

Highlights from IMW 2021

1-2 febbraio 2022
Bologna
Royal Hotel Carlton

Niccolò Bolli

Alterazioni epigenetiche nel mieloma

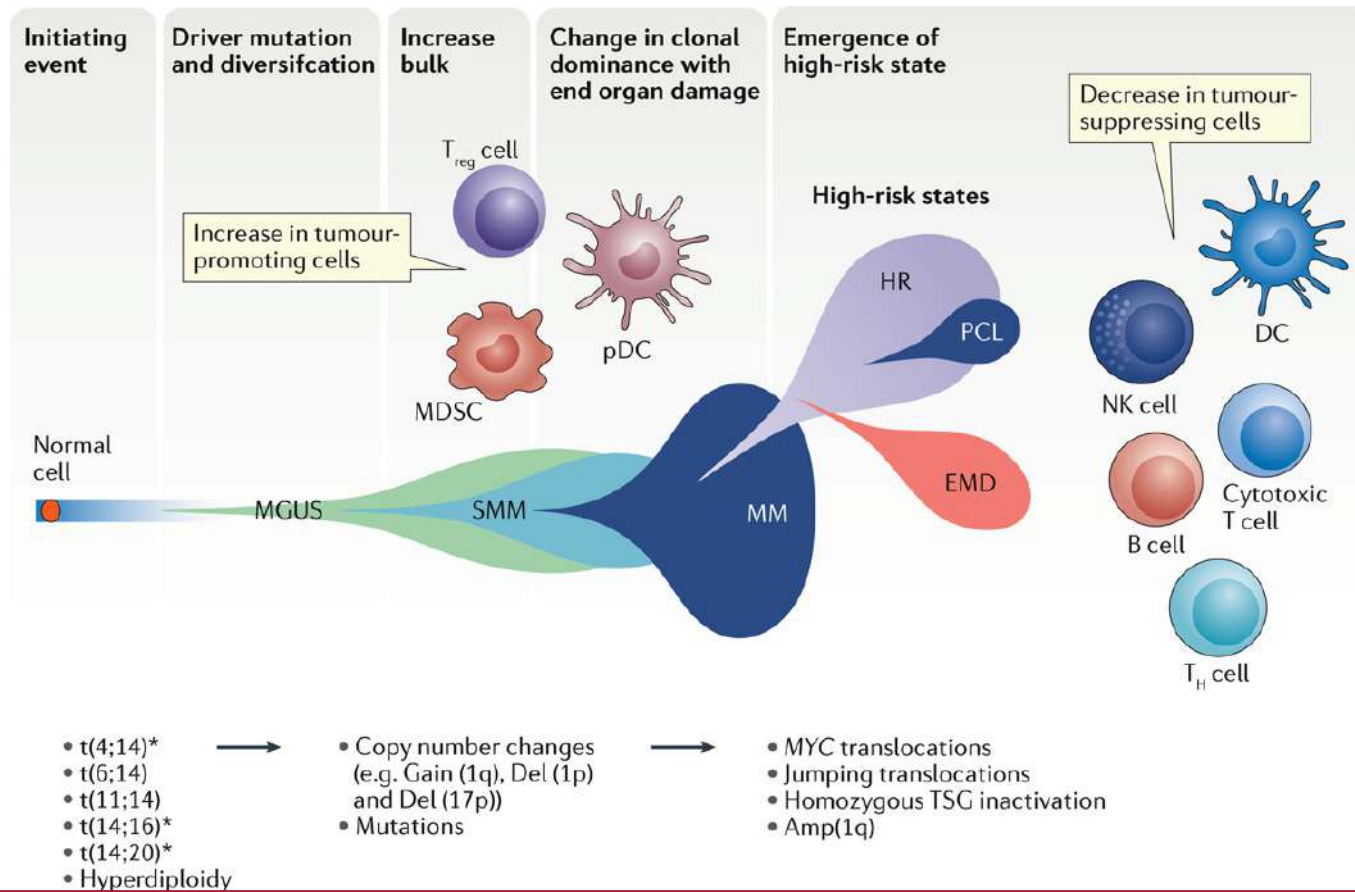
Coordinatore Scientifico
Michele CAVO

Comitato Scientifico
Michele CAVO
Maria Teresa PETRUCCI

Outline

- What is epigenetics?
 - DNA methylation
 - Histone modification
 - 3D genomic structure
- Epigenetics in myeloma
- Epigenetic modifiers of special interest
 - MMSET/NSD2
 - PRC2 complex (EZH2, PHF19)

Myeloma disease evolution



Initiation and progression mediated by myeloma cell intrinsic and extrinsic factors

Epigenetics

The study of heritable changes in gene expression without changes to the underlying DNA sequence

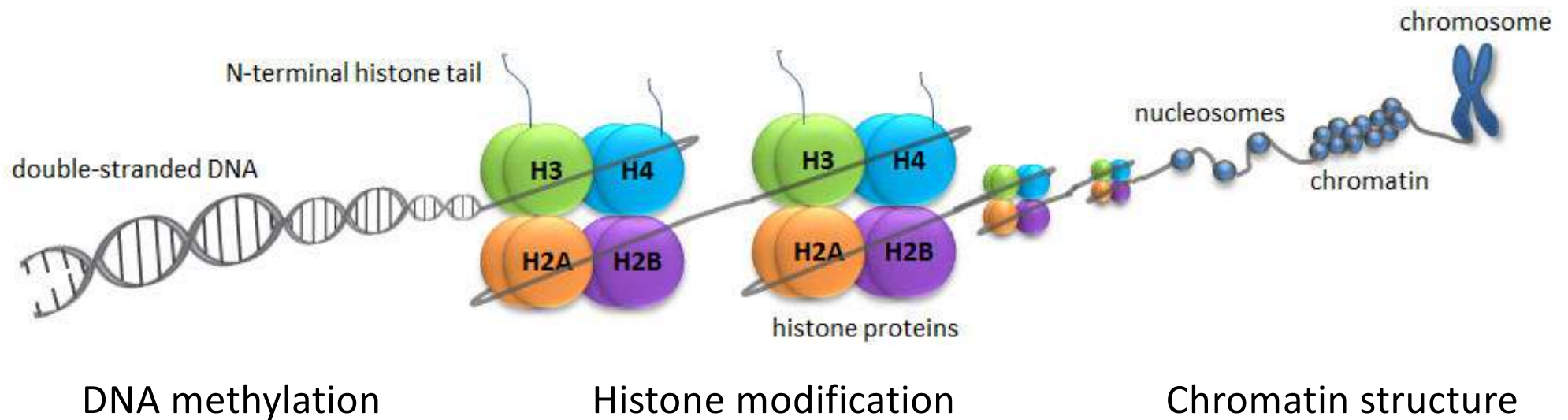
- Please note again, access can only be provided to fully vaccinated or previously COVID19-infected and recovered participants.

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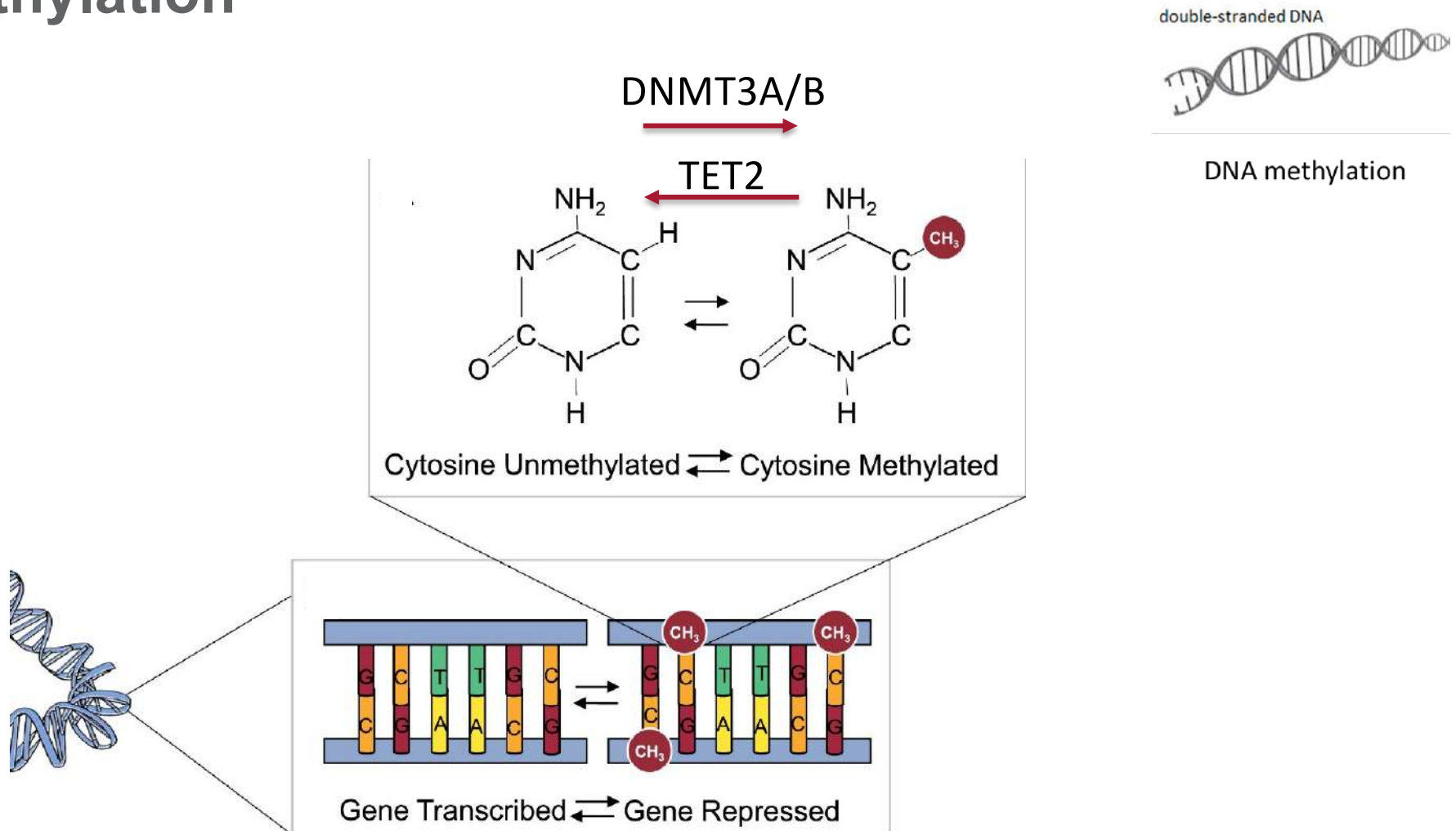
Epigenetics

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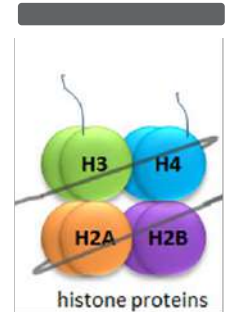
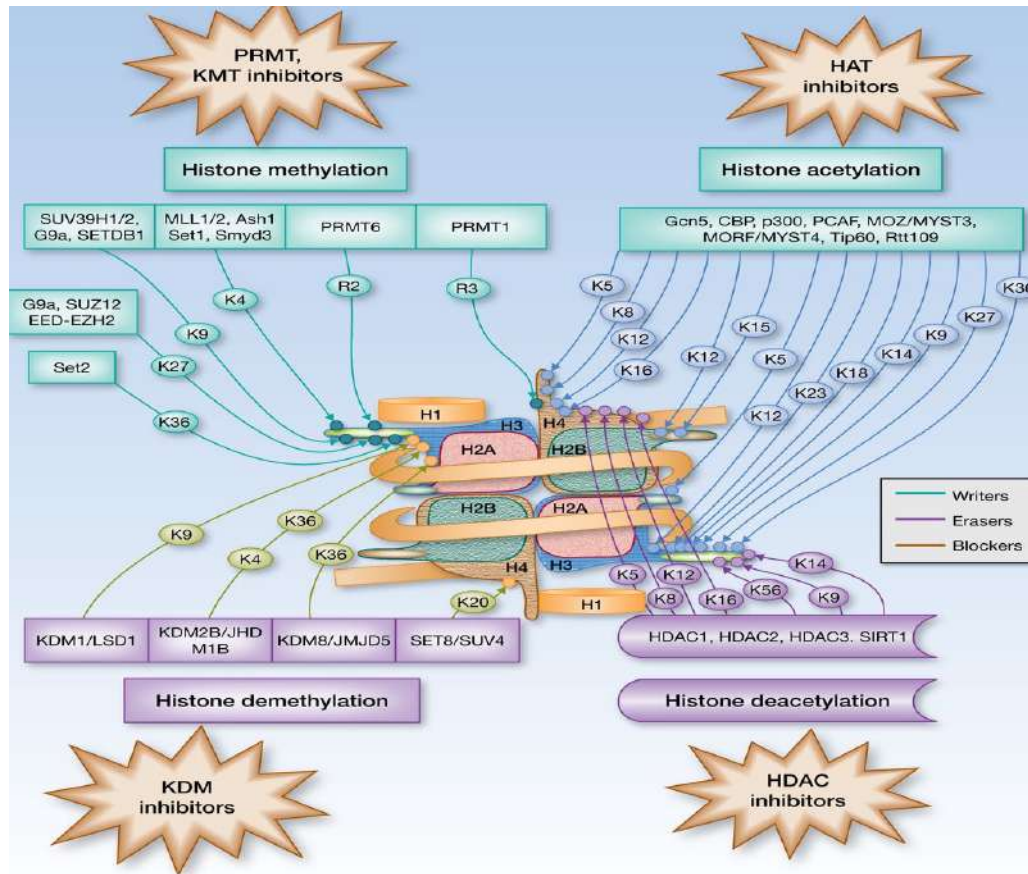


Potentially modifiable with targeted therapy

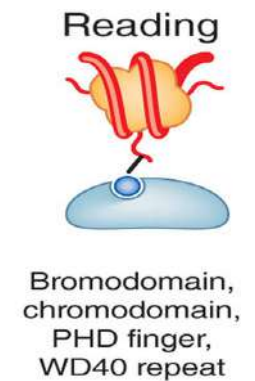
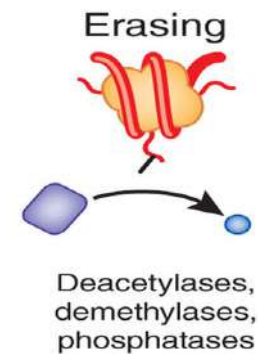
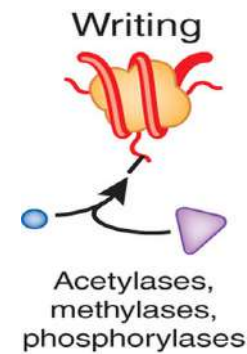
DNA methylation



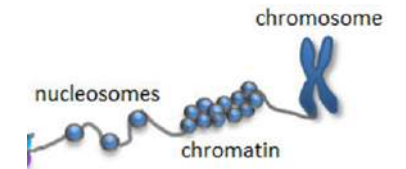
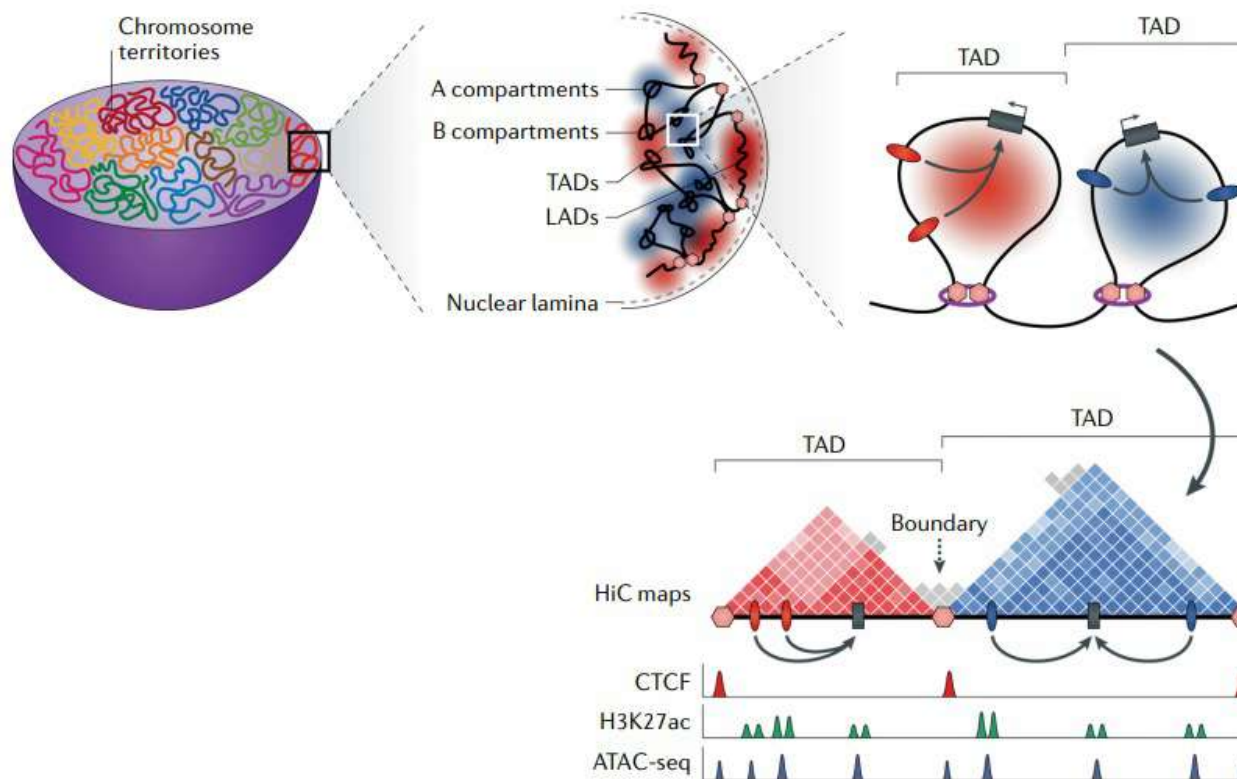
Histone modification



Histone modification



Chromatin structure

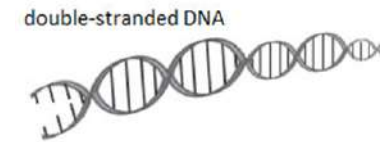


Chromatin structure

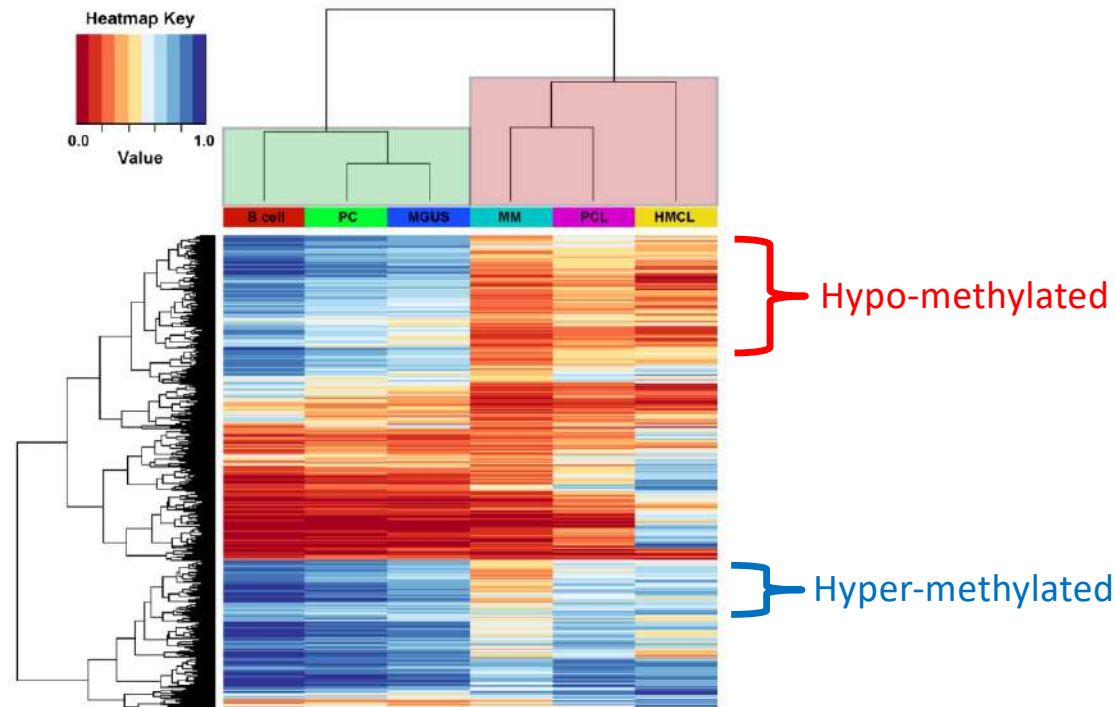
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DNA methylation levels change as disease progresses



DNA methylation

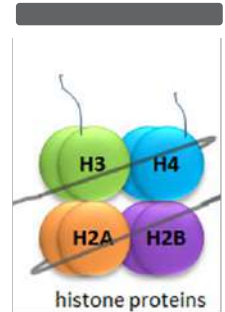
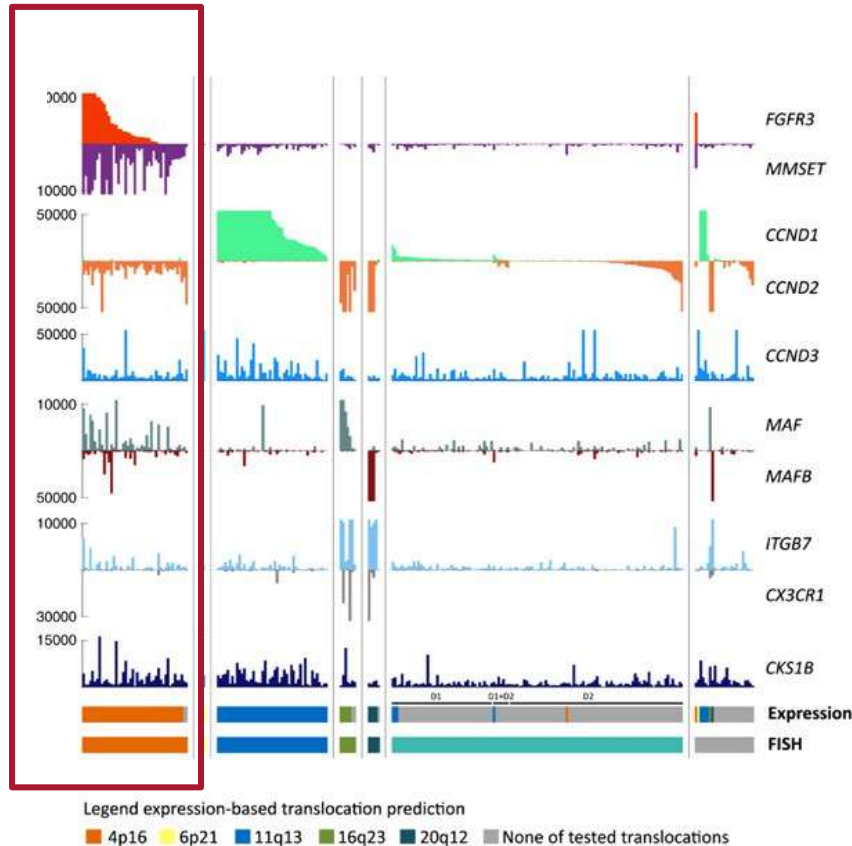


	B cell	PC	MGUS	MM	PCL	HMCL
Hypo	637	14	3407	3	41	
Hyper	222	9	82	2151	426	

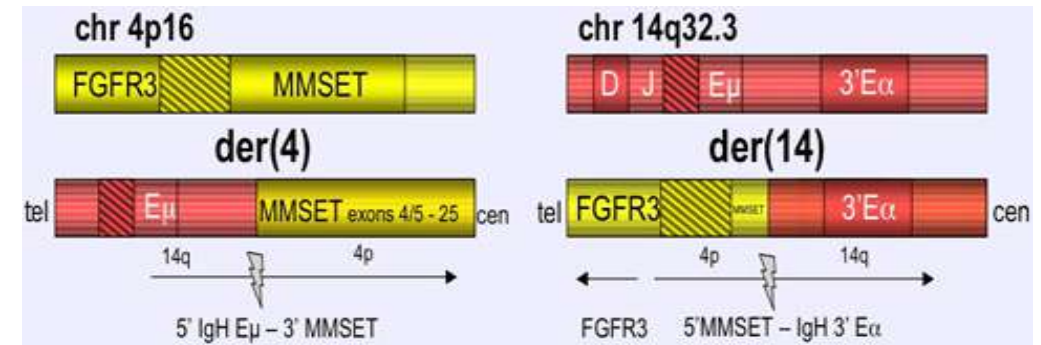
Global hypomethylation
Gene specific hypermethylation

t(4;14)

~15% newly diagnosed patients

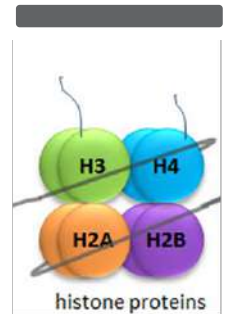
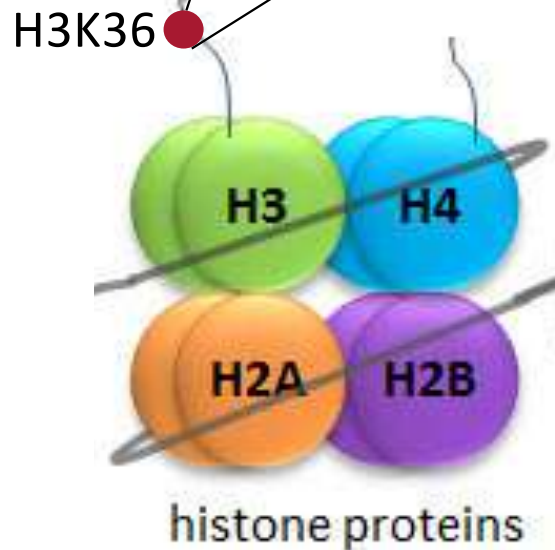
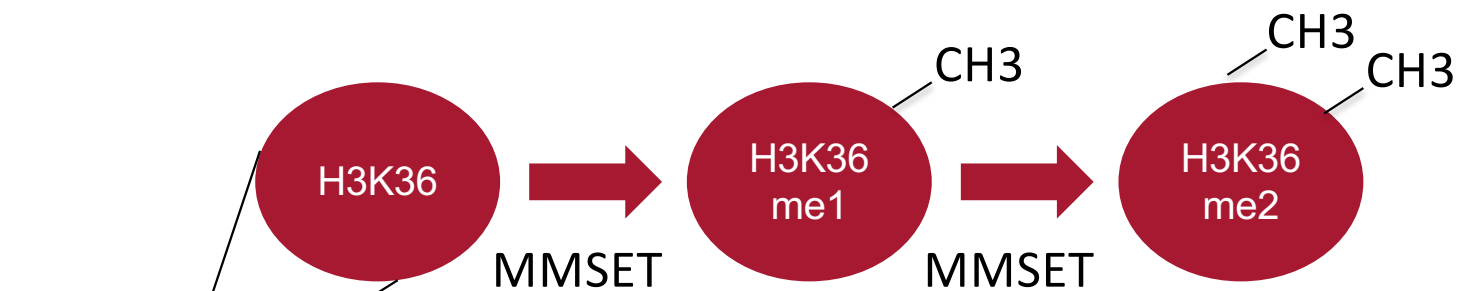


Histone modification

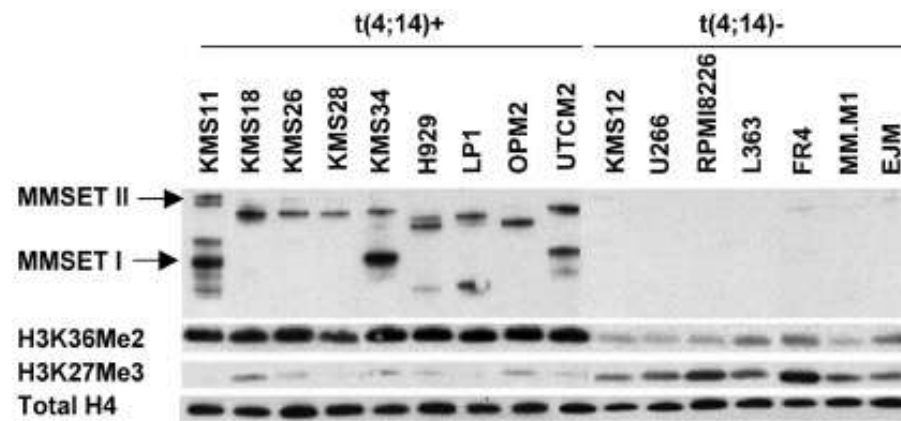


Upregulation of:
FGFR3 (lost in 20% of cases)
MMSET/NSD2 – H3K36 methyltransferase

MMSET/NSD2

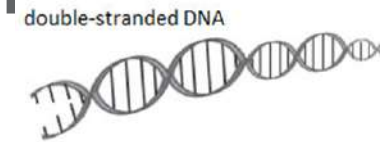


Histone modification

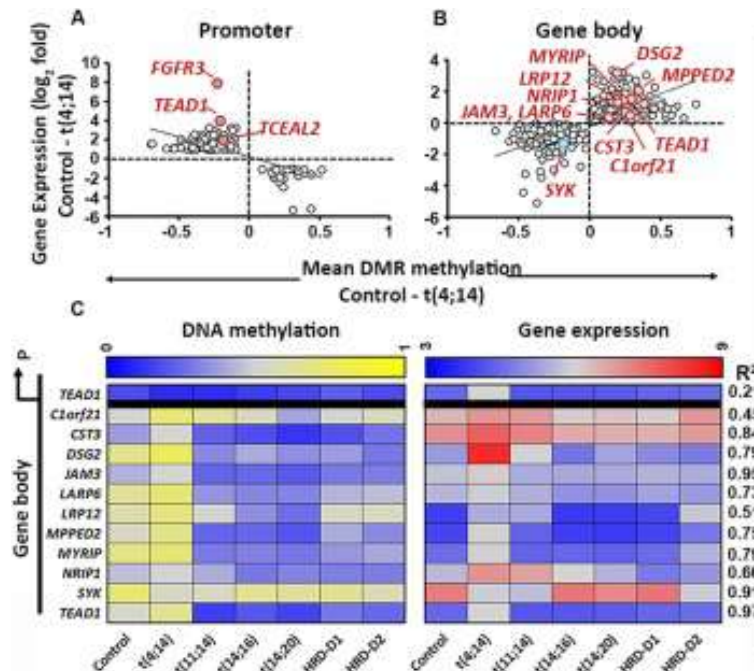
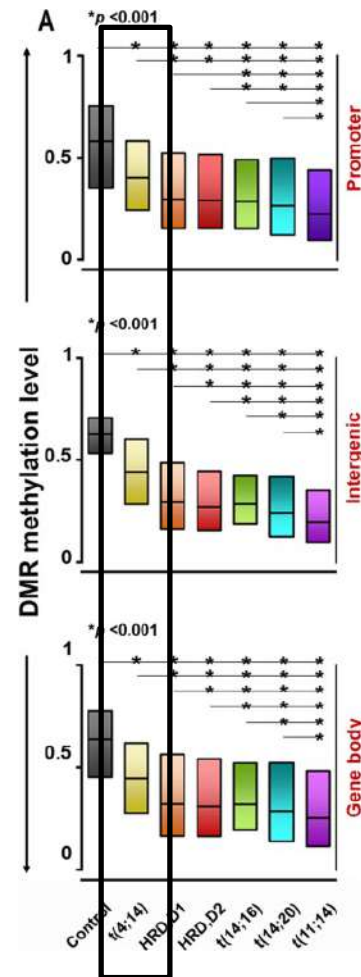
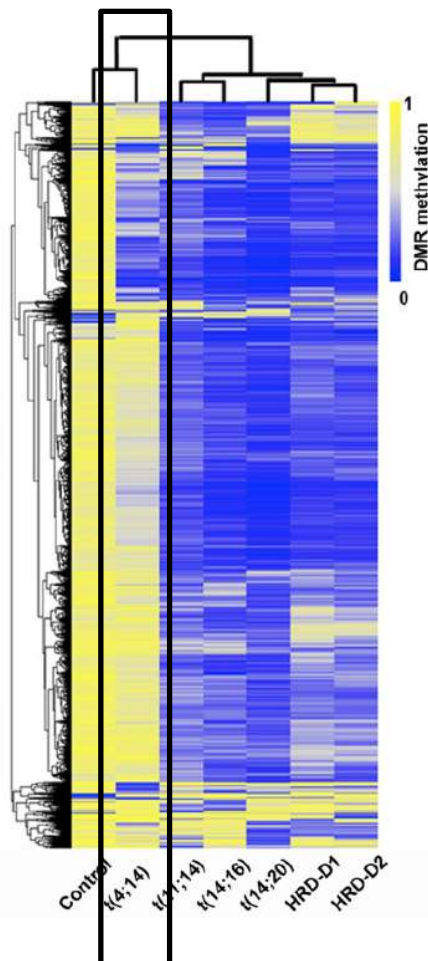


t(4;14) drives high levels of MMSET and H3K36me2

t(4;14) patients - distinct DNA methylation pattern

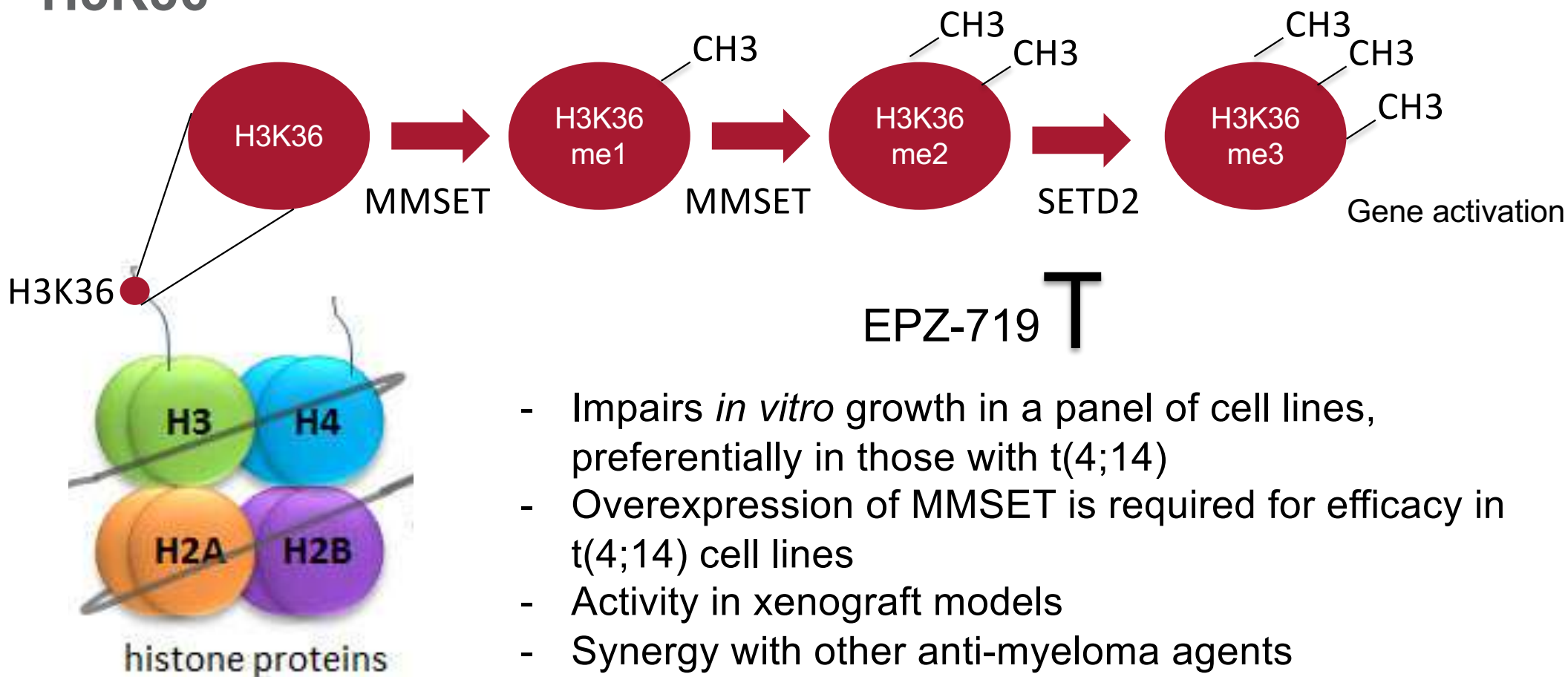


DNA methylation



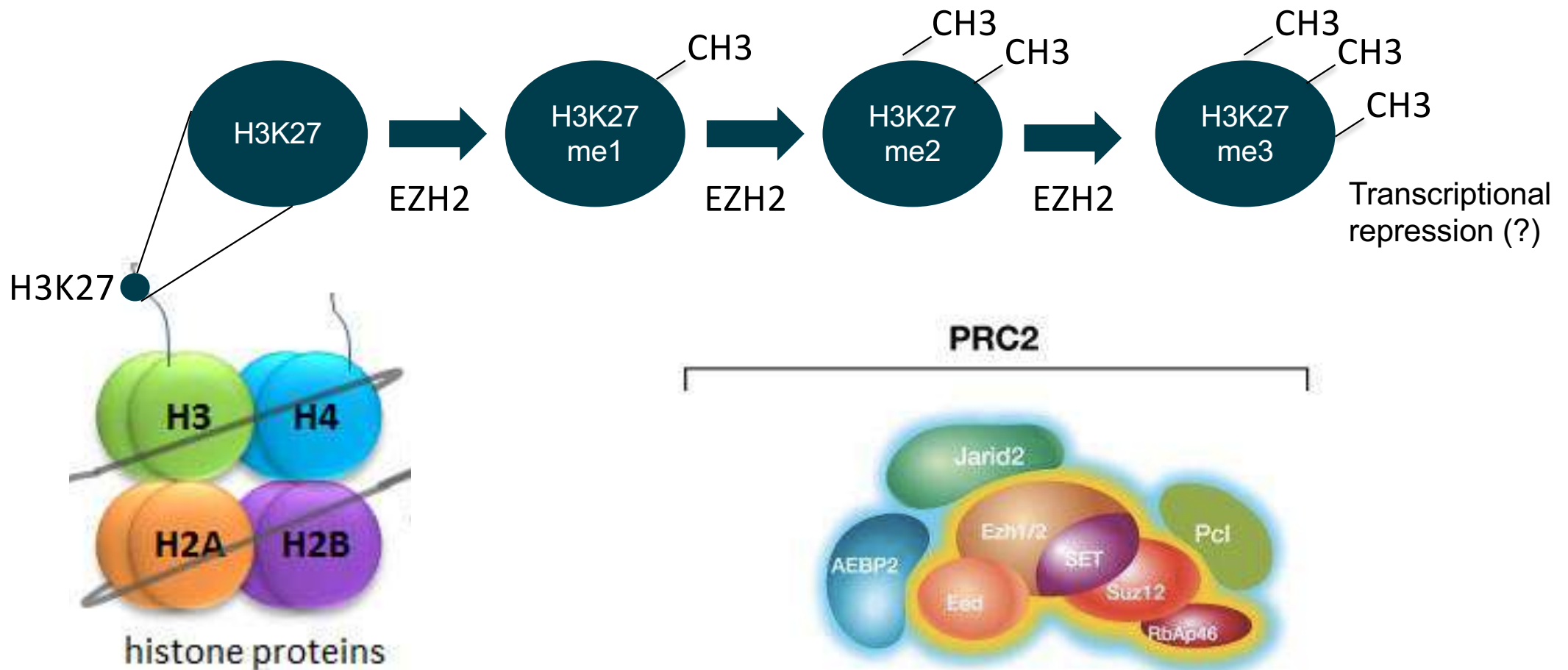
Choudhury S et al, *Journal of Haematology and Oncology*, 2020

H3K36



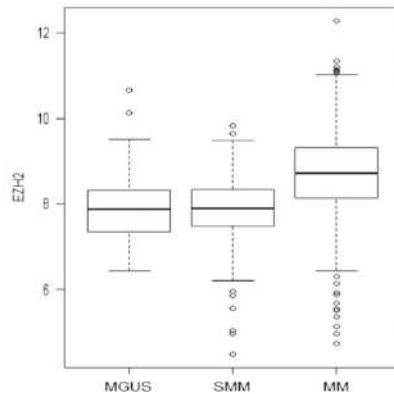
SETD2 inhibitor given fast track designation by FDA and now in clinical trials

EZH2

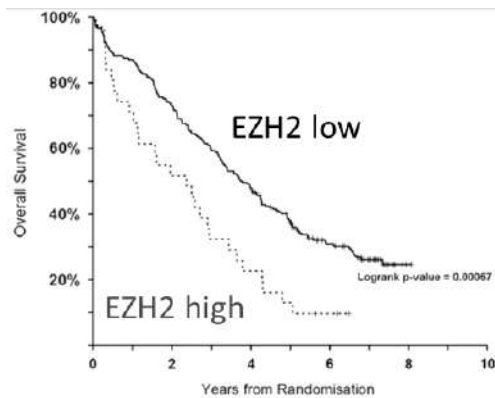


EZH2

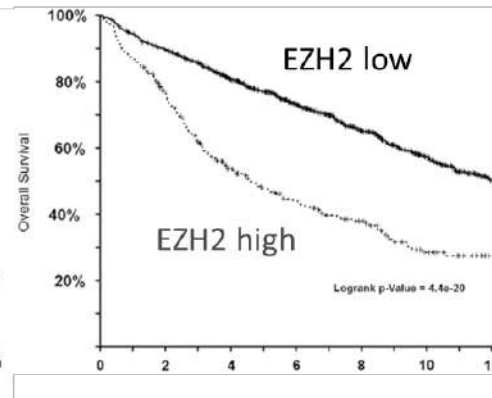
H3K27me3 methyltransferase implicated in aggressive disease biology



Myeloma IX

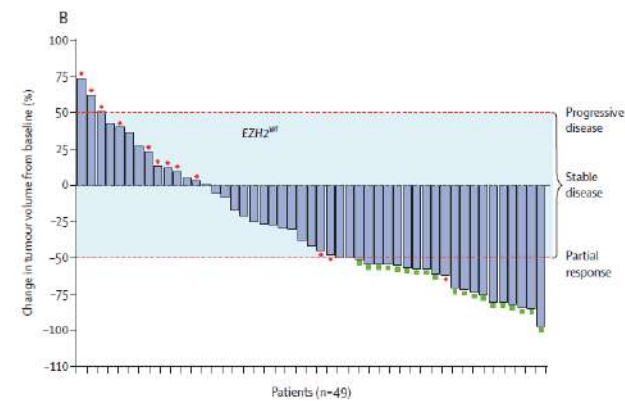
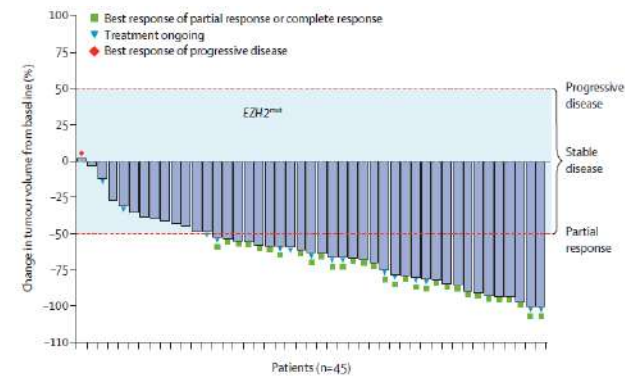


UAMS

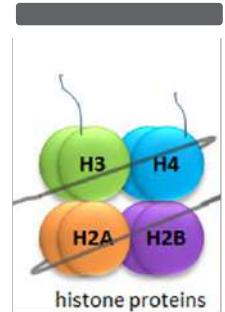


Pawlyn C et al, *Blood Cancer Journal*, 2017
Goldsmith SR et al, *Clin Lymph Myel Leuk*, 2019

EZH2 inhibitor Tazemetostat active in lymphoma



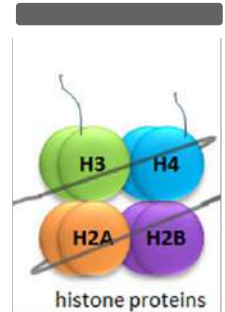
Morschhauser F et al, *Lancet Oncology*, 2020



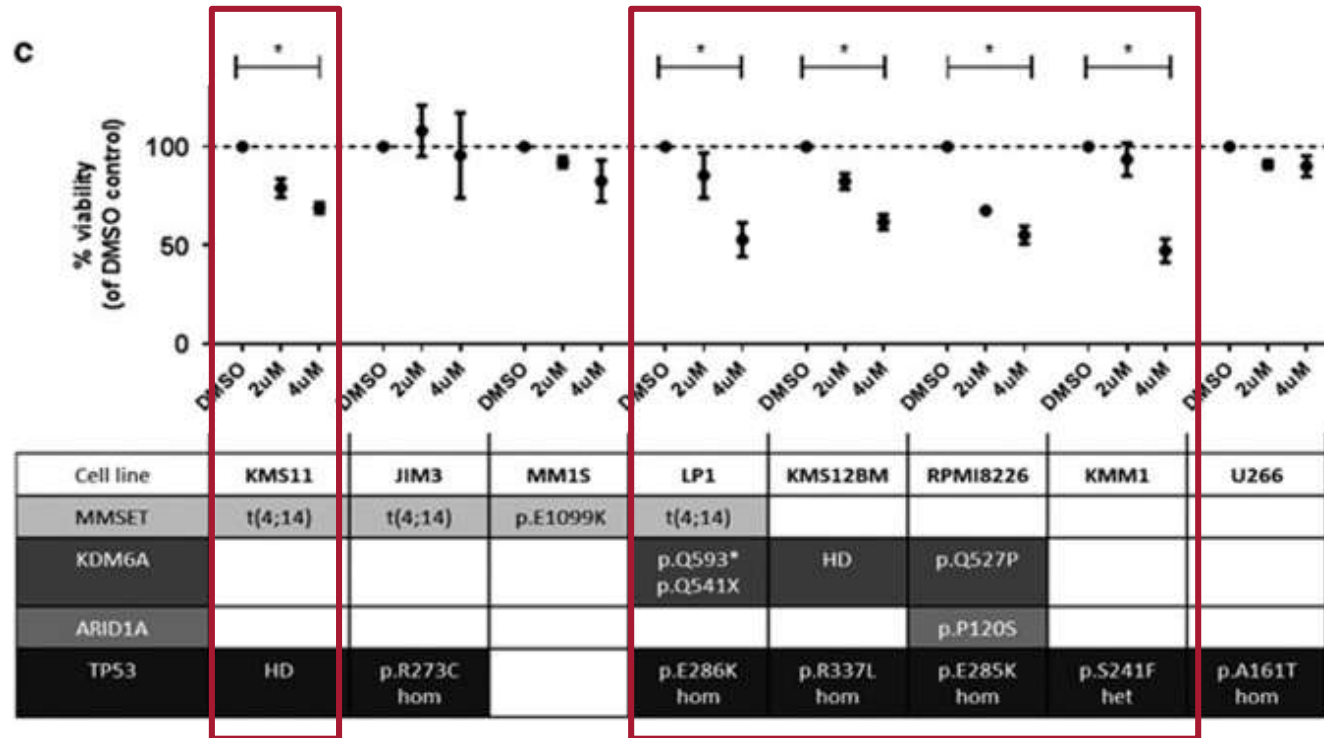
Histone modification

EZH2

H3K27me3 methyltransferase

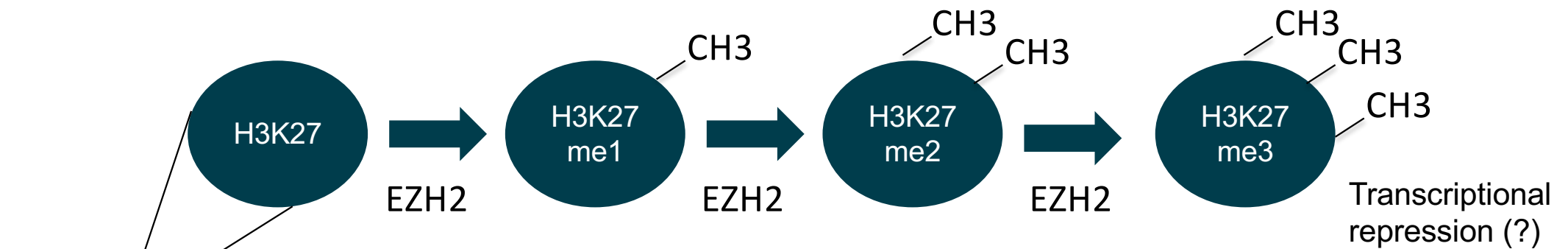


Histone modification

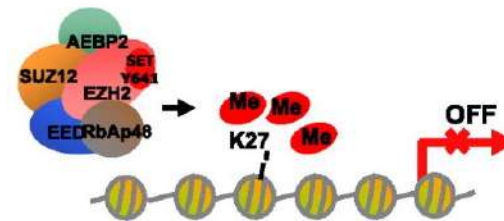


EZH2 inhibition led to upregulation of cell cycle control genes, cell cycle arrest and apoptosis

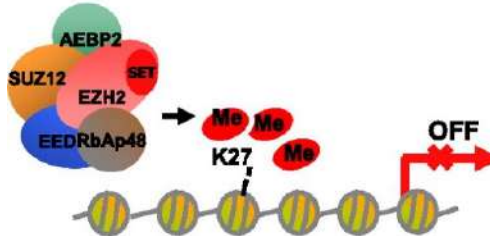
Increased H3K27me3



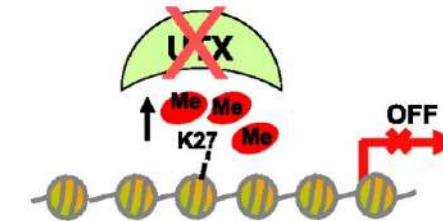
A *EZH2* Mutation



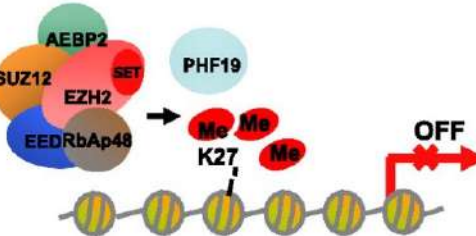
B *EZH2* overexpression



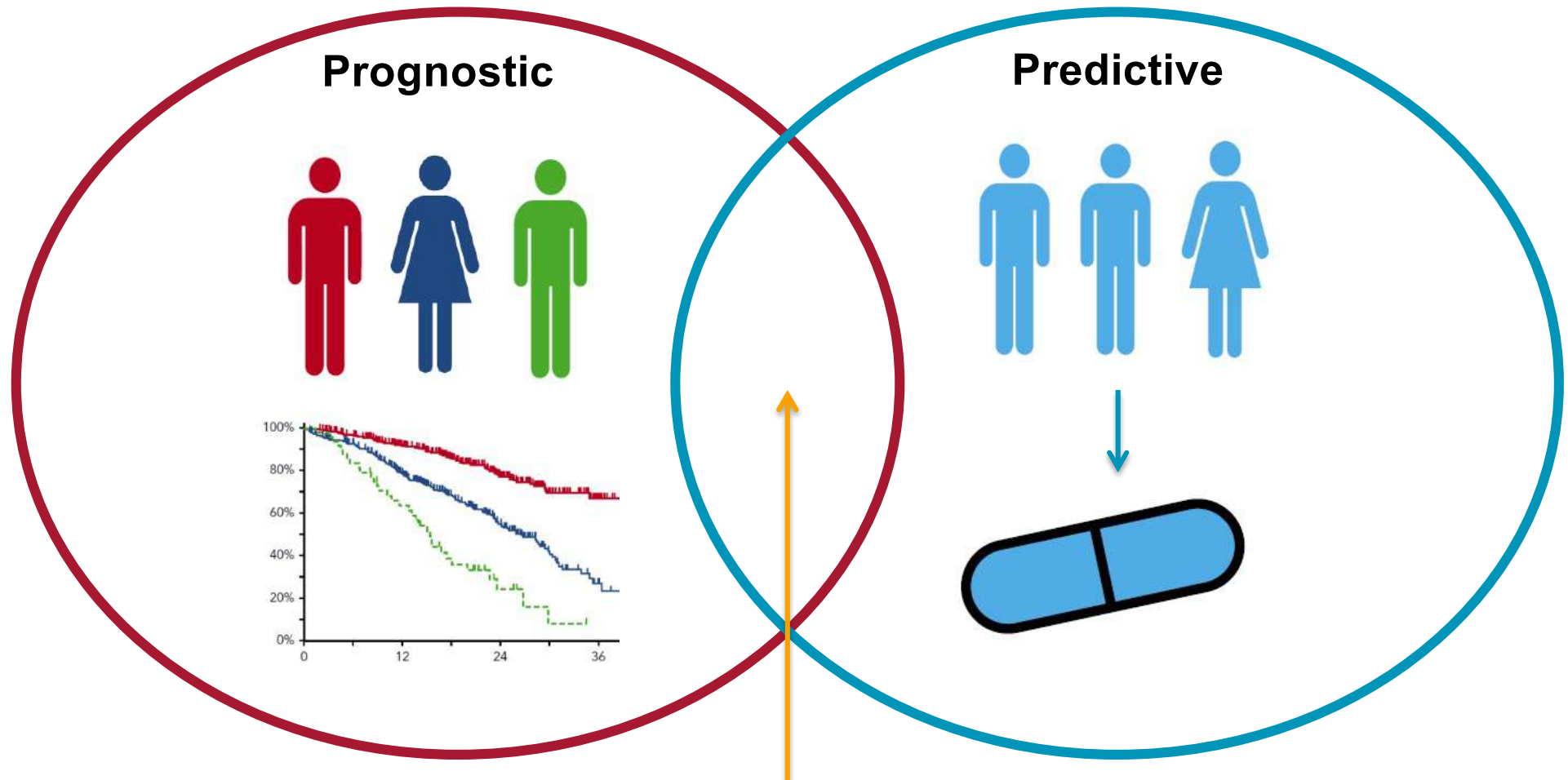
C *KDM6A/UTX* mutation



D *PHF19/PCL3* overexpression



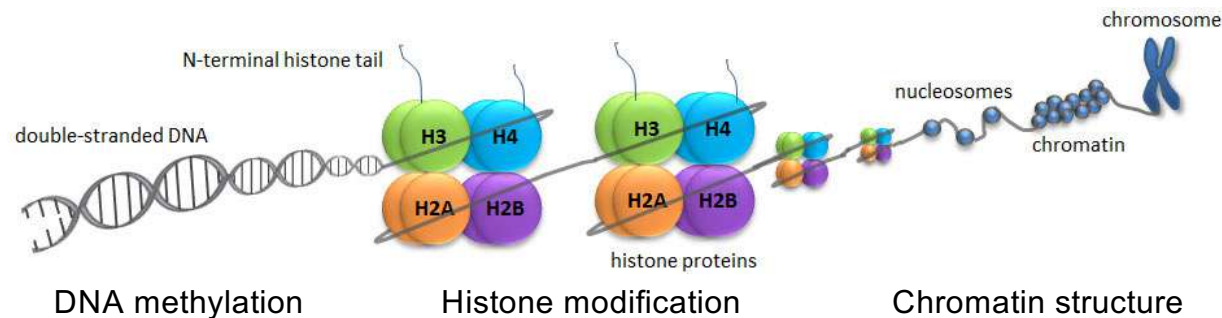
Biology-based drive to improve outcome for high-risk



Ideal targets: MMSET, MAF, Myc....SETD2, EZH2, PHF19??

Summary

- Epigenetics refers to the structure and packaging of DNA within a cell which can alter how the genetic code is interpreted.
- Epigenetic modifications regulate the process of normal B-cell development and plasma cell differentiation and several epigenetic changes are implicated in myeloma pathogenesis.



- Key epigenetic factors that may be possible targets in myeloma include IDH2, DNMT3A/B, MMSET (WHSC1/NSD2), SETD2 and the PRC2 complex (EZH2/PHF19). (but not only these!)
- Targeting biomarkers that are both prognostic and predictive is likely to improve outcomes for patients with high-risk myeloma fastest.



**If they ask you anything you don't know, just
say it's due to epigenetics.**