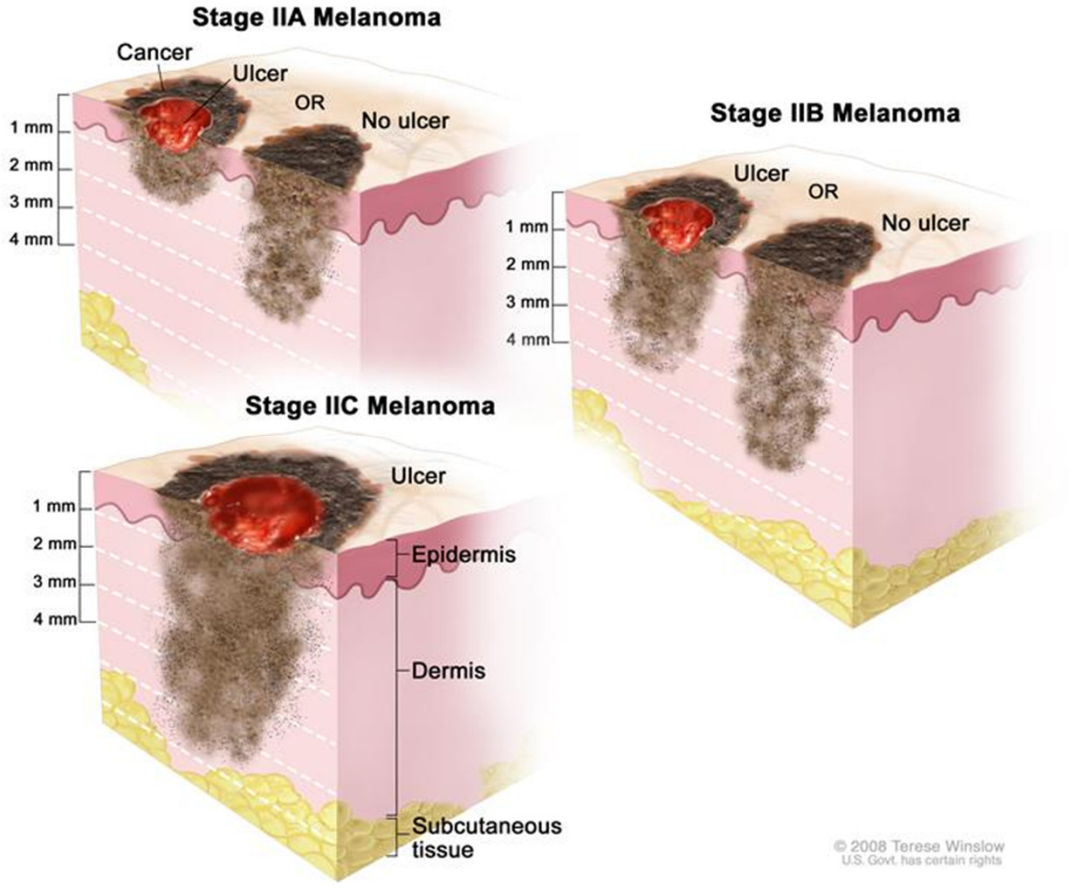




National Cancer Institute
Balch et al 2001

Stages of Melanoma: Stage 2

Stage	Description
2a	Tumor >1 but ≤2mm w/ ulcer **OR** >2 but ≤4mm w/no ulcer
2b	Tumor >2 but ≤4mm w/ulcer **OR** >4 w/o ulcer
2c	Tumor >4mm w/ ulcer

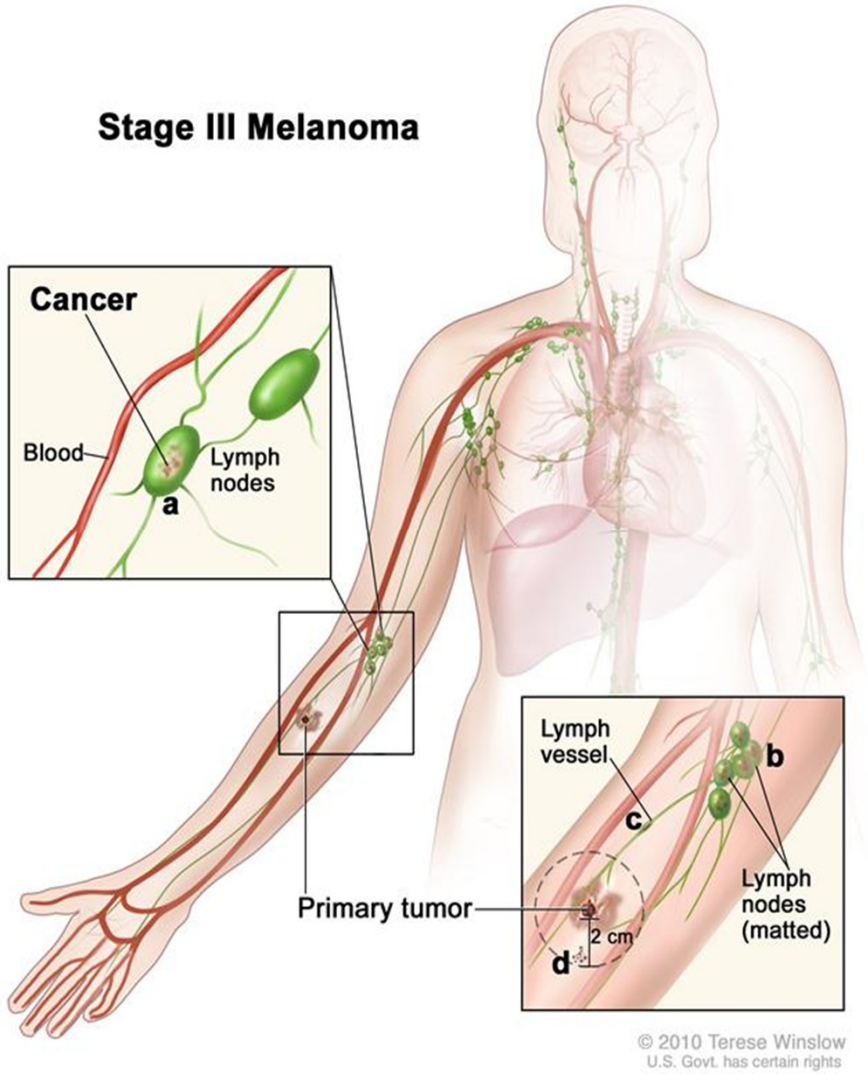


National Cancer Institute

Stages of Melanoma: Stage 3

Stage	Description
3	Tumor can be any thickness, w/ or w/o ulceration, cancer has spread to 1 or > lymph nodes, cancer is present in lymph vessel

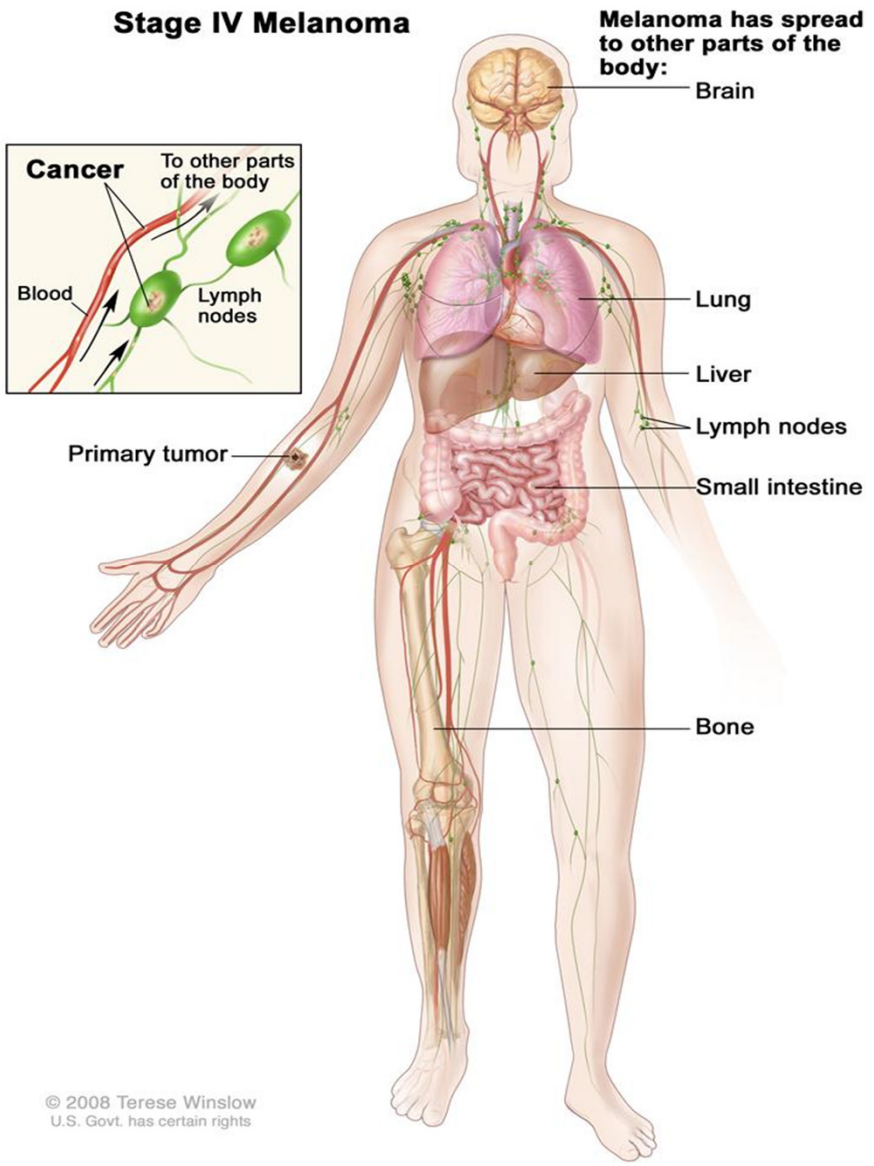
Prognosis is bleak, little response to chemotherapy or radiation treatments



National Cancer Institute

Stages of Melanoma: Stage 4

Stage	Description
4	Cancer has spread into other tissues such as: brain, kidneys, bone, lung, liver, soft tissue or GI tract



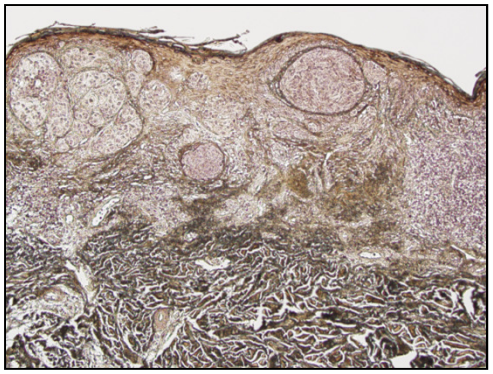
Prognosis is bleak, little response to chemotherapy or radiation treatments

National Cancer Institute

Melanoma survival by stage

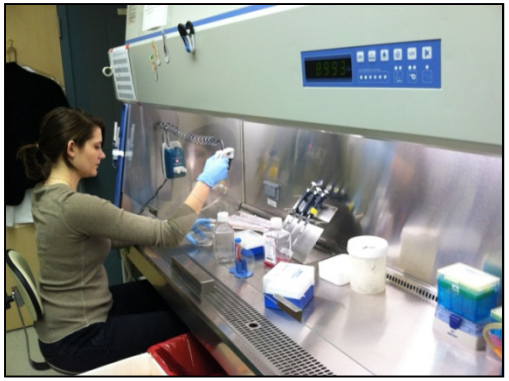
Stage	5-year survival (%)
IA	97
IB	92
IIA	81
IIB	70
IIC	53
IIIA	78
IIIB	59
IIIC	40
IV	10

Our Approach



- Exploit the extensive archive of patient melanoma biopsies at UAMS

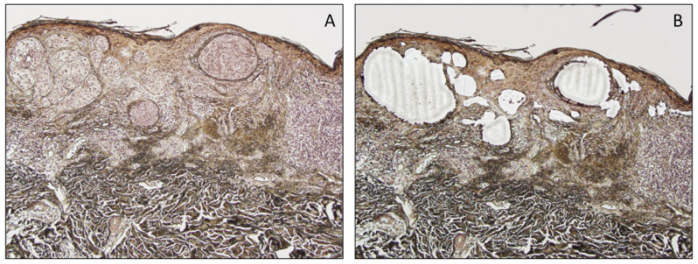
- Utilize the state of the art Proteomics Facility assembled by Dr. Tackett to find biomolecules in these samples to improve diagnosis, prognosis and treatment



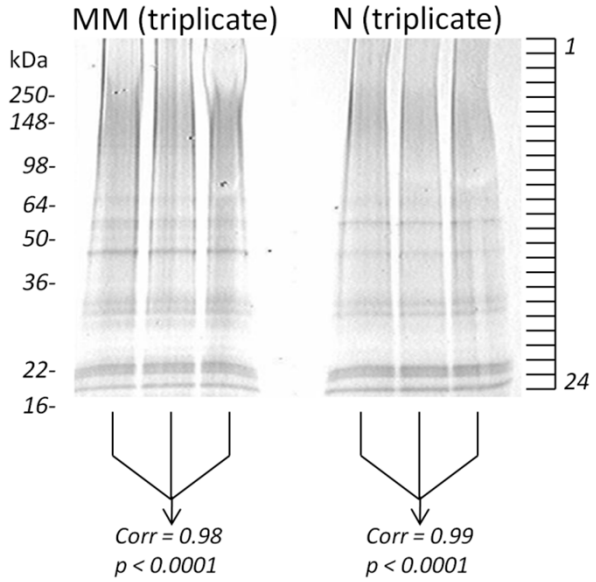
- Bring our findings back into Dr. Tackett's research laboratory to understand how these biomolecules activate the cancer phenotype (*study melanoma cells directly*)

Proteomics of FFPE Human Melanoma

Laser microdissection of melanoma cells

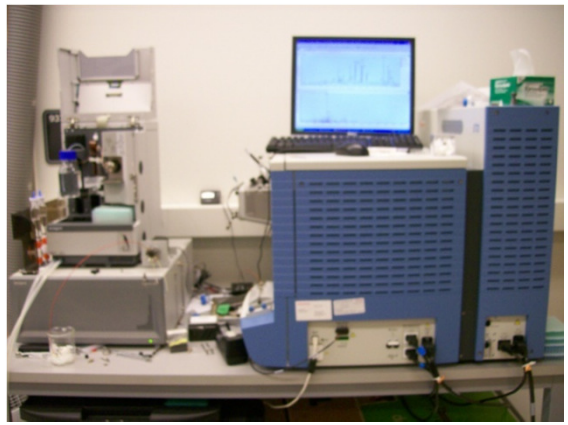


GeLC-MS/MS



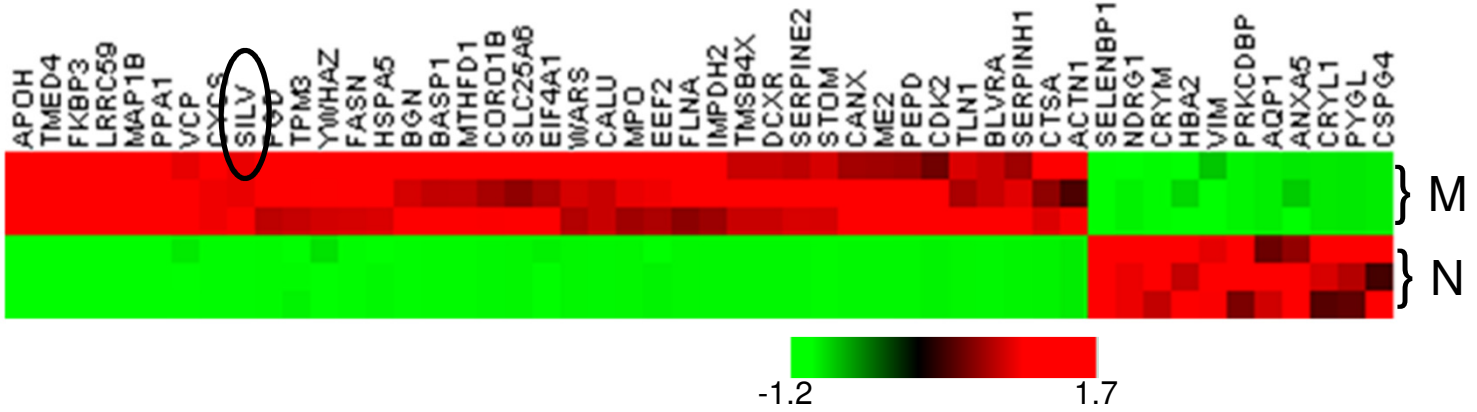
Normalized Spectral Abundance Factor

$$\frac{(\frac{SpC}{L})k}{\sum_{i=1}^{N}(\frac{SpC}{L})_i}$$



Thermo LTQ-XL

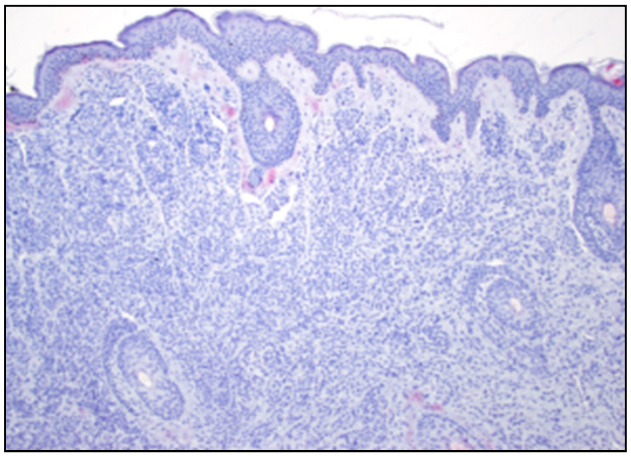
Candidate Biomarkers for Melanoma Diagnosis and Prognosis



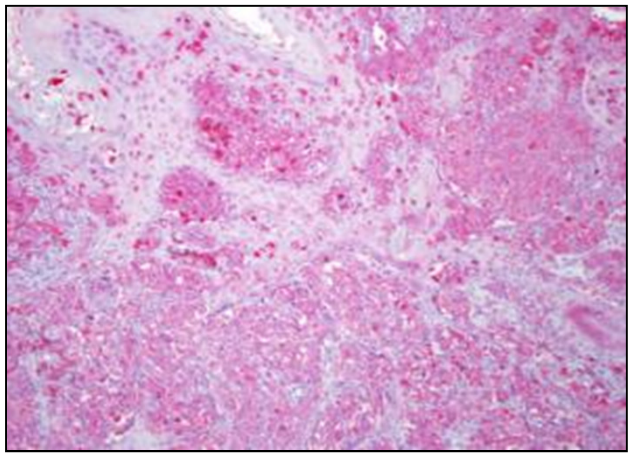
390 Proteins Differentially Regulated in Melanoma

SILV is Up-regulated in Melanoma

Benign melanocytic nevus

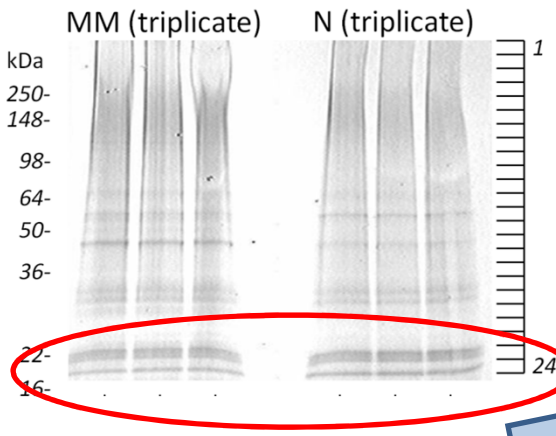


Malignant melanoma



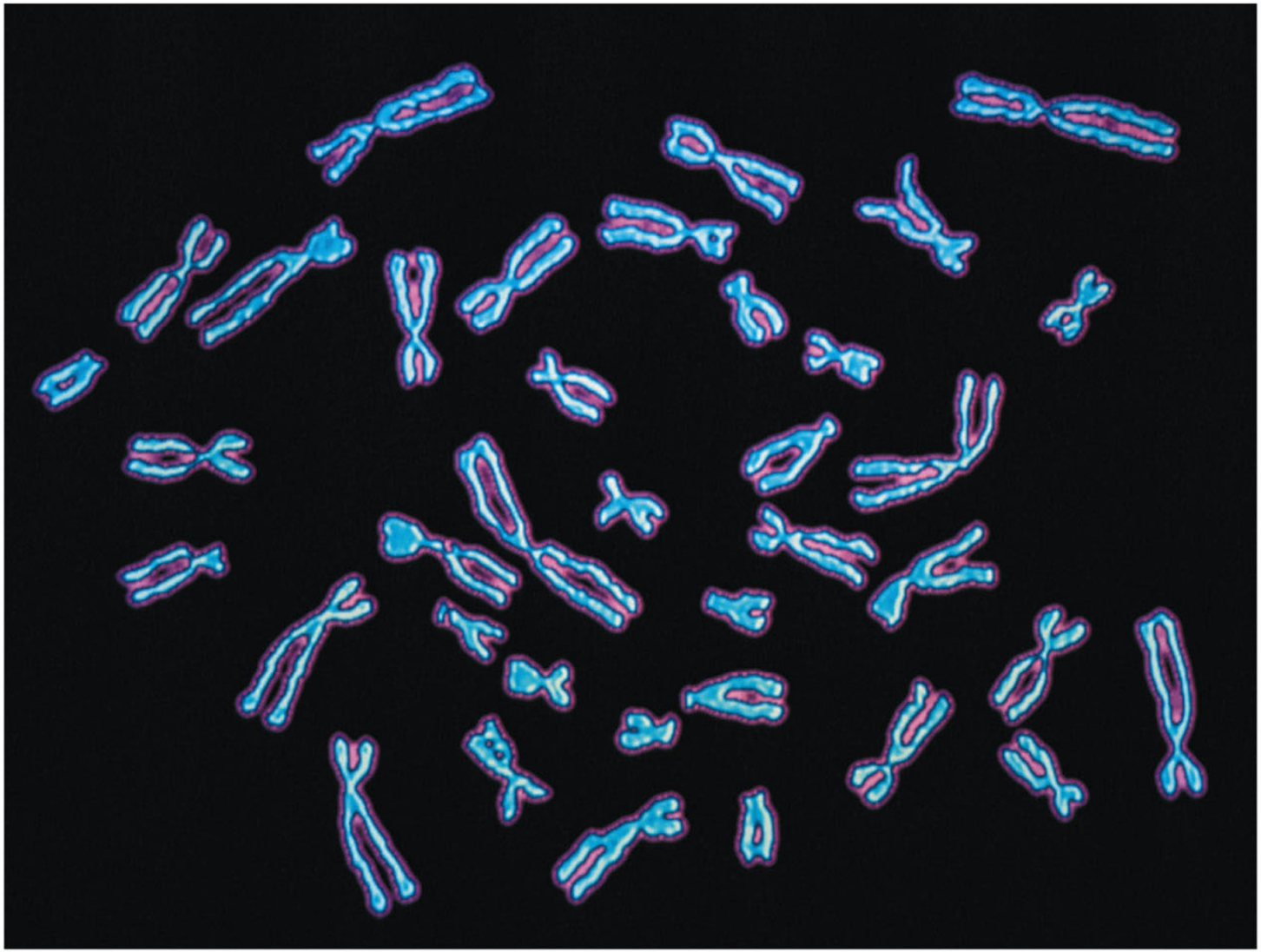
100X

What about these low molecular weight proteins?

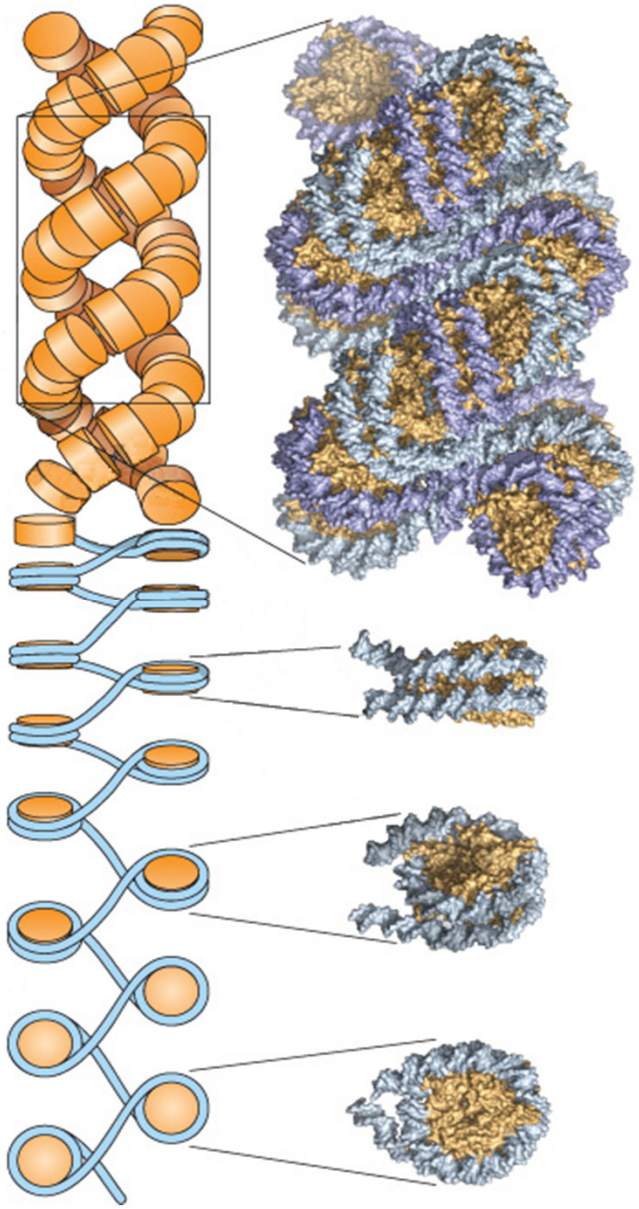


Histones

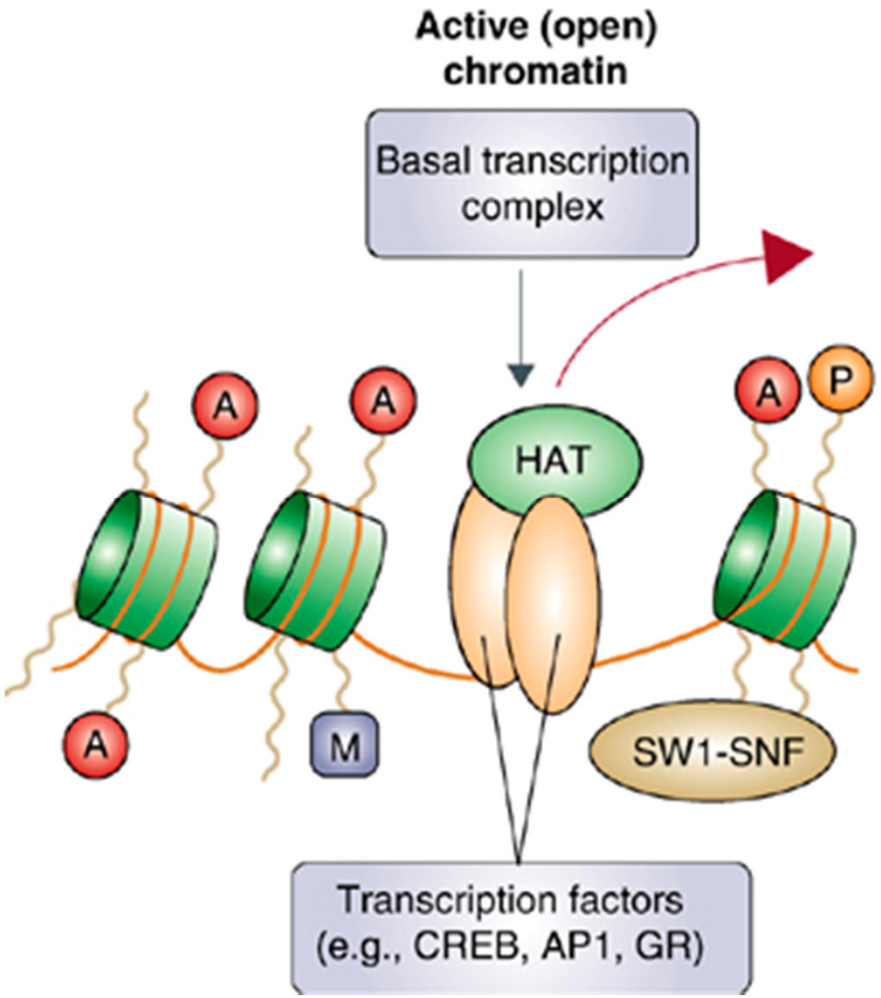
DNA Wraps Around Histones to Form Chromosomes



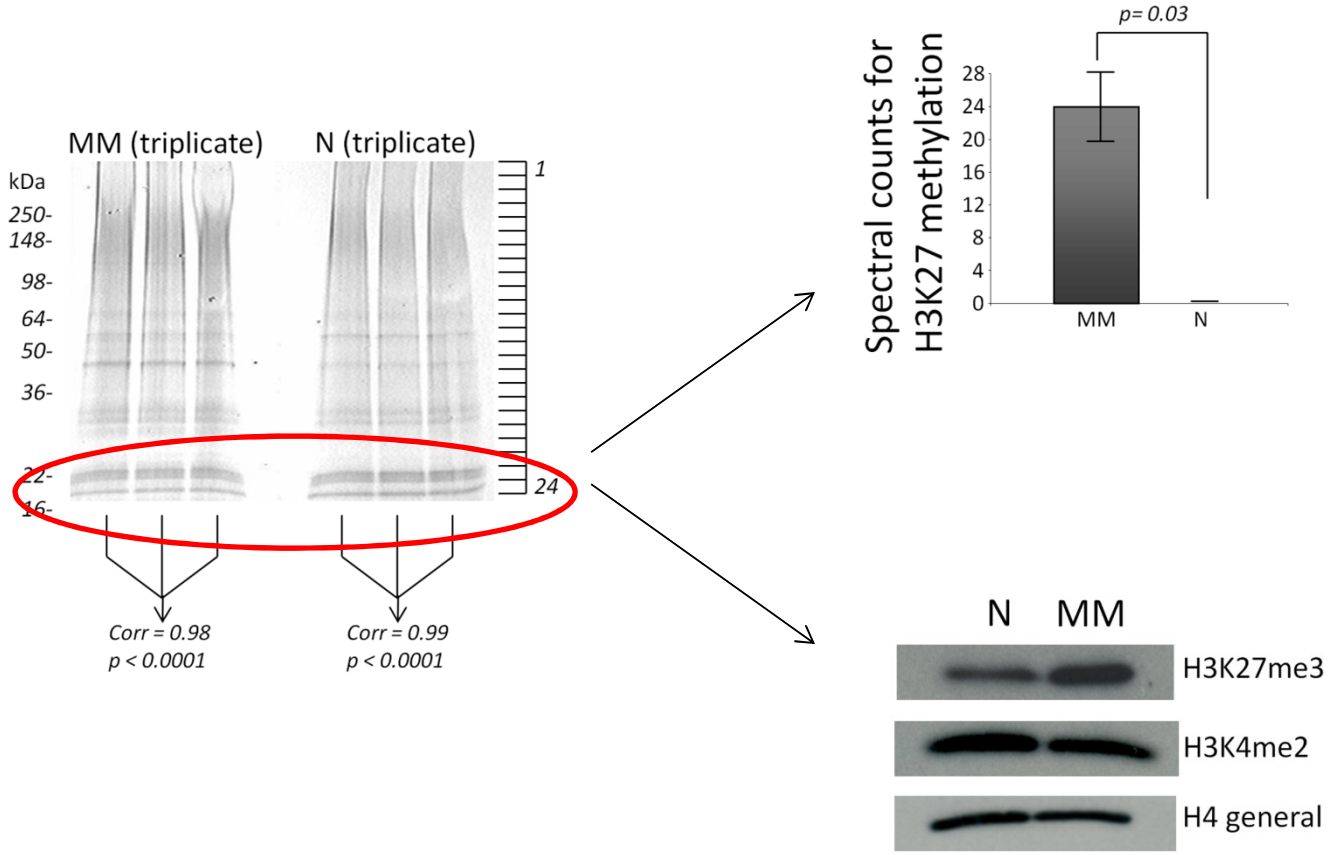
Unraveling a Chromosome



Natural Modifications to Histones Regulate Gene Expression

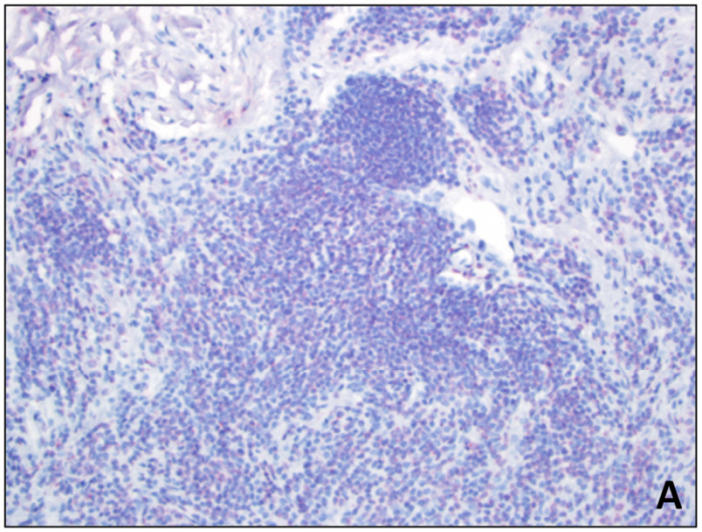


Modifications of Histones in Patient Melanoma

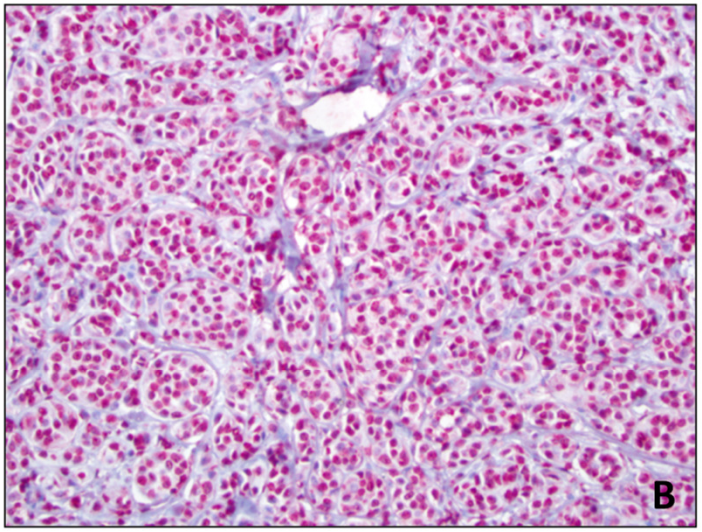


H3K27me3 is Up-regulated in Melanoma

Benign melanocytic nevus



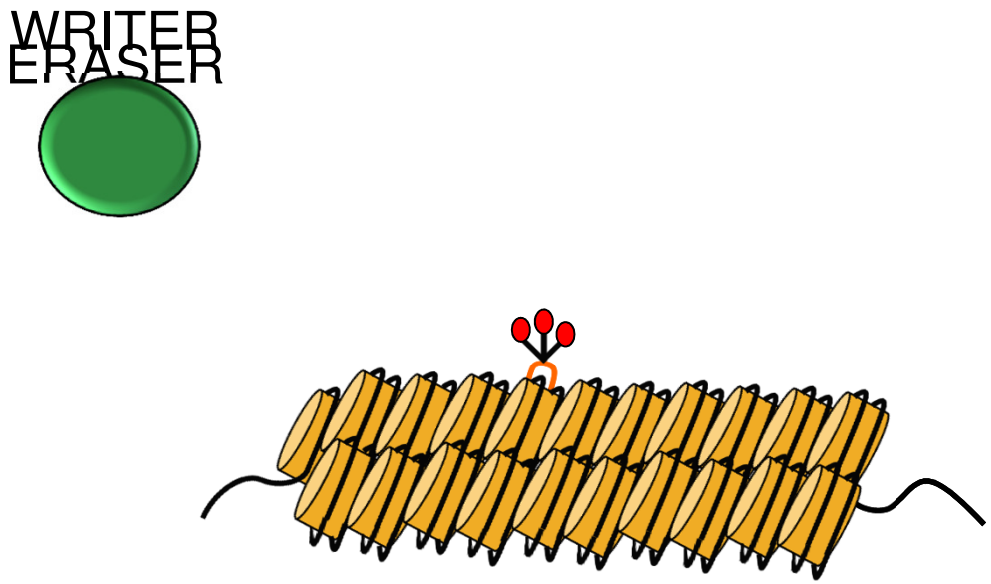
Malignant melanoma



	Low or no expression	High expression
Benign nevus	13	4
Melanoma	0	14

200X

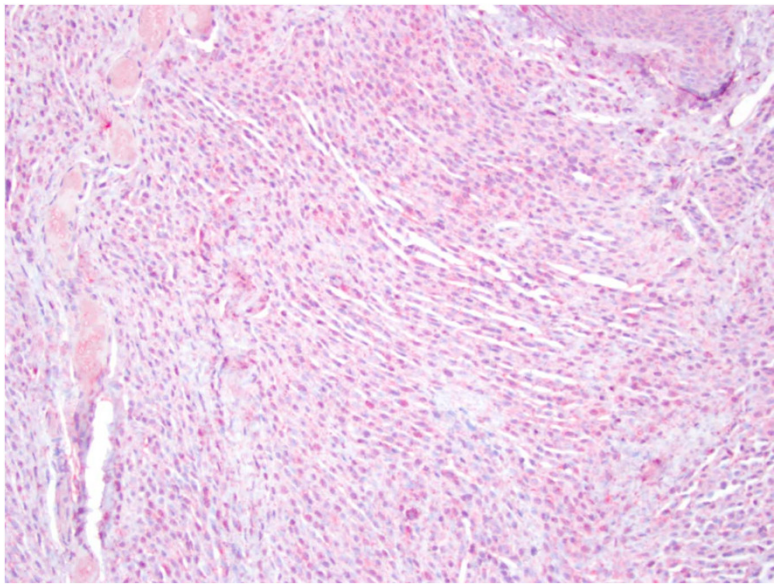
Maintaining an Epigenetic Mark



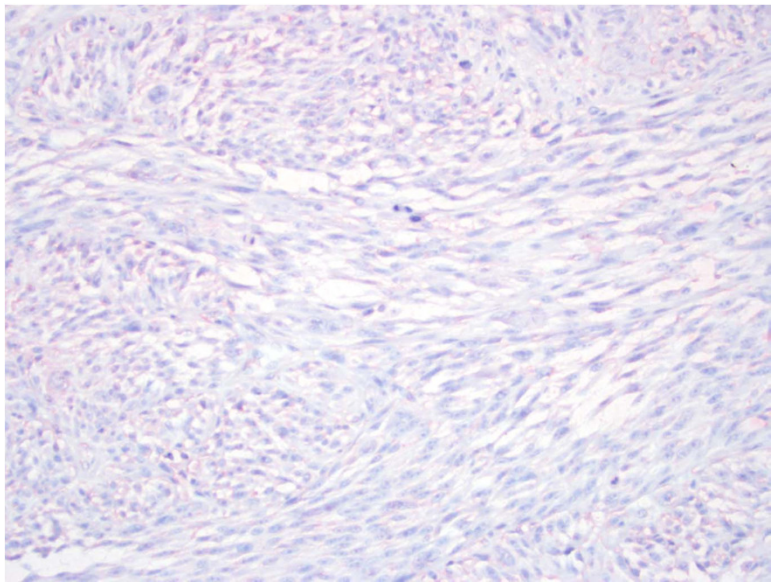
H3K27me3 “WRITER” is Over-expressed and “ERASER” is Repressed in Melanoma

JMJD3 “ERASER”

Benign melanocytic nevus

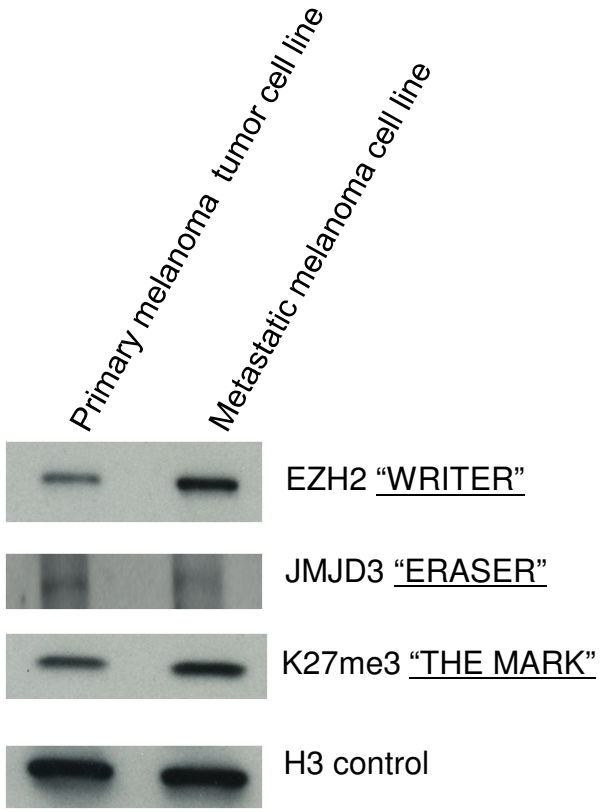


Malignant melanoma

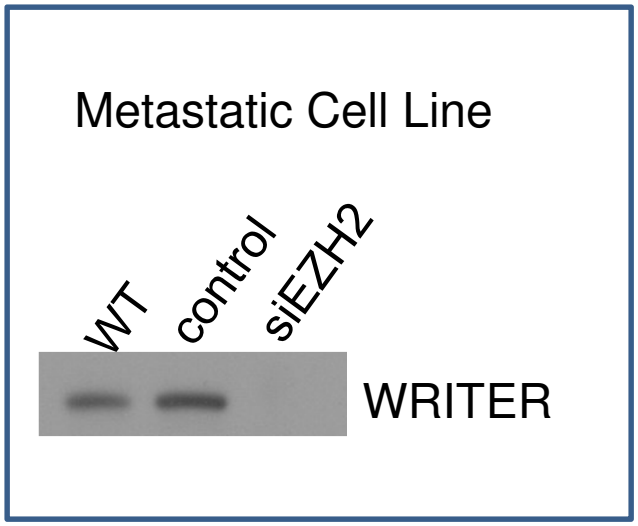


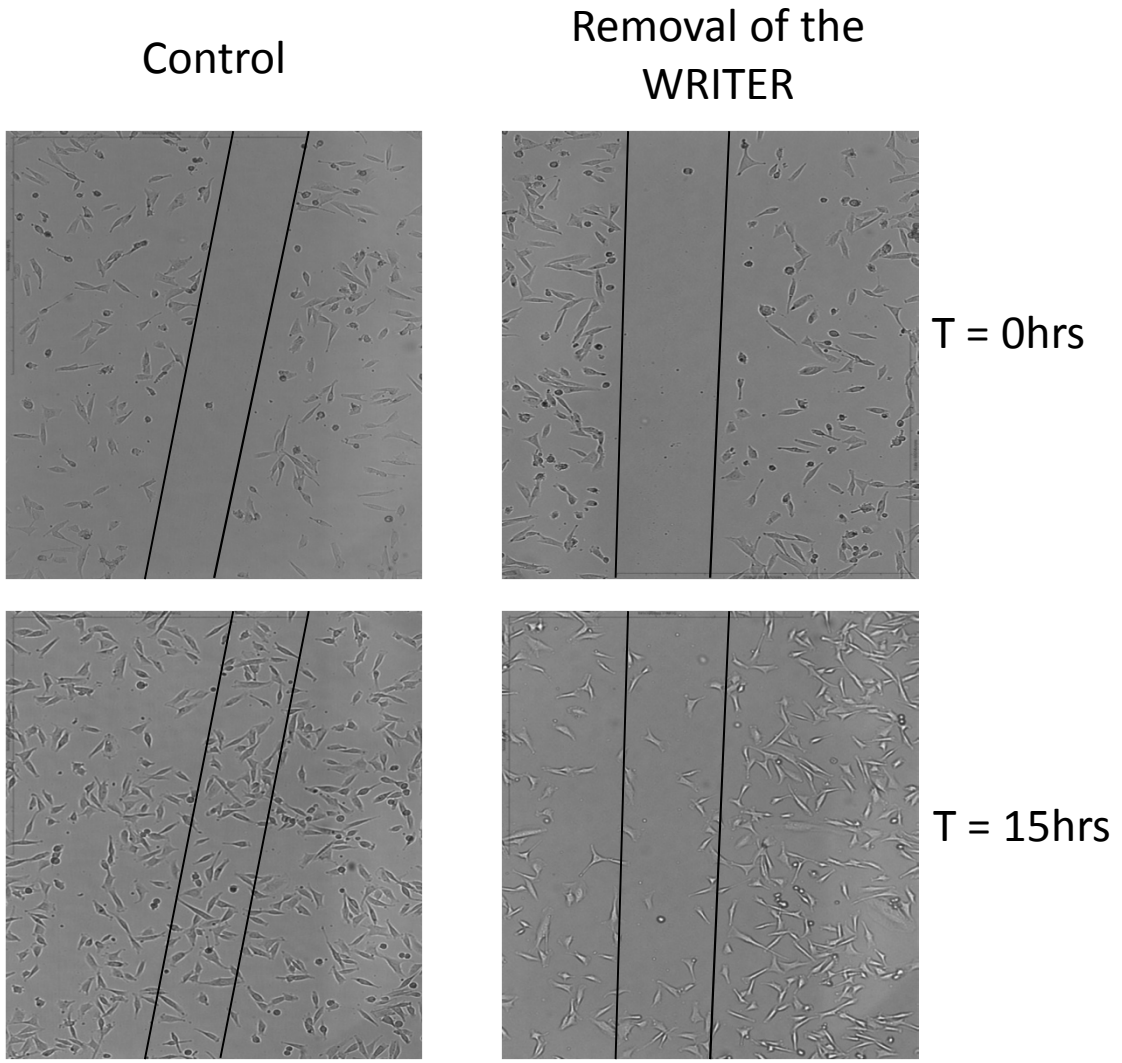
•Tissue microarrays show JMJD3 “eraser” and EZH2 “writer” are differentially expressed (*p<0.0001*)

A Cell Culture Model for Studying Melanoma in the Lab

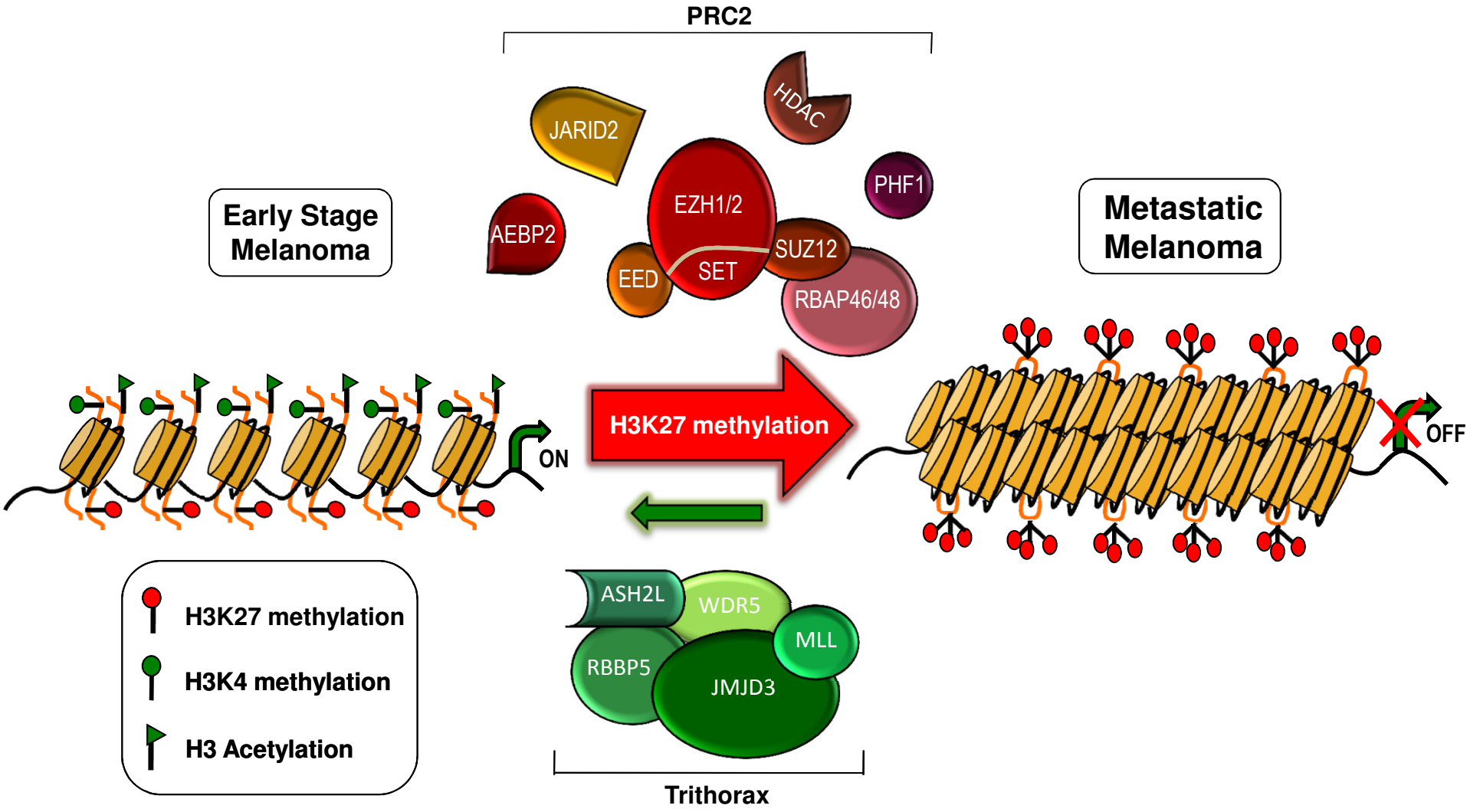


The “WRITER” is Necessary for Melanoma Cells to Migrate





A Novel Epigenetic Program Activated in Melanoma



Summary

- Described a translational research approach for identifying novel targets for melanoma diagnosis, prognosis and treatment
  - Extensive archive of patient skin biopsies at UAMS
  - Cutting-edge Proteomic technologies
  - A laboratory model to determine mechanism
- Uncovered 390 putative melanoma biomarkers that will move to the validation stage
- Found an epigenetic program involving proteins that WRITE and ERASE the H3K27me3 mark
  - Important for the migration phenotype of melanoma cells
  - Moving forward in elucidating how this epigenetic program “sets” the cancer “clock”

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