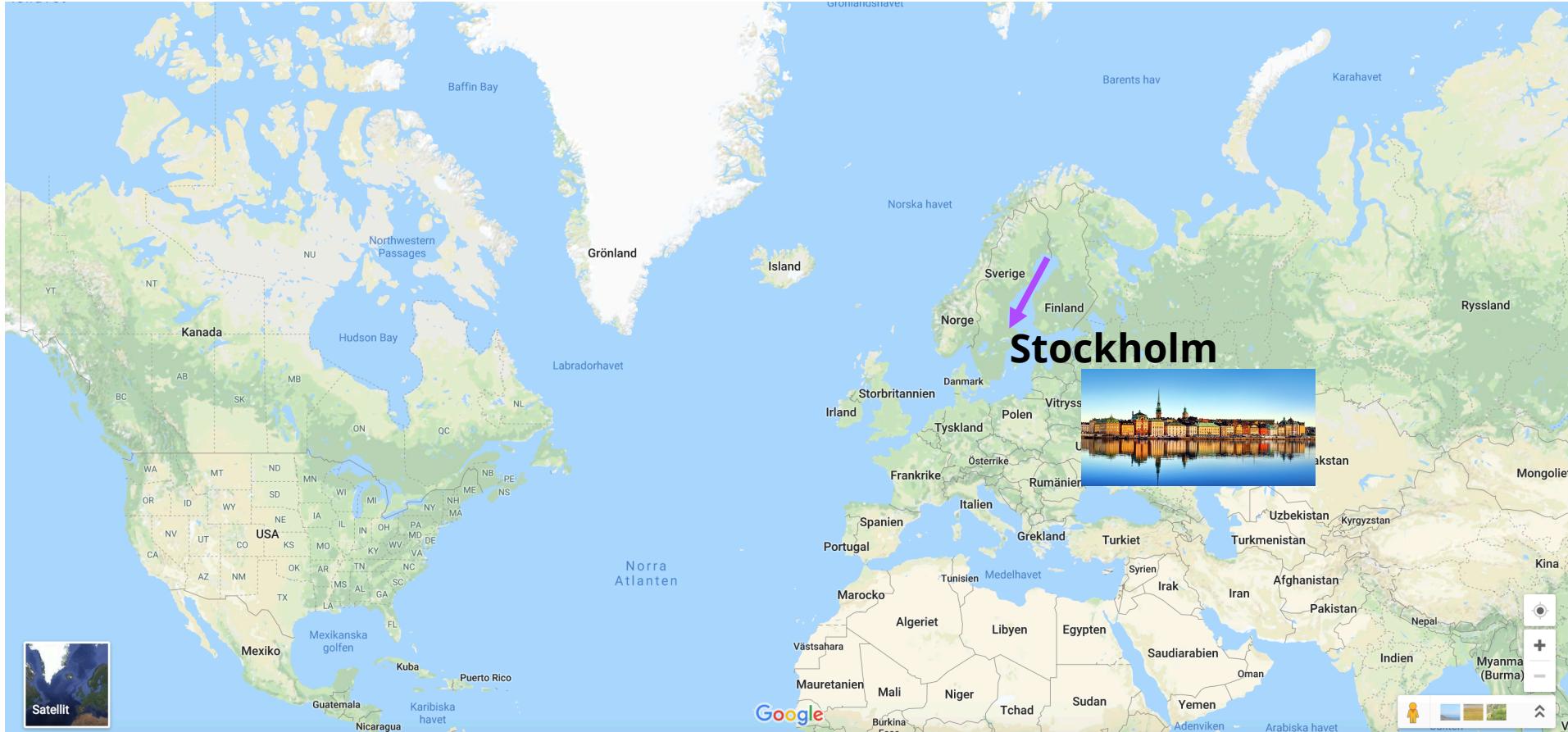


# Spatial Transcriptomics

Stefania Giacomello  
UC Davis, 21.06.2018

# Where the technology was developed

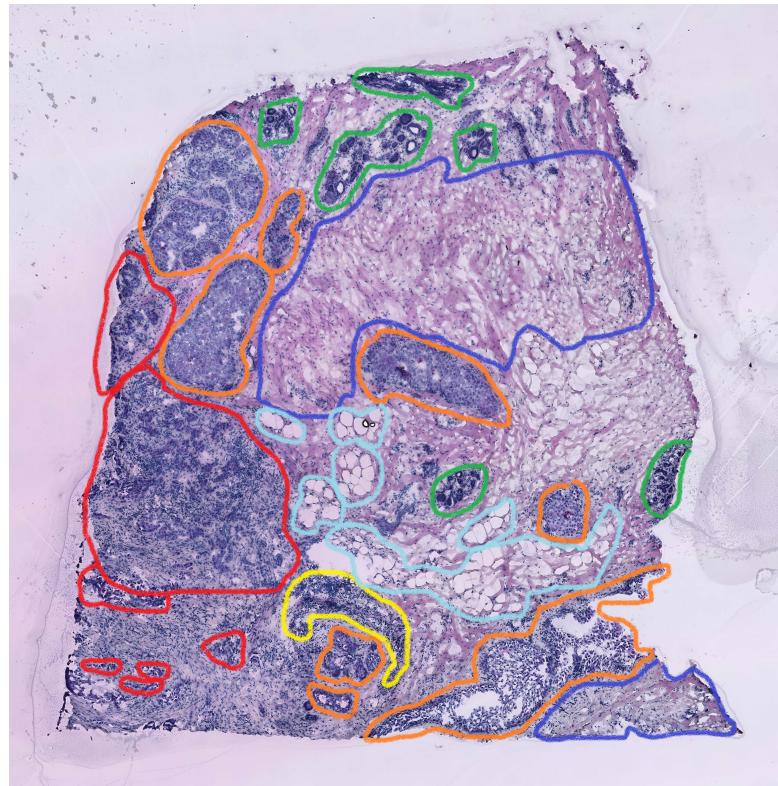


SciLifeLab



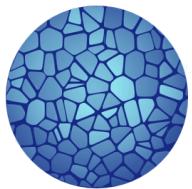
SPATIAL  
TRANSCRIPTOMICS

# The concept



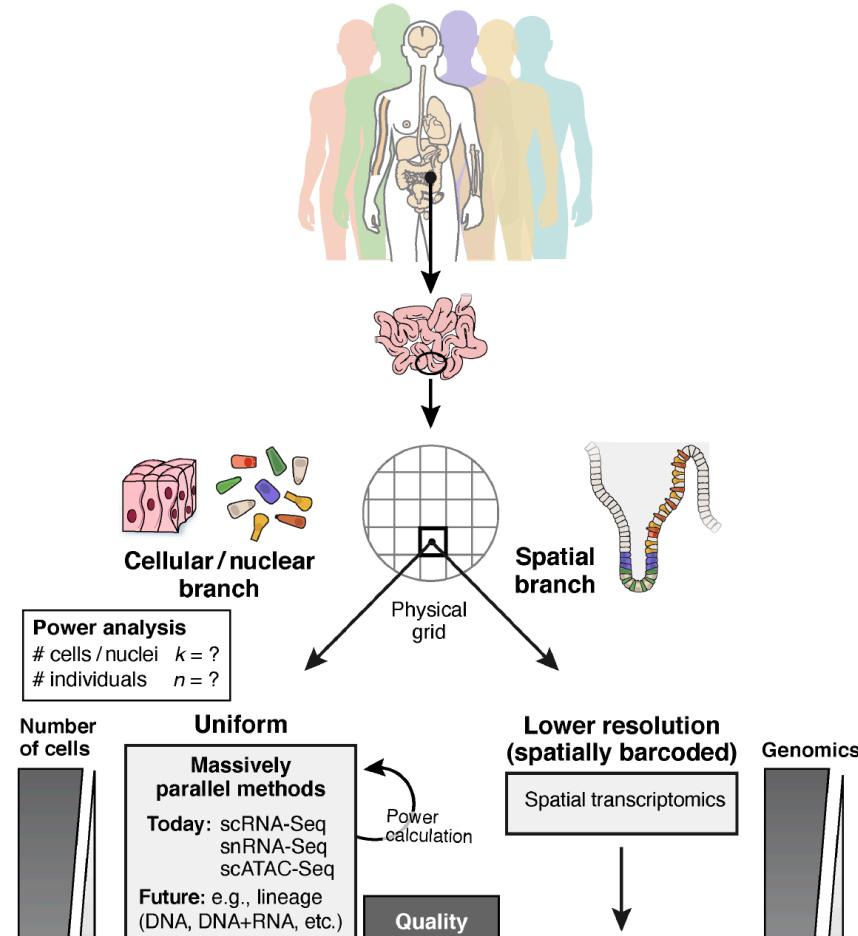
- Invasive cancer (tumor cells + stroma)
- Inflammatory cells
- Fibrous tissue
- Fat tissue
- Normal breast glands
- Cancer *in situ*

# The concept



HUMAN  
CELL  
ATLAS

*The Human Cell Atlas –  
White Paper – October 18, 2017*



# Available methods

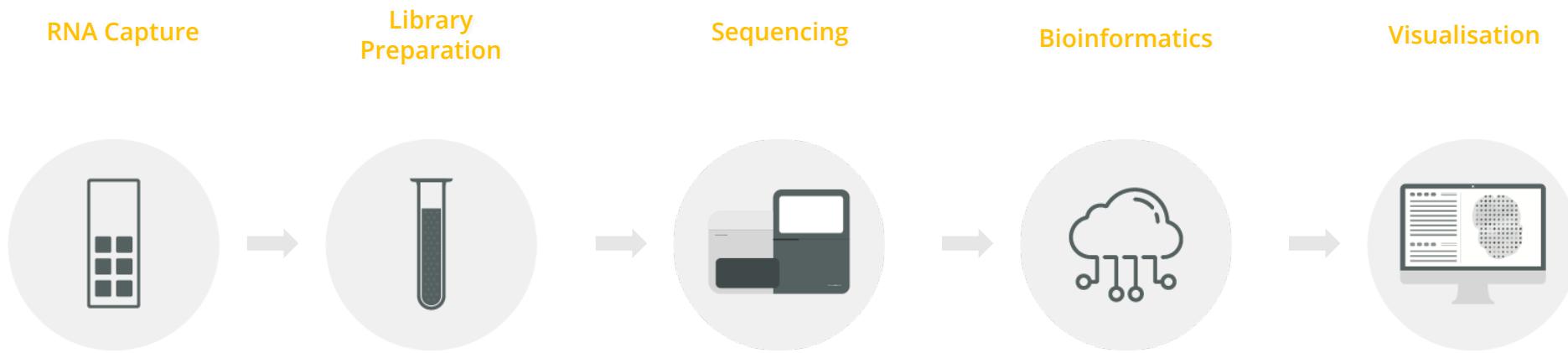
**smFISH** *Raj A, et al., Nature Methods 2008*

**ISS** *Ke R, et al., Nature Methods 2013*

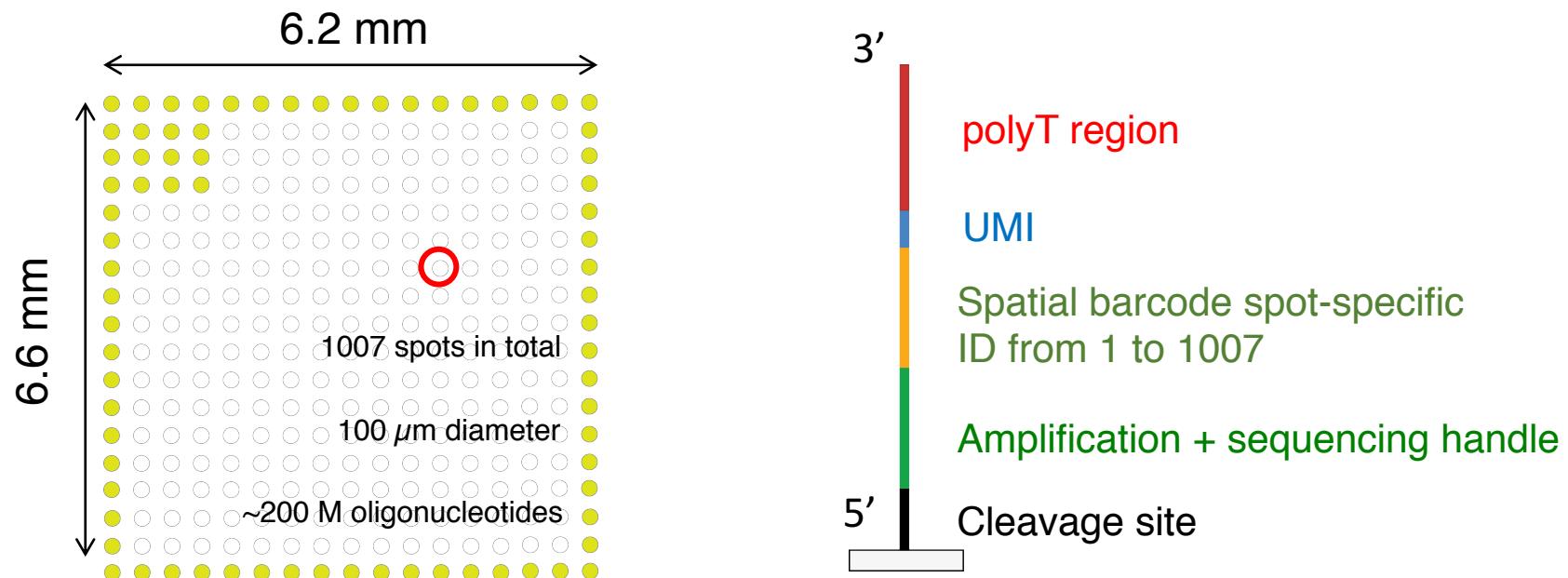
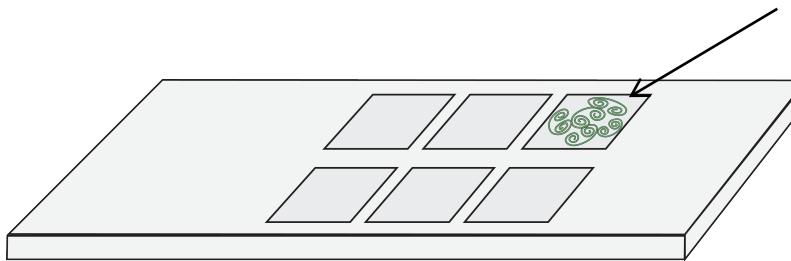
**FISSEQ** *Lee JH, et al., Science 2014*

**ST** *Ståhl P, et al., Science 2016*

# Workflow

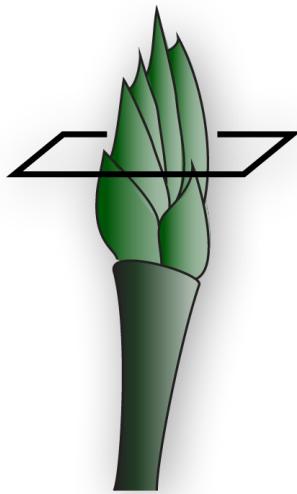


# The array

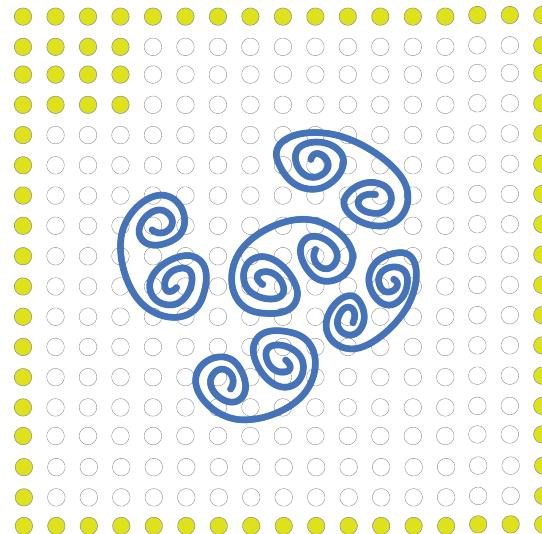


# The Technology

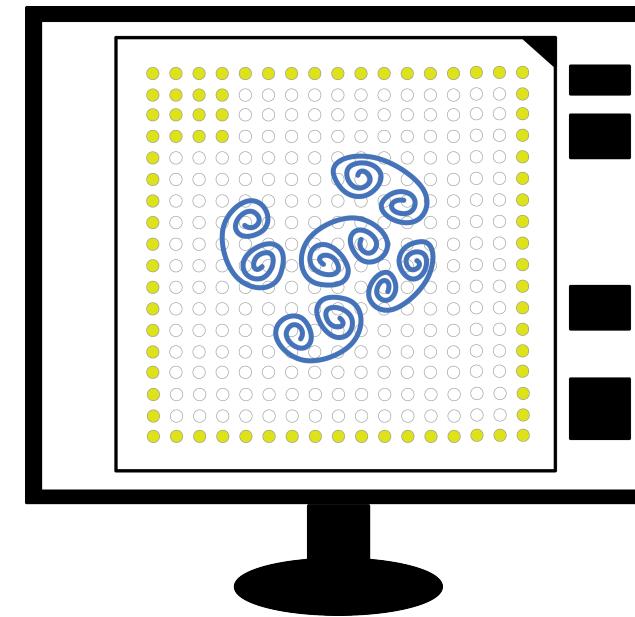
Cryosectioning



Staining

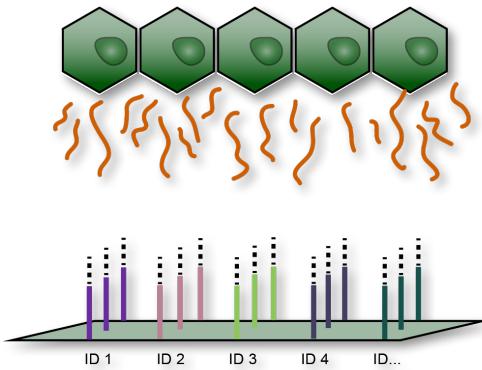


High resolution imaging

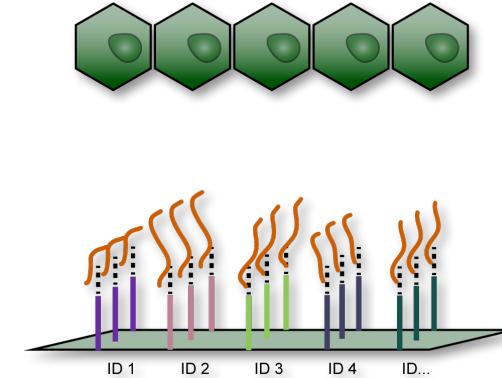


# The Technology

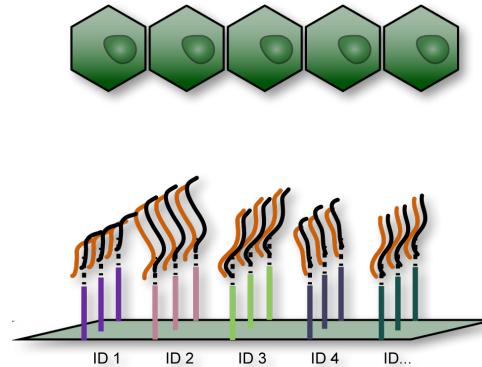
Permeabilization



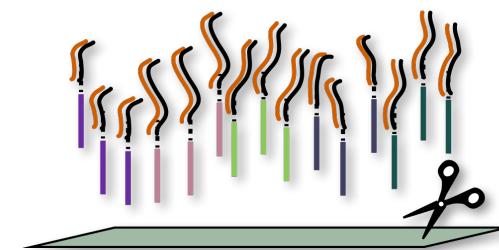
Poly-T capture of transcripts



On surface cDNA synthesis



Tissue removal and release

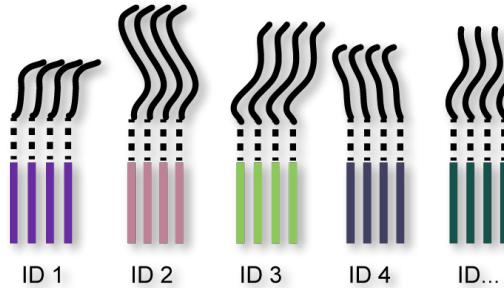


# The Technology

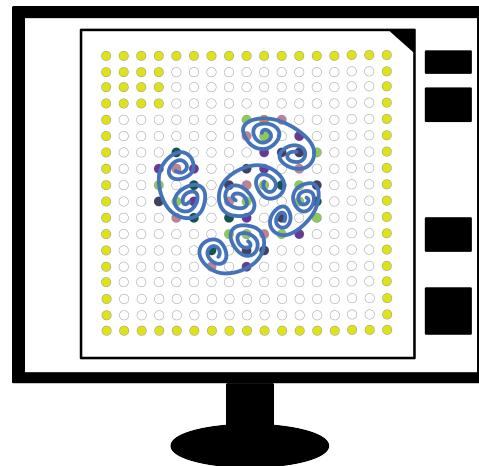
## Illumina sequencing

```
GTACCTATTAAGCGCGTATGCACCG  
GCATGGCACGGCGCTCGCGTATGCAC  
GTACCTATTAAGCGCGTATGCACCG  
TTAACGCGGTATGCATTAGCCCACCG  
GCCATATATATTGCTATAATGCTGC  
GCCACGGGCTACGATGCATTGCTAT  
GTACCTATTAAGCGCGTATGCACCG  
GCATGGCACGGCGCTCGCGTATGCAC  
GTACCTATTAAGCGCGTATGCACCG  
TTAACGCGGTATGCATTAGCCCACCG  
GCCATATATATTGCTATAATGCTGC  
GCCACGGGCTACGATGCATTGCTAT
```

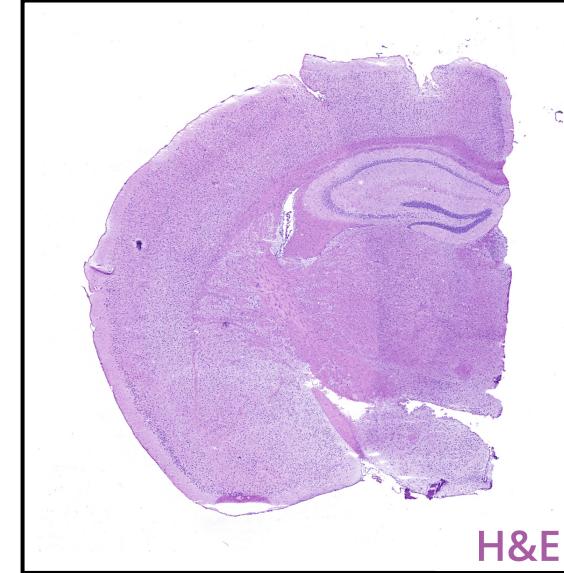
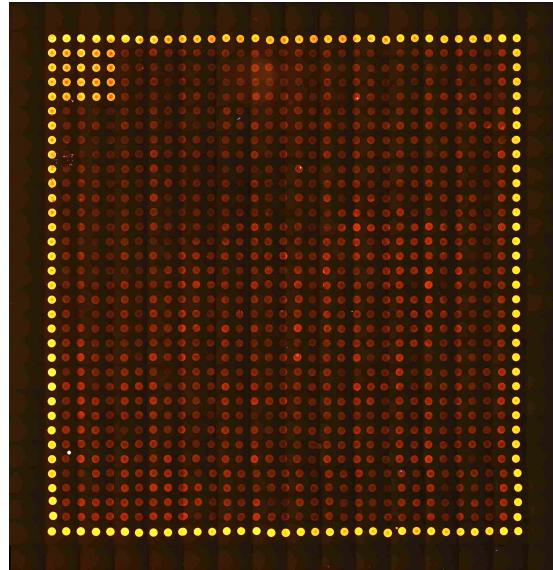
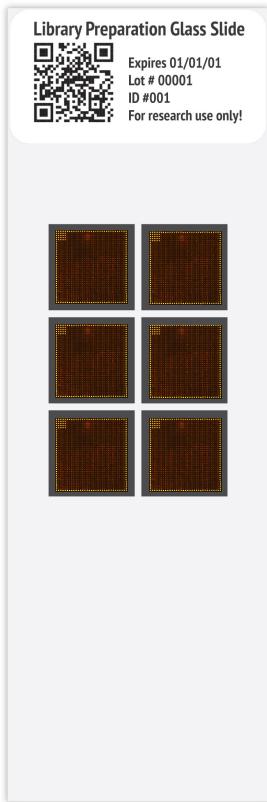
## Alignment and sorting of barcodes



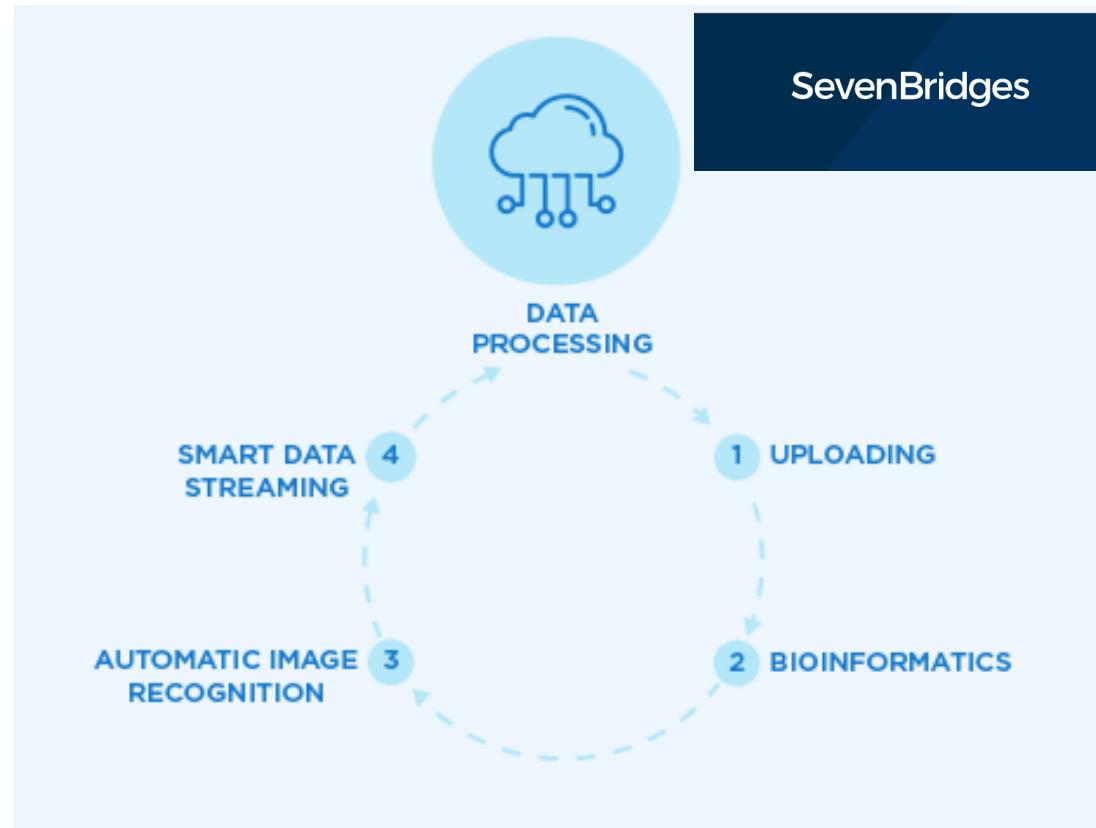
## Alignment of image and barcoded transcripts



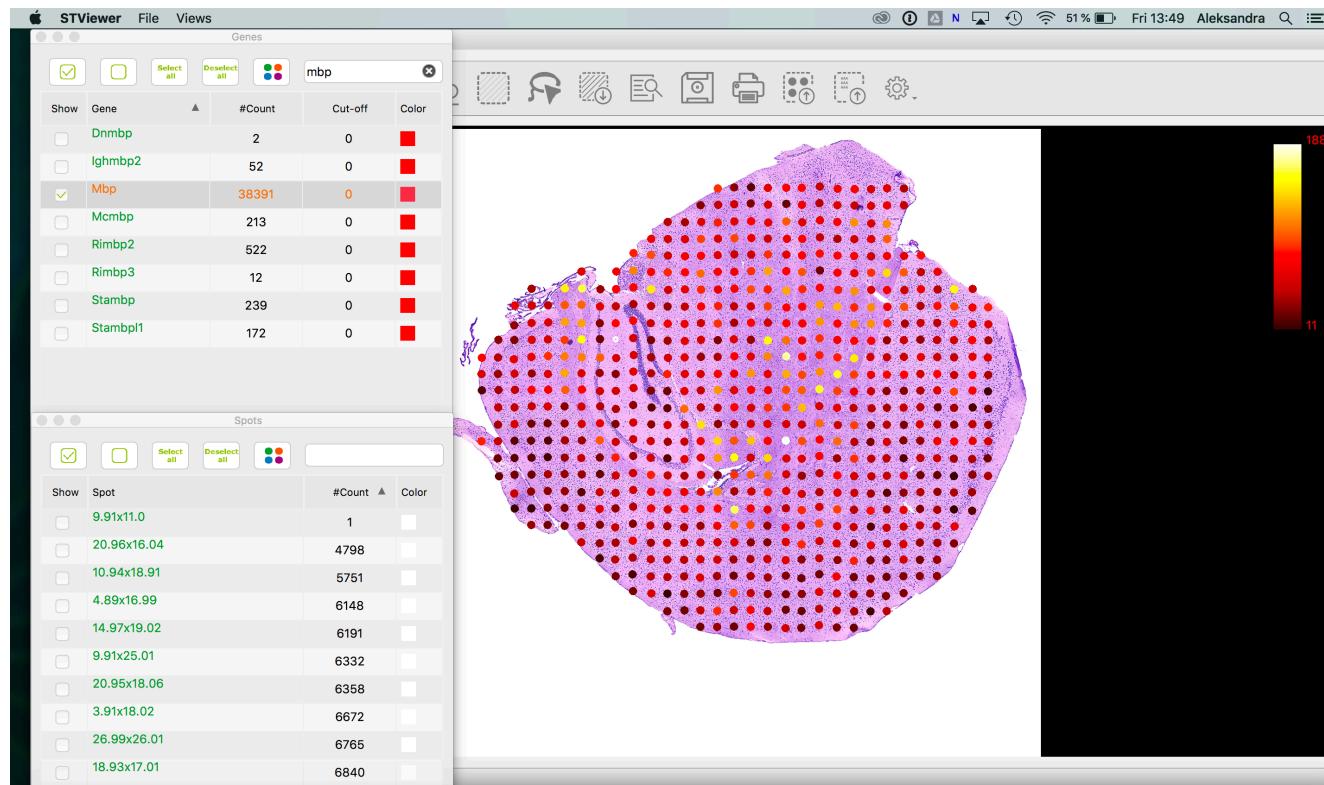
# The Technology



# Analysis



# Spatial Transcriptomics Viewer



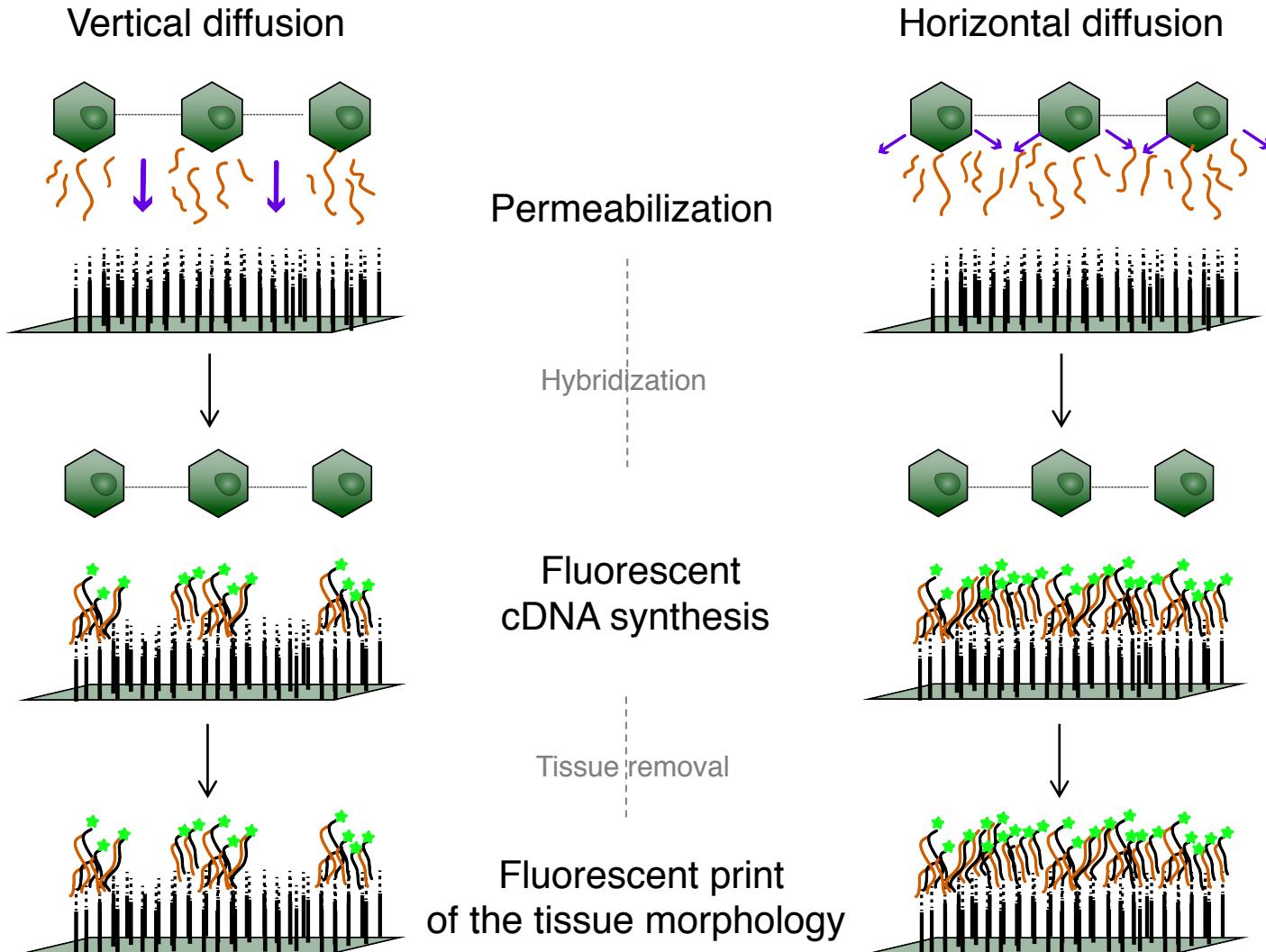
# Lateral Diffusion?

How do we know

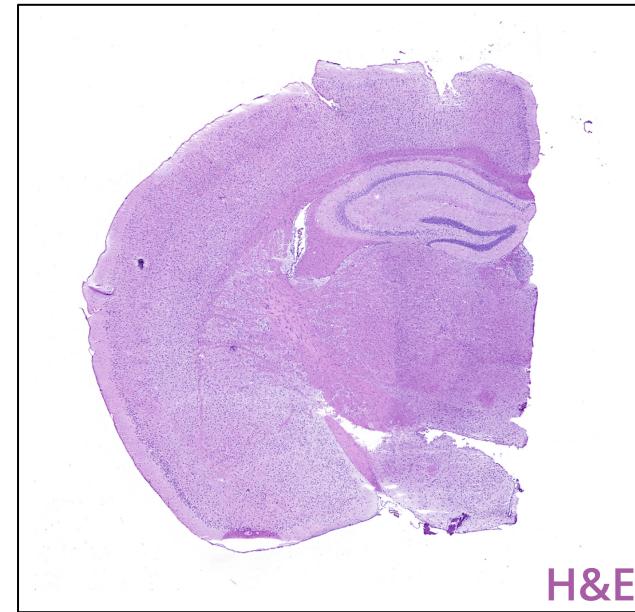
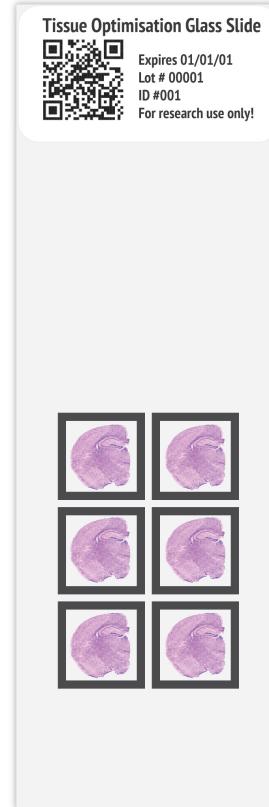
that transcripts are **directly** transferred

to the array surface?

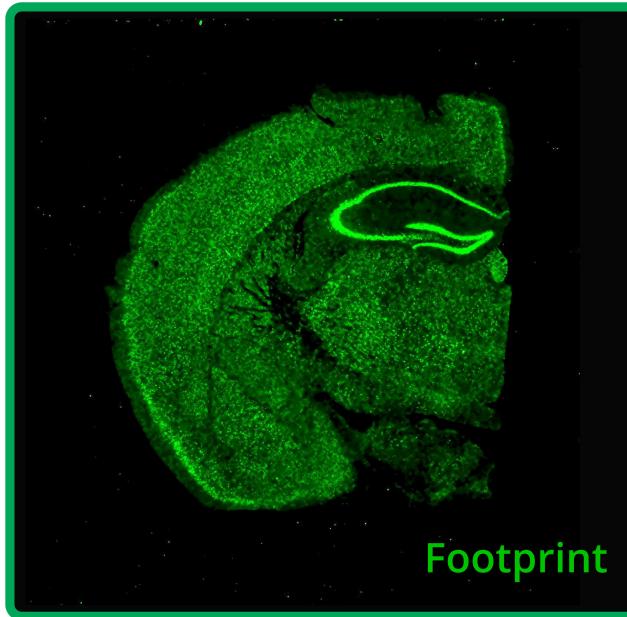
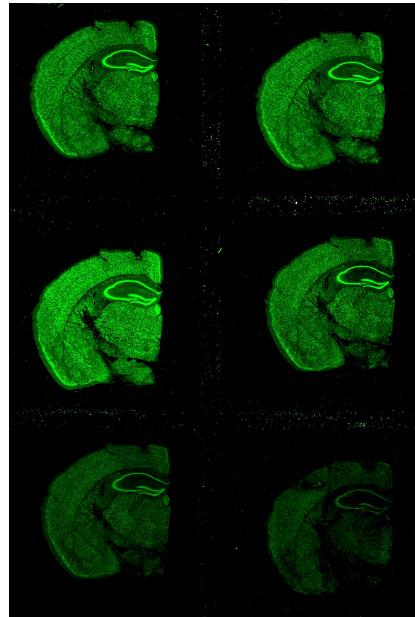
# Lateral Diffusion?



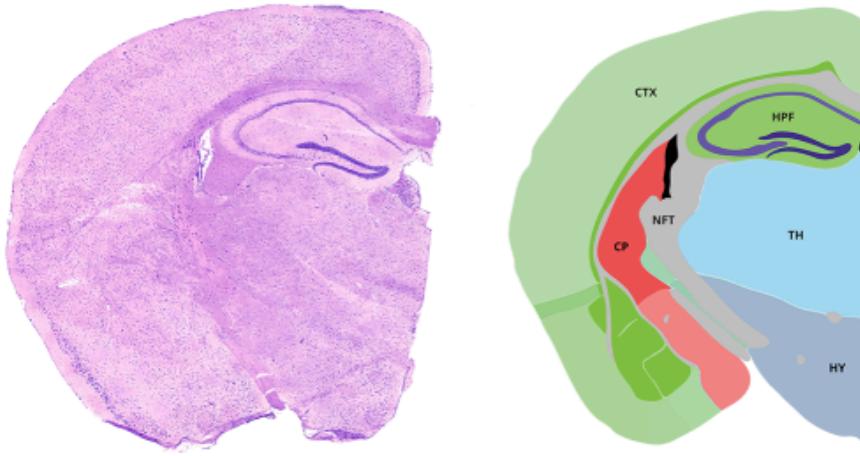
# Tissue Optimization Experiment



# Tissue Optimization Results



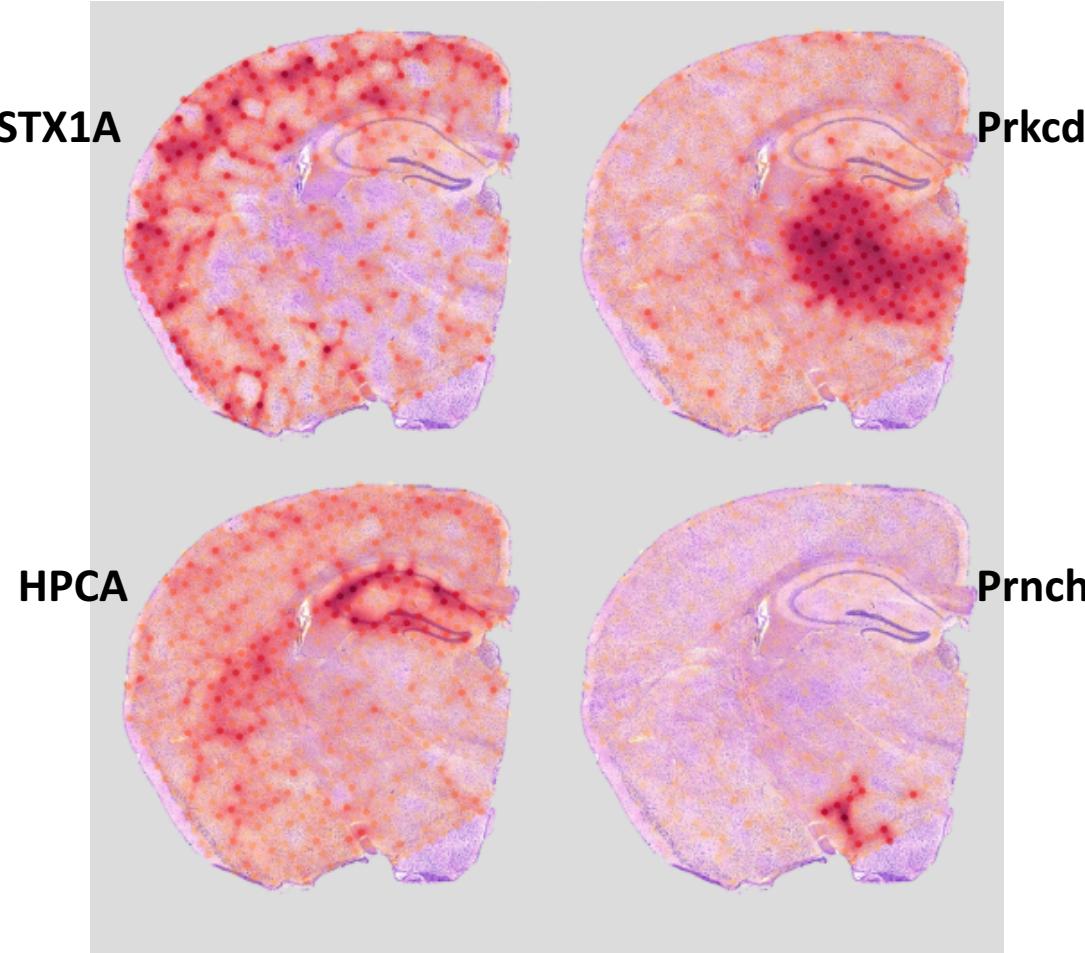
# What can we do?



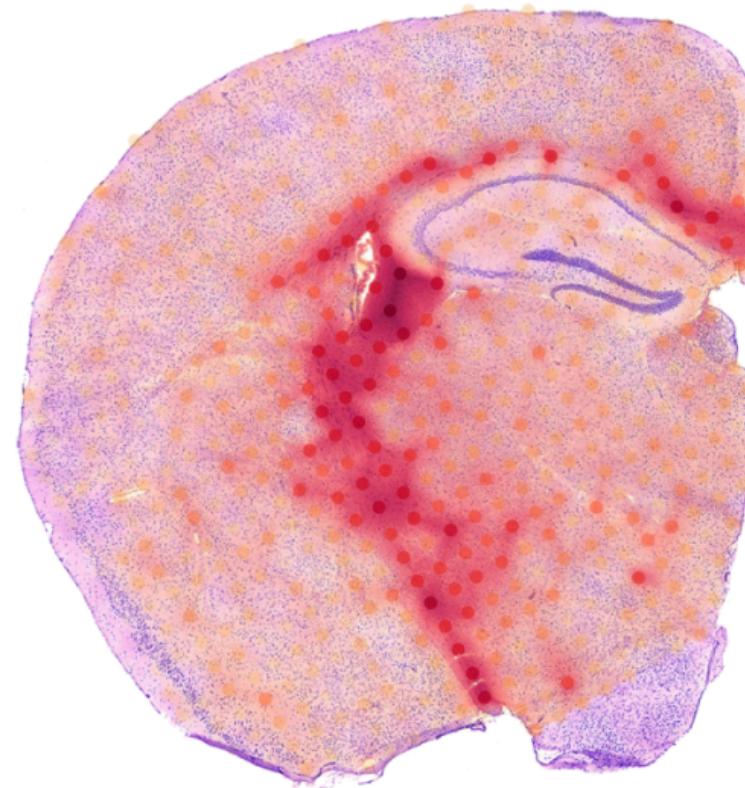
The region abbreviations correspond to:

- CTX – Cortex
- HPF – Hippocampus
- CP – Caudate putamen
- NFT – Nerve fiber tracts
- TH – Thalamus
- HY – Hypothalamus

# Choose a gene

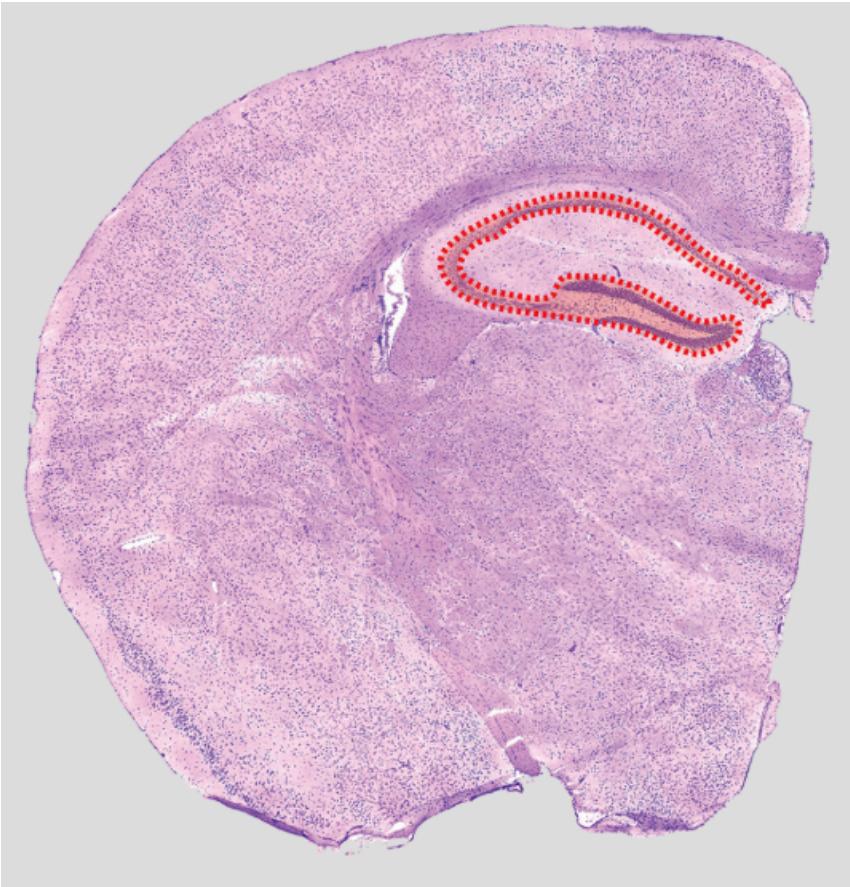


# Combine genes



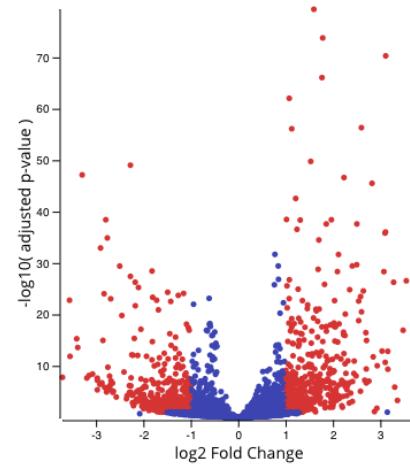
**Myelin production  
genes in nerve fiber  
tract**

# Select a region



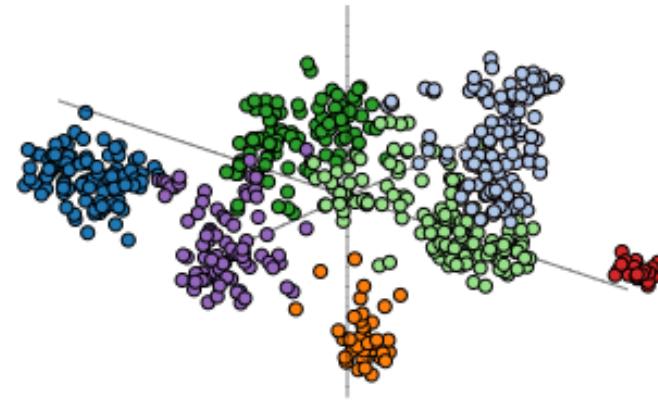
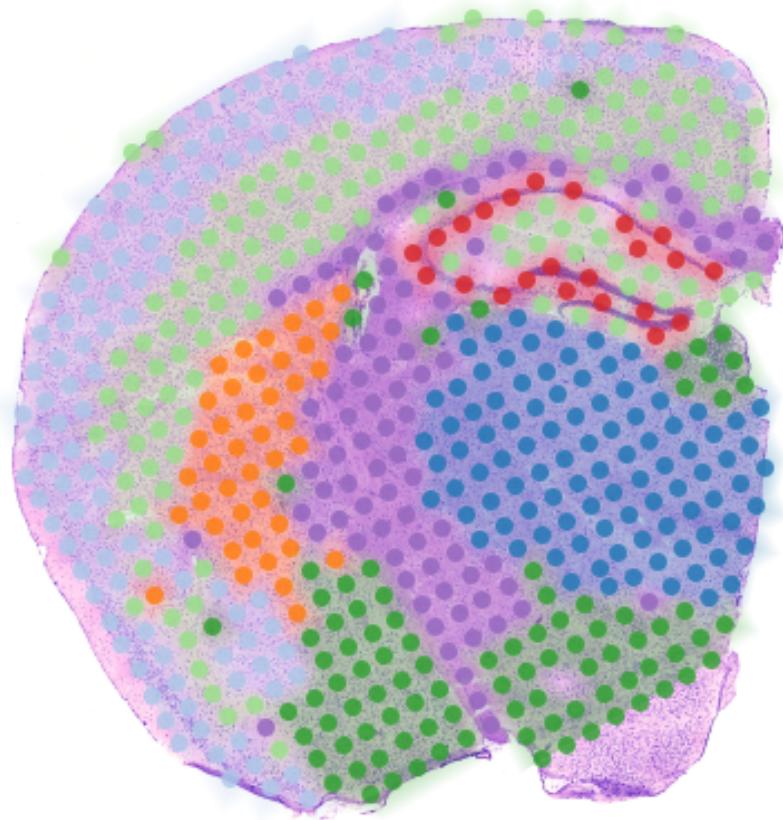
Rank	Gene	Number Unique Molecules Detected
1	Yam1	9139
2	Ppp3ca	5171
3	Nrgn	4768
4	Malat1	3567
5	Tmsb4x	3567
6	Calm1	3409
7	Actb	3160
8	Olfm1	3039
9	Snap25	2808
10	Fth1	2775

# Compare regions

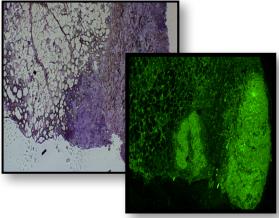


Name	Log2 Fold Change	adjusted p-value
Chn1	1.60	4.31e-80
Tmsb4x	1.78	1.62e-74
Hpc1	3.11	4.97e-71
Cnih2	1.77	8.42e-67
Ppp3ca	1.08	8.86e-63
Ptk2b	2.60	4.59e-57
Nrgn	1.13	7.49e-57
Gria2	1.53	1.68e-50
Ptpn4	-2.27	9.32e-50
Rora	-3.29	7.01e-48

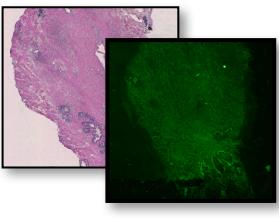
# Machine learning



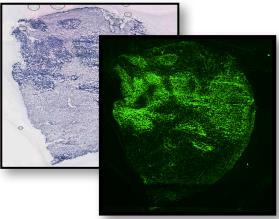
Breast cancer



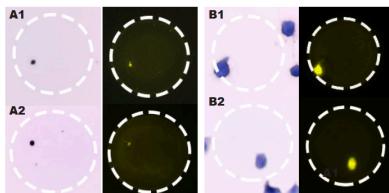
Prostate cancer



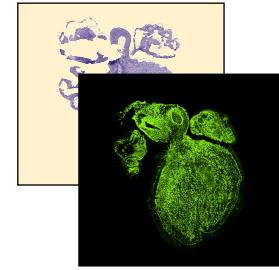
Melanoma



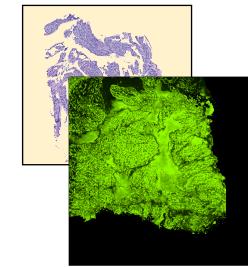
Chronic Lymphocytic Leukemia



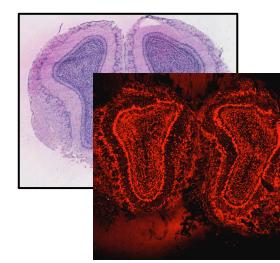
Fetal Human Heart



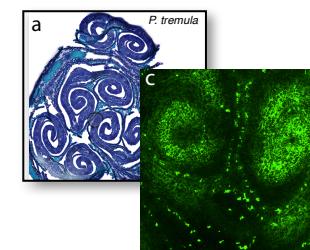
Adult Human Heart



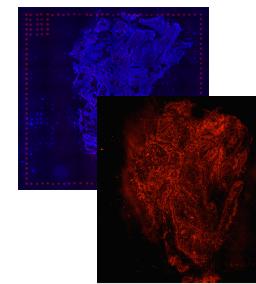
Mouse brain



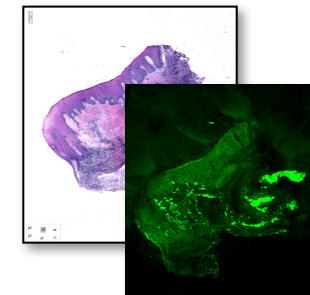
Plants



Rheumatoid arthritis

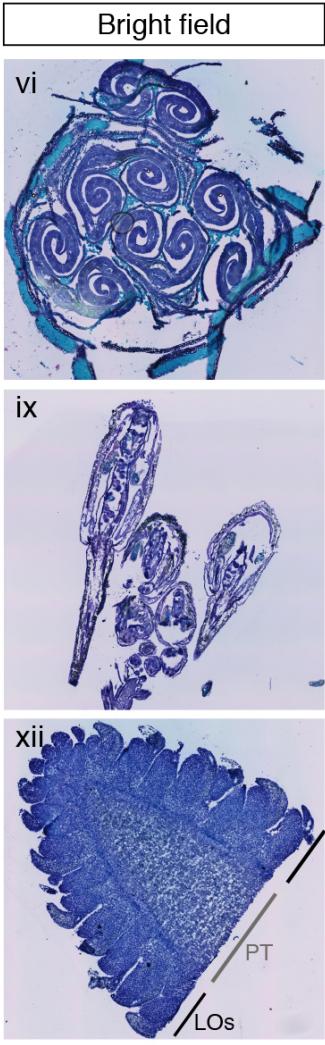


Periodontitis



# Plant Species

Angiosperms



*Populus tremula*



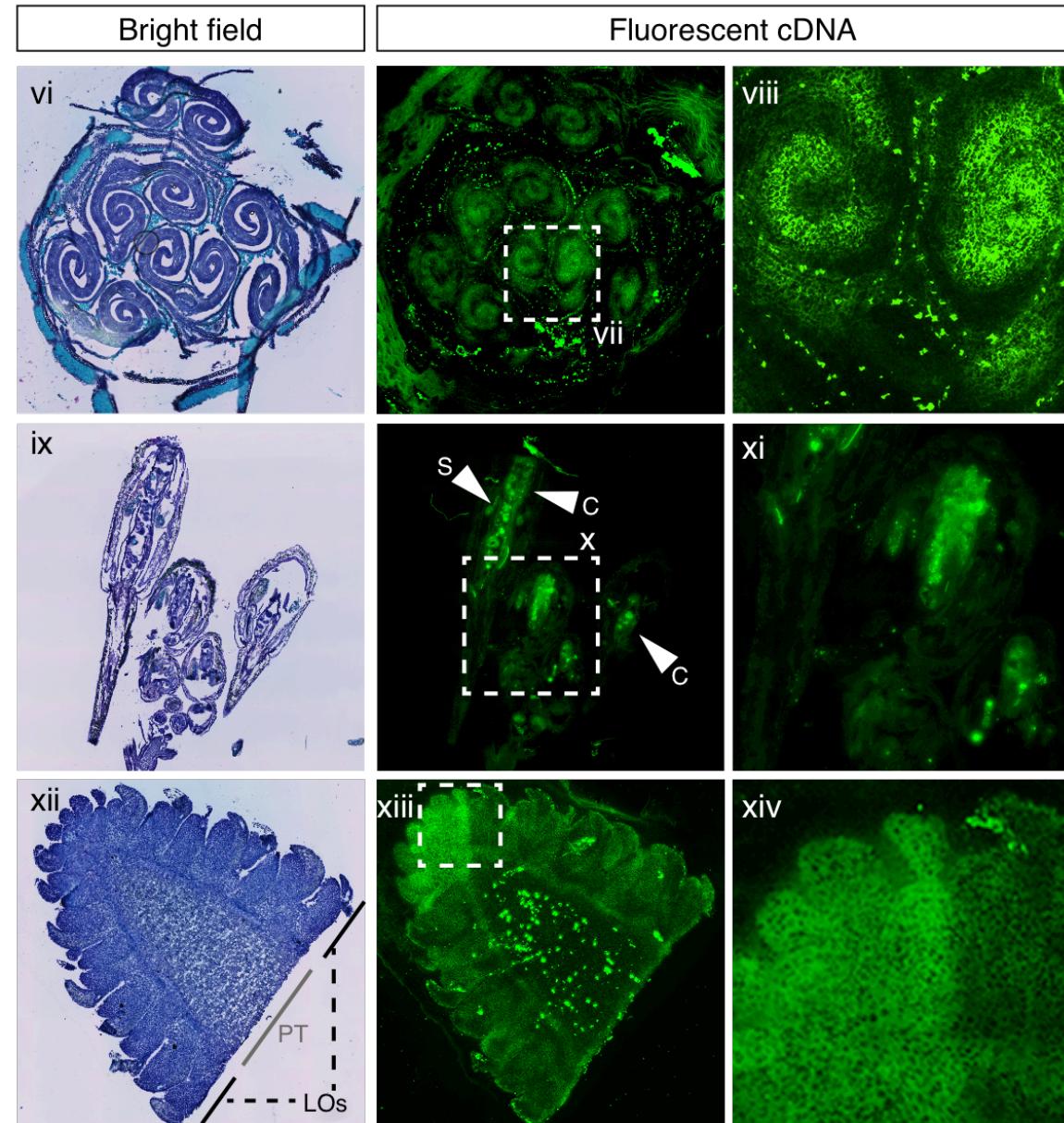
*Arabidopsis thaliana*



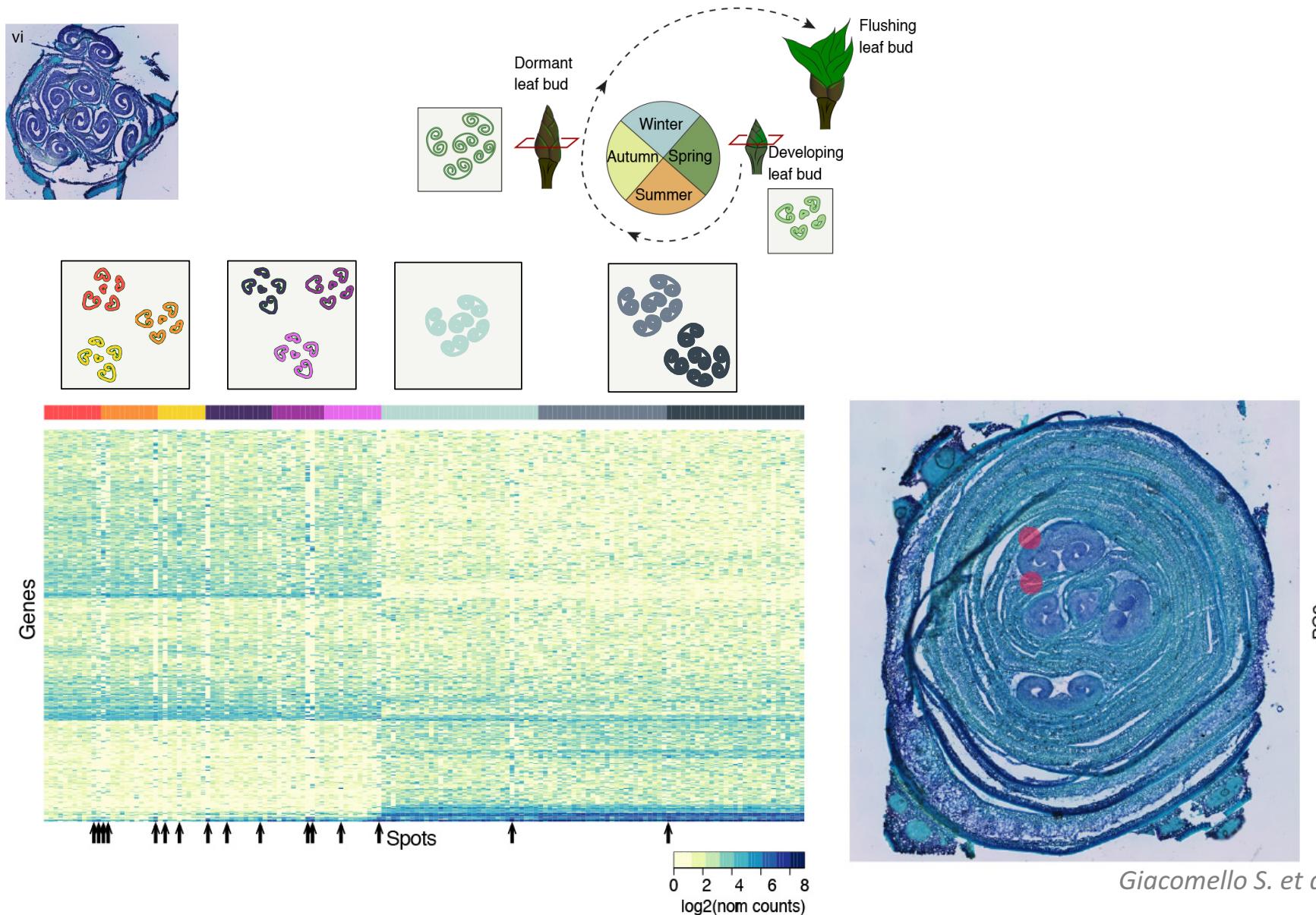
*Picea abies*



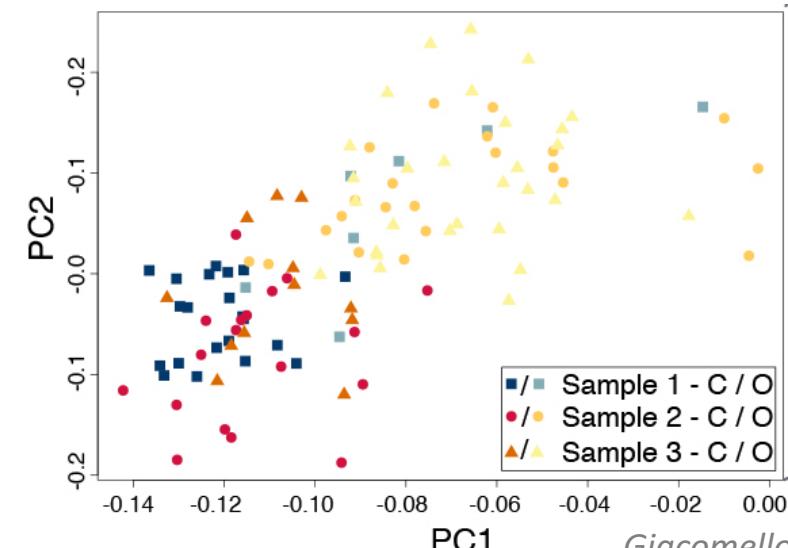
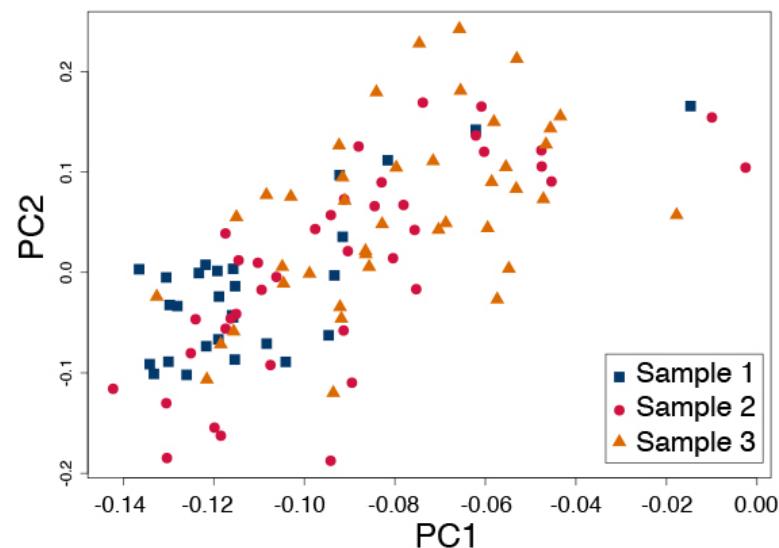
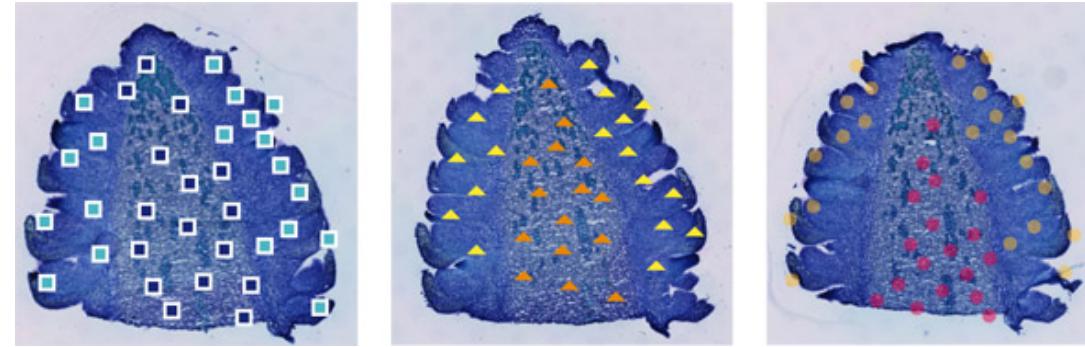
# Lateral Diffusion?



# Leaf Development

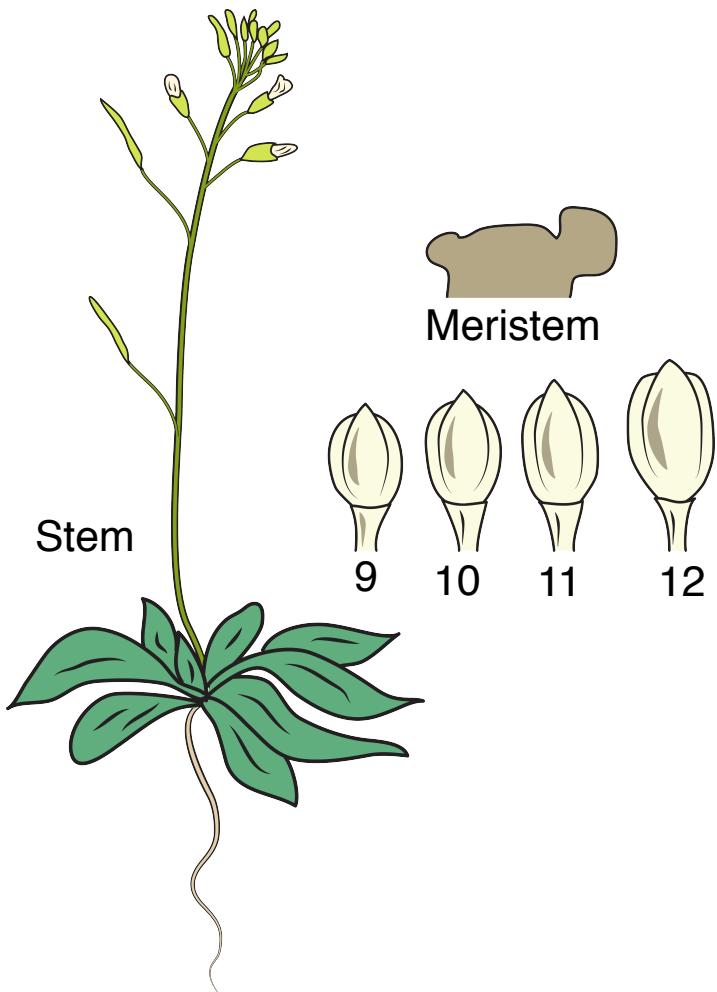


# Cone Development



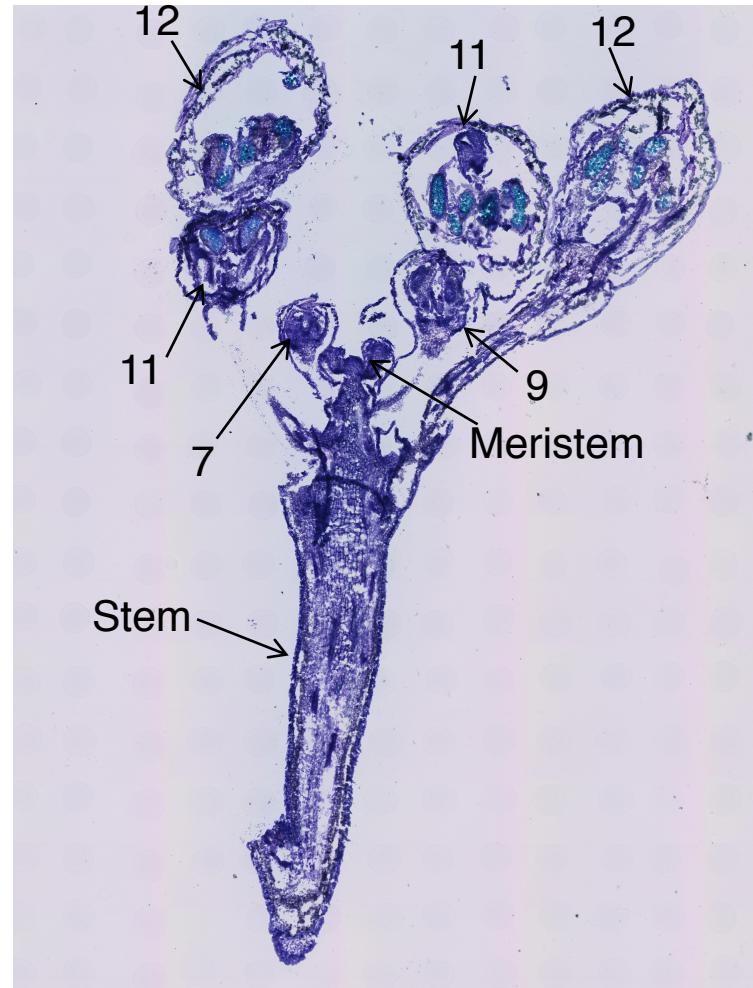
# Validation

eFP browser



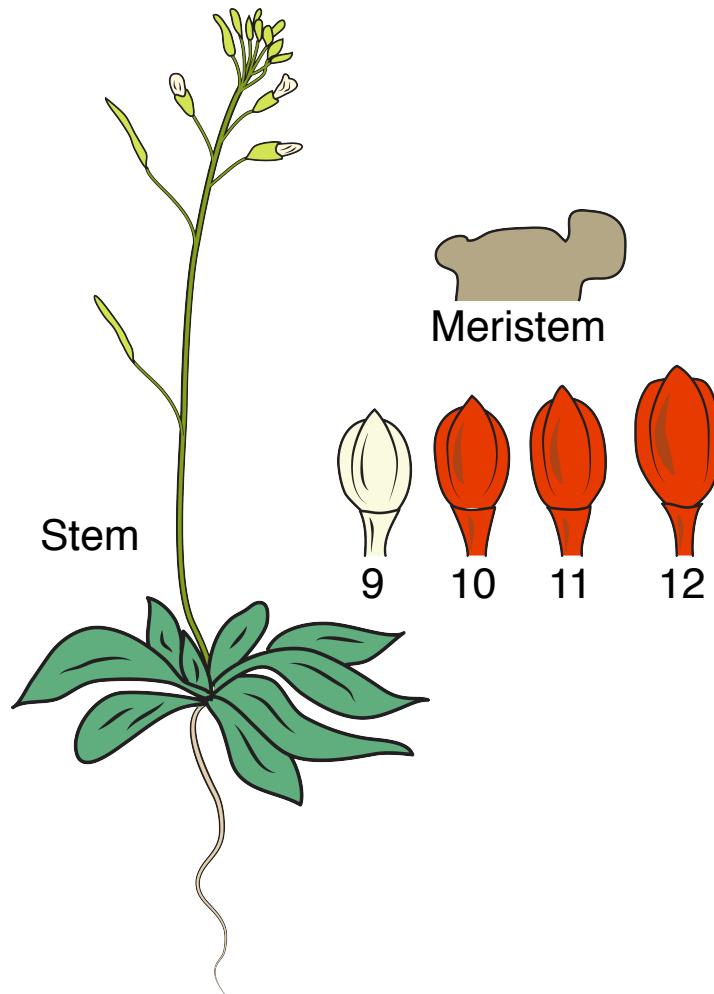
Schmid et al., *Nature Genetics* 2005  
“Atlas of *Arabidopsis* Development”

Spatial Transcriptomics



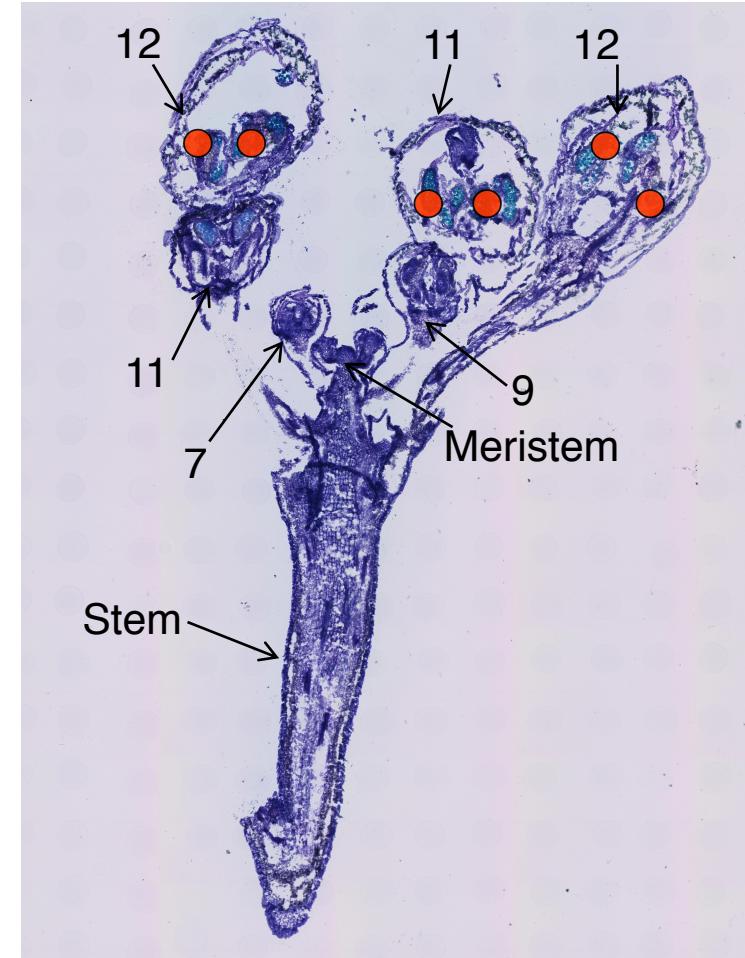
# Validation – ATA27

eFP browser

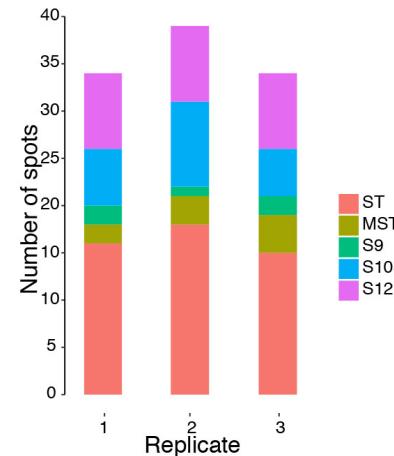
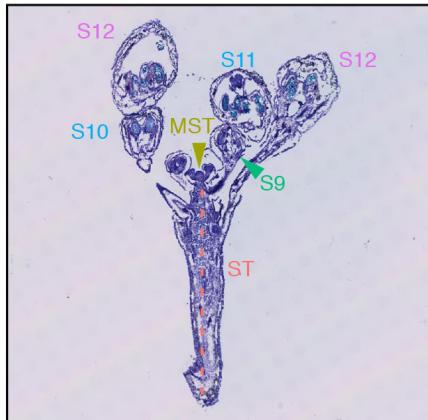


Schmid et al., *Nature Genetics* 2005

Spatial Transcriptomics

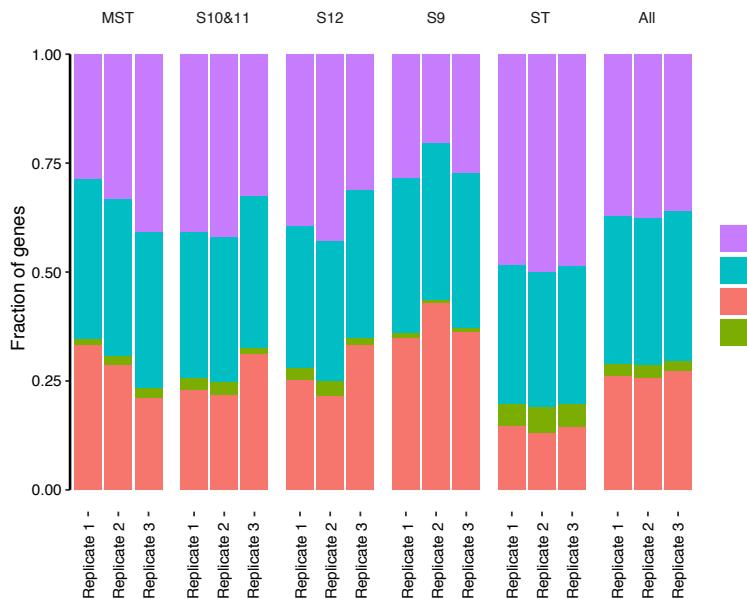


# Validation – Atlas of Development



~16,000 genes

107 spots



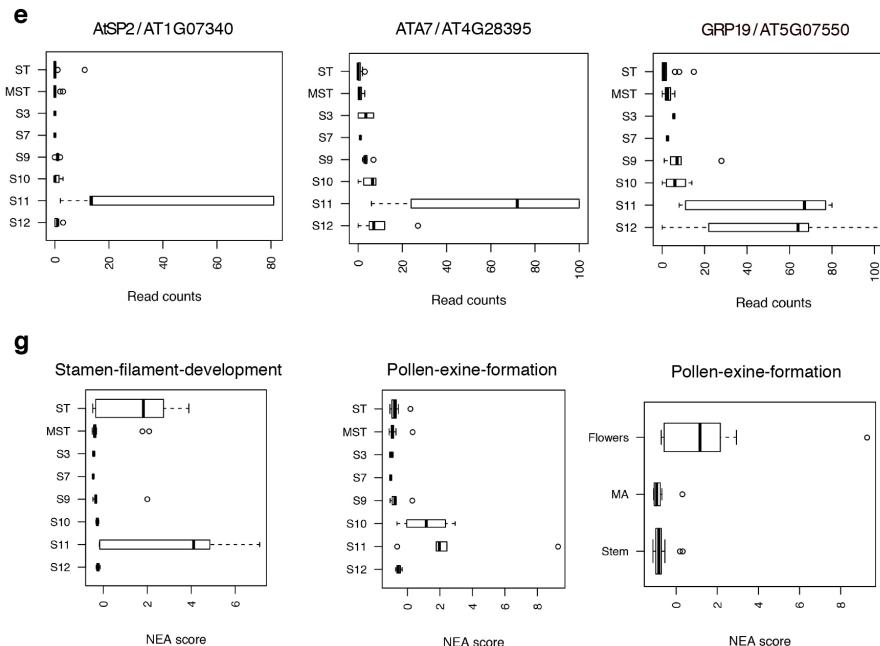
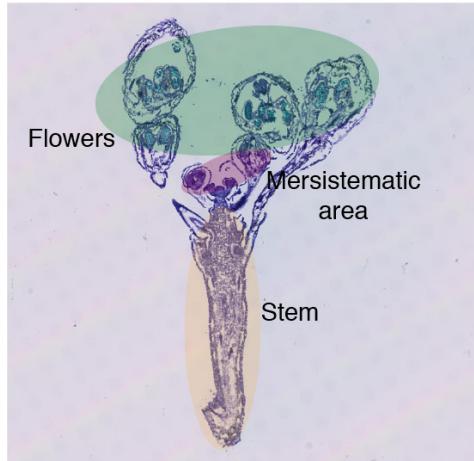
Specificity: 92.9%

Accuracy: 71.2%

Sensitivity: 58.5%

False Positive Rate: 6.5%

# Global spatial gene expression



Replicates

Tissue categories

Spots

293 DE genes at macro- level  
141 DE genes at micro- level

128 pathways at macro- level  
189 pathways at micro- level

# Our Products

Library Preparation and Tissue Optimization Glass Slides



# Our Products

## Tissue Optimization Reagent Kit

