

# A comprehensive genome wide characterization of Meis1 induced leukemic transformation.

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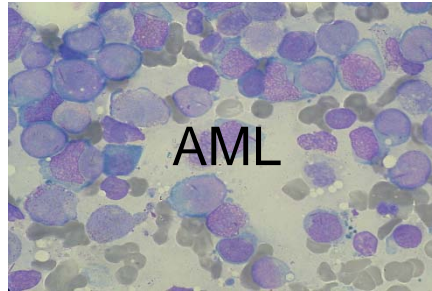


BC Cancer Agency  
CARE & RESEARCH  
An agency of the Provincial Health Services Authority

# AML: A Heterogenous Disease

MLL translocations (5-6%)

NPM1 mutants (35%)



Upregulation of **HOX genes** and **MEIS1**

- Engineered co-overexpression of **HOX** or **NUP98-HOX** fusions with **MEIS1** are sufficient for leukemic transformation
- MEIS1 is rate limiting for MLL-induced leukemias

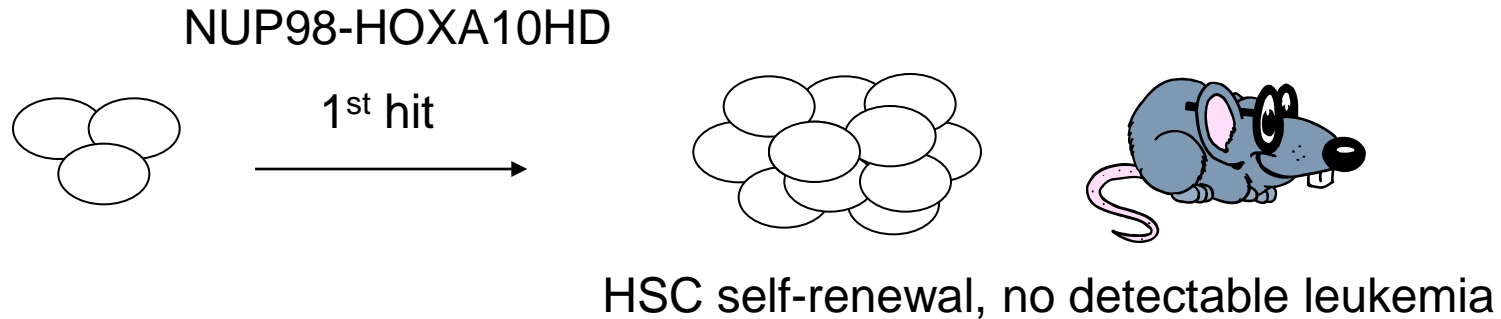
Meis1 is important as a HOX transcription factor co-factor – but what are its **targets**, and its **impact on gene expression**?

# Our Goal

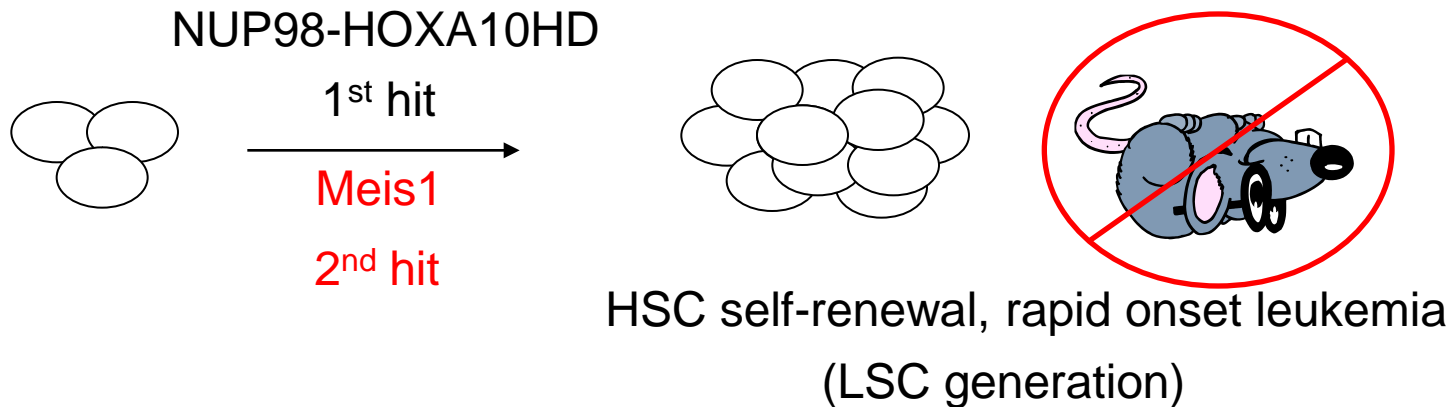
- To develop a comprehensive genome-wide map of Meis1 binding sites
- To define its associated epigenetic changes in key histone marks
- To determine its effects on the overall transcriptome

**AIM:** To ultimately identify key **mechanisms** and **pathways** associated with leukemic transformation.

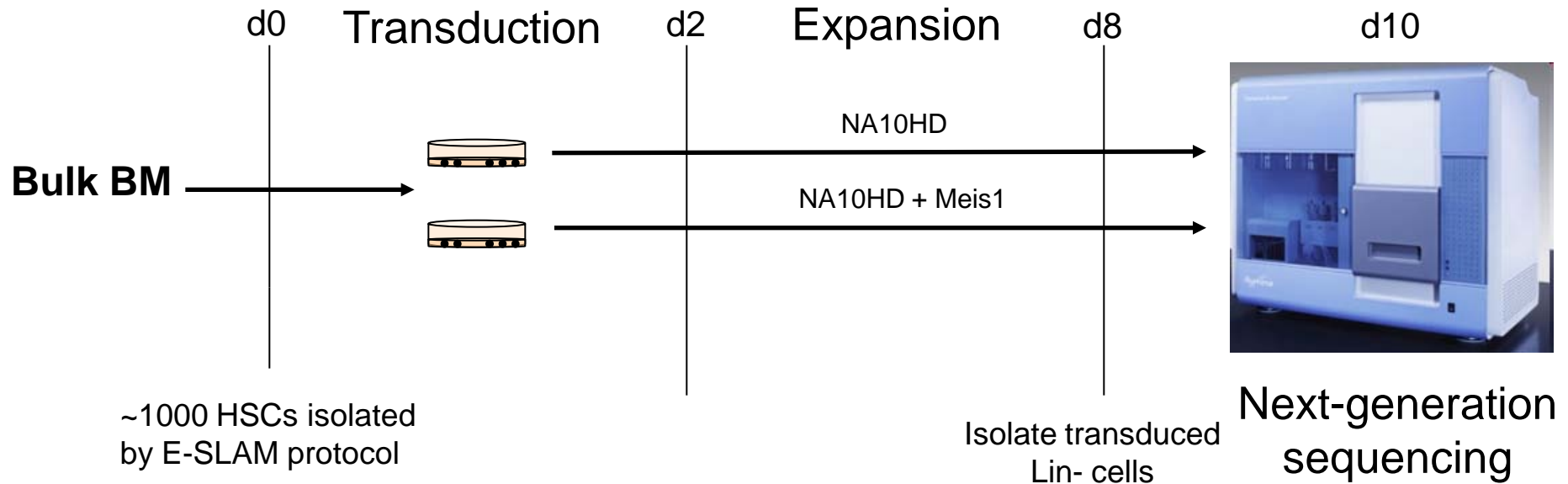
# Our models



(Ohta and Sekulovic et al., Exp Hematol. 2007 May; 35(5): 817–830)  
(Sekulovic et al. Blood 2011, Sekulovic et al. Blood 2011).



# Experimental Procedure



## Key features:

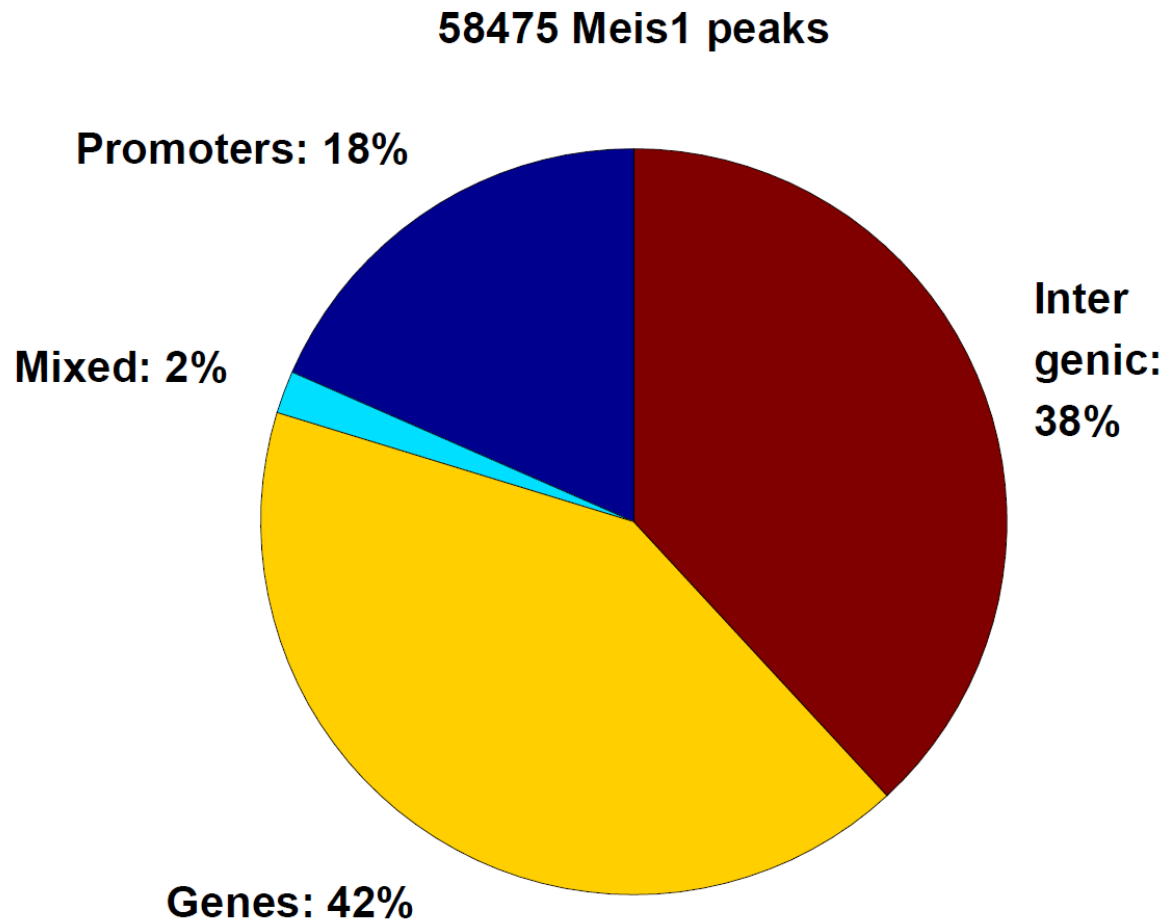
- start with high purity HSCs, obtain large numbers of cells required for sequencing

## Results:

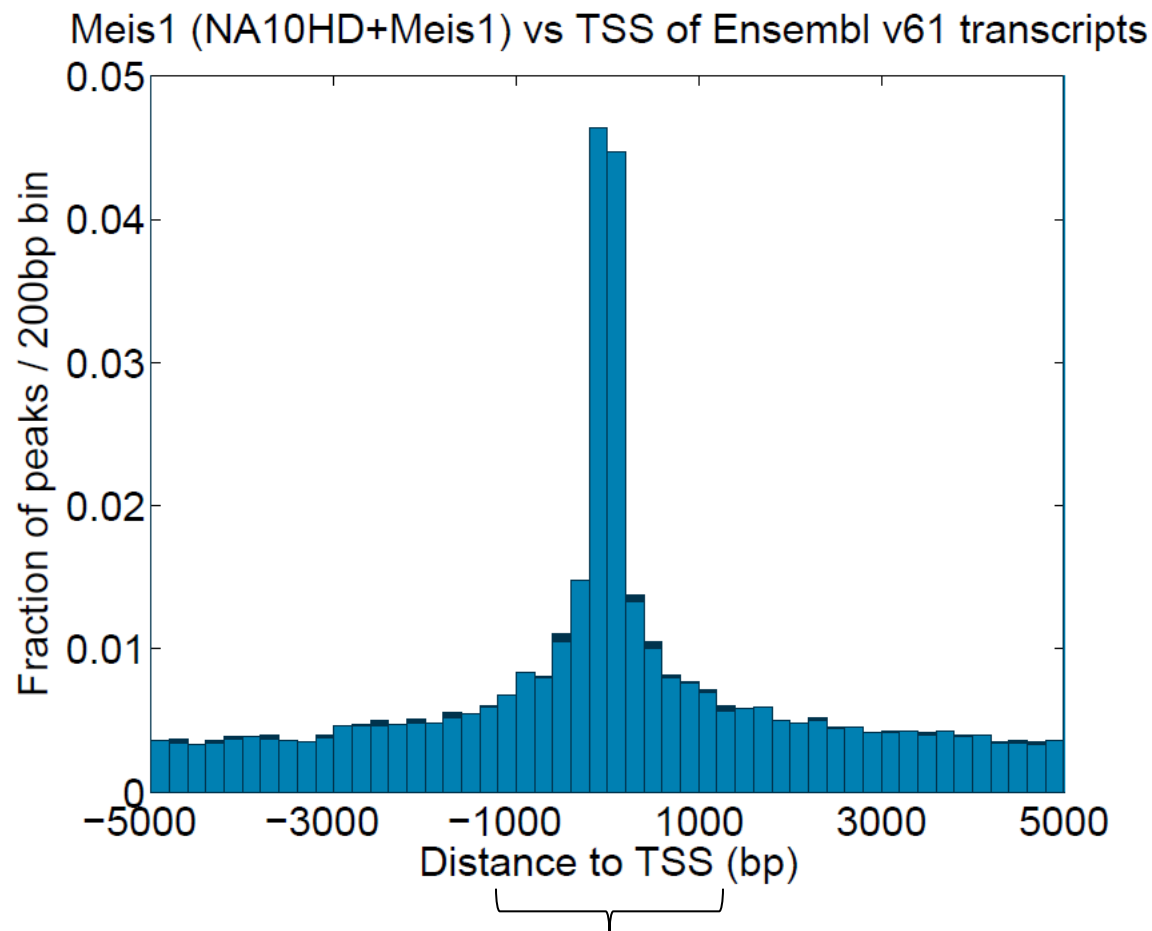
- we study epigenetics via ChIP-Seq of H3K4me3, H3K27me3 and H3K9me3
- we study Meis1 binding via ChIP-Seq of anti-HA Ab HA-Meis1
- we study transcriptome changes via RNA-seq



# Characterizing Meis1 binding in the genome

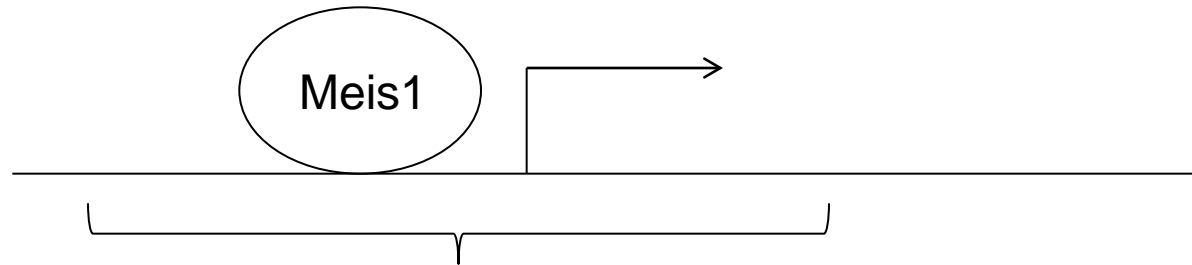


# Characterizing Meis1 binding in the genome



17% of all Meis1 binding

# Characterizing Meis1 binding in the genome



DNA motifs?

**RUNX1** **TGTTGGTT** 24% (13958 peaks)

**C-EBP** **TTCAAA** 21% (12060 peaks)

**ETS** **AGGAAAG** 76% (44680 peaks)

# Gene Expression changes upon Meis1 overexpression

**RNA-seq (21484 from protein coding transcripts)**



Distinguish changes in gene transcripts (based on whole gene coverage)



**78 upregulated genes**

(eg. Flt3, Hlf, Ddx4, Msi2)

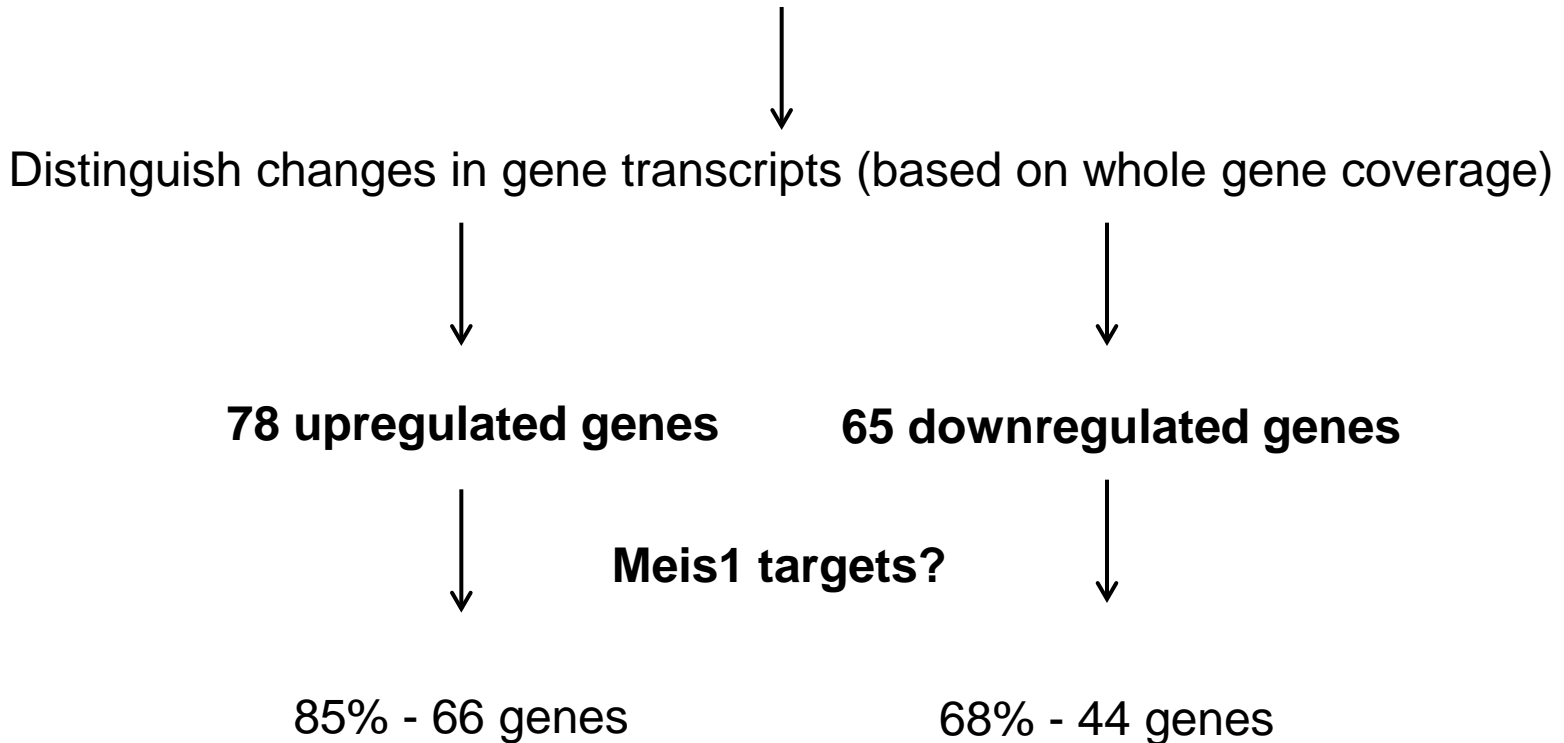


**65 downregulated genes**

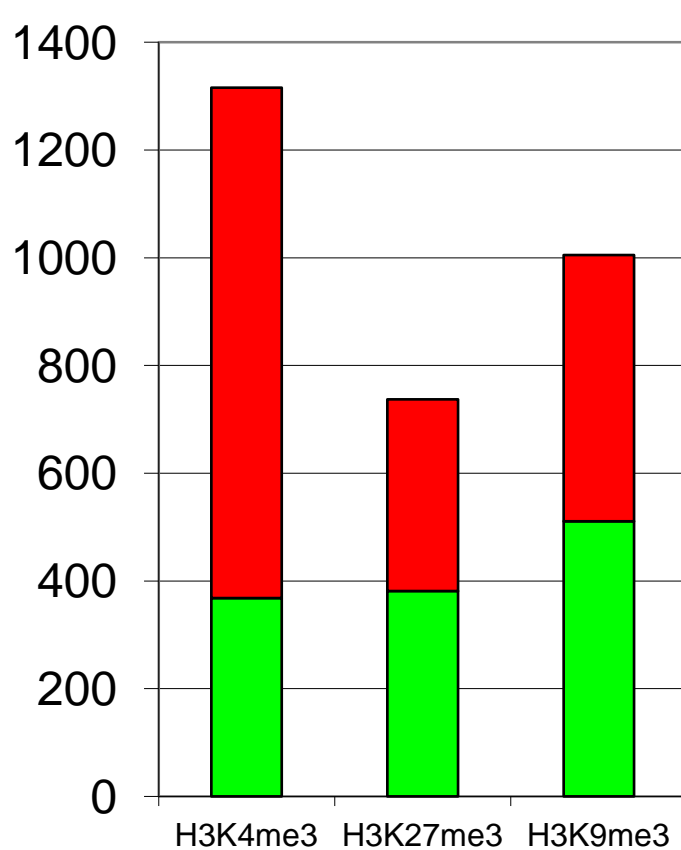
(eg. Sfpi1, Mmp12)

# Gene Expression changes upon Meis1 overexpression

**RNA-seq (21484 from protein coding transcripts)**



# Meis1 Induced progression to leukemia affects a subset of genes



31510 genes analyzed looking either side of the transcription start site

**H3K4me3**

~4% of genes affected,  
944 down, 366 up

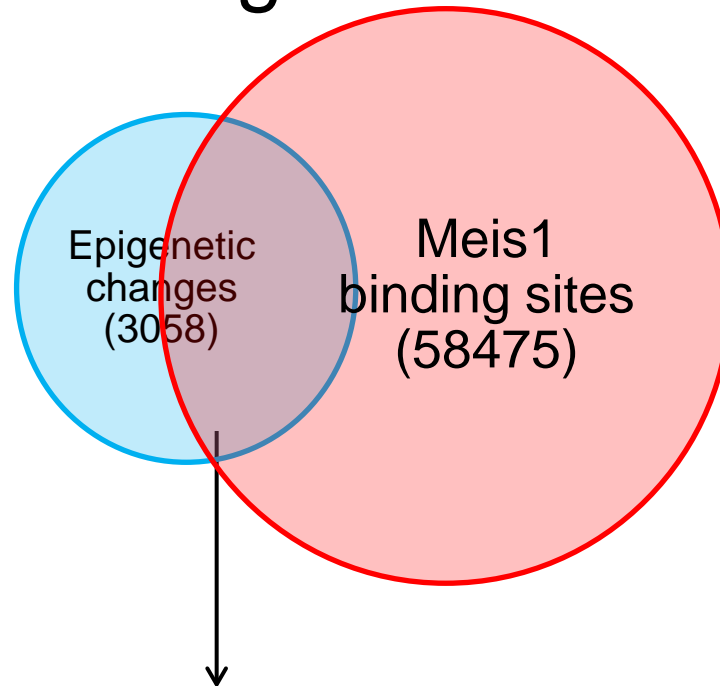
**H3K27me3**

~2% of genes affected,  
356 down, 377 up

**H3K9me3**

~3% of genes affected,  
494 down, 511 up

# Epigenetic changes with Meis1 binding



771 of 1285 (60%) H3K4me3 changes correlate with Meis1 binding  
389 of 724 (54%) H3K27me3 changes correlate with Meis1 binding  
323 of 980 (33%) H3K9me3 changes correlate with Meis1 binding

**Examples:** Flt3 → loss of H3K27me3  
Rara → loss of H3K4me3  
HoxA3 → gain of H3K9me3



# Summary

1) Meis1 binds 13005 gene locations

2) **2-4%** of genes (3058 total) are affected epigenetically (H3K4me3, H3K27me3 and H3K9me3) upon Meis1 overexpression

3) Epigenetic changes correlate well with Meis1 binding locations – especially if you consider H3K4me3 and H3K27me3 which associate with promoters

3) only **143 total genes** are affected by Meis1 overexpression

Substantial number of Meis1 binding sites are epigenetically changed but not transcript level changes.

# Summary

**Question** – Is there an epigenetic state associated with leukemic cell function which may not be reflected immediately by gene expression changes?

A smaller number of Meis1 targets are associated with both epigenetic and gene expression changes → **Question** – Are these the top candidates for genes and pathways for Meis1-induced leukemogenesis?

**Next steps:** Deeper analysis of the datasets for potential pathways/gene networks and tests of candidate genes.

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