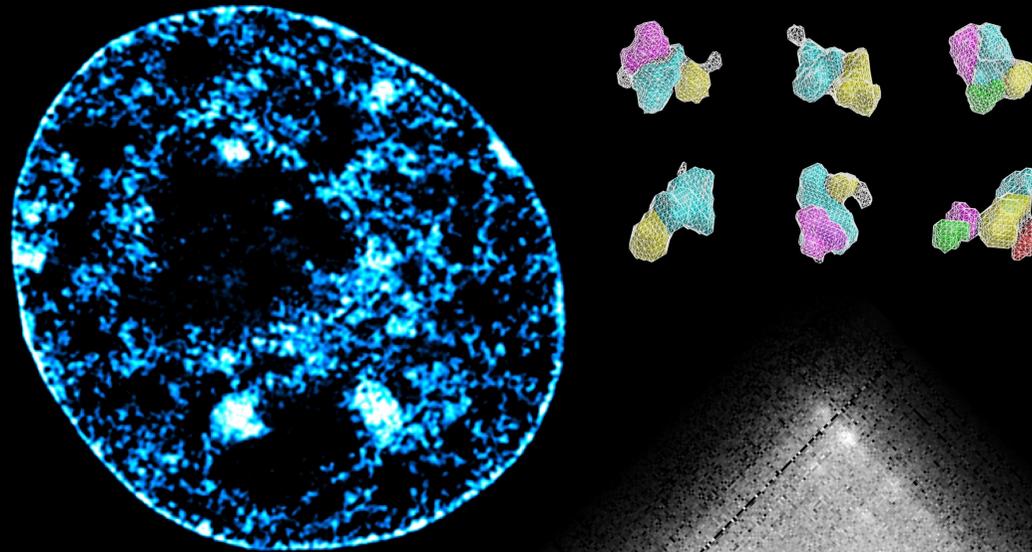


# The role of histone acetylation in sub-megabase chromatin folding

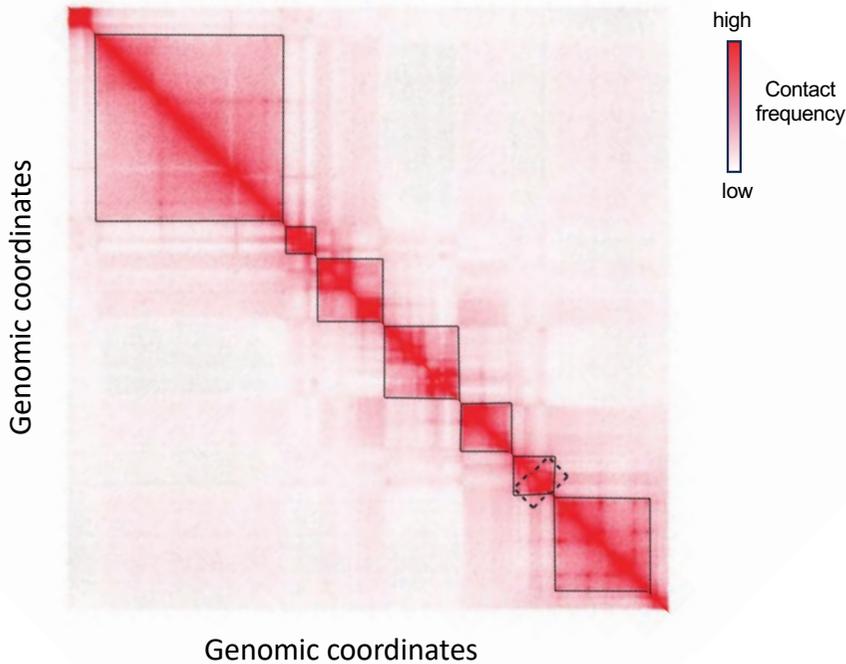


Frédéric Bantignies / Cavalli lab

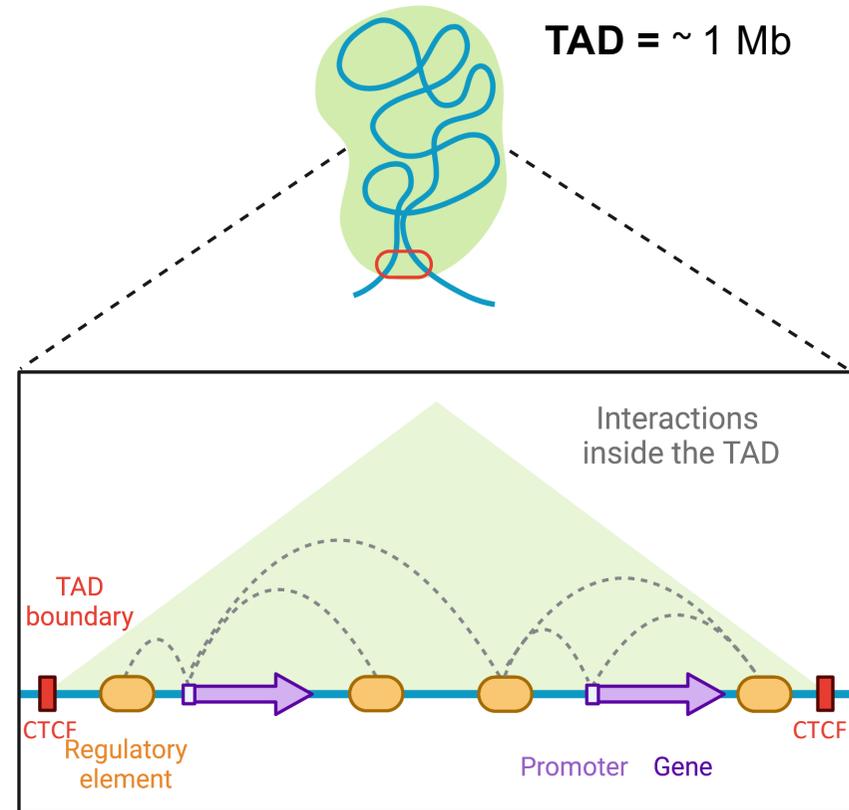
GdR ADN&G, Lyon, May 30 - 31 2024

# Topologically Associating Domain or TAD

Cell population in situ Hi-C  
Contact density map



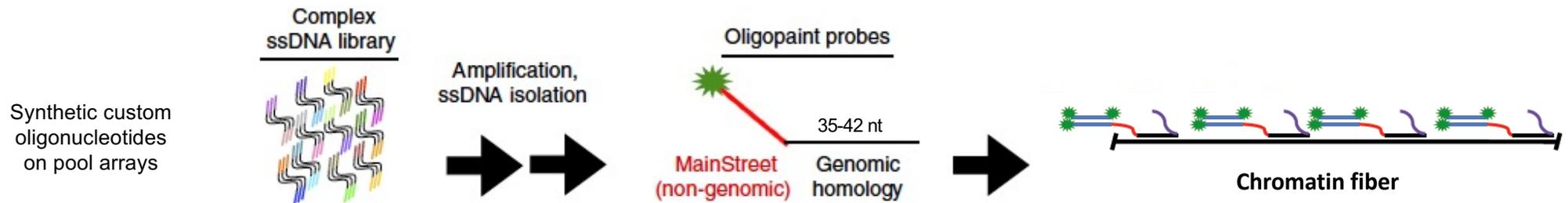
Hi-C map from Human GM12878  
B-lymphoblastoid cells



➤ TAD organization in single cell ?

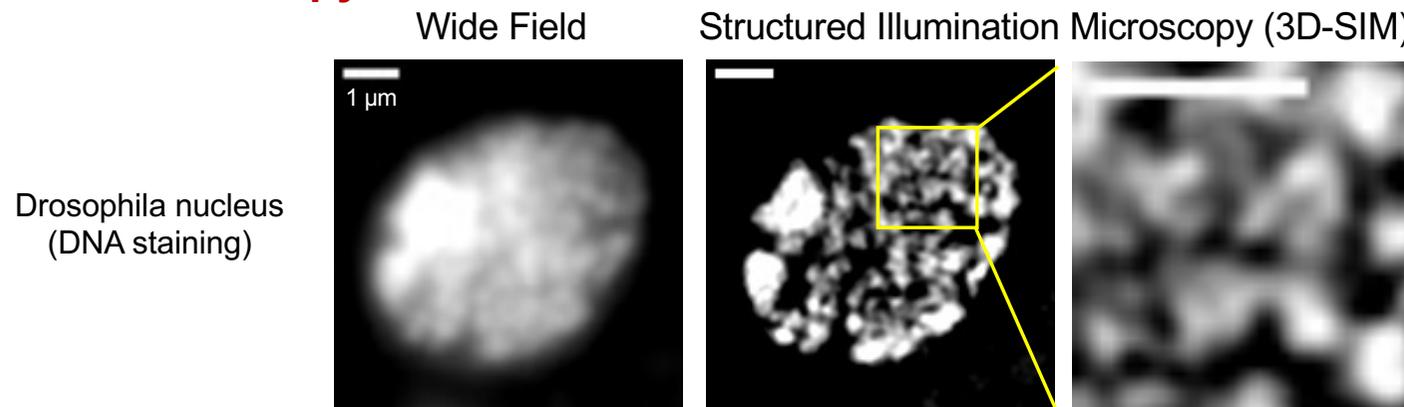
# TAD organization in single-cell

## ❖ FISH with Oligopaint



Beliveau *et al.*, Nature communications 2015; Beliveau *et al.*, PNAS 2018  
<https://oligopaints.hms.harvard.edu> & <https://paintshop.io>

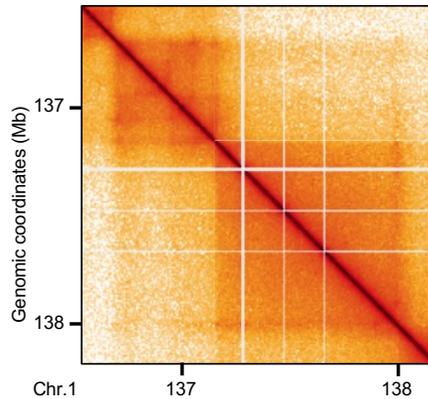
## ❖ Super-resolution microscopy



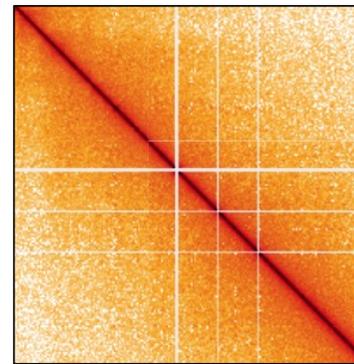
➤ Resolution: approx. 120 nm (2 times more than a regular confocal/ 8 times if we consider the z -axis)

Oligopaint probes

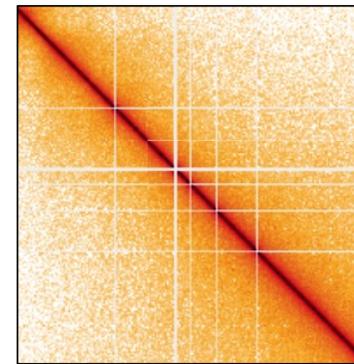
within TAD  
between TADs



WT mESC



CTCF-AID  
+ Auxin



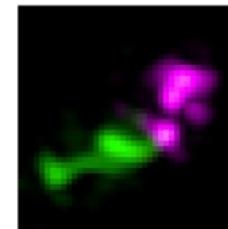
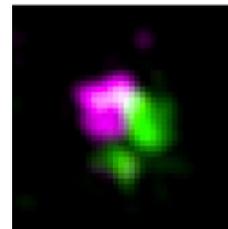
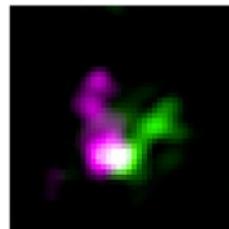
RAD21-AID  
+ Auxin

Micro-C

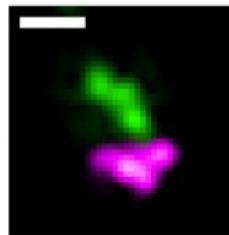
CTCF

Cohesin/RAD21

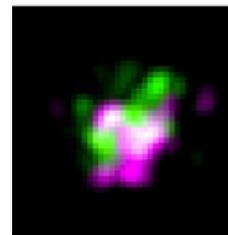
within TAD  
102a-102b



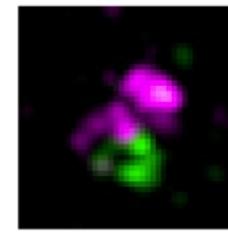
between TADs  
101-102a



Scale bar: 500 nm



> More intermingling  
between adjacent TADs

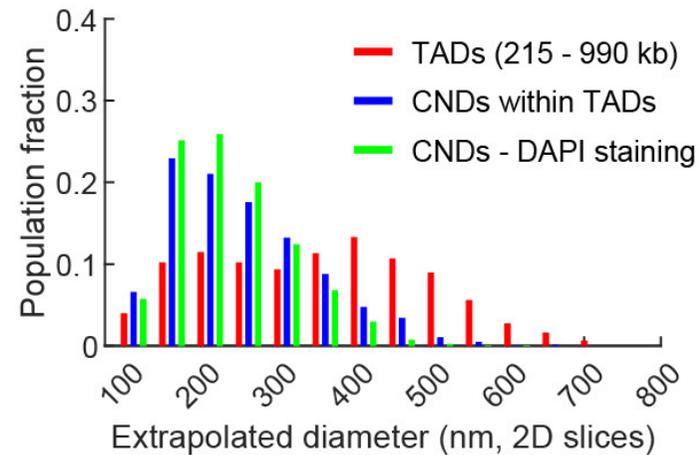
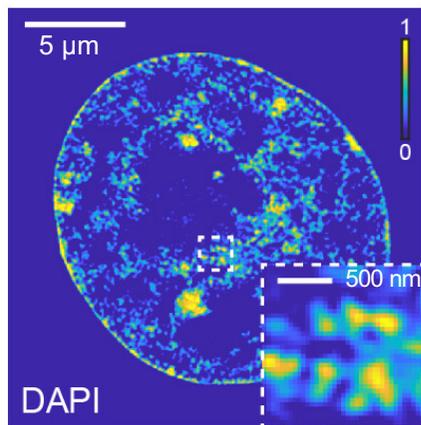
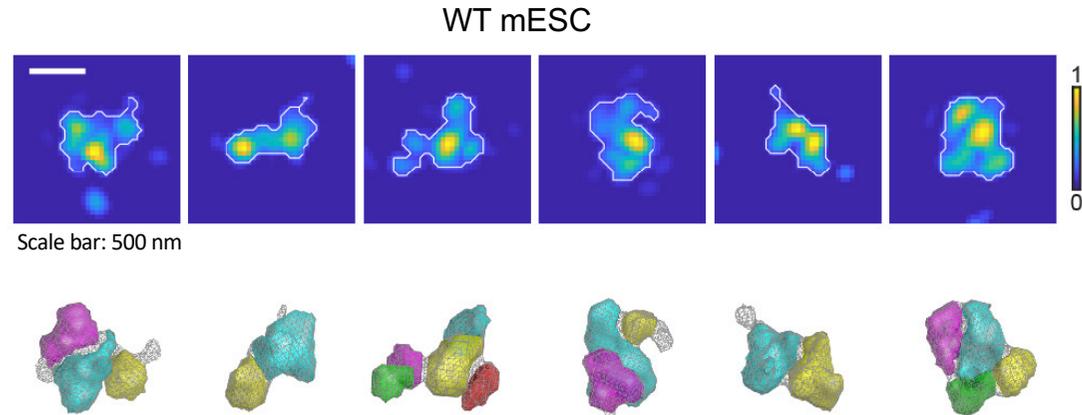
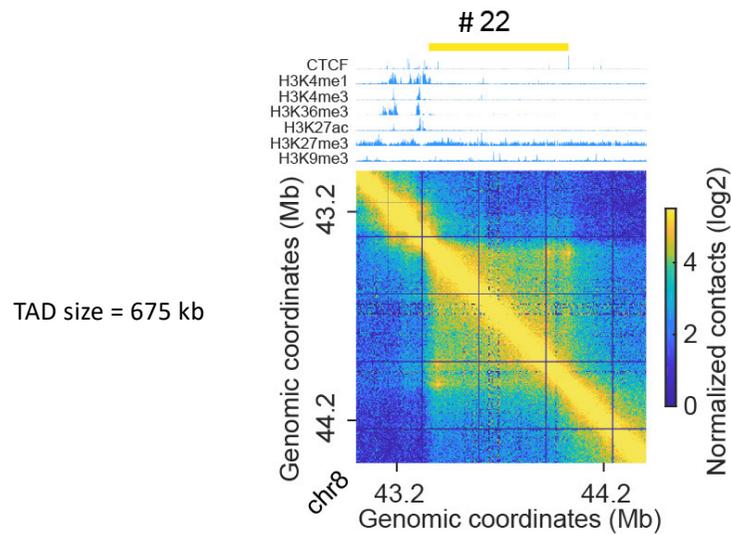


> Less folding/interactions  
inside TAD

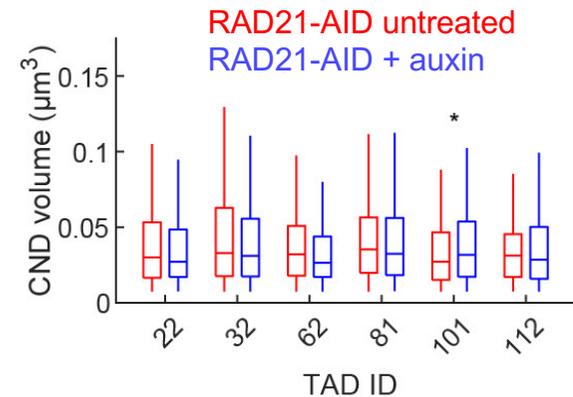
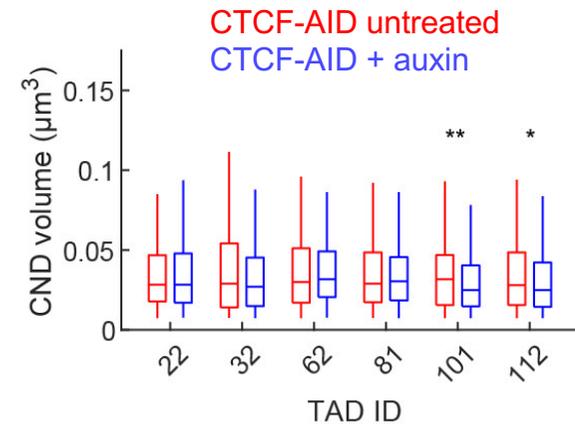
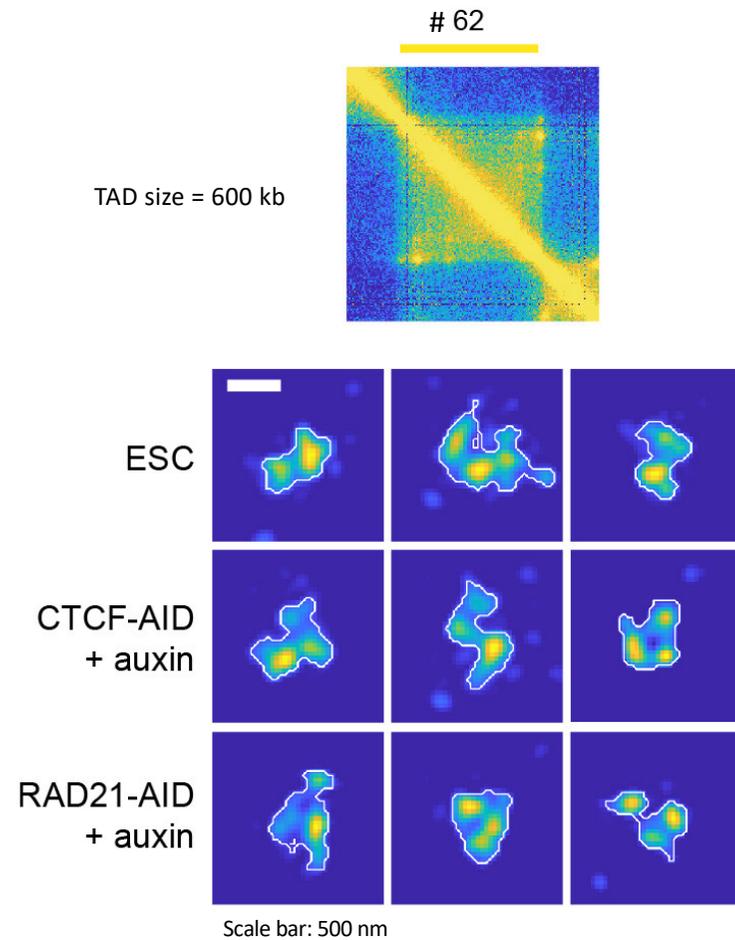
3D-SIM

Szabo *et al.*, Nature Genetics 2020

# TADs are subdivided into discrete Chromatin NanoDomains or CNDs



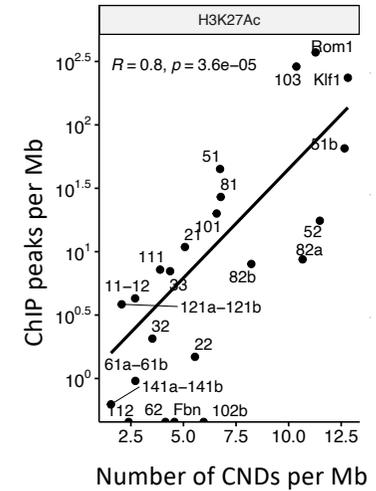
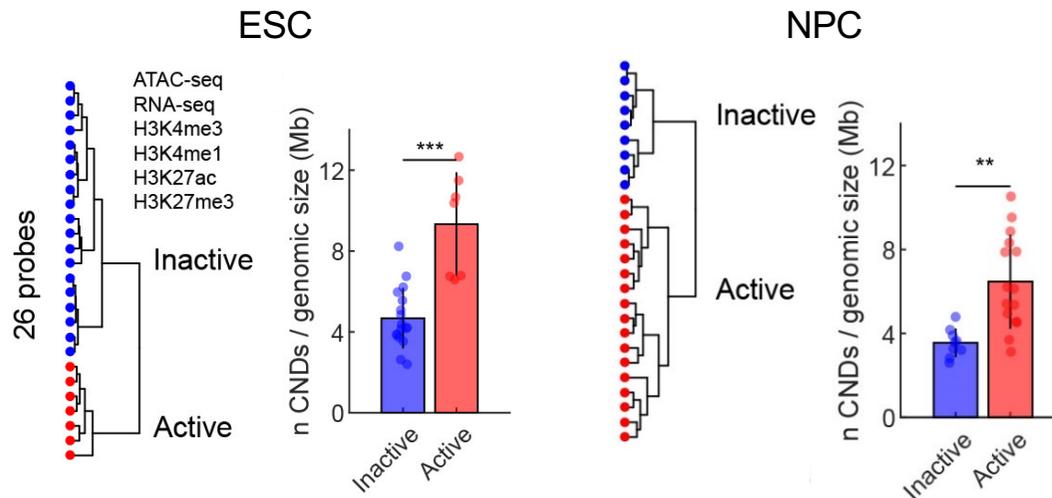
# CNDs persist in cells depleted for CTCF or Cohesin



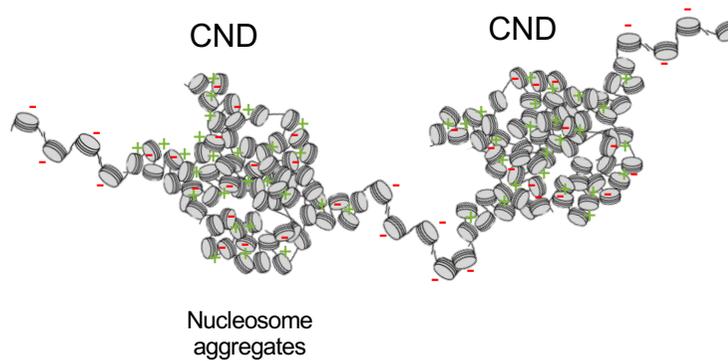
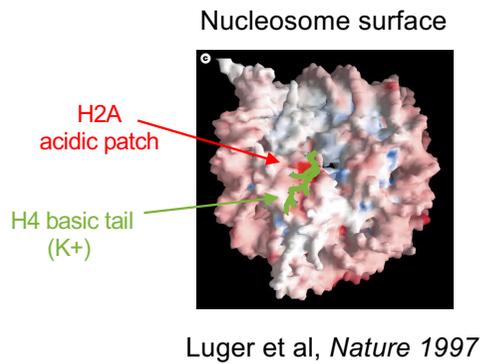
➤ **A different mechanism is involved in CND formation**

# CND folding depends on chromatin state

Epigenetic mark Clusters:  
Inactive vs. Active



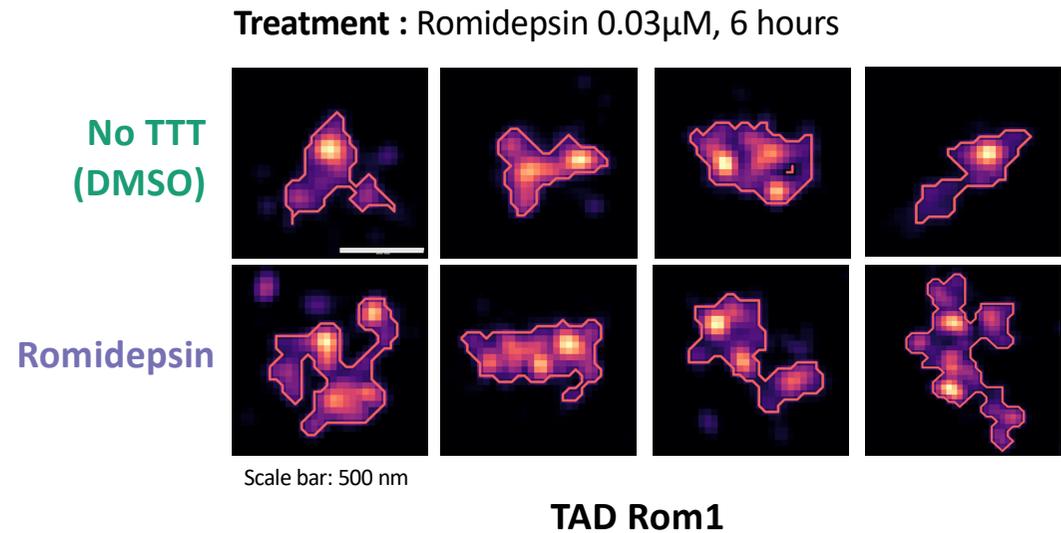
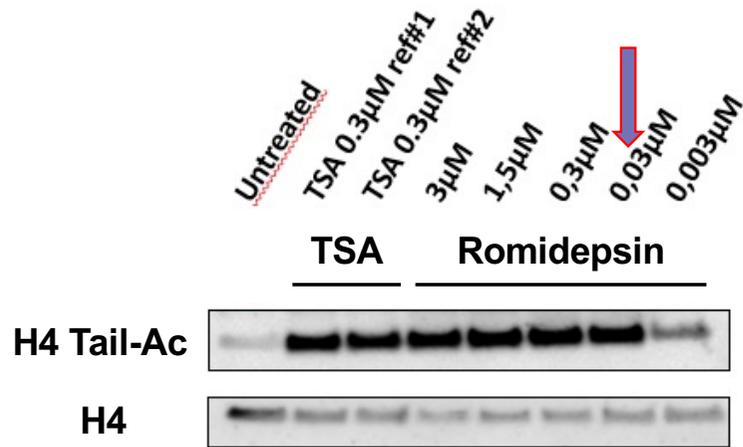
## Role of Histone Acetylation ?



➤ **Acetylation**, by neutralizing the + charge of Lysine residues, would prevent nucleosome-nucleosome interactions, and may play an important role in this chromatin organization.

# CNDs depend on histone acetylation – effect of global hyperAcetylation

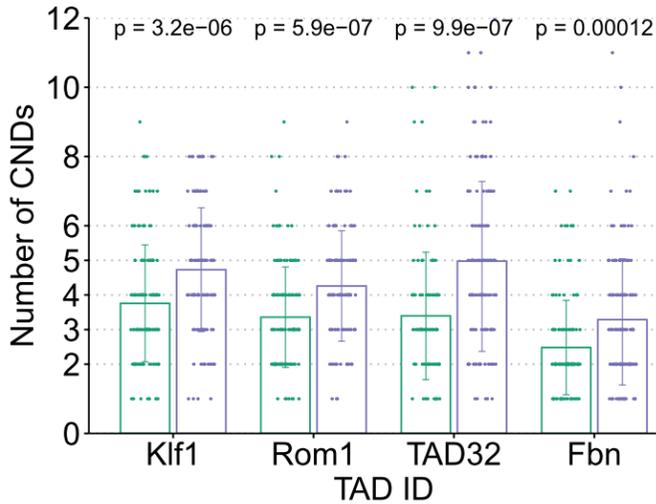
- ❖ **Romidepsin**, a potent inhibitor of nuclear HDACs (specific of Class I HDACs 1, 2 and 3)



# CNDs depend on histone acetylation – effect of global hyper-Acetylation

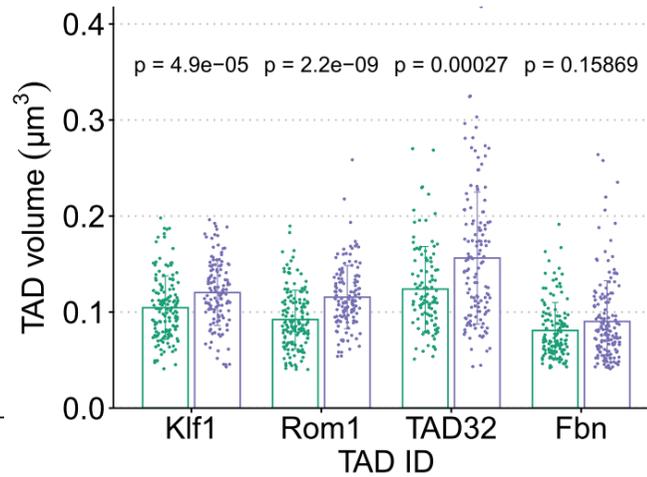
**CNDs per TAD**

■ NoTTT 
 ■ Romi

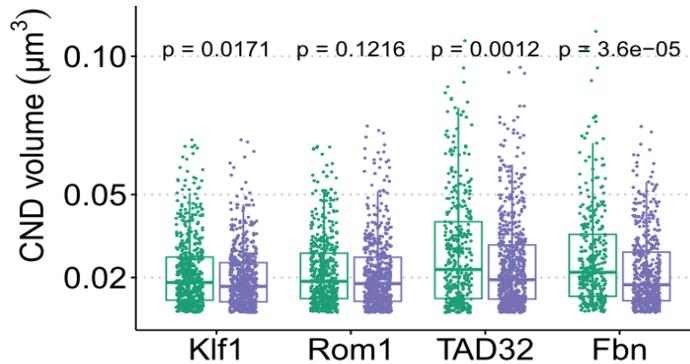


**TAD volume**

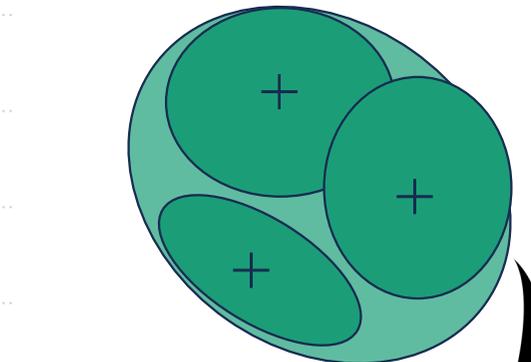
■ NoTTT 
 ■ Romi



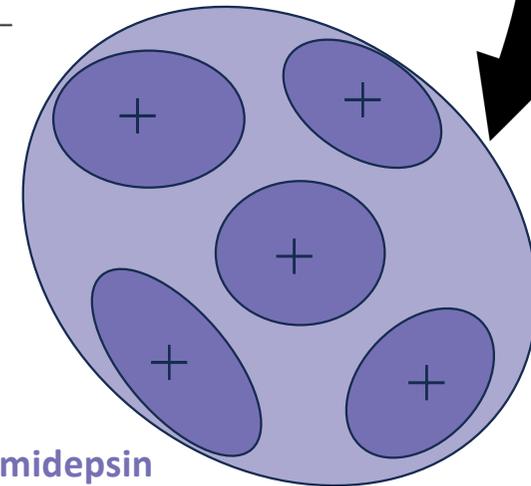
**CND volume**



**No Treatment**



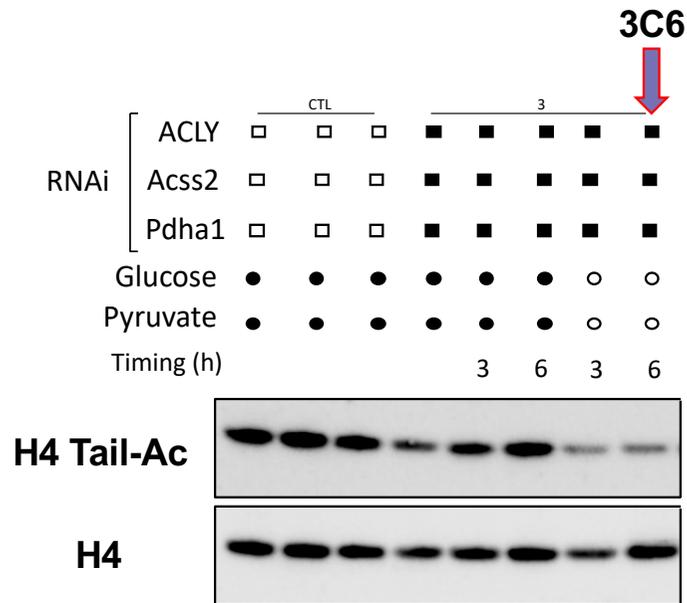
**Global HyperAcetylation**



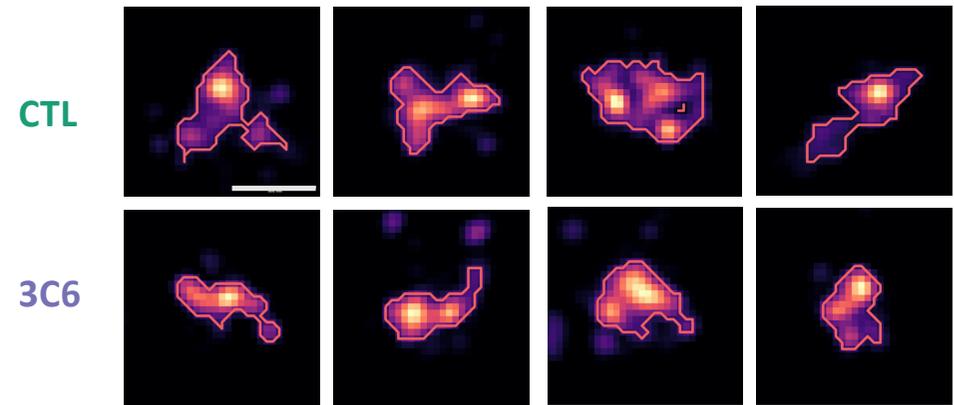
**Romidepsin**

# CNDs depend on histone acetylation – effect of global hypo-Acetylation

❖ Inhibition of Acetyl-CoA metabolism, the substrate for histone acetylation



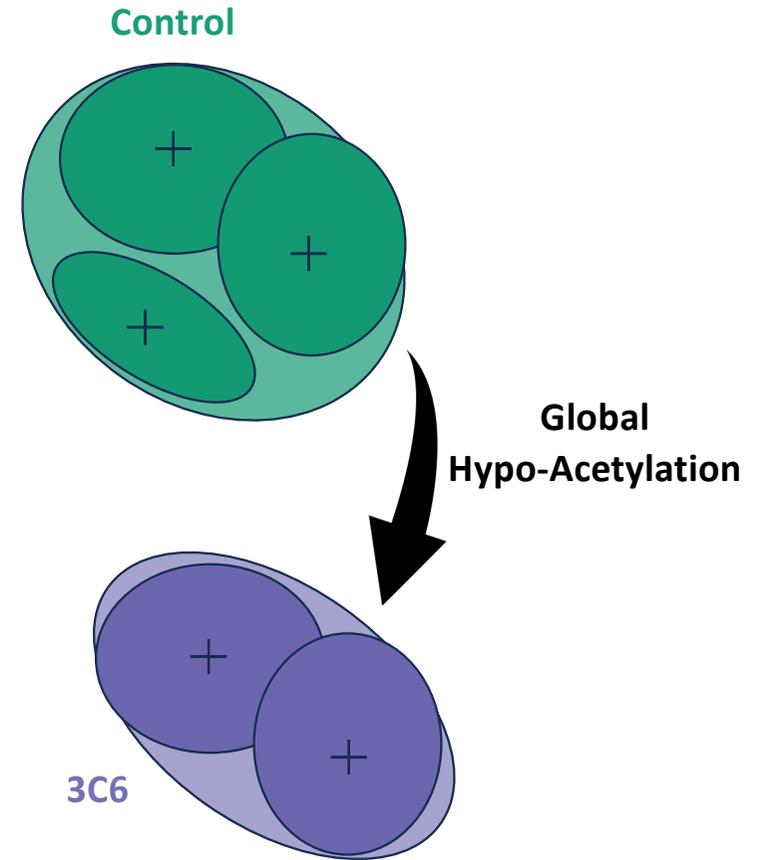
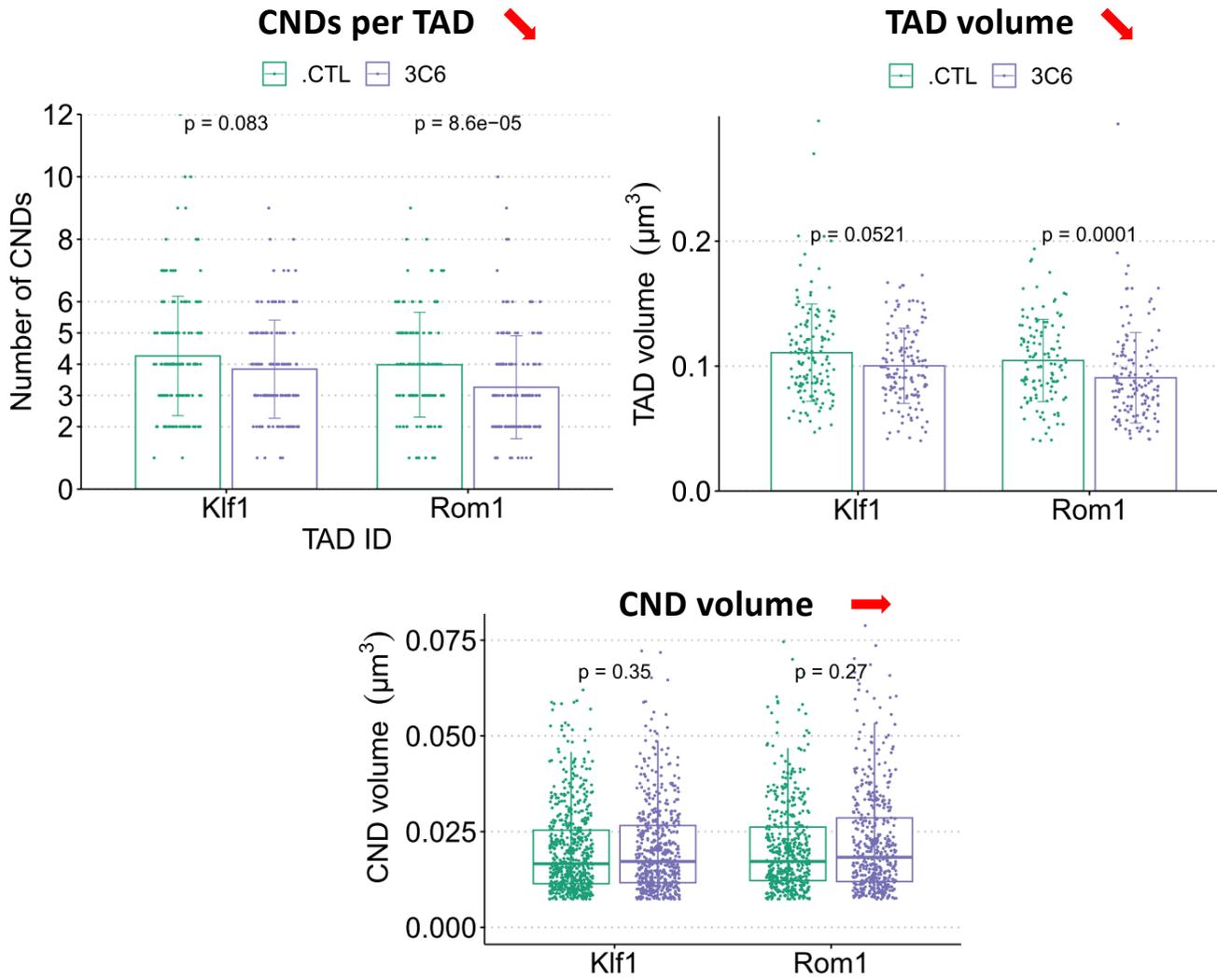
Treatment : Acetyl-CoA pool reduction, 3C6



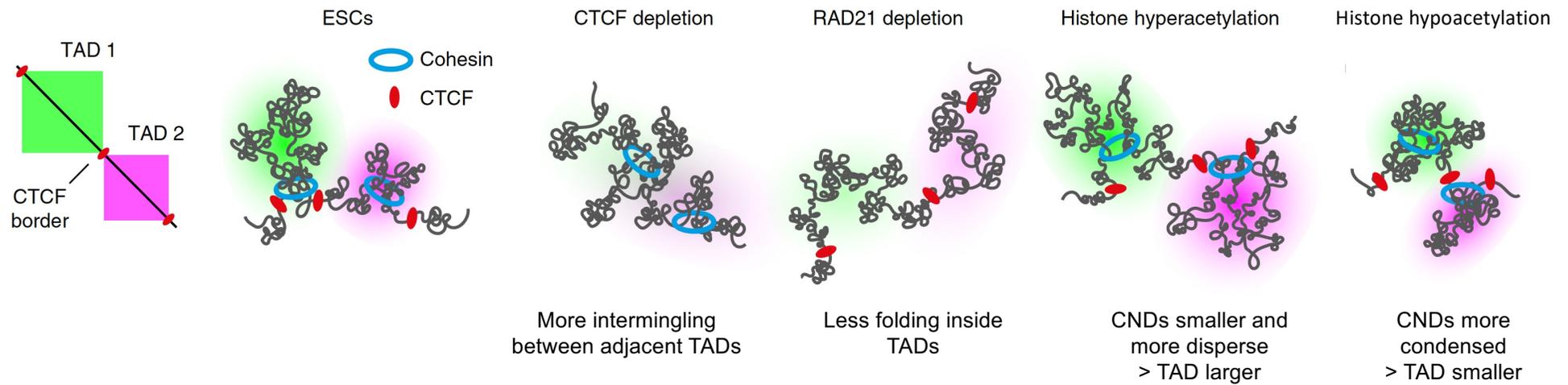
TAD Rom1

- **ACLY:** ATP Citrate Lyase (produces Acetyl-CoA from Citrate)
- **Acss2:** Acyl-CoA Synthetase Short chain family member 2 (produces Acetyl-CoA from Acetate)
- **Pdha1:** Pyruvate Dehydrogenase Complex (produces Acetyl-CoA from Pyruvate)

# CNDs depend on histone acetylation – effect of global hypo-Acetylation



# The sub-megabase chromatin folding involves different mechanisms





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