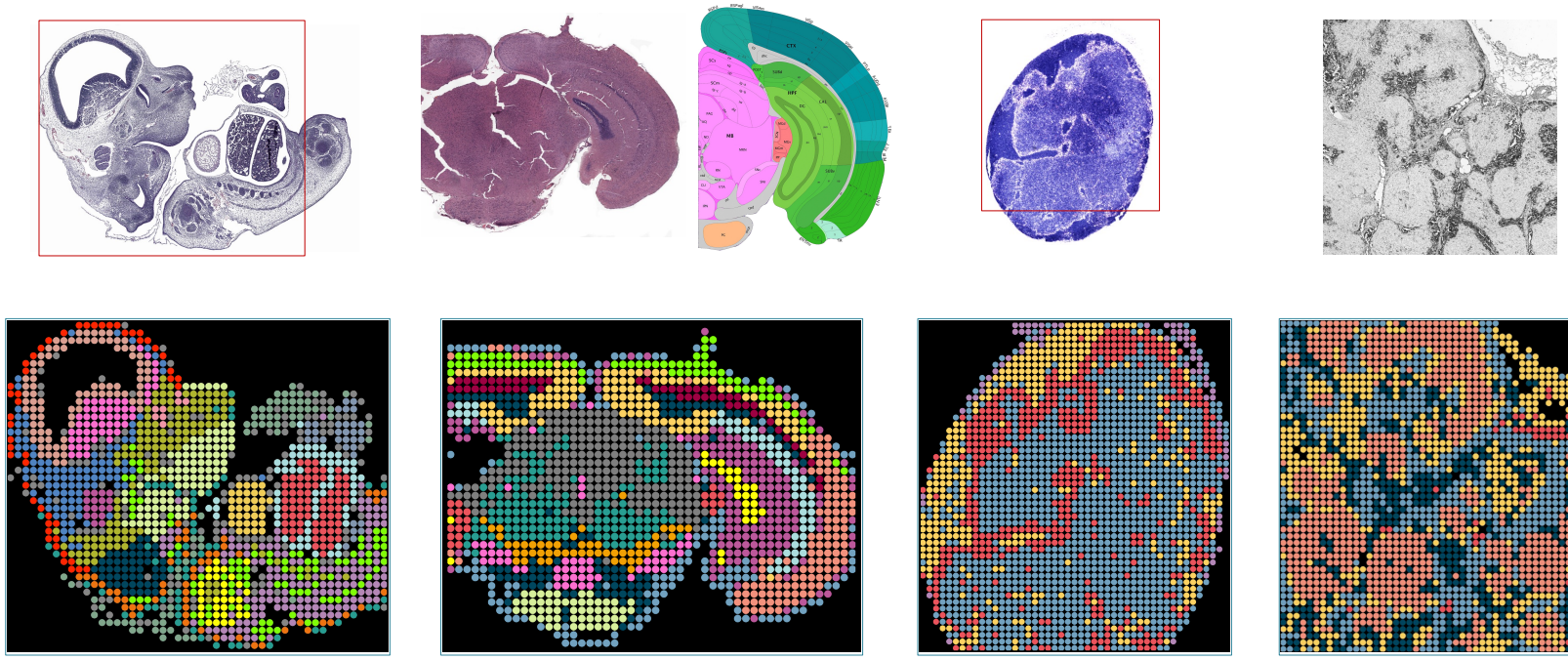
Sequencing-based Spatial Multi-Omics Mapping



Rong Fan, Ph.D.

Harold Hodgkinson Professor of Biomedical Engineering, Yale University
Professor of Pathology, Yale School of Medicine

Conflict of Interest (COI) Disclosure

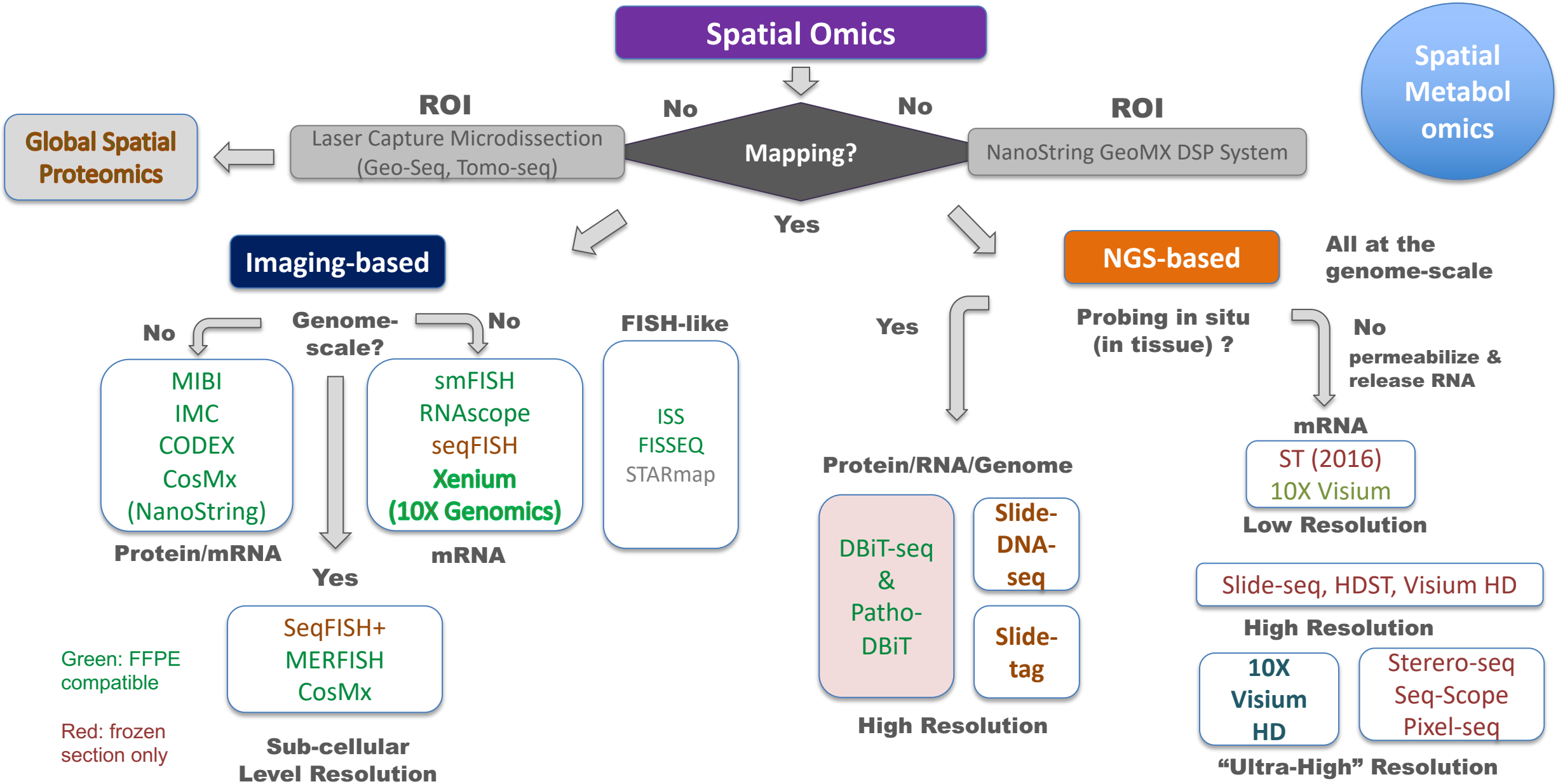
IsoPlexis (NASDAQ: ISO / CELL / Bruker)
Dr. Fan is Co-founder & SAB member of IsoPlexis Corporation.

Singleron Biotechnologies
Dr. Fan is Co-founder & SAB member of Singleron Biotechnologies Co., Ltd

AtlasXomics
Dr. Fan is Co-founder & SAB member of AtlasXomics, INC.

Bio-Techne (NASDAQ: TECH)
Dr. Fan served on the Scientific Advisory Board (SAB) of Bio-Techne. cv

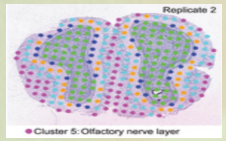
Spatial Omics Technology Family



The Rise of NGS-Based High-Throughput Spatial Omics Mapping

Take mRNAs Out

2016



ST Method
Lundeberg Lab
Science (2016)
mRNA expression
100μm spot size

2017

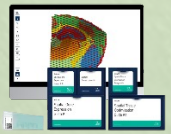
2018

2019

mRNA ST

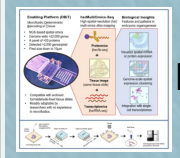
Slide-seq
10μm spot

HDST
2μm spot



Visium
55μm spot

Spatial Multi-omics
mRNA ST + 22 proteins



DBiT-seq

10μm pixel size

Liu et al., bioRxiv (2019)
doi.org/10.1101/788992

2020

ST for RNA isoform sequencing

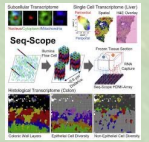
Visium for FFPE
Lundeberg et al.

SM-OMICS
Sanja Vickovic
ST+proteins

DBiT-seq for FFPE tissue spatial transcriptome at cellular level
(10μm pixel size)

DBiT-seq
Liu et al, Cell (2020)

2021

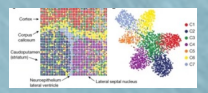


Seq-scope
<1μm spot

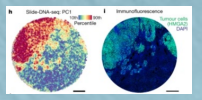
Cho et al., Cell, 2021

Visium FFPE
probe-based

Spatial-CUT&Tag

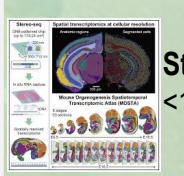


Spatial-ATAC-seq



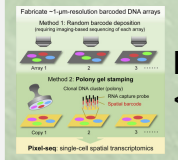
Slide-DNA-seq

2022



Stereo-seq
<1μm spot

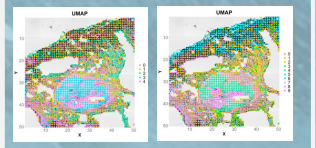
Chen et al., Cell (2022)



PIXEL-seq
<1μm spot

Fu et al., Cell (2022)

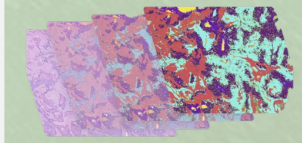
Scale Up Spatial Multi-Omics



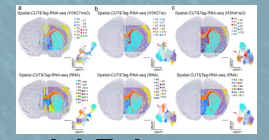
Spatial-CITE-seq

2023-2024

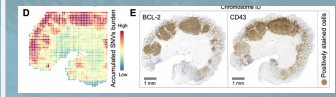
10X Genomics Visium HD



Spatial Profiling of Gene Expression – probe based (ready for preorder 2024)



Spatial-Epigenome-Transcriptome-co-seq



Spatial RNA Biology in Archival FFPE Tissues

2016 2017 2018 2019 2020 2021 2022 2023

Send Barcodes In

Barcoded Solid-Phase RNA Capture for Spatial Transcriptomics Profiling

TRANSCRIPTION

Science

Visualization and analysis of gene expression in tissue sections by spatial transcriptomics

Patrik L. Ståhl,[1,2]* Fredrik Salmén,[2]* Sanja Vickovic,[2]† Anna Lundmark,[2,3]† José Fernández Navarro,[1,2] Jens Magnusson,[1] Stefania Giacomello,[2] Michaela Asp,[2] Jakub O. Westholm,[4] Mikael Huss,[4] Annelie Mollbrink,[2] Sten Linnarsson,[5] Simone Codeluppi,[5,6] Åke Borg,[7] Fredrik Pontén,[8] Paul Igor Costea,[2] Pelin Sahlén,[2] Jan Mulder,[9] Olaf Bergmann,[1] Joakim Lundeberg,[2]‡ Jonas Frisén[1]

Analysis of the pattern of proteins or messenger RNAs (mRNAs) in histological tissue sections is a cornerstone in biomedical research and diagnostics. This typically involves the visualization of a few proteins or expressed genes at a time. We have devised a strategy, which we call "spatial transcriptomics," that allows visualization and quantitative analysis of the transcriptome with spatial resolution in individual tissue sections. By positioning histological sections on arrayed reverse transcription primers with unique positional barcodes, we demonstrate high-quality RNA-sequencing data with maintained two-dimensional positional information from the mouse brain and human breast cancer. Spatial transcriptomics provides quantitative gene expression data and visualization of the distribution of mRNAs within tissue sections and enables novel types of bioinformatics analyses, valuable in research and diagnostics.

nature protocols

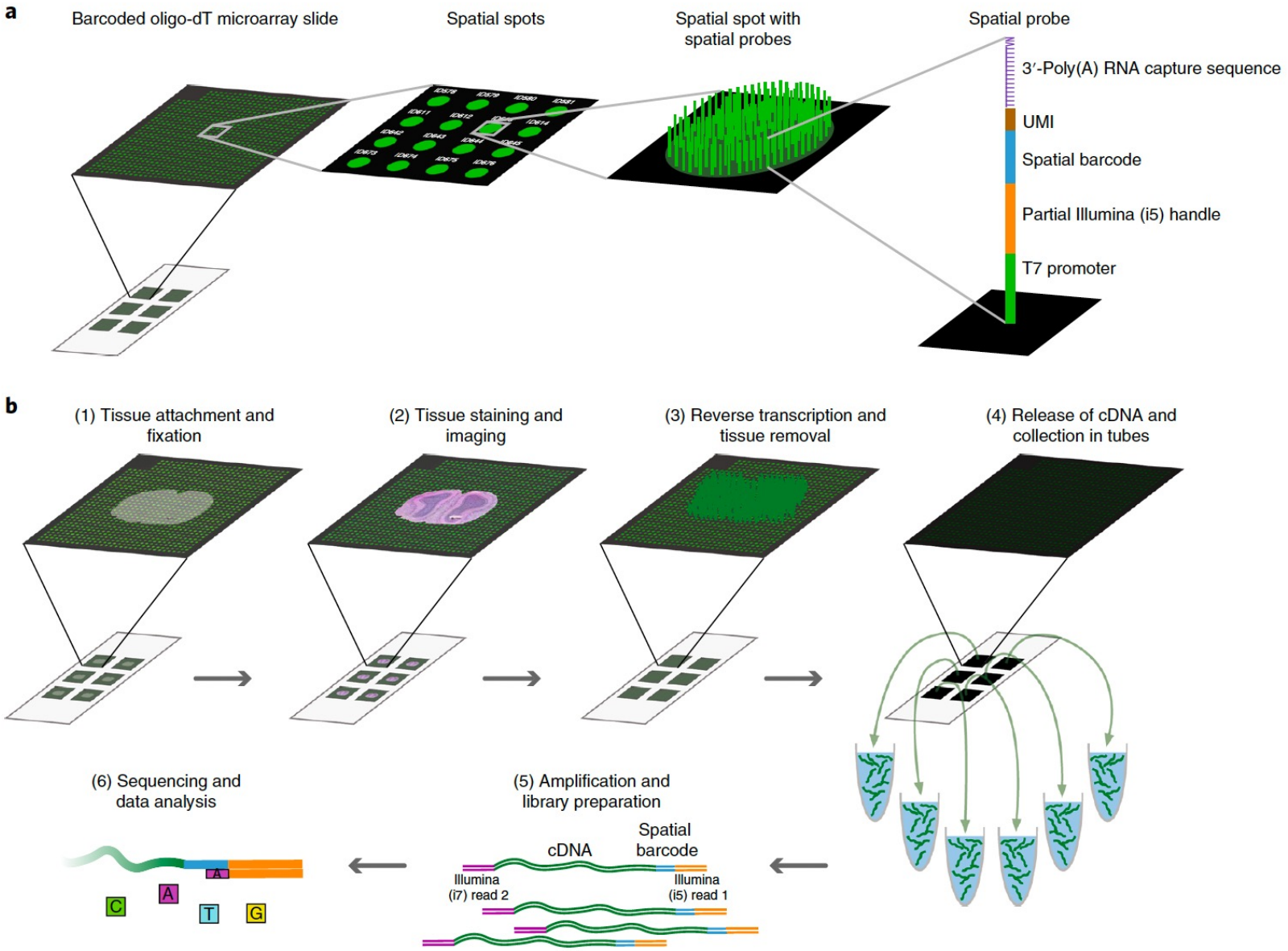
PROTOCOL

https://doi.org/10.1038/s41596-018-0045-2

Barcoded solid-phase RNA capture for Spatial Transcriptomics profiling in mammalian tissue sections

Fredrik Salmén[1,2,5], Patrik L. Ståhl[1,5*], Annelie Mollbrink[1], José Fernández Navarro[1], Sanja Vickovic[1,3], Jonas Frisén[4], Joakim Lundeberg[1*]

Spatial resolution of gene expression enables gene expression events to be pinpointed to a specific location in biological tissue. Spatially resolved gene expression in tissue sections is traditionally analyzed using immunohistochemistry (IHC) or in situ hybridization (ISH). These technologies are invaluable tools for pathologists and molecular biologists; however, their throughput is limited to the analysis of only a few genes at a time. Recent advances in RNA sequencing (RNA-seq) have made it possible to obtain unbiased high-throughput gene expression data in bulk. Spatial Transcriptomics combines the benefits of traditional spatially resolved technologies with the massive throughput of RNA-seq. Here, we present a protocol describing how to apply the Spatial Transcriptomics technology to mammalian tissue. This protocol combines histological staining and spatially resolved RNA-seq data from intact tissue sections. Once suitable tissue-specific conditions have been established, library construction and sequencing can be completed in ~5–6 d. Data processing takes a few hours, with the exact timing dependent on the sequencing depth. Our method requires no special instruments and can be performed in any laboratory with access to a cryostat, microscope and next-generation sequencing.



Slide-seq and Curio Bio

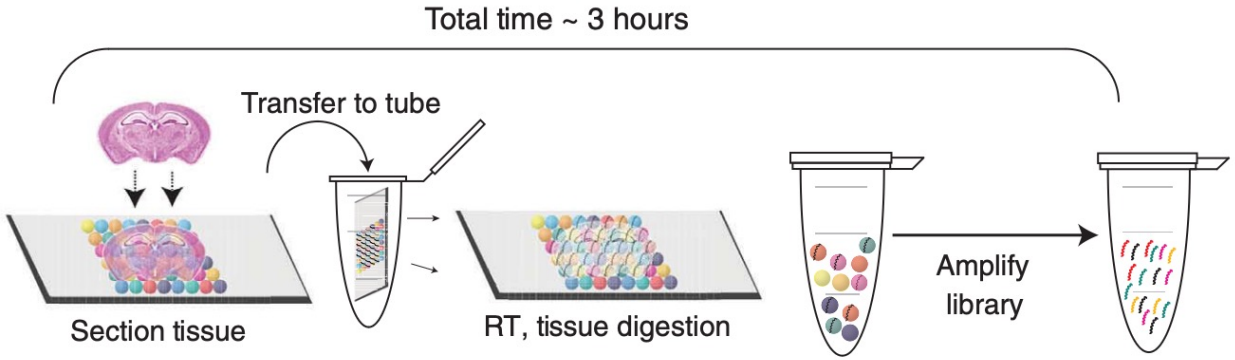
Science

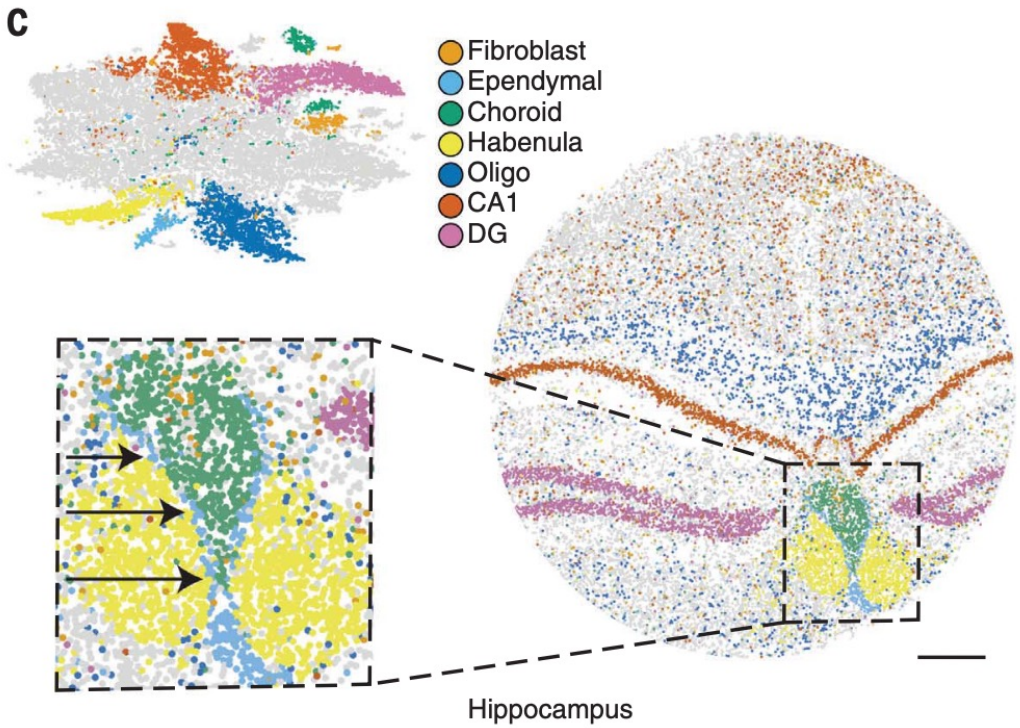
RNA SEQUENCING

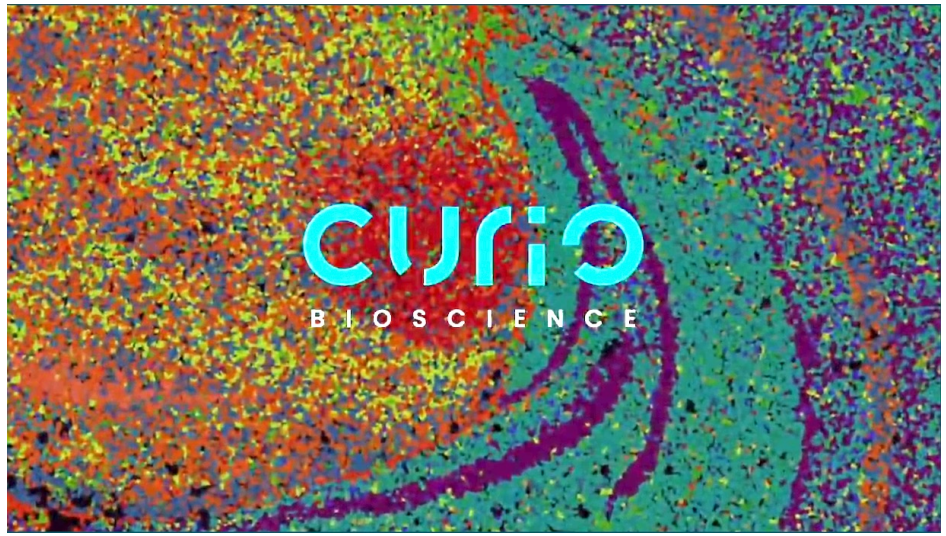
Slide-seq: A scalable technology for measuring genome-wide expression at high spatial resolution

Samuel G. Rodriques[1,2,3]*, Robert R. Stickels[3,4,5]*, Aleksandrina Goeva[3], Carly A. Martin[3], Evan Murray[3], Charles R. Vanderburg[3], Joshua Welch[3], Linlin M. Chen[3], Fei Chen[3]†‡, Evan Z. Macosko[3,6]†‡

Spatial positions of cells in tissues strongly influence function, yet a high-throughput, genome-wide readout of gene expression with cellular resolution is lacking. We developed Slide-seq, a method for transferring RNA from tissue sections onto a surface covered in DNA-barcoded beads with known positions, allowing the locations of the RNA to be inferred by sequencing. Using Slide-seq, we localized cell types identified by single-cell RNA sequencing datasets within the cerebellum and hippocampus, characterized spatial gene expression patterns in the Purkinje layer of mouse cerebellum, and defined the temporal evolution of cell type–specific responses in a mouse model of traumatic brain injury. These studies highlight how Slide-seq provides a scalable method for obtaining spatially resolved gene expression data at resolutions comparable to the sizes of individual cells.







Spatial Transcriptome Sequencing at Subcellar Resolution

Cell

CellPress

Resource

Microscopic examination of spatial transcriptome using Seq-Scope

Chun-Seok Cho,[1,4] Jingyue Xi,[2,4] Yichen Si,[2] Sung-Rye Park,[1] Jer-En Hsu,[1] Myungjin Kim,[1] Goo Jun,[3] Hyun Min Kang,[2] and Jun Hee Lee[1,5,*]

[1]Department of Molecular and Integrative Physiology, University of Michigan Medical School, Ann Arbor, MI 48109, USA
[2]Department of Biostatistics, University of Michigan School of Public Health, Ann Arbor, MI 48109, USA
[3]Human Genetics Center, University of Texas Health Science Center at Houston, Houston, TX 77030, USA
[4]These authors contributed equally
[5]Lead contact
*Correspondence: leeju@umich.edu
https://doi.org/10.1016/j.cell.2021.05.010

Cell

CellPress
OPEN ACCESS

Resource

Spatiotemporal transcriptomic atlas of mouse organogenesis using DNA nanoball-patterned arrays

Ao Chen,[1,2,26] Sha Liao,[1,26] Mengnan Cheng,[1,3,26] Kailong Ma,[1,26] Liang Wu,[1,3,4,26] Yiwei Lai,[1,5,26] Xiaojie Qiu,[6,7,26] Jin Yang,[8] Jiangshan Xu,[1,3] Shijie Hao,[1,3] Xin Wang,[1] Huifang Lu,[1] Xi Chen,[1] Xing Liu,[1] Xin Huang,[1,3] Zhao Li,[1] Yan Hong,[1] Yujia Jiang,[1,9] Jian Peng,[1] Shuai Liu,[1] Mengzhe Shen,[1] Chuanyu Liu,[1,10] Quanshui Li,[1] Yue Yuan,[1] Xiaoyu Wei,[1] Huiwen Zheng,[1,9] Weimin Feng,[1,3] Zhifeng Wang,[1,4] Yang Liu,[1] Zhaohui Wang,[1] Yunzhi Yang,[1,9] Haitao Xiang,[1,3] Lei Han,[1] Baoming Qin,[5] Pengcheng Guo,[5] Guangyao Lai,[5] Pura Muñoz-Cánoves,[11,12] Patrick H. Maxwell,[13] Jean Paul Thiery,[14] Qing-Feng Wu,[15] Fuxiang Zhao,[1] Bichao Chen,[1] Mei Li,[1] Xi Dai,[1,3] Shuai Wang,[1,3] Haoyan Kuang,[1] Junhou Hui,[1] Liqun Wang,[16] Ji-Feng Fei,[16] Ou Wang,[1] Xiaofeng Wei,[17] Haorong Lu,[17] Bo Wang,[17] Shiping Liu,[1,4] Ying Gu,[1,18] Ming Ni,[8] Wenwei Zhang,[1,19] Feng Mu,[8] Ye Yin,[1,20] Huanming Yang,[1,21] Michael Lisby,[2] Richard J. Cornall,[22] Jan Mulder,[23,24] Mathias Uhlén,[23,24] Miguel A. Esteban,[1,5,25,*] Yuxiang Li,[1,*] Longqi Liu,[1,9,10,*] Xun Xu,[1,18,27,*] and Jian Wang[1,21,*]

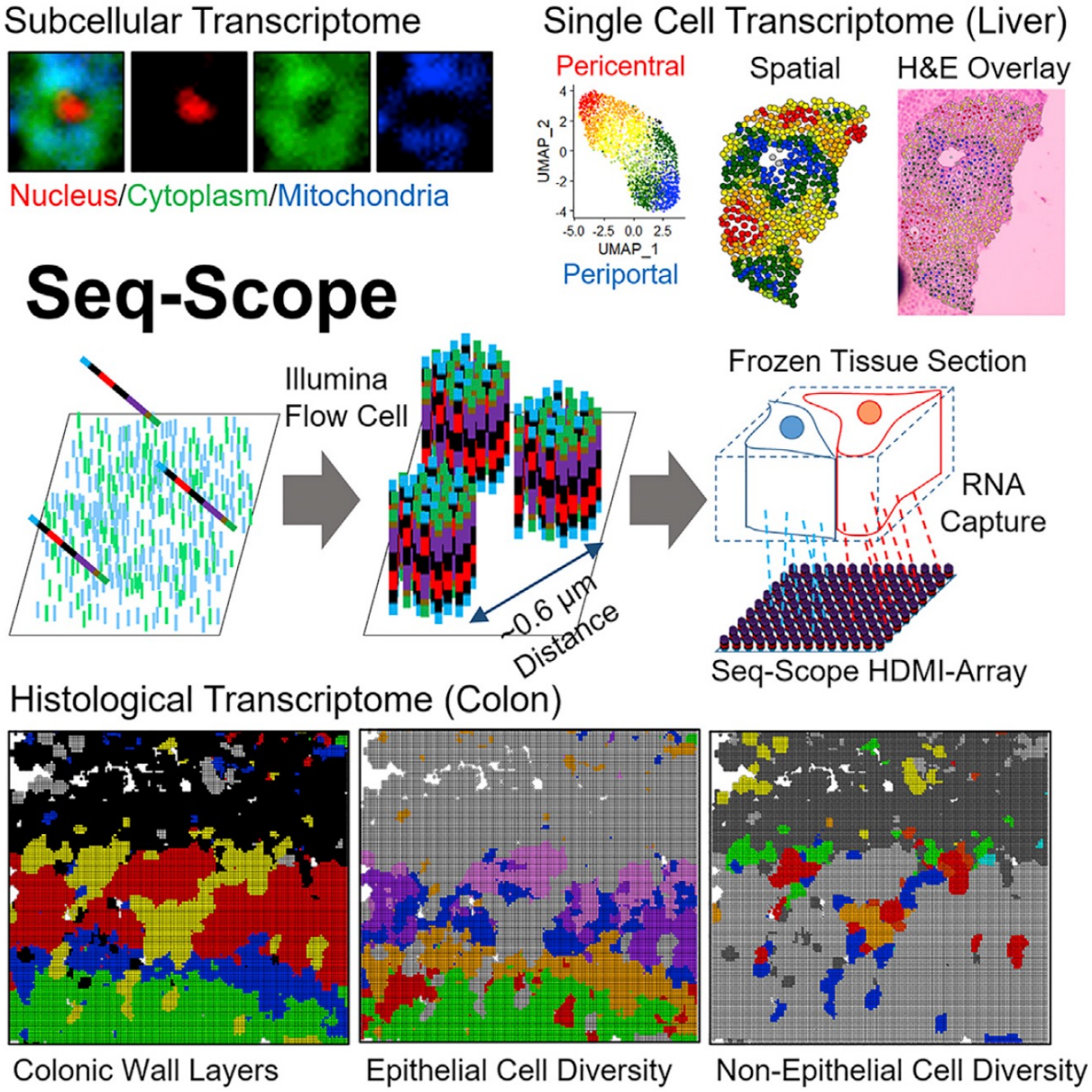
Cell

CellPress

Resource

Polony gels enable amplifiable DNA stamping and spatial transcriptomics of chronic pain

Xiaonan Fu,[1,2,9] Li Sun,[1,2,3,9] Runze Dong,[1,2,4,9] Jane Y. Chen,[1,5] Runglawan Silakit,[1,6] Logan F. Condon,[1,5,7] Yiing Lin,[8] Shin Lin,[6] Richard D. Palmiter,[1,5] and Liangcai Gu[1,2,10,*]

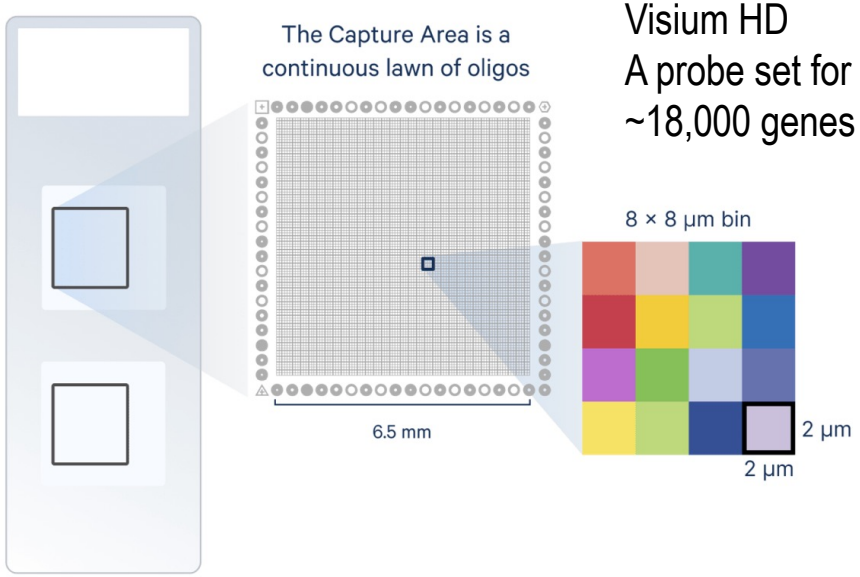


10X Genomics Visium, Visium FFPE, and Visium HD

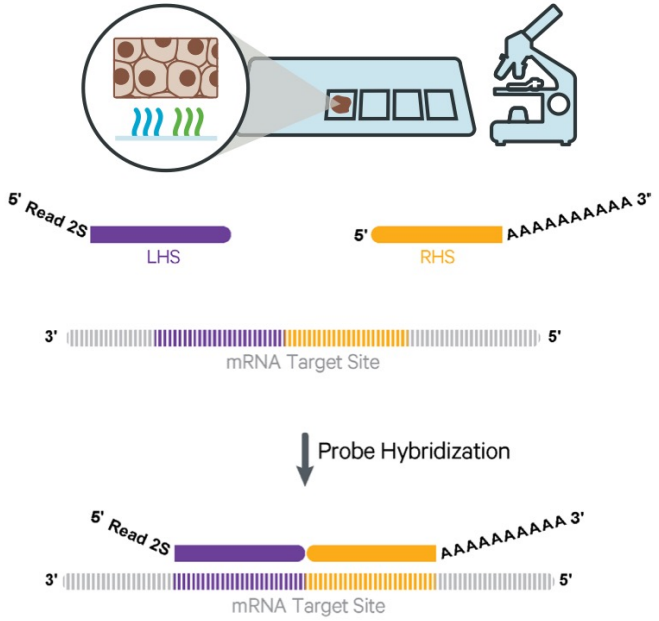
Visium Spatial Gene Expression

Map the whole transcriptome within the tissue context

Visium Spatial Gene Expression is a next-generation molecular profiling solution for classifying tissue based on total mRNA. Map the whole transcriptome with morphological context in FFPE or fresh frozen tissues to discover novel insights into normal development, disease pathology, and clinical translational research.



Visium FFPE
Visium HD
A probe set for ~18,000 genes



Access more sample types

Compatible with both FFPE and fresh frozen tissue samples.

Whole tissue section profiling

No need to select regions of interest—analyze the whole transcriptome from an entire section.

High cellular resolution

1–10 cell resolution on average per spot depending on tissue type.

Diverse sample compatibility

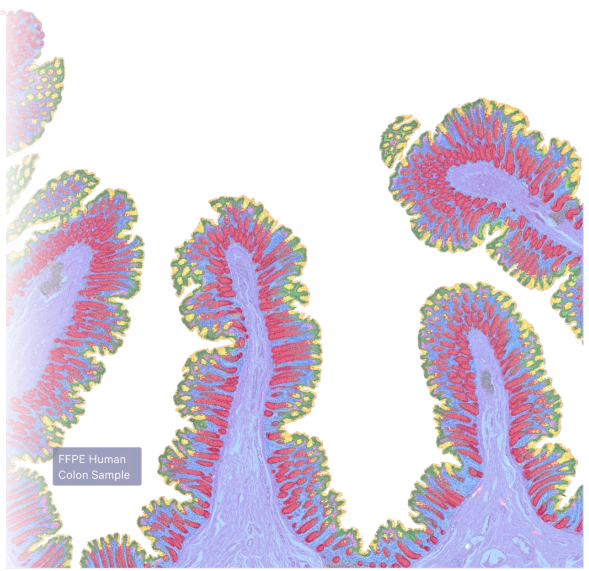
Demonstrated data on a diverse set of organs across species (human, mouse, rat, and more).

Protein co-detection

Combine whole transcriptome spatial analysis with immunofluorescence protein detection.

Streamlined data analysis

Combine histological and gene expression data with easy-to-use software.



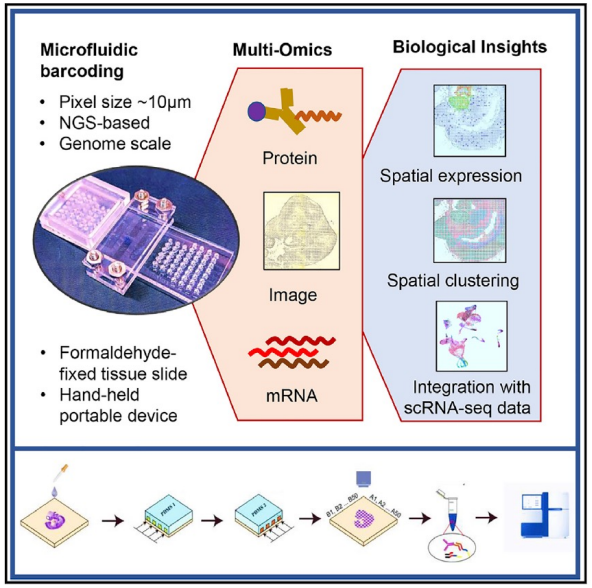
Deterministic Barcoding in Tissue for Spatial Multi-Omics

Cell

Resource

High-Spatial-Resolution Multi-Omics Sequencing via Deterministic Barcoding in Tissue

Graphical Abstract



Authors

Yang Liu, Mingyu Yang, Yanxiang Deng, ..., Yang Xiao, Stephanie Halene, Rong Fan

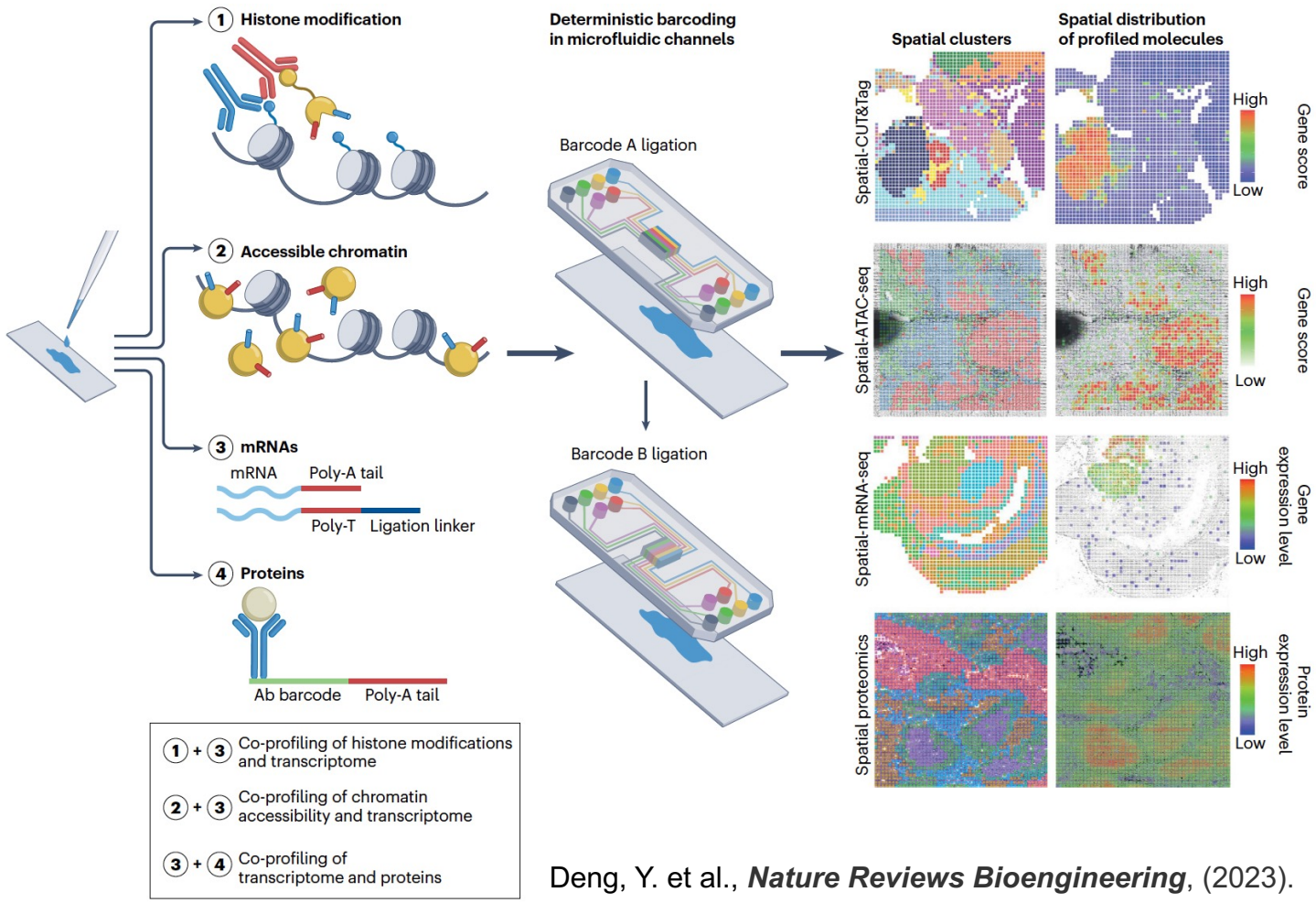
Correspondence

rong.fan@yale.edu

In Brief

DBiT-seq is a microfluidic-based method to deliver barcodes to the surface of a tissue slide to allow for spatial omics sequencing with 10-μm pixel size.

Liu, Y. et al., ***bioRxiv*** 788992 (2019).
Liu, Y. et al., ***Cell***, 10;183(6):1665-1681 (2020).



Deng, Y. et al., ***Nature Reviews Bioengineering***, (2023).

Other In-Tissue Barcoding Methods

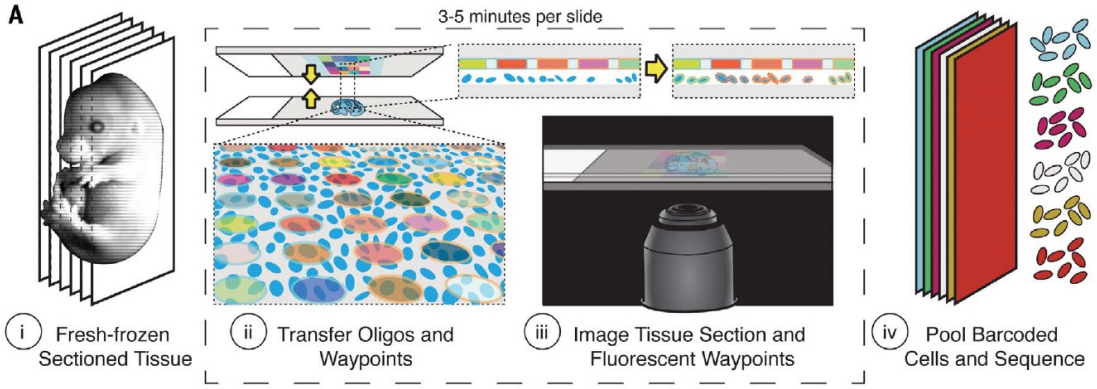
Science

SPATIAL GENETICS

Embryo-scale, single-cell spatial transcriptomics

Sanjay R. Srivatsan[1]†, Mary C. Regier[2,3]†, Eliza Barkan[1,4], Jennifer M. Franks[1], Jonathan S. Packer[5], Parker Grosjean[2], Madeleine Duran[1], Sarah Saxton[2], Jon J Ladd[6], Malte Spielmann[7,8], Carlos Lois[9], Paul D. Lampe[6], Jay Shendure[1,10,11,12]*, Kelly R. Stevens[2,3,12,13]*, Cole Trapnell[1,10,12]*

Spatial patterns of gene expression manifest at scales ranging from local (e.g., cell-cell interactions) to global (e.g., body axis patterning). However, current spatial transcriptomics methods either average local contexts or are restricted to limited fields of view. Here, we introduce sci-Space, which retains single-cell resolution while resolving spatial heterogeneity at larger scales. Applying sci-Space to developing mouse embryos, we captured approximate spatial coordinates and whole transcriptomes of about 120,000 nuclei. We identify thousands of genes exhibiting anatomically patterned expression, leverage spatial information to annotate cellular subtypes, show that cell types vary substantially in their extent of spatial patterning, and reveal correlations between pseudotime and the migratory patterns of differentiating neurons. Looking forward, we anticipate that sci-Space will facilitate the construction of spatially resolved single-cell atlases of mammalian development.



nature

Article

Spatial genomics enables multi-modal study of clonal heterogeneity in tissues

https://doi.org/10.1038/s41586-021-04217-4
Received: 1 February 2021
Accepted: 8 November 2021
Published online: 15 December 2021

Tongtong Zhao[1,2,7], Zachary D. Chiang[1,2,3,7], Julia W. Morriss[1,2], Lindsay M. LaFave[2,4,5], Evan M. Murray[1,2], Isabella Del Priore[4,5], Kevin Meli[4,5], Caleb A. Lareau[1,2], Naeem M. Nadaf[1], Jilong Li[1], Andrew S. Earl[1,2,3], Evan Z. Macosko[1,6], Tyler Jacks[1,4,5], Jason D. Buenrostro[1,2,3,8]✉ & Fei Chen[1,2,3,8]✉

nature

Article

Slide-tags enables single-nucleus barcoding for multimodal spatial genomics

https://doi.org/10.1038/s41586-023-06837-4
Received: 26 March 2023
Accepted: 6 November 2023
Published online: 13 December 2023
Open access

Andrew J. C. Russell[1,2,15], Jackson A. Weir[1,3,15], Naeem M. Nadaf[1,15], Matthew Shabet[1], Vipin Kumar[1], Sandeep Kambhampati[1,4], Ruth Raichur[1], Giovanni J. Marrero[1], Sophia Liu[1,5,6], Karol S. Balderrama[1], Charles R. Vanderburg[1], Vignesh Shanmugam[1,7], Luyi Tian[1,13], J. Bryan Iorgulescu[1,8,9,10,14], Charles H. Yoon[11], Catherine J. Wu[1,8,9,10], Evan Z. Macosko[1,12]✉ & Fei Chen[1,2]✉

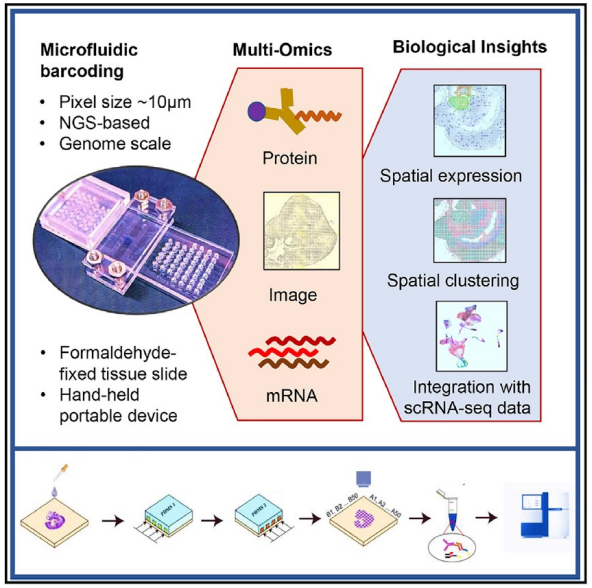
Deterministic Barcoding in Tissue for Spatial Multi-Omics

Cell

Resource

High-Spatial-Resolution Multi-Omics Sequencing via Deterministic Barcoding in Tissue

Graphical Abstract



Authors

Yang Liu, Mingyu Yang, Yanxiang Deng, ..., Yang Xiao, Stephanie Halene, Rong Fan

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rong.fan@yale.edu

In Brief

DBiT-seq is a microfluidic-based method to deliver barcodes to the surface of a tissue slide to allow for spatial omics sequencing with 10-μm pixel size.

Liu, Y. et al., ***bioRxiv*** 788992 (2019).
Liu, Y. et al., ***Cell***, 10;183(6):1665-1681 (2020).

Check for updates

research highlights

SEQUENCING

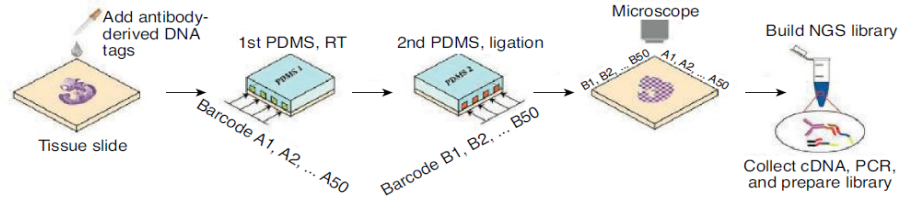
Multiomics sequencing goes spatial

Microfluidic channels provide a means to deliver barcodes encoding spatial information to a tissue, which allows co-profiling of gene expression and proteins of interest in a spatially resolved manner.

The plethora of sequencing tools have broadened our understanding of how cells function and develop. Yet the majority of sequencing tools leave out the spatial context where cells reside. Such spatial context can be essential to understanding how cells organize within a three-dimensional environment and how cells interact with each other.

Back in 2013, Rong Fan from Yale University was intrigued by a conversation with colleague Kathryn Miller-Jensen: they noticed that trypsinizing cancer cells off the substrate could perturb the measurements of the signaling network. Since then, Fan has been thinking about how to fix and measure cellular states on a substrate or in a tissue without cell dissociation. Barcoding strategies were introduced in massively parallel single-cell RNA sequencing and have substantially advanced the single-cell field. Yet, Fan says, "I was never satisfied with the random barcoding approach." He hoped to have a method for 'deterministic barcoding' of a tissue — delivering barcodes to a given cell in a specific location.

In a sense, the advent of spatially resolved transcriptomics, our Method of the Year 2020, solved Fan's problem. Sequencing-based Visium from 10x Genomics, Slide-seq, and high-definition spatial transcriptomics (HDST), among



Schematic workflow of DBiT-seq. PDMS, polydimethylsiloxane microfluidic chip; RT, reverse transcription; NGS, next-generation sequencing. Reproduced with permission from Liu et al. *Cell* **183**, 1665–1681.e18, (2020), Elsevier.

to poly(A)-tailed mRNAs; this step is followed by in situ reverse transcription. The strip-like confinement, however, only provides one-dimensional information. To achieve a two-dimensional array of pixels, Fan and his colleagues applied a crossflow scheme, in which they removed the first microfluidic chip and clamped on a second chip to deliver a separate set of DNA barcodes in the perpendicular direction. The two sets of barcodes are joined via the ligation linker and store the spatial information of the respective mRNA. After two rounds of microfluidic flow, the tissue retains its morphology and allows optical or fluorescence imaging to associate individual pixels with gene expression patterns.

gene expression patterns. Furthermore, the integration of DBiT-seq and single-cell transcriptomics data allowed the annotation of cell types and the visualization of cell distributions.

In addition to mouse embryos, Fan notes, "As of today, we have performed DBiT-seq on not only mouse embryos but also adult heart, vessel, tonsil, lymph node, kidney, pancreas and skin." Moreover, DBiT-seq is compatible with immunostained tissue slides and allows the study of transcriptome and protein expression and of cell morphology. Fan says, "We are thinking about how to better integrate tissue histology images and machine learning to deconvolve single cell-transcriptomes in DBiT-seq pixels."

Spatially Resolved Joint Proteome-Transcriptome Profiling

Dr. Yang Liu

Yale Pathology

Prof. Stephanie Halene

Prof. Joe Craft

Prof. Mina Xu

Prof. David Hafler

nature biotechnology

Brief Communication

https://doi.org/10.1038/s41587-023-01676-0

High-plex protein and whole transcriptome co-mapping at cellular resolution with spatial CITE-seq

Received: 28 March 2022

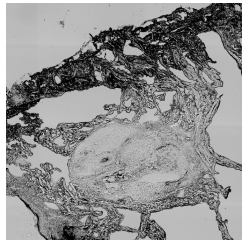
Accepted: 12 January 2023

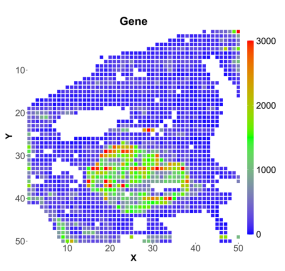
Published online: 23 February 2023

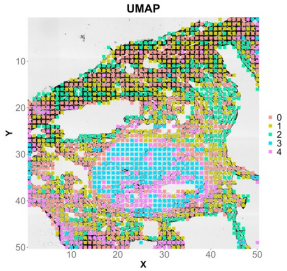
Check for updates

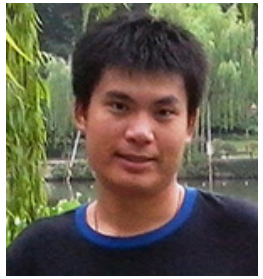
Yang Liu[1,2,3,4,5], Marcello DiStasio[3,4,5], Graham Su[1,2], Hiromitsu Asashima[4,5], Archibald Enninful[1,2], Xiaoyu Qin[1,2], Yanxiang Deng[1,2], Jungmin Nam[1], Fu Gao[4], Pino Bordignon[6], Marco Cassano[6], Mary Tomayko[3,7], Mina Xu[3], Stephanie Halene[4], Joseph E. Craft[4,8,9], David Hafler[4,5,8,9] & Rong Fan[1,2,3,4,9]

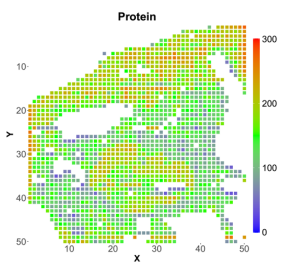
In this study, we extended co-indexing of transcriptomes and epitopes (CITE) to the spatial dimension and demonstrated high-plex protein and whole transcriptome co-mapping. We profiled 189 proteins and whole transcriptome in multiple mouse tissue types with spatial CITE sequencing and then further applied the method to measure 273 proteins and transcriptome in human tissues, revealing spatially distinct germinal center reactions in tonsil and early immune activation in skin at the Coronavirus Disease 2019 mRNA vaccine injection site.

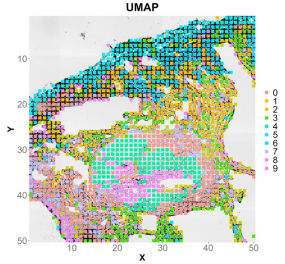




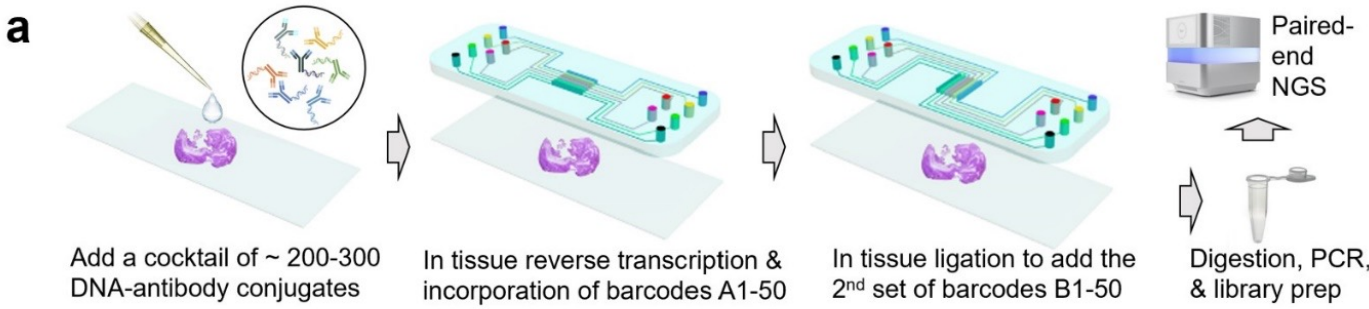


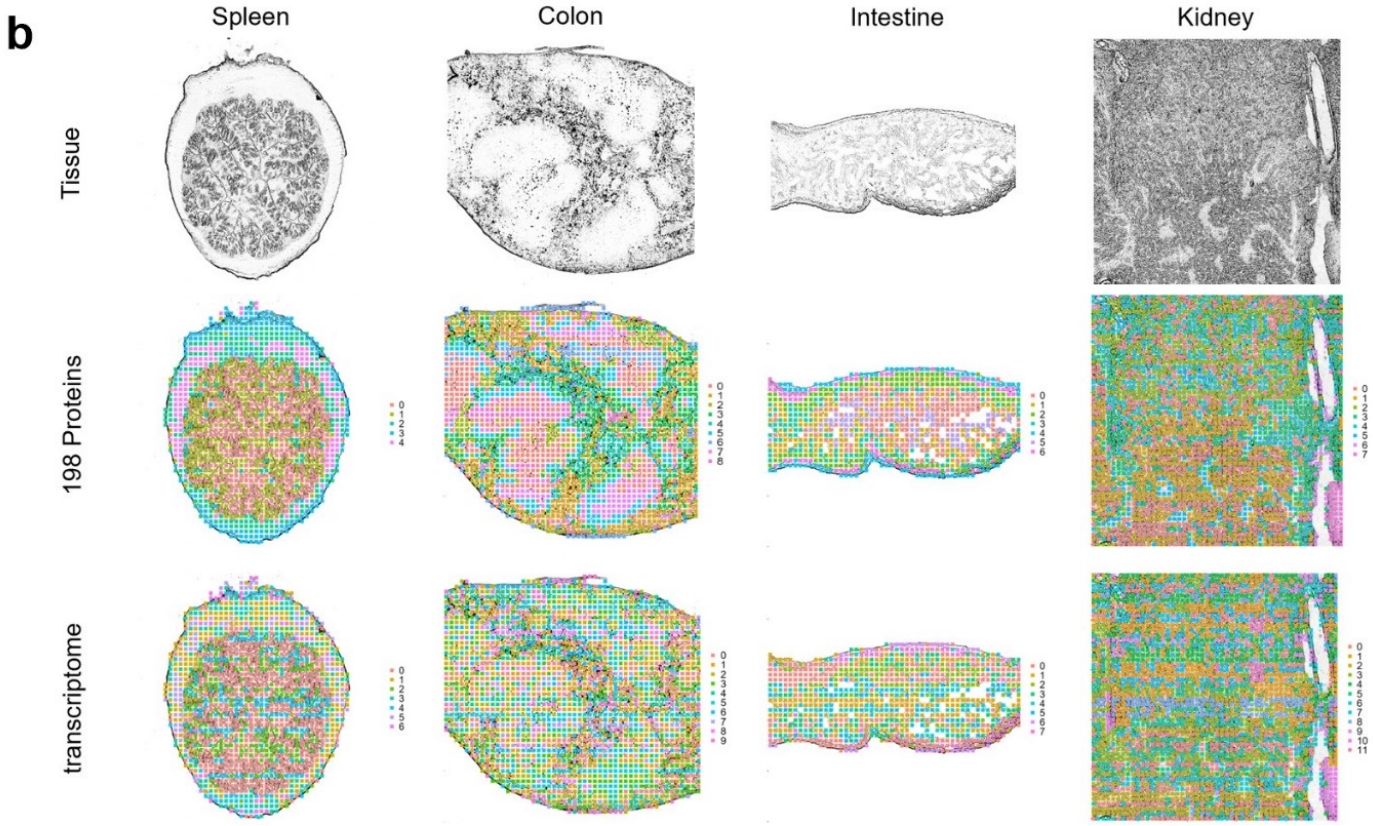






Dr. Yang Liu (Yale Pathology)





Liu Y. et al, *Nature Biotechnology* (2023)

Beyond Spatial Transcriptomics

and a Panel of Proteins

nature

Article

Spatial profiling of chromatin accessibility in mouse and human tissues

https://doi.org/10.1038/s41586-022-05094-1

Received: 5 August 2021

Accepted: 8 July 2022

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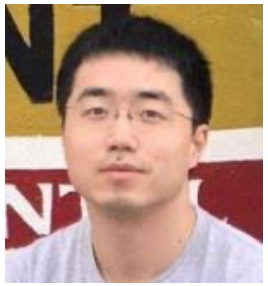
Open access

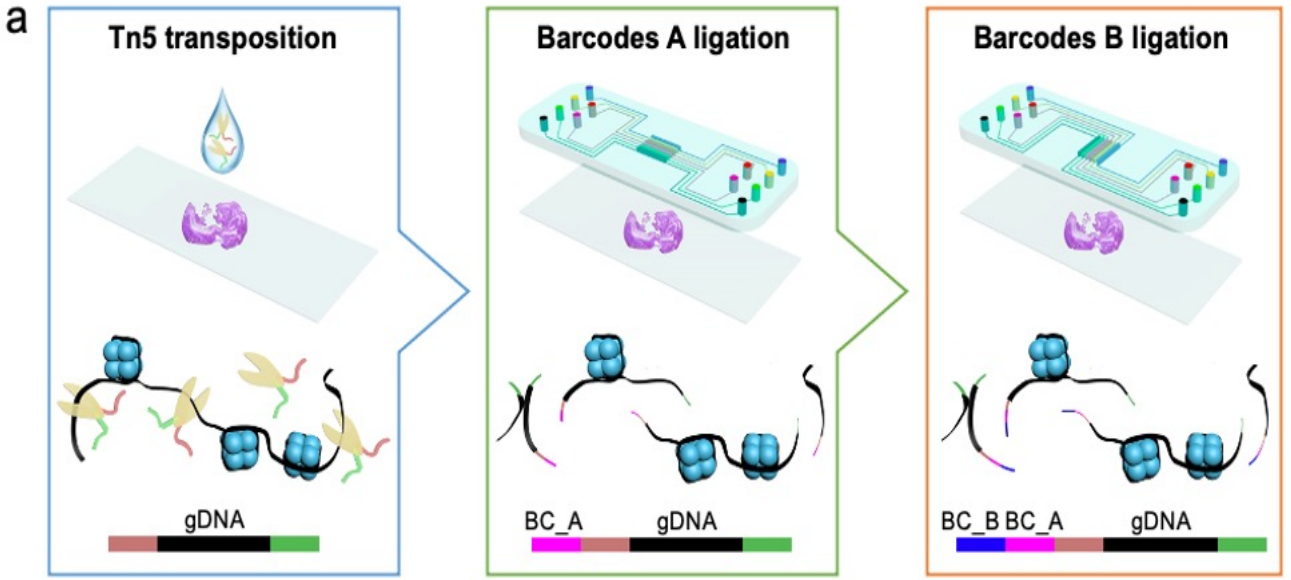
Check for updates

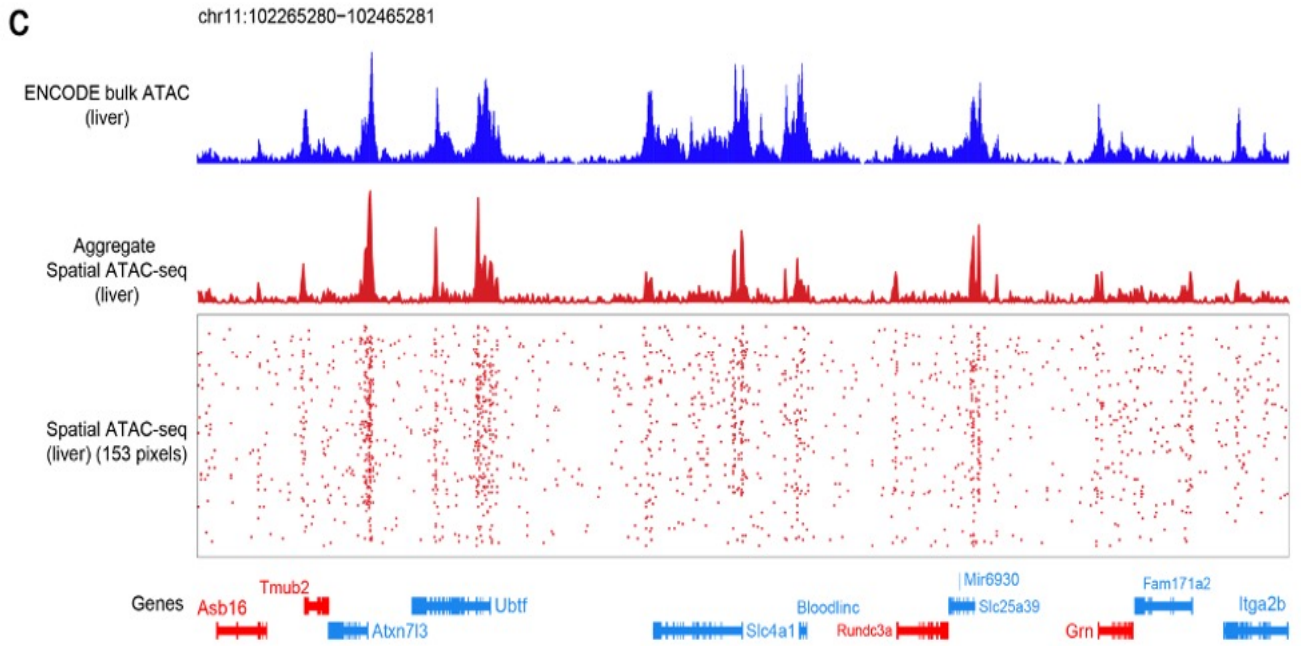
Yanxiang Deng[1,2], Marek Bartosovic[3], Sai Ma[4], Di Zhang[1], Petra Kukanja[3], Yang Xiao[5], Graham Su[1,2], Yang Liu[1,2], Xiaoyu Qin[1,2], Gorazd B. Rosoklija[6,7,8], Andrew J. Dwork[6,7,8,9], J. John Mann[6,7,10], Mina L. Xu[11], Stephanie Halene[2,12,13], Joseph E. Craft[14], Kam W. Leong[5,15], Maura Boldrini[6,7], Gonçalo Castelo-Branco[3,16] ✉ & Rong Fan[1,2,11,17] ✉

Cellular function in tissue is dependent on the local environment, requiring new methods for spatial mapping of biomolecules and cells in the tissue context[1]. The emergence of spatial transcriptomics has enabled genome-scale gene expression mapping[2–5], but the ability to capture spatial epigenetic information of tissue at the cellular level and genome scale is lacking. Here we describe a method for spatially resolved chromatin accessibility profiling of tissue sections using next-generation sequencing (spatial-ATAC-seq) by combining in situ Tn5 transposition chemistry[6] and microfluidic deterministic barcoding[5]. Profiling mouse embryos using spatial-ATAC-seq delineated tissue-region-specific epigenetic landscapes and identified gene regulators involved in the development of the central nervous system. Mapping the accessible genome in the mouse and human brain revealed the intricate arealization of brain regions. Applying spatial-ATAC-seq to tonsil tissue resolved the spatially distinct organization of immune cell types and states in lymphoid follicles and extrafollicular zones. This technology progresses spatial biology by enabling spatially resolved chromatin accessibility profiling to improve our understanding of cell identity, cell state and cell fate decision in relation to epigenetic underpinnings in development and disease.



Dr. Yanxiang Deng (Upenn)





Yanxiang Deng, et al, ***Nature*** 609, 375–383 (2022)

Science

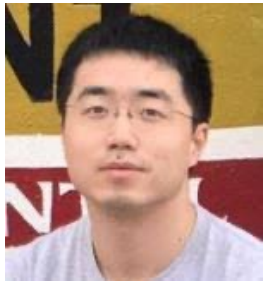
RESEARCH

SPATIAL EPIGENOMICS

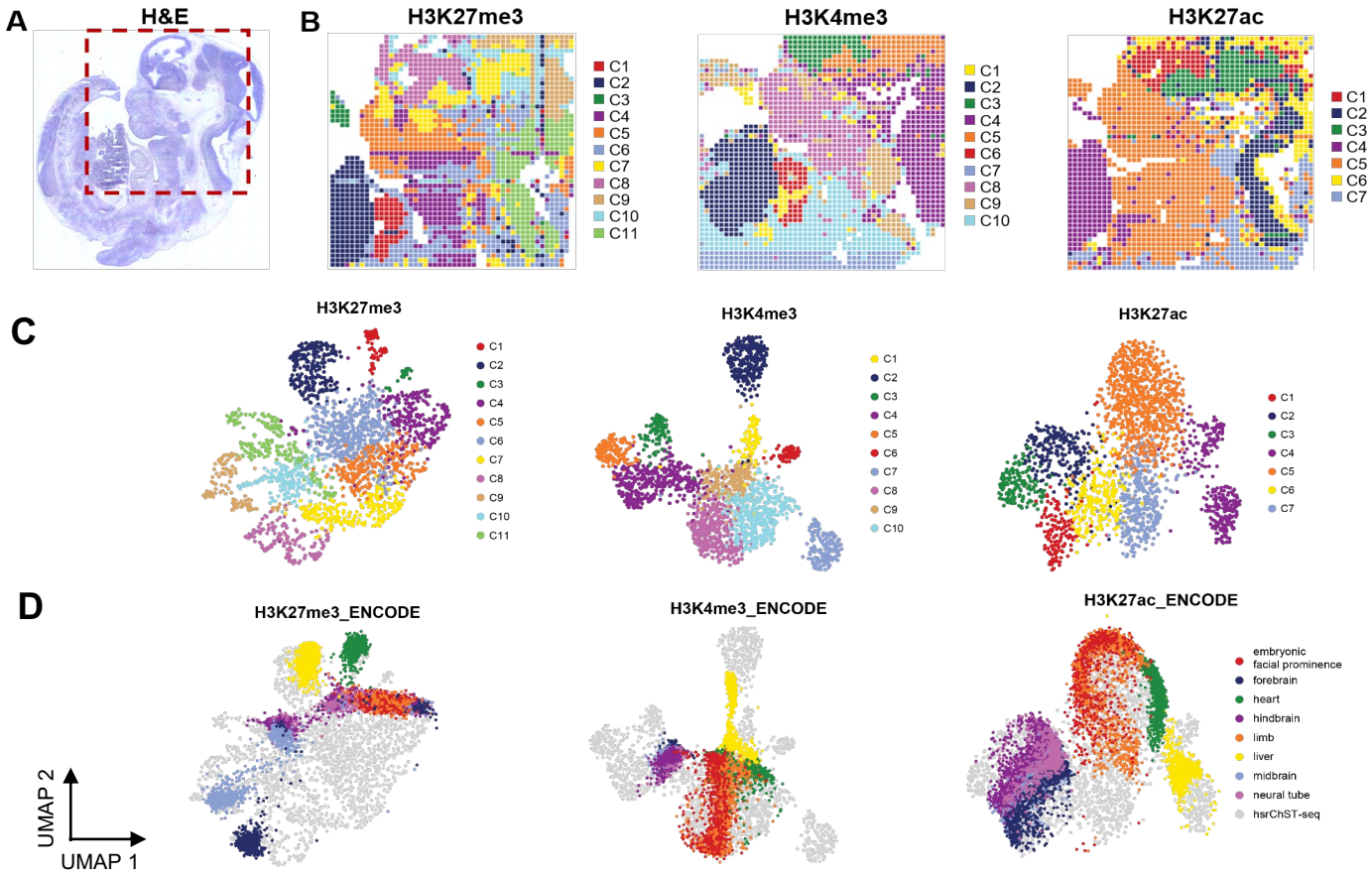
Spatial-CUT&Tag: Spatially resolved chromatin modification profiling at the cellular level

Yanxiang Deng[1,2], Marek Bartosovic[3], Petra Kukanja[3], Di Zhang[1], Yang Liu[1,2], Graham Su[1,2], Archibald Enninful[1,2], Zhiliang Bai[1], Gonçalo Castelo-Branco[3,4], Rong Fan[1,2,5]*

Spatial omics emerged as a new frontier of biological and biomedical research. Here, we present spatial-CUT&Tag for spatially resolved genome-wide profiling of histone modifications by combining in situ CUT&Tag chemistry, microfluidic deterministic barcoding, and next-generation sequencing. Spatially resolved chromatin states in mouse embryos revealed tissue-type-specific epigenetic regulations in concordance with ENCODE references and provide spatial information at tissue scale. Spatial-CUT&Tag revealed epigenetic control of the cortical layer development and spatial patterning of cell types determined by histone modification in mouse brain. Single-cell epigenomes can be derived in situ by identifying 20-micrometer pixels containing only one nucleus using immunofluorescence imaging. Spatial chromatin modification profiling in tissue may offer new opportunities to study epigenetic regulation, cell function, and fate decision in normal physiology and pathogenesis.



Dr. Yanxiang Deng (Upenn)



Deng *et al.*, *Science* **375**, 681–686 (2022) 11 February 2022

nature

Article

Spatial epigenome–transcriptome co-profiling of mammalian tissues

https://doi.org/10.1038/s41586-023-05795-1

Received: 6 June 2022

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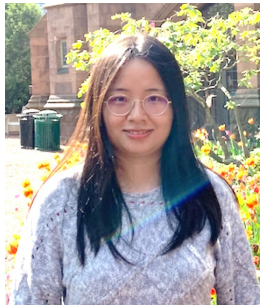
Open access

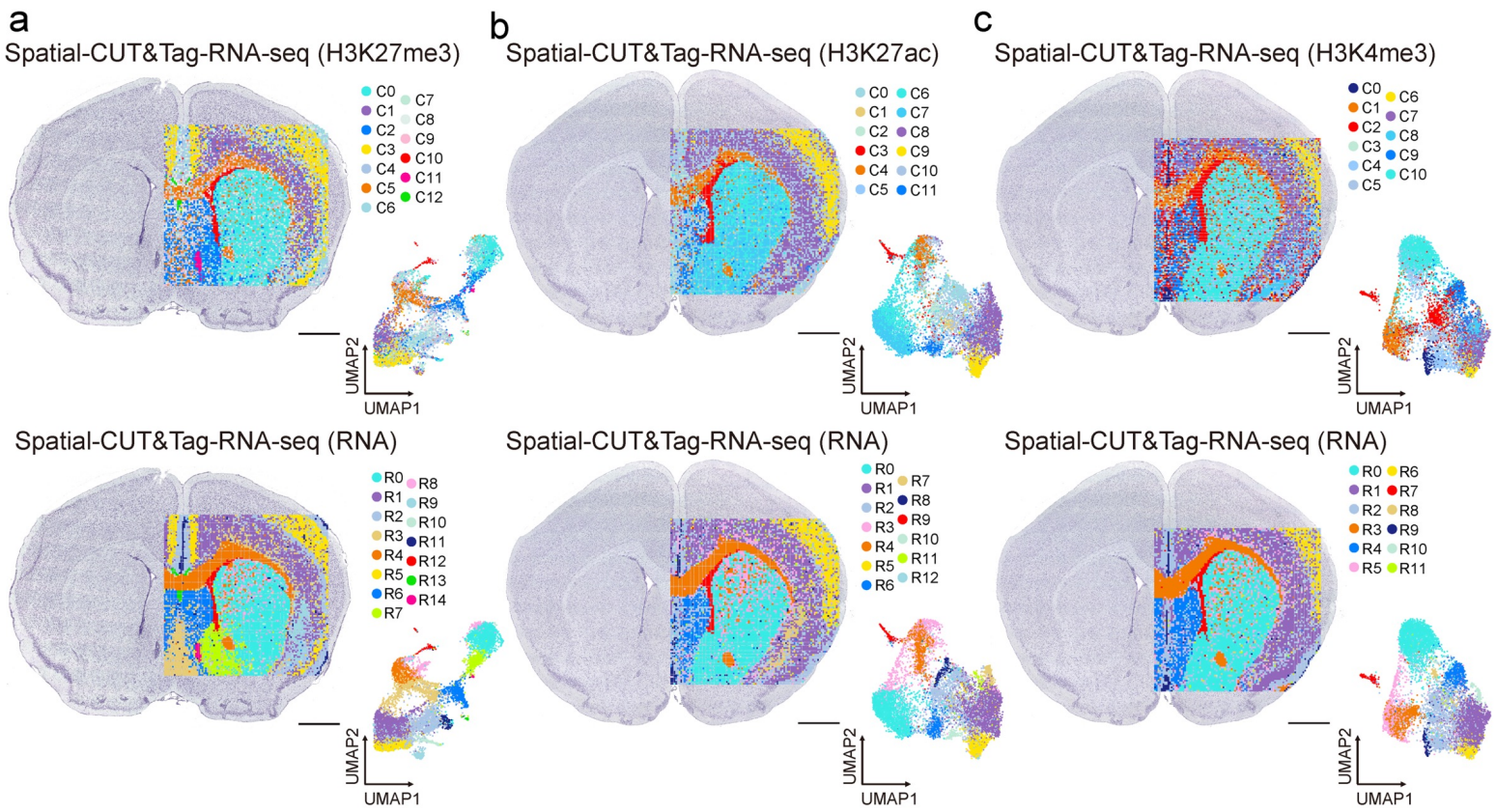
Check for updates

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[9,10,13], Kam W. Leong[8,14], 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]

Emerging spatial technologies, including spatial transcriptomics and spatial epigenomics, are becoming powerful tools for profiling of cellular states in the tissue context[1–5]. However, current methods capture only one layer of omics information at a time, precluding the possibility of examining the mechanistic relationship across the central dogma of molecular biology. Here, we present two technologies for spatially resolved, genome-wide, joint profiling of the epigenome and transcriptome by cosequencing chromatin accessibility and gene expression, or histone modifications (H3K27me3, H3K27ac or H3K4me3) and gene expression on the same tissue section at near-single-cell resolution. These were applied to embryonic and juvenile mouse brain, as well as adult human brain, to map how epigenetic mechanisms control transcriptional phenotype and cell dynamics in tissue. Although highly concordant tissue features were identified by either spatial epigenome or spatial transcriptome we also observed distinct patterns, suggesting their differential roles in defining cell states. Linking epigenome to transcriptome pixel by pixel allows the uncovering of new insights in spatial epigenetic priming, differentiation and gene regulation within the tissue architecture. These technologies are of great interest in life science and biomedical research.

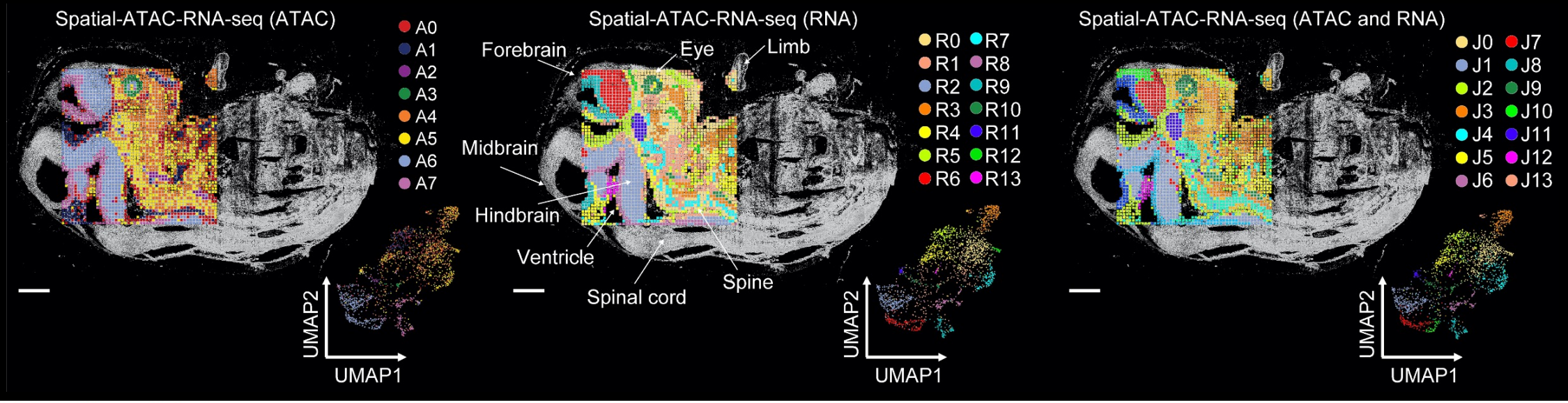


Dr. Di Zhang (Yale)

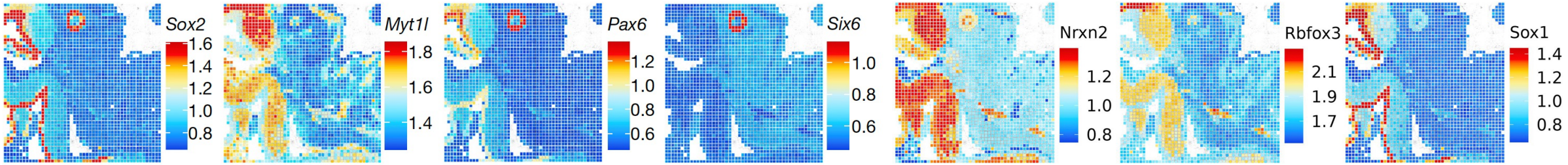


Di Zhang, et al, ***Nature*** (2023)

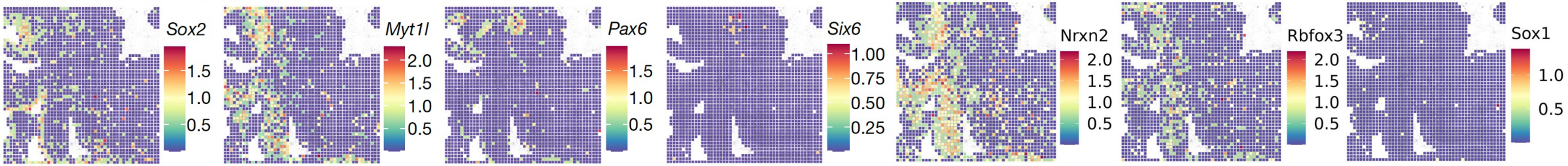
Spatial-ATAC-RNA-Co-Profiling of Embryonic Mouse Brain



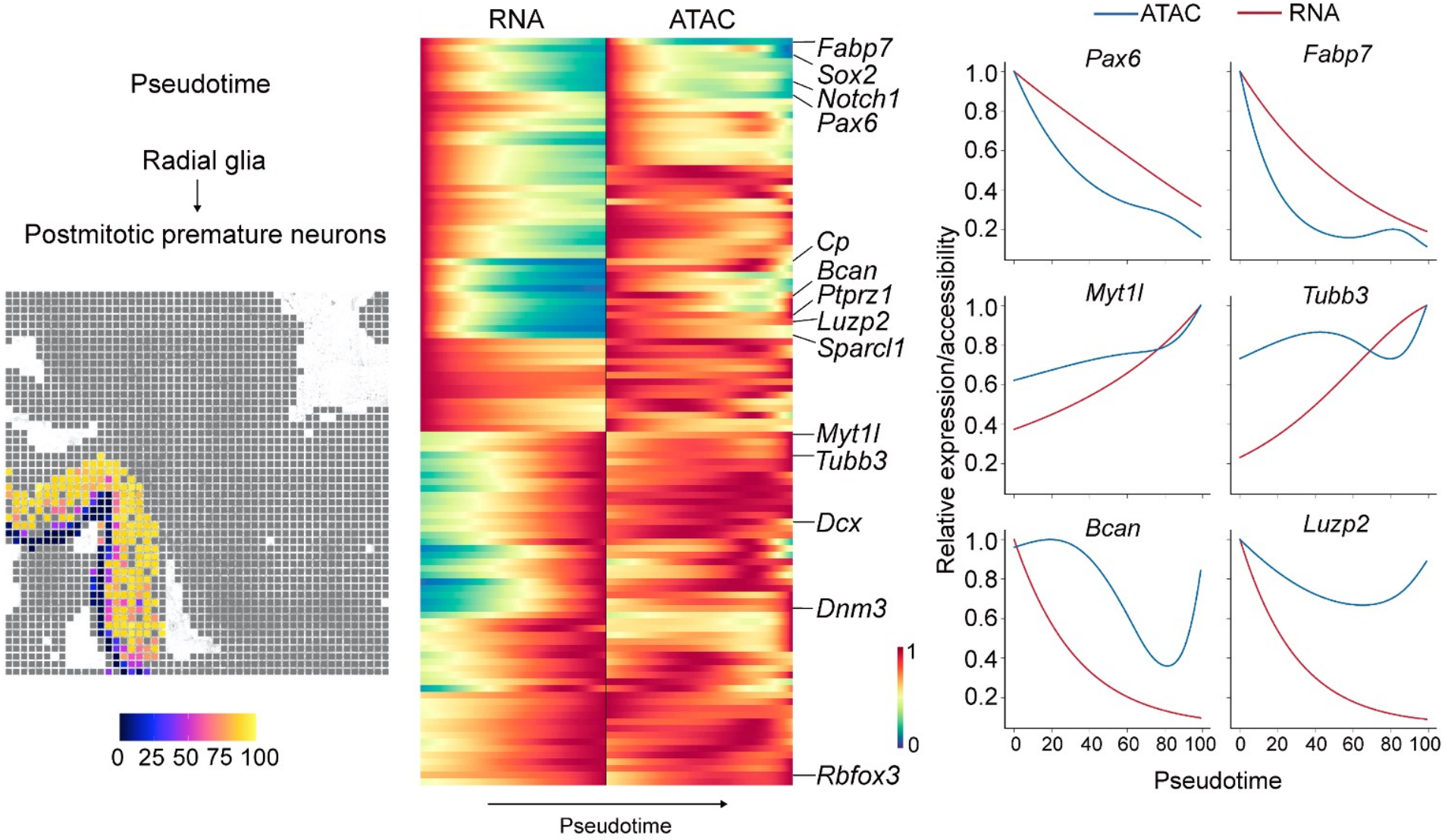
Spatial ATAC–RNA-seq (ATAC)



Spatial ATAC–RNA-seq (RNA)

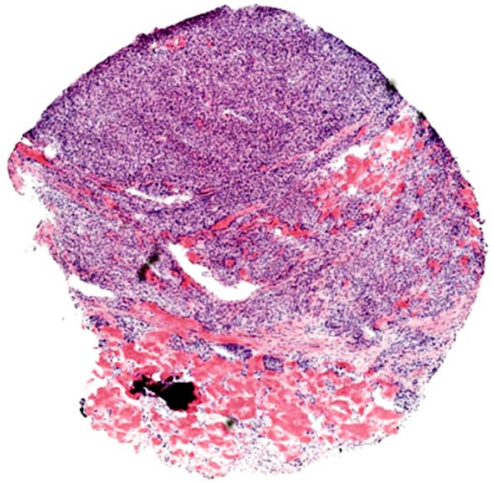


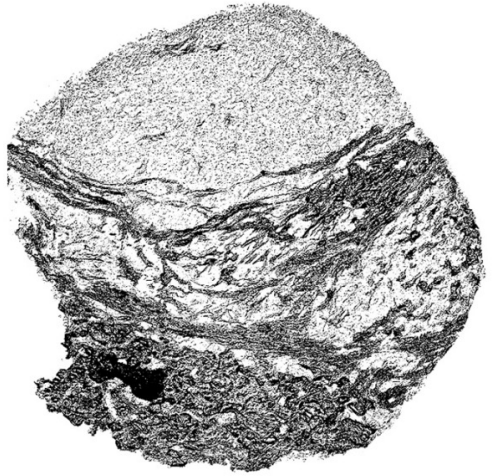
Spatially Resolved Pseudo Time Analysis of Both Epigenetic and Transcriptional State from Radial Glia to PPN



Hope you will join the hands-on computational data analysis session later today

	Session Four: Practical Methods in Spatial Omics		
13:15 - 15:00	**Chair:** Rong Fan, PhD Rong Fan and members of his group from Yale University (Shuozhen Bao, Alev Baysoy, Zhiliang Bai) lead a practical tutorial with Jupyter notebooks and GitHub software, to teach 'hands-on' experimental methods and computational tools for spatial omics and data analysis	Webinar via Zoom	Coming Soon





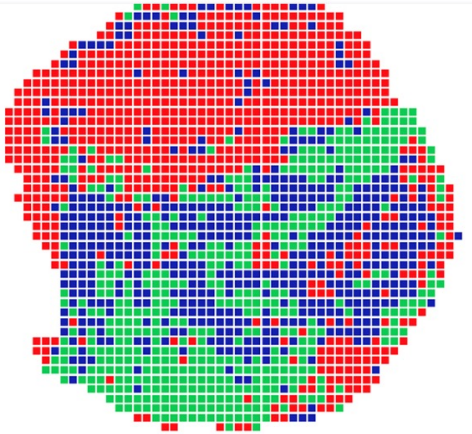
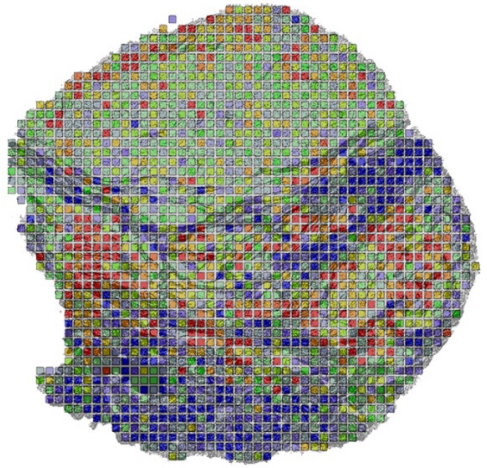


Image Courtesy Rong Fan



Spatially Exploring RNA Biology in FFPE Tissue

Dr. Zhiliang Bai

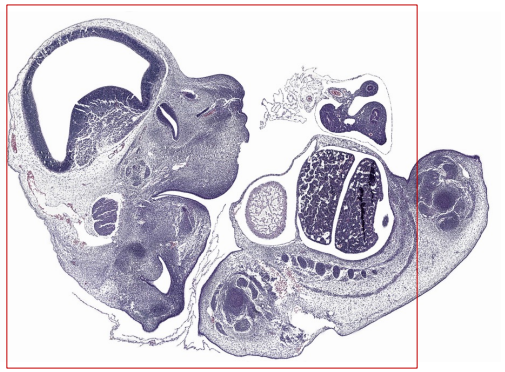
Prof. Mina Xu
(Yale Pathology)

Prof. Jun Lu
(Yale Genetics)

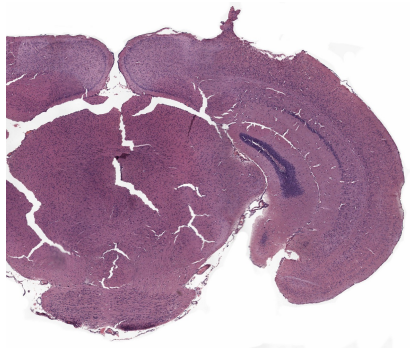
Prof. Yi Xing
(Upenn/CHOP)

Patho-DBiT-seq: clinical pathology FFPE tissue spatial RNA biology profiling

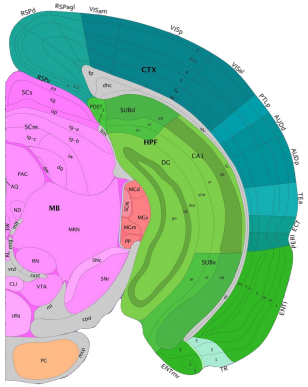
Highly sensitive spatial transcriptomic sequencing of formalin-fixed paraffin-embedded tissue



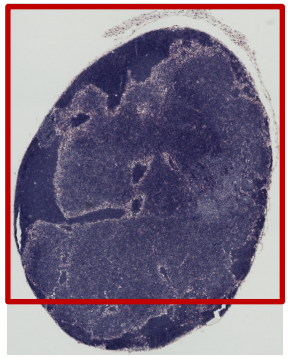
H&E Stain



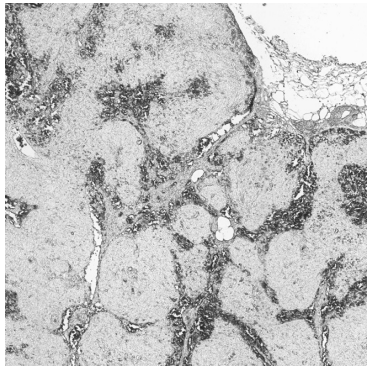
H&E Stain



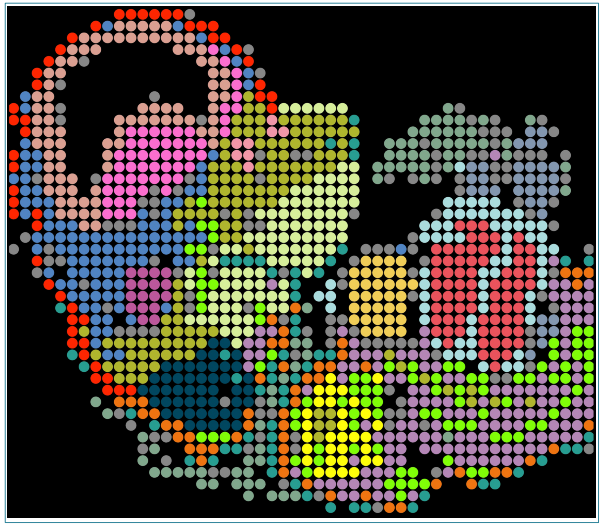
Allen Reference



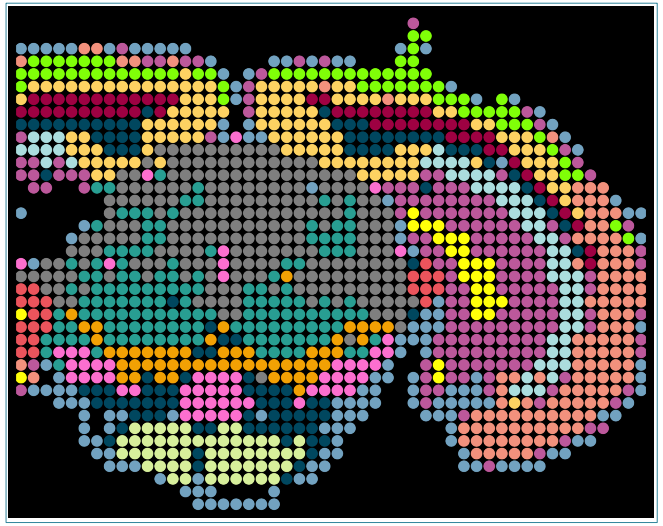
H&E Stain



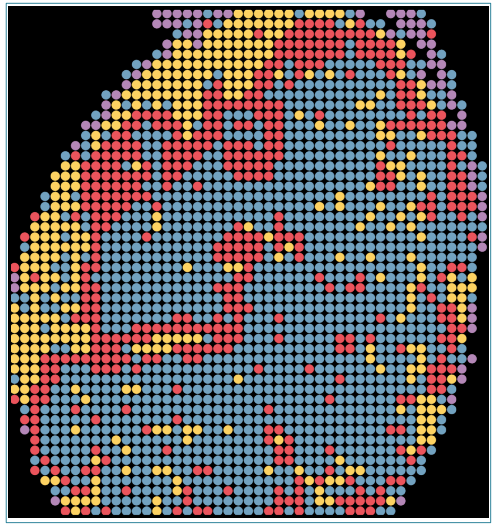
Tissue Scan



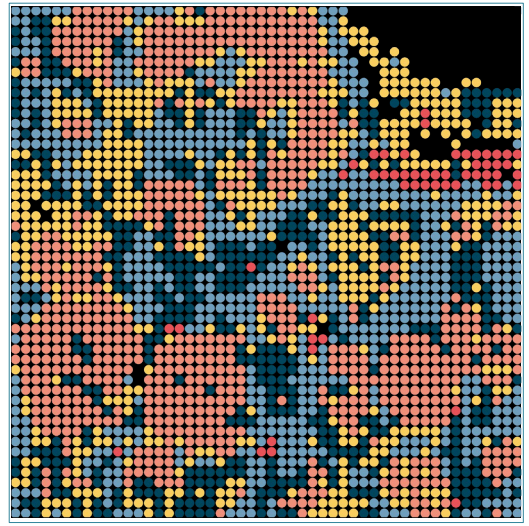
Mouse Embryo E13



Mouse Brain



Mouse Lymph Node

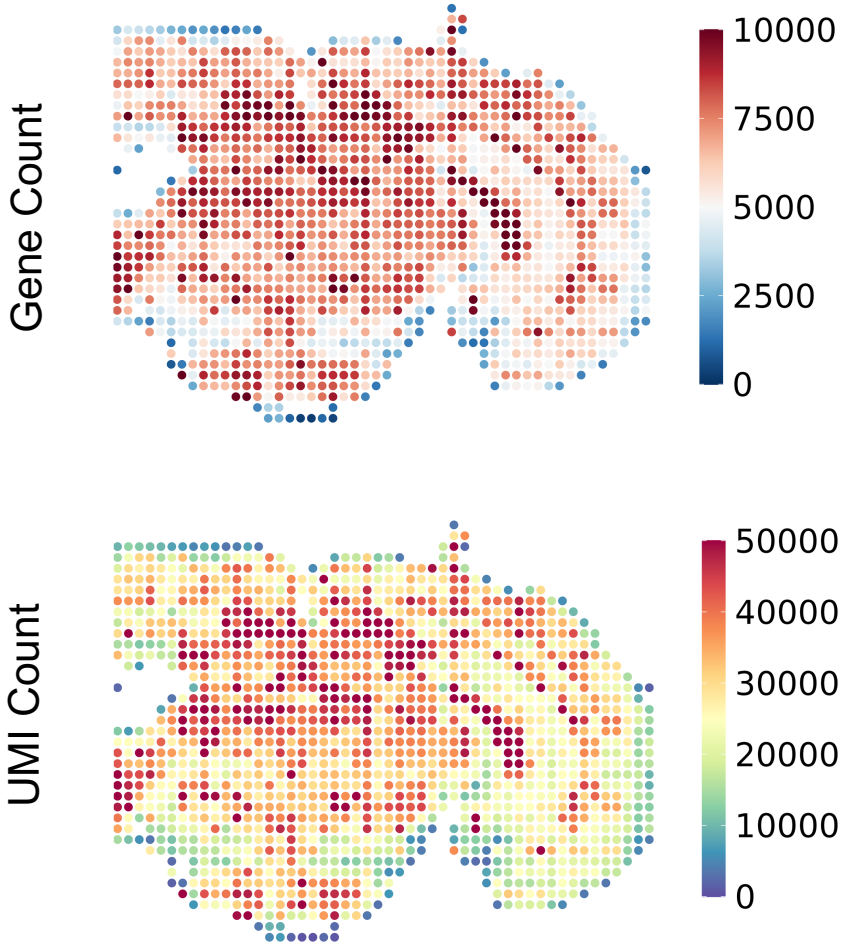


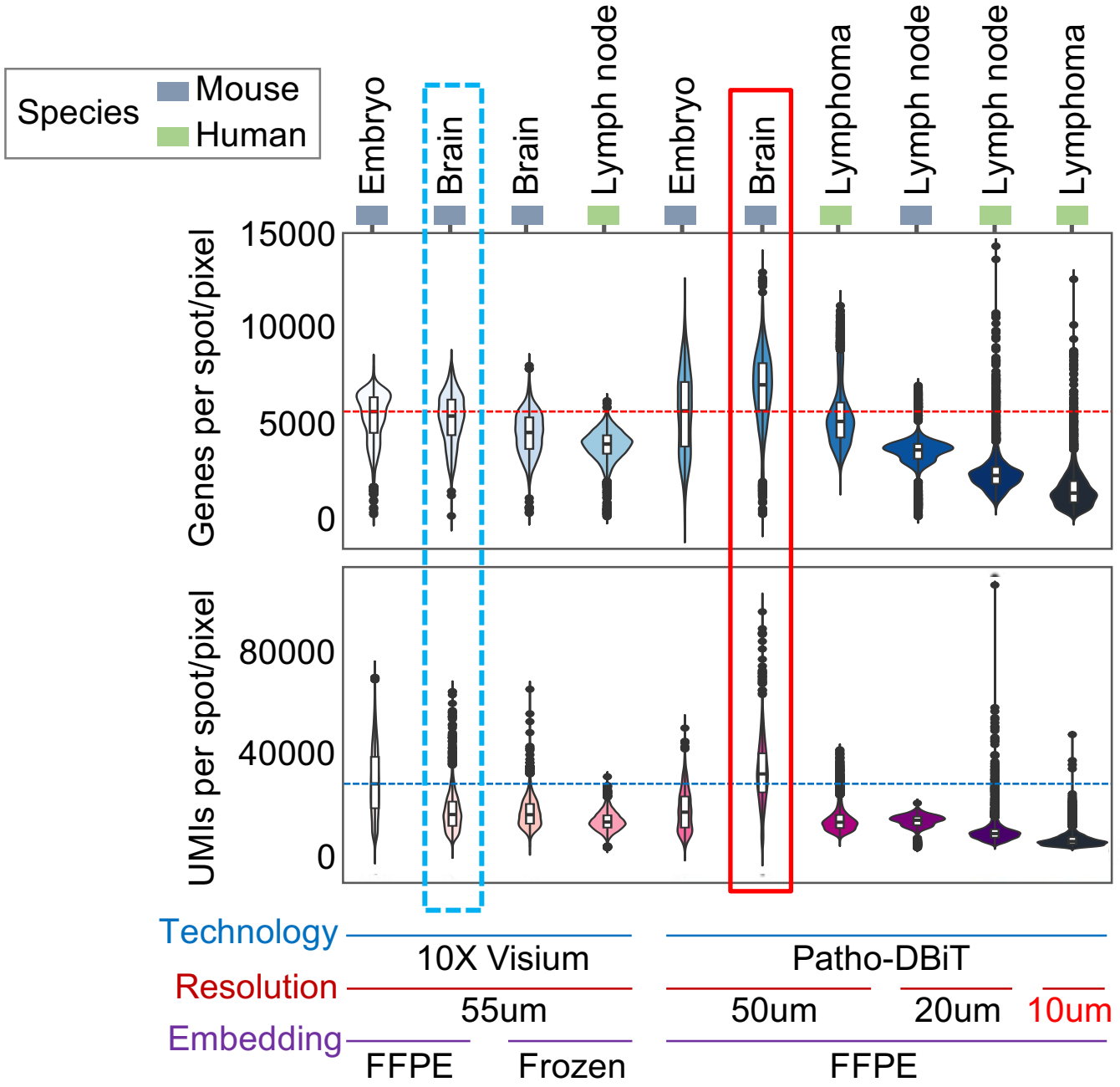
Human Lymph Node

https://www.biorxiv.org/content/10.1101/2024.02.06.579143v1

High-Quality Spatial RNA Biology Profiling Data from FFPE

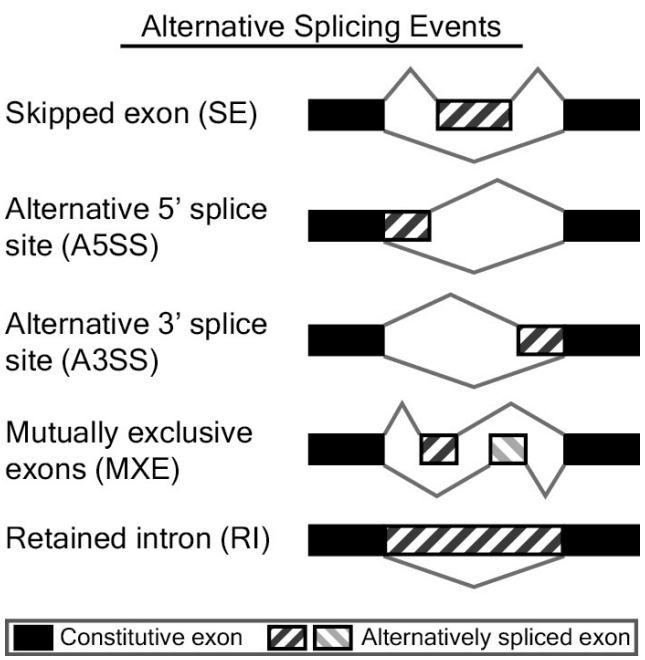
Mean: 6,751 Genes/Pixel, 30,896 UMIs/Pixel

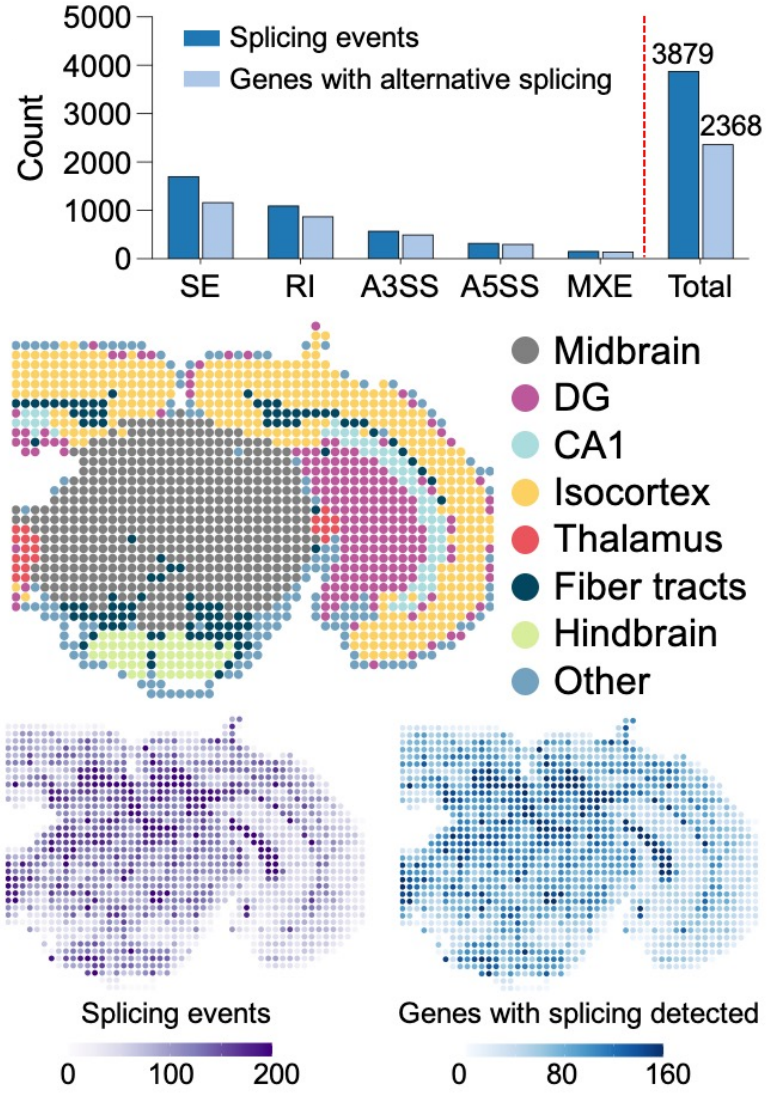




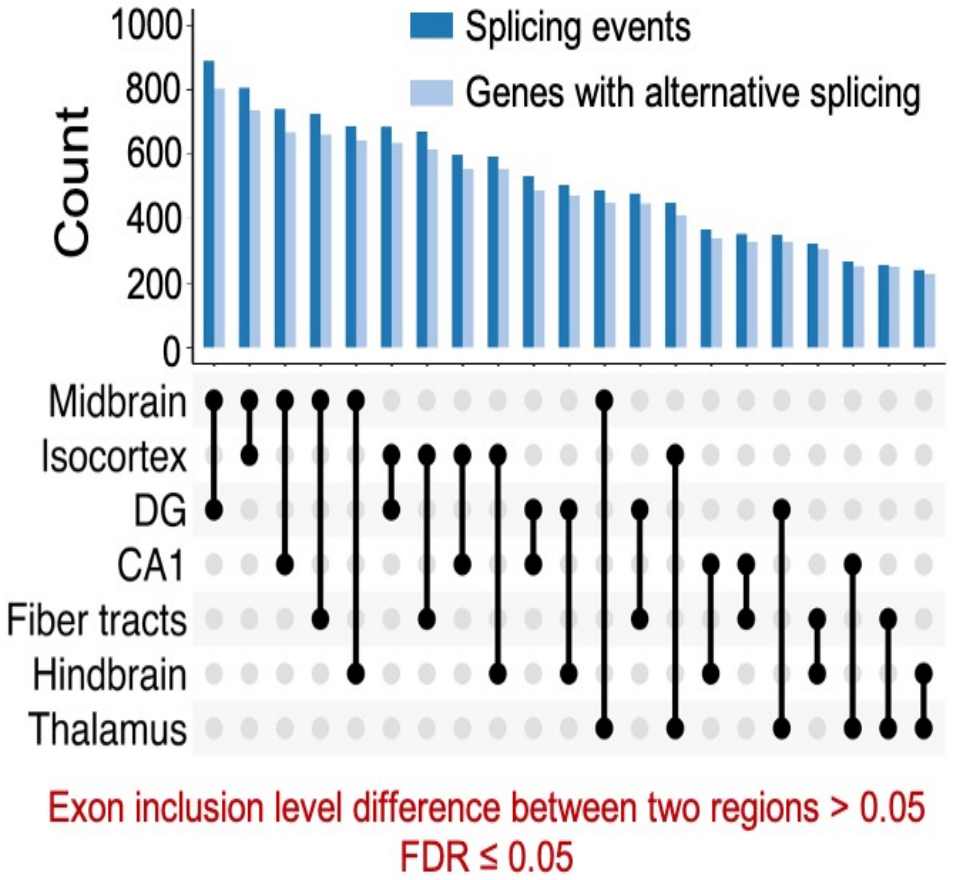
https://www.biorxiv.org/content/10.1101/2024.02.06.579143v1

Spatial Profiling of Alternative Splicing in FFPE Tissue



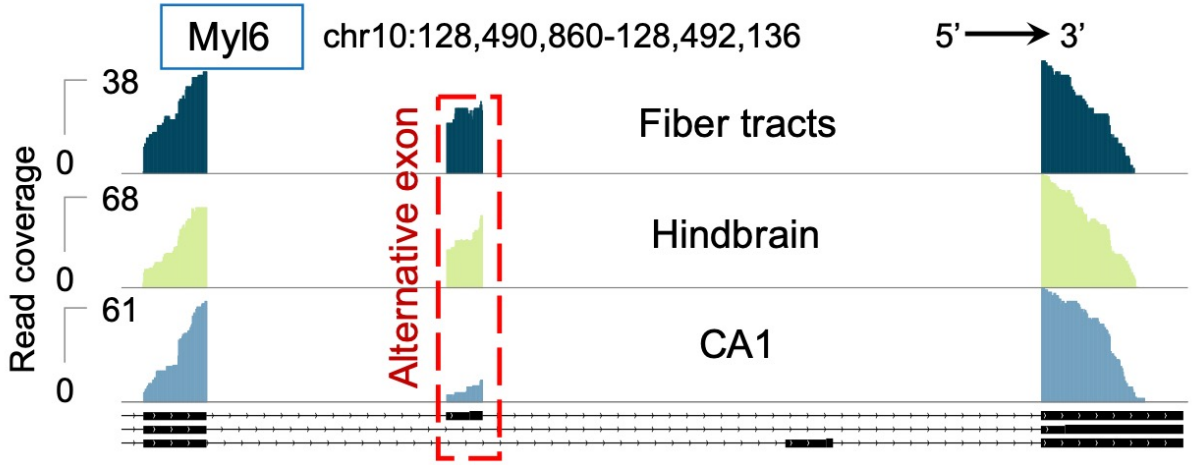


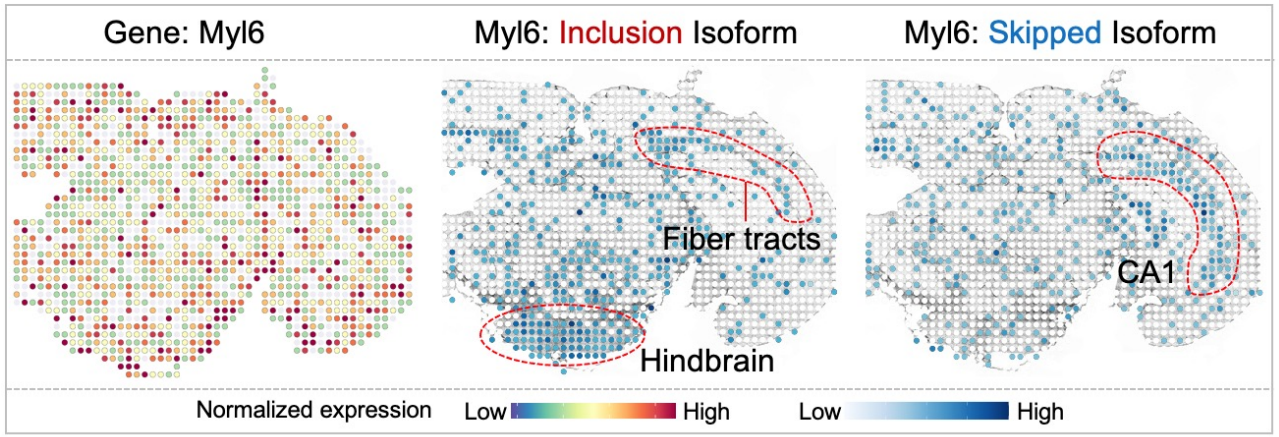
- Distinct alternative splicing in different brain regions

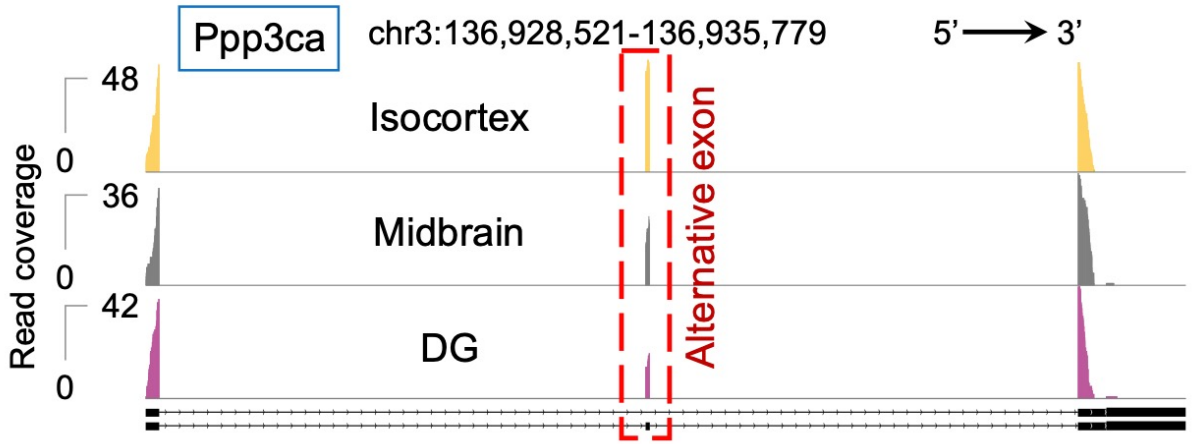


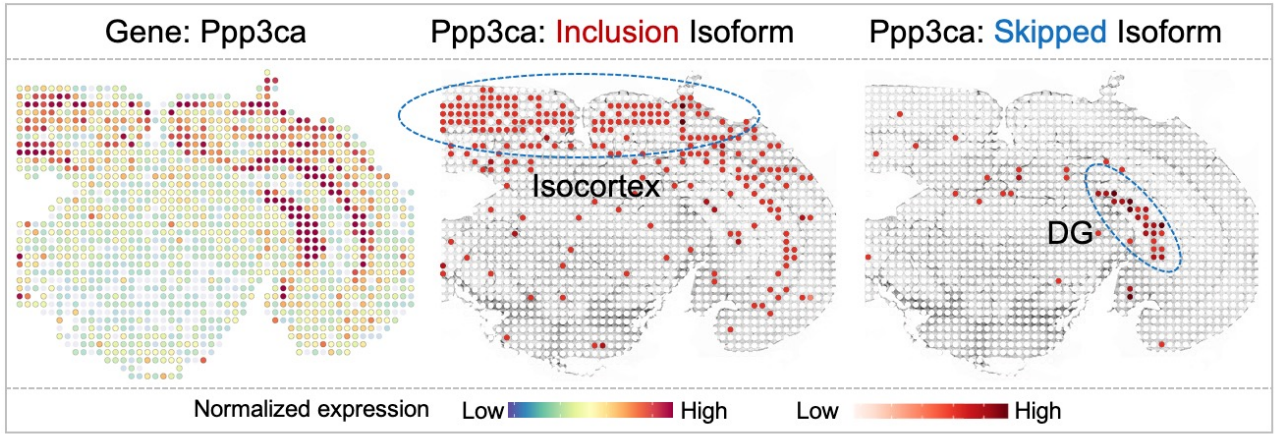
https://www.biorxiv.org/content/10.1101/2024.02.06.579143v1

Spatial Profiling of Alternative Splicing in FFPE Tissue





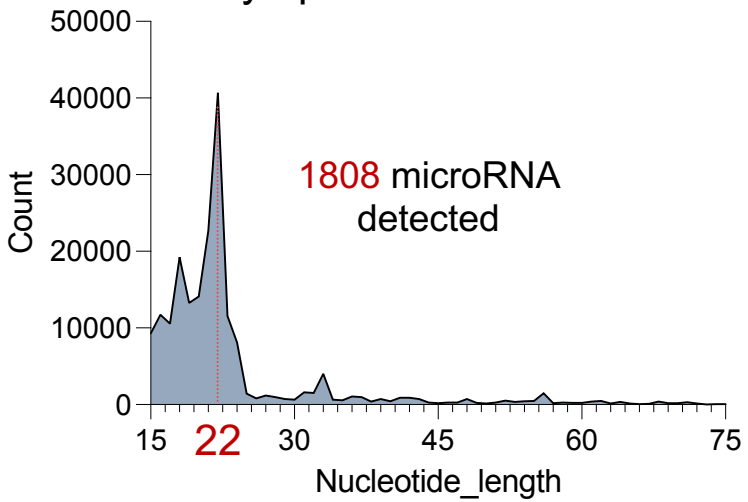


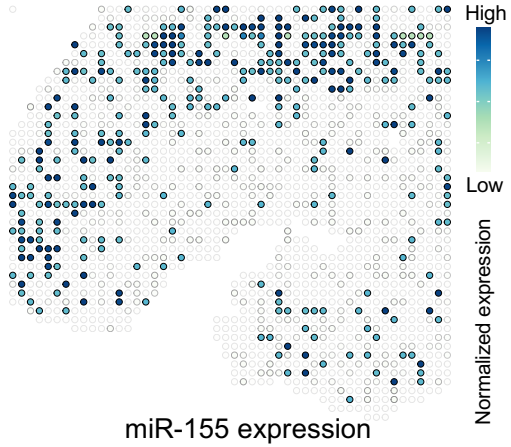


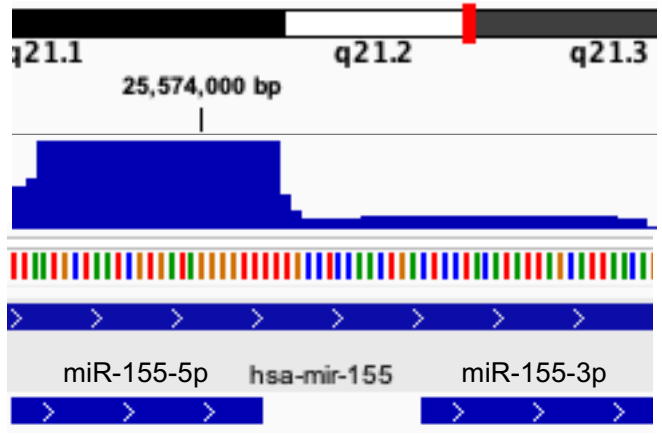
https://www.biorxiv.org/content/10.1101/2024.02.06.579143v1

Spatially Resolved Unbiased microRNA and mRNA Co-Profiling of Clinical FFPE Tissue Identified the Potential Regulation of NF-κB Signaling by miR-155 in Human Lymphoma

- Lymphoma B cells have a 10- to 30-fold higher miR-155 copy number than do normal B cells.







- We detected abundant miR-155 expression in the tumor B and plasma cells
- The reads were accurately mapped to the reference genome position

Plasma cell Score	B cell Score
IGKC, IGLC2, IGHA2, IGHG3	*CD19, MS4A1, CD74*

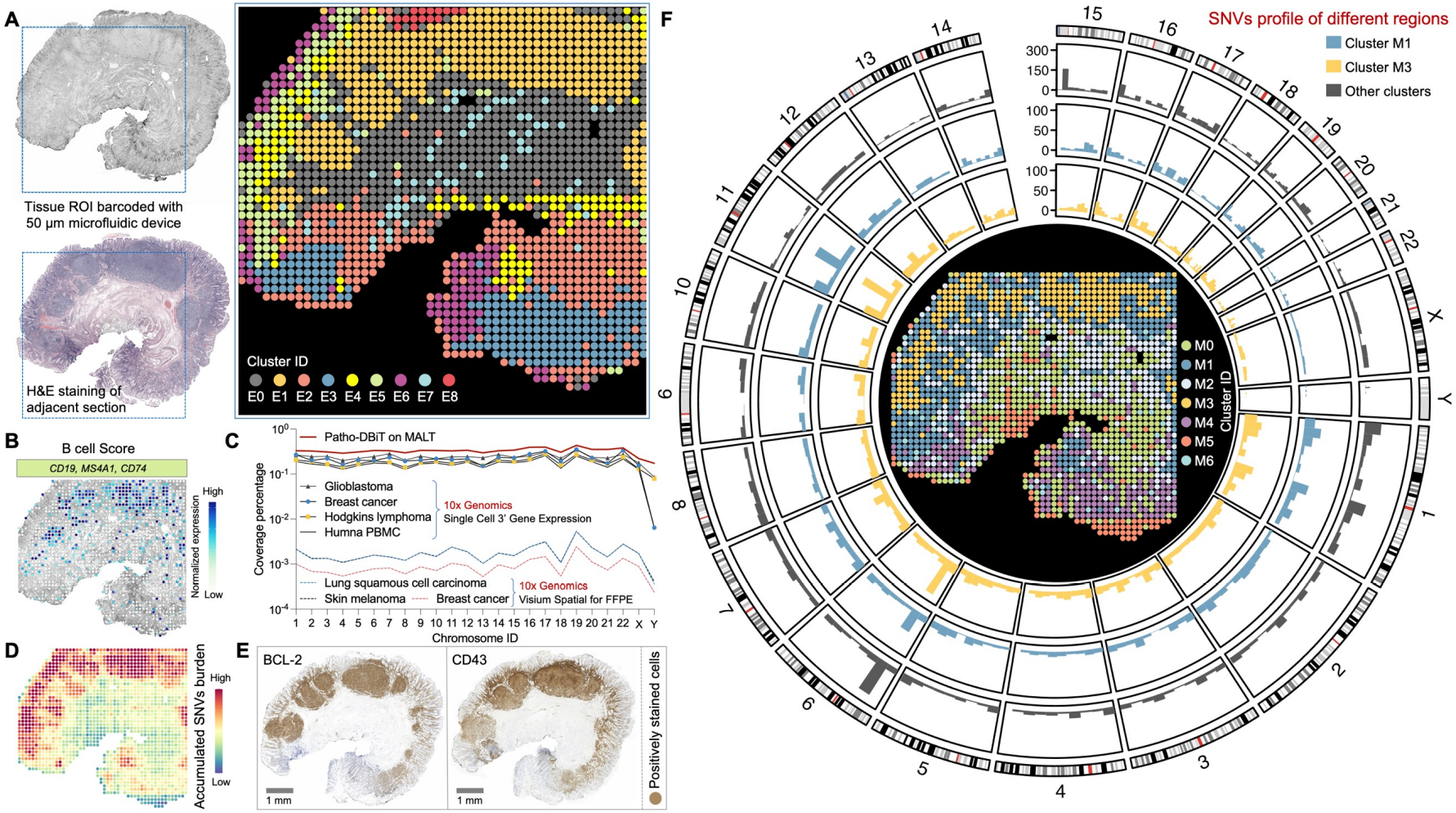
Spatial expression of gene module regulating NF-kB signaling

miR-155 is an NF-κB trans-activational target

https://www.biorxiv.org/content/10.1101/2024.02.06.579143v1

Spatial “TMB” Profiling

marginal zone lymphoma of mucosa associated lymphoid tissue



The patient is a 58-year-old man who had incidental finding of retroperitoneal lymphadenopathy on imaging originally performed for an orthopedic visit. Upper endoscopy revealed multiple areas of erosion in the stomach.

These results suggest that our FFPE tissue spatial DBIT-seq has the capacity to differentiate tumor from non-tumor regions based on the genetic variation level such as SNV and potentially further distinguish tumor subclones.

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