Single Cell Epigenomics

Fides Zenk

Learning Objectives of this week

General strategies of single cell isolation

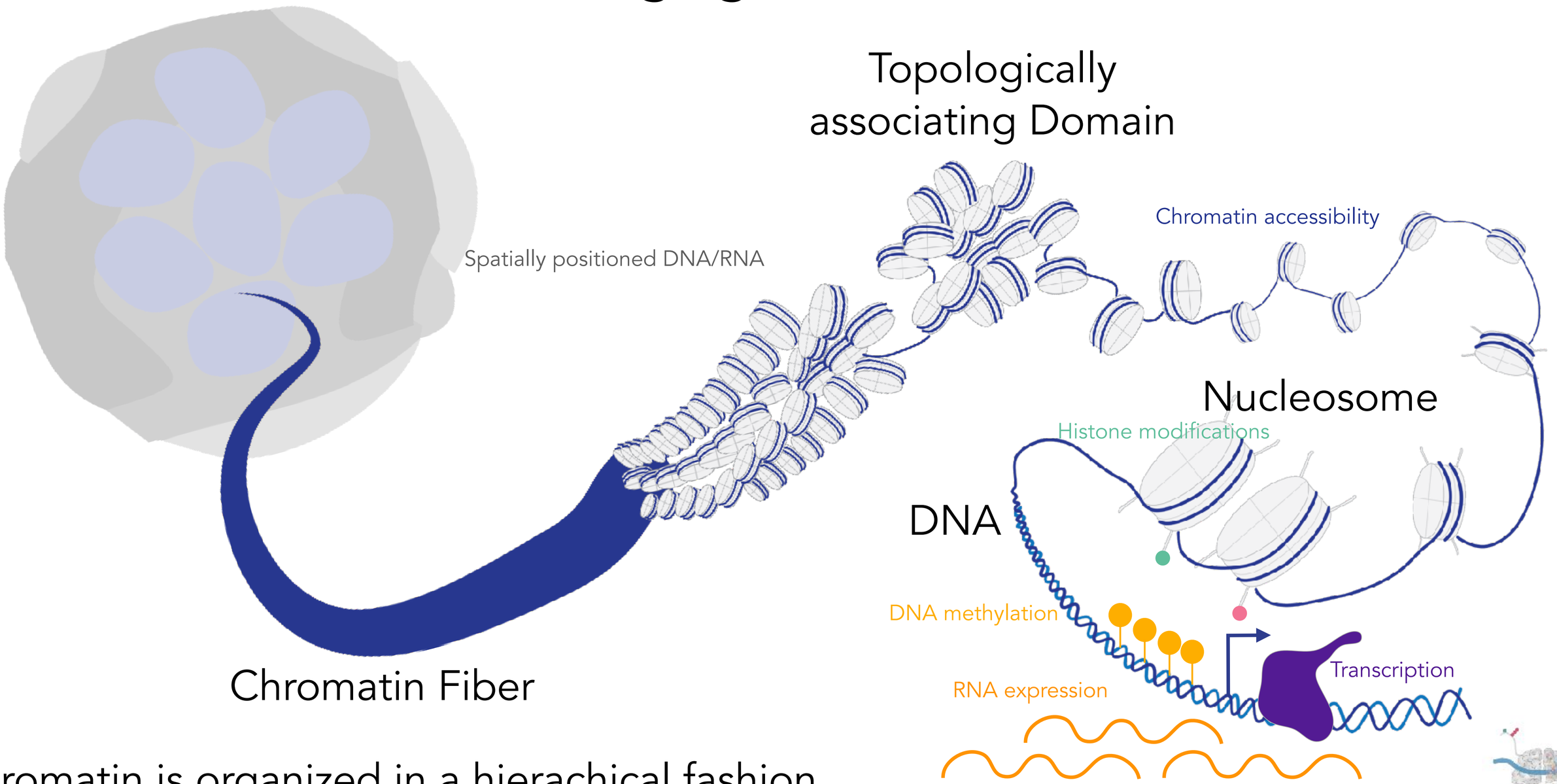
Getting to know technologies to study gene regulation in single cells

Possibilities to read out different layers of chromatin organisation

Reading out multiple modalities at once

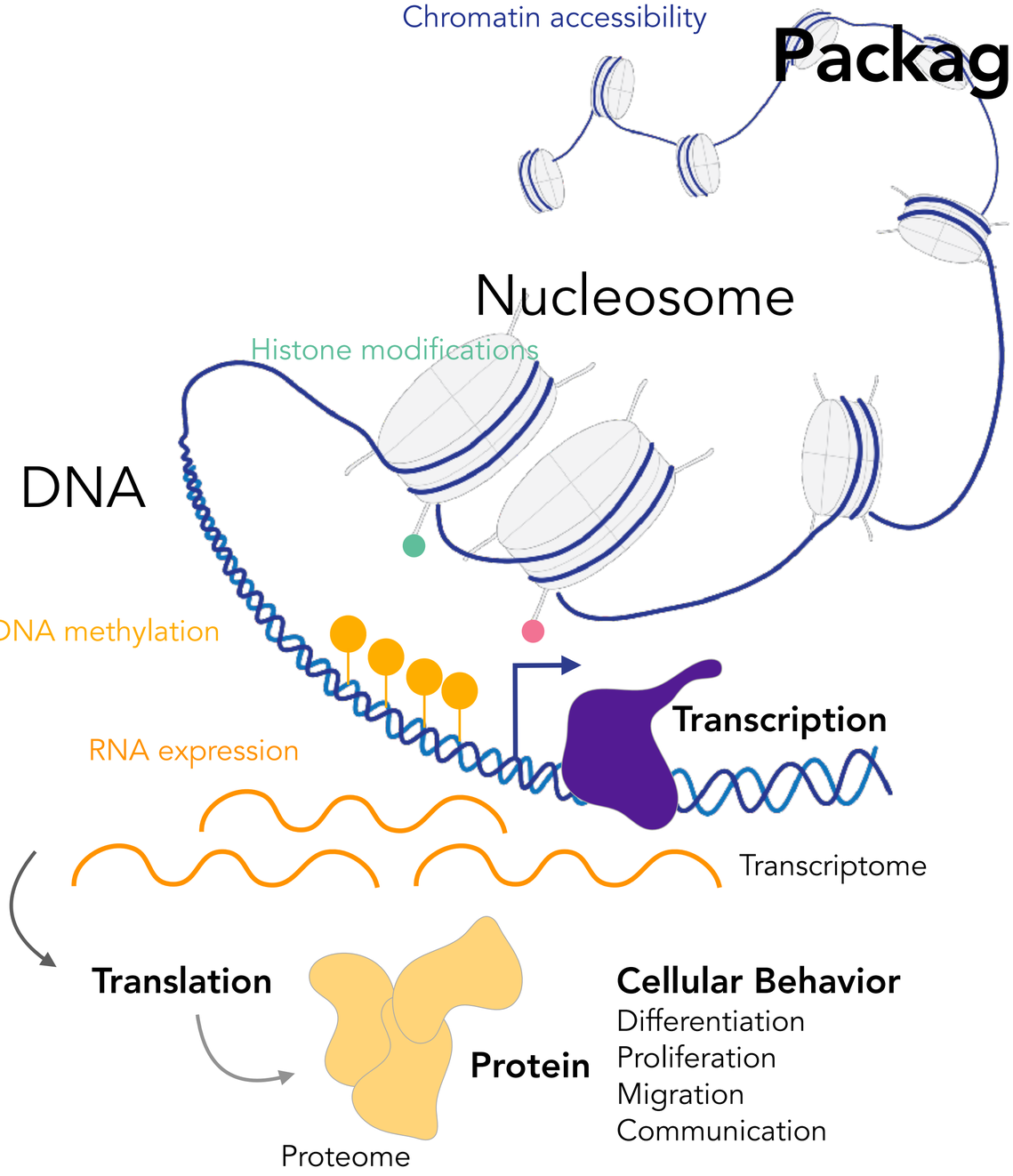
Open questions in chromatin biology and how to address them

Packaging of Chromatin inside the Nucleus



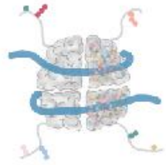
Chromatin is organized in a hierachical fashion

Packaging of Chromatin inside the Nucleus

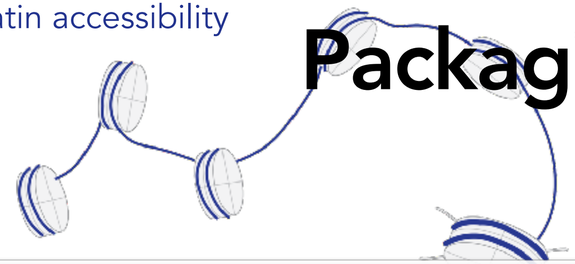


Modalities to measure to characterize cell states

Protein
mRNA
DNA
DNA methylation
Chromatin accessibility
Chromatin/Histone modification
Chromatin-Protein interactions
DNA/chromosomal structure
Other RNAs (miRNA, lncRNA…)

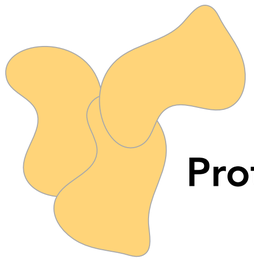


Packaging of Chromatin inside the Nucleus



Modalities to measure to characterize cell states	
Protein	Function/Phenotype
mRNA	Function/Phenotype (indirect)
DNA	Genotype (somatic mutations, CNVs, lineage)
DNA methylation	Gene regulation - e.g. Transcriptional repression
Chromatin accessibility	Gene regulation - Regulatory regions, TF binding sites
Chromatin/Histone modification	Gene regulation - Active/Repressed genes, enhancers, functional el.
Chromatin-Protein interactions	Gene regulation - TF/ enzyme binding to DNA
DNA/chromosomal structure	Gene regulation - physical contacts enhancers/genes
Other RNAs (miRNA, lncRNA…)	Other RNAs (miRNA, lncRNA…)

Translation

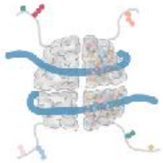


Protein

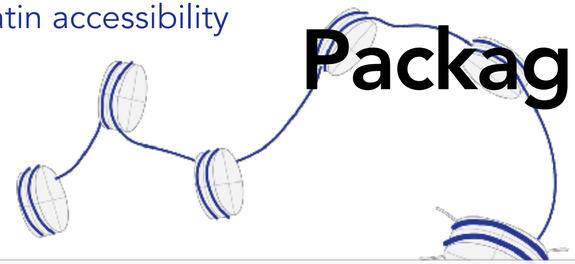
Proteome

Cellular Behavior

Differentiation
Proliferation
Migration
Communication



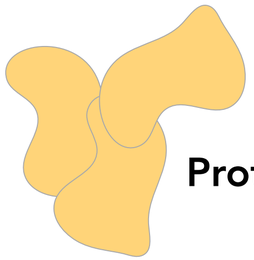
Packaging of Chromatin inside the Nucleus



Modalities to measure to characterize cell states

Protein	Mass Cytometry, Mass Spectrometry, scPEA, CITE-seq,	Function/Phenotype
mRNA	scRNA-seq	Function/Phenotype (indirect)
DNA	scDNA-seq	Genotype (somatic mutations, CNVs, lineage)
DNA methylation	scBisulfite-seq	Gene regulation - e.g. Transcriptional repression
Chromatin accessibility	scATAC-seq, scMNase	Gene regulation - Regulatory regions, TF binding sites
Chromatin/Histone modification	scCHIC-seq, scCut&Tag	Gene regulation - Active/Repressed genes, enhancers, functional el.
Chromatin-Protein interactions		Gene regulation - TF/ enzyme binding to DNA
DNA/chromosomal structure	scHI-C, SPRITE, GAM	Gene regulation - physical contacts enhancers/genes
Other RNAs (miRNA, lncRNA…)	smallRNA-seq	Other RNAs (miRNA, lncRNA…)

Translation

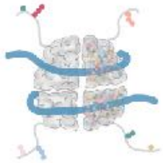


Protein

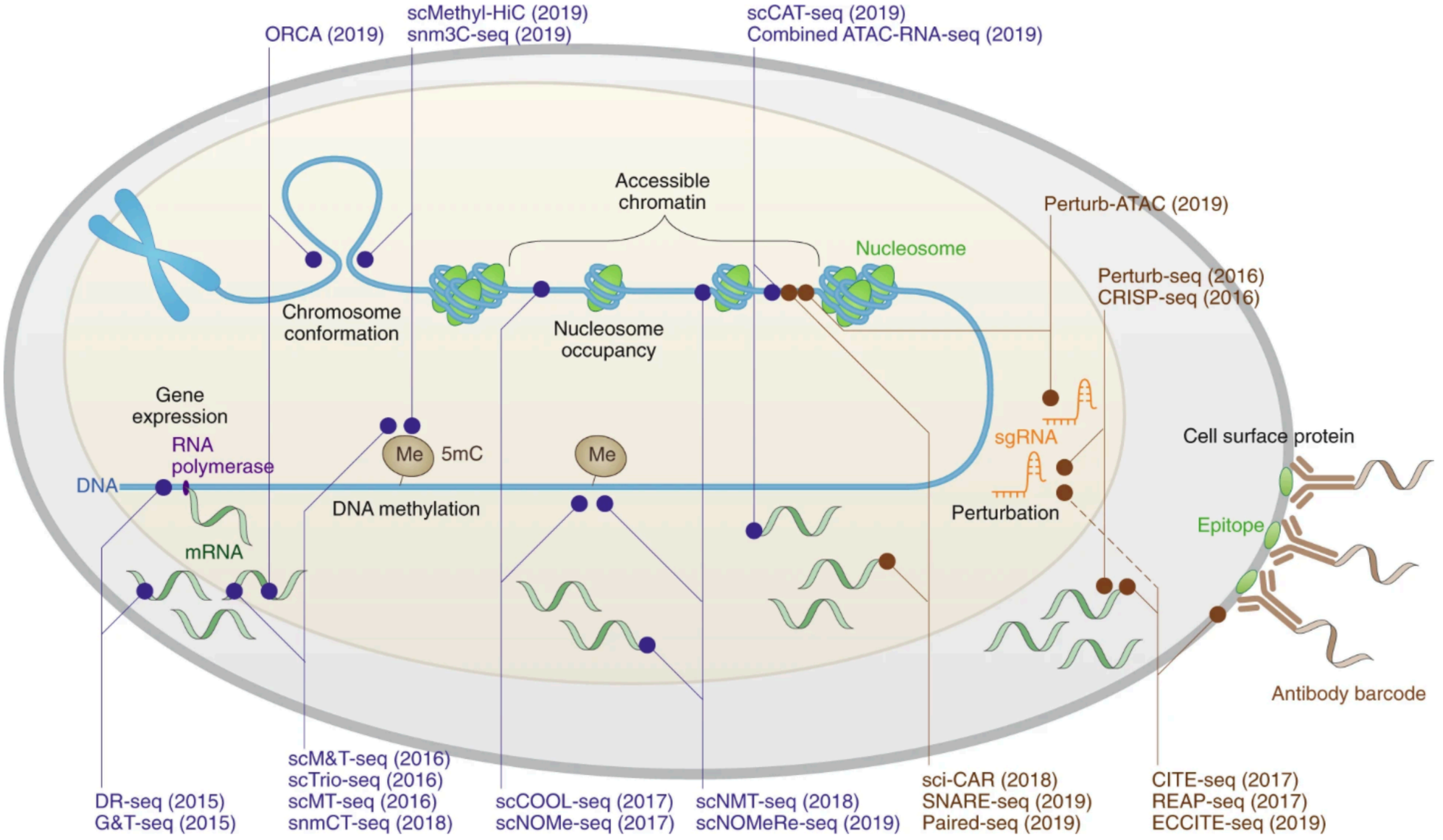
Proteome

Cellular Behavior

Differentiation
Proliferation
Migration
Communication

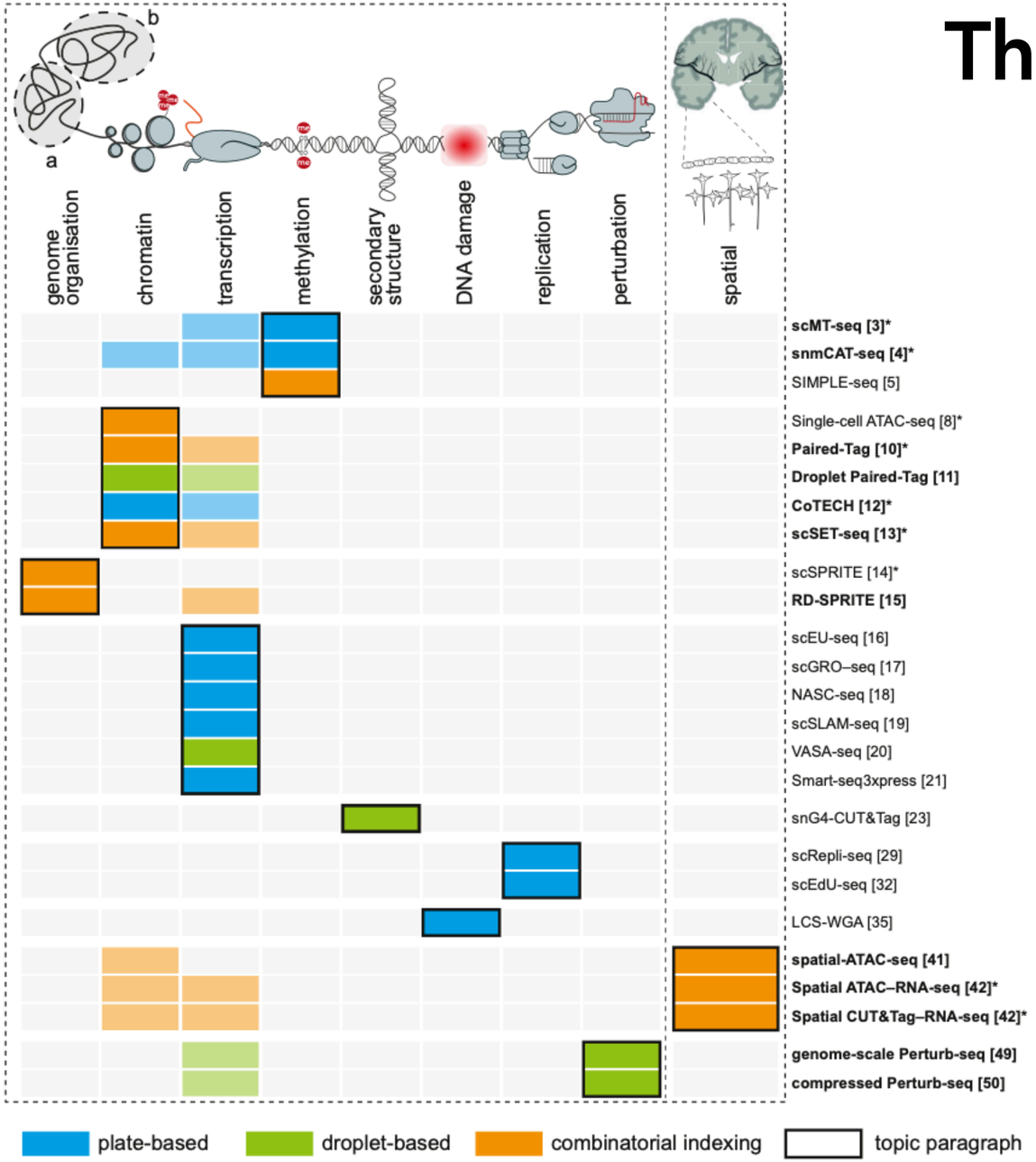


The dream of single-cell multiomics



Zhu Ren (2020) Nature Methods

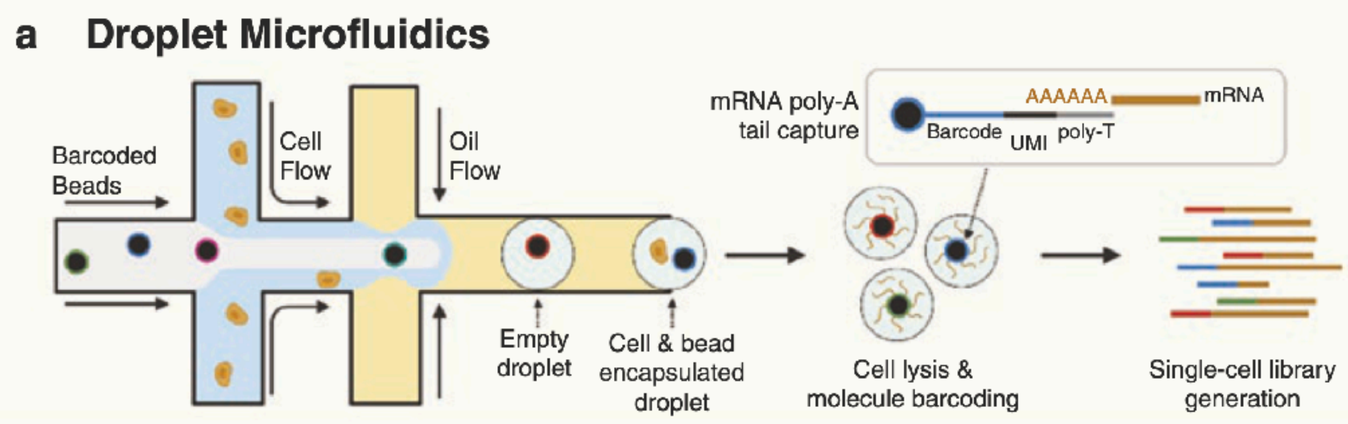
The dream of single-cell multiomics



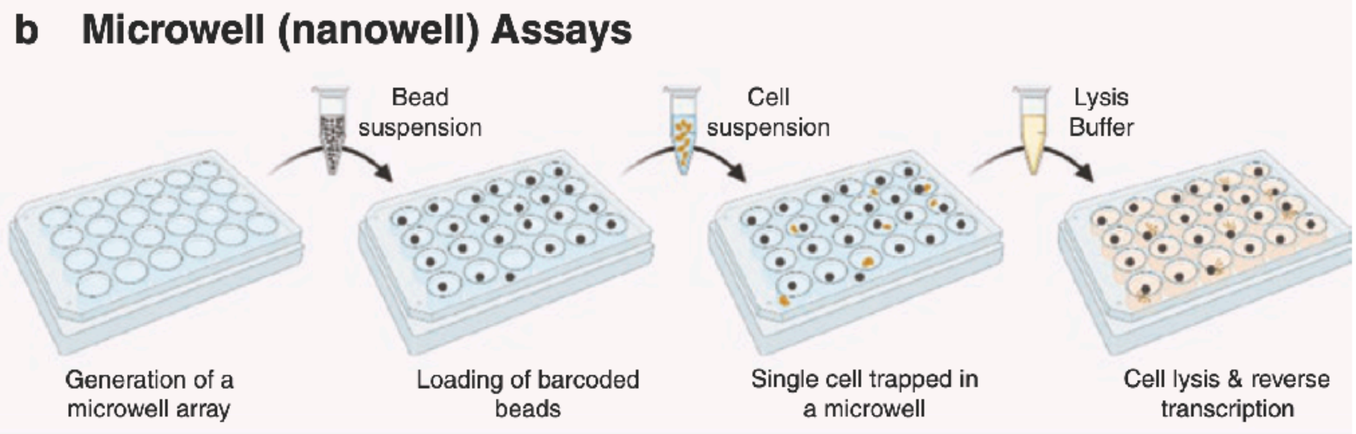
Many different technologies cover chromatin organization and nuclear processes

Van den Berg, Zeller (2025) Current Opinion in Cell Biology

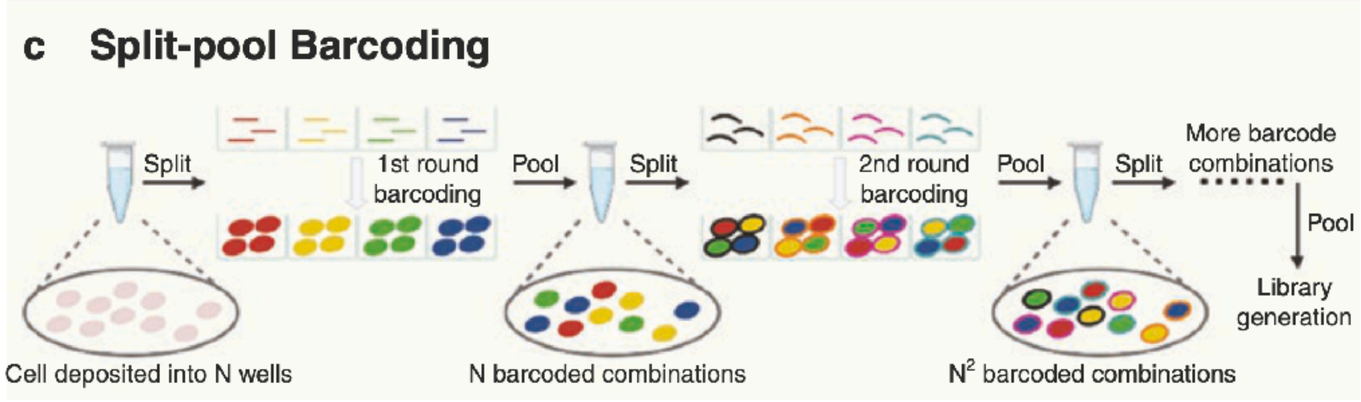
Basic differences between single cell technologies



e.g. 10x Genomics



e.g. Fluidigm (usually low throughput)



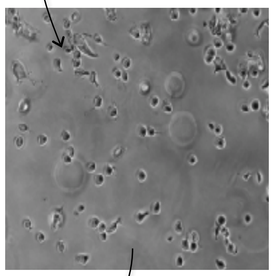
e.g. Parse, Scale Biosciences

Muto, Humphreys (2022) Innovations in Nephrology

Workflow of single cell genomics experiments

Optional: Imaging of cell

Optional: Disaggregation of complex tissue
(mostly enzymatic digestion)

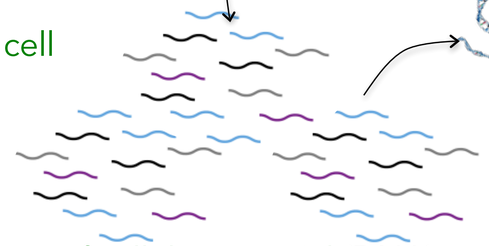


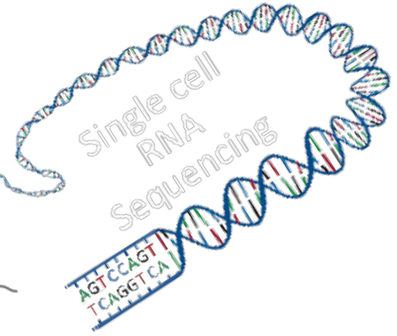
Generation of single cell suspension
(Removing aggregates/debris by filtering)

Isolation of single cell

Optional: Imaging of cell

Lysis of cell





Amplification and Enrichment of cellular material (DNA)

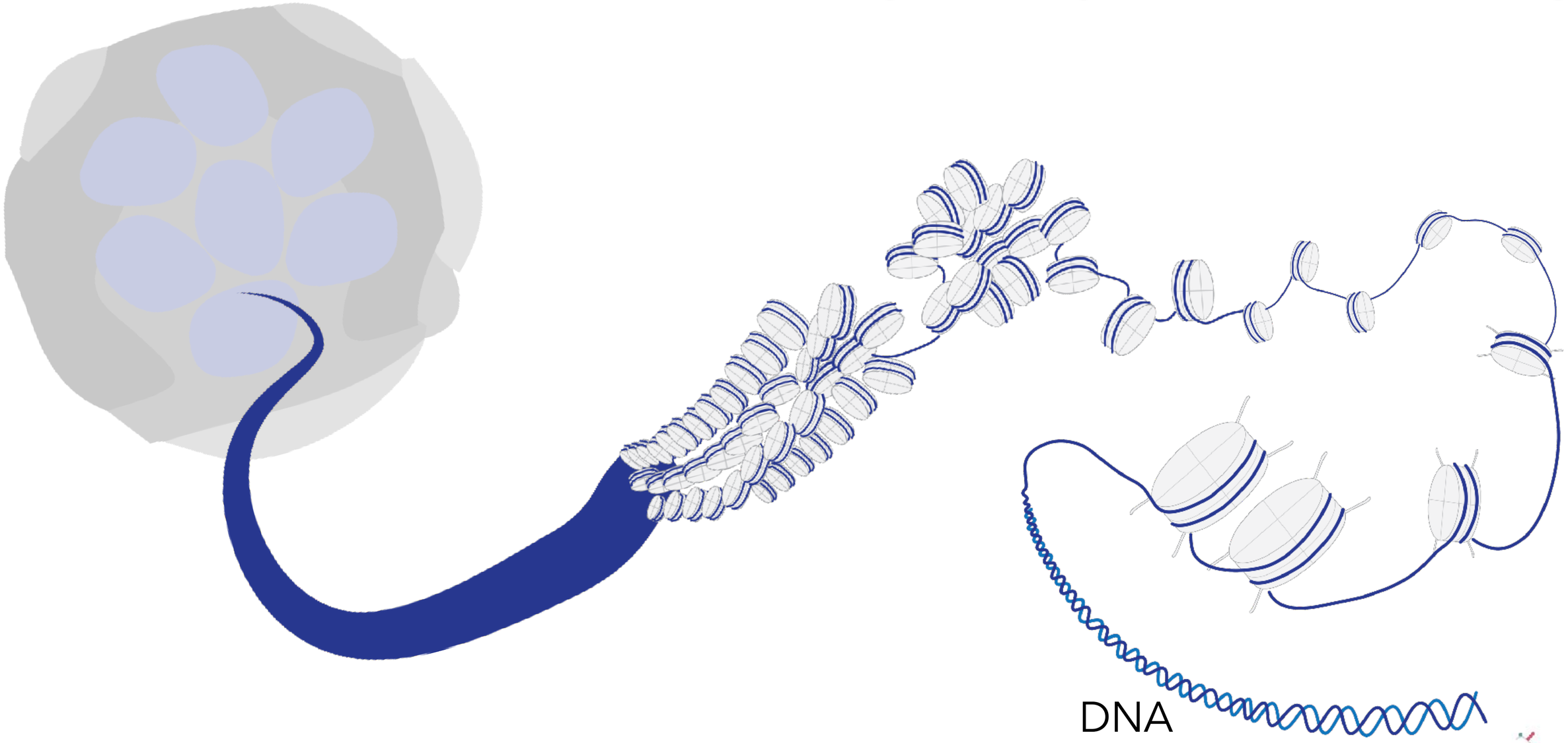
Preparation of sequencing libraries
(multiplexing of cells)

High-throughput
sequencing

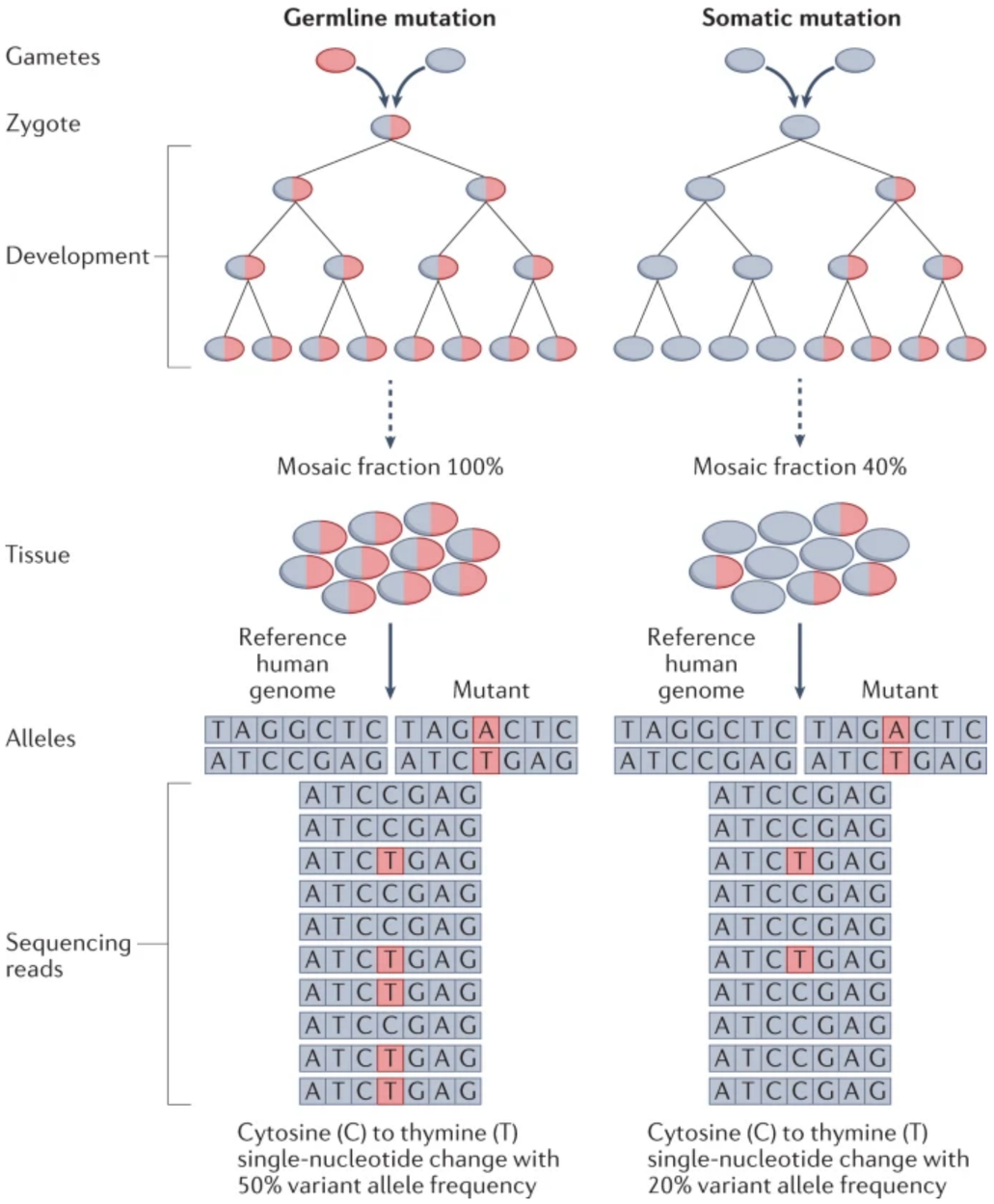
Computational analyses

Challenge:
Very low input:
2 copies of DNA
→ Contamination
→ Bias due to amplification
→ Noise (technical & biological)

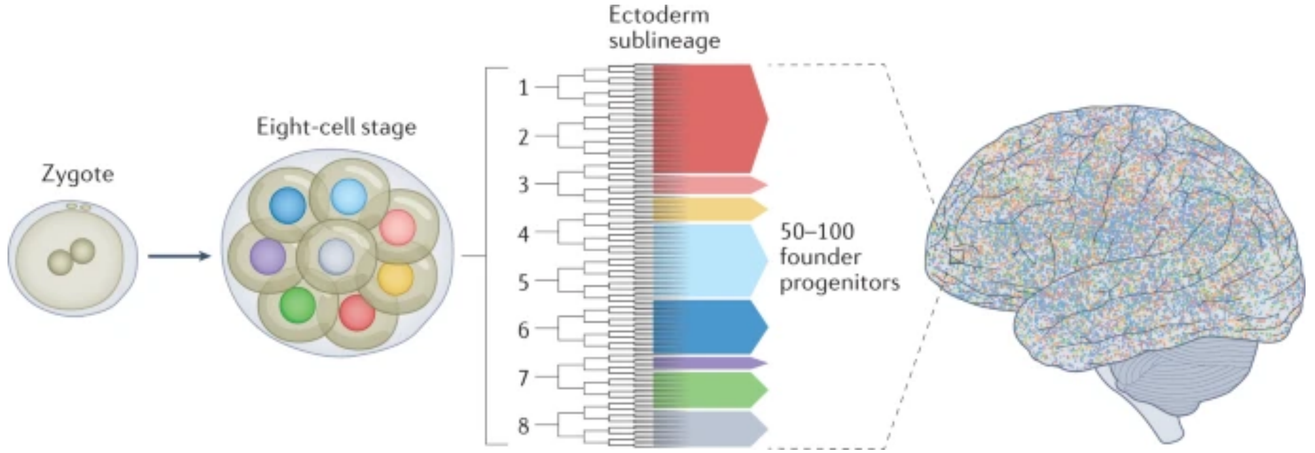
Single-cell genome sequencing



What can we learn from single-cell DNA sequencing?

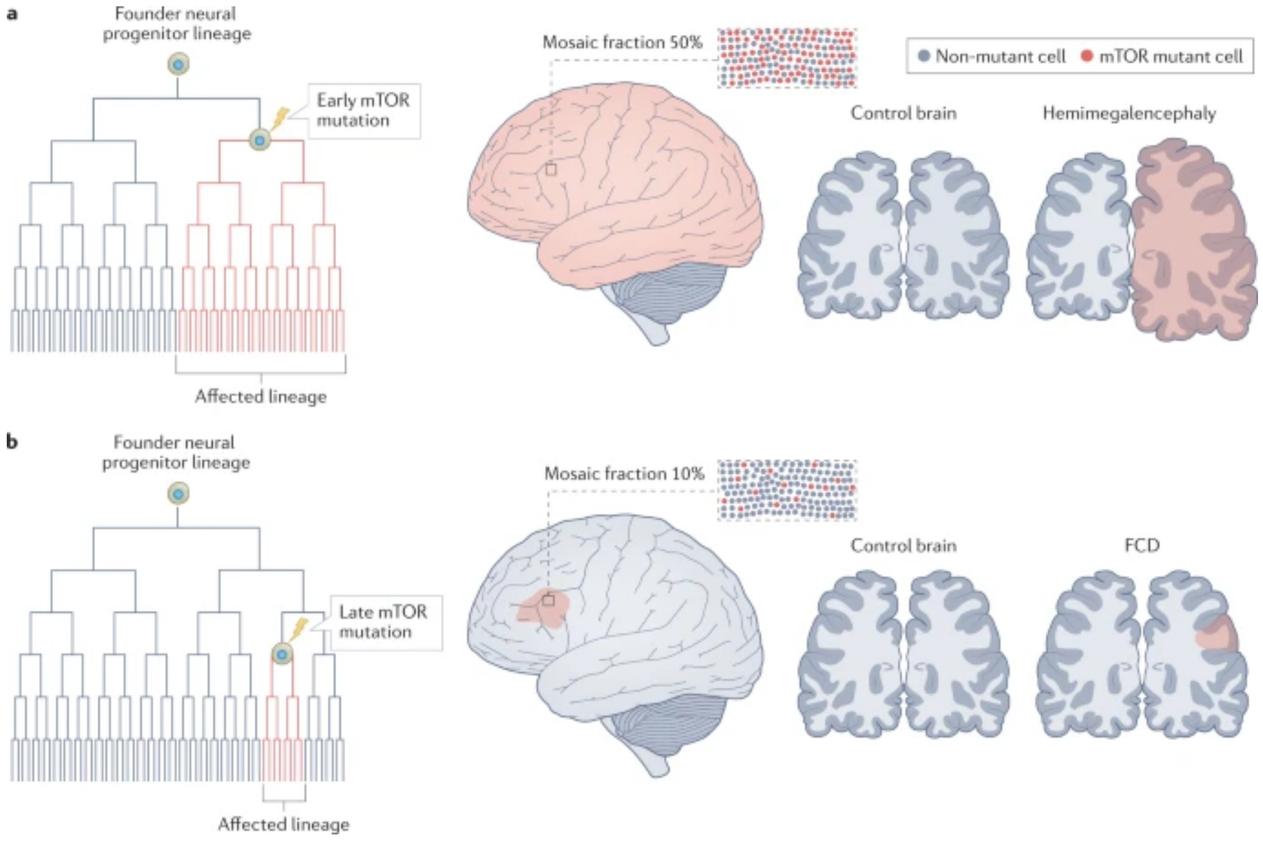


Tracing developmental lineages
Mutation rates during development and ageing
Understanding somatic mosaicism
Human diseases - cortical malformations, cancer

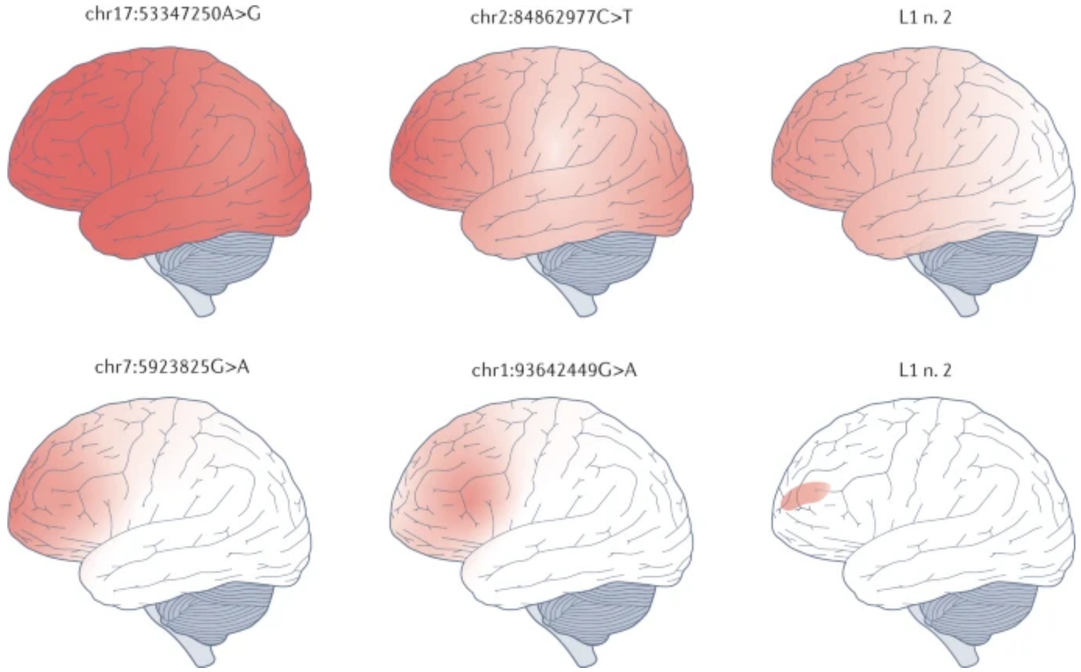


Bizzotto and Welsh Nat. Neuro 2022

What can we learn from single-cell DNA sequencing?

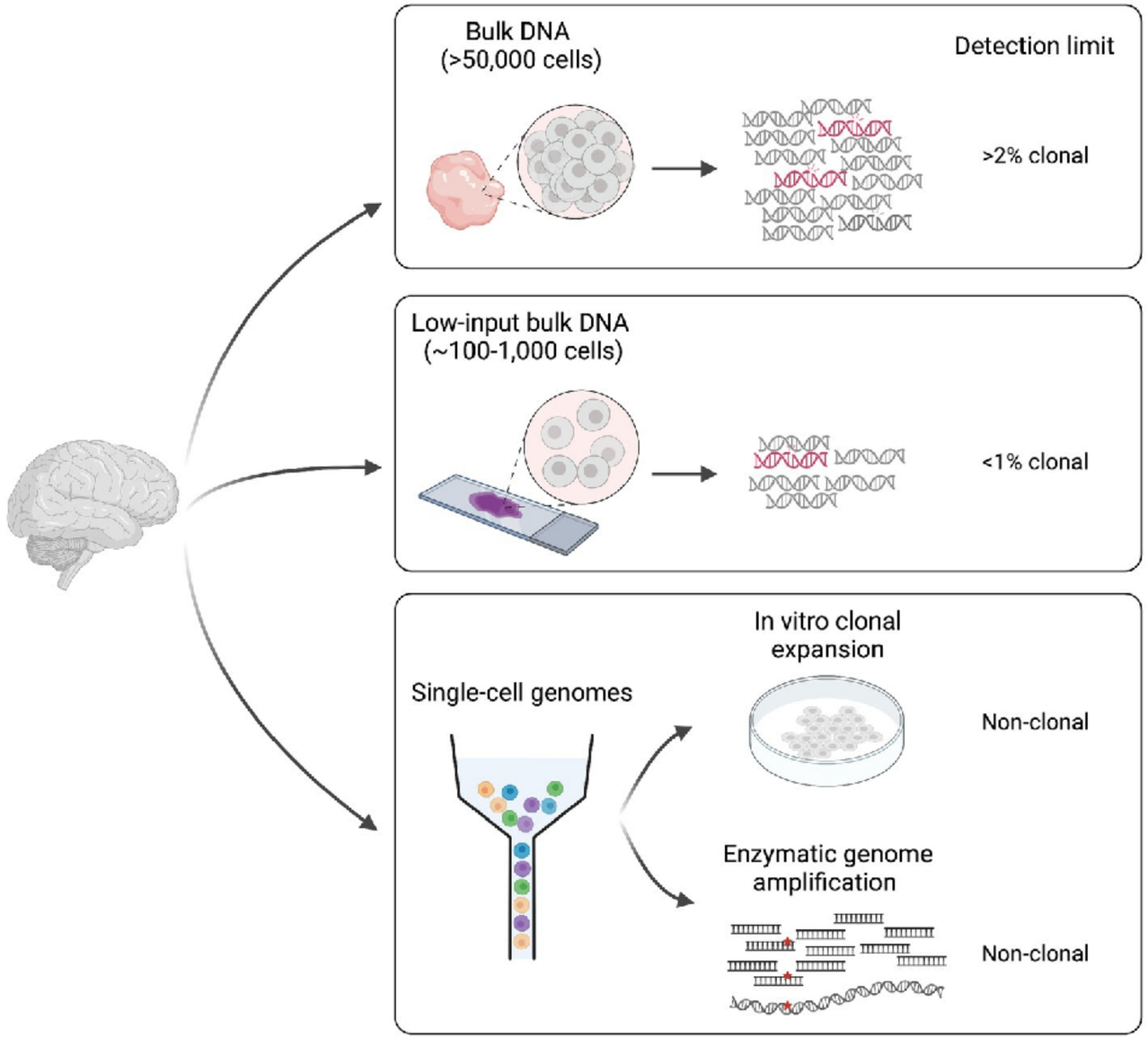


Tracing developmental lineages
Mutation rates during development and ageing
Understanding somatic mosaicism
Human diseases - cortical malformations, cancer



Bizzotto and Welsh Nat. Neuro 2022

What can we learn from single-cell DNA sequencing?



To study cell-type-specific effects (e.g. in postmitotic cells), single-cell RNA sequencing is needed

Technically challenging, require very deep sequencing

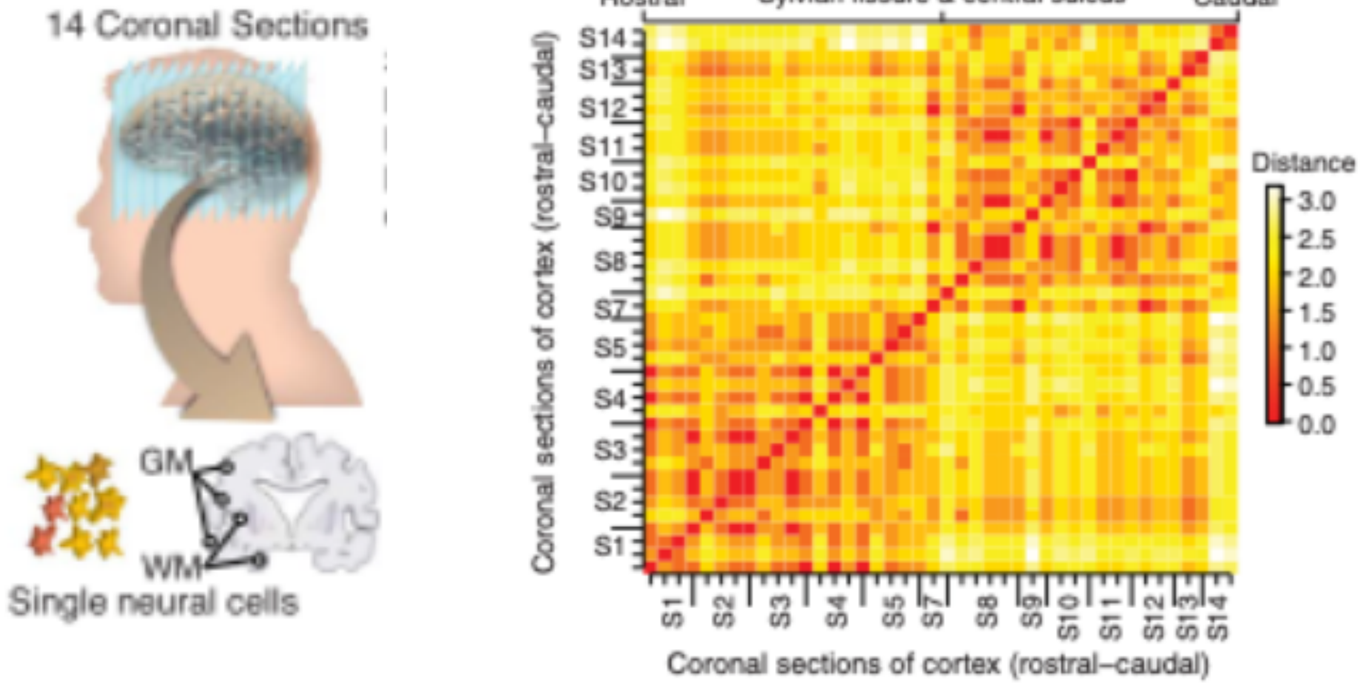
Bizzotto Frontiers in Neuroscience 2023

What can we learn from single-cell DNA sequencing?

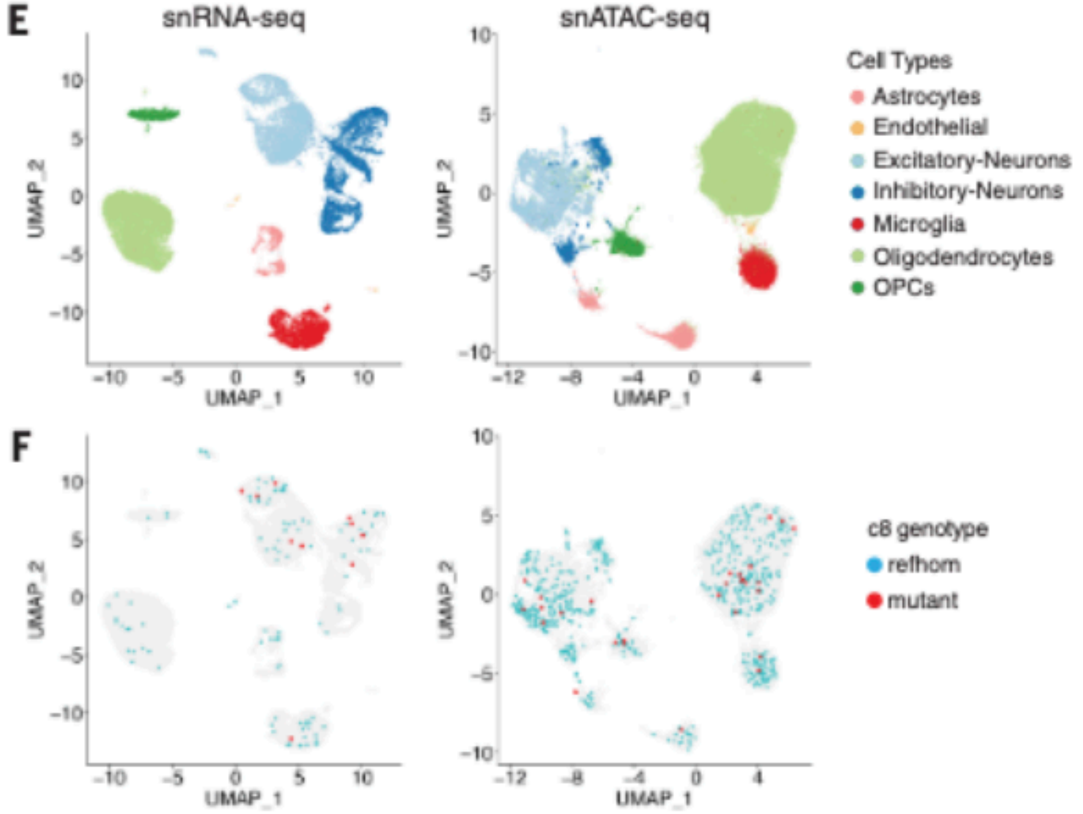
DEVELOPMENT

Landmarks of human embryonic development inscribed in somatic mutations

Sara Bizzotto[1,2,3]*, Yanmei Dou[4]*, Javier Ganz[1,2,3]*, Ryan N. Doan[1], Minseok Kwon[4], Craig L. Bohrson[4], Sonia N. Kim[1,2,3,5], Taejeong Bae[6], Alexej Abyzov[6], NIMH Brain Somatic Mosaicism Network†, Peter J. Park[4,7]‡, Christopher A. Walsh[1,2,3]‡



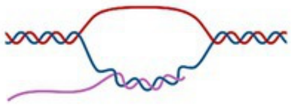
Hindbrain and forebrain form distinct clusters based on DNA sequence



Annotated mutations can be recovered from scRNA and scATAC-Seq (6% vs. 12%, respectively)

What can we learn from single-cell DNA sequencing?

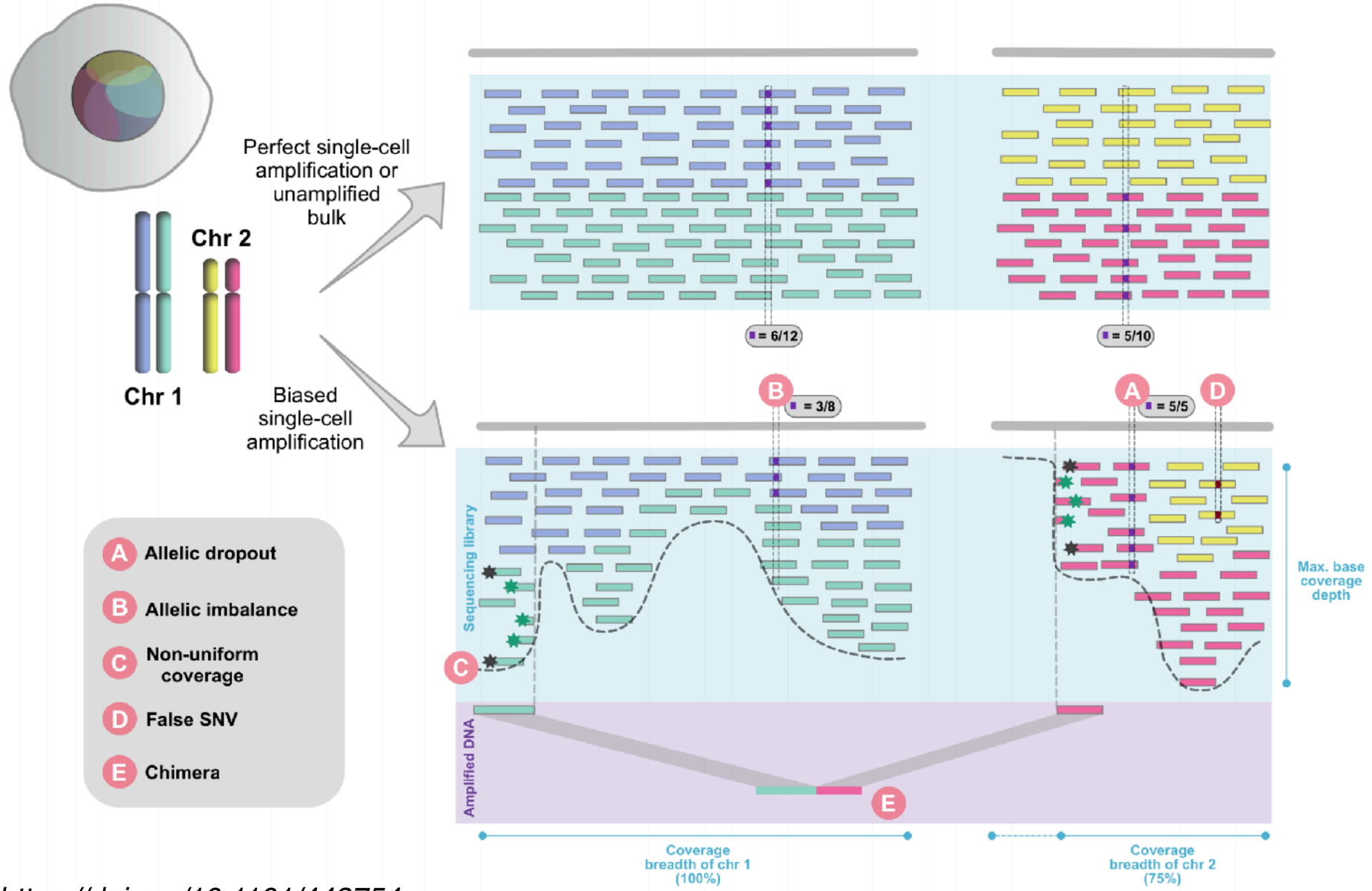
Somatic mutation in the aging human brain

Cell type	Rates (genome/year)		Genomic enrichment	COSMIC signatures		Mechanism
Neurons 	sSNVs	indels	• Transcriptionally active regions • Brain-specific regulatory regions • Neuronal enhancers	sSNVs	indels	Transcription 
	~16-17	~2-3		SBS5 SBS89 SBS16	ID5 ID4 ID8	
Oligodendrocytes 	sSNVs	indels	• Inactive genomic regions	sSNVs	indels	Cell division (OPCs) 
	~27	~1-2		SBS5 SBS89 SBS1 SBS32	ID5 ID8 ID9	

Non-dividing cells accumulate mutations at transcriptionally active sites
Dividing cell accumulate mutations in inactive genomic regions

Bizzotto Frontiers in Neuroscience 2023

Whole genome amplification can introduce technical errors



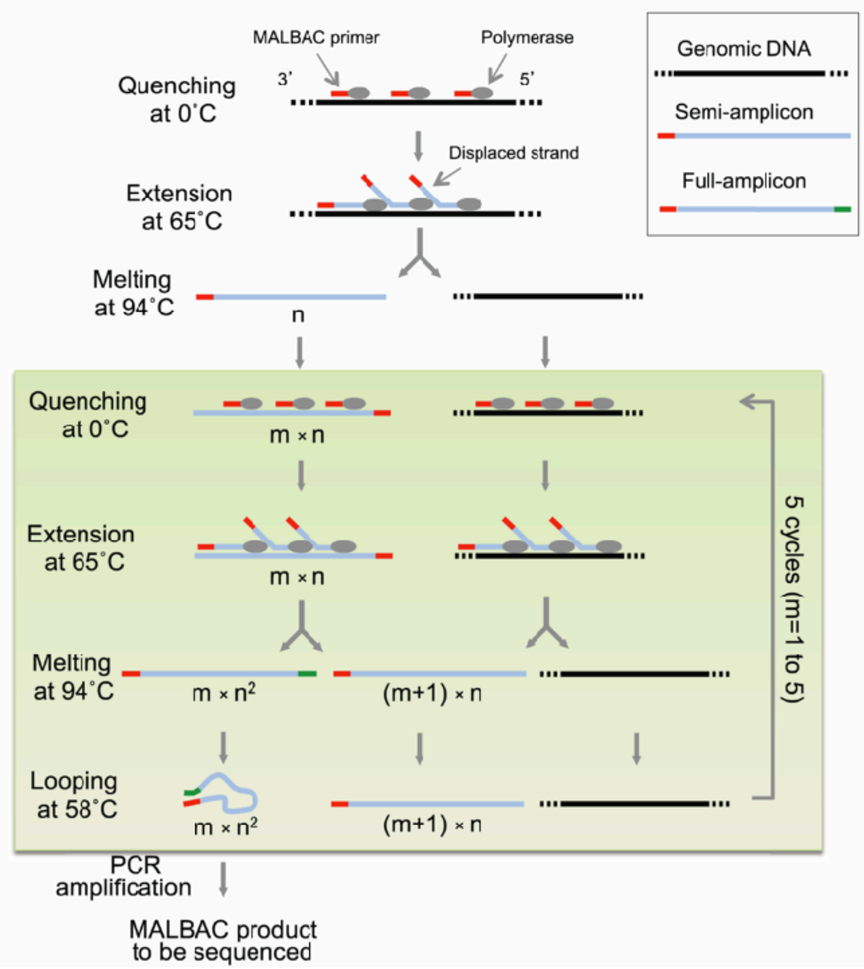
https://doi.org/10.1101/443754

Methods for single-cell whole genome amplification

MALBAC - Multiple annealing & looping-based amplification

Zong et al., Science

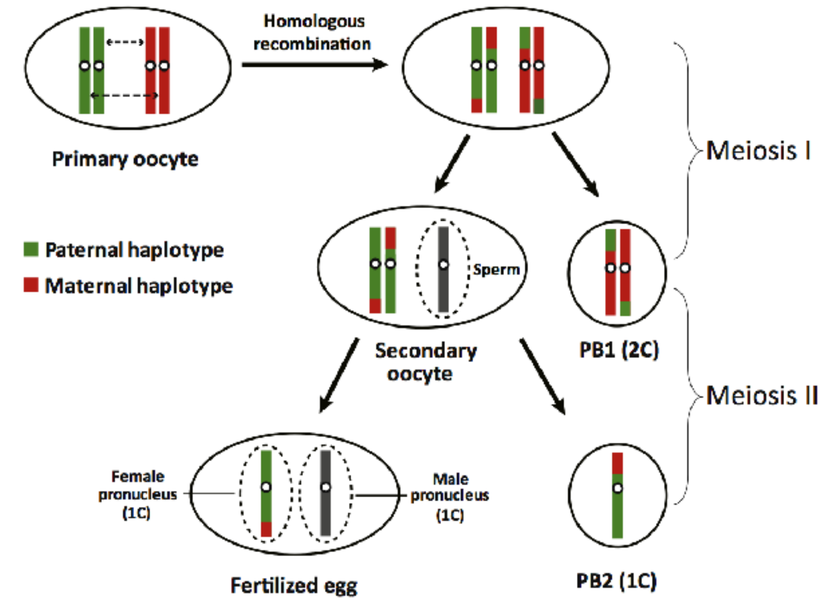
- Pyrophage polymerase
- MALBAC primer: GTGAGTGATGGTTGAGGTAGTGTGGAGNNNNNGGG



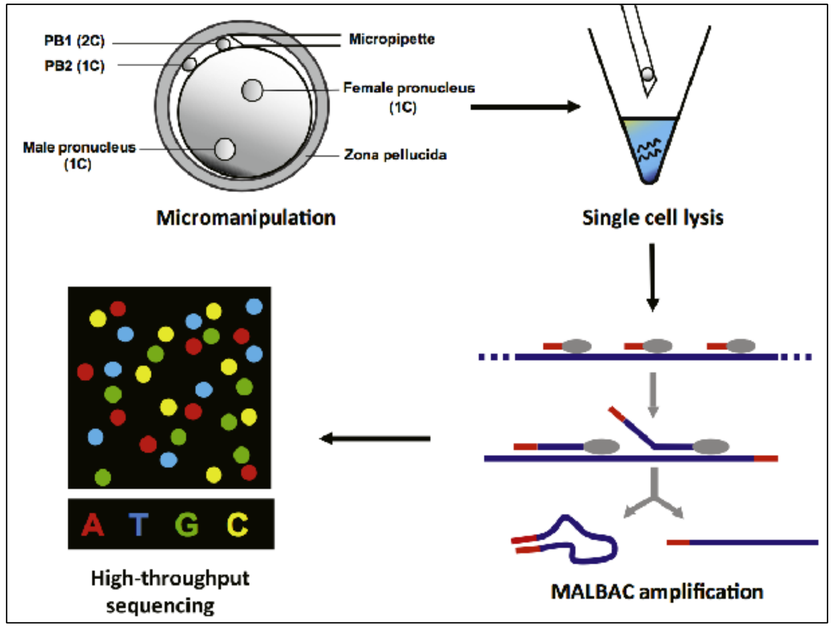
Looping prevents exponential amplification

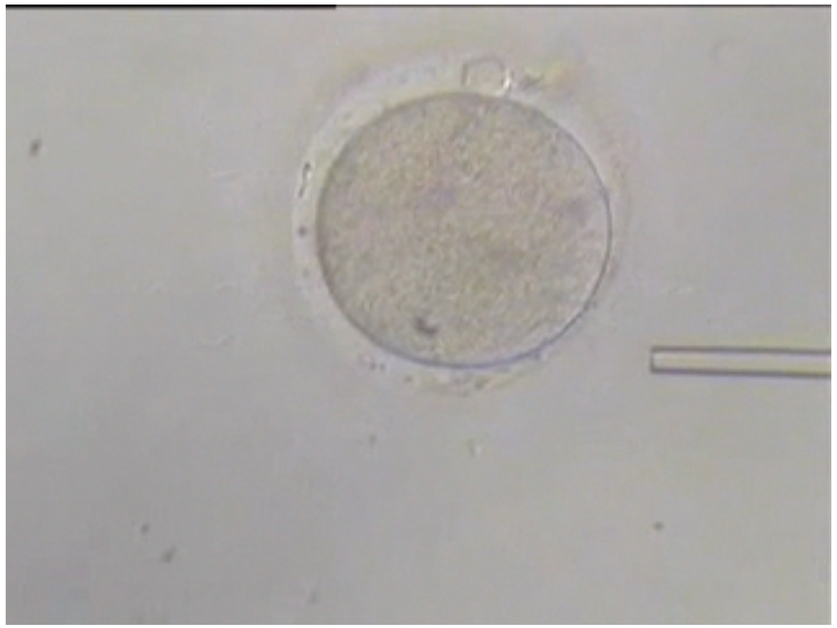
Random priming allows to almost linearly ampliy the whole genome

Applications scDNA-seq: Genome analyses of single human oocytes



Polar Bodies 1&2
not required for
embryogenesis

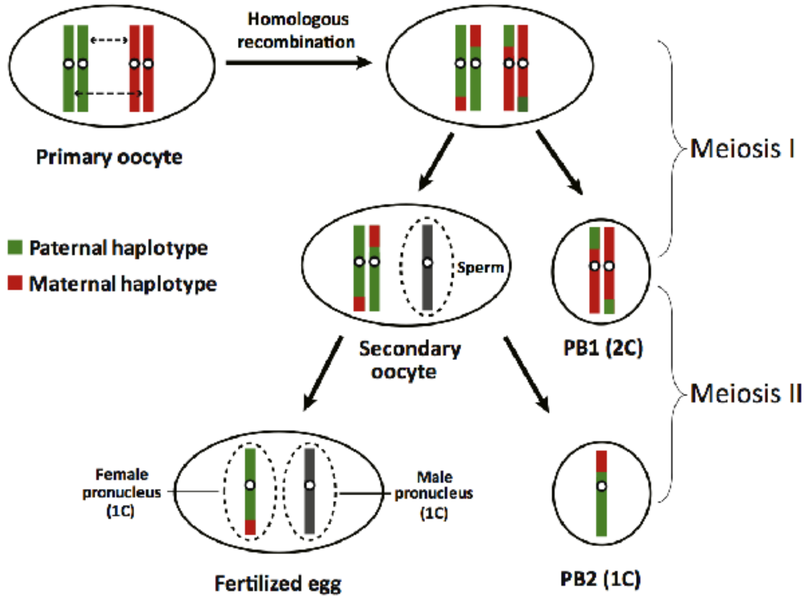




Applications scDNA-seq: Genome analyses of single human oocytes

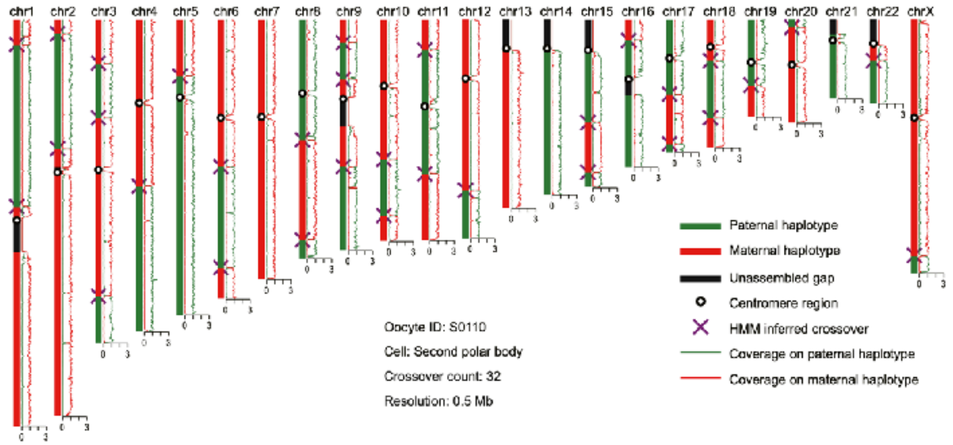
Sequencing genome of PB1 & PB2:
Information on aneuploidy and SNPs in disease-associated alleles

➡Accurate and cost-effective method to screen fertilized eggs prior to implantation in IVF

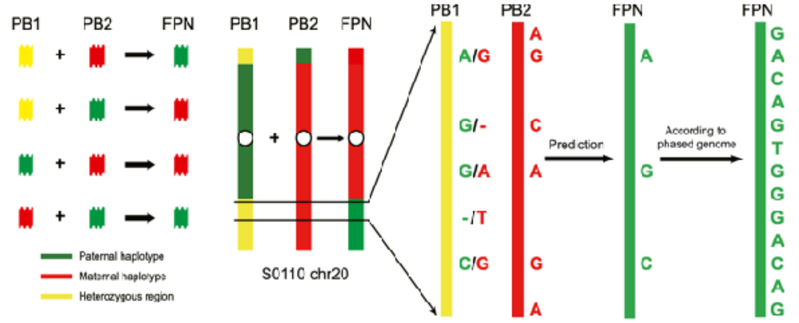


Polar Bodies 1&2 not required for embryogenesis

Crossover distribution map for PB2



Deduction of FPN Haplotype through Genomes of PB1



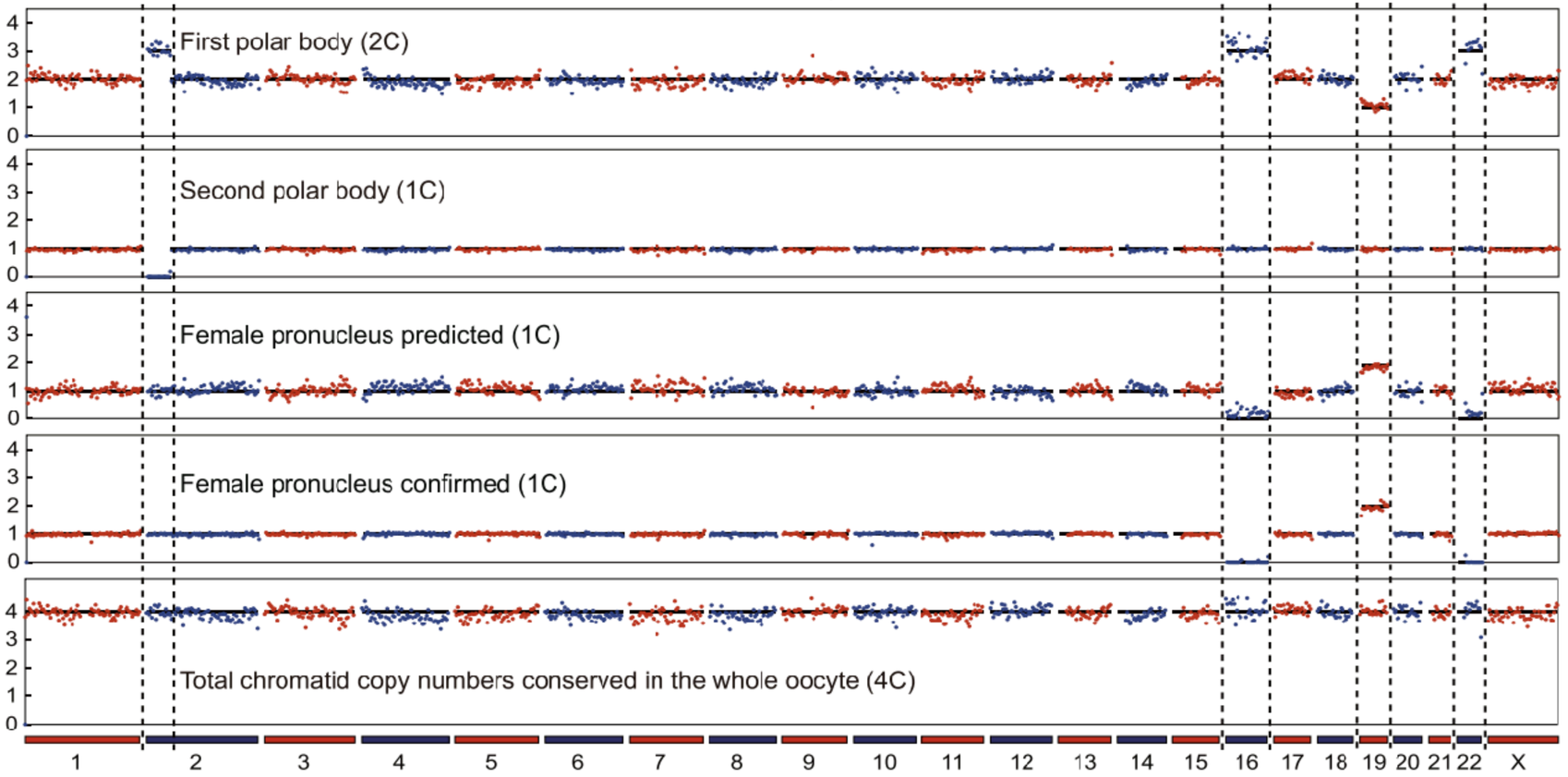
FPN - female pronucleus

Applications scDNA-seq: Genome analyses of single human oocytes

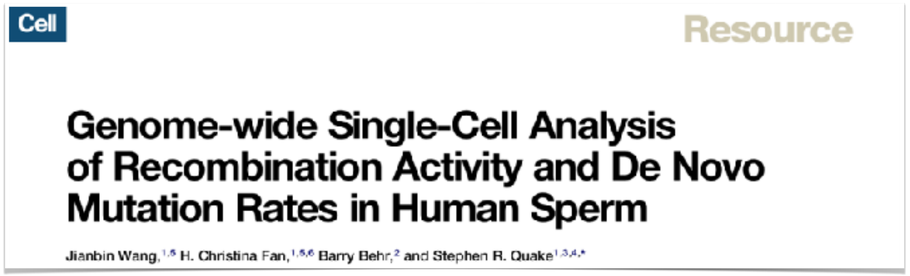
Sequencing genome of PB1 & PB2:
Information on aneuploidy and SNPs in disease-associated alleles

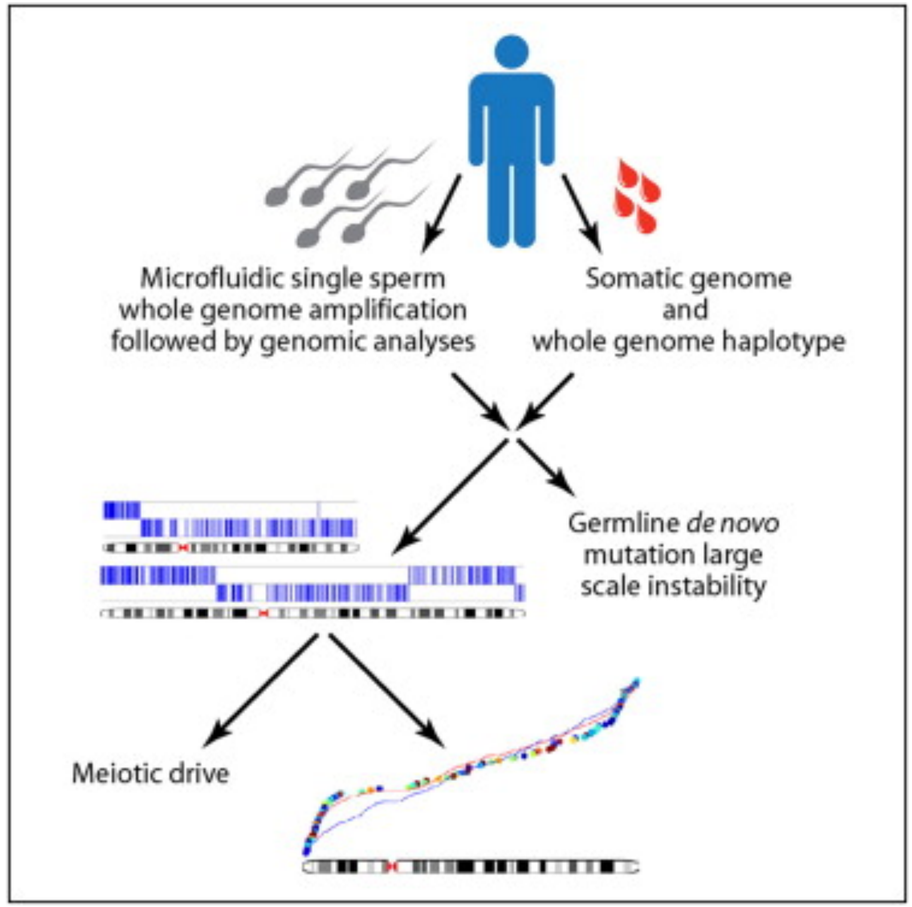
➡Accurate and cost-effective method to screen fertilized eggs prior to implantation in IVF

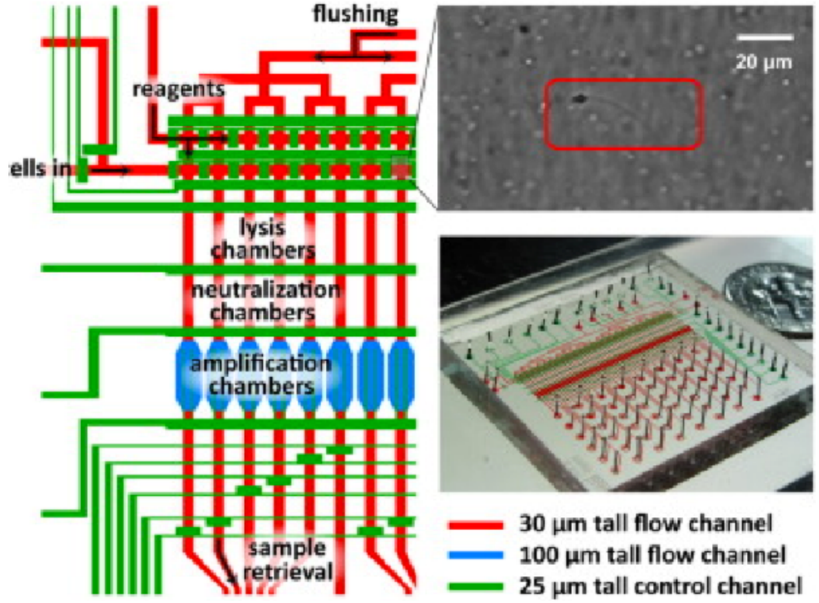
Deduction of Aneuploidy for IVF



Applications scDNA-seq: Recombination and mutation in sperm







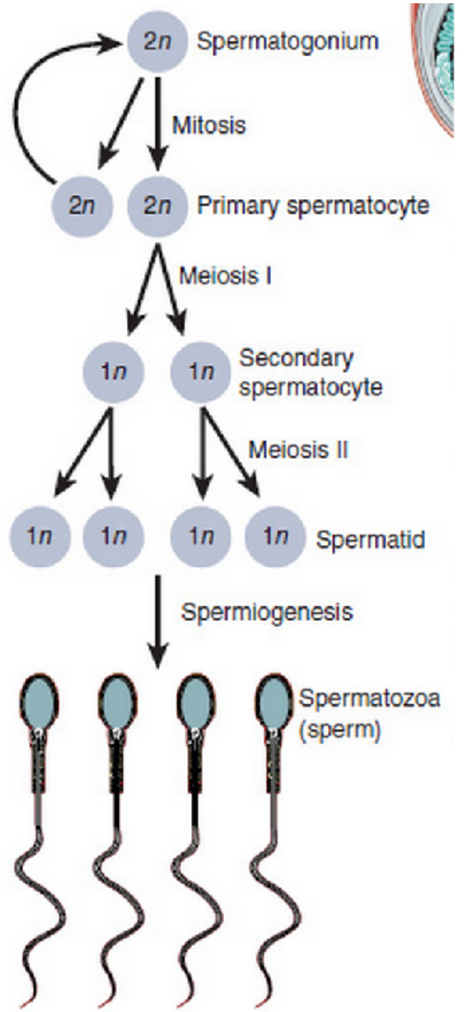
MDA

➡Whole genome sequencing of single sperm cells

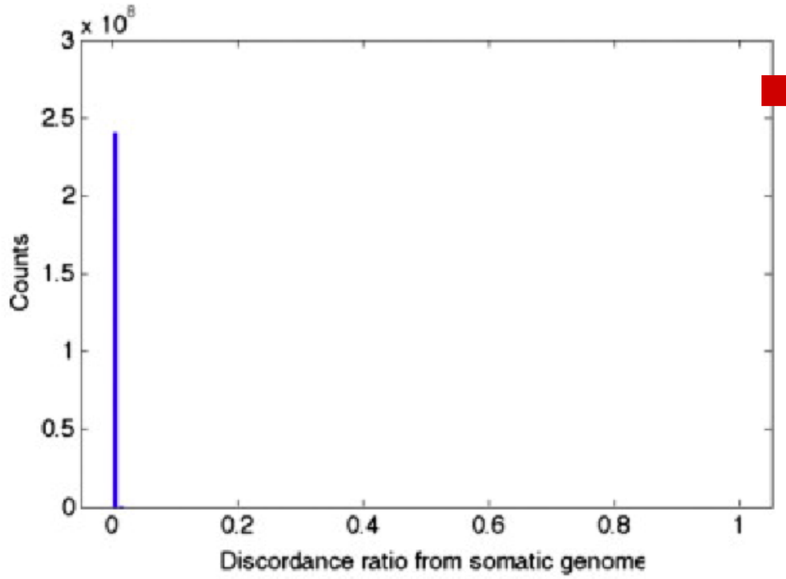
- Meiotic recombination: shuffling of two haploid somatic genomes
- Point mutations due to replication errors

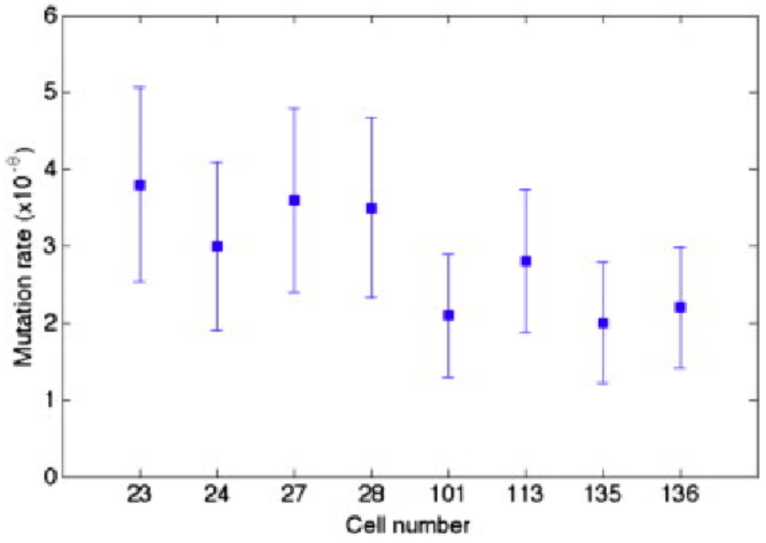
➡ Enormous variety of new genomes created in gametes

Spermatogenesis



Applications scDNA-seq: Recombination and mutation in sperm

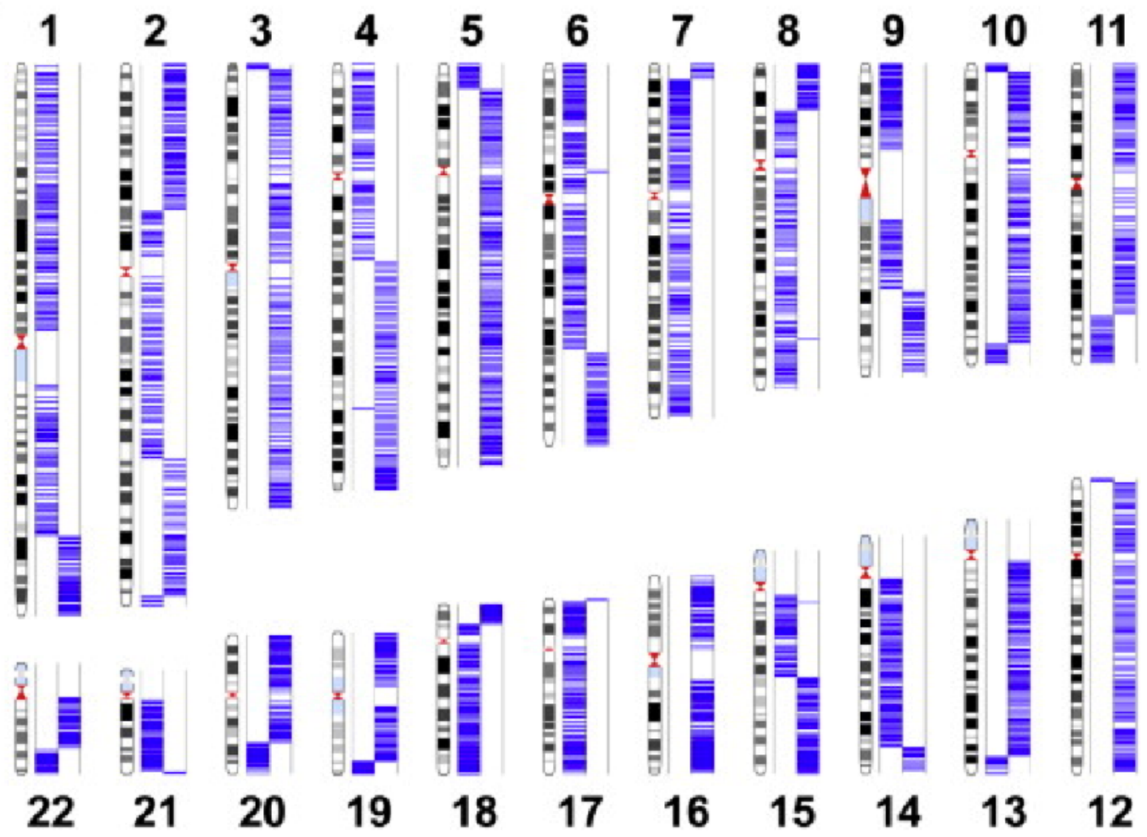




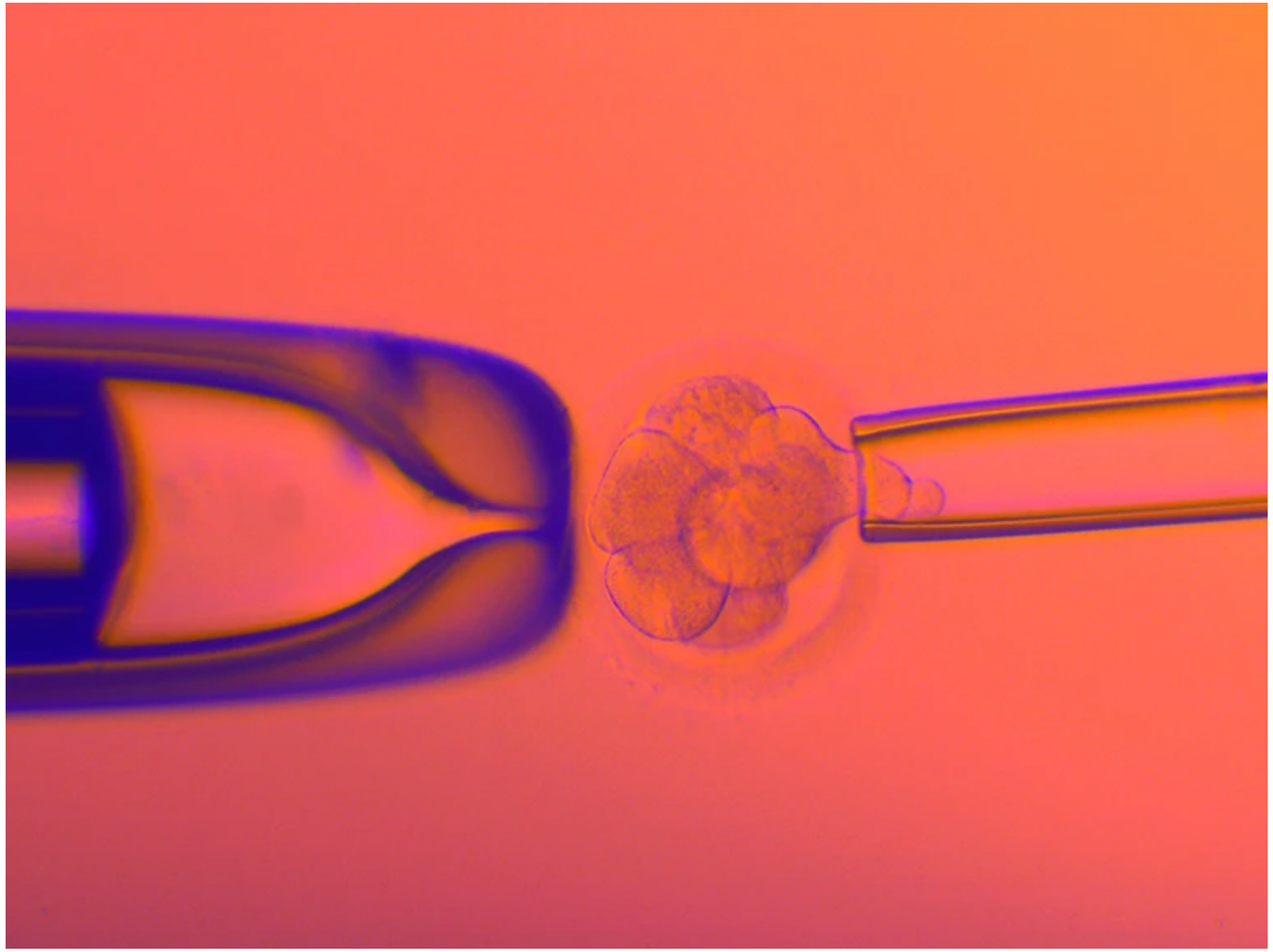
Single sperm mutation rate: 2-4 x 10^{-8}

Amplification/ Sequencing error: 2.7 × 10^{-4}

Personal sperm recombination map

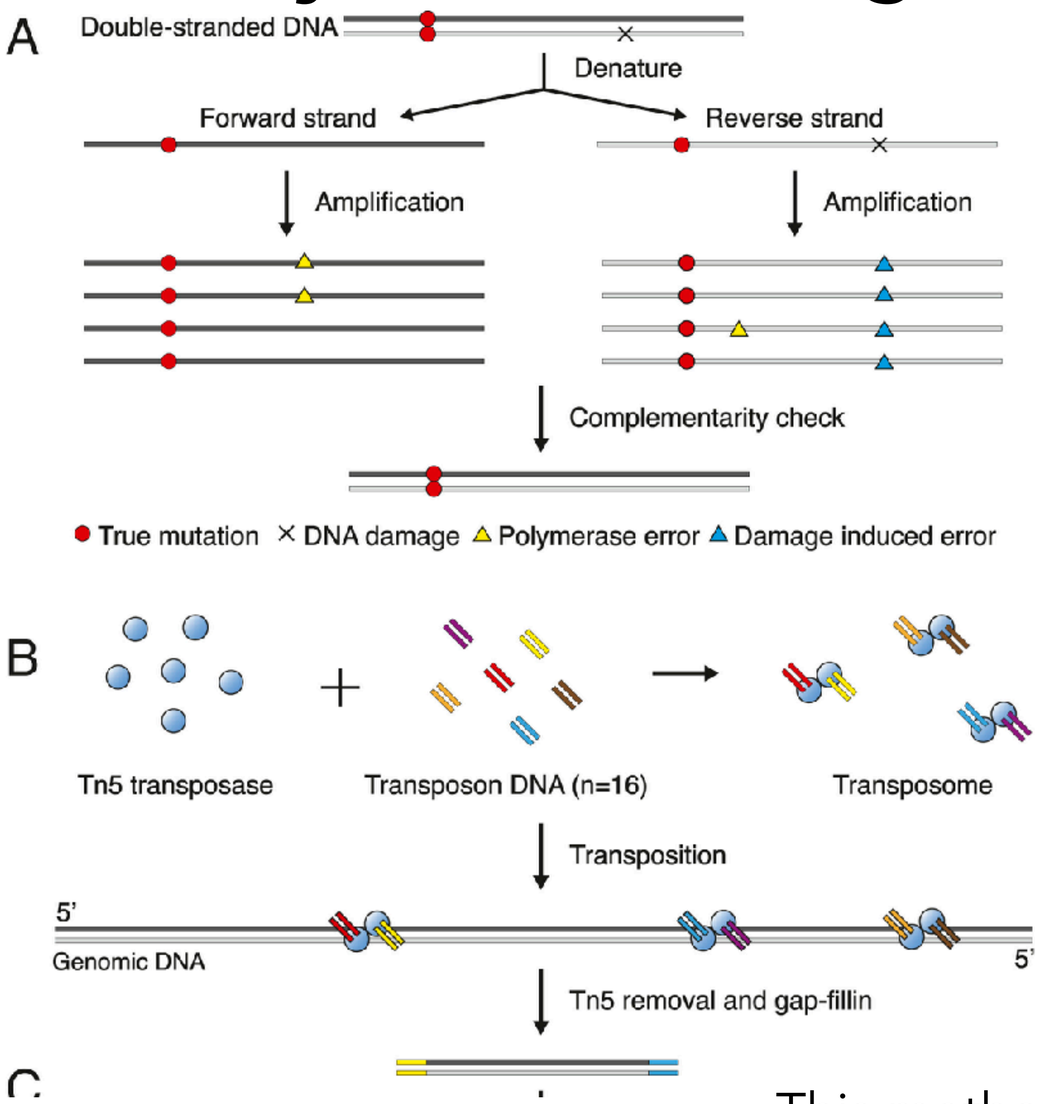


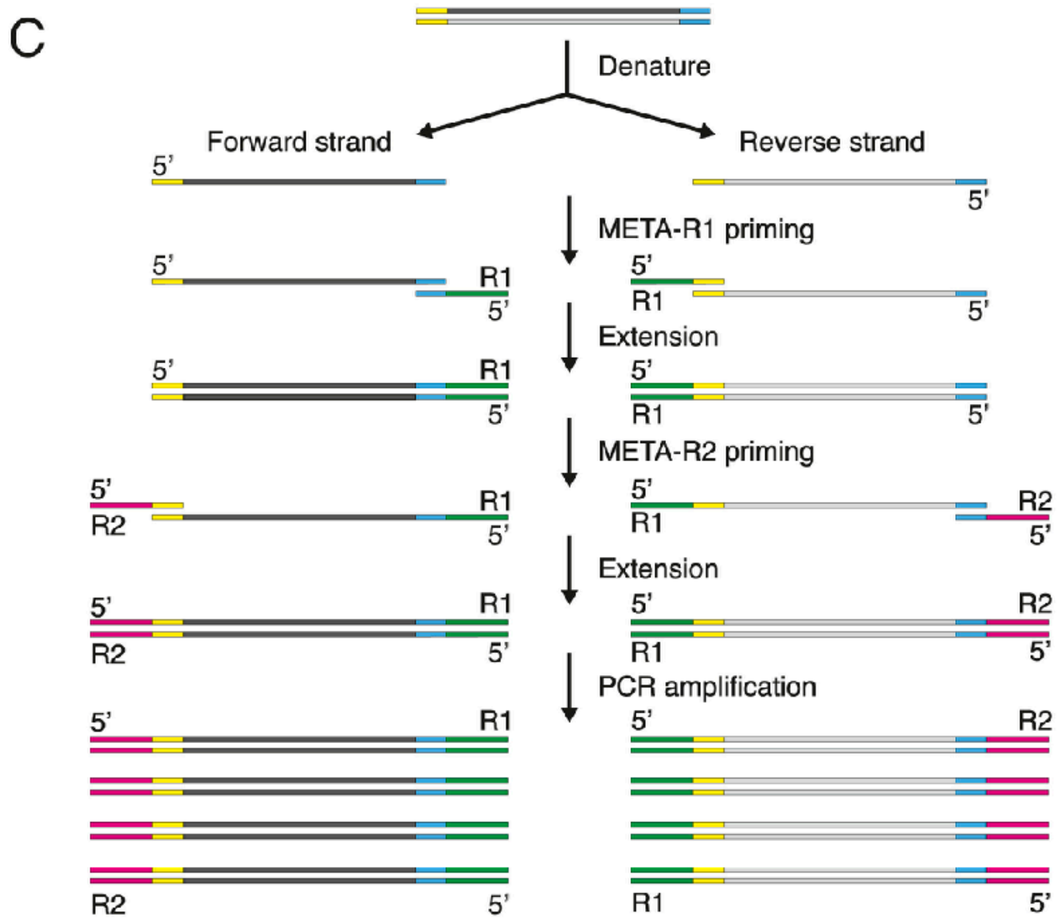
Single-cell genotyping in IVF



A cell is plucked from a human embryo created using *in vitro* fertilization so that it can be screened for genetic disorders. (This is done at the cleavage stage 6-8 cell embryo or blastocyst stage)

Enzymatic whole genome amplification to detect CNV

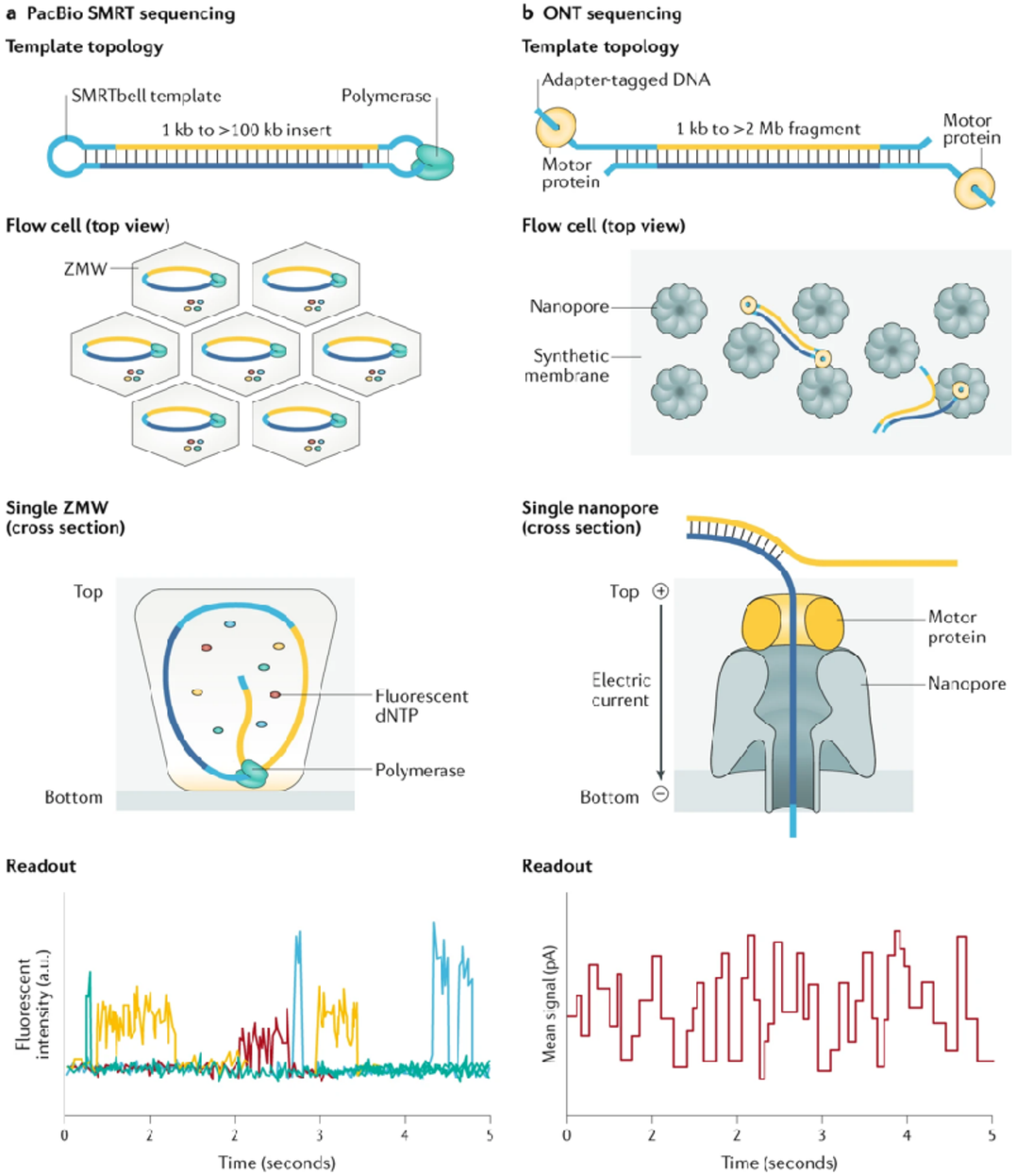




This method allows to discriminate true mutations from preparation induced sequencing errors

Xing et al. (2021) PNAS (Sunney Xie lab)

Long-read sequencing helps in genome sequencing



Long-read sequencing is Nature Method of the year 2023

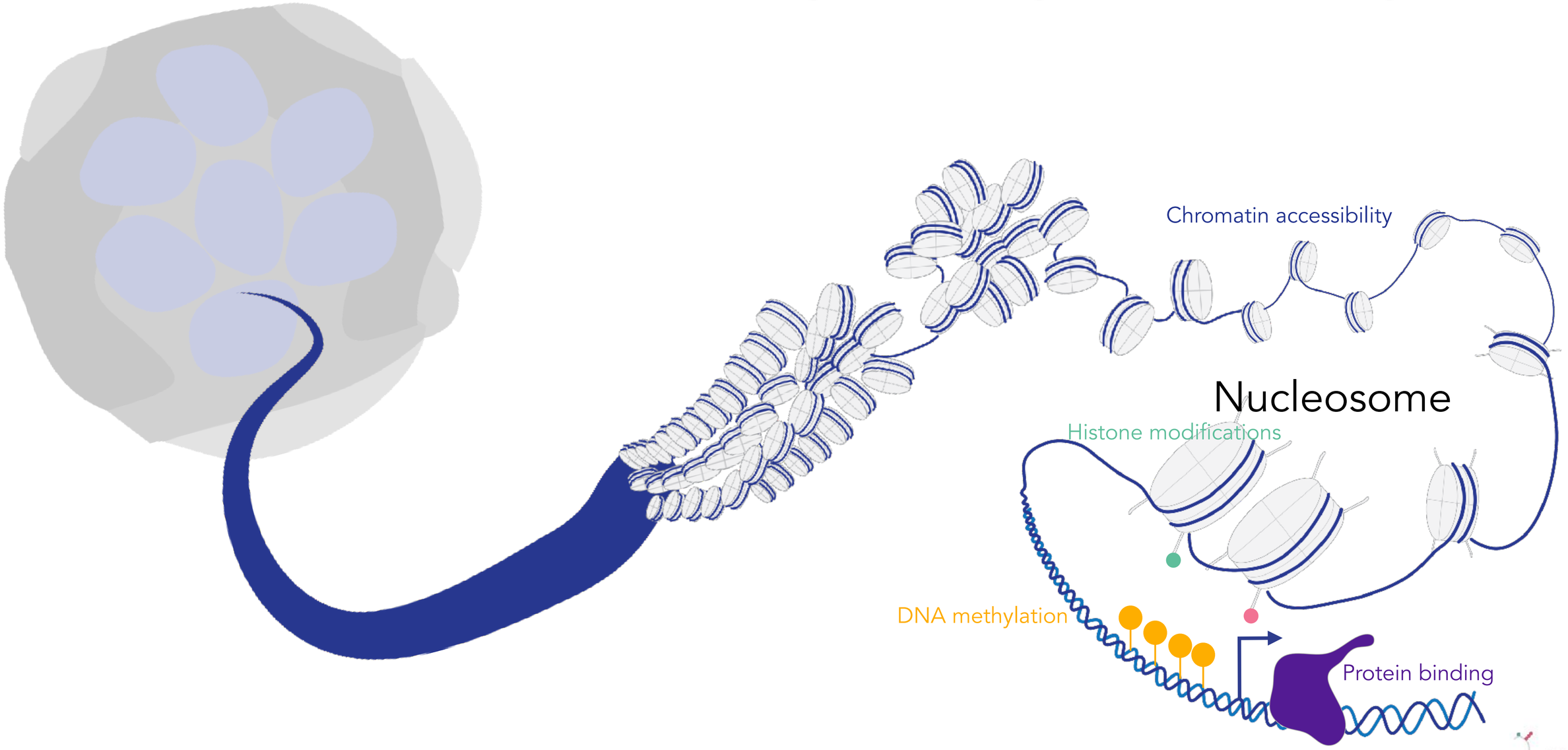
Long reads can help to quantify indels and repetitive regions

Long reads are needed for genome assembly

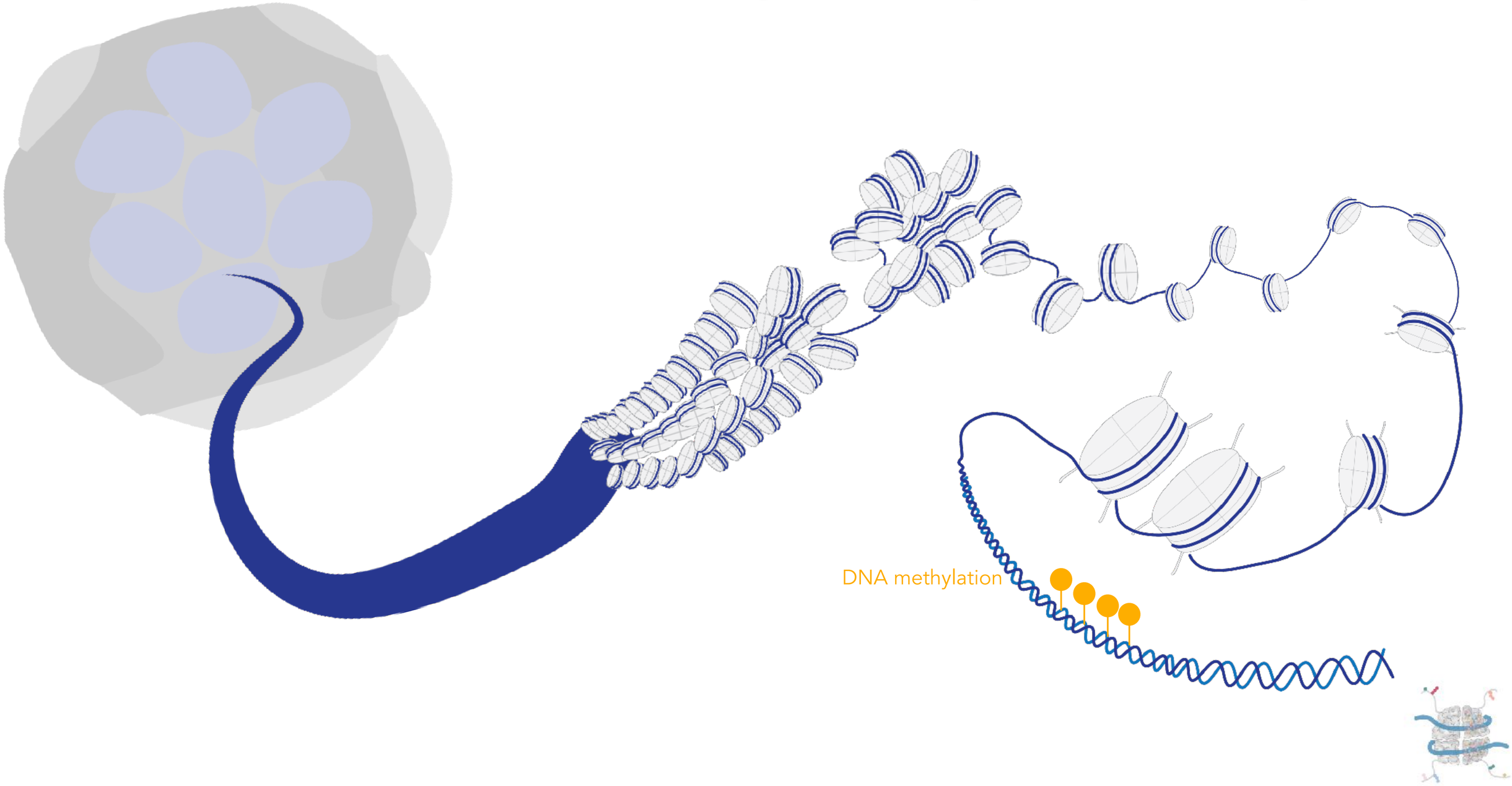
Two main methods from PacBio and Oxford Nanopore

Logsdon et al. (2020) Nature Rev. Gen.

Profiling the epigenome in single cells

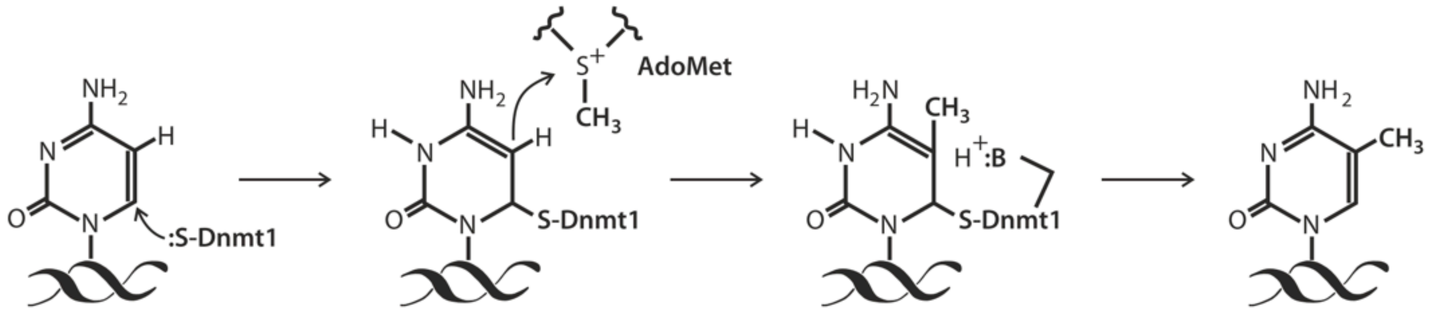


Profiling the epigenome in single cells

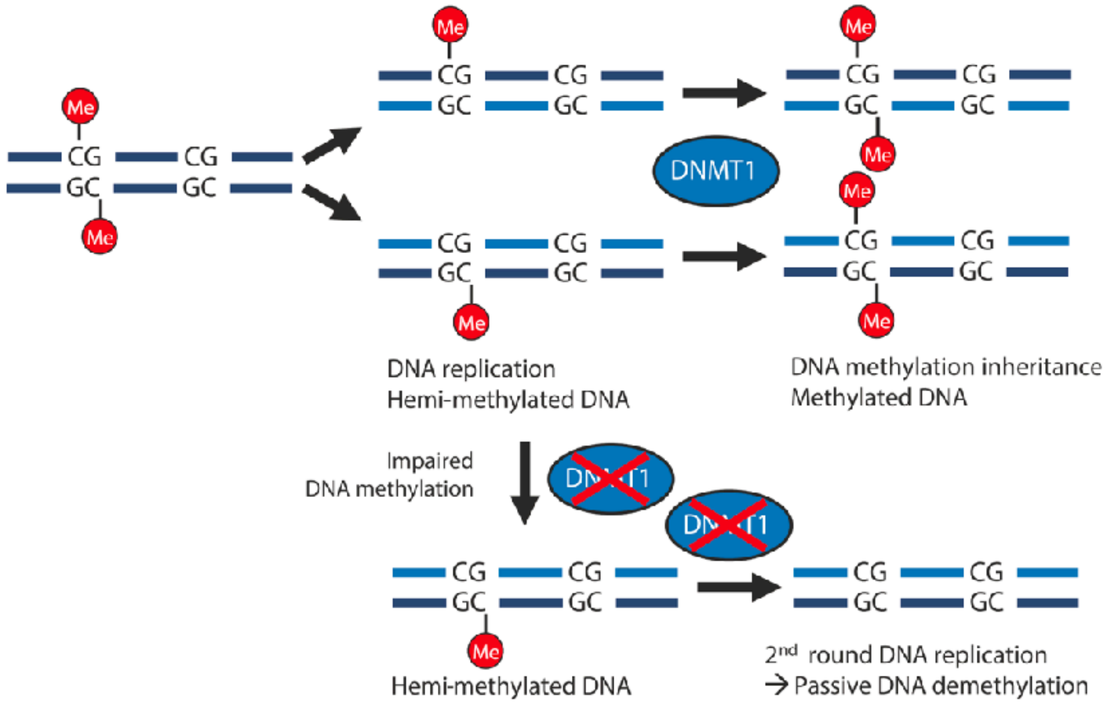


Cytosin bases can be methylated

Dnmt1 is important for maintenance of DNA-methylation



In mammalian genomes CG methylation is the most common type of DNA-methylation



70-80% of CpGs are methylated

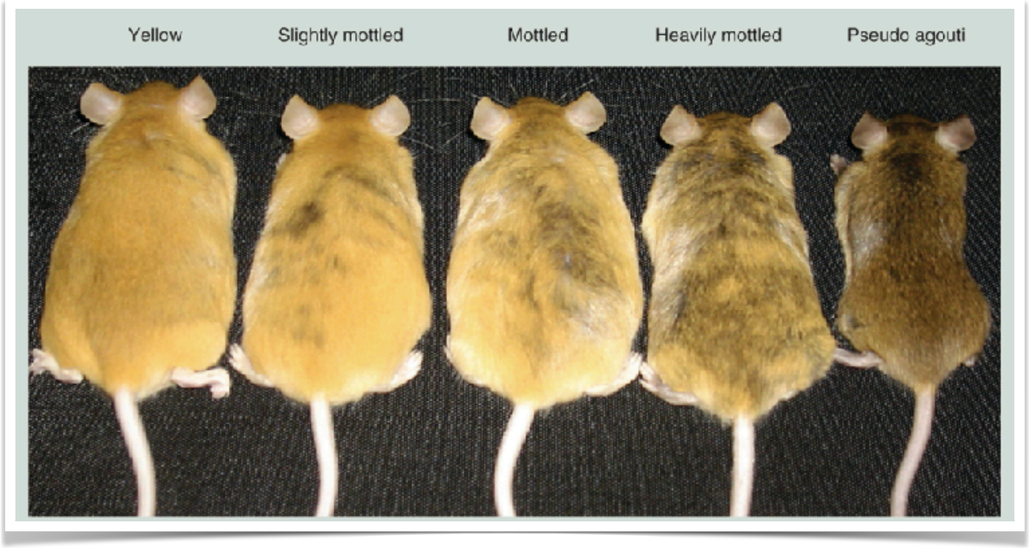
Mammalian promoters and regulatory elements often contain CpG islands - which are not methylated

Promoter methylation is usually associated with silencing

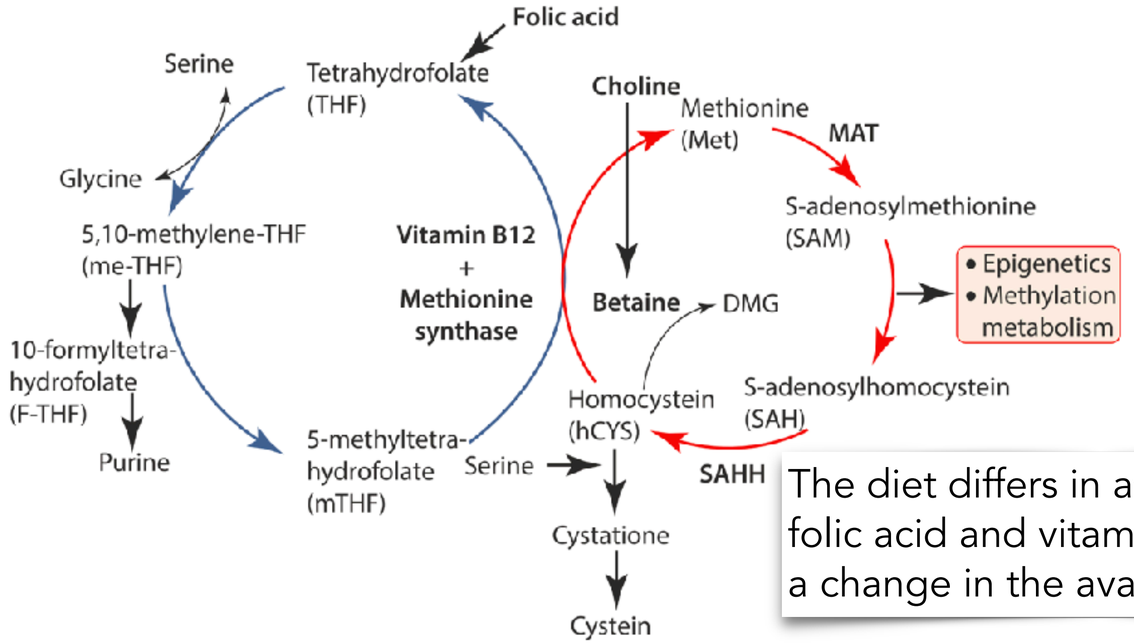
Transposons are often methylated

Paro (2021) Introduction to Epigenetics

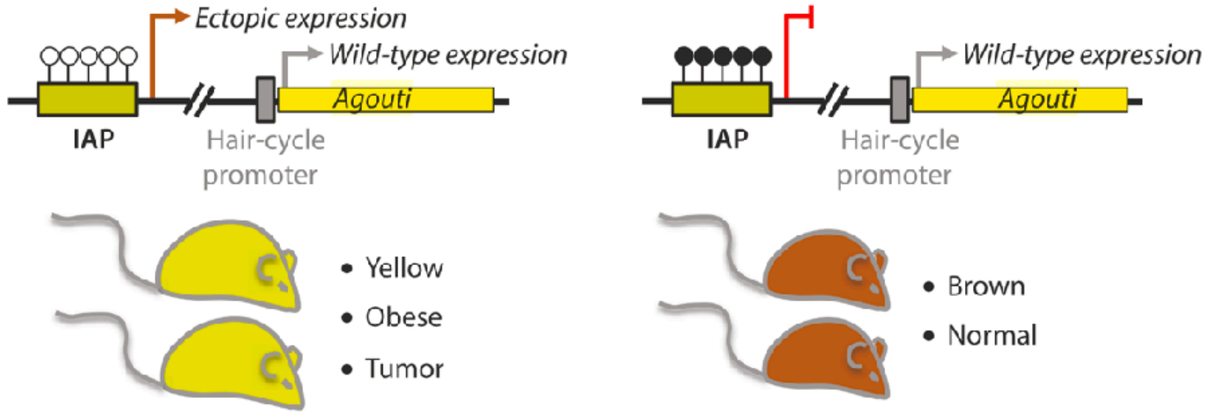
DNA methylation suppresses retroelements



Genetically identical mice fed with 5 different diets during pregnancy



The diet differs in availability of folic acid and vitamin B12 causing a change in the availability of SAM



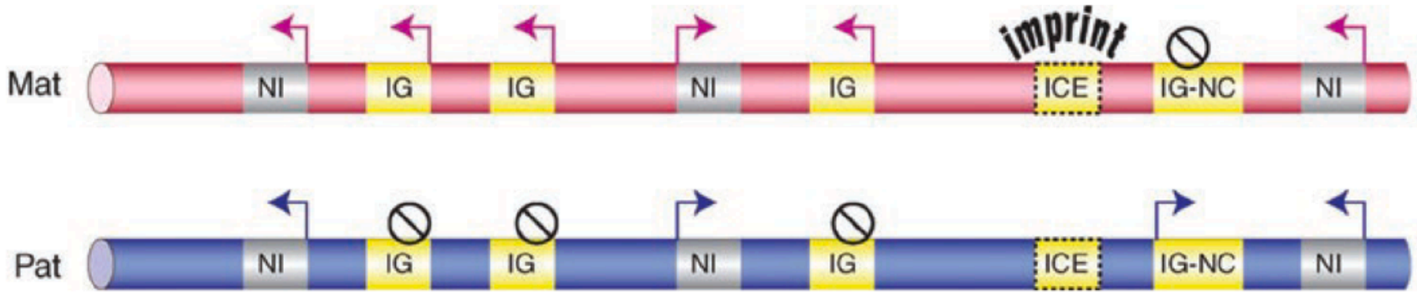
IAP is a retroelement that is silenced by DNA methylation

Agouti viable yellow is a very specific example!

Dolinoy et al. (2006) Environ. Health Perspect (Randy Jirtle lab)

Paro (2021) Introduction to Epigenetics

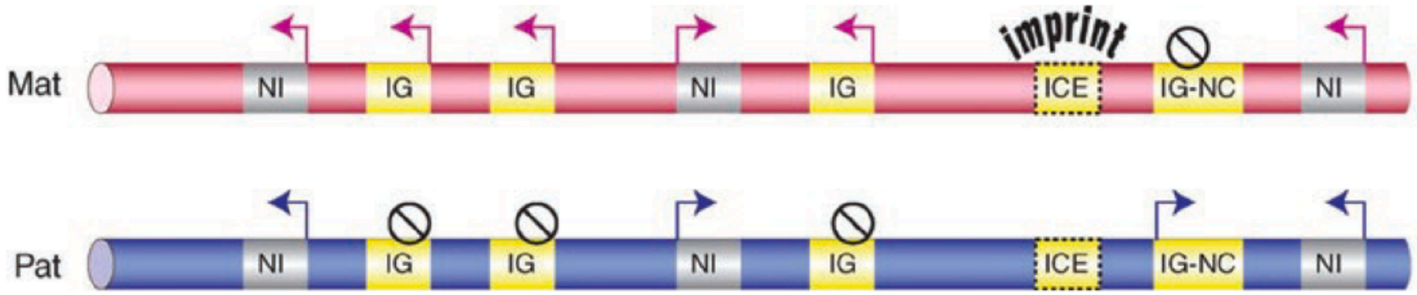
DNA methylation controls imprinting - parent of origin expresion



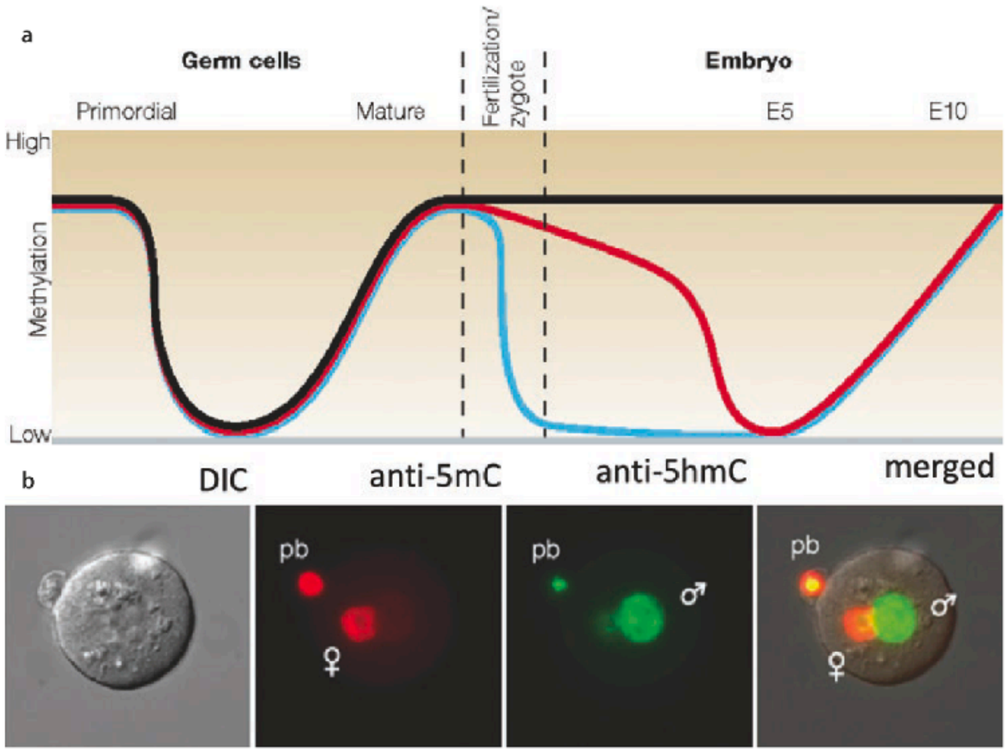
Typical imprinted gene cluster with constitutive genes and non-coding RNA

Paro (2021) Introduction to Epigenetics

DNA methylation controls imprinting - parent of origin expresion



Typical imprinted gene cluster with constitutive genes and non-coding RNA



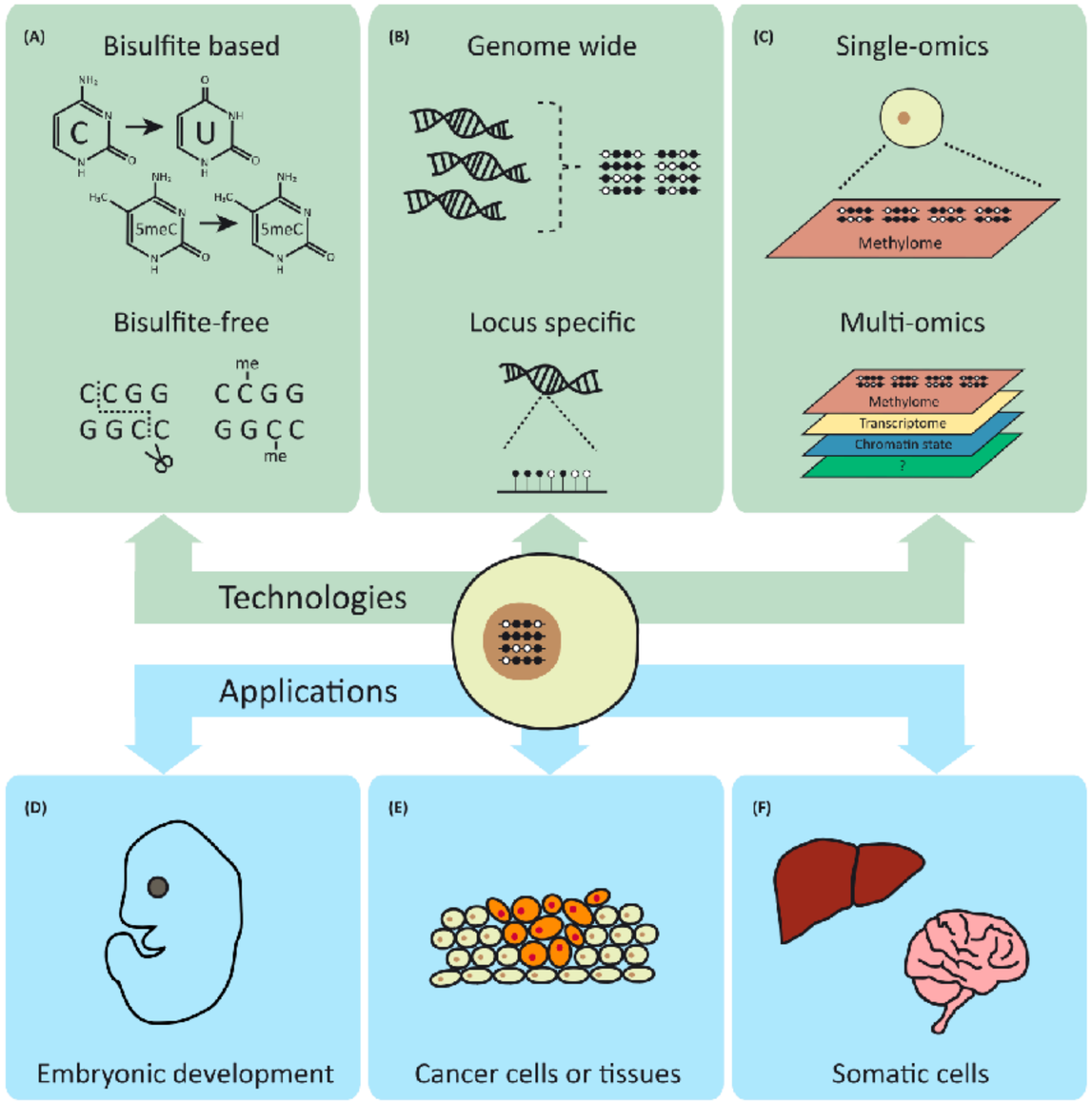
imprinted genes
maternal genome
paternal genome

Imprints are reset during germline development

Global DNA-methylation is erased and reestablished
during early embryonic development

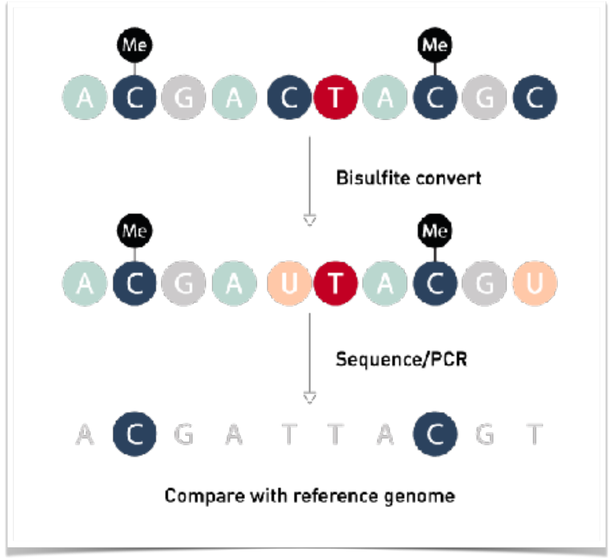
Paro (2021) Introduction to Epigenetics

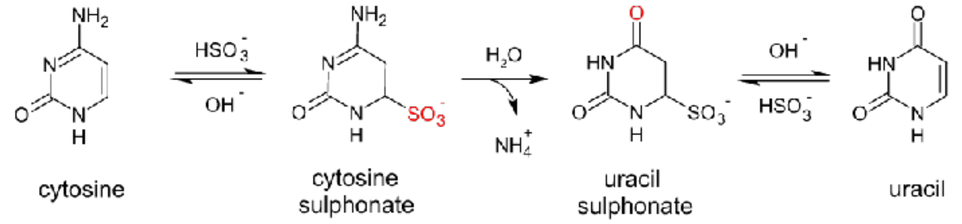
DNA methylation controls imprinting - parent of origin expresion

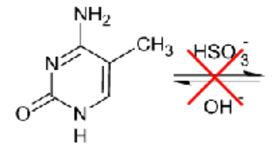


Karemaker (2018) Trends in Biotechnology

Bisulfite treatment







5-methylcytosine

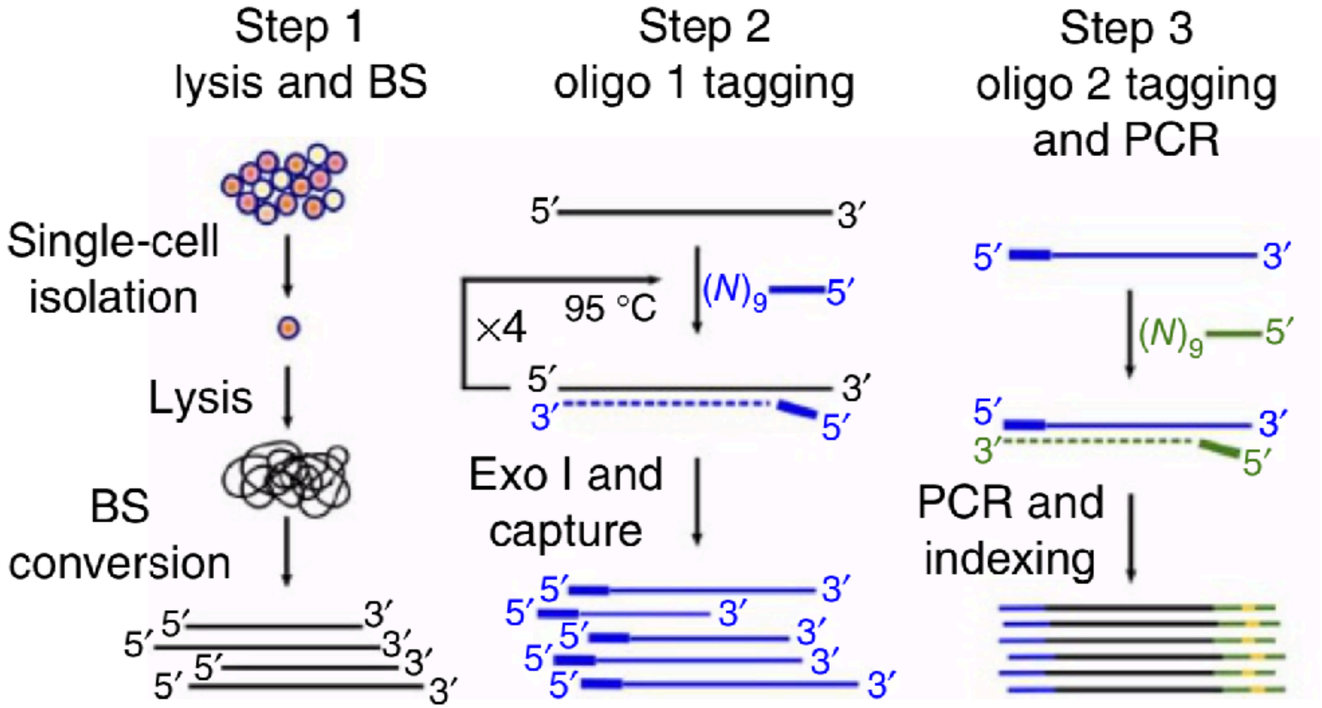
unmethylated Cytosine is converted to Uracil (read as Thymine)

DNA methylation analyses in single cells

Single-cell genome-wide bisulfite sequencing for assessing epigenetic heterogeneity

Sébastien A Smallwood[1,6], Heather J Lee[1,2,6], Christof Angermueller[3], Felix Krueger[4], Heba Saadeh[1], Julian Peat[1], Simon R Andrews[4], Oliver Stegle[3], Wolf Reik[1,2,5,7] & Gavin Kelsey[1,5,7]

We report a single-cell bisulfite sequencing (scBS-seq) method that can be used to accurately measure DNA methylation at up to 48.4% of CpG sites. Embryonic stem cells grown in serum or in 2i medium displayed epigenetic heterogeneity, with '2i-like' cells present in serum culture. Integration of 12 individual mouse oocyte datasets largely recapitulated the whole DNA methylome, which makes scBS-seq a versatile tool to explore DNA methylation in rare cells and heterogeneous populations.

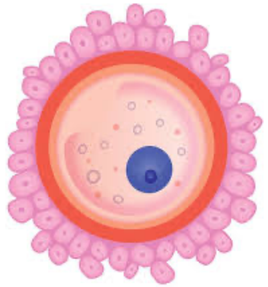


BS treatment:
DNA fragmentation &
conversion of unmethylated
cytosine to thymine

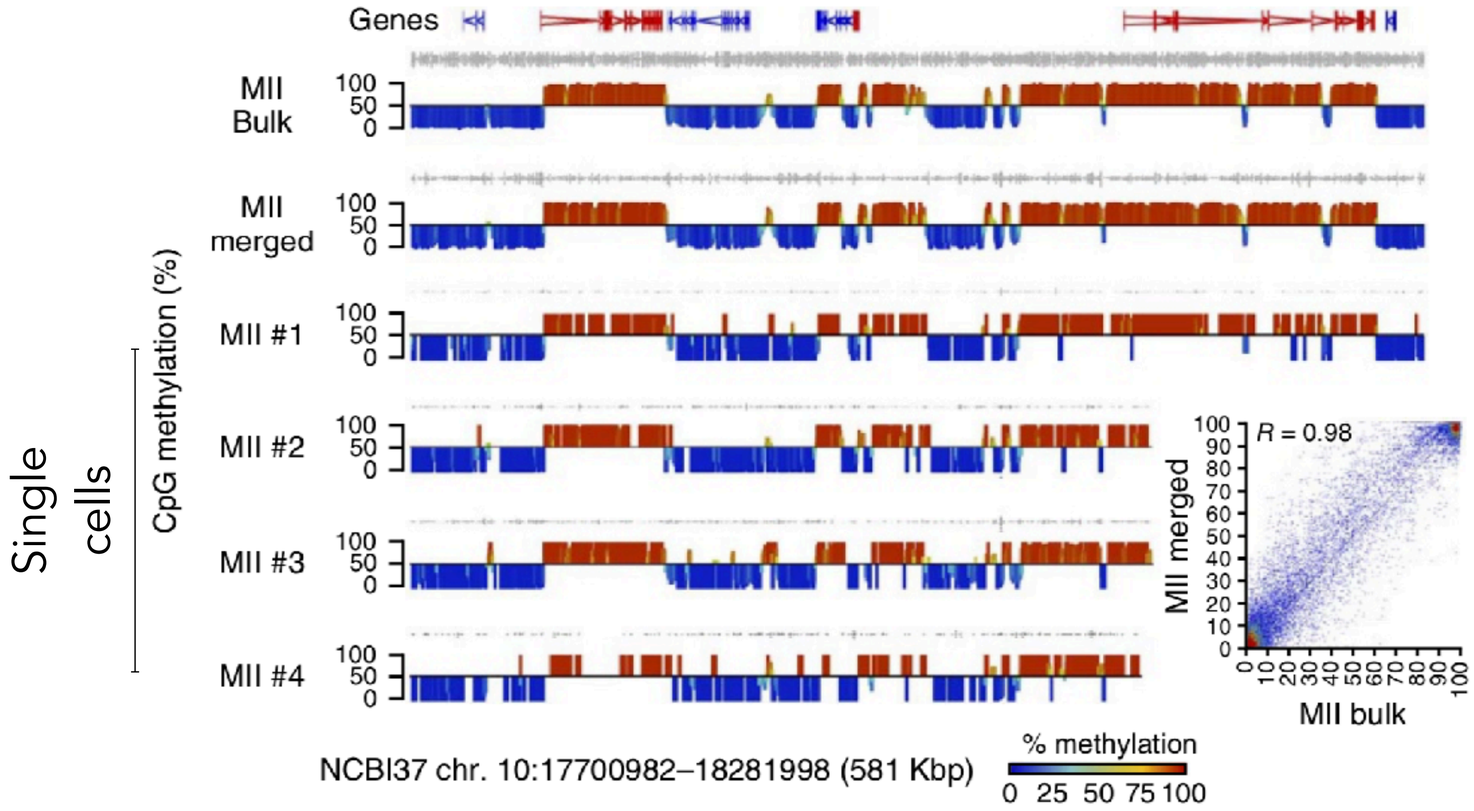
- 2 steps of random priming & extension to introduce sequencing adapters
- PCR amplification

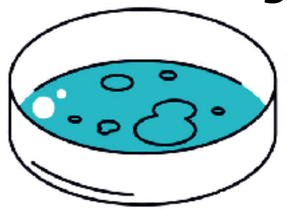
Smallwood et al., Nature Methods 2014

DNA methylation analyses in single cells

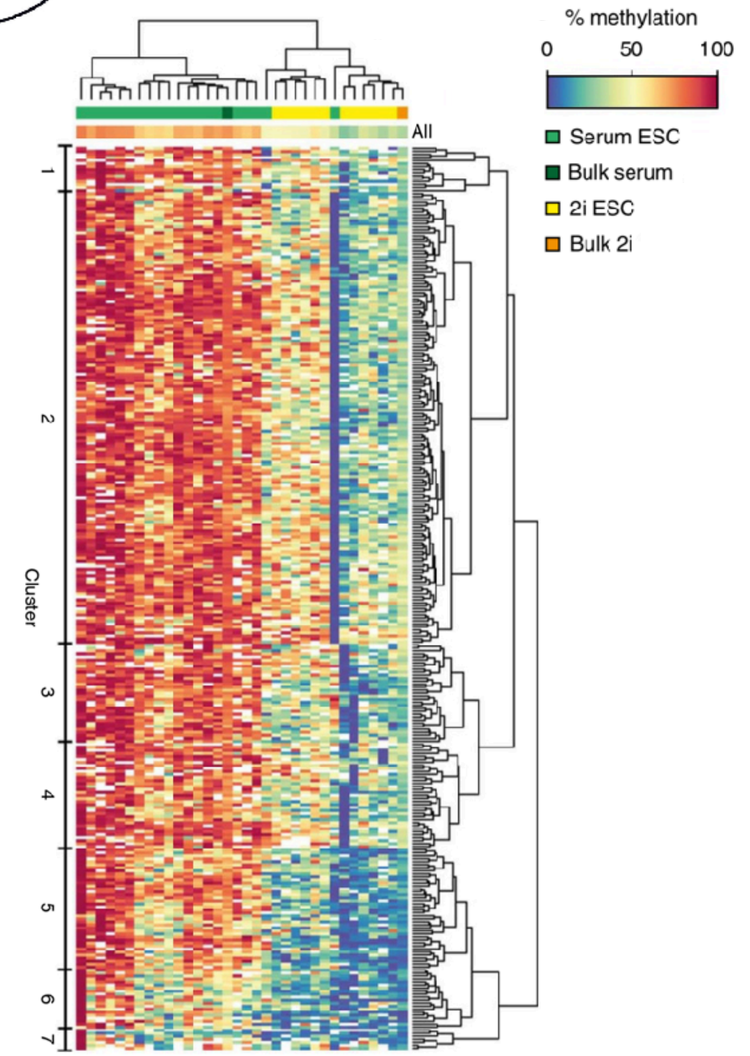


CpG methylation percentage quantified over 2-kb windows in mouse oocytes





DNA methylation heterogeneity in mESCs



Smallwood et al., Nature Methods 2014

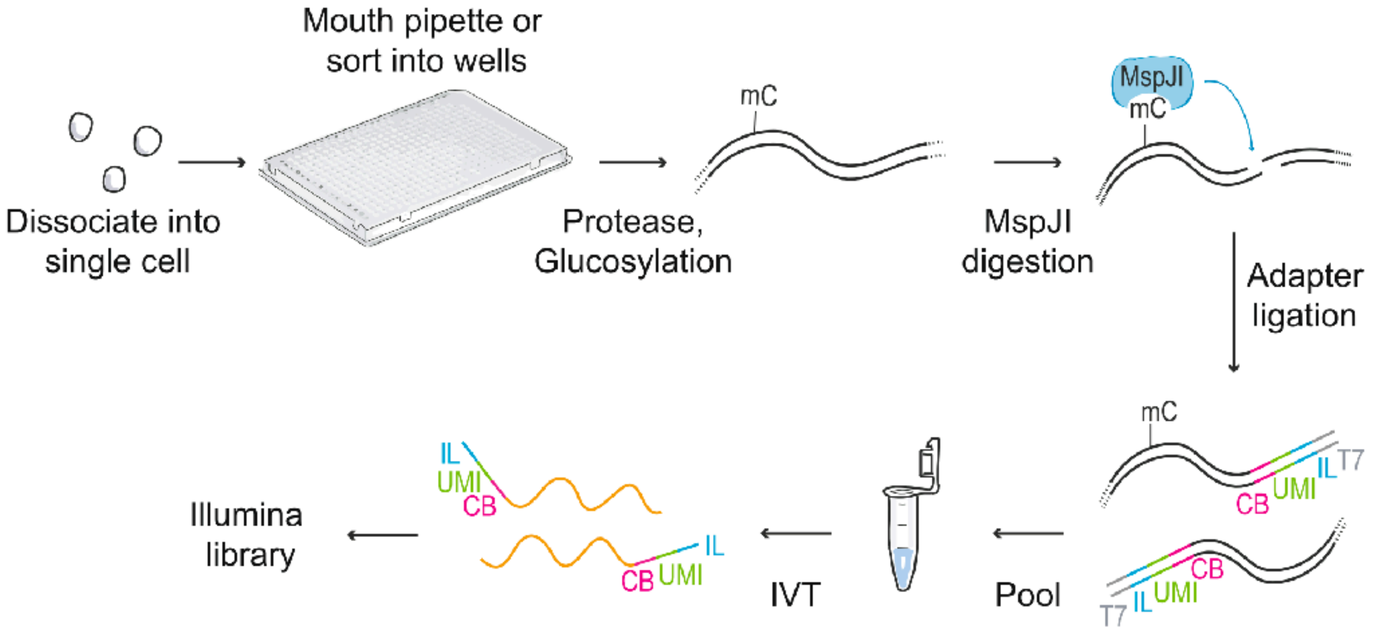
DNA methylation analyses in single cells - bisulfite independent approach

ARTICLE

https://doi.org/10.1038/s41467-021-21532-6 OPEN

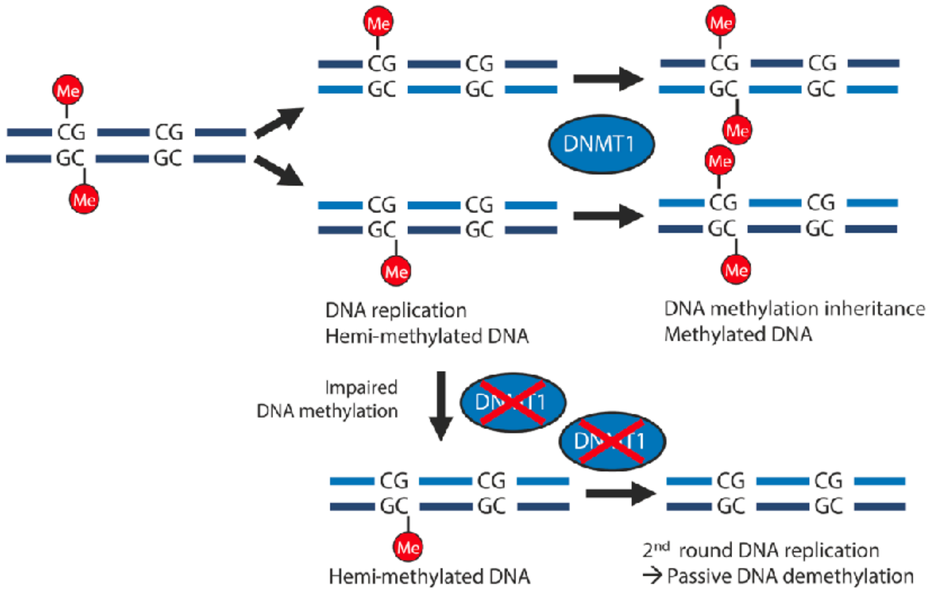
Strand-specific single-cell methylomics reveals distinct modes of DNA demethylation dynamics during early mammalian development

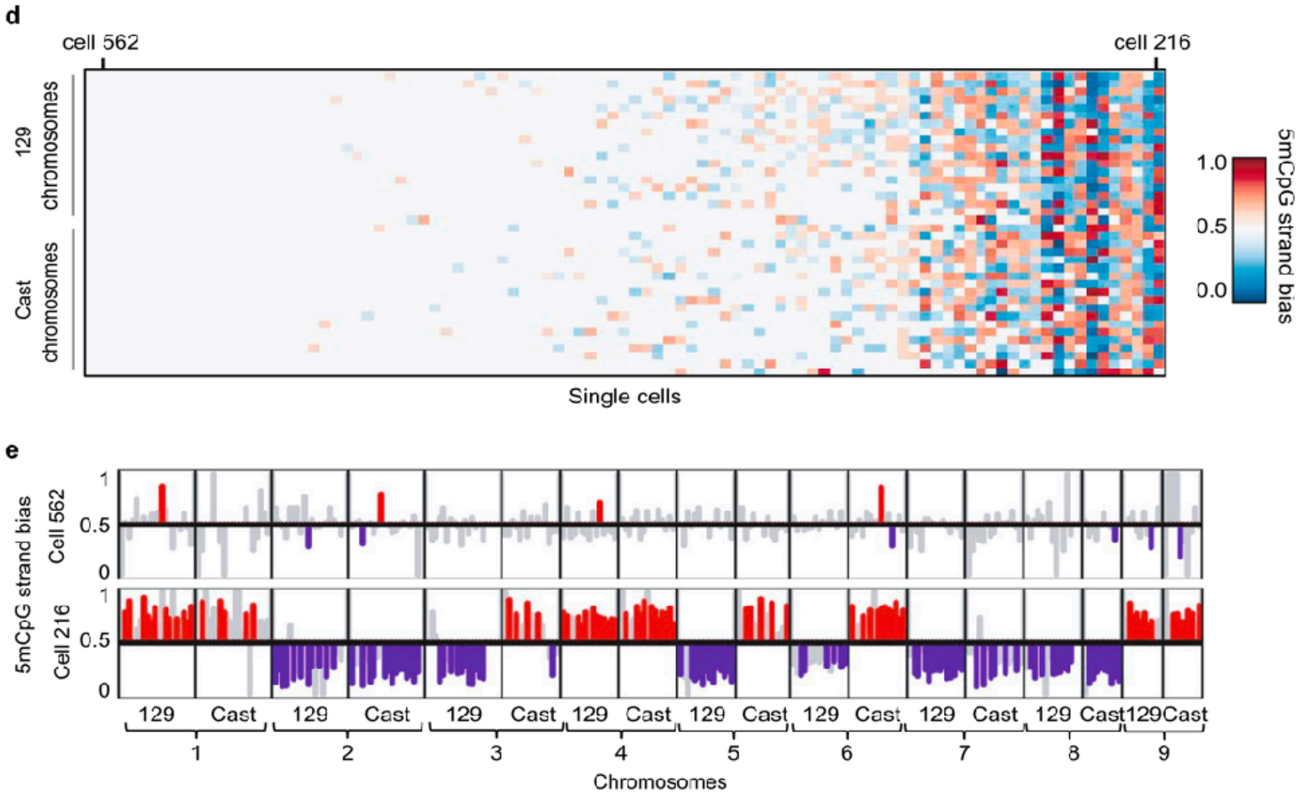
Maya Sen[1,8], Dylan Mooijman[1,7,8], Alex Chialastri[2,3,8], Jean-Charles Boisset[1], Mina Popovic[4], Björn Heindryckx[4], Susana M. Chuva de Sousa Lopes[4,5], Siddharth S. Dey[2,3,6✉] & Alexander van Oudenaarden[1✉]



Sen et al., Nature Comm. 2021

DNA methylation analyses in single cells - bisulfite independent approach



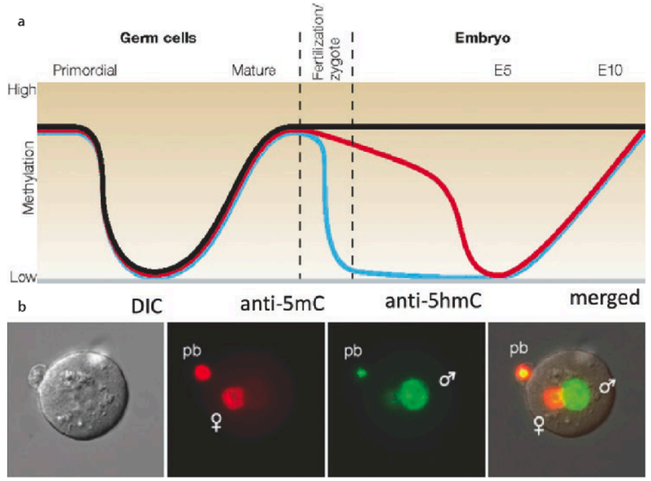


DNA-methylation distribution between DNA strands is heterogeneous

suggesting loss of maintenance DNA-methylation in some cells

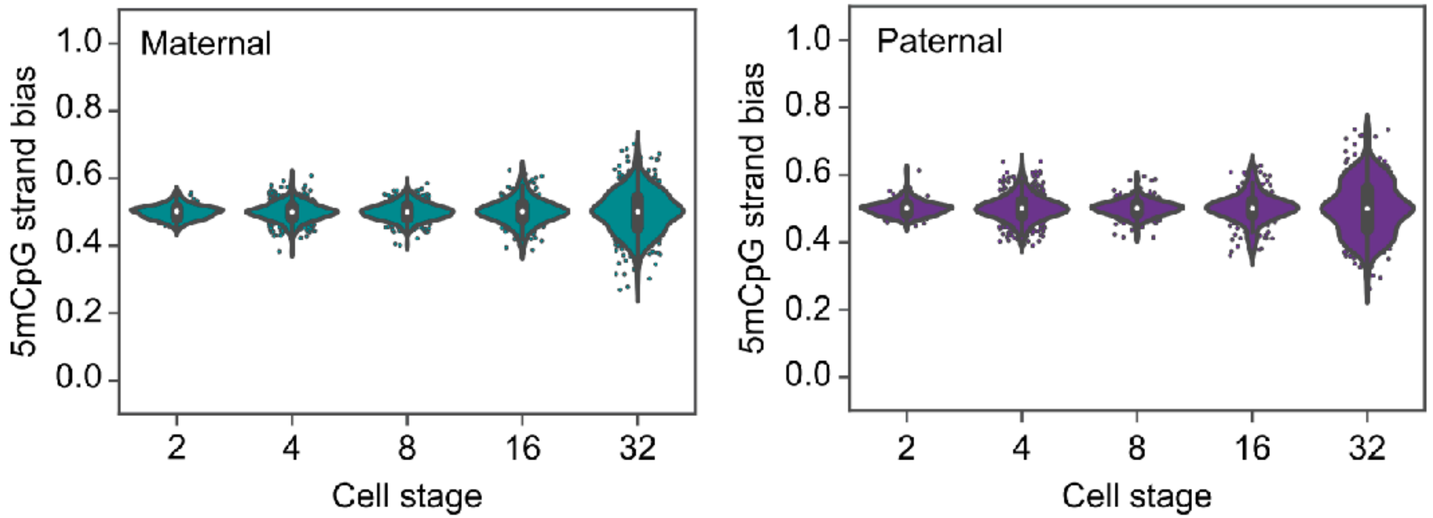
Sen et al., Nature Comm. 2021

DNA methylation analyses in single cells - bisulfite independent approach



Is DNA-methylation passively lost in early embryos, because of inactive DNMT1?

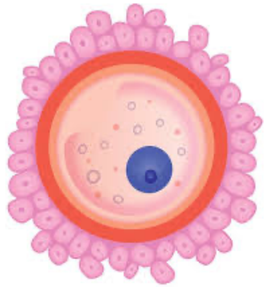
332 cells from 42 embryos



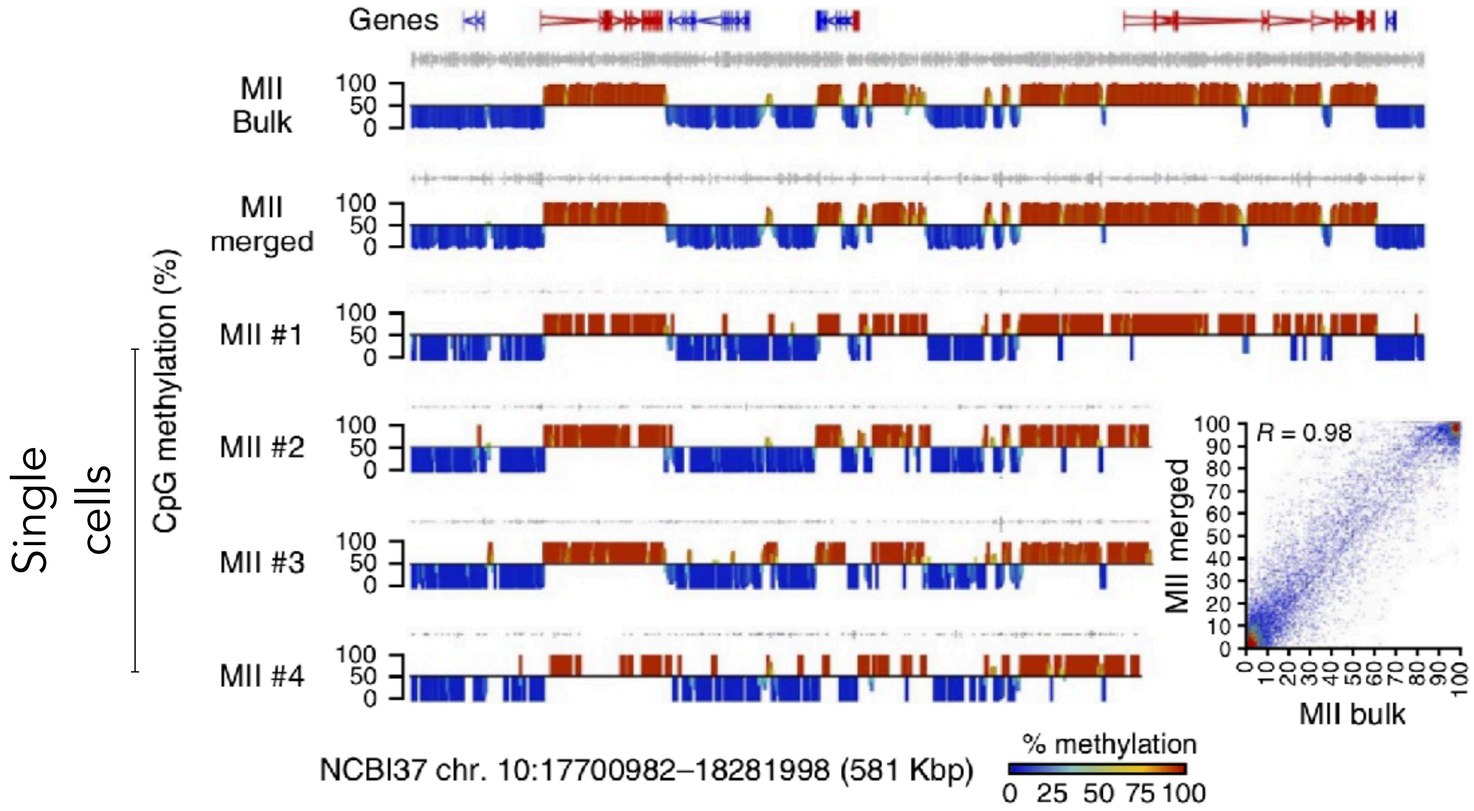
In early embryos DNA-methylation is not strand specific (indicating maintenance of methylation)
After the 16-cell stage strand biased methylation starts to appear.

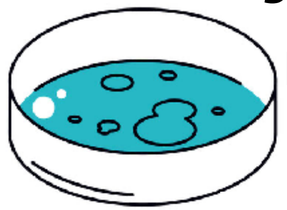
Sen et al., Nature Comm. 2021

DNA methylation analyses in single cells

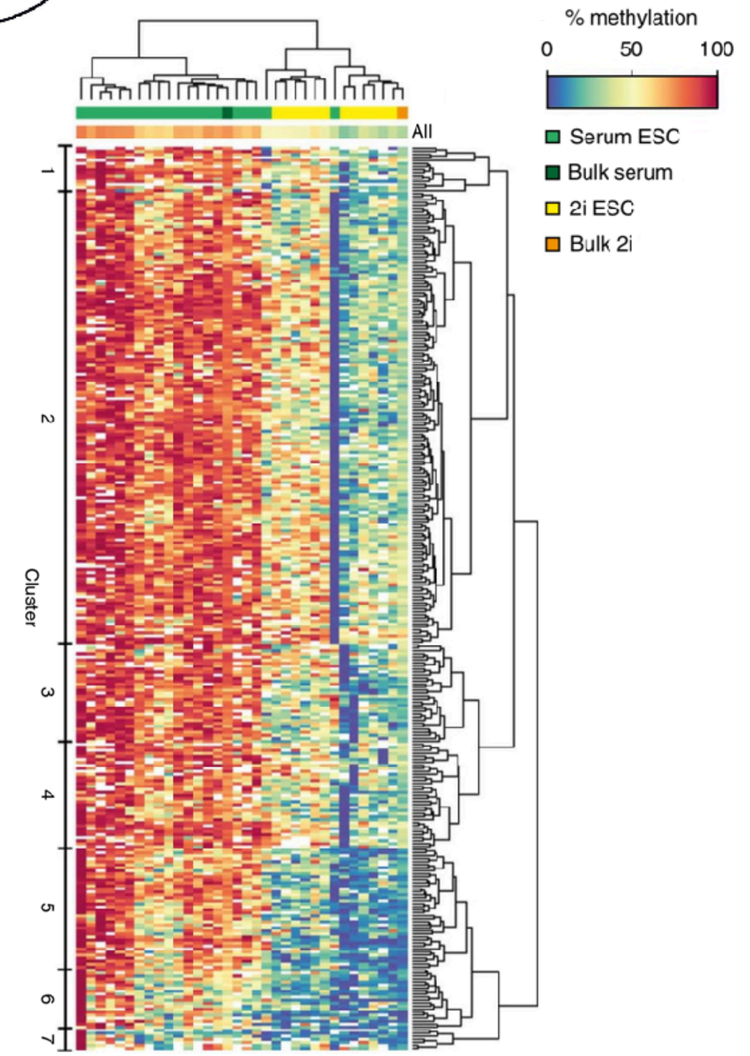


CpG methylation percentage quantified over 2-kb windows in mouse oocytes



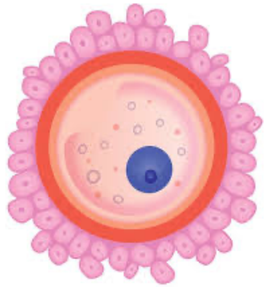


DNA methylation heterogeneity in mESCs

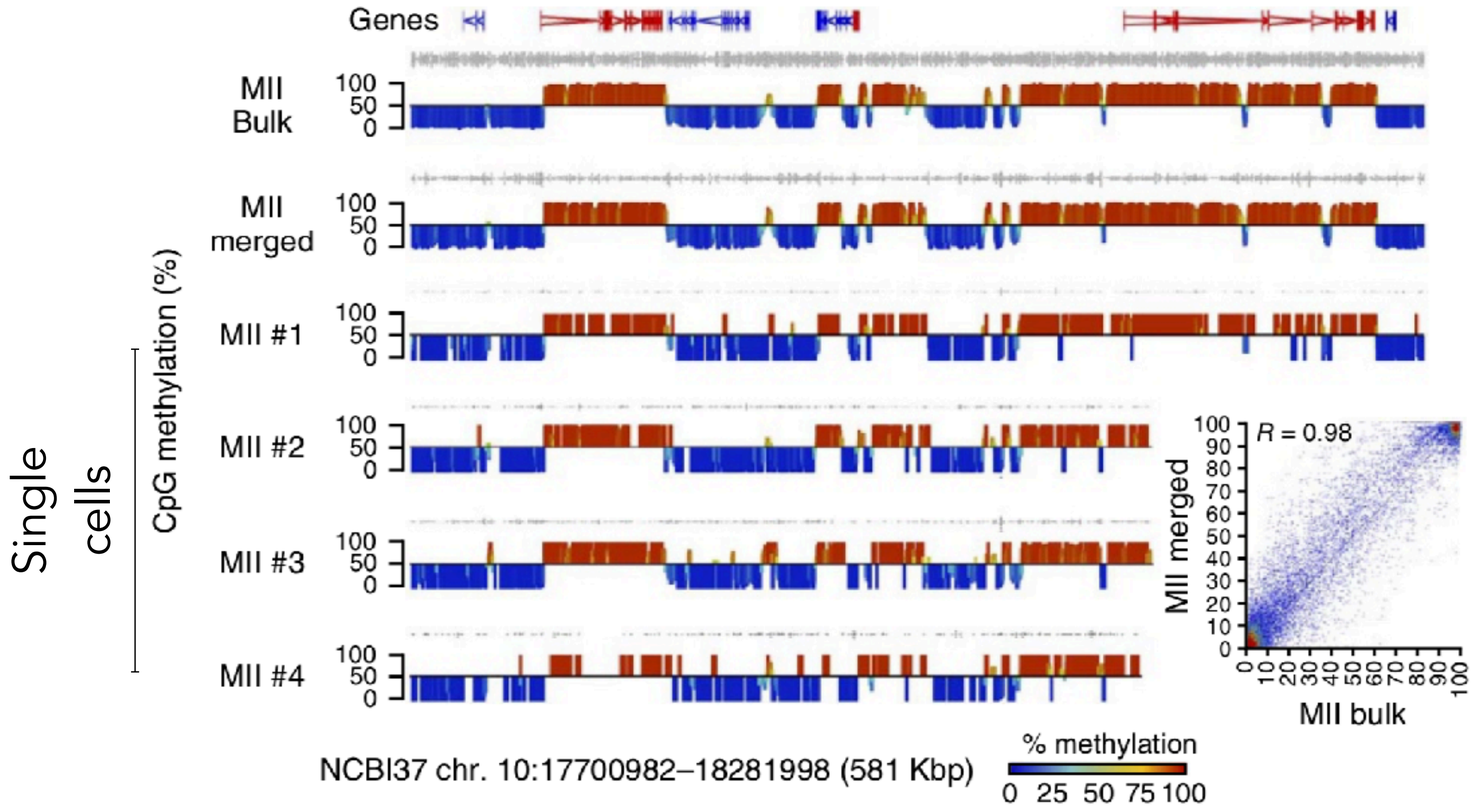


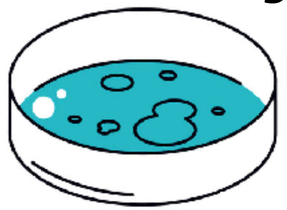
Smallwood et al., Nature Methods 2014

DNA methylation analyses in single cells

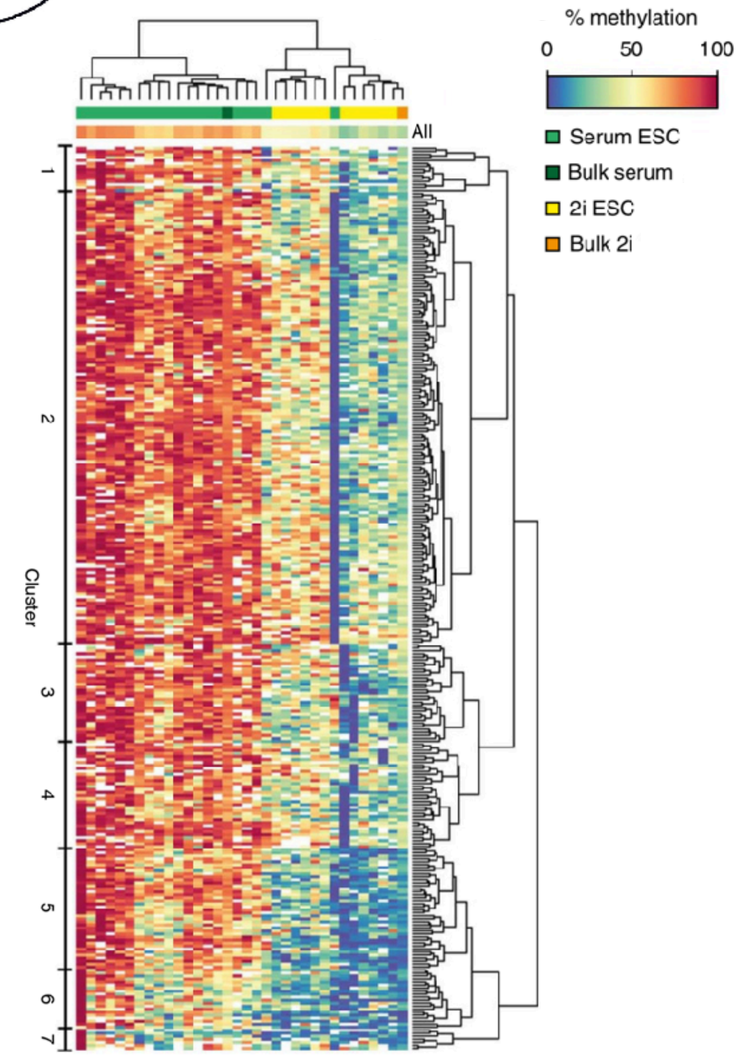


CpG methylation percentage quantified over 2-kb windows in mouse oocytes



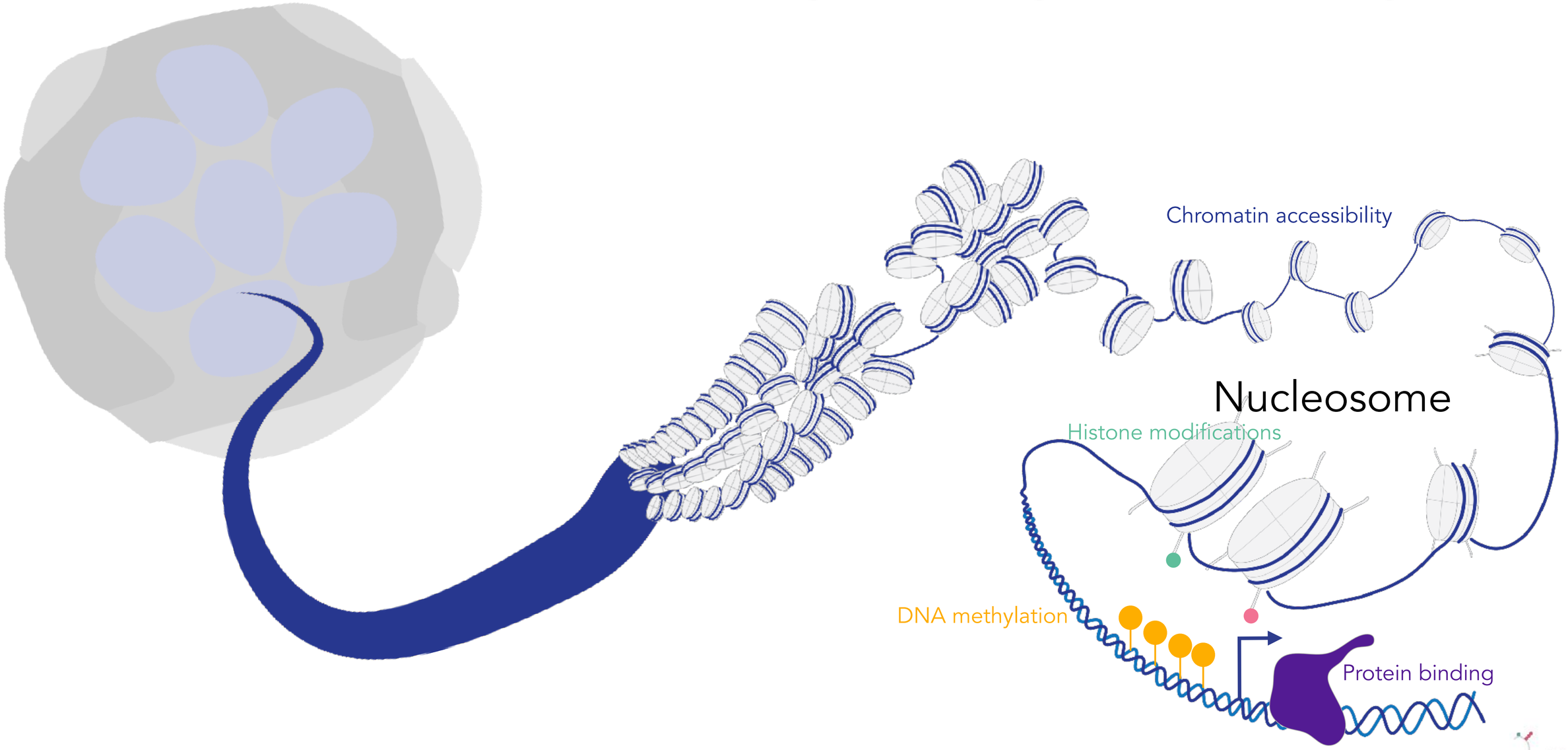


DNA methylation heterogeneity in mESCs

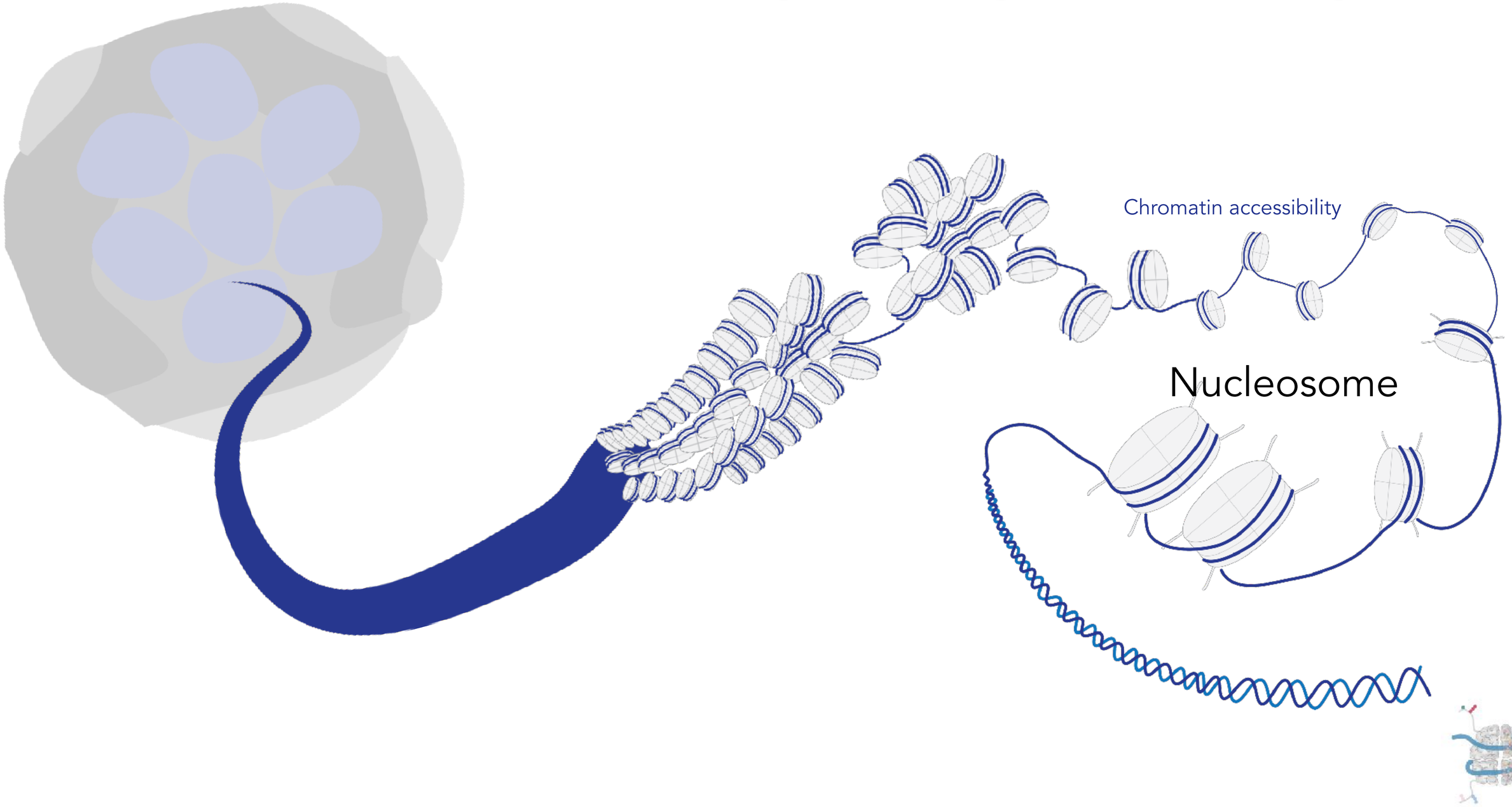


Smallwood et al., Nature Methods 2014

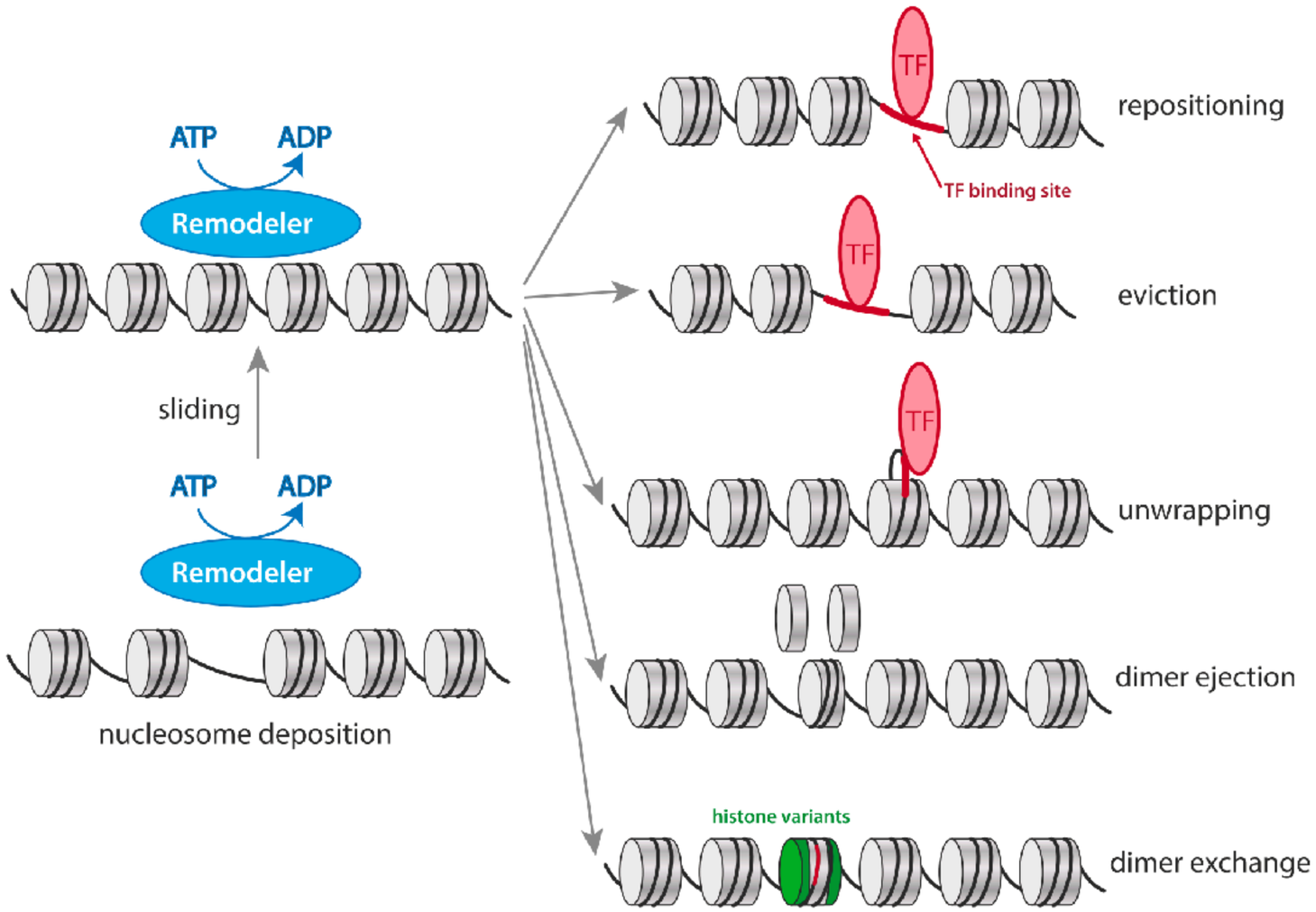
Profiling the epigenome in single cells



Profiling the epigenome in single cells



How do chromatin remodelers act?

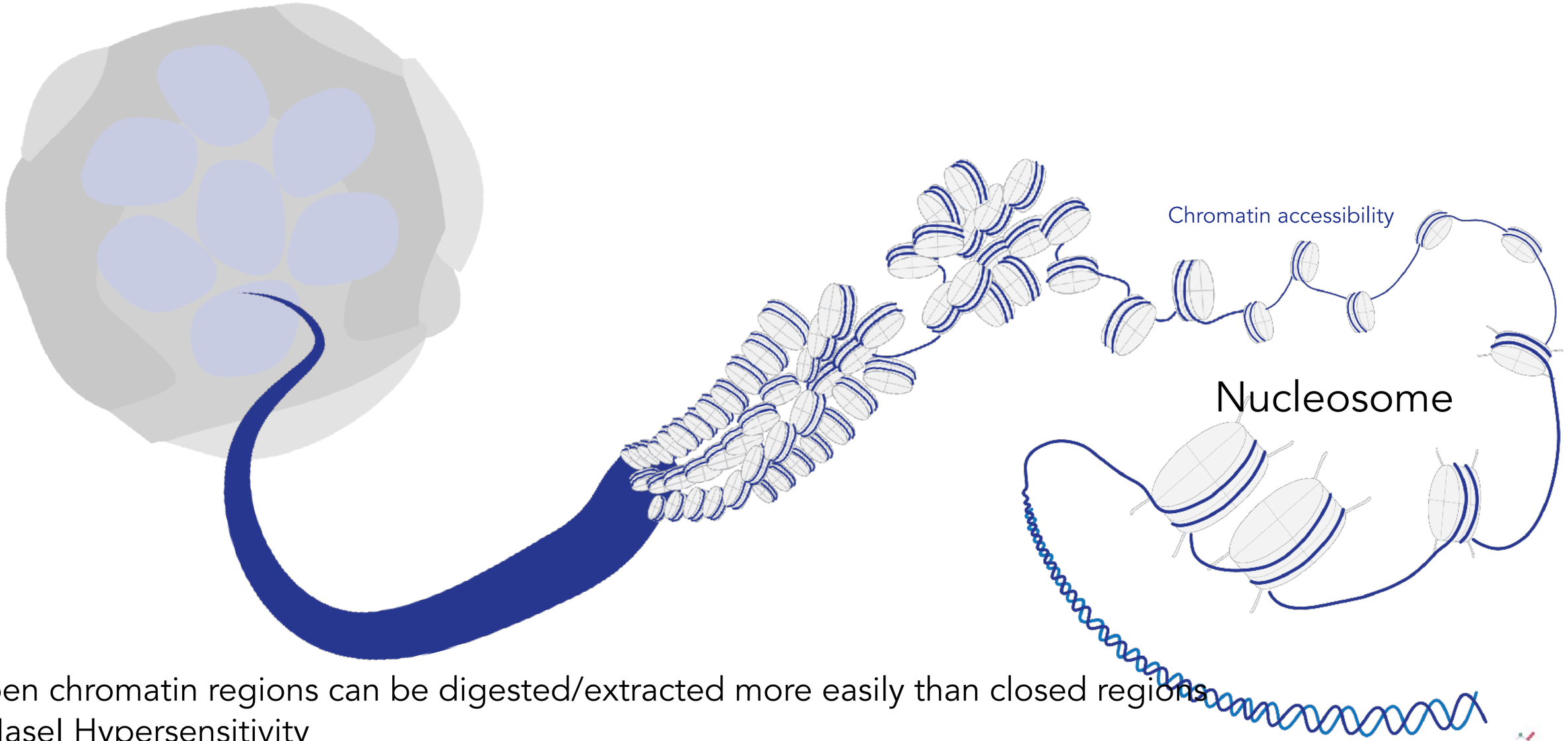


Remodelers can alter the nucleosome positioning at a givenlocus or change the histone composition

In general opening of chromatin is mostly

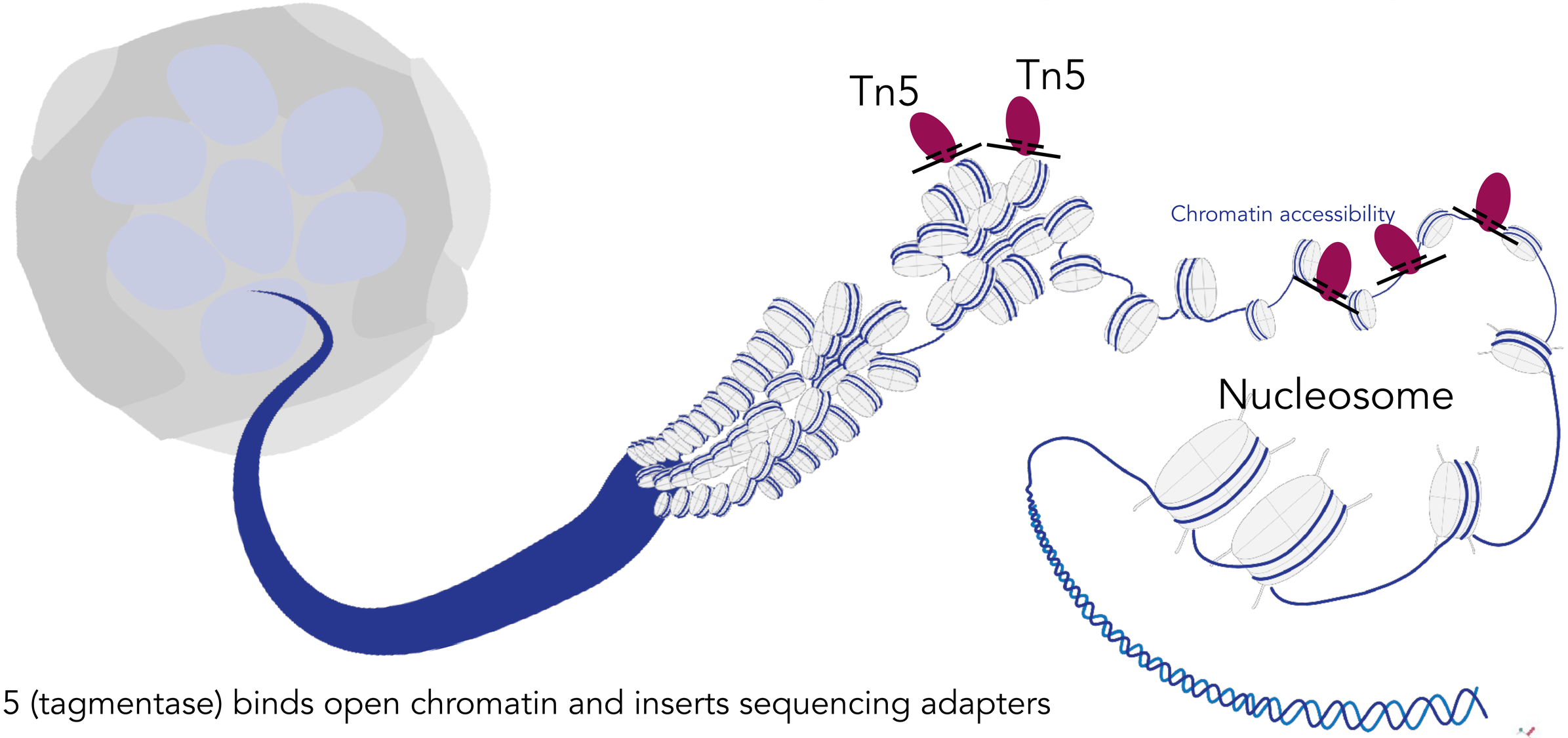
Paro (2021) Introduction to Epigenetics

Profiling the epigenome in single cells



Open chromatin regions can be digested/extracted more easily than closed regions
DNaseI Hypersensitivity
MNase-Seq
Formaldehyde assisted isolation of regulatory elements (FAIRE)

Profiling the epigenome in single cells



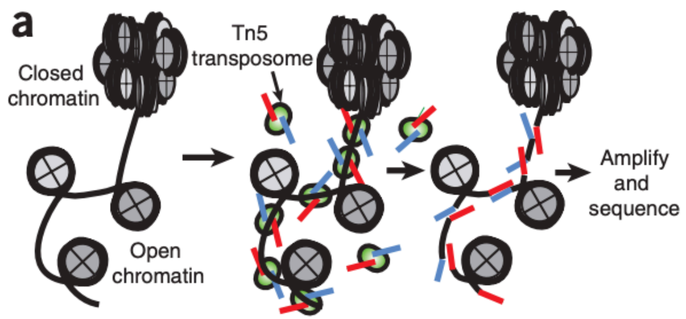
Tn5 (tagmentase) binds open chromatin and inserts sequencing adapters

We have already looked in detail into scATAC-seq - there are a few other methods

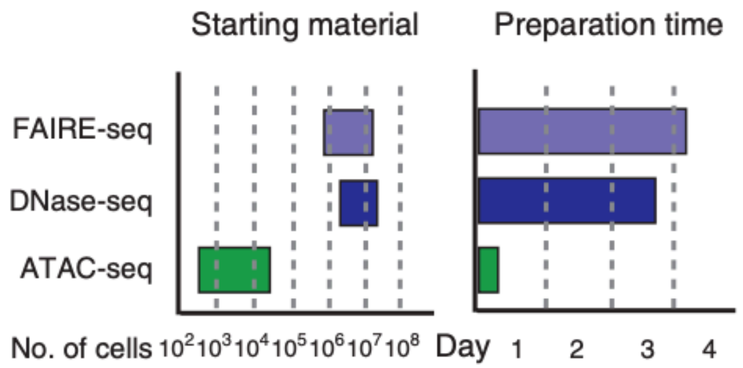
Nucleosome positioning and open chromatin profiling

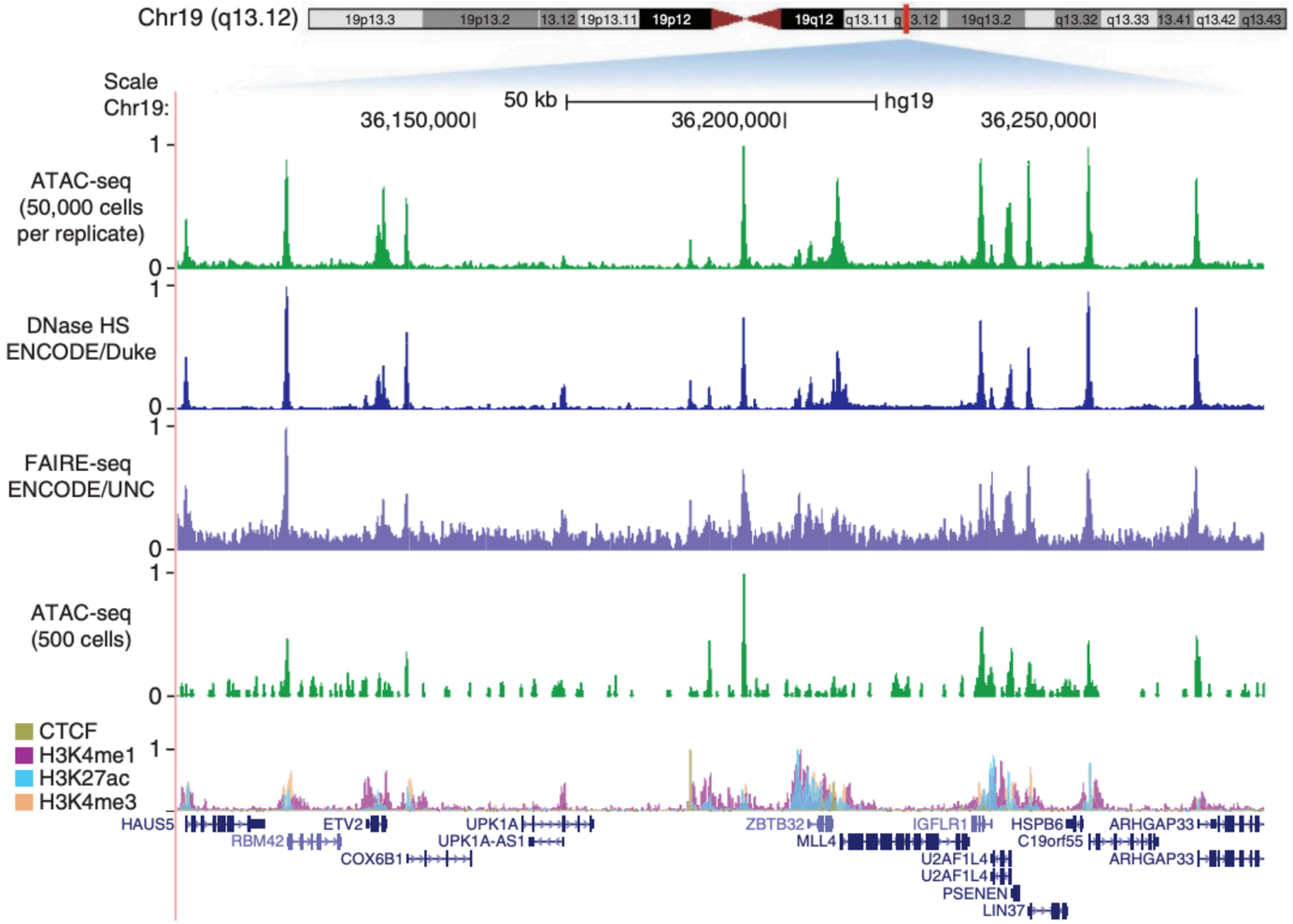
Transposition of native chromatin for fast and sensitive epigenomic profiling of open chromatin, DNA-binding proteins and nucleosome position

Jason D Buenrostro[1–3], Paul G Giresi[2,3], Lisa C Zaba[2,3], Howard Y Chang[2,3] & William J Greenleaf



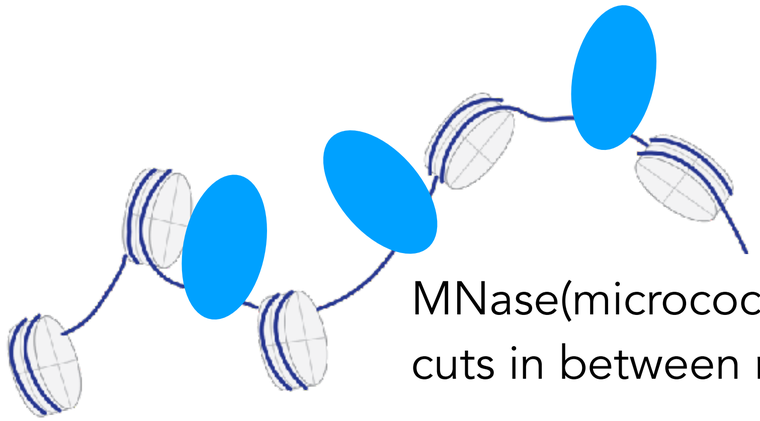
- Hyperactive mutant Tn5 Transposase
- Tagmentation: Cleave and tag dsDNA with sequencing adapters





Buenrostro et al. (2012) Nature Methods

Nucleosome positioning and open chromatin profiling



MNase(micrococcal nuclease)
cuts in between nucleosomes

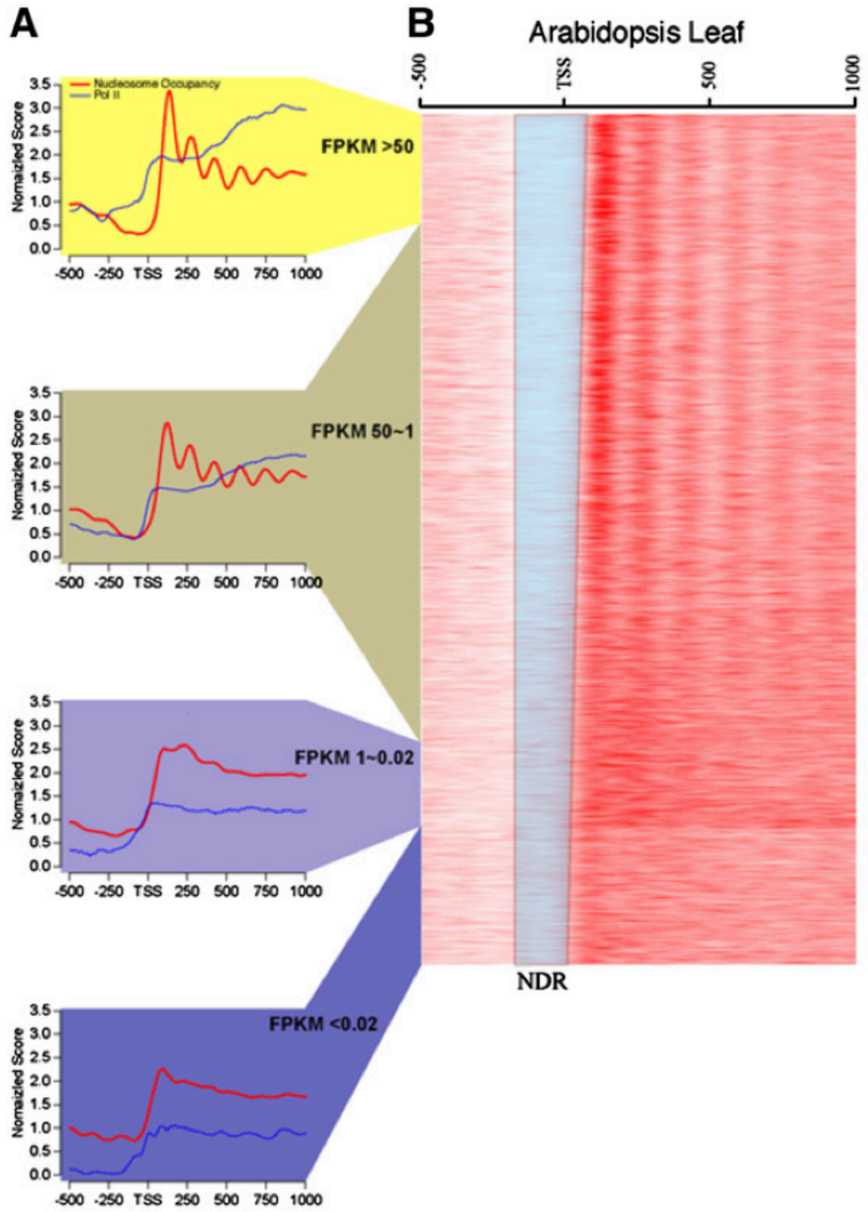
TSS is most of the times nucleosome-free

Highly expressed genes have a well positioned +1 nucleosome

Active genes show homogenous distribution of nucleosome

Inactive genes do not have uniform distribution of nucleosome (are they still regularly spaced?)

Highly expressed genes



Lowly expressed genes

Zhang, Jiang (2015) Plant Physiology

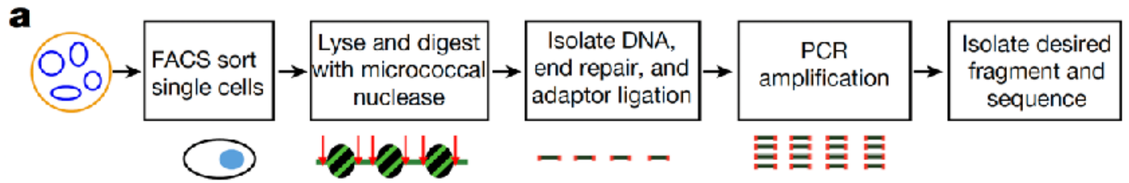
LETTER

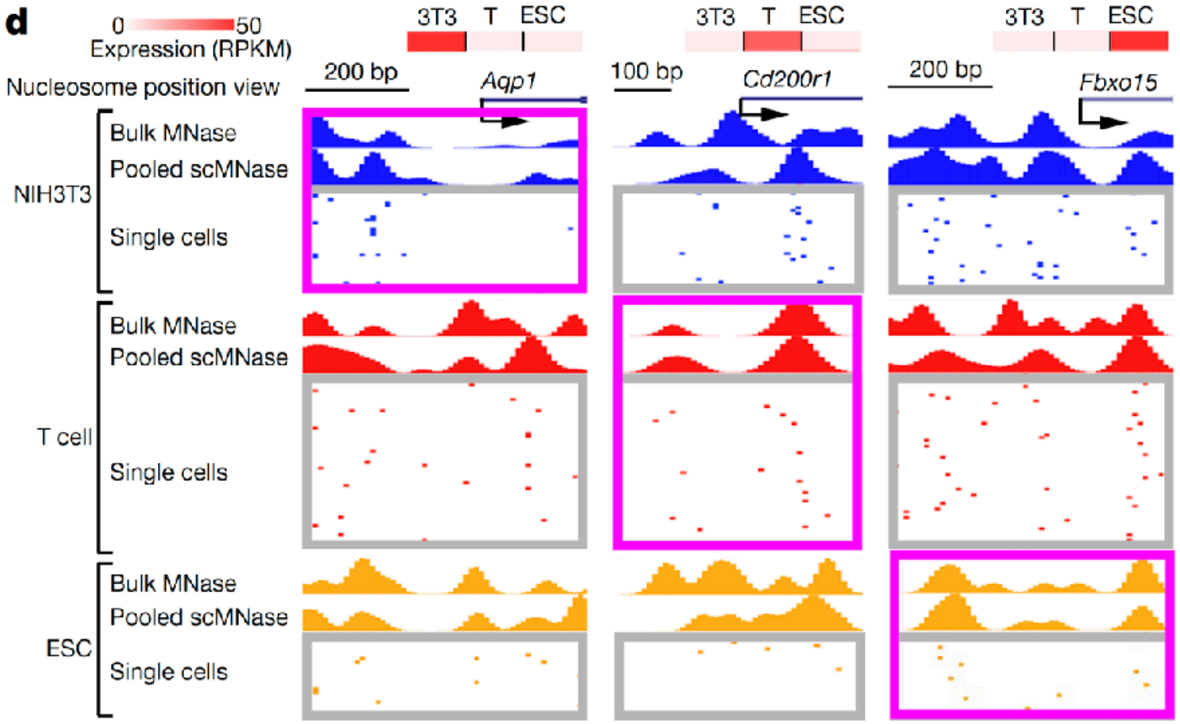
Corrected: Publisher Correction

https://doi.org/10.1038/s41586-018-0567-3

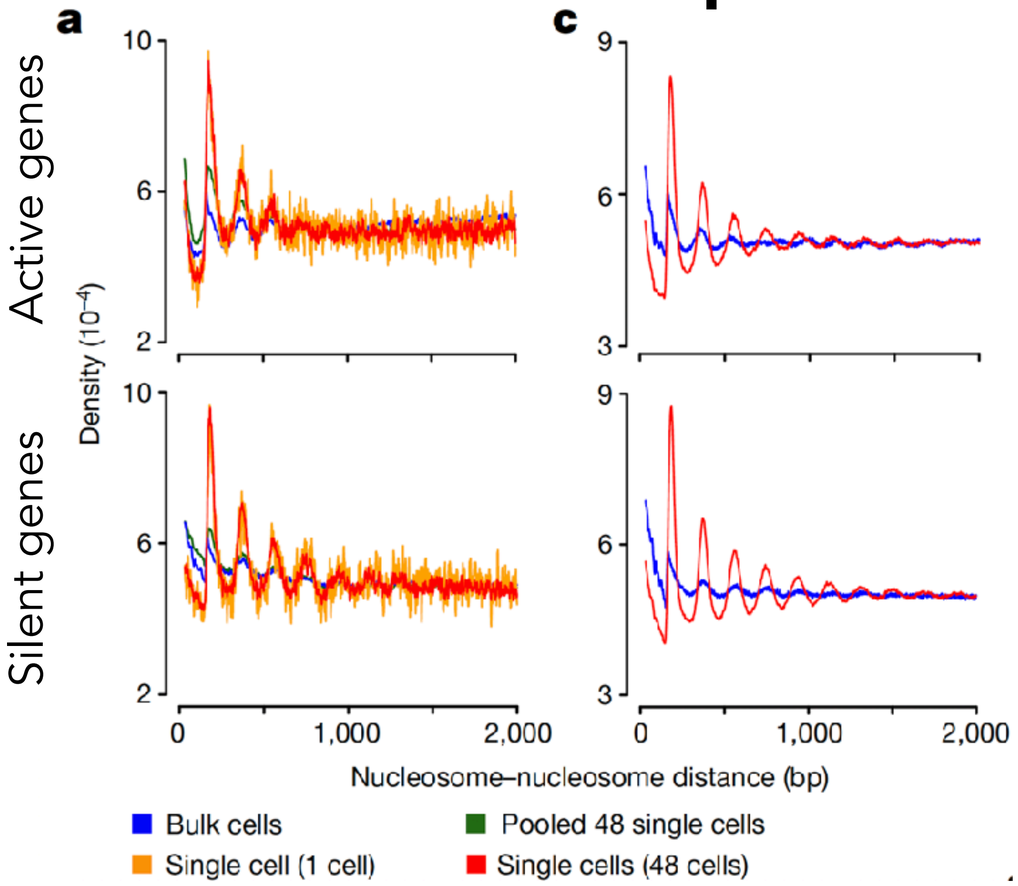
Principles of nucleosome organization revealed by single-cell micrococcal nuclease sequencing

Binbin Lai[1], Weiwu Gao[1,2], Kairong Cui[1], Wanli Xie[1,3], Qingsong Tang[1], Wenfei Jin[4], Gangqing Hu[1], Bing Ni[2] & Keji Zhao[1]*





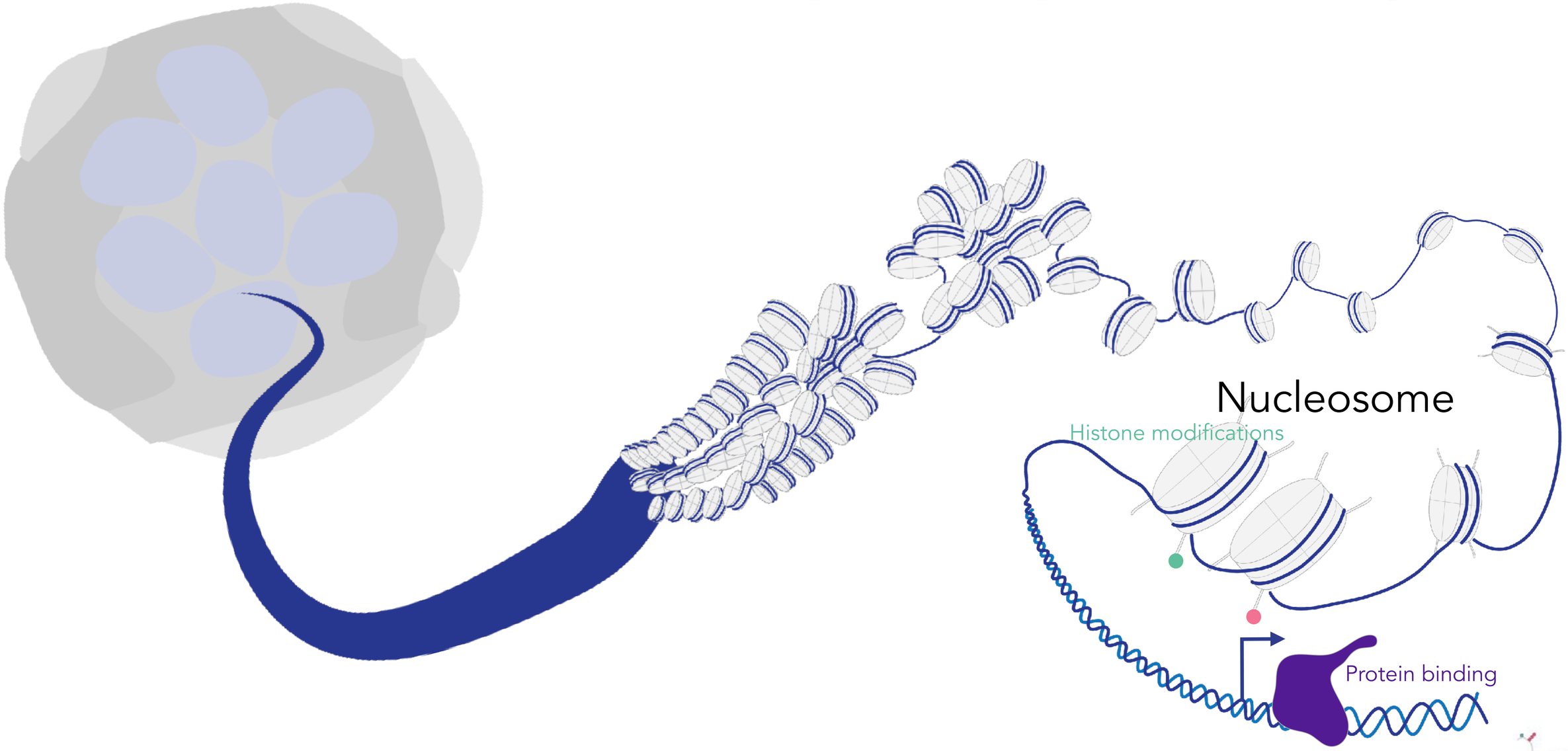
Nucleosome positioning



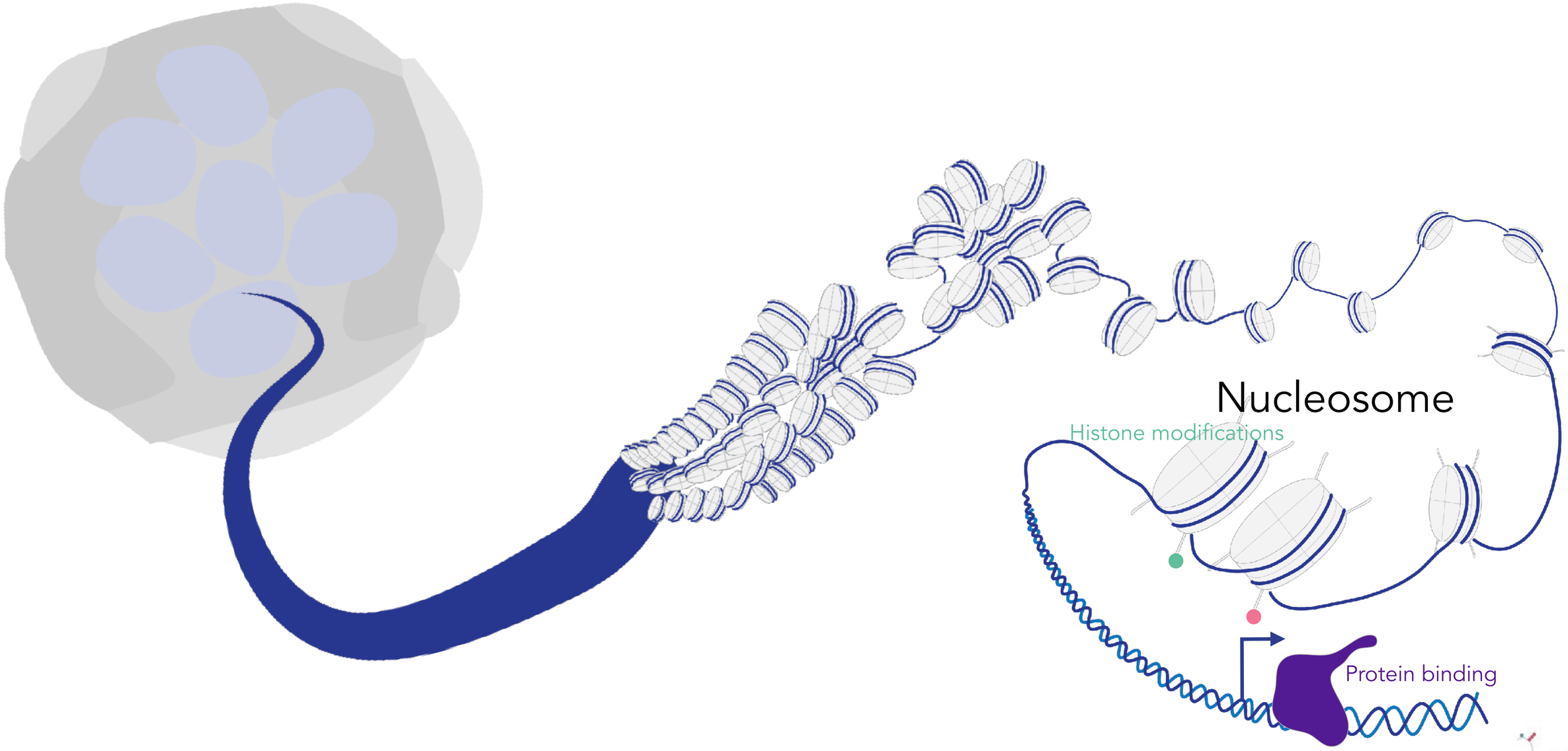
For active genes nucleosomes are positioned but not regularly spaced

For silent gene nucleosomes are highly regularly spaced

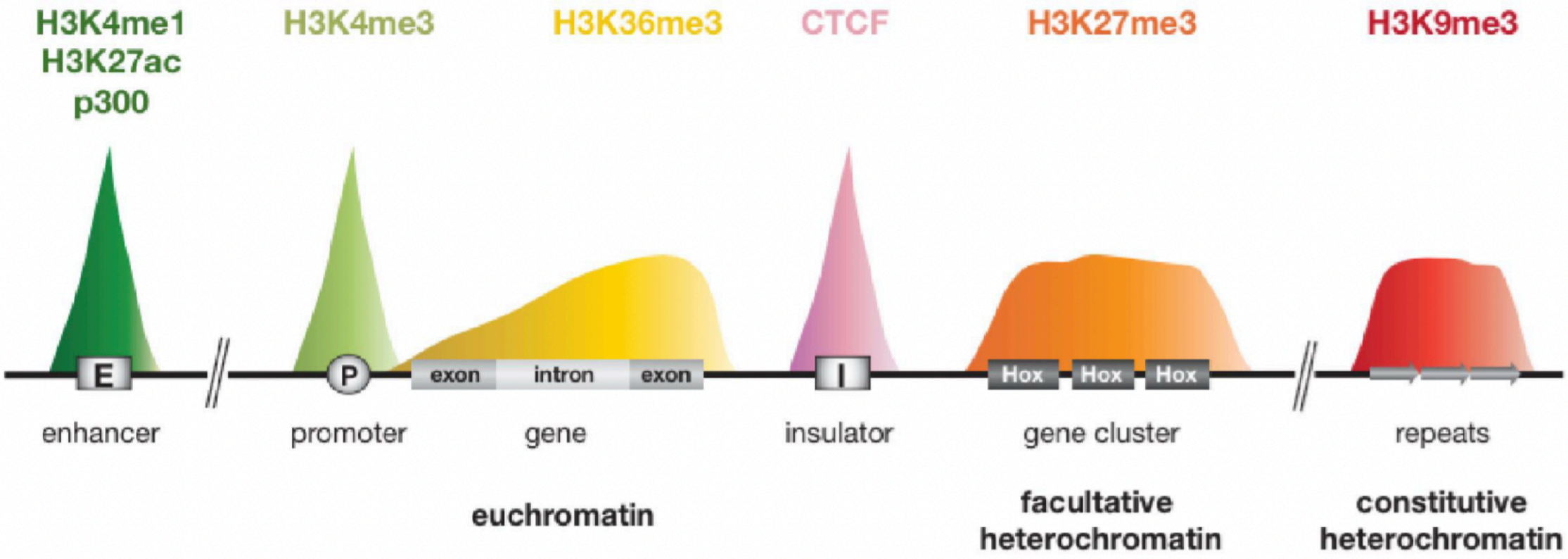
Profiling the epigenome in single cells



Profiling the epigenome in single cells



Histone modifications are differentially enriched in the genome



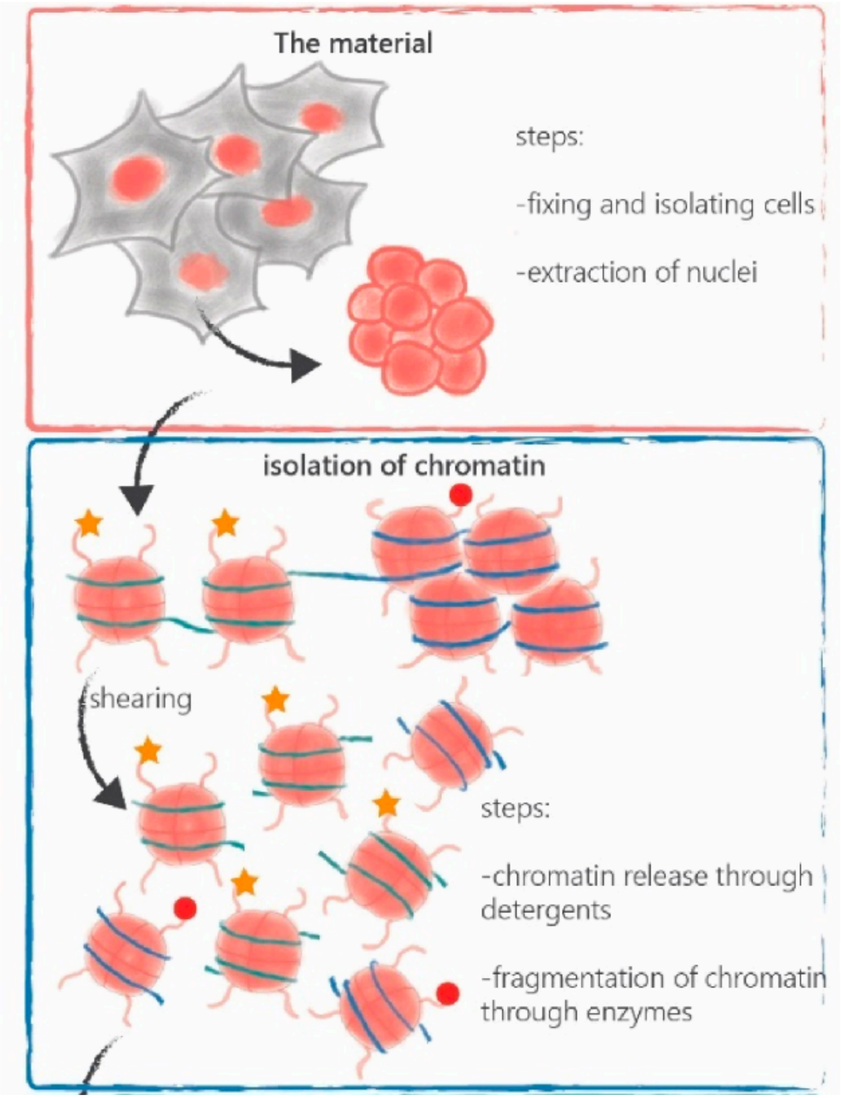
Jenuwein & Allis Epigenetics (2009)

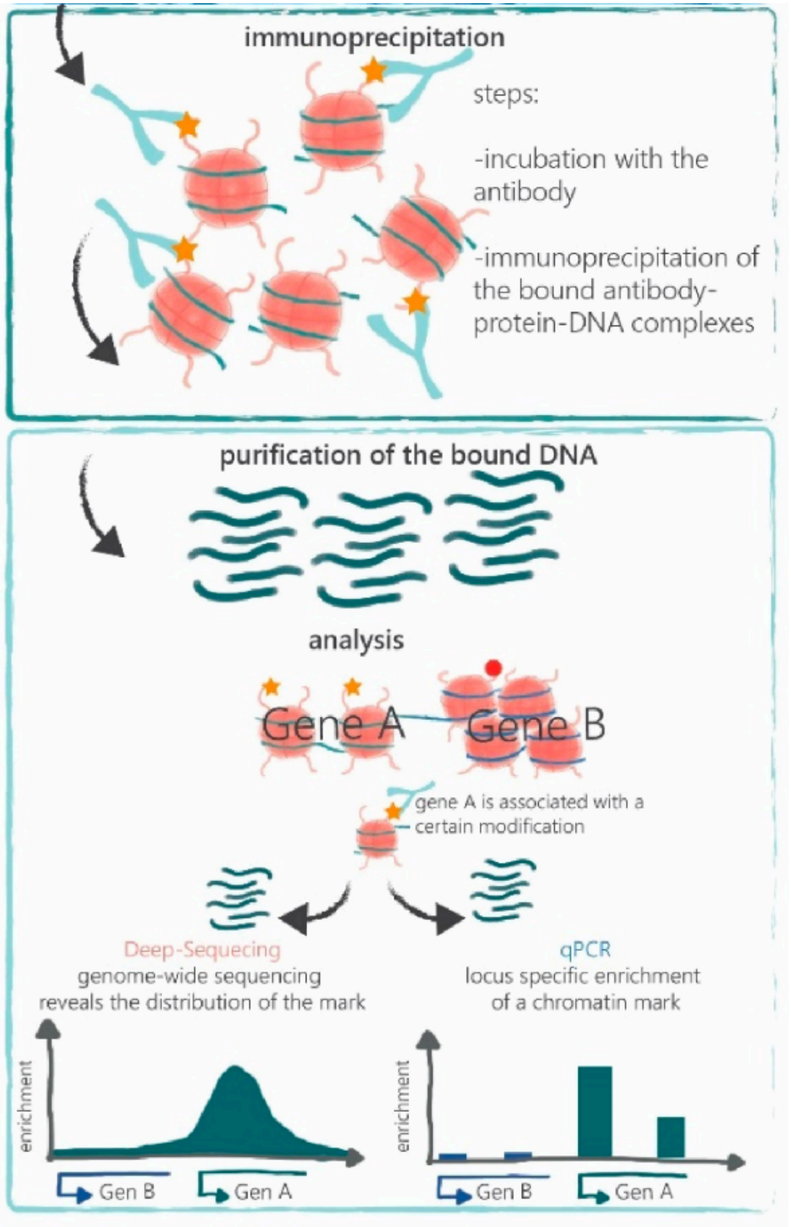
Classical analysis in bulk through ChIP sequencing

Requires crosslinking

Requires a lot of material

Not easily feasible in single cells





Classical analysis in bulk through ChIP sequencing

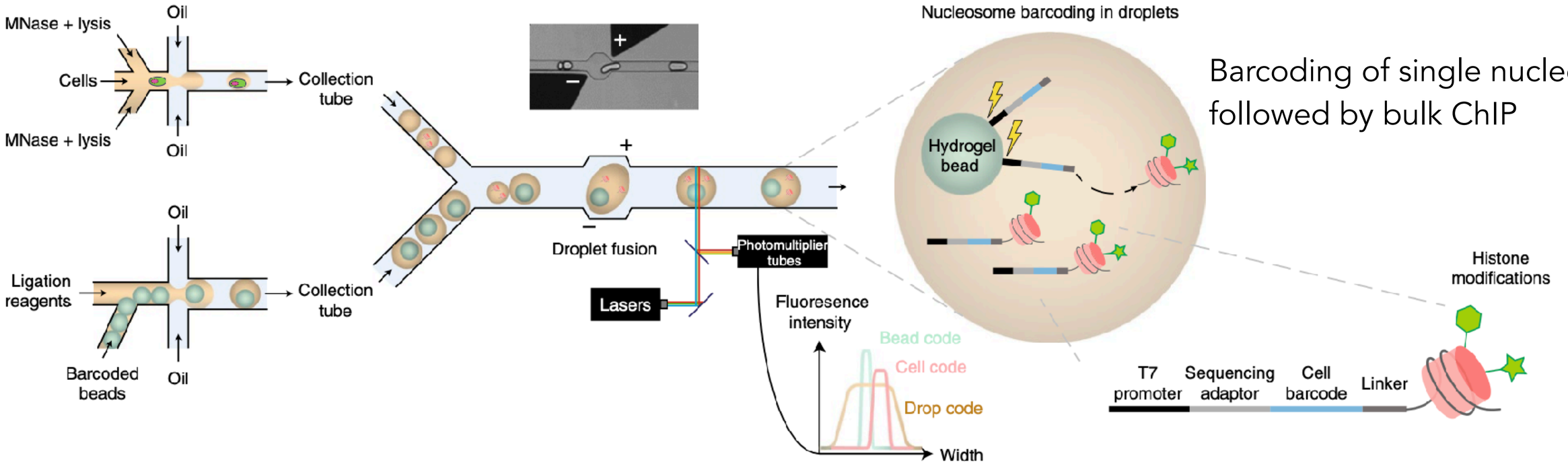
TECHNICAL REPORT
https://doi.org/10.1038/s41588-019-0424-9
nature genetics

High-throughput single-cell ChIP-seq identifies heterogeneity of chromatin states in breast cancer

Kevin Grosselin[1,2,9], Adeline Durand[3,4], Justine Marsolier[3,4], Adeline Poitou[1,10], Elisabetta Marangoni[4], Fariba Nemati[4], Ahmed Dahmani[4], Sonia Lameiras[5], Fabien Reyal[4,6,7], Olivia Frenoy[1,11], Yannick Pousse[1], Marcel Reichen[1,12], Adam Woolfe[1], Colin Brenan[1,8], Andrew D. Griffiths[2,13*], Céline Vallot[3,4,13*] and Annabelle Gérard[1,13*]

Problem scaling down ChIP-seq to single cells:

- High background
- Epitope masking due to cross-linking
- Low yields/signal -> requires large number of cells



Barcoding of single nucleosomes followed by bulk ChIP

Cleavage under target (CUT&X technologies)

2004: ChIC–chromatin immunocleavage

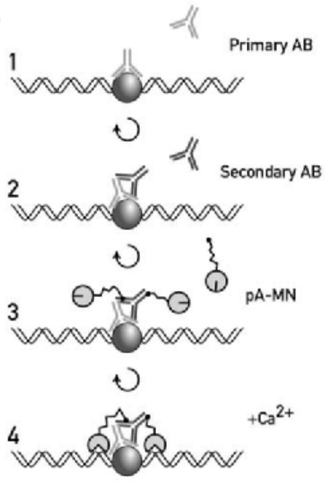
Molecular Cell, Vol. 16, 147–157, October 8, 2004, Copyright ©2004 by Cell Press

ChIC and ChEC: Genomic Mapping of Chromatin Proteins **Technique**

Manfred Schmid, Thérèse Durussel, and Ulrich K. Laemmli*
Departments of Biochemistry and Molecular Biology
NCCR Frontiers in Genetics
University of Geneva
30, Quai Ernest-Ansermet
CH1211, Geneva 4
Switzerland

ble, and significant amounts are lost into the pellet during centrifugation.

While ChIP is highly successful when applied to soluble proteins, such as transcription regulatory proteins, unpublished experiments with insoluble-type proteins (such as scaffolding components) in this laboratory appeared less promising. ChIP analyses with such insoluble-type proteins appear afflicted with increased back-



- Permeabilized cells without cross-linking
- Protein A/ Micrococcal Nuclease (pA-MNase) fusion protein binds to AB
- MNase activation by calcium
- DNA fragments released to supernatant

2017: CUT & RUN –Cleavage Under Target and Release Using Nuclease

PROTOCOL

Targeted *in situ* genome-wide profiling with high efficiency for low cell numbers

Peter J Skene[1–3], Jorja G Henikoff[1] & Steven Henikoff[1,2]

[1]Basic Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA. [2]Howard Hughes Medical Institute, Seattle, Washington, USA. [3]Present address: NanoString Technologies, Seattle, Washington, USA. Correspondence should be addressed to S.H. (steveh@fhcrc.org).

Published online 12 April 2018; doi:10.1038/nprot.2018.015

eLIFE elifesciences.org TOOLS AND RESOURCES

An efficient targeted nuclease strategy for high-resolution mapping of DNA binding sites

Peter J Skene, Steven Henikoff*

Howard Hughes Medical Institute, Basic Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, United States

Cleavage under target (CUT&X technologies)

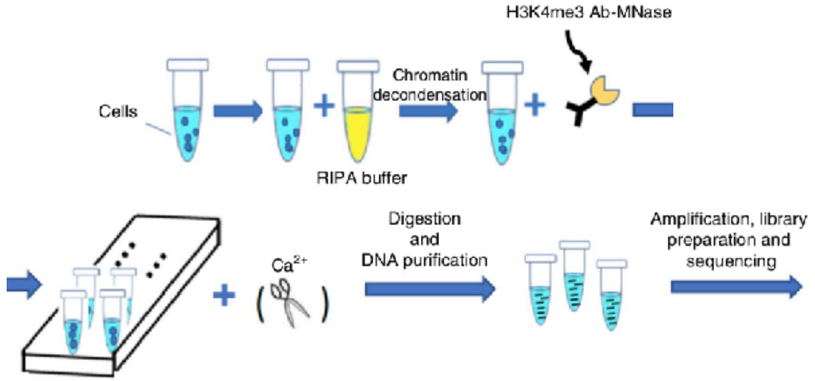
2019: CUT & RUN –in single cells - scChIC

nature methods
BRIEF COMMUNICATION
https://doi.org/10.1038/s41592-019-0361-7

Single-cell chromatin immunocleavage sequencing (scChIC-seq) to profile histone modification

Wai Lim Ku[1,4], Kosuke Nakamura[1,2,4], Weiwu Gao[1,3,4], Kairong Cui[1], Gangqing Hu[1], Qingsong Tang[1], Bing Ni[3]* and Keji Zhao[1]*

- Recruitment of MNase-AB conjugate to histone modification
- DNA cleavage induced by Ca2+



2023: CUT & RUN –in single cells - scChIC

nature genetics
Technical Report
https://doi.org/10.1038/s41588-022-01260-3

Single-cell sortChIC identifies hierarchical chromatin dynamics during hematopoiesis

Received: 22 May 2021
Accepted: 1 November 2022
Published online: 20 December 2022

Peter Zeller[1,2,4], Jake Yeung[1,2,3,4], Helena Viñas Gaza[1,2], Buys Anton de Barbanson[1,2], Vivek Bhardwaj[1,2], Maria Florescu[1,2], Reinier van der Linden[1,2] & Alexander van Oudenaarden[1,2]

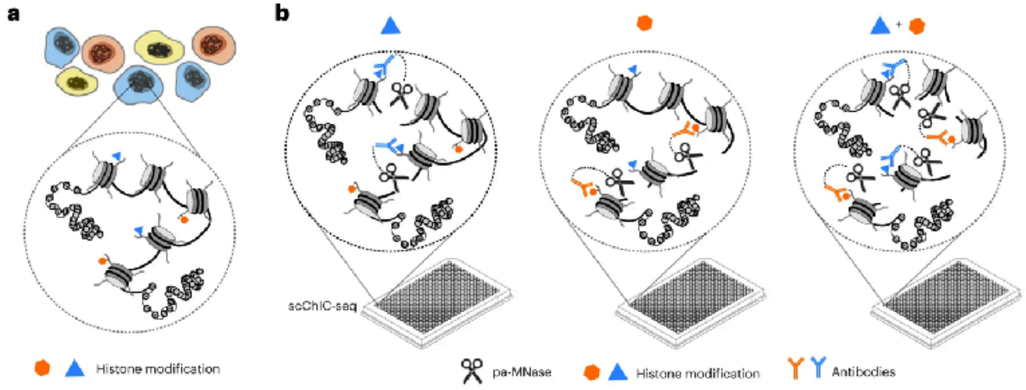
Journal Club!

nature biotechnology
Article
https://doi.org/10.1038/s41587-022-01560-3

scChIX-seq infers dynamic relationships between histone modifications in single cells

Received: 27 April 2021
Accepted: 12 October 2022
Published online: 2 January 2023

Jake Yeung[1,2,3], Maria Florescu[1,3], Peter Zeller[1,3], Buys Anton de Barbanson[1], Max D. Wellenstein[1] & Alexander van Oudenaarden[1]



Use CUT&Run in larger scale to adress a biological question

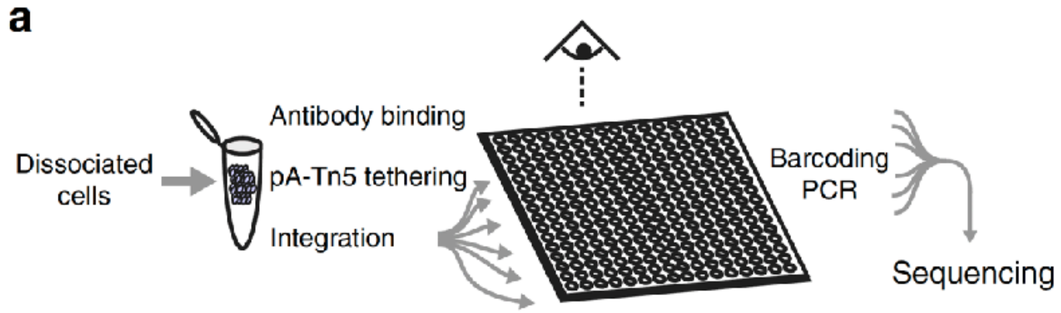
Bottlenecks: plate-based, adapter ligation

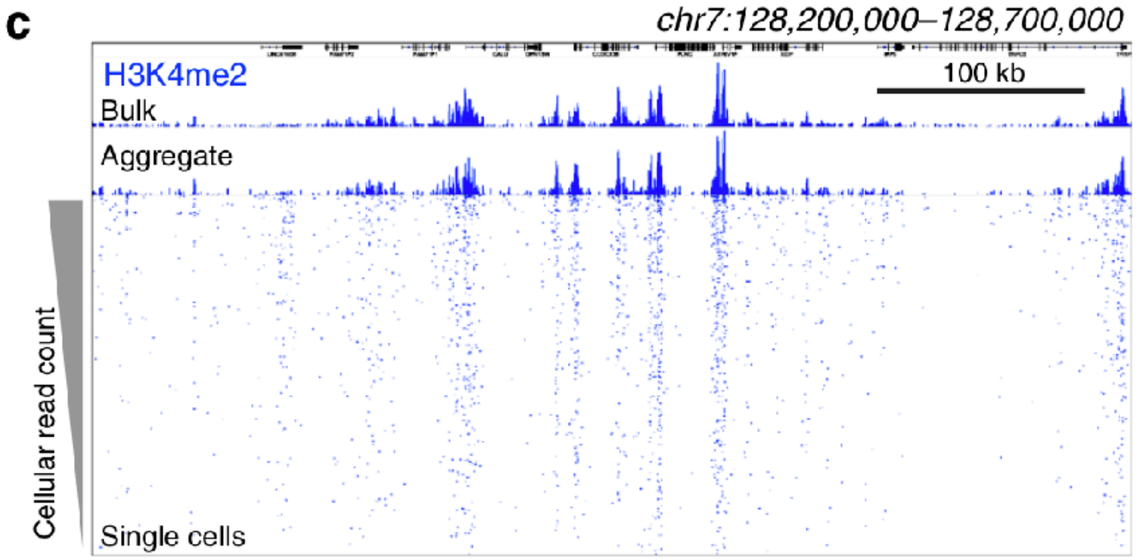
Cleavage under target (CUT&X technologies)

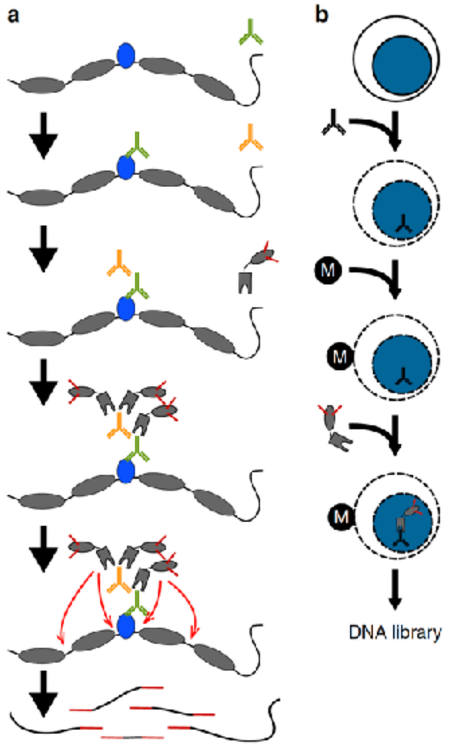
2019: CUT&Tag –in single cells

Cut&Tag for H3K4me2 on K562 cells

single cell profiling SMARTer ICELL8 systemTAKARA



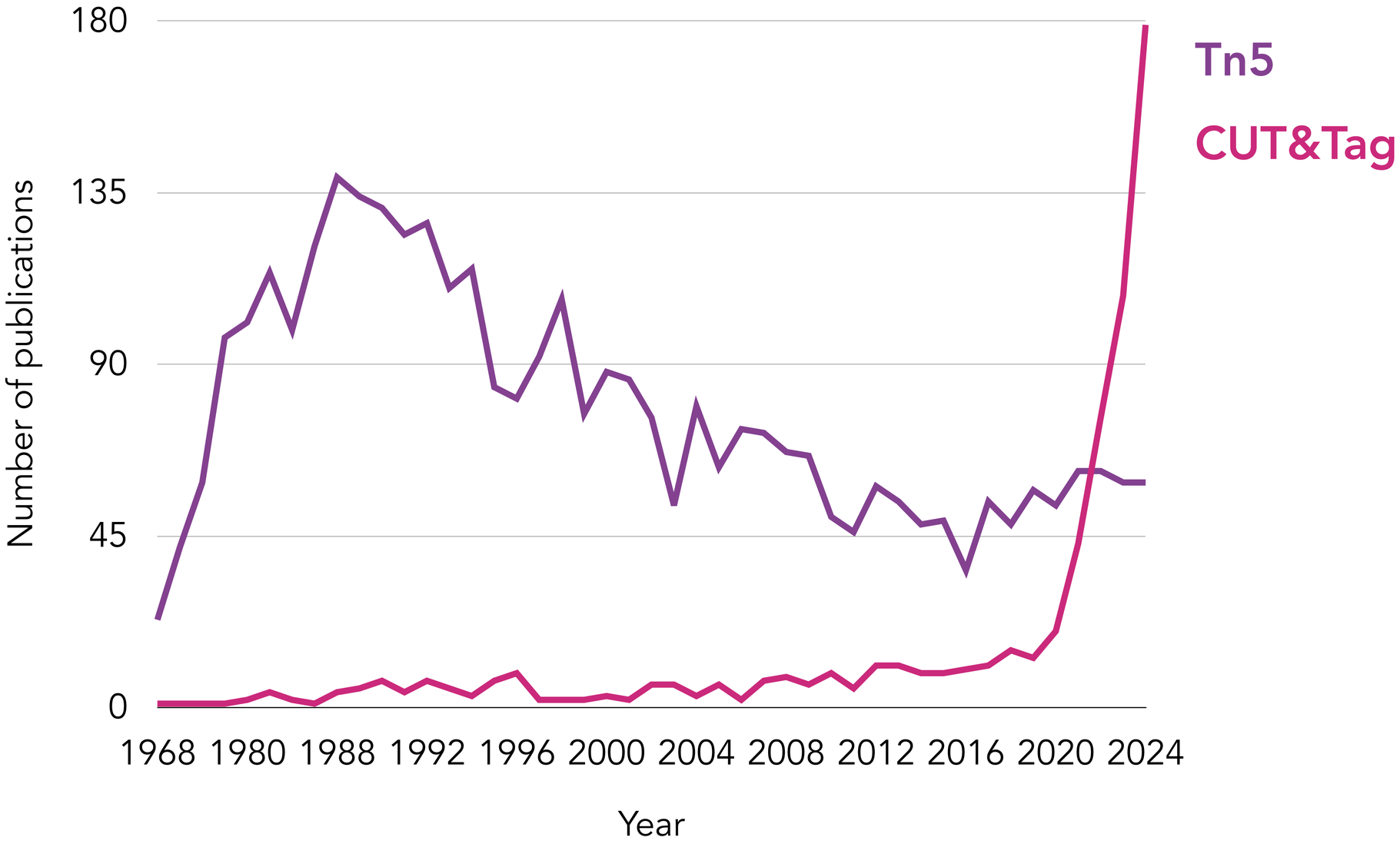




Chromatin is cleaved by Tn5 coupled to protein A (the same enzyme used for ATAC)

Libraries are just PCR amplified from DNA fragments

Publications on CUT&Tag and Tn5



Cleavage under target (CUT&X technologies)

nature biotechnology

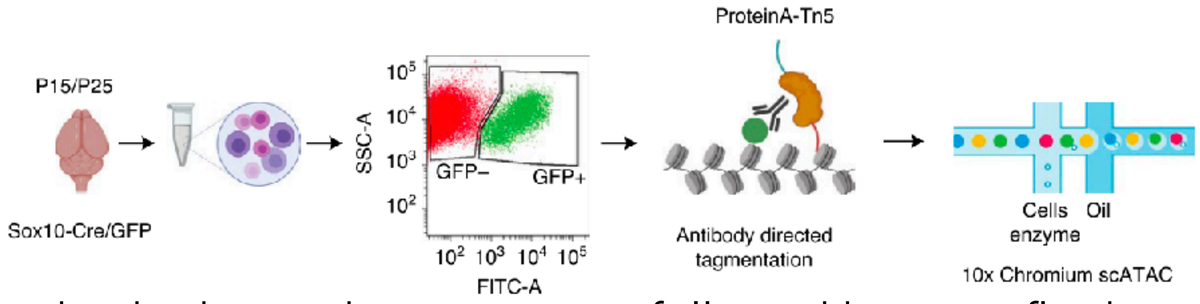
ARTICLES

https://doi.org/10.1038/s41587-021-00869-9

Check for updates

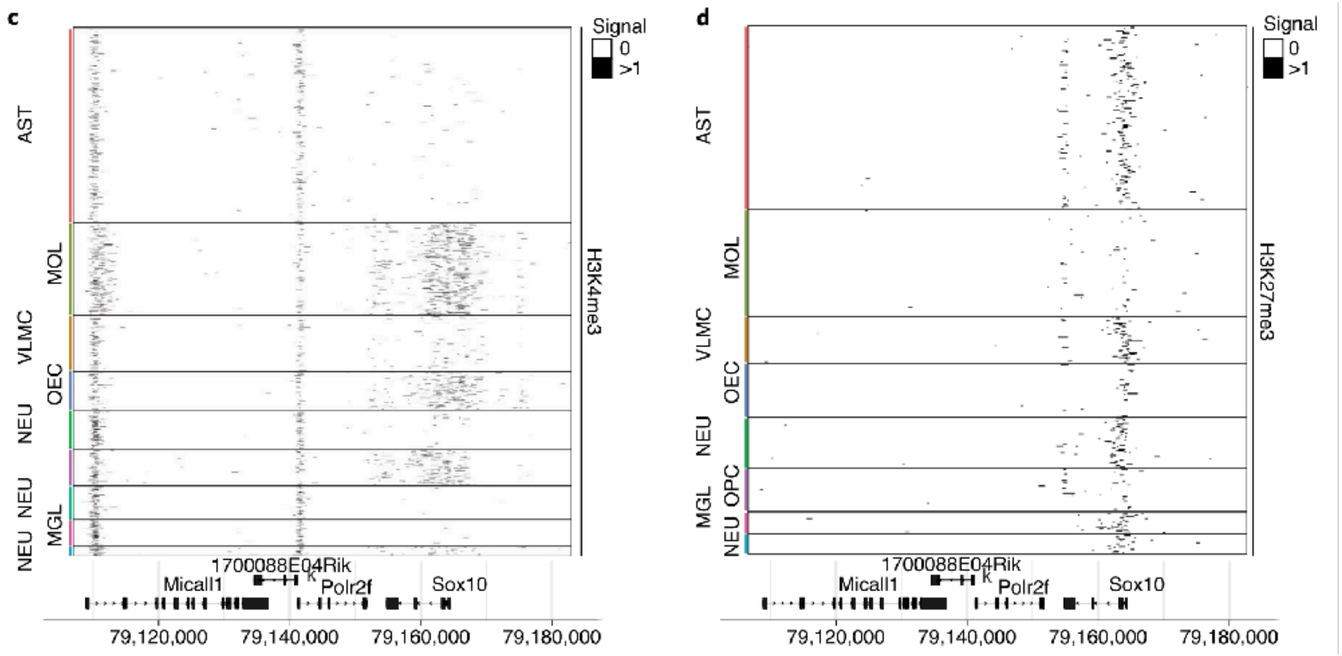
Single-cell CUT&Tag profiles histone modifications and transcription factors in complex tissues

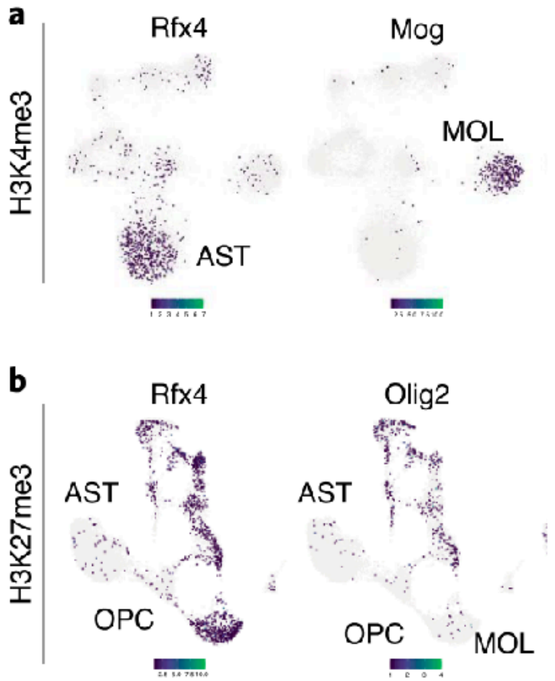
Marek Bartosovic[1], Mukund Kabbe[1] and Gonçalo Castelo-Branco[1,2]



Antibody-directed tagmentationfollowed by microfluidics to isolate single nuclei

H3K4me3 (active) and H3K27me3 (inactive) are anticorrelated





Cleavage under target (CUT&X technologies)

nature methods

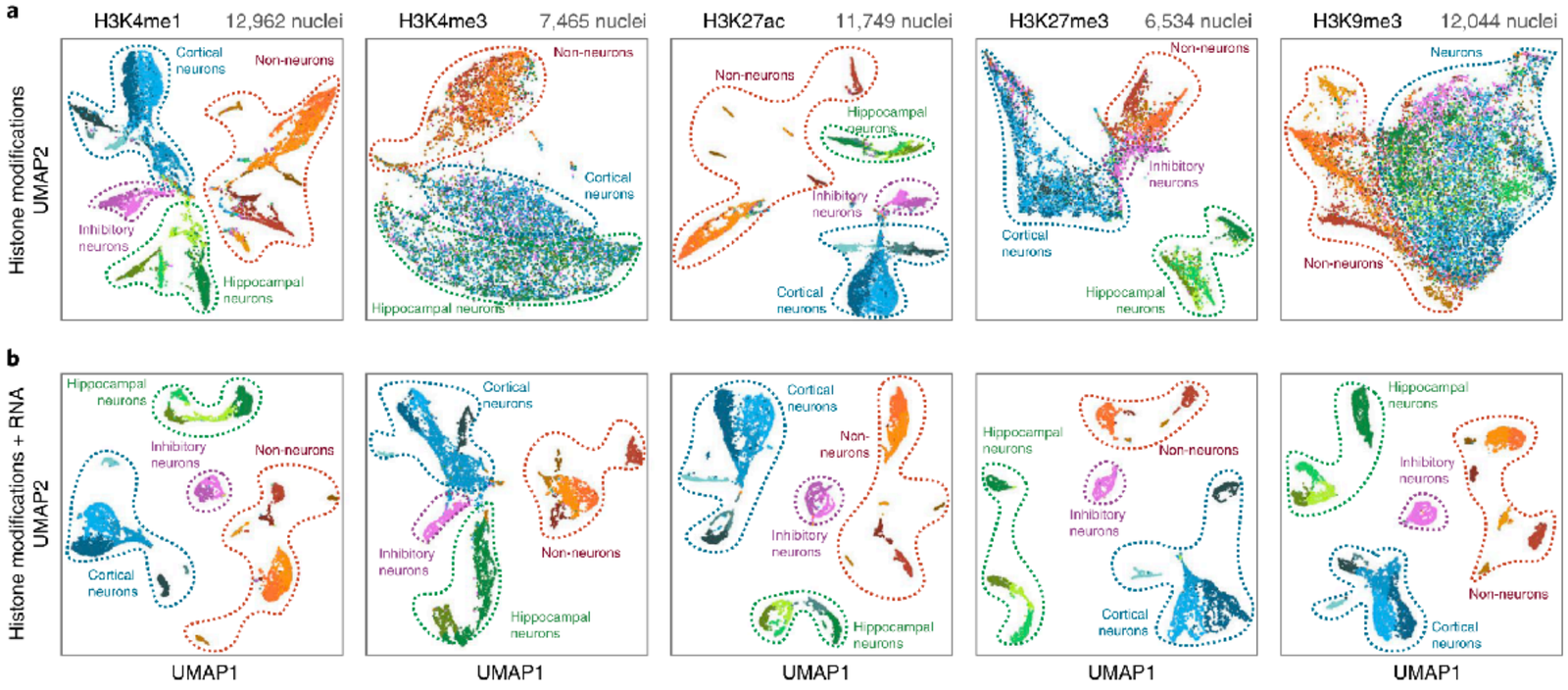
ARTICLES

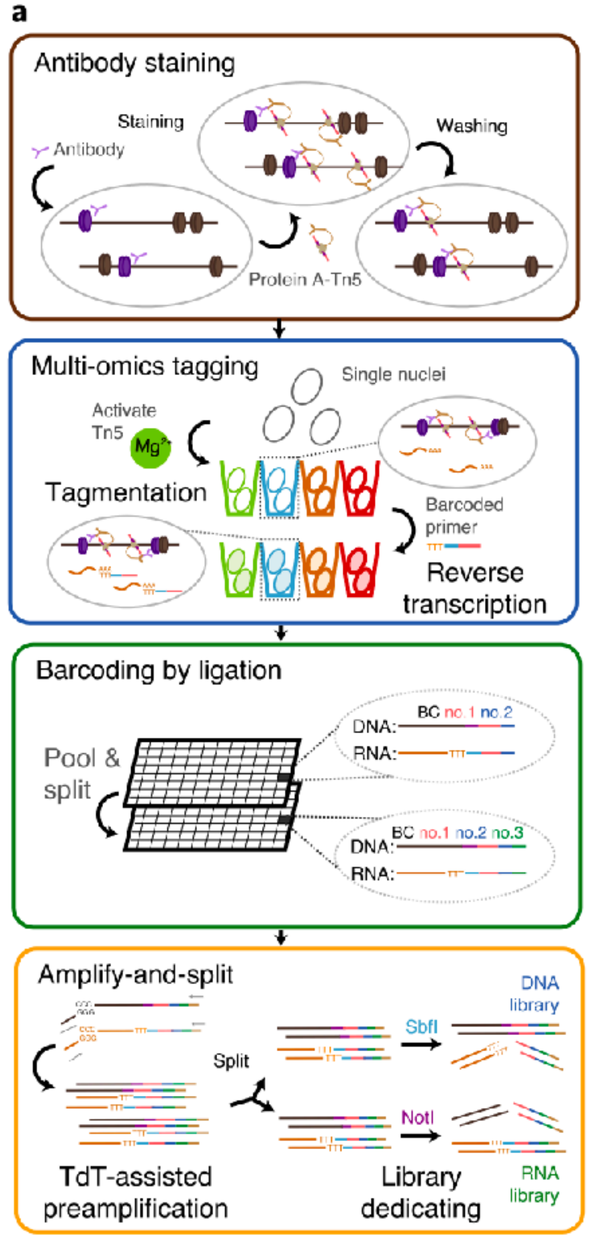
https://doi.org/10.1038/s41592-021-01060-3

Check for updates

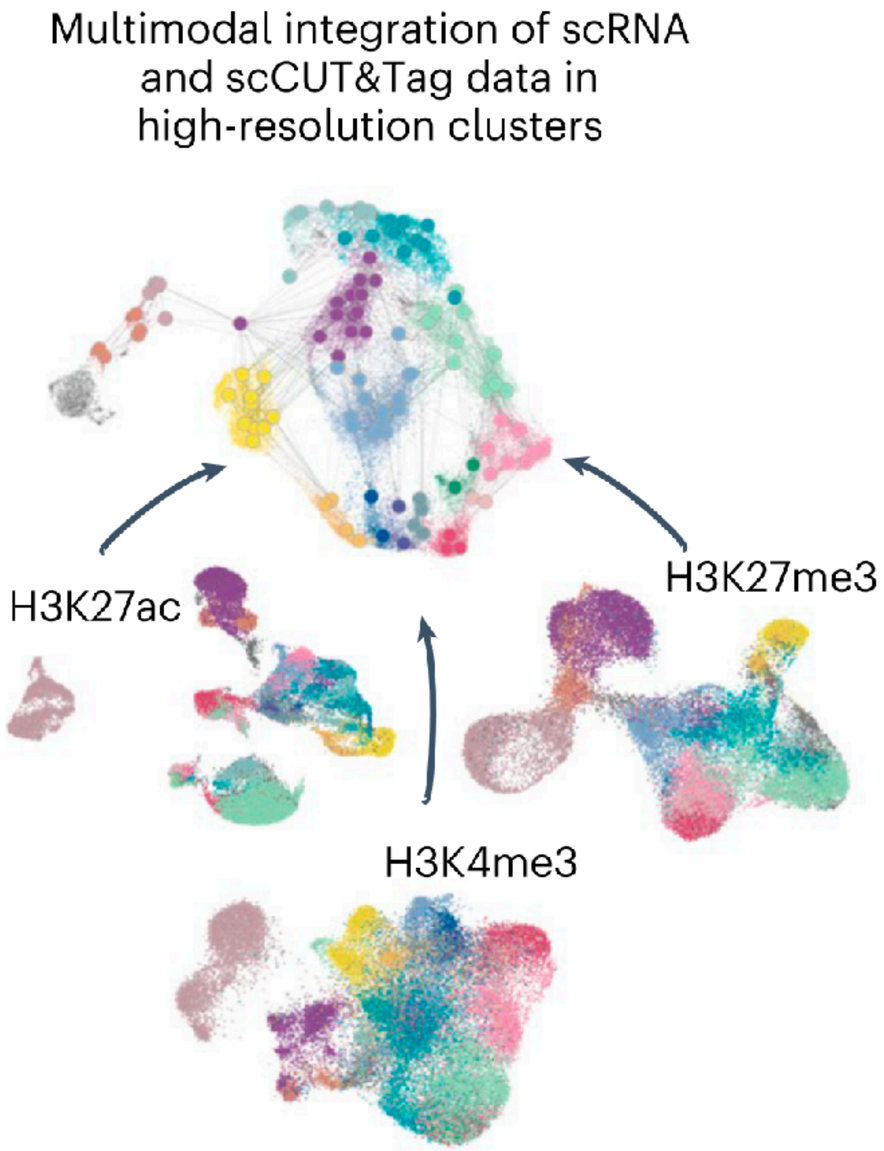
Joint profiling of histone modifications and transcriptome in single cells from mouse brain

Chenxu Zhu[1], Yanxiao Zhang[1], Yang Eric Li[2], Jacinta Lucero[3], M. Margarita Behrens[3] and Bing Ren[1,2,4,5,6]





Integrating RNA expression and histone modifications



nature neuroscience

Resource

https://doi.org/10.1038/s41593-024-01652-0

Single-cell epigenomic reconstruction of developmental trajectories from pluripotency in human neural organoid systems

Received: 20 April 2023

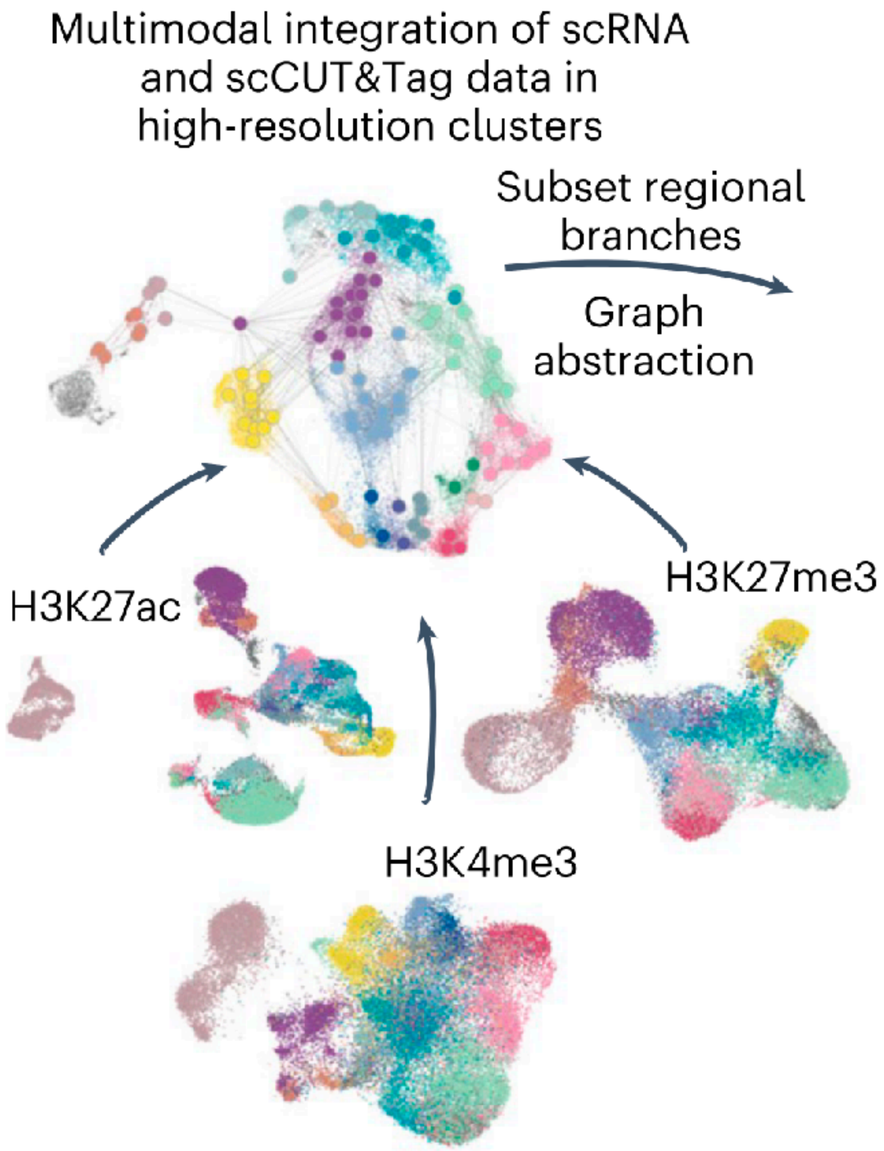
Accepted: 17 April 2024

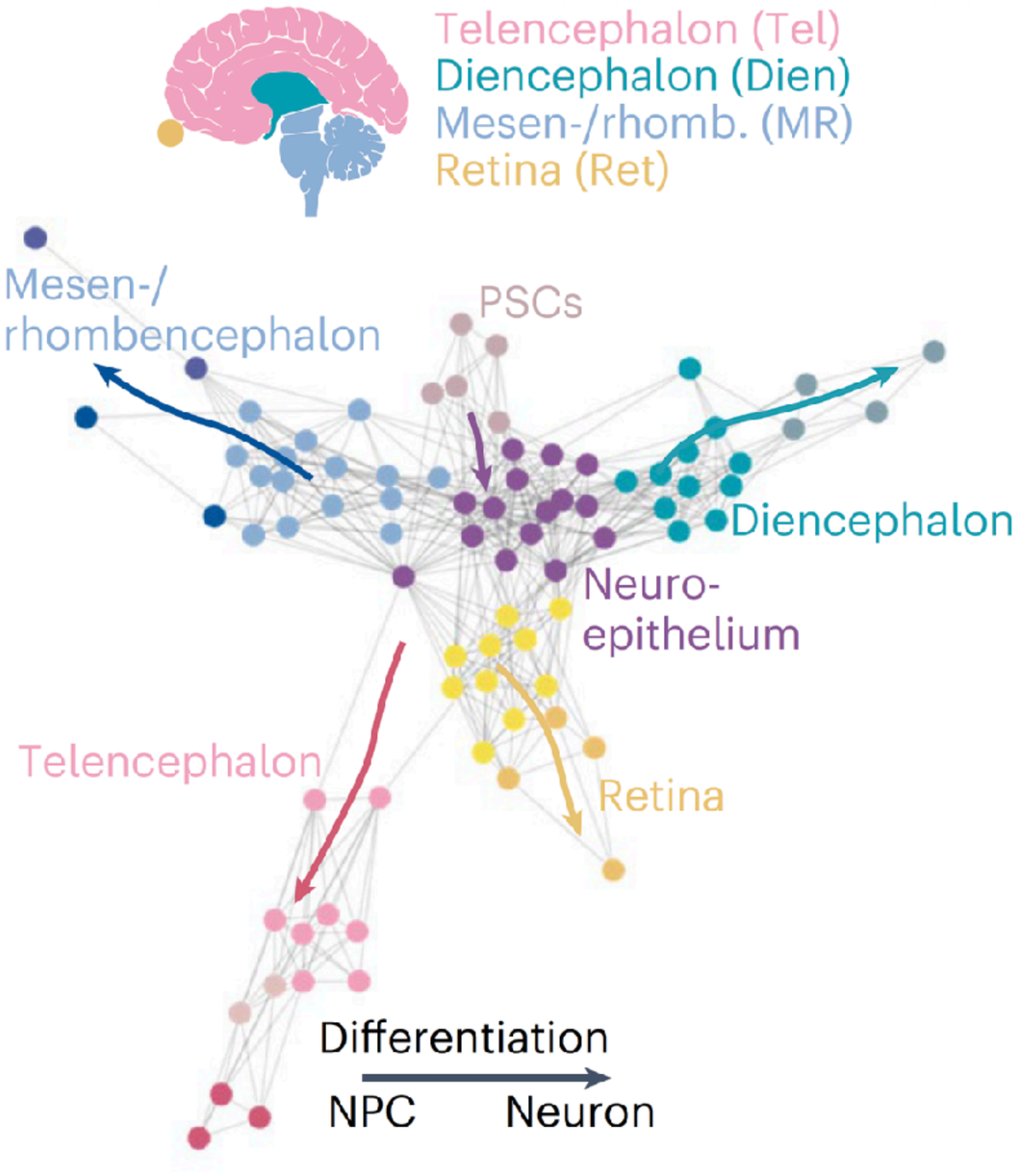
Published online: 24 June 2024

Fides Zenk[1,3,4] ✉, Jonas Simon Fleck[1,2,4], Sophie Martina Johanna Jansen[1], Bijan Kashanian[1], Benedikt Eisinger[1], Małgorzata Santel[1], Jean-Samuel Dupré[2], J. Gray Camp[2] ✉ & Barbara Treutlein[1] ✉

Zenk & Fleck et al. 2024, Nature Neuroscience

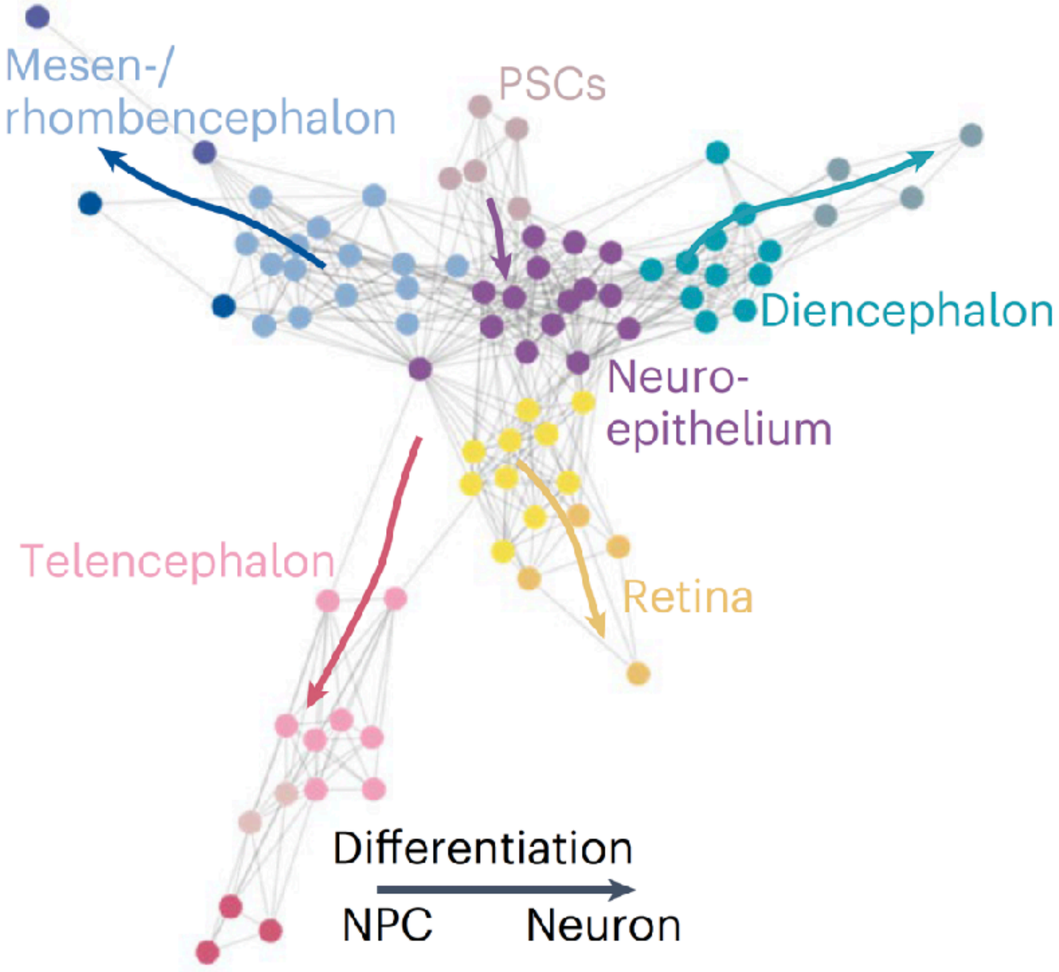
Integrating RNA expression and histone modifications

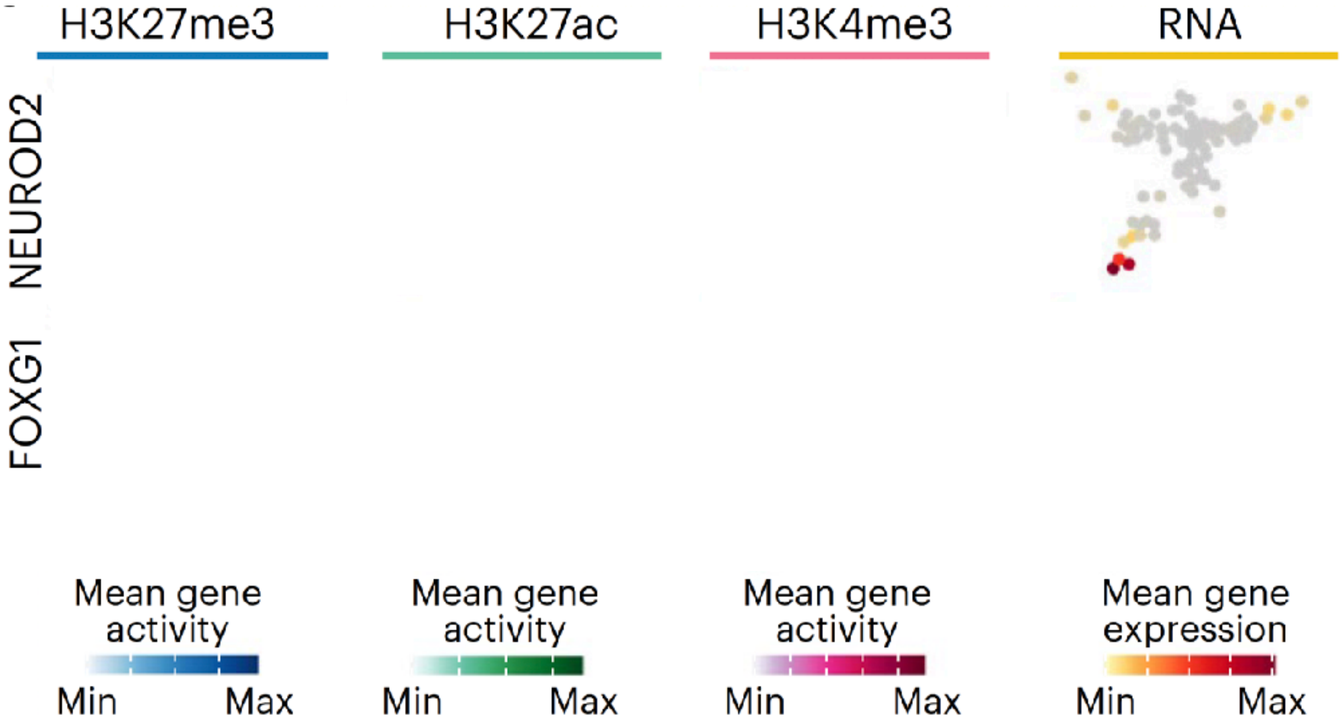




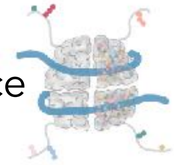
Building a model of gene regulation during brain development

Telencephalon (Tel)
Diencephalon (Dien)
Mesen-/rhomb. (MR)
Retina (Ret)

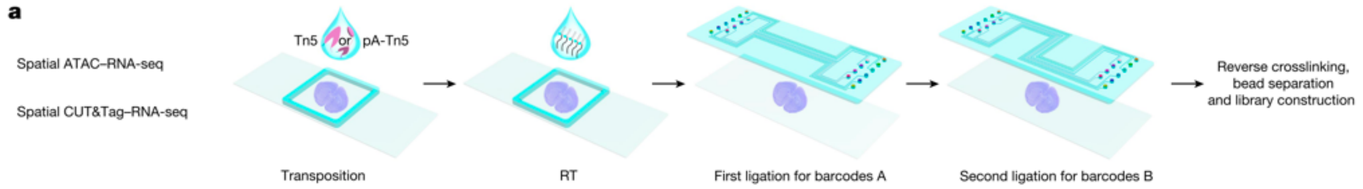




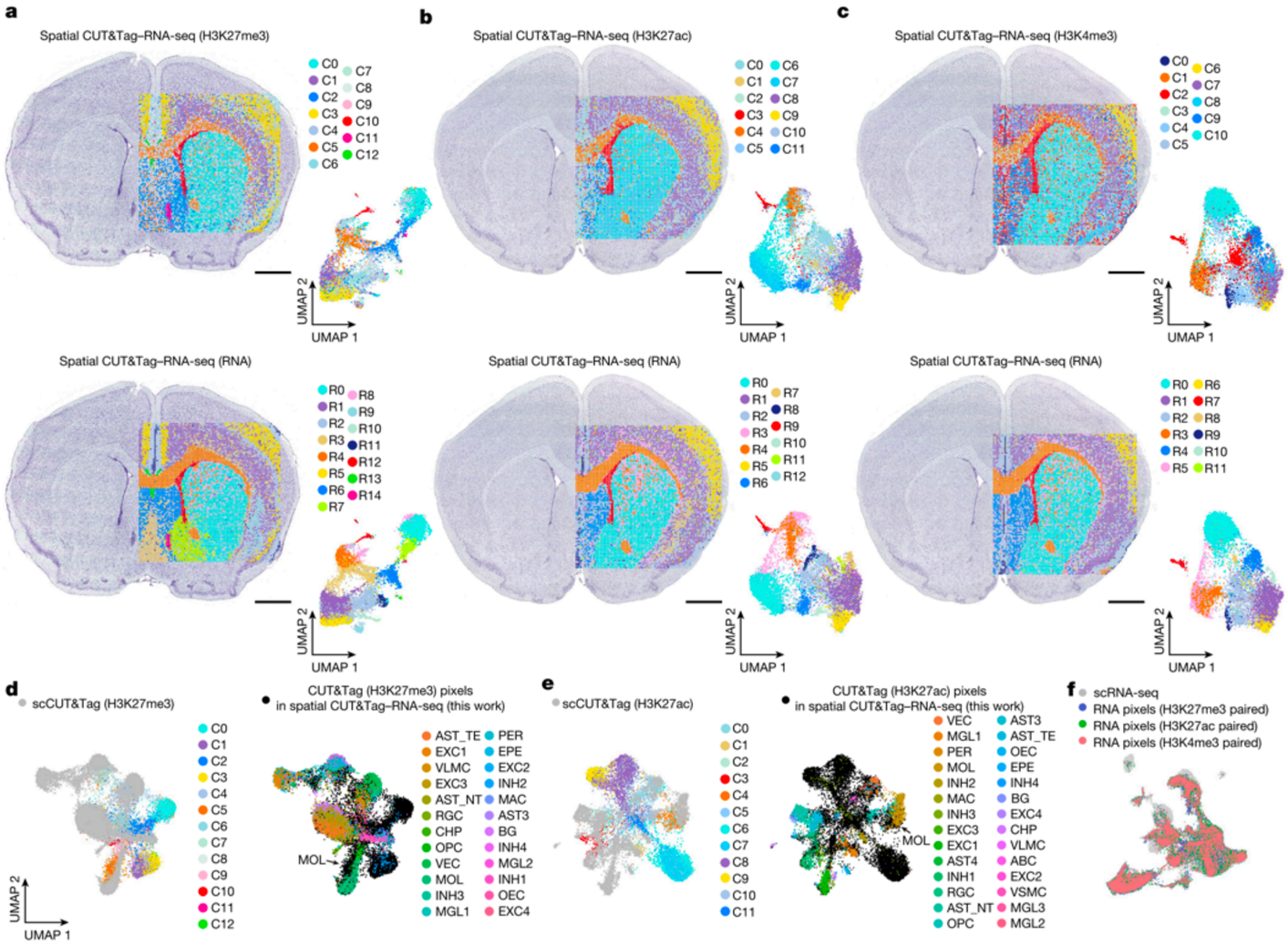
Zenk & Fleck et al. 2024, Nature Neuroscience



Spatially resolved CUT&Tag



Mouse brain slides on microfluidic device for barcoding



Article

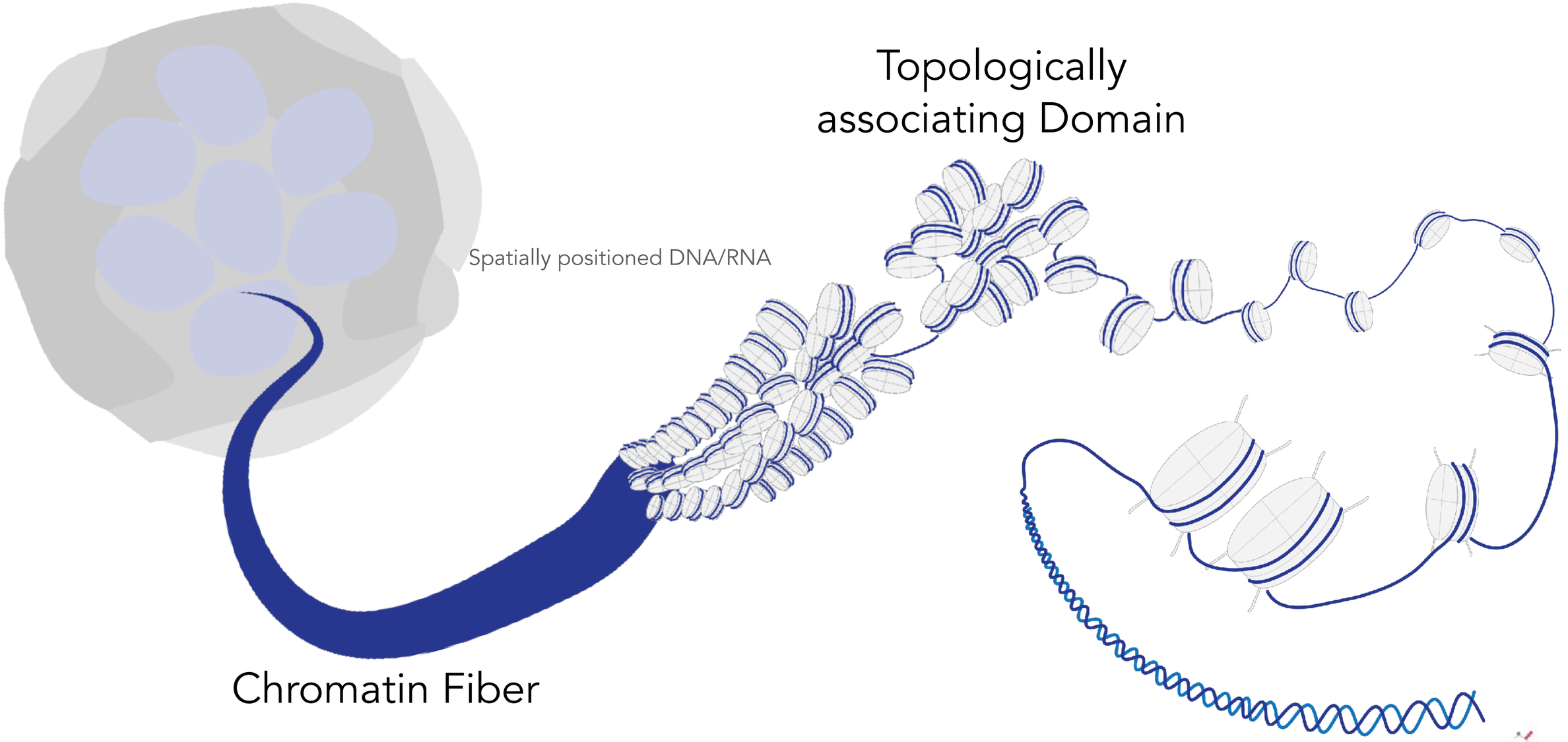
Spatial epigenome–transcriptome co-profiling of mammalian tissues

https://doi.org/10.1038/s41586-023-05795-1
Received: 6 June 2022
Accepted: 3 February 2023
Published online: 15 March 2023

Di Zhang[1,21], Yanxiang Deng[1,2,20,21], Petra Kukanja[3], Eneritz Agirre[3], Marek Bartosovic[3], Mingze Dong[4,5], Cong Ma[6], Sai Ma[7], Graham Su[1,2], Shuozhen Bao[1], Yang Liu[1,2], Yang Xiao[8], Gorazd B. Rosoklija[9,10,11], Andrew J. Dwork[9,10,11,12], J. John Mann[8,10,13], Kam W. Leong[6,14], Maura Boldrini[9,10], Liya Wang[15], Maximilian Haeussler[16], Benjamin J. Raphael[6], Yuval Kluger[4,5,17], Gonçalo Castelo-Branco[3,18] & Rong Fan[1,2,4,19]

No nuclei resolution but spatially resolved RNA and histone modification profiles

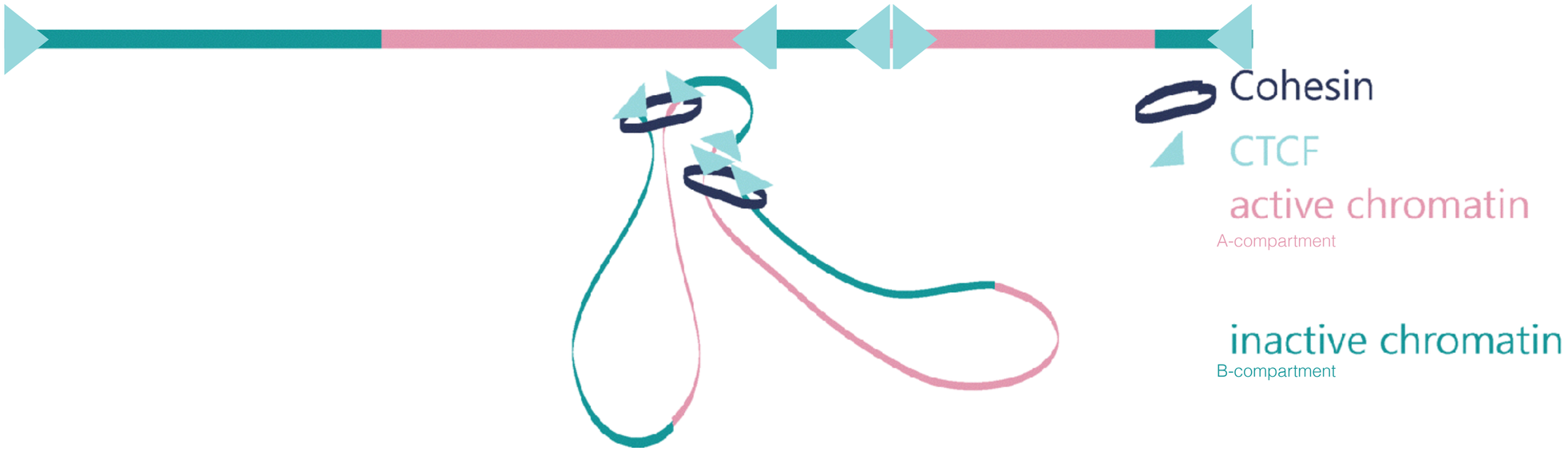
Packaging of Chromatin inside the Nucleus



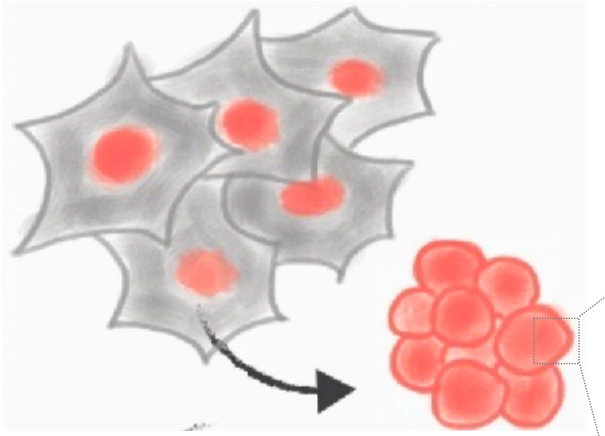
Chromatin is organized in a hierachical fashion

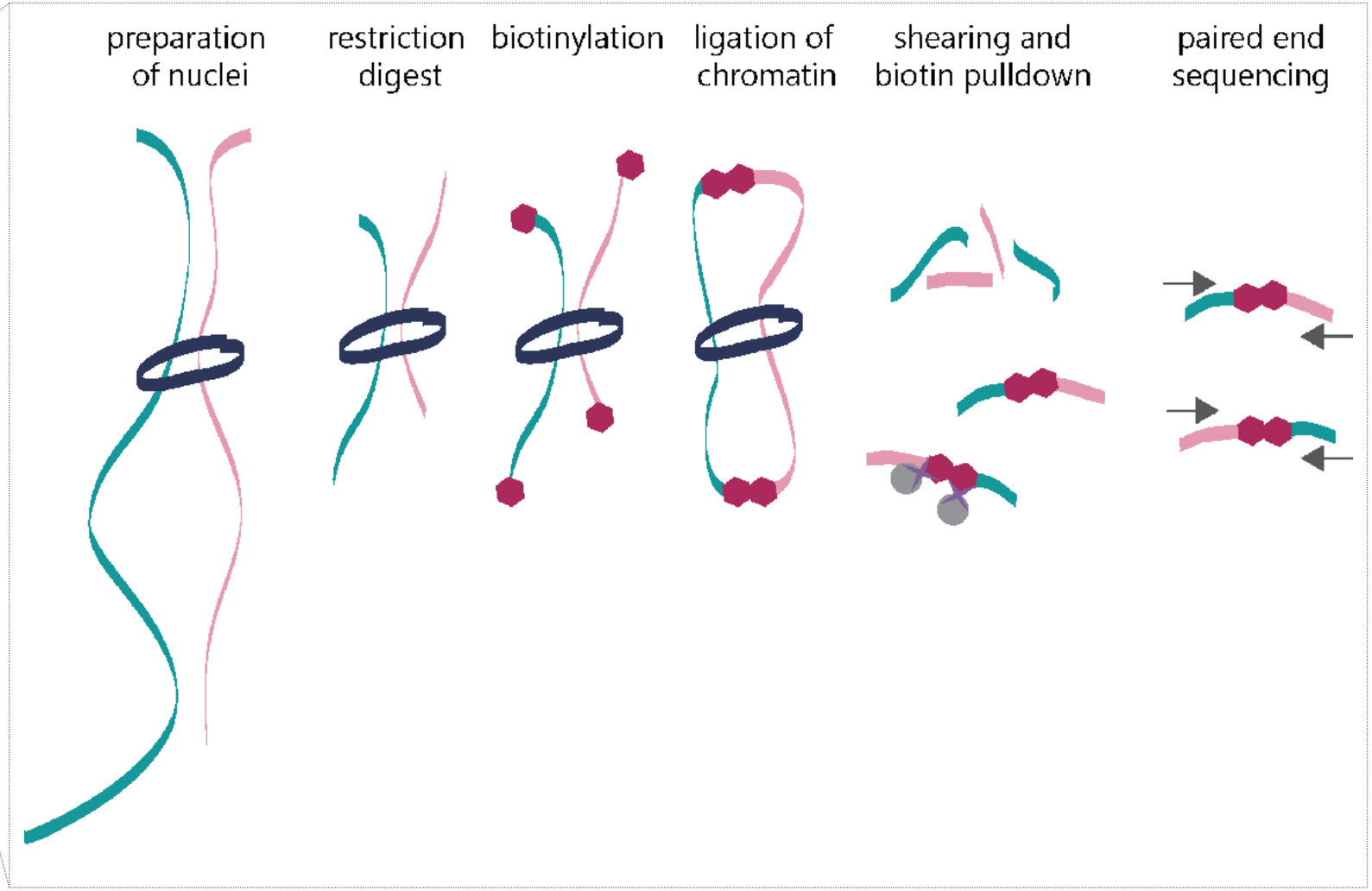
Packaging of Chromatin inside the Nucleus

Packaging of Chromatin inside the Nucleus

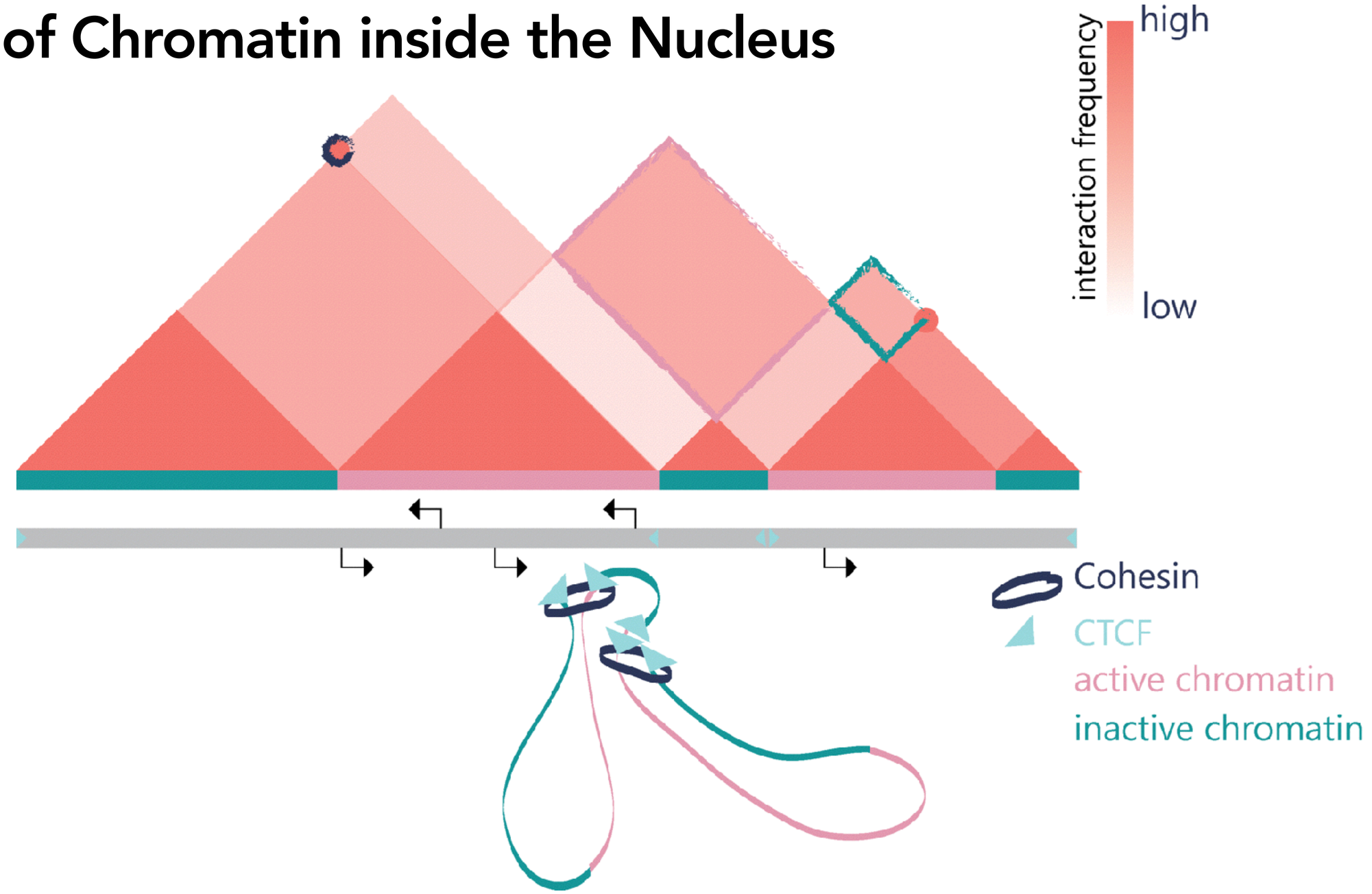


Studying chromatin structure using *in situ* HiC



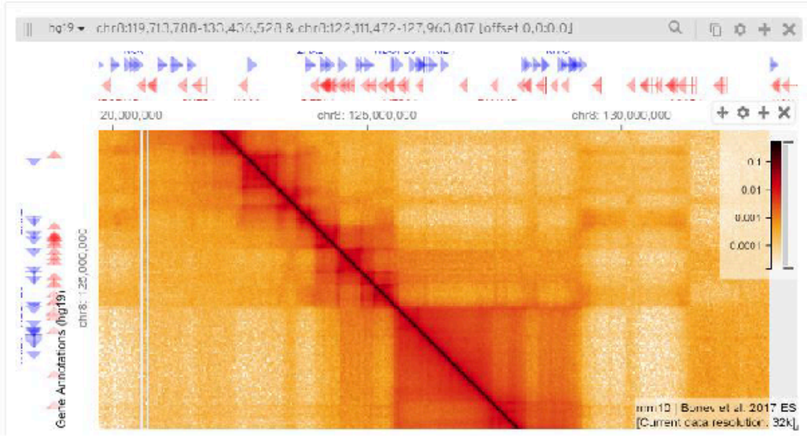


Packaging of Chromatin inside the Nucleus

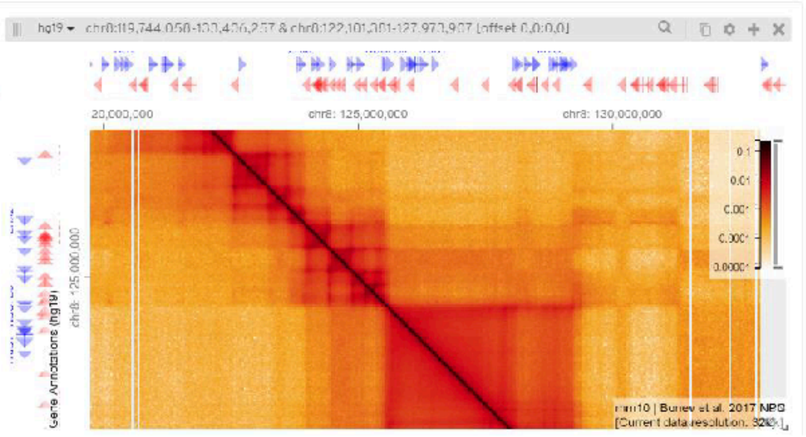


Changes in genome topology are small between cell types

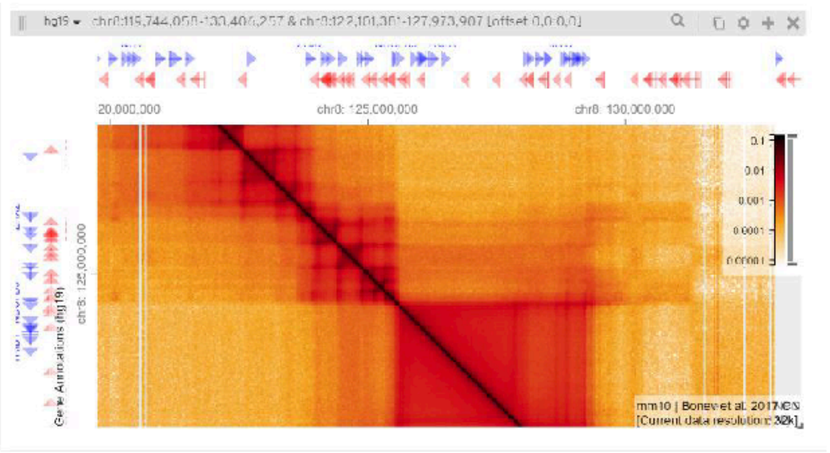
Mouse ES cells



Mouse neural progenitors



Cortical neurons



Are TADs features of single cells or is it a population effect?

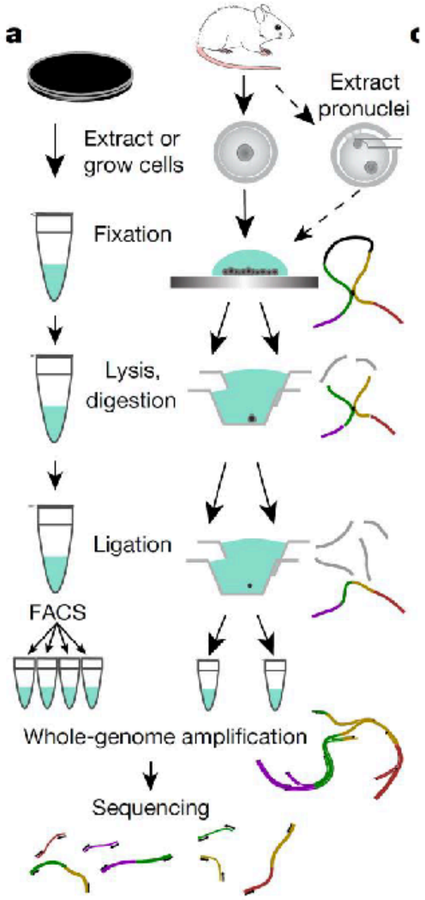
Chromatin 3D interactions

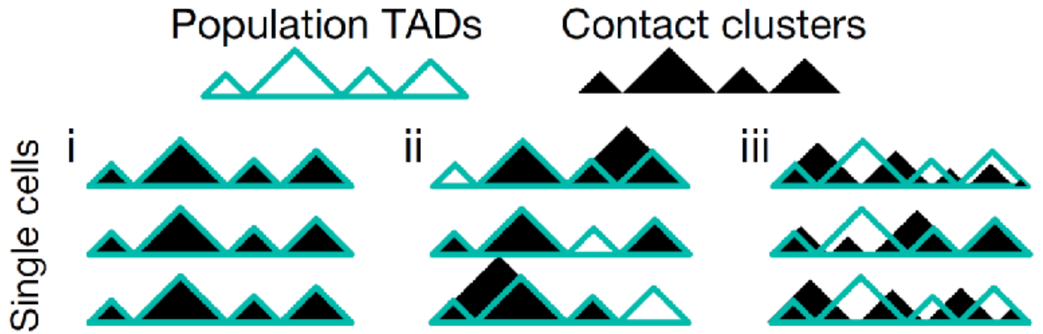
LETTER

doi:10.1038/nature21711

Single-nucleus Hi-C reveals unique chromatin reorganization at oocyte-to-zygote transition

Ilya M. Flyamer[1,2,3]*†, Johanna Gassler[1]*, Maxim Imakaev[4,5]*, Hugo B. Brandão[6], Sergey V. Ulianov[2,3], Nezar Abdennur[7], Sergey V. Razin[2,3], Leonid A. Mirny[4,5,6]§ & Kikuë Tachibana-Konwalski[1]§



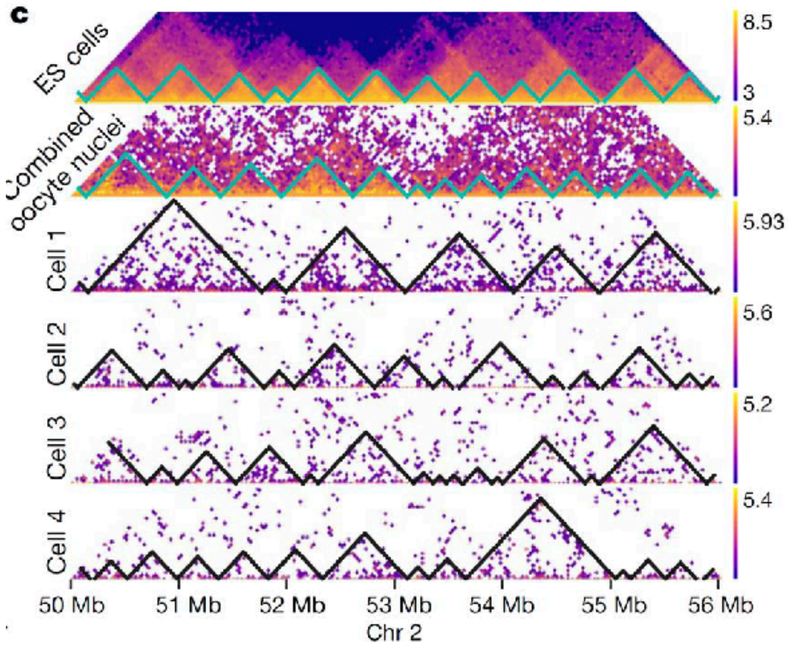


TAD present in every cell

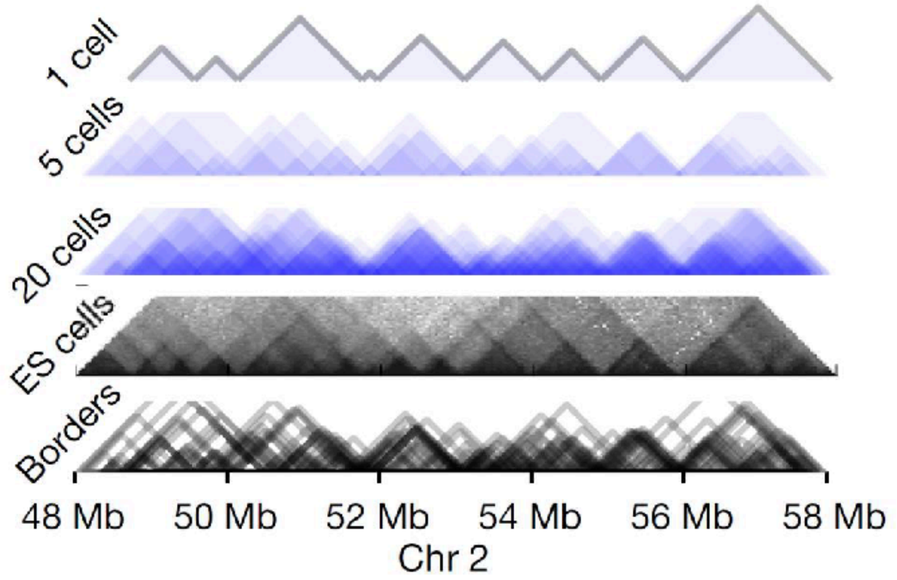
Population TAD boundaries

Contact clusters that match TADs only as average feature

Single oocyte HiC



Single cell HiC



Chromatin 3D interactions

nature genetics

Article

https://doi.org/10.1038/s41588-024-01745-3

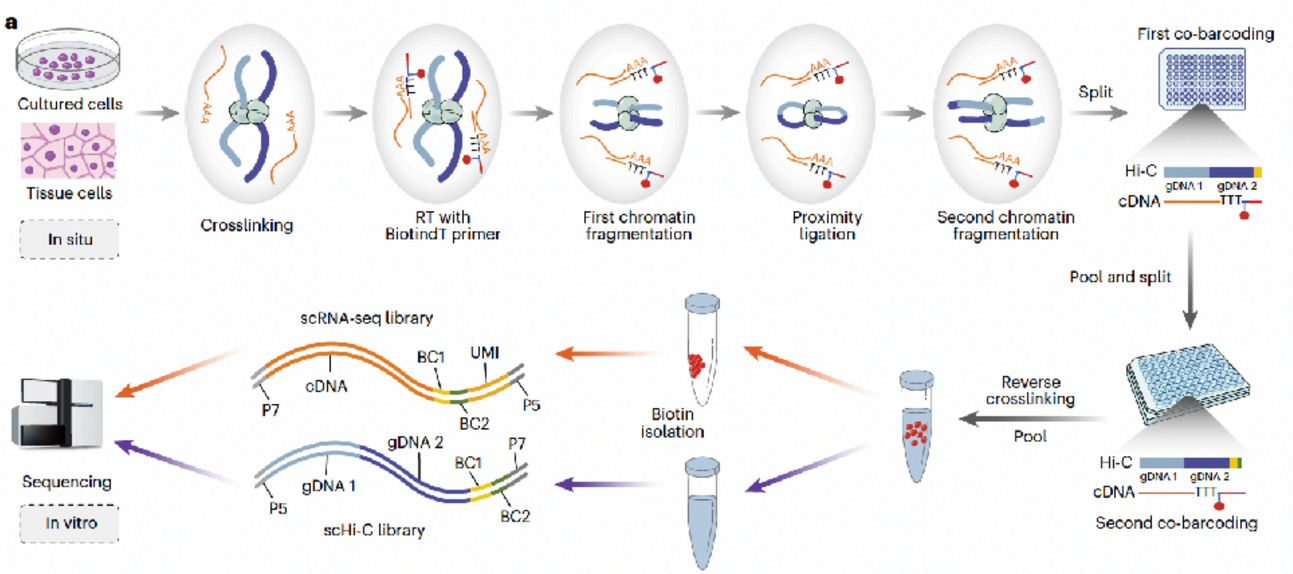
GAGE-seq concurrently profiles multiscale 3D genome organization and gene expression in single cells

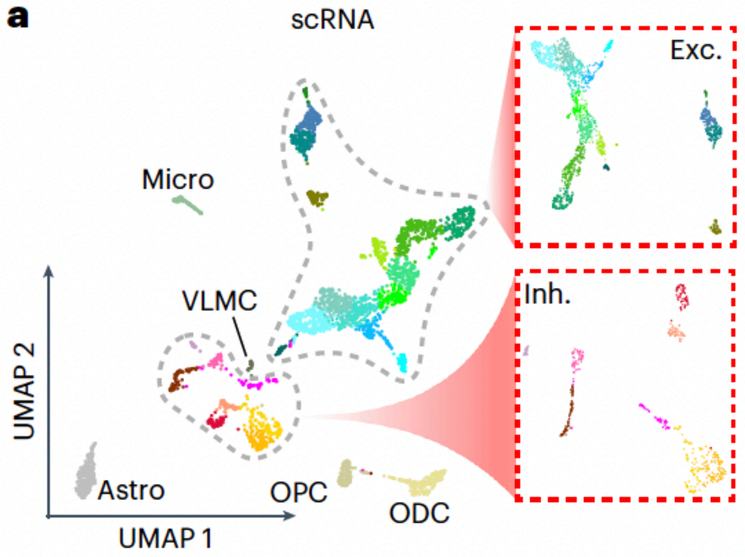
Received: 21 July 2023

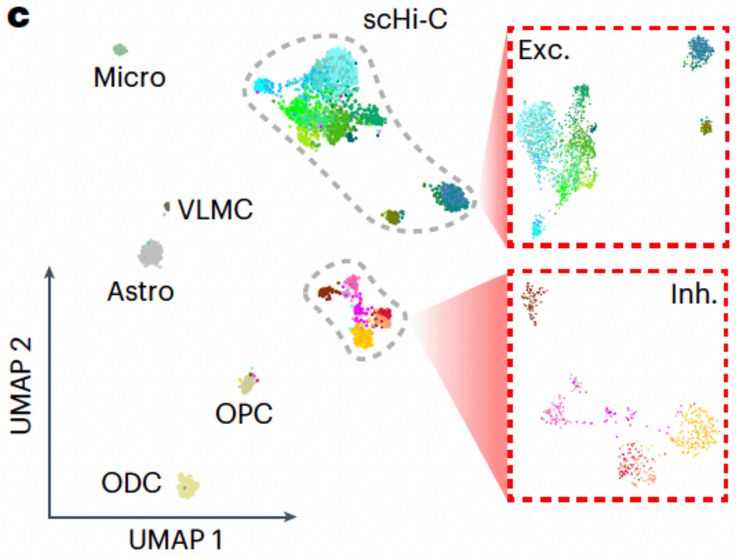
Accepted: 5 April 2024

Published online: 14 May 2024

Tianming Zhou[1], Ruochi Zhang[1,5], Deyong Jia[2], Raymond T. Doty[3], Adam D. Munday[3], Daniel Gao[4,6], Li Xin[2,4], Janis L. Abkowitz[3,4], Zhijun Duan[3,4] ✉ & Jian Ma[1] ✉







Excitatory neuron
- L2 IT RvPP
- L2/3 IT RSP
- L2/3 IT CTX a
- L2/3 IT CTX b
- L2/3 IT CTX c
- L4 IT CTX
- L4/5 IT CTX
- L5 IT RSP
- L5 IT CTX
- L6 IT CTX
- L5 PT CTX
- L6 CT CTX a
- L6 CT CTX b
- L5/6 NP CTX
- L6b CTX

Inhibitory neuron
- Pvalb a
- Pvalb b
- Sst a
- Sst b
- Vip
- Sncg
- Lamp5
- Meis2

Glia
- Astro
- OPC
- ODC
- VLMC
- Micro

Article

Cell-type specialization is encoded by specific chromatin topologies

https://doi.org/10.1038/s41586-021-04081-2

Received: 4 August 2020

Accepted: 30 September 2021

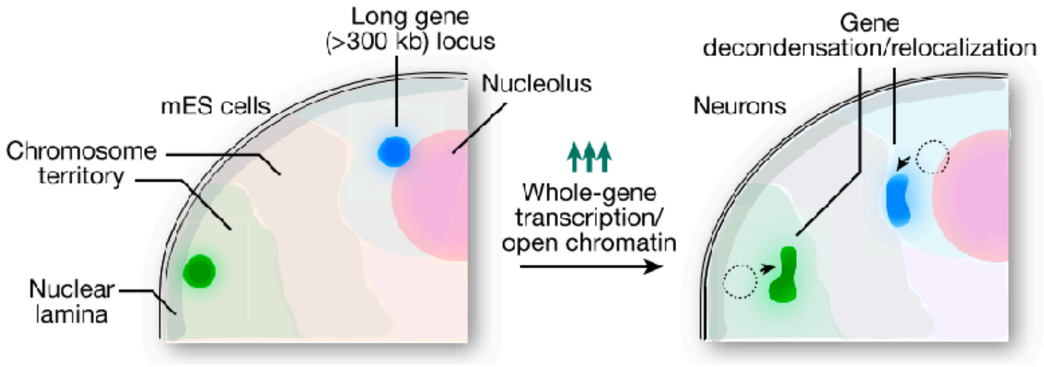
Published online: 17 November 2021

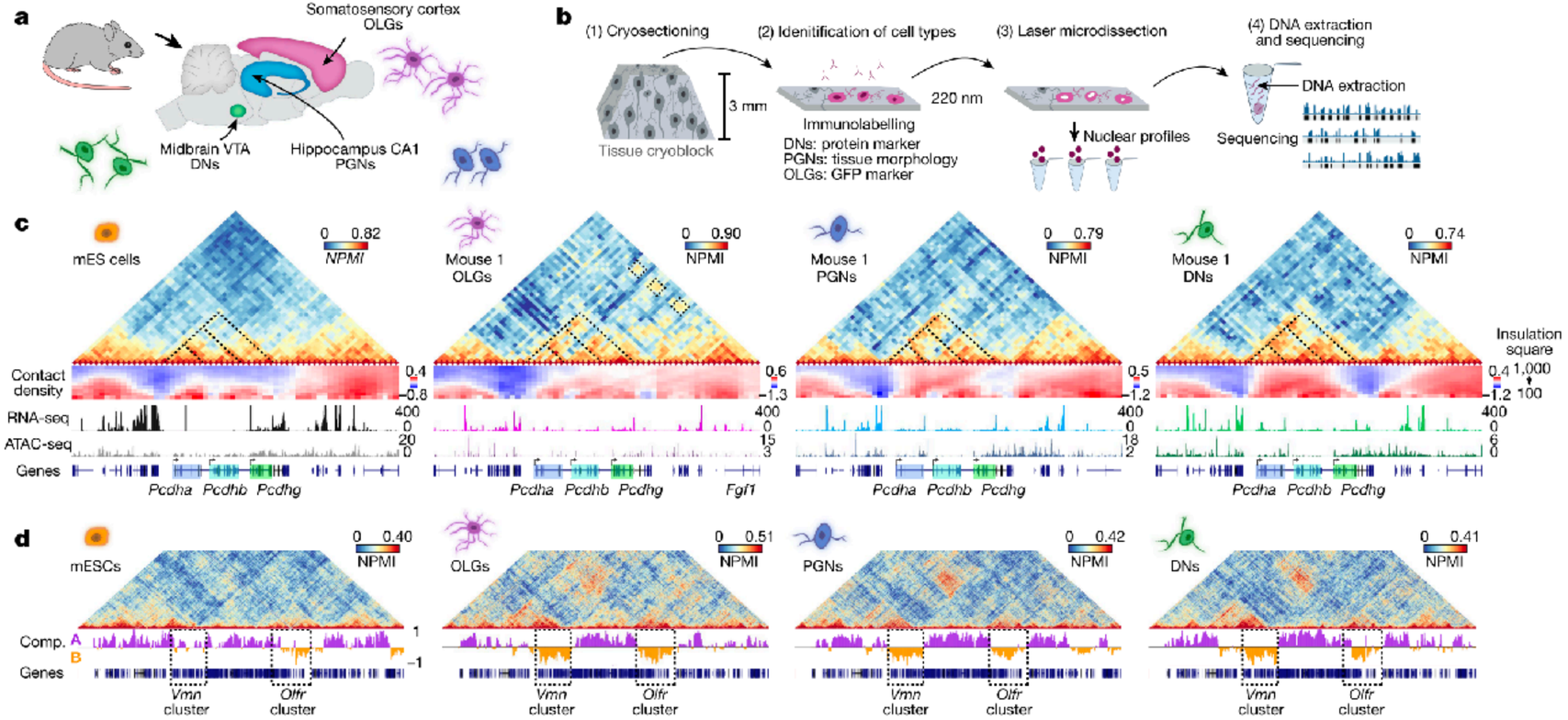
Open access

Check for updates

Warren Winick-Ng[1,22]✉, Alexander Kukalev[1,22], Izabela Harabula[1,2,22], Luna Zea-Redondo[1,2,22], Dominik Szabó[1,2,22], Mandy Meijer[3], Leonid Serebreni[1,16], Yingnan Zhang[4], Simona Bianco[5], Andrea M. Chiariello[5], Ibai Irastorza-Azcarate[1], Christoph J. Thieme[1], Thomas M. Sparks[1], Sílvia Carvalho[1,6,7,8], Luca Fiorillo[5], Francesco Musella[5], Ehsan Irani[1,9], Elena Torlai Triglia[1,17], Aleksandra A. Kolodziejczyk[10,11,18], Andreas Abentung[12,19], Galina Apostolova[12], Eleanor J. Paul[13,20,21], Vedran Franke[14], Rieke Kempfer[1,2], Altuna Akalin[14], Sarah A. Teichmann[10,11], Georg Dechant[12], Mark A. Ungless[13], Mario Nicodemi[5,9], Lonnie Welch[4], Gonçalo Castelo-Branco[3,15] & Ana Pombo[1,2,9]✉

Chromatin 3D interactions





Microscopy based technologies

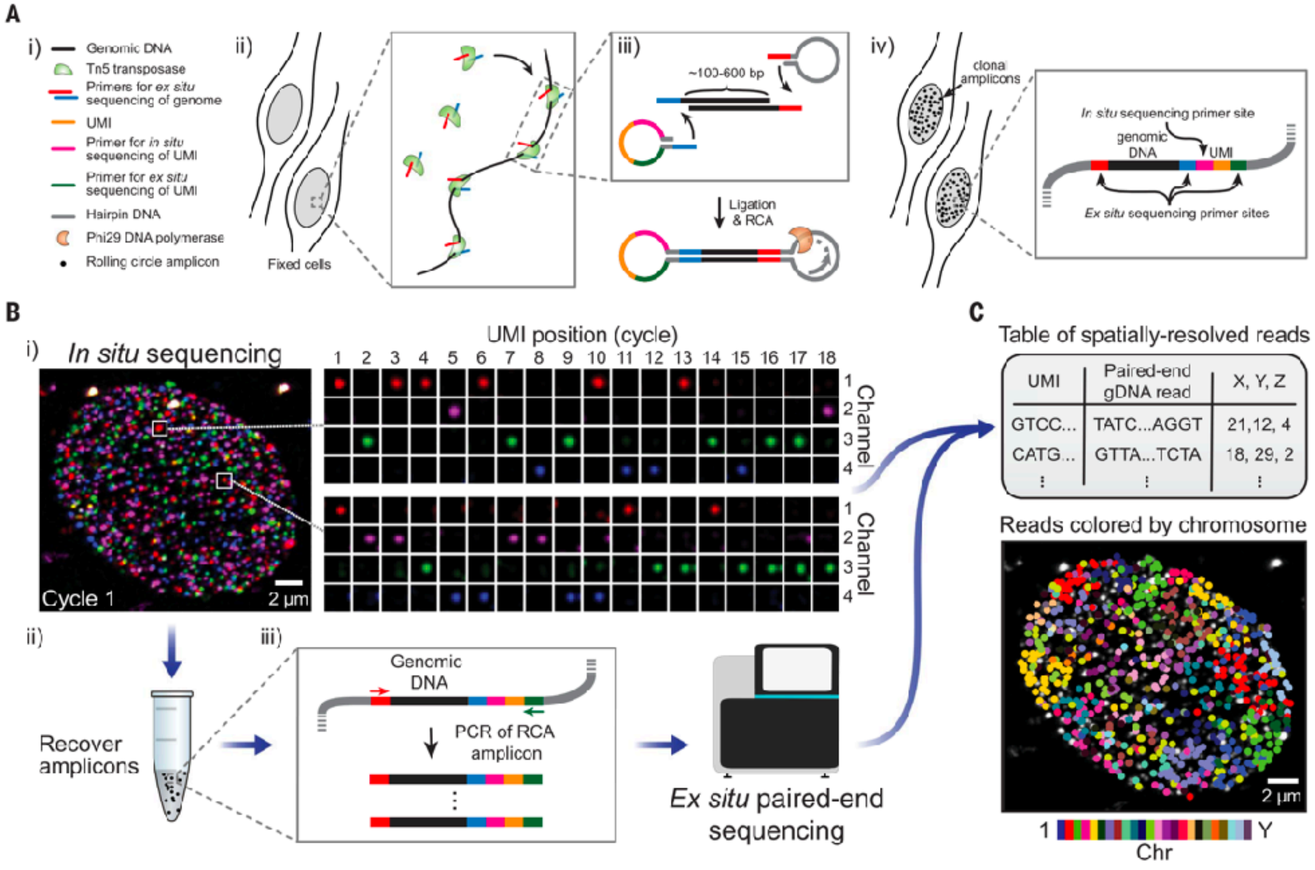
RESEARCH ARTICLE SUMMARY

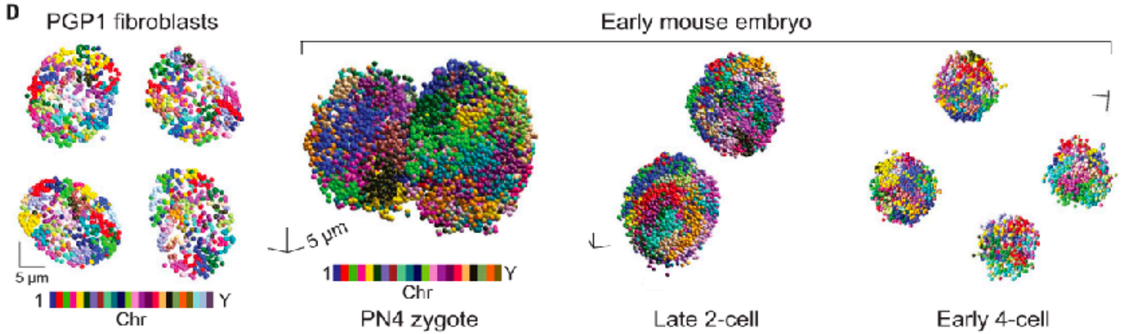
3D GENOMICS

In situ genome sequencing resolves DNA sequence and structure in intact biological samples

Andrew C. Payne*, Zachary D. Chiang*, Paul L. Reginato*, Sarah M. Mangiameli, Evan M. Murray, Chun-Chen Yao, Styliani Markoulaki, Andrew S. Earl, Ajay S. Labade, Rudolf Jaenisch, George M. Church, Edward S. Boyden†‡, Jason D. Buenrostro†‡, Fei Chen†‡

Journal Club!





Microscopy based technologies

Science

RESEARCH ARTICLES

Cite as: Y. Takei *et al.*, *Science* 10.1126/science.abj1966 (2021).

Single-cell nuclear architecture across cell types in the mouse brain

Journal Club!

Yodai Takei[1], Shiwei Zheng[2], Jina Yun[1], Sheel Shah[1], Nico Pierson[1], Jonathan White[1], Simone Schindler[1], Carsten H. Tischbirek[1], Guo-Cheng Yuan[2], Long Cai[1]*

[1]Division of Biology and Biological Engineering, California Institute of Technology, Pasadena, CA, USA. [2]Department of Genetics and Genomic Sciences and Charles Bronfman Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA.

*Corresponding author. Email: lcai@caltech.edu