Marc Elosua Bayes

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Ivo Gut lab - Biomedical Genomics Group
Holger Heyn Lab - Single-Cell Genomics Group

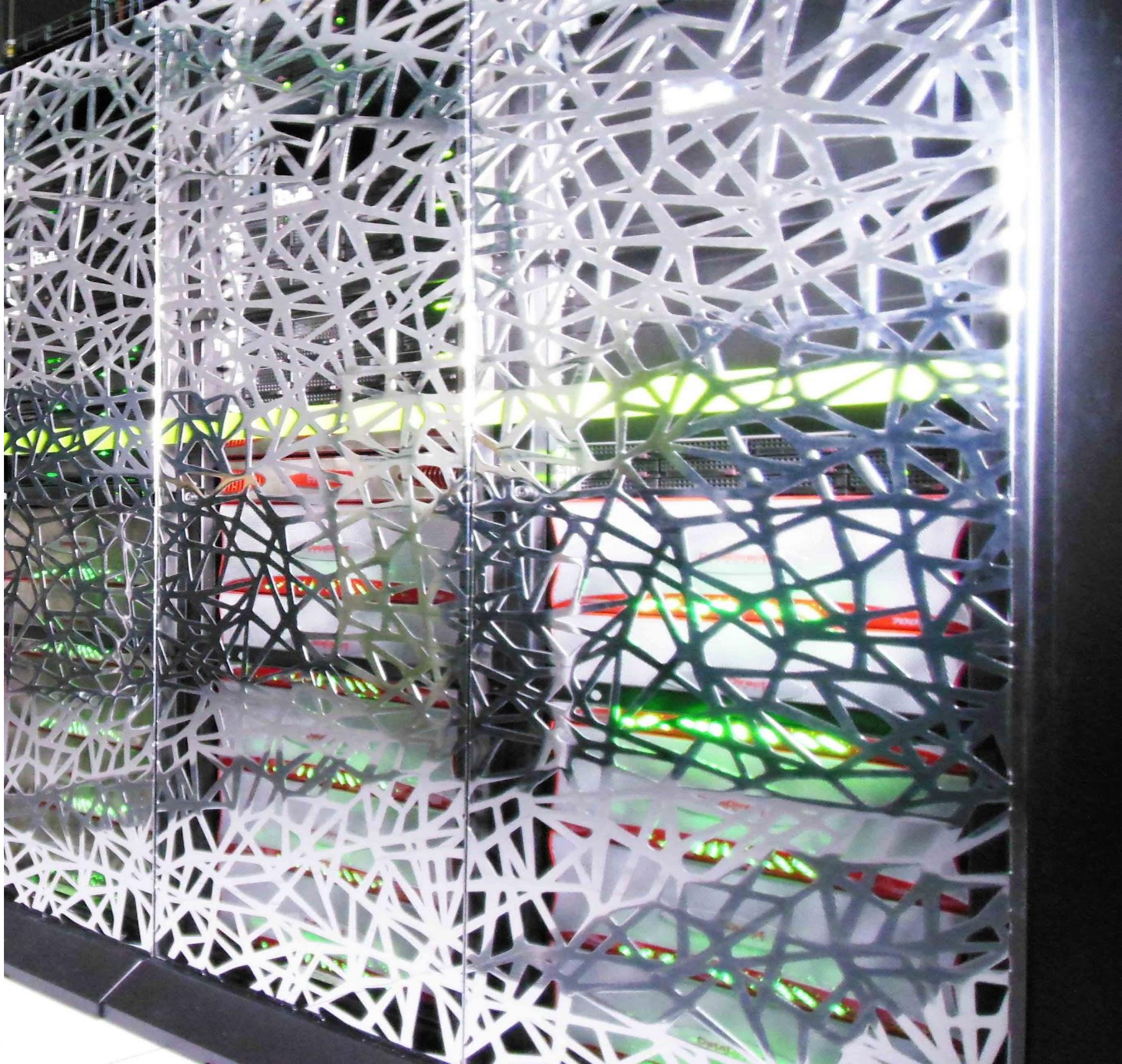
Advanced Spatial Analysis
SincellTE-2022

12/01/2022

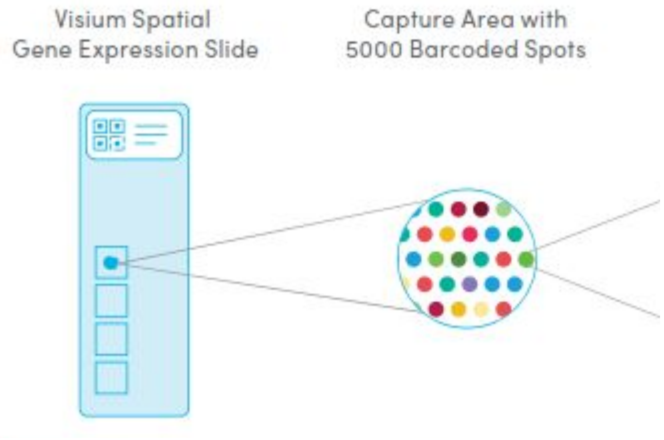
cnag
centre nacional d'anàlisi genòmica
centro nacional de análisis genómico

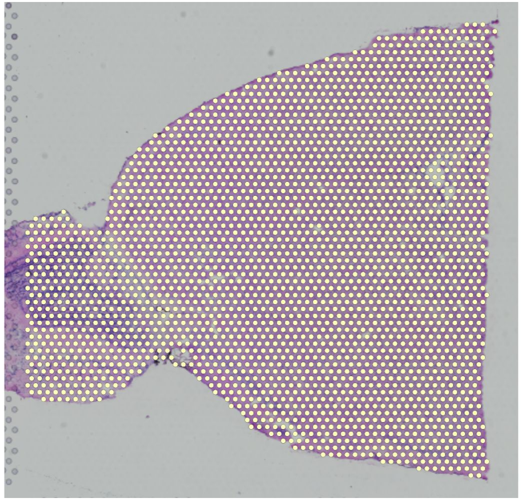
CRG
Centre for Genomic Regulation

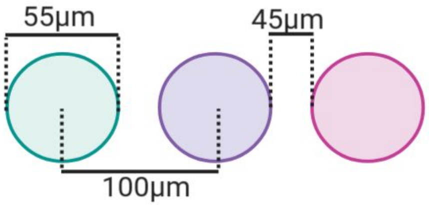
@elosua_bayes



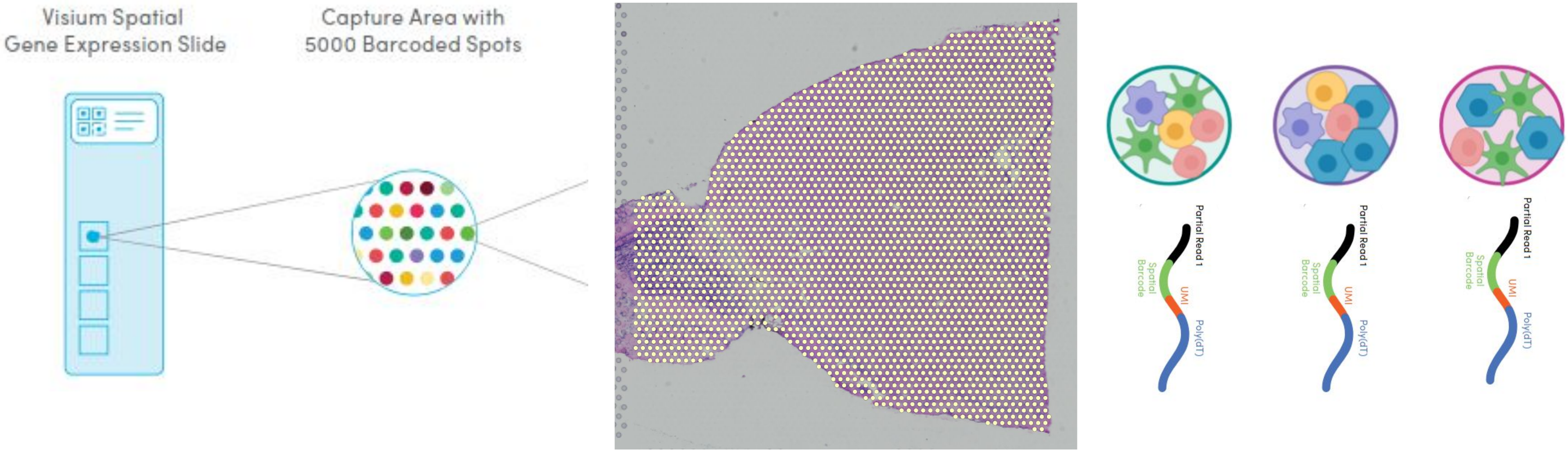
Array based spatial transcriptomics







Array based spatial transcriptomics



Cell type deconvolution tools

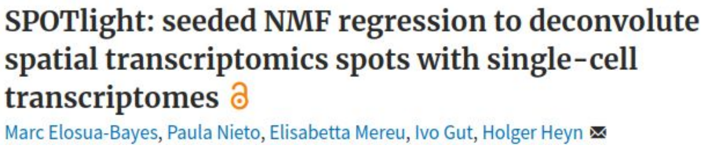
Article | Published: 18 February 2021

Robust decomposition of cell type mixtures in spatial transcriptomics

Dylan M. Cable, Evan Murray, Luli S. Zou, Aleksandrina Goeva, Evan Z. Macosko, Fei Chen & Rafael A. Irizarry

Deep learning and alignment of spatially resolved single-cell transcriptomes with Tangram

Tommaso Biancalani, Gabriele Scalia, Lorenzo Buffoni, Raghav Avasthi, Ziqing Lu, Aman Sanger, Neriman Tokcan, Charles R. Vanderburg, Åsa Segerstolpe, Meng Zhang, Inbal Avraham-Davidi, Sanja Vickovic, Mor Nitzan, Sai Ma, Ayshwarya Subramanian, Michal Lipinski, Jason Buenrostro, Nik Bear Brown, Duccio Fanelli, Xiaowei Zhuang, Evan Z. Macosko & Aviv Regev



SPOTlight: seeded NMF regression to deconvolute spatial transcriptomics spots with single-cell transcriptomes

Marc Elosua-Bayes, Paula Nieto, Elisabetta Mereu, Ivo Gut, Holger Heyn

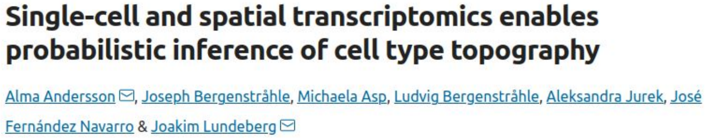
CellDART: Cell type inference by domain adaptation of single-cell and spatial transcriptomic data

Sungwoo Bae, Kwon Joong Na, Jaemoon Koh, Dong Soo Lee, Hongyoon Choi, Young Tae Kim

doi: https://doi.org/10.1101/2021.04.26.441459

Comprehensive mapping of tissue cell architecture via integrated single cell and spatial transcriptomics

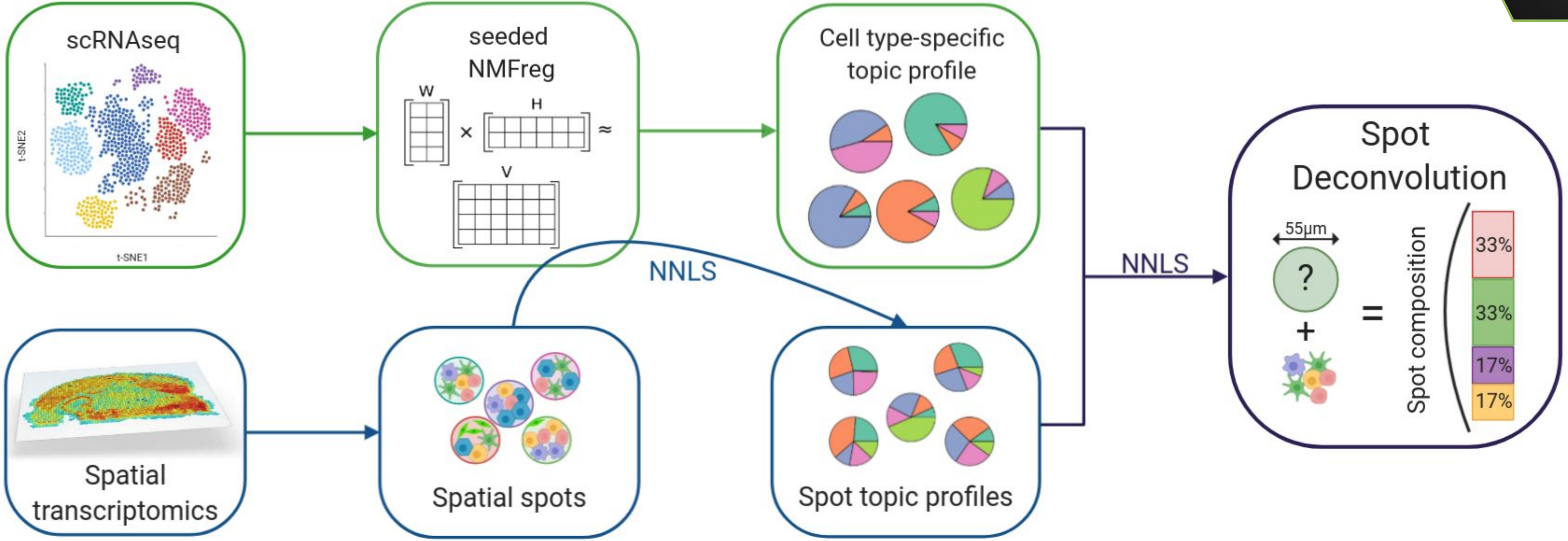
Vitalii Kleshchevnikov, Artem Shmatko, Emma Dann, Alexander Aivazidis, Hamish W King, Tong Li, Artem Lomakin, Veronika Kedlian, Mika Sarkin Jain, Jun Sung Park, Lauma Ramona, Elizabeth Tuck, Anna Arutyunyan, Roser Vento-Tormo, Moritz Gerstung, Louisa James, Oliver Stegle, Omer Ali Bayraktar



Single-cell and spatial transcriptomics enables probabilistic inference of cell type topography

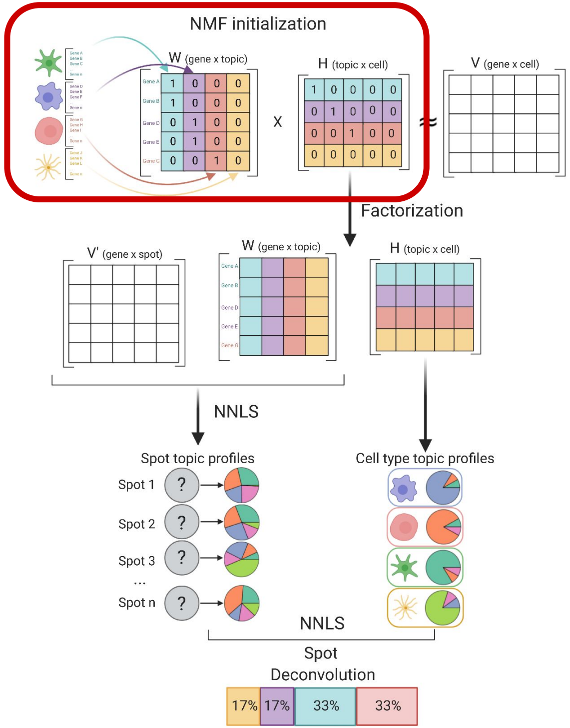
Alma Andersson, Joseph Bergenstråhle, Michaela Asp, Ludvig Bergenstråhle, Aleksandra Jurek, José Fernández Navarro & Joakim Lundeberg

SPOTlight

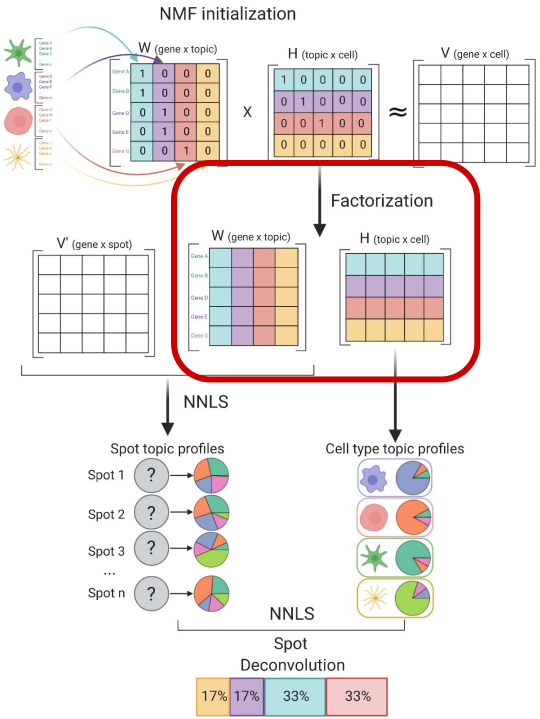

scRNAseq
t-SNE2
t-SNE1
seeded NMFreg
W
H
V
Cell type-specific topic profile
NNLS
Spot Deconvolution
55µm
?
Spot composition
33%
33%
17%
17%
Spatial transcriptomics
Spatial spots
Spot topic profiles
NNLS

SPOTlight

1st- Matrix initialization with marker genes.



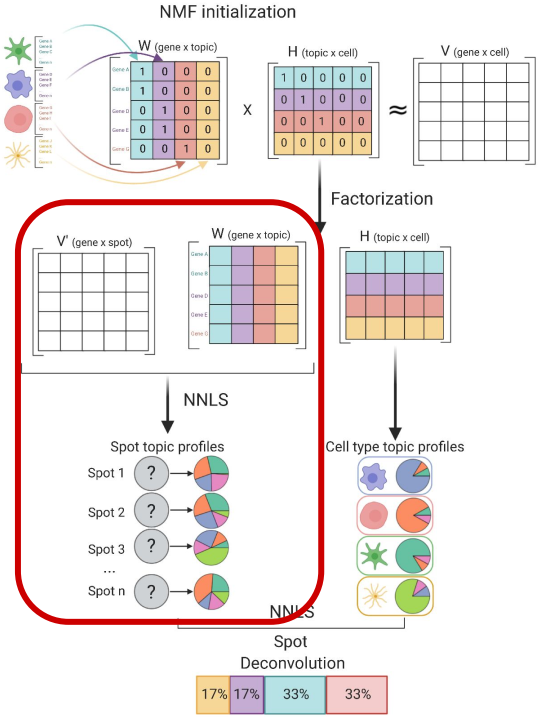
SPOTlight



$$
W = \begin{array}{c|cccc}
\text{Gene A} & 1 & 0 & 0 & 0 \\
\text{Gene B} & 1 & 0 & 0 & 0 \\
\text{Gene D} & 0 & 1 & 0 & 0 \\
\text{Gene E} & 0 & 1 & 0 & 0 \\
\text{Gene G} & 0 & 0 & 1 & 0
\end{array}
\quad \times \quad
H = \begin{pmatrix}
1 & 0 & 0 & 0 & 0 \\
0 & 1 & 0 & 0 & 0 \\
0 & 0 & 1 & 0 & 0 \\
0 & 0 & 0 & 0 & 0
\end{pmatrix}
\approx V
$$

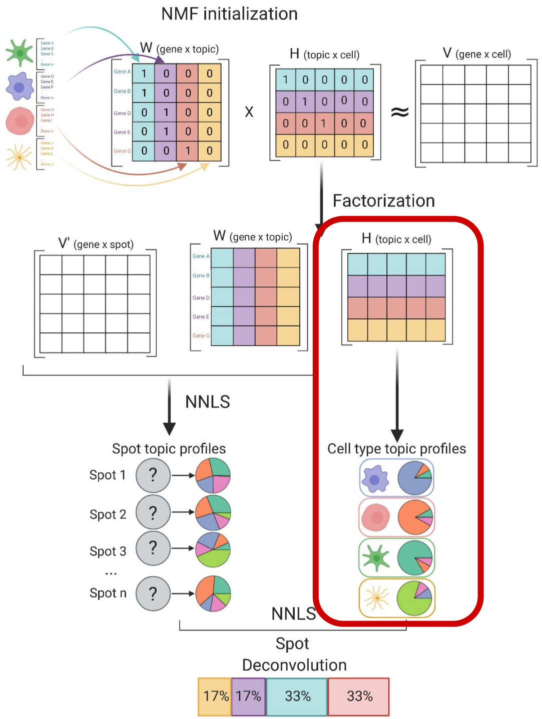
2nd- Non-negative Matrix Factorization

SPOTlight



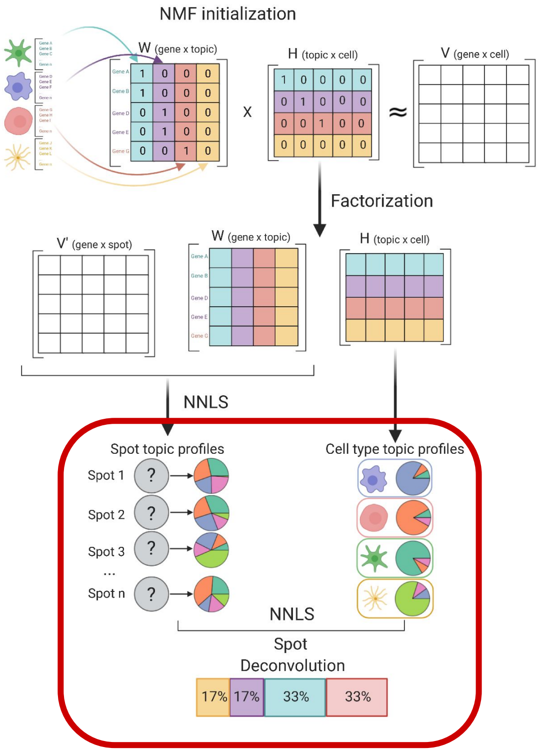
3rd- Non-negative least squares regression to obtain the spot's topic profile

SPOTlight



4th- Cell-type specific topic profiles

SPOTlight



5th- Non-negative least squares regression to deconvolute spots

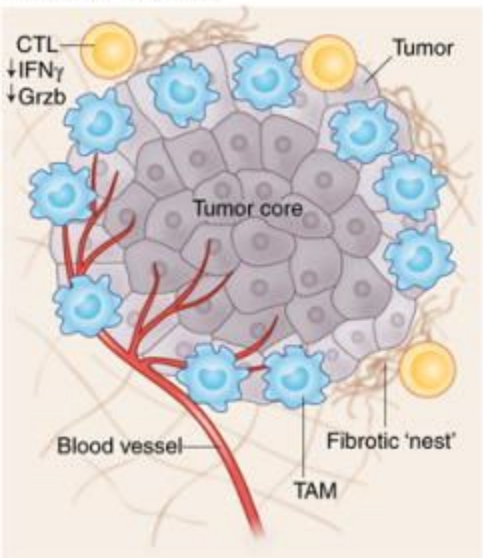
A practical example

A single-cell tumor immune atlas
for precision oncology

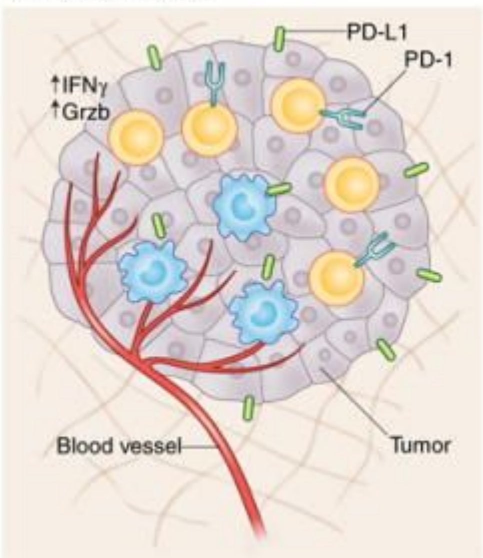
Cell Type Deconvolution & Tumor Immune Microenvironment

The TIME is defined as the ensemble of immune cells that surround and infiltrate a tumor, which can significantly change cancer behavior and conversely, are modulated by the tumor itself.

Tumor Immune Microenvironment



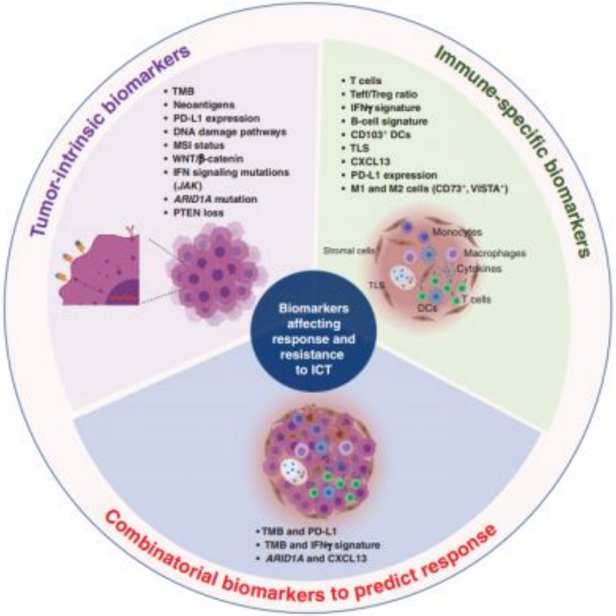
Cold tumor



Hot tumor

Binnewies M. et al. Nature Medicine 2018

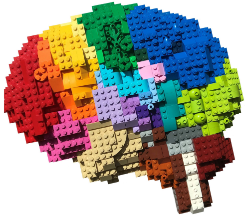
Tumor Immune Microenvironment



- Immune cells **affect and are affected** by the tumor
- The presence or absence of certain **cell populations** indicate **tumor response**
- **Biomarkers** for ICT prognosis and treatment response **lack precision**
- A **comprehensive compendium of cells in the TIME** is required to find predictive cellular states and their spatial localization

Sharma P. et al. Cancer Discovery 2021

How to study the TIME



Bulk RNA-seq

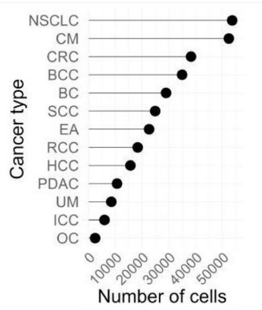
Single-cell RNA-seq

Spatial Transcriptomics

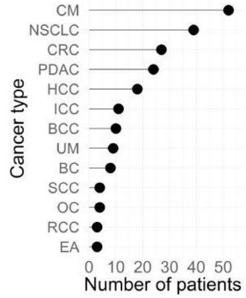
A Tumor Immune Cell Atlas

A single-cell tumor immune atlas for precision oncology

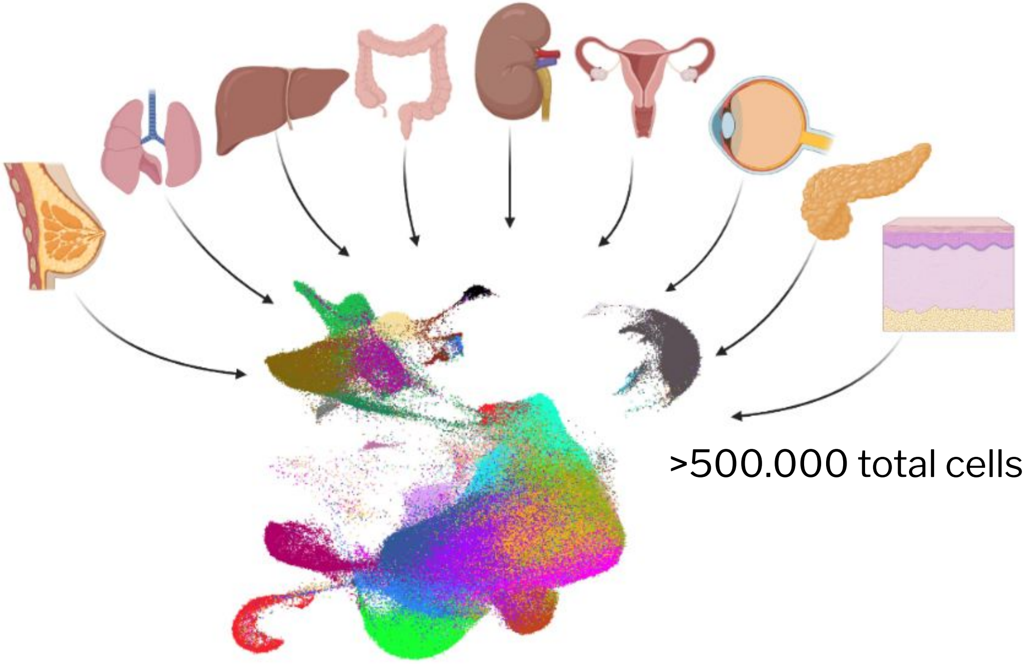
Paula Nieto,[1] Marc Elosua-Bayes,[1] Juan L. Trincado,[1] Domenica Marchese,[1] Ramon Massoni-Badosa,[1] Maria Salvany,[2] Ana Henriques,[2] Juan Nieto,[1] Sergio Aguilar-Fernández,[1] Elisabetta Mereu,[1] Catia Moutinho,[1] Sara Ruiz,[1] Patricia Lorden,[1] Vanessa T. Chin,[3,4,5] Dominik Kaczorowski,[3] Chia-Ling Chan,[3] Richard Gallagher,[5,6] Angela Chou,[7,8,9] Ester Planas-Rigol,[10] Carlota Rubio-Perez,[10] Ivo Gut,[1] Josep M. Piulats,[11] Joan Seoane,[10,12,13,14] Joseph E. Powell,[3,15] Eduard Batlle,[2,12,14] and Holger Heyn[1,16]



x13 Tumor types

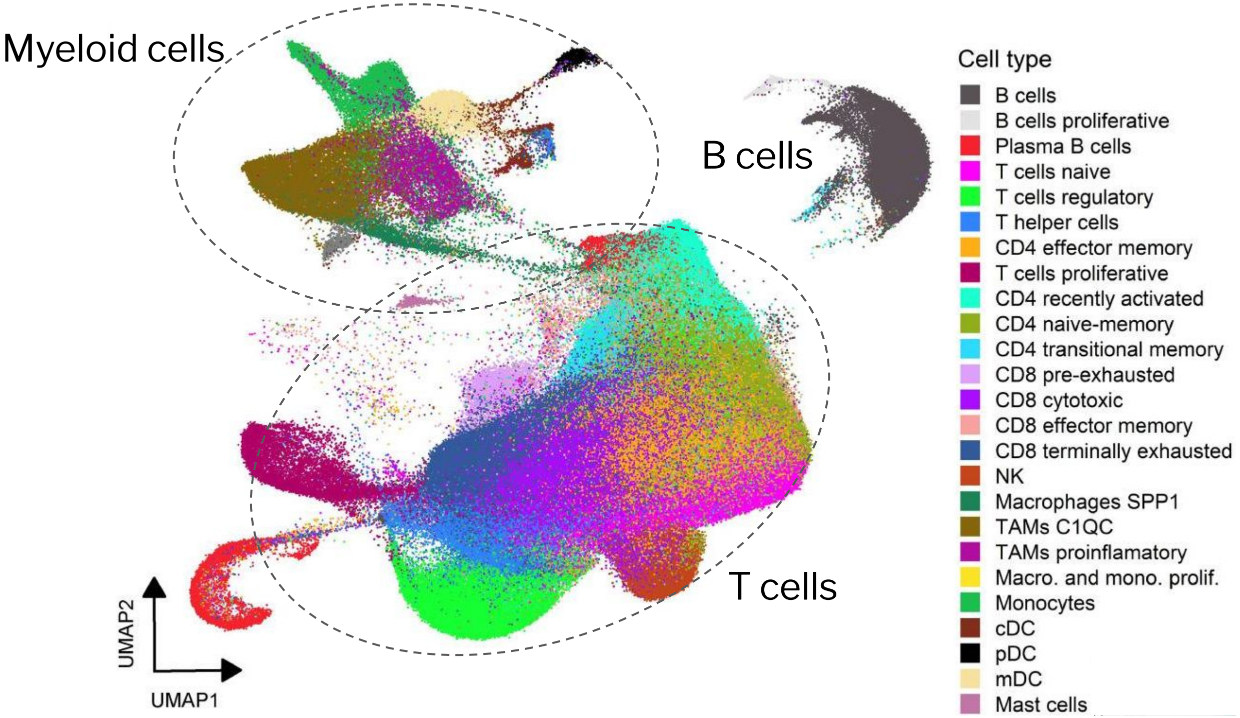


>217 Patients



>500.000 total cells

A Tumor Immune Cell Atlas

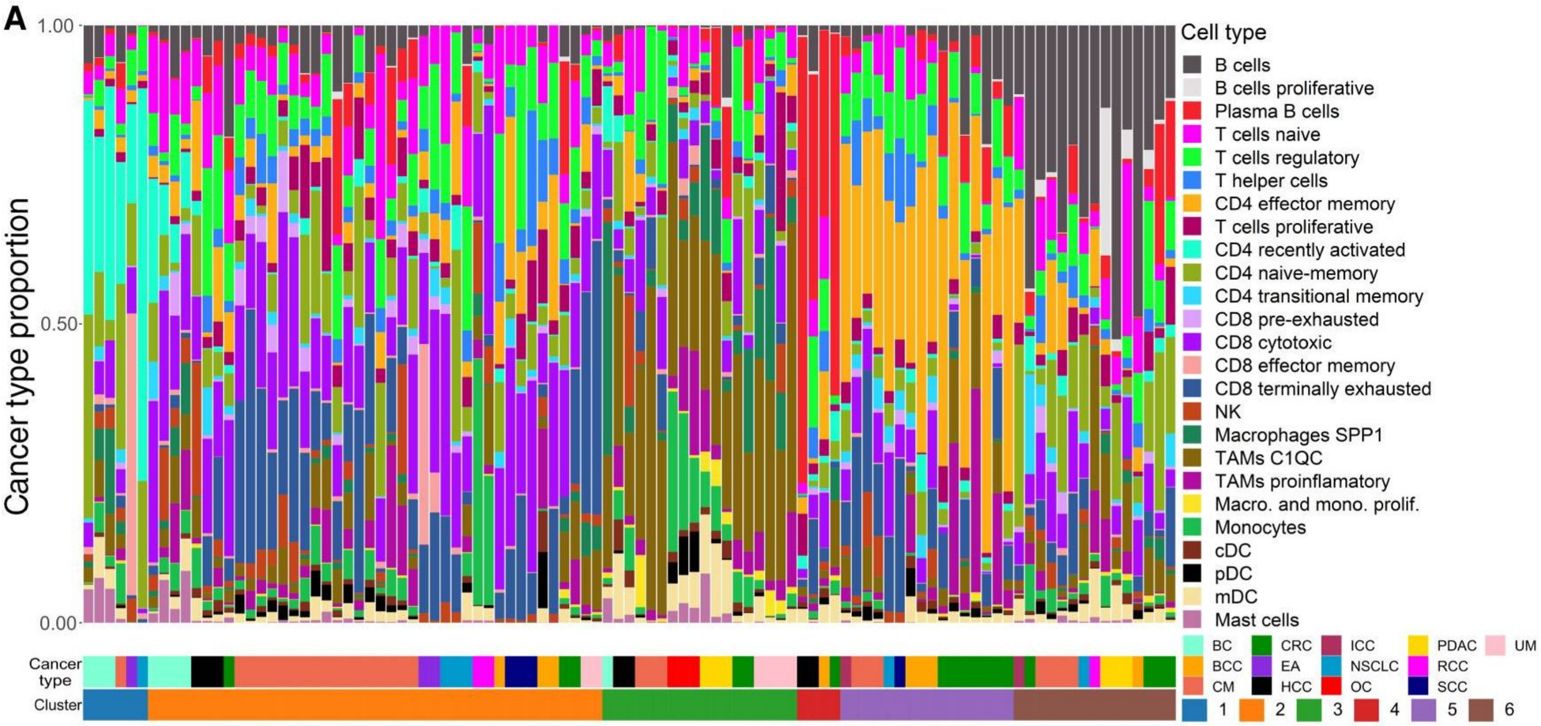


Myeloid cells

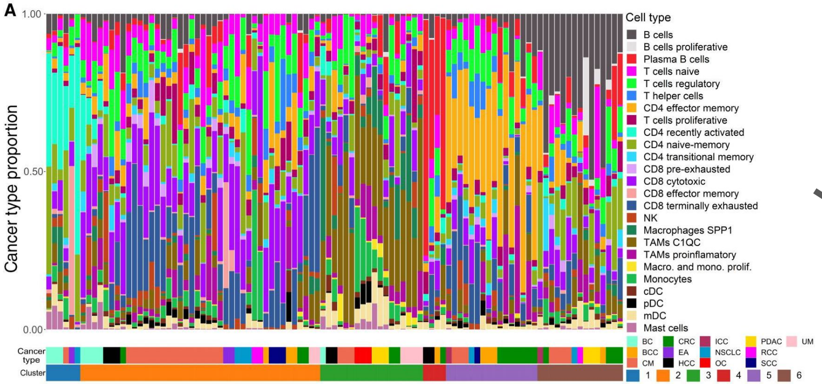
B cells

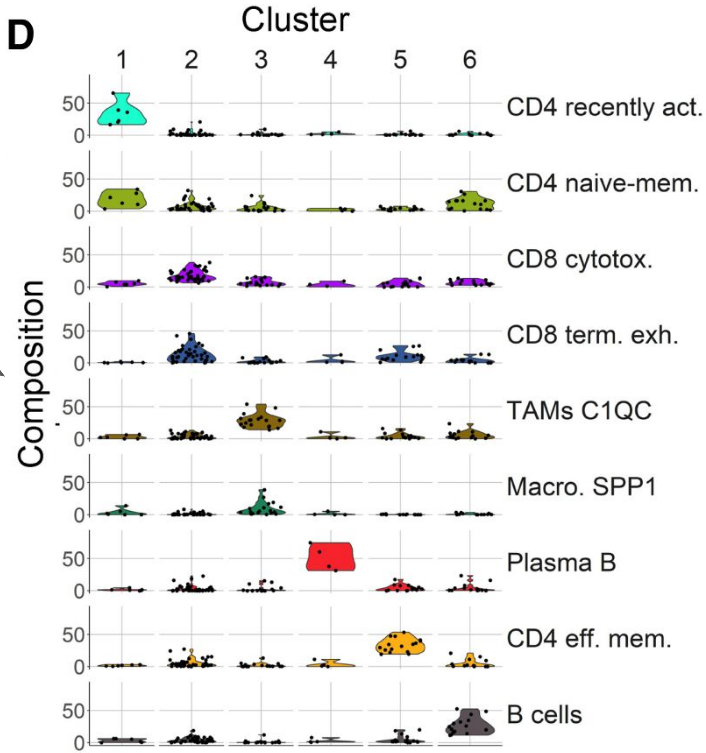
T cells

Tumor Immune Profiles

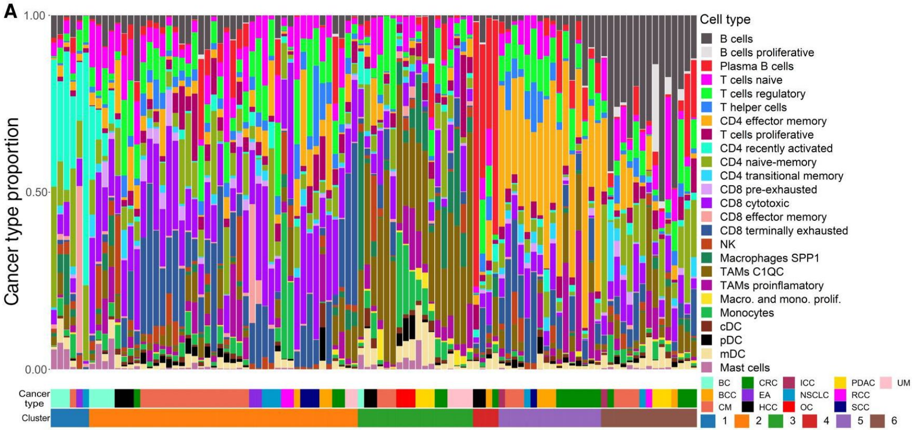


Tumor Immune Profiles



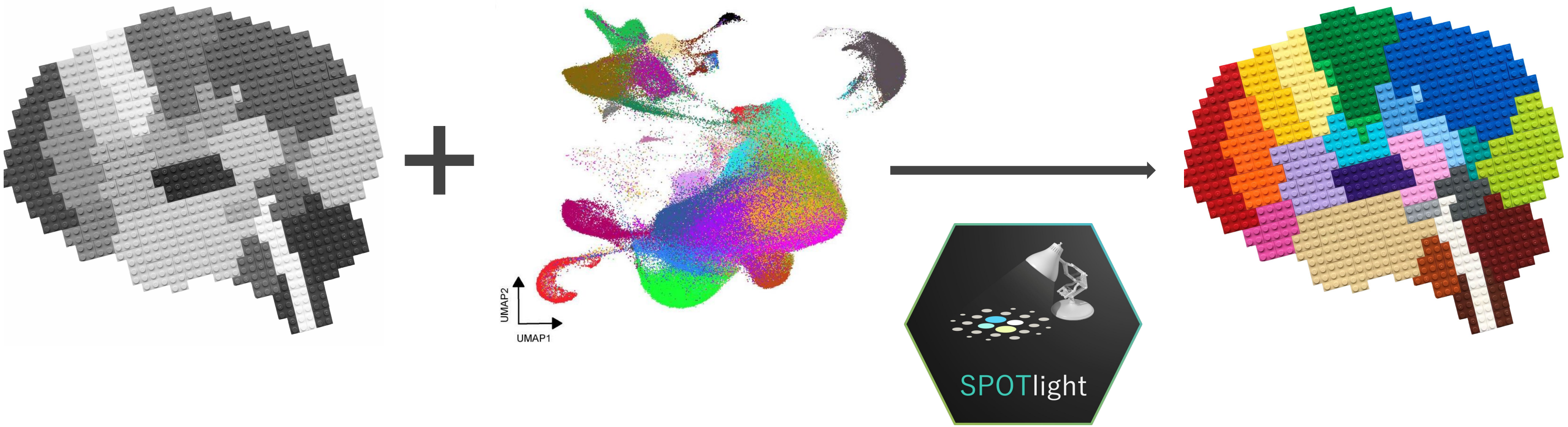


Immune profiles linked to ICT response



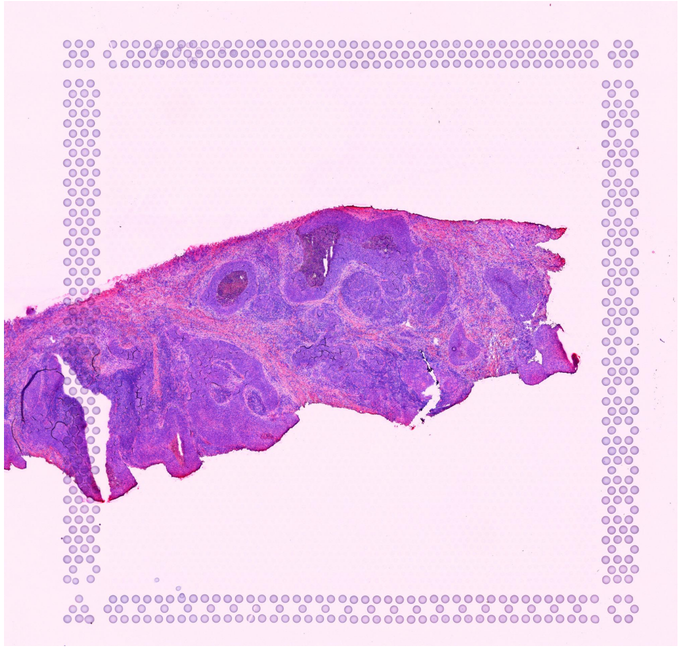
- Cluster 5 showed **exhaustion markers** on CD8 cells with levels of **LAG3, PDCD1, and CTLA4** target for ICT.
- Cluster 5 tumors may be **more susceptible to ICT treatment**.
- The presence of **specific immune cell** states (regulatory T cells or anti-inflammatory TAMs) is linked to **ICT efficacy**.
- Patient clusters could **differ in their response to ICTs**.

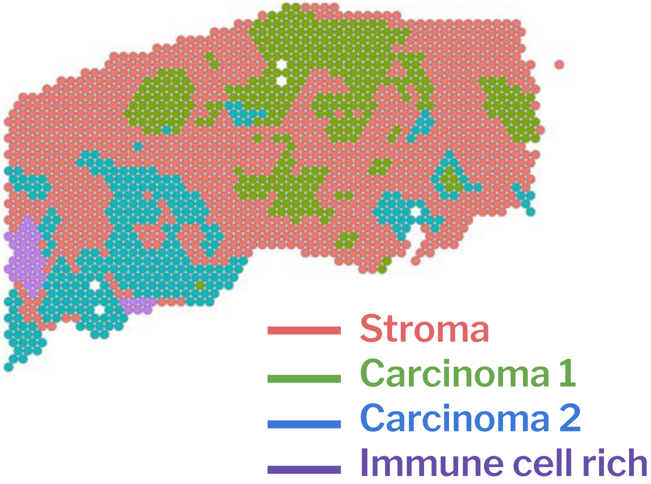
Spatial Mapping Of Immune Populations



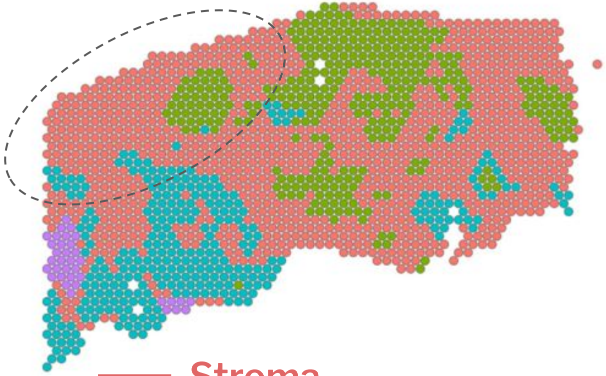
Elosua M. et al.
Nucleic Acids Research 2020

Oropharyngeal Carcinoma

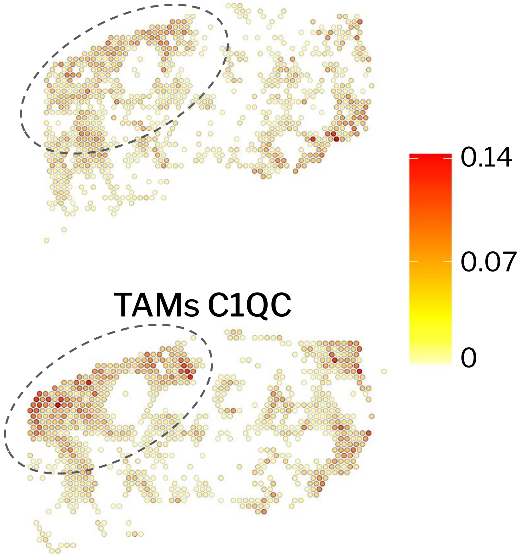




Oropharyngeal Carcinoma



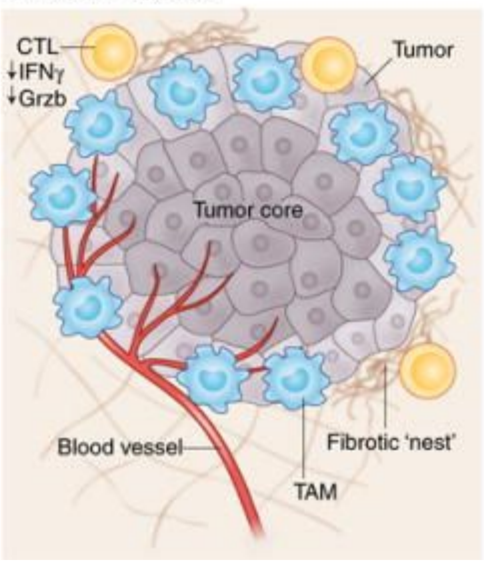
- Stroma
- Carcinoma 1
- Carcinoma 2
- Immune cell rich



CD8 terminally exhausted

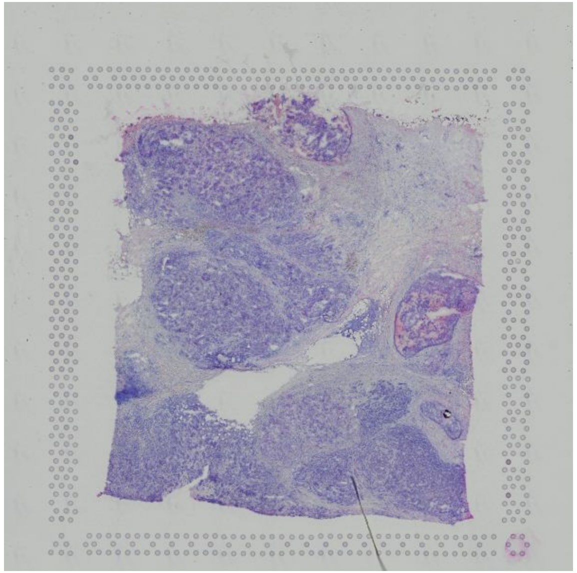
TAMs C1QC

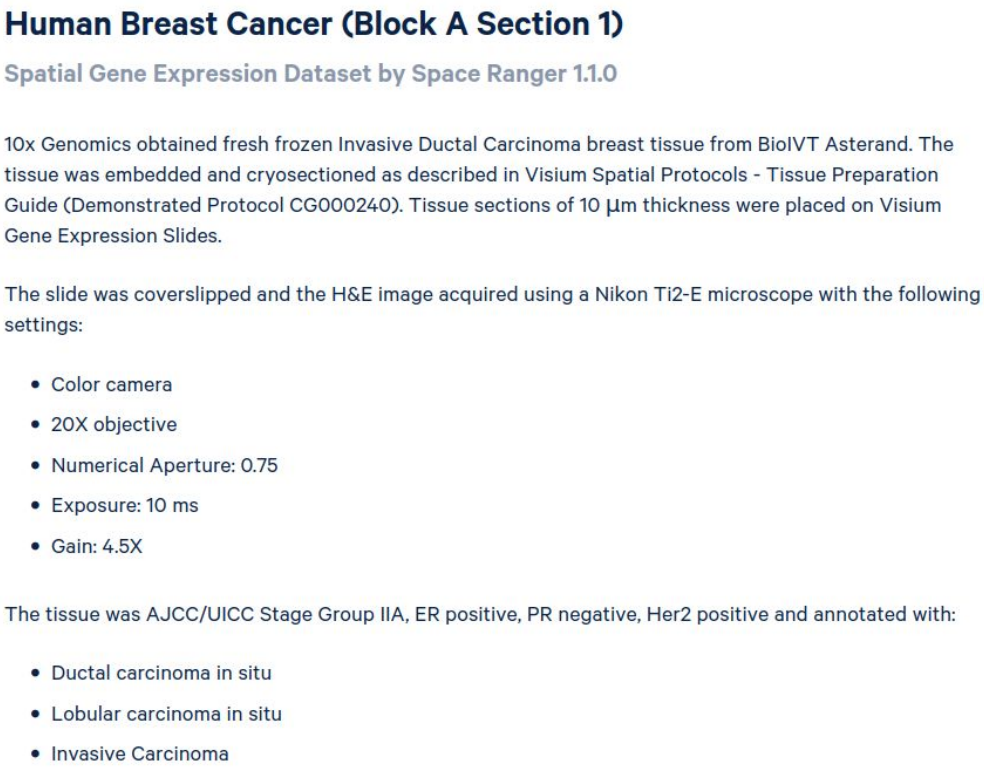
Cold tumor



Binnewies M. et al. Nature Medicine 2018

Breast Carcinoma





Human Breast Cancer (Block A Section 1)

Spatial Gene Expression Dataset by Space Ranger 1.1.0

10x Genomics obtained fresh frozen Invasive Ductal Carcinoma breast tissue from BioIVT Asterand. The tissue was embedded and cryosectioned as described in Visium Spatial Protocols - Tissue Preparation Guide (Demonstrated Protocol CG000240). Tissue sections of 10 µm thickness were placed on Visium Gene Expression Slides.

The slide was coverslipped and the H&E image acquired using a Nikon Ti2-E microscope with the following settings:

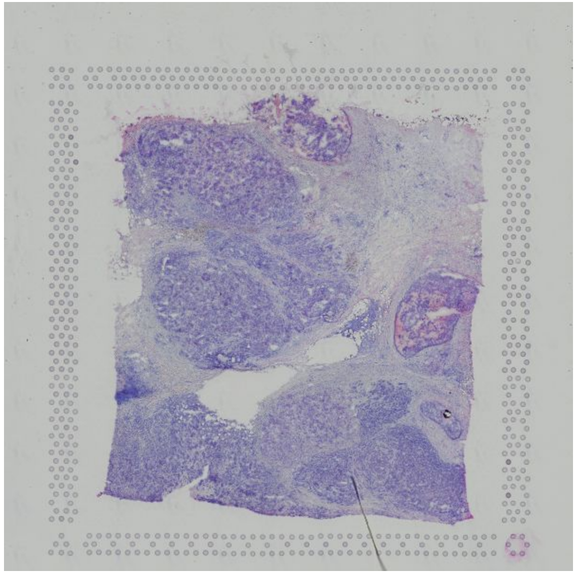
- Color camera
- 20X objective
- Numerical Aperture: 0.75
- Exposure: 10 ms
- Gain: 4.5X

The tissue was AJCC/UICC Stage Group IIA, ER positive, PR negative, Her2 positive and annotated with:

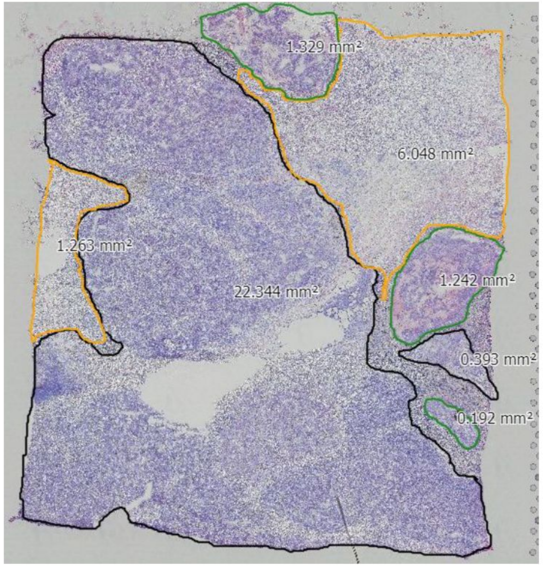
- Ductal carcinoma in situ
- Lobular carcinoma in situ
- Invasive Carcinoma

10X public dataset

Breast Carcinoma - Pathologist annotation

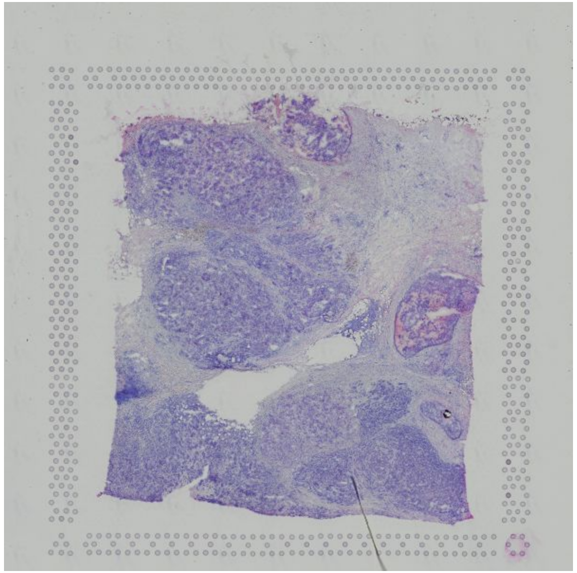


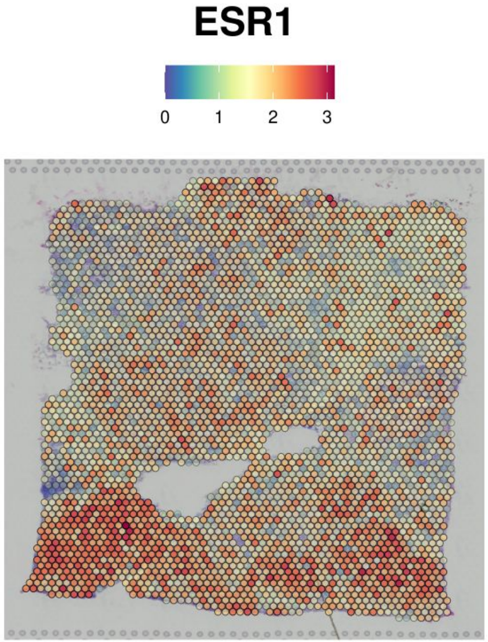
▬ Invasive carcinoma
🟧 Fibrous tissue
🟩 Ductal Cancer In Situ (DCIS)

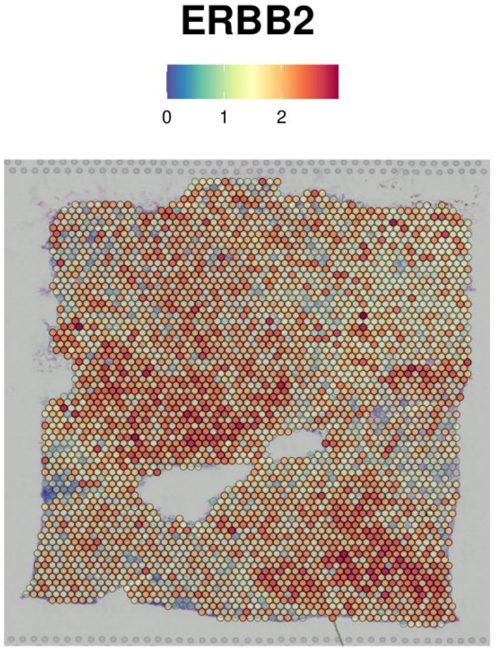


10X public dataset

Breast Carcinoma - Tissue Annotation

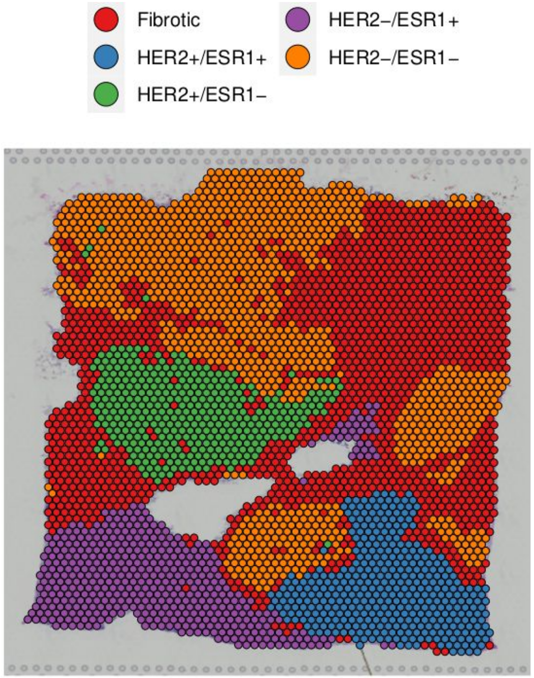


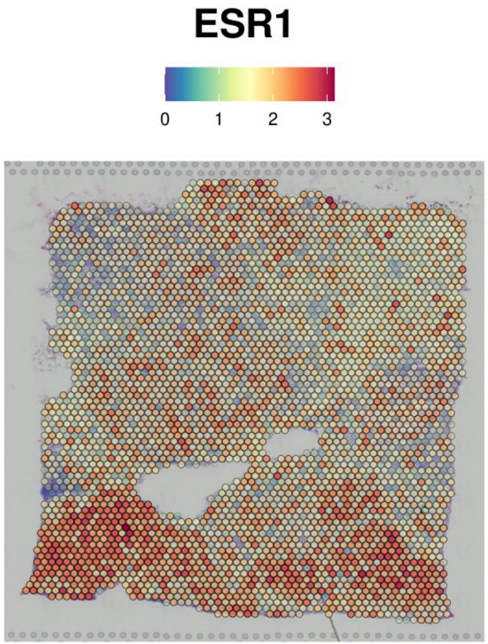


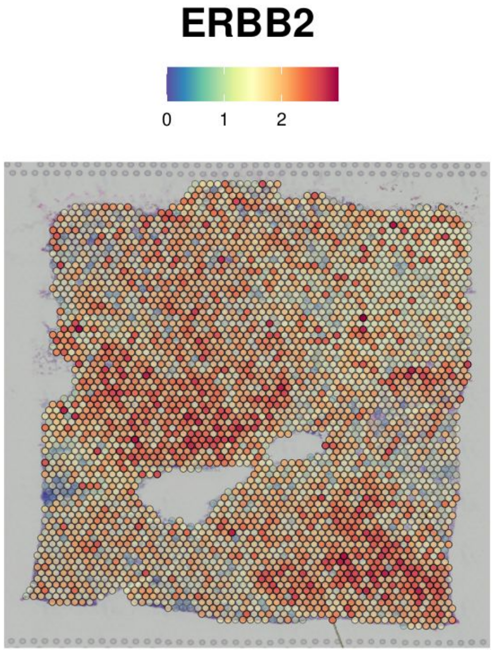


10X public dataset

Breast Carcinoma - Tissue Annotation

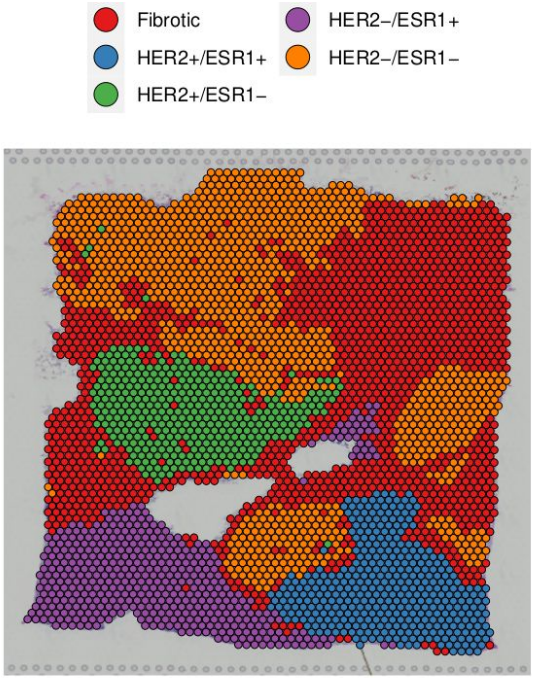


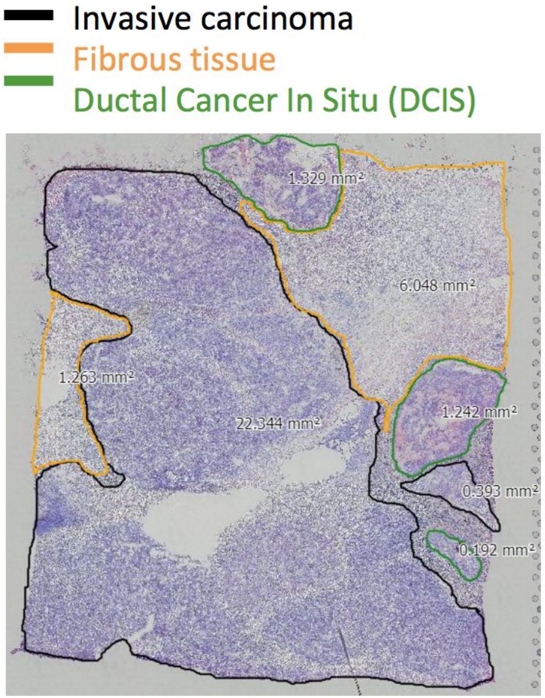

ESR1


ERBB2

10X public dataset

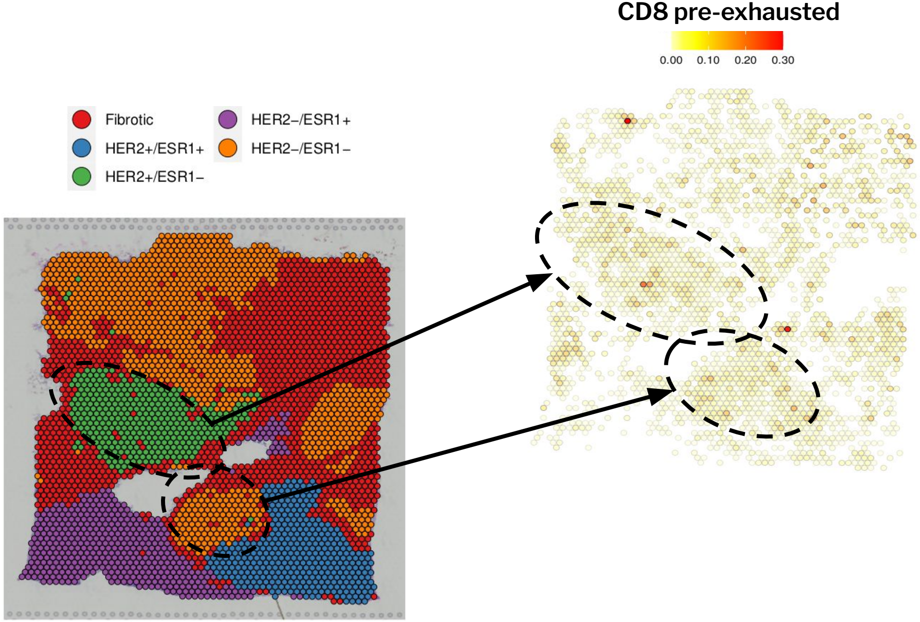
Breast Carcinoma - Tissue Annotation

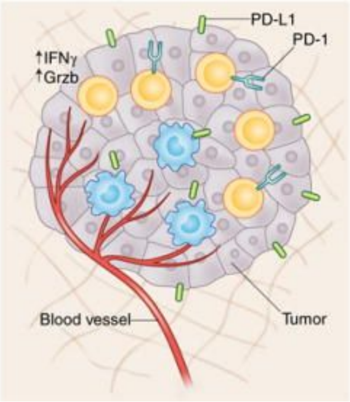




10X public dataset

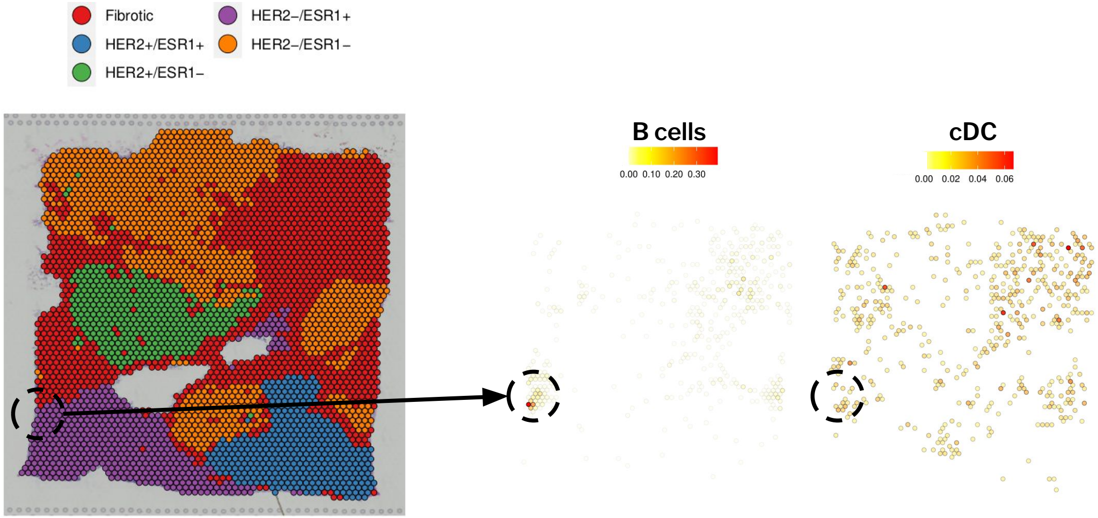
Cell type propotions from Paula



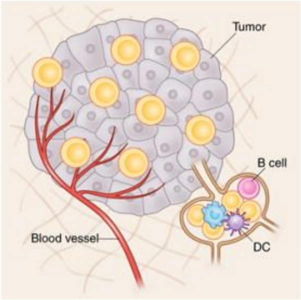


Binnewies M. et al.
Nature Medicine 2018

Cell type propotions from Paula



Tertiary Lymphoid structures



Binnewies M. et al.
Nature Medicine 2018

Take-home message

- We identified **25 immune populations** shared across patients and cancer types, for personalized medicine applications.
- Based on immune cell composition we grouped **patients into 6 different clusters**.
- This classification can be highly informative and clinically **predictive of patient survival and therapy response** and could be extended to additional cancer types and drive the design of clinical trials.
- By detecting **striking regional immune cell enrichments** in tumoral regions and adjacent areas, we foresee an application in digital pathology to guide immunotherapy decisions.
- In combination with **SPOTlight-based spatial mapping of ST data**, enables a harmonized assessment of tumor infiltrating immune cells, a first step toward an automated digital pathology framework.

Acknowledgements

CHAN ZUCKERBERG INITIATIVE

La Marató

erc

HUMAN CELL ATLAS

MARIE CURIE ACTIONS

Unión Europea

HORIZON 2020

Generalitat de Catalunya