

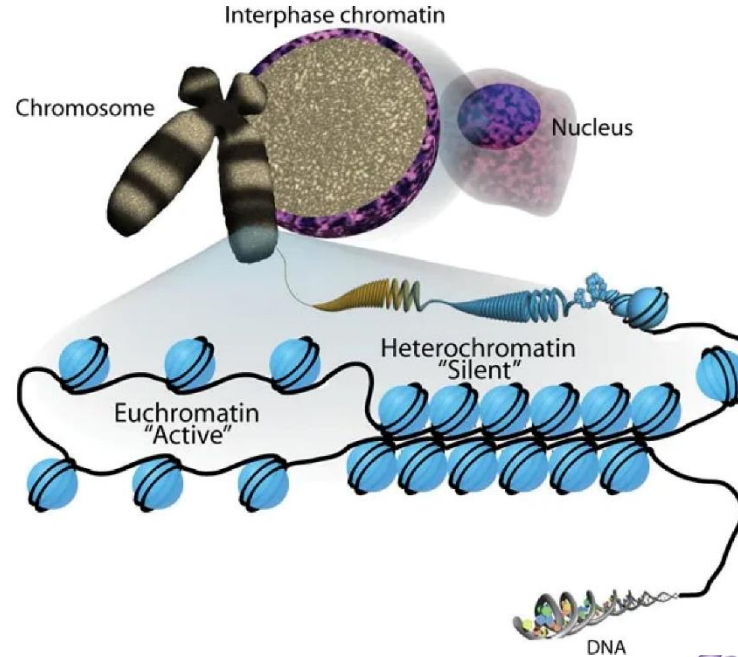
# **Structural study of epigenetic regulation**

**Jikui Song**

**Department of Biochemistry  
University of California, Riverside**

**10/23/2024**

# Heterochromatin vs Euchromatin

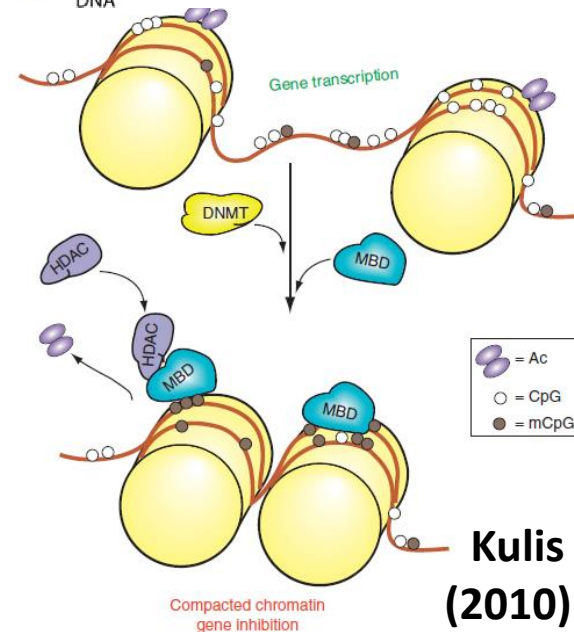
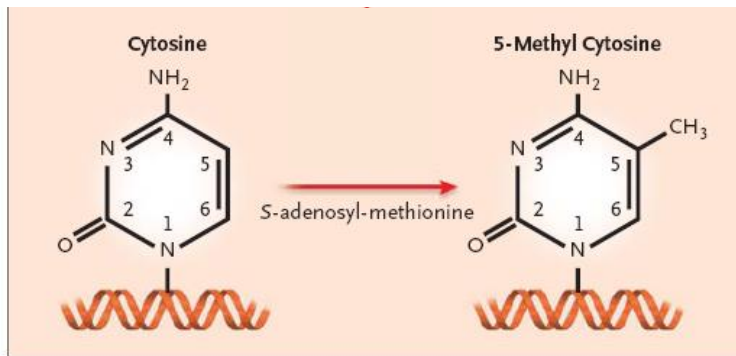


## Euchromatin

- Low DNA density
- Hyper-acetylation
- H3K4me3, H3K36me3
- Low DNA methylation

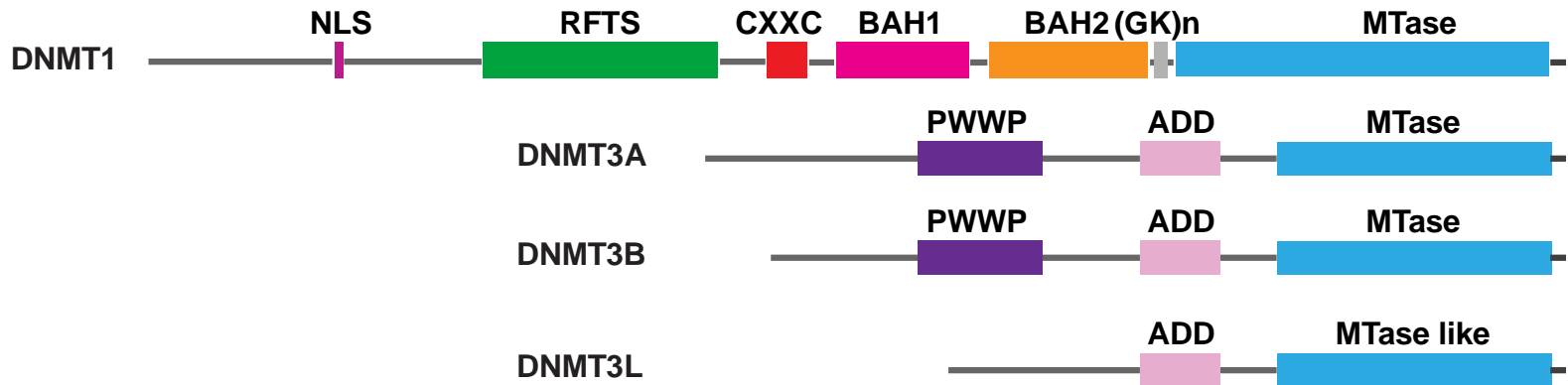
## Heterochromatin

- High DNA density
- Hypo-acetylation
- H3K9me3, H4K20me3, HP1
- High DNA methylation

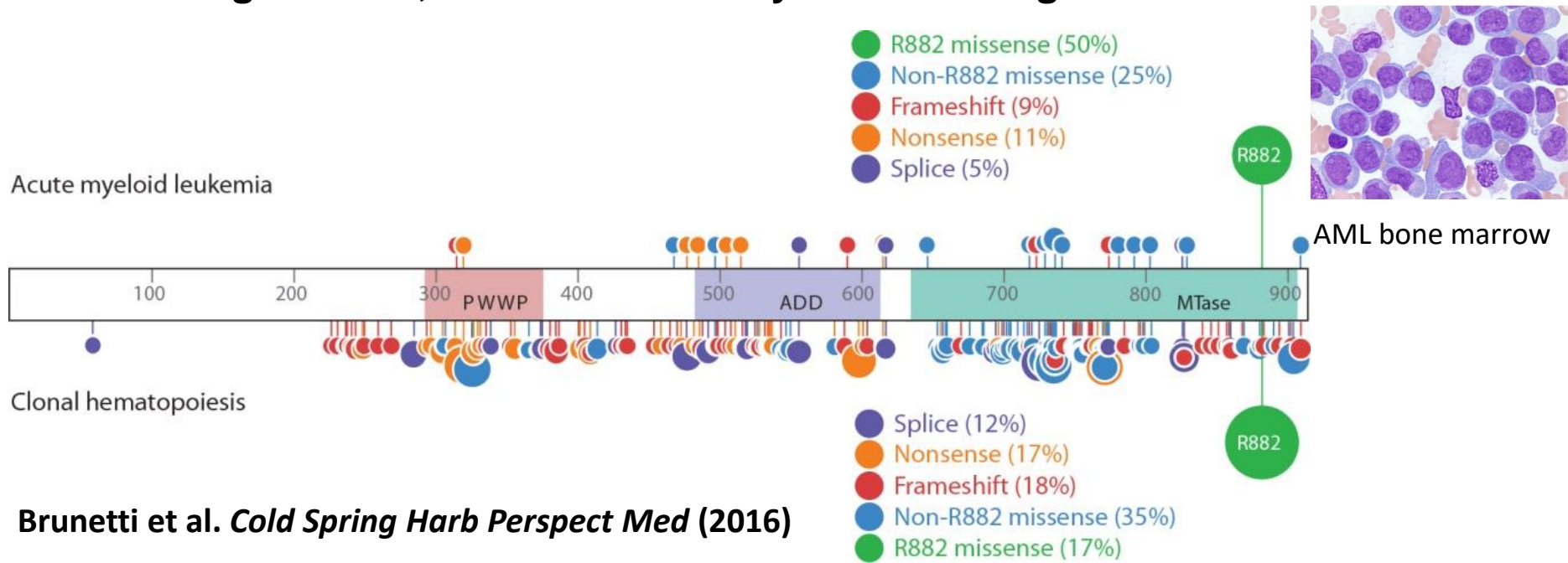


**Kulis & Esteller  
(2010) Adv Genet**

# Mammalian DNA methyltransferases (DNMTs)



Dysregulation of DNMTs have been linked to a variety of human diseases, including cancers, immunodeficiency and neurological disorder

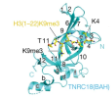
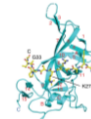


# Mechanistic study of DNA/histone methylation by X-ray crystallography



R35GM119721

## Histone methylation

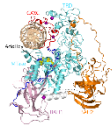


BAHCC1-H3K27me3 TNRC18-H3K9me3

Fan et al. *Nat Genet.* (2020)

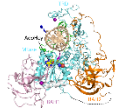
Zhao et al. *Nature* (2023)

## Maintenance DNA methylation



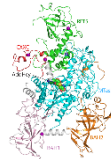
DNMT1-CpG

Song et al. *Science.* (2011)



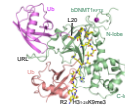
DNMT1-mCpG

Song et al. *Science.* (2012)



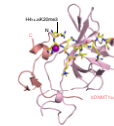
Apo DNMT1

Zhang et al. *JMB.* (2015)



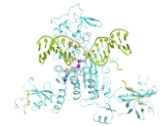
DNMT1-H3K9me3/H3ub

Ren et al. *PNAS* (2020)



DNMT1-H4K20me3

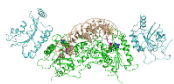
Ren et al. *Nat Commun* (2021)



ZMET2-DNA

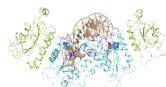
Fang et al. *Nat Commun* (2022)

## De novo DNA methylation



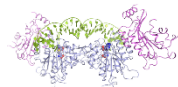
3A-3L-DNA

Zhang et al. *Nature* (2018)



3B-3L-DNA

Gao et al. *Nat Commun* (2020)



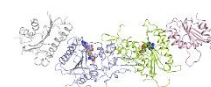
3A<sup>R882H</sup>-3L-DNA

Anteneh et al. *Nat Commun* (2020)



3B Polymer

Gao et al. *Nat Commun* (2022)



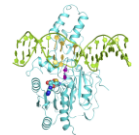
3A<sup>R882H</sup>

Lu et al. *Nat Commun* (2024)



3C-3L

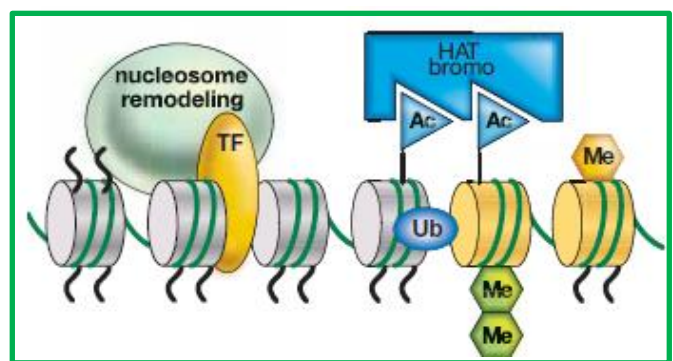
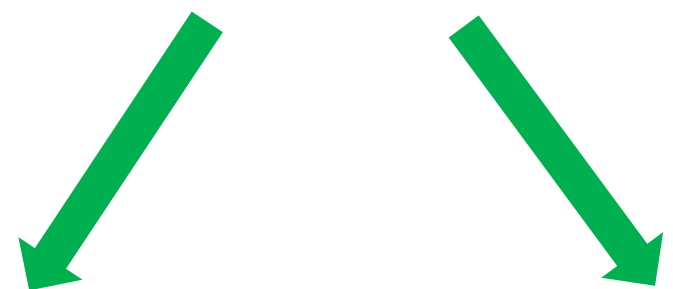
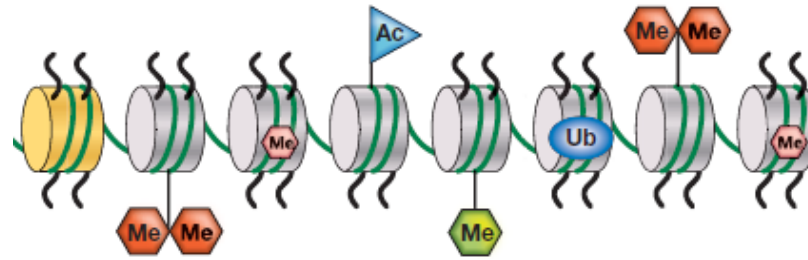
Khudaverdyan et al. (2024)



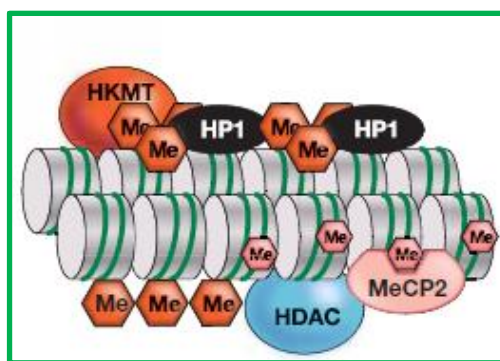
DRM2-DNA

Fang et al. *Sci Adv* (2021)

# Structural study of epigenetic regulation at nucleosome level



Actively transcribed region  
(Euchromatin)



Transcription repressed region  
(Heterochromatin)

# Cryo-EM structural study of epigenetic regulation at UC Riverside

## Opportunities

- *In vitro* reconstitution of epigenetically modified nucleosome has been well established
- Conformational heterogeneity of epigenetic complexes
- Low sample yield

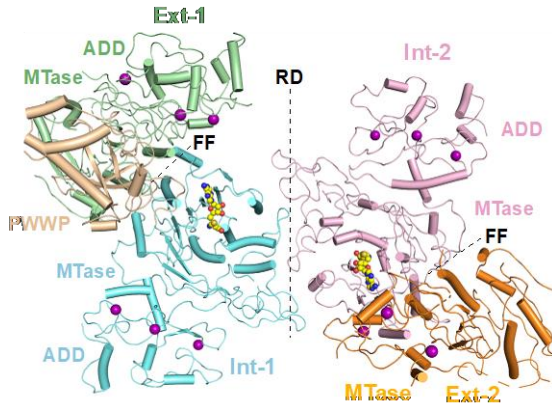
## Challenges

- The EM facility at UC Riverside lacks a capacity for cryo-EM data collection
- Limited access to the cryo-EM facilities of local institutes

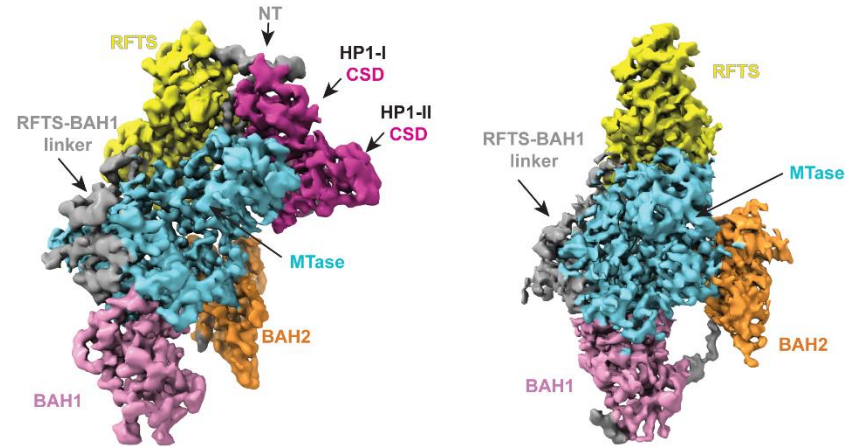


Talos120

# Published cryo-EM structural work from the Song lab in collaboration with National Cryo-EM Facility (NCEF)



DNMT3B homo-oligomeric assembly  
Lu et al. *Nucleic Acids Res* (2023)

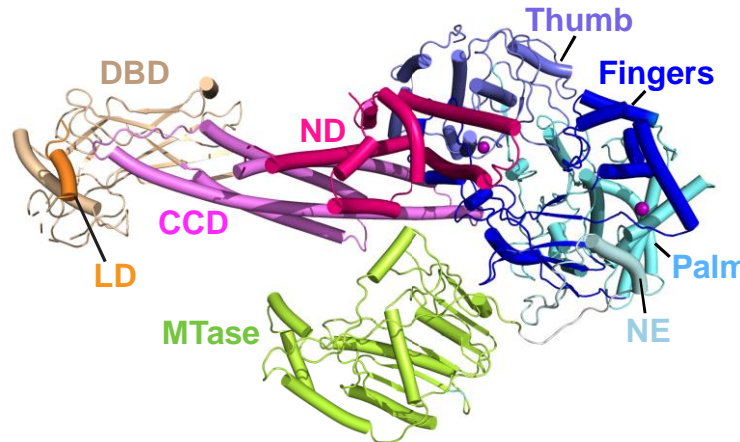


Heterochromatin regulation of DNA methyltransferase DIM2, homologue of human DNMT1  
Shao et al. *Nat Commun.* (2024)

**Overexpression of DNMT3B and DNMT1 have been associated with cancers**



NCEF team

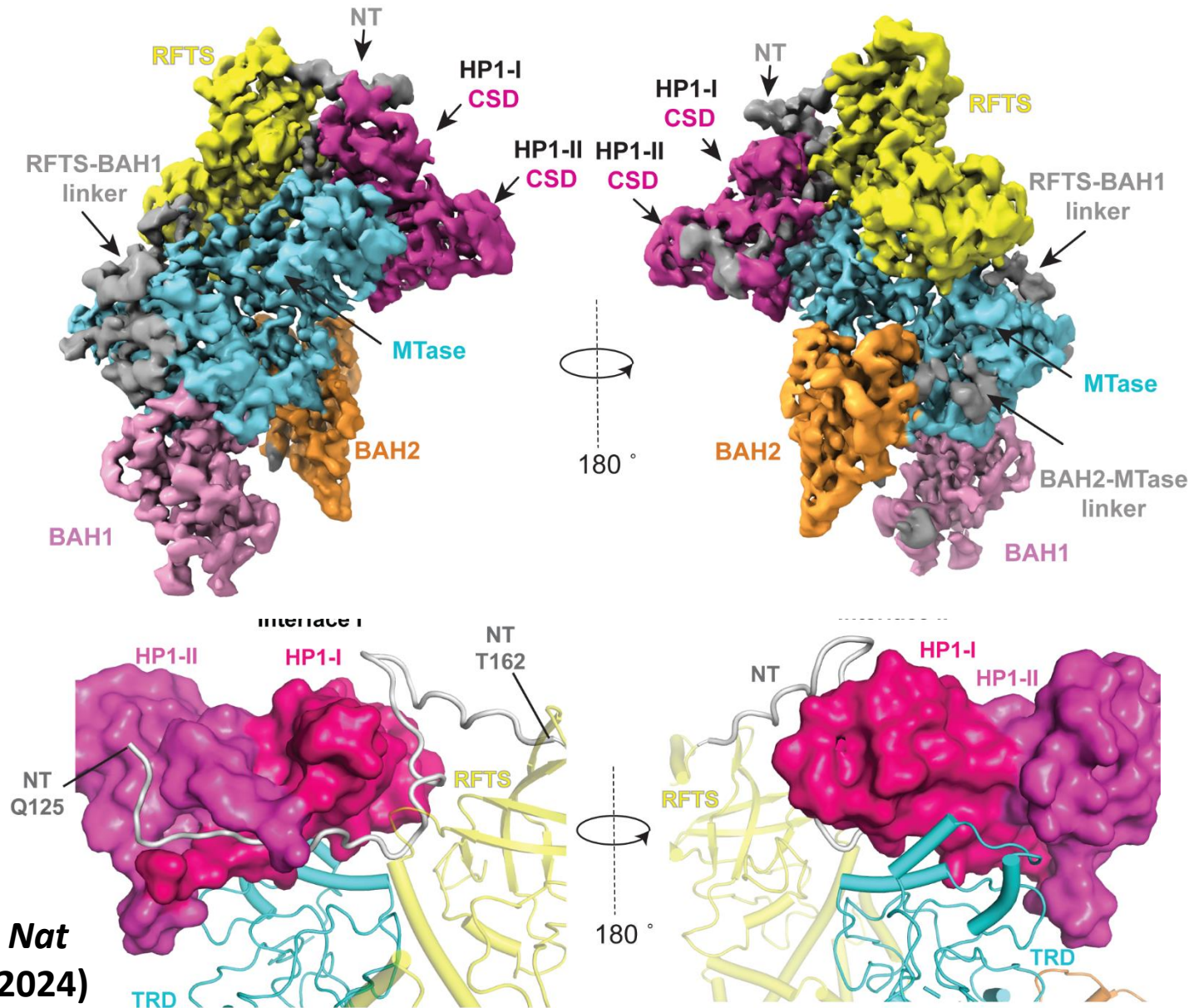


DENV2 NS5 – hSTAT2 complex  
Biswal et al. *Commun. Biol* (2024)

**hSTAT2 regulates antitumor immunity**

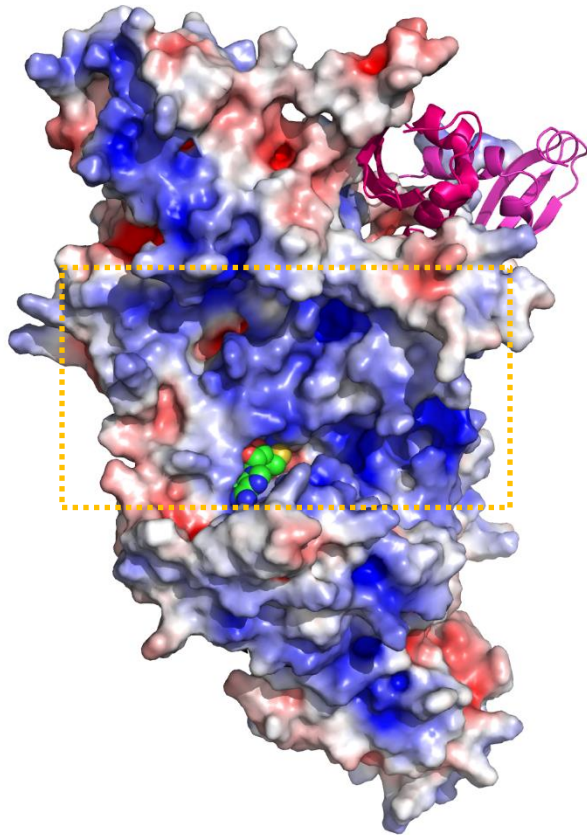
More to come!

# Structure of the DIM2 - HP1 complex

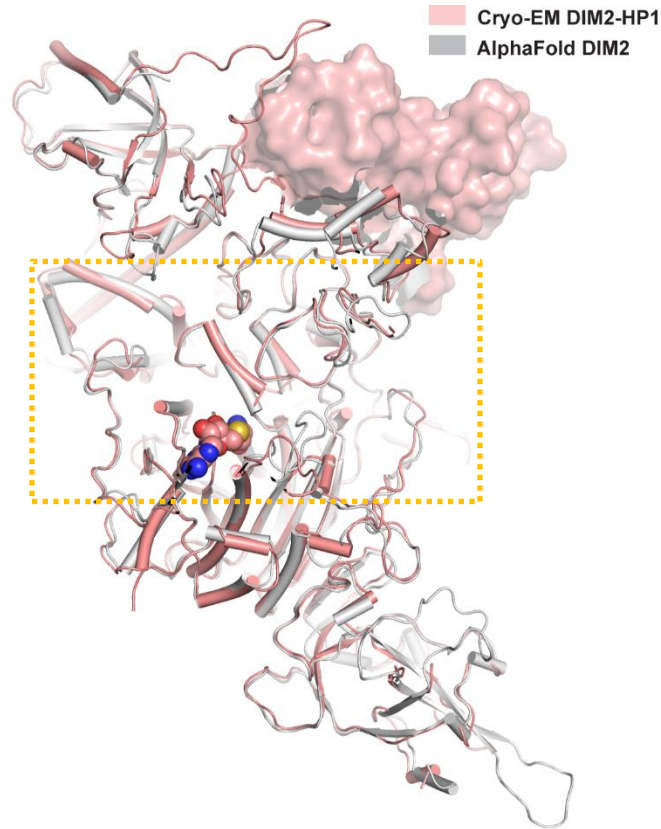




# Functional regulation of DIM2 by HP1

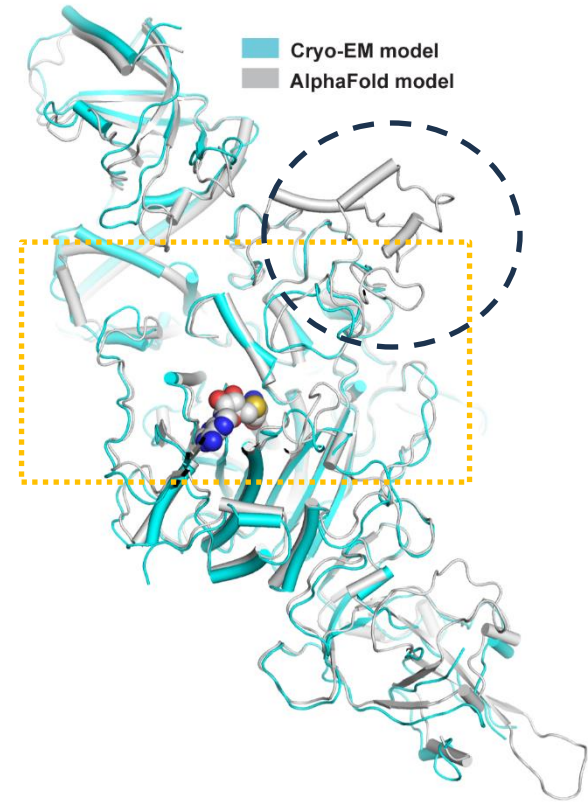


**DIM2-HP1**



**DIM2-HP1**

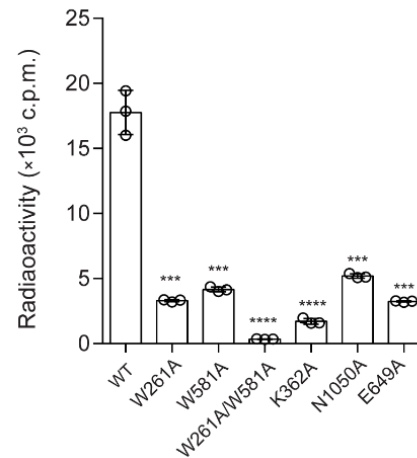
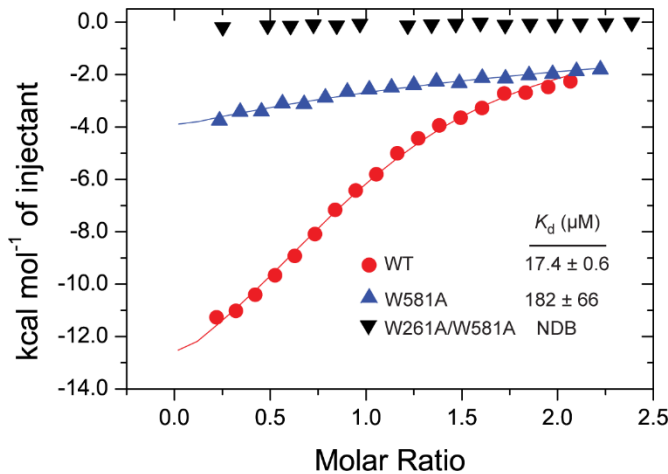
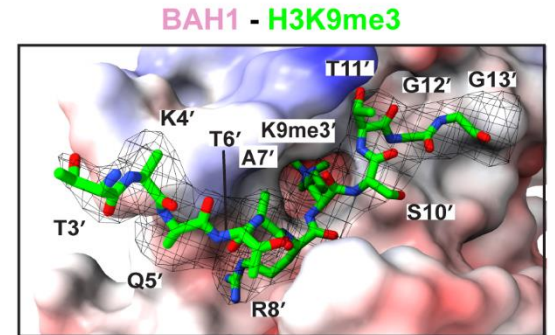
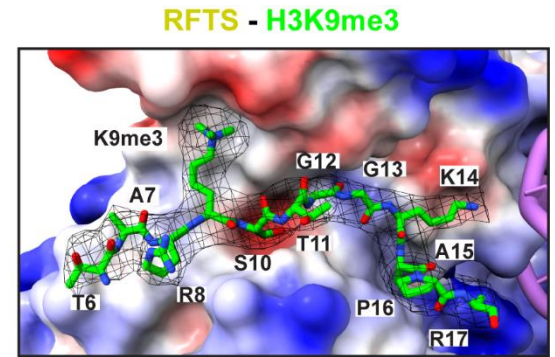
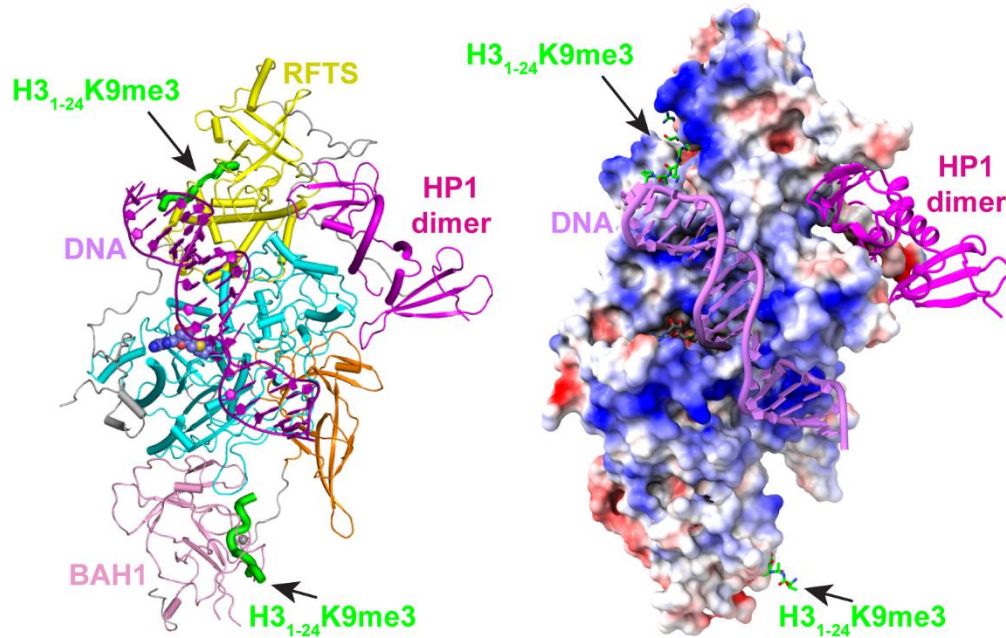
Apo-DIM2 (AlphaFold)



**Apo-DIM2 (Cryo-EM)**

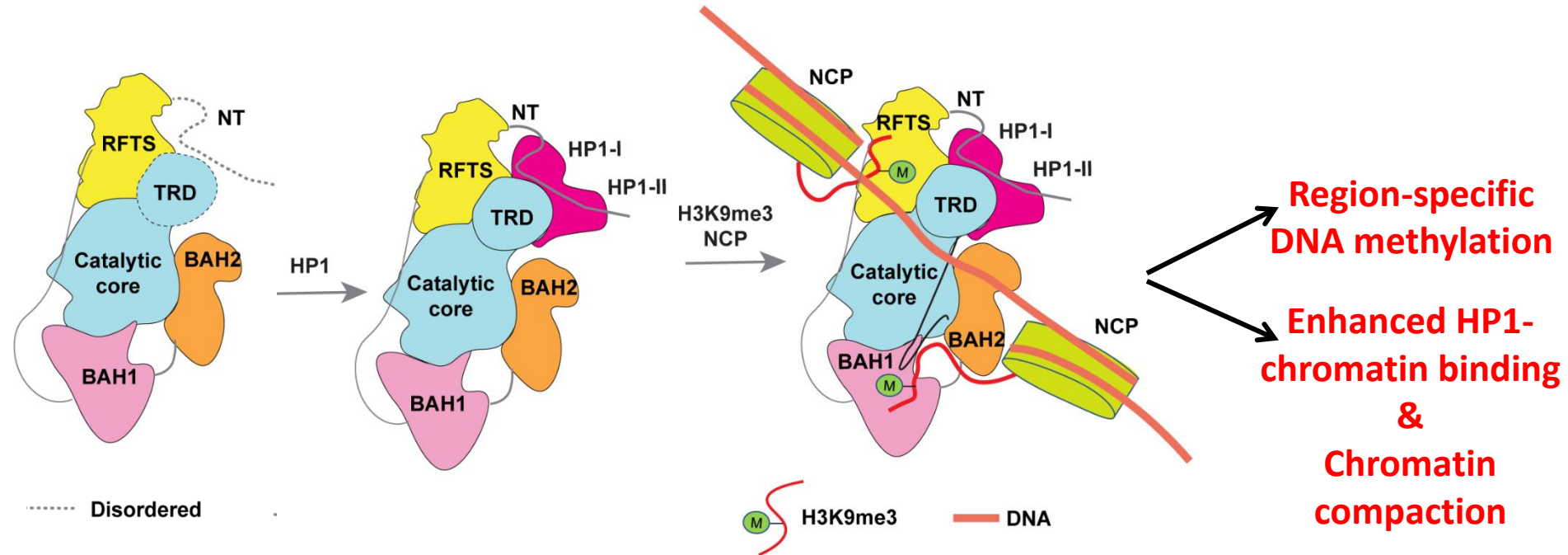
Apo-DIM2 (AlphaFold)

# Allosteric regulation DIM2 by H3K9me3

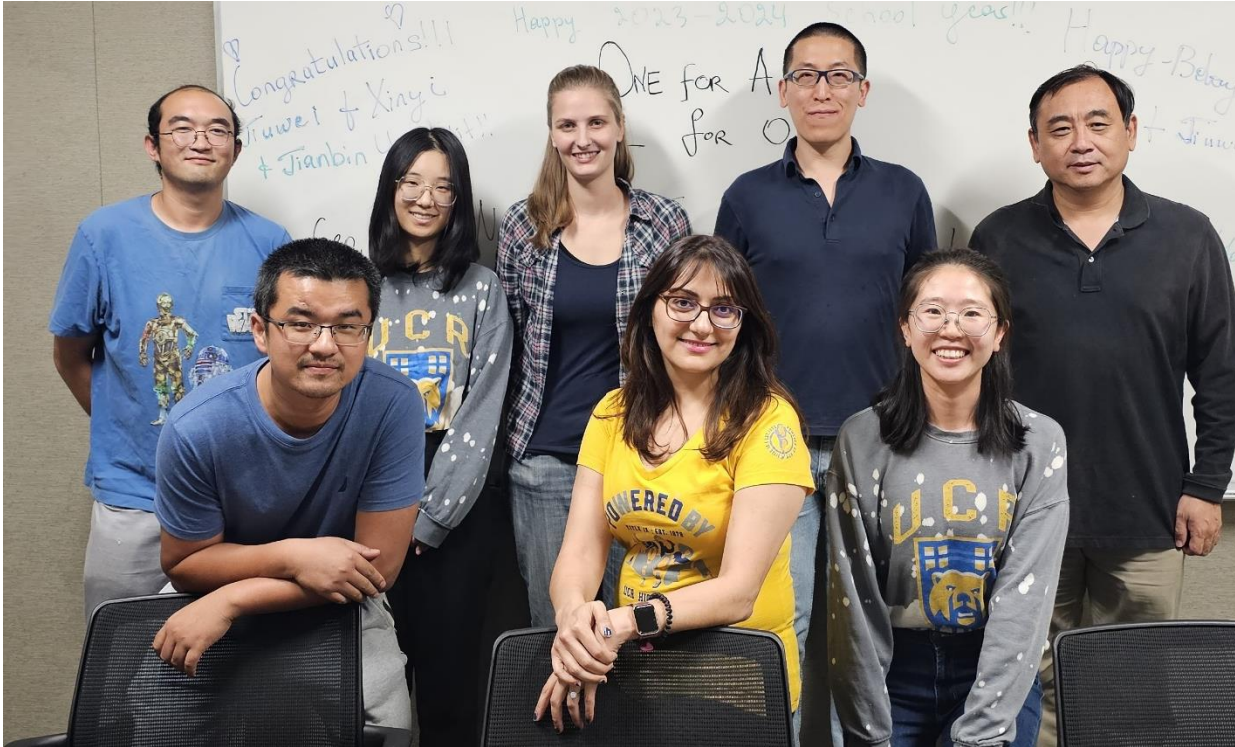


Shao et al. *Nat Commun* (2024)

# Multi-layered heterochromatin interaction as a switch for DIM2-mediated DNA methylation



# Acknowledgements



## **Song Lab**

Jianbin Chen

Xinyi Chen

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Linfeng Gao

Wendan Ren

Zhi-Min Zhang

Hiwot Anteneh



**NCEF Team!**