Spatial Transcriptomics: background and promise

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About me

- Lecturer in Translational Medicine, Centre for 3D Models of Health and Disease, UCL
- Previously Trinity College Dublin, Cold Spring Harbour Laboratory (USA)
- Interested in using human tissue to test new treatments for cancer
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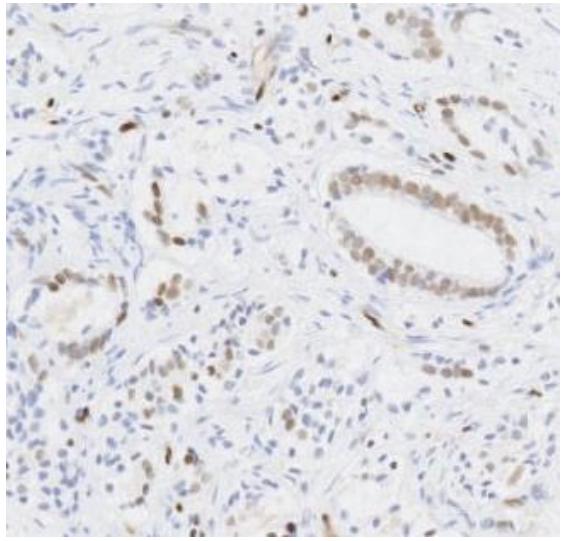
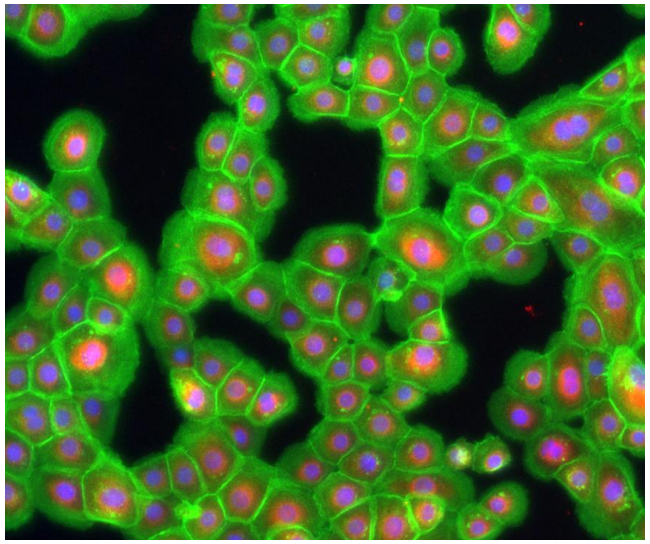
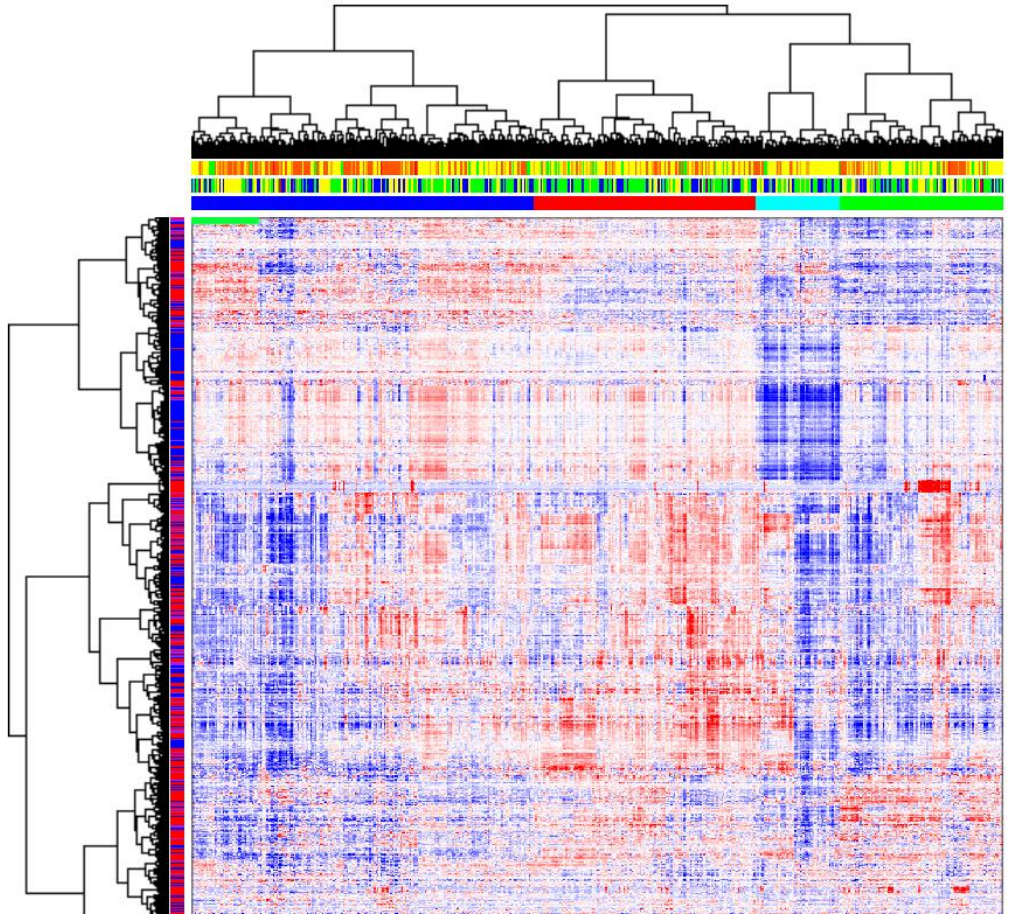
Spatial Transcriptomics

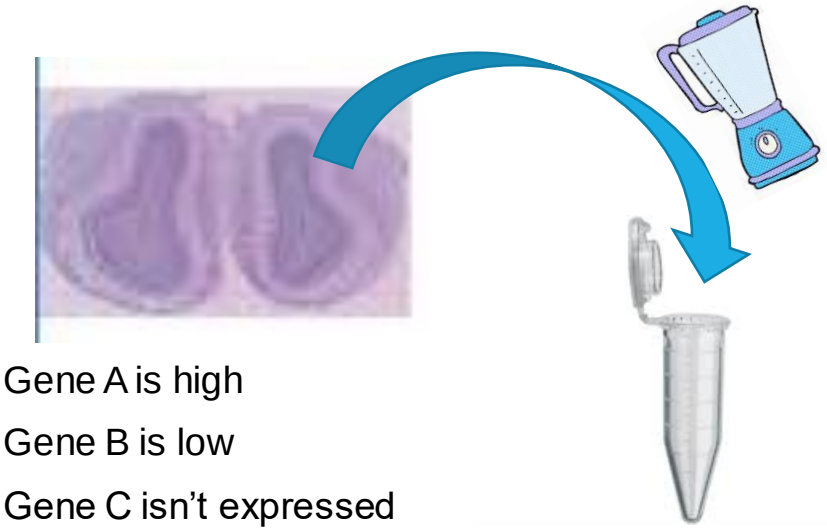






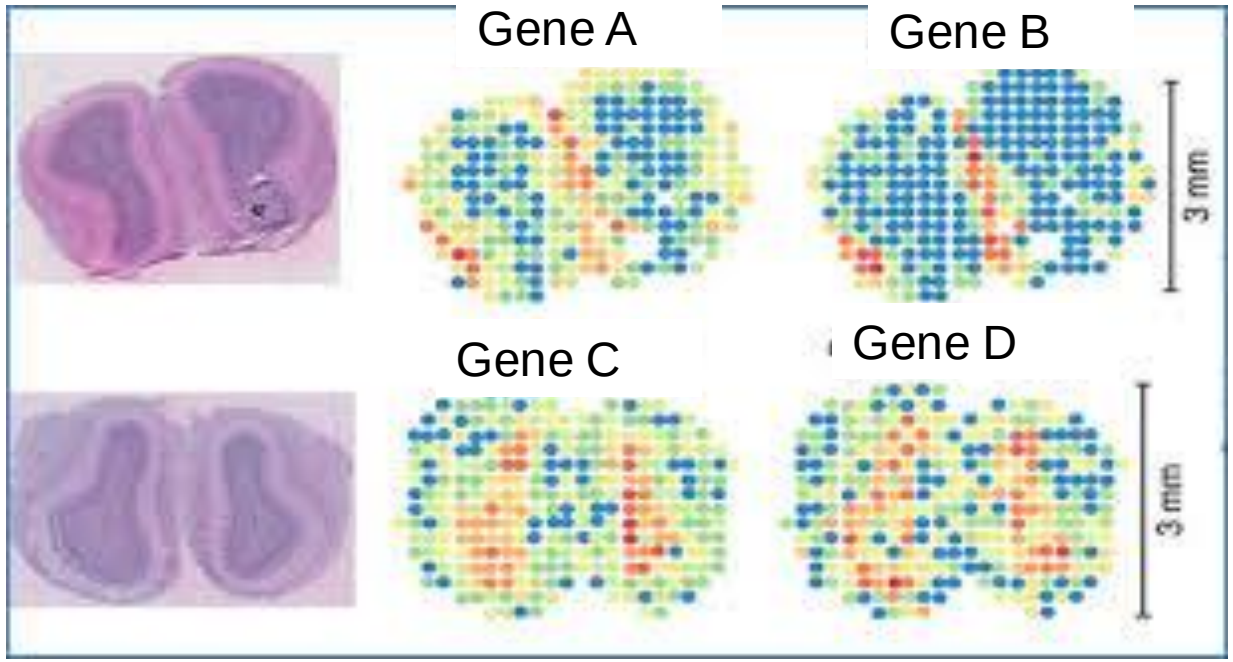
TCGA Firehose data, prostate adenocarcinoma

Next Generation Sequencing vs Spatial Transcriptomics



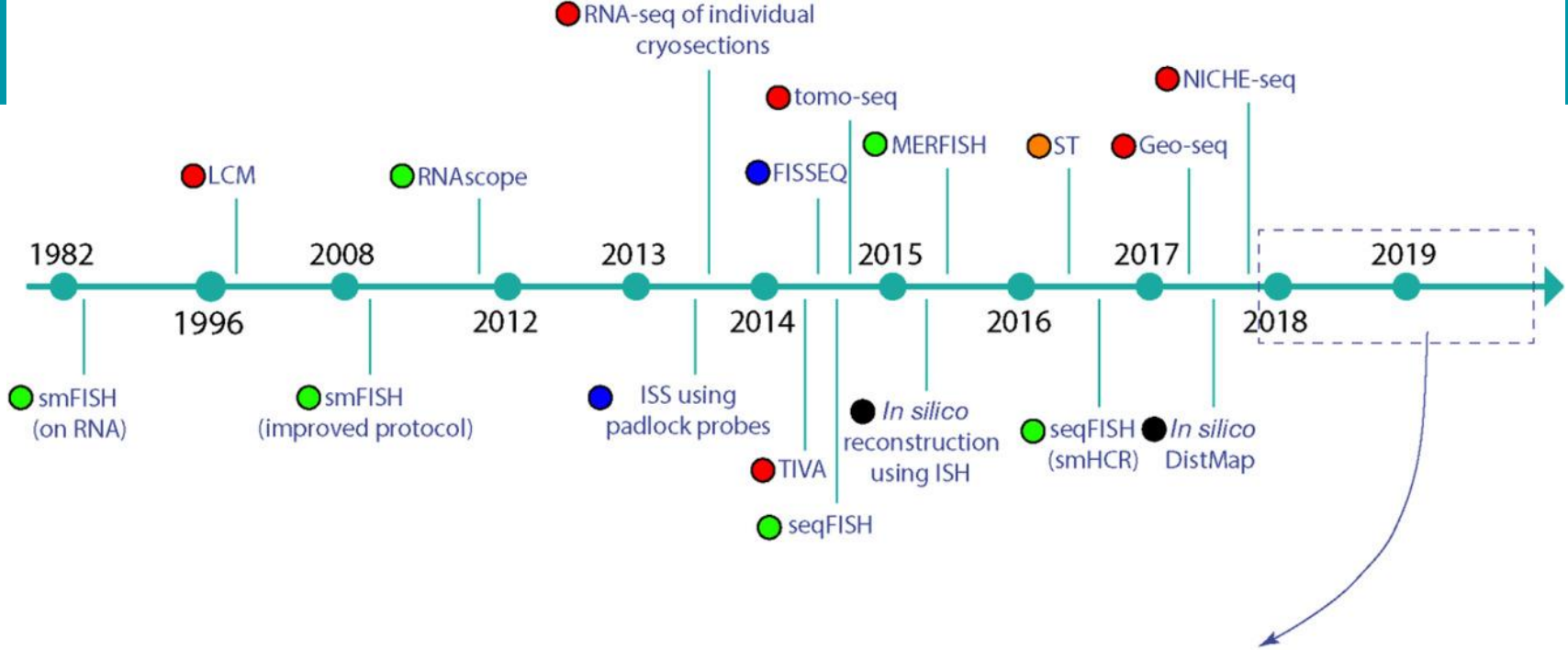
- Gene A is high
- Gene B is low
- Gene C isn't expressed
- Gene D is high

- (one data point per gene per sample)



https://rna-seqblog.com/identification-of-spatial-expression-trends-in-single-cell-gene-expression-data/

(many data points mapped to location per gene per sample)



Section 1. Technologies based on microdissected gene expression

Section 2. *In situ* hybridization technologies

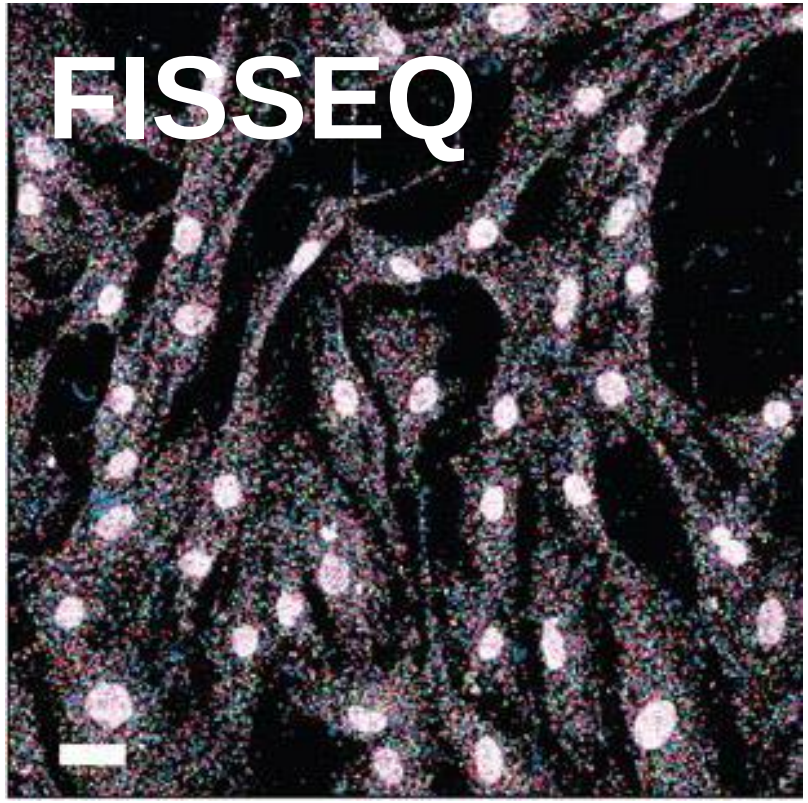
Section 3. *In situ* sequencing technologies

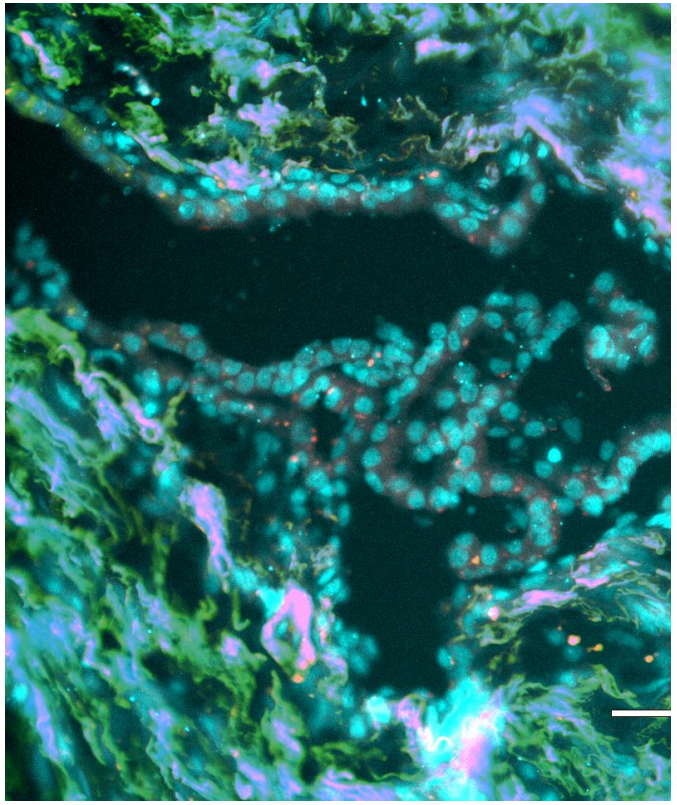
Section 4. *In situ* capturing technologies

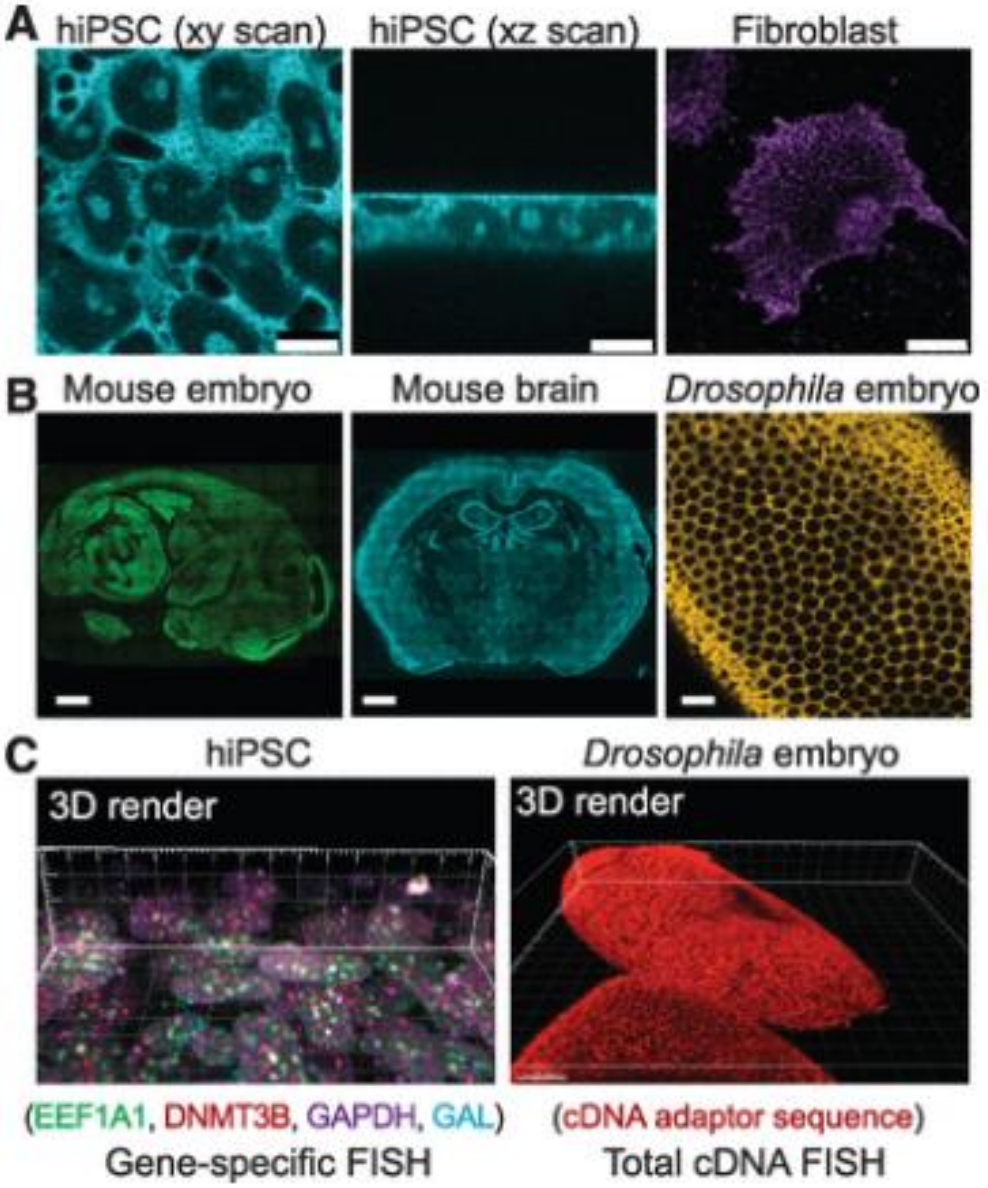
Section 5. *In silico* reconstruction of spatial data

https://onlinelibrary.wiley.com/doi/epdf/10.1002/bies.201900221

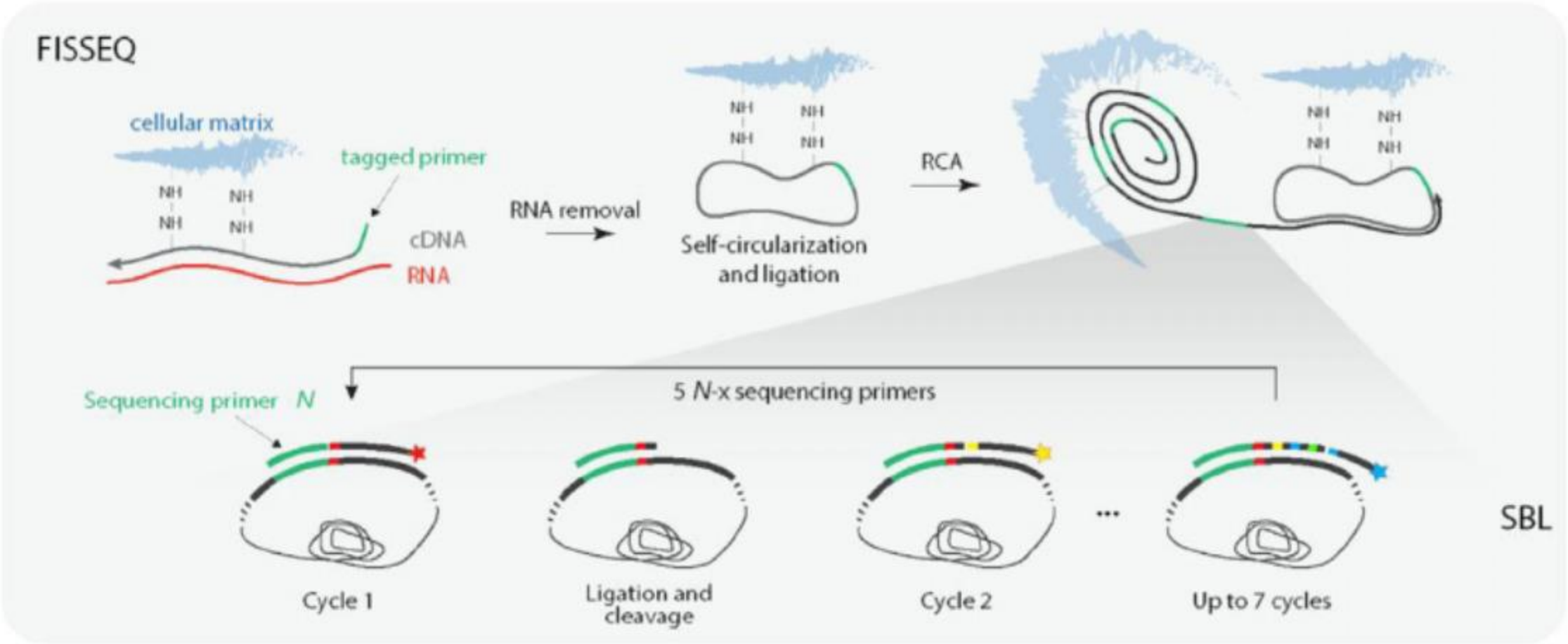
Cold Spring Harbour Laboratory







- FISSEQ = fluorescent in situ RNA sequencing
- Published in Science & Nature Methods
- Not commercialised – developed by Je Lee & George Church



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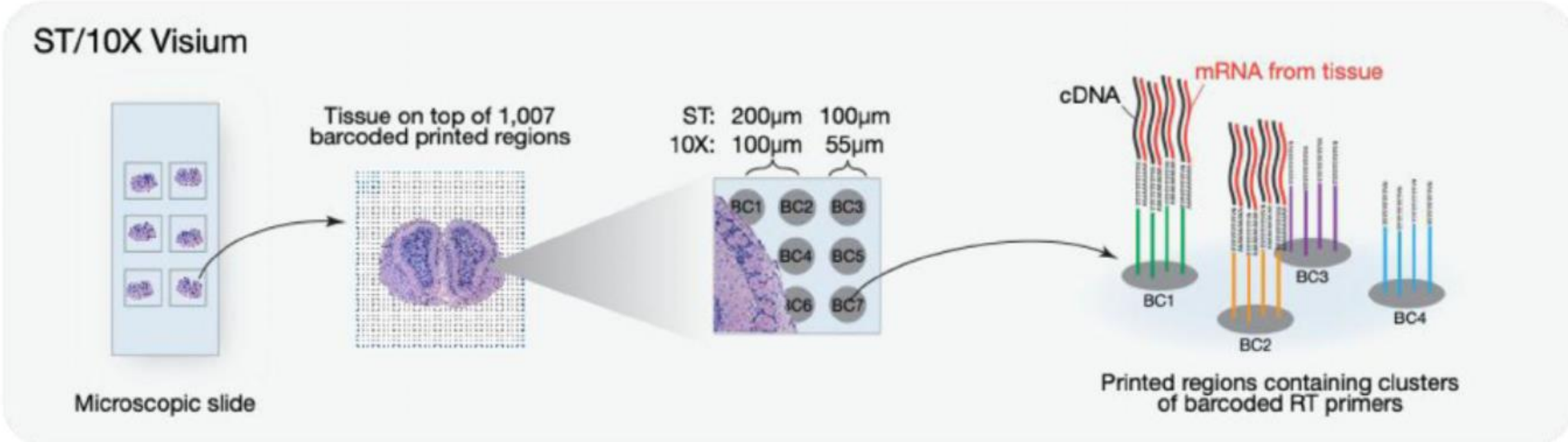
10X Visium



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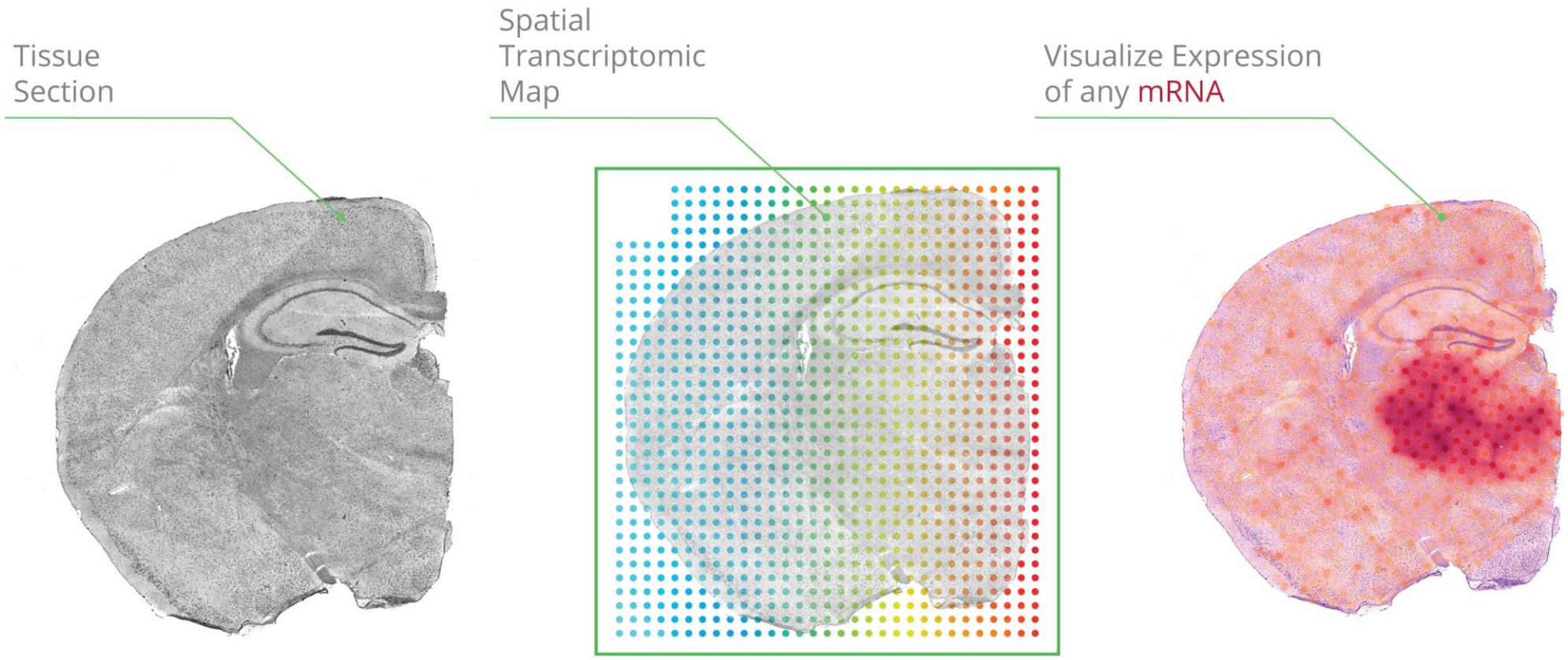
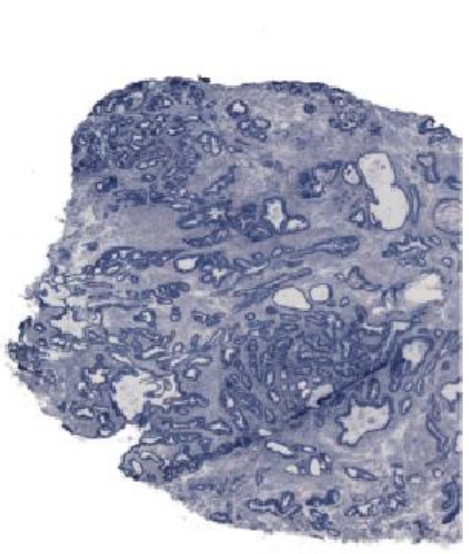
10X Visium

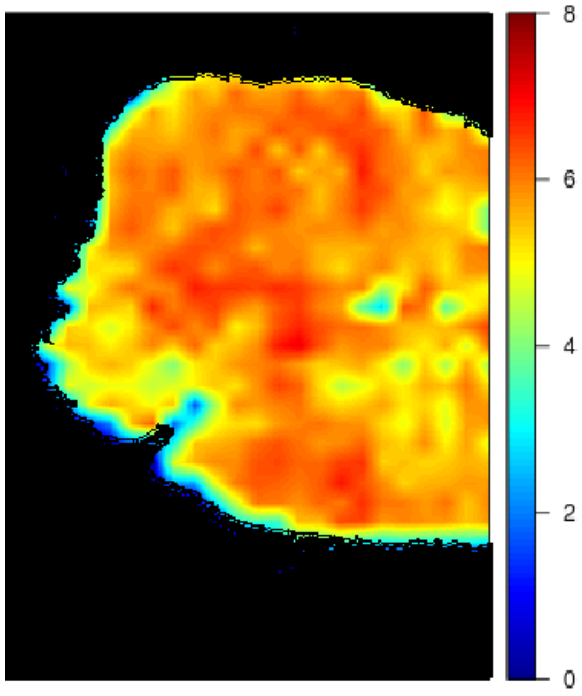

Tissue
Section
Spatial
Transcriptomic
Map
Visualize Expression
of any mRNA

10X Visium

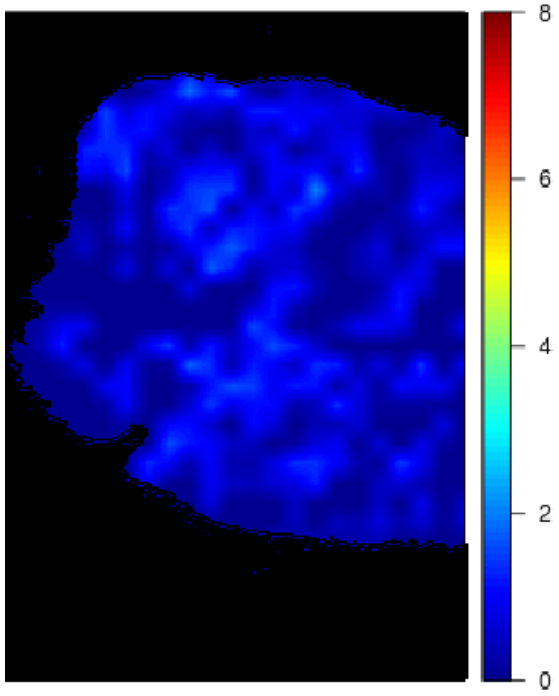
https://spatialtranscriptomics3d.shinyapps.io/STProstateResearch/



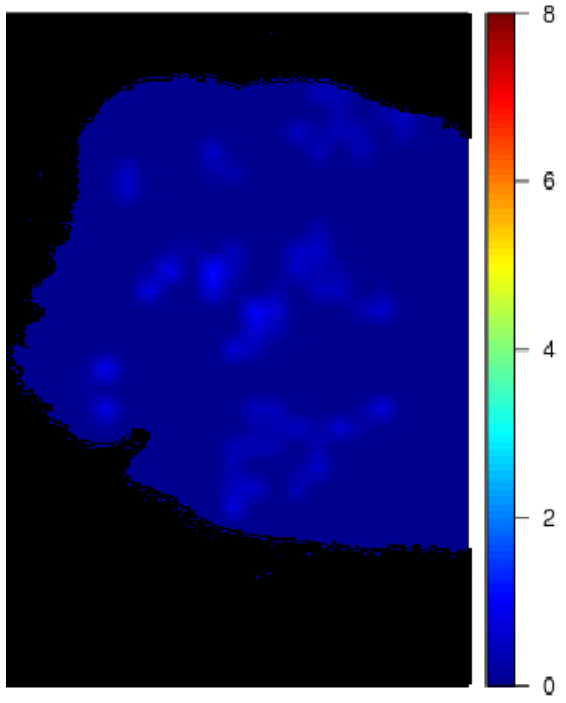
H&E



ACTB



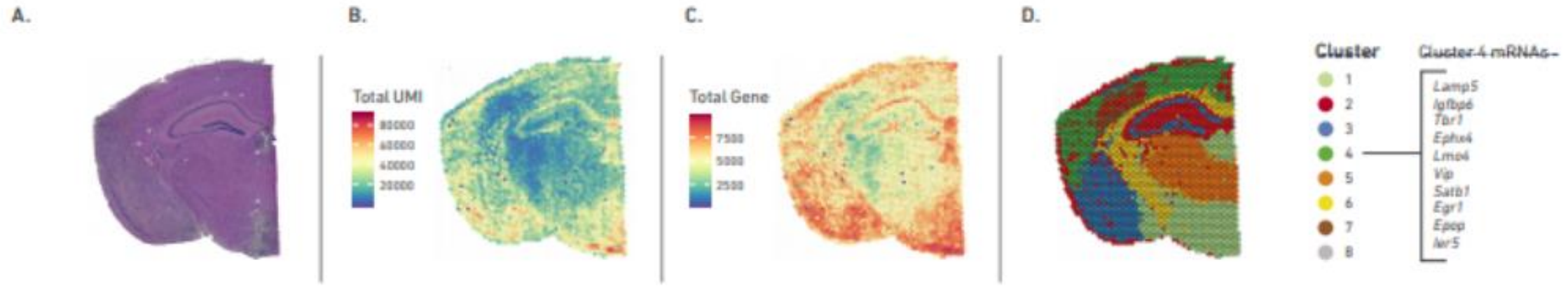
PTEN



MYC

10X Visium – latest version, more dots, analysis pipeline:

Visium with H&E: Use H&E staining for morphological context:



So you've decided you want to use Spatial Transcriptomics.

What next?

- Usual considerations: cost, equipment needed, time etc.
- Sample type (live cells / fixed cells / frozen sections / FFPE)
- Sample type (auto fluorescence?)
- Targeted or transcriptome-wide?
- Spatial resolution: anatomical features? Subcellular?
- Has it been demonstrated outside of originator's lab?

Considerations when choosing a method:

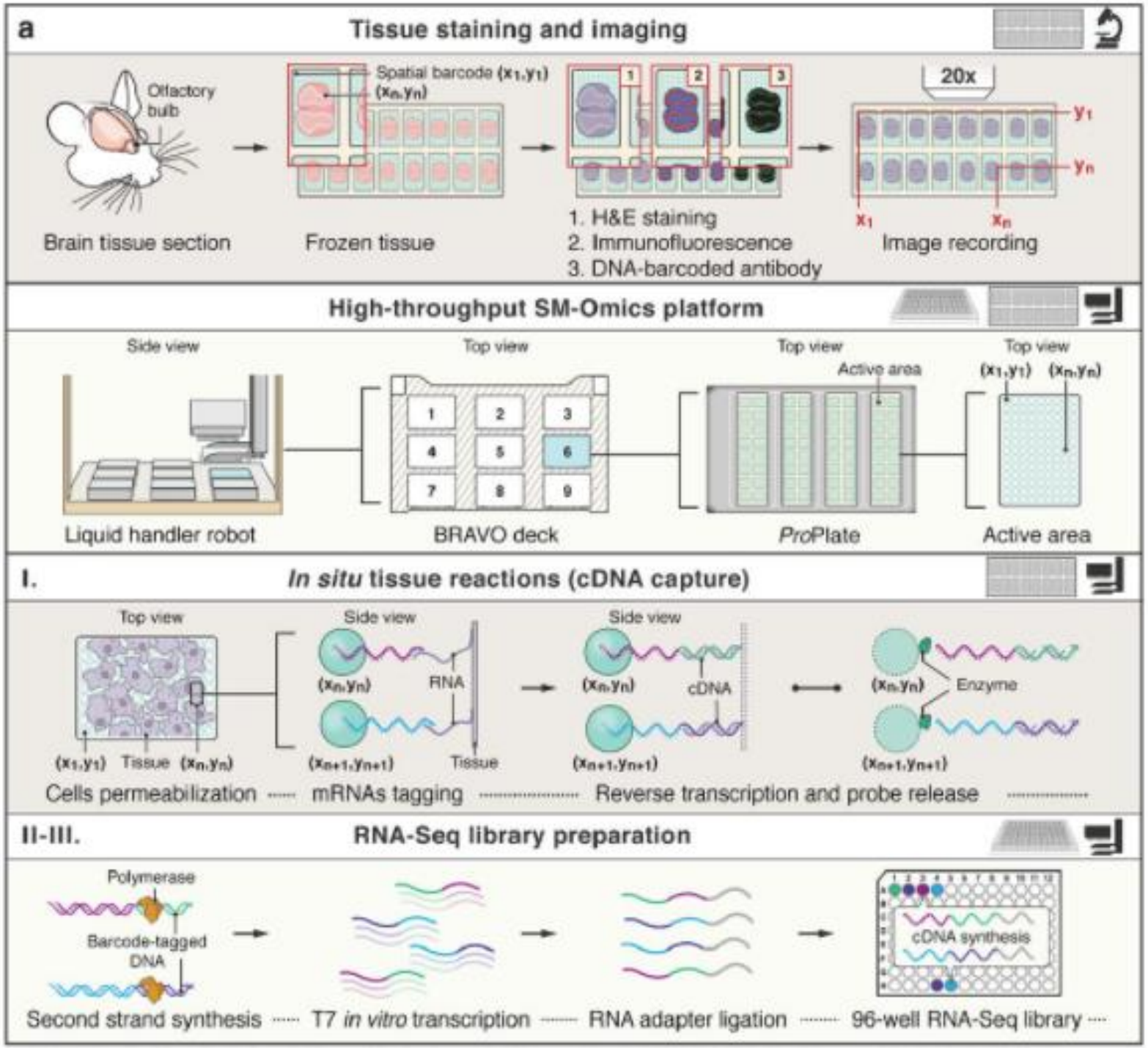
Method	Sample type	Spatial resolution	Approach	Detection efficiency	Advantages/Drawbacks	Demonstrated outside of originators lab
FISSEQ	Fresh-frozen or FFPE[60]	Subcellular	Transcriptome-wide	<0.005%[61]	+ Non-targeted – Low sensitivityLimited field of view	No
ST/10X Visium	Fresh-frozen	Anatomical features of 100 µm/55 µm	Transcriptome-wide	ST: 6.9%[41] 10X: higher than ST	+ Whole-mRNA analysis – Barcoded regions contain multiple cells	Yes
Nanostring GeoM	Fresh-frozen and FFPE	Custom down to 10µm	Targeted	Not specified	+ FFPE compatibleChoose between protein/RNA profilingHigh level of automation – Low sensitivity when using smaller ROIsRequire manual choice of regions	Yes

Spatially Resolved Transcriptomes—Next Generation Tools for Tissue Exploration
Michaela Asp, Joseph Bergenstråhle, and Joakim Lundeberg

https://onlinelibrary.wiley.com/doi/epdf/10.1002/bies.201900221

Future of Spatial Transcriptomics

- cBioportal/Cancertool for spatial datasets?
- Larger cohorts – spatial equivalent of TCGA?
- Automated spatial transcriptomics?
- High content spatial transcriptomics?
- Combining with spatial proteomics?
- Combining with spatial metabolomics?
- Combining with spatial epigenomics?

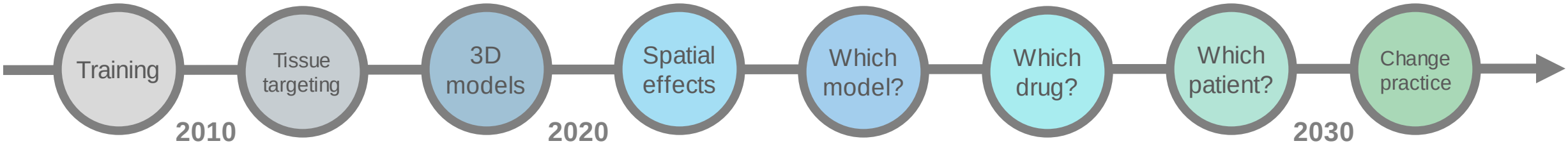


"Here, we advance the application of ST at scale, by presenting Spatial Multiomics (SM-Omics) as a fully automated high-throughput platform for combined and spatially resolved transcriptomics and antibody-based proteomics."

https://www.biorxiv.org/content/10.1101/2020.10.14.338418v1.full

Vickovic et al, 2020, preprint

Translational use of ST in my own work



Development of human tissue models for drug development & personalised medicine

Currently 96% of cancer drugs fail. *And that's just the ones that make it as far as Phase I!*

Cancer research demystified

PEOPLE: Using MRI to target areas of prostate tumour...

New research! Our latest work on prostate cancer...

How close can we get to studying real cancer in...

How and WHY are we putting human prostates in 3D...

Acknowledgements

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Hayley Pye

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Eleftheria Panagiotaki

Edward Johnston

Shonit Punwani

Bernard Siow

Surgery:

Greg Shaw

Ashwin Sridhar

John Kelly

Genomics England:

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Adrienne Flanagan

Manuel Rodriguez-Justo

Pathology:

Alex Freeman

Aiman Haider

FISSEQ:

Je Hyuk Lee

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PROSTATE CANCER UK