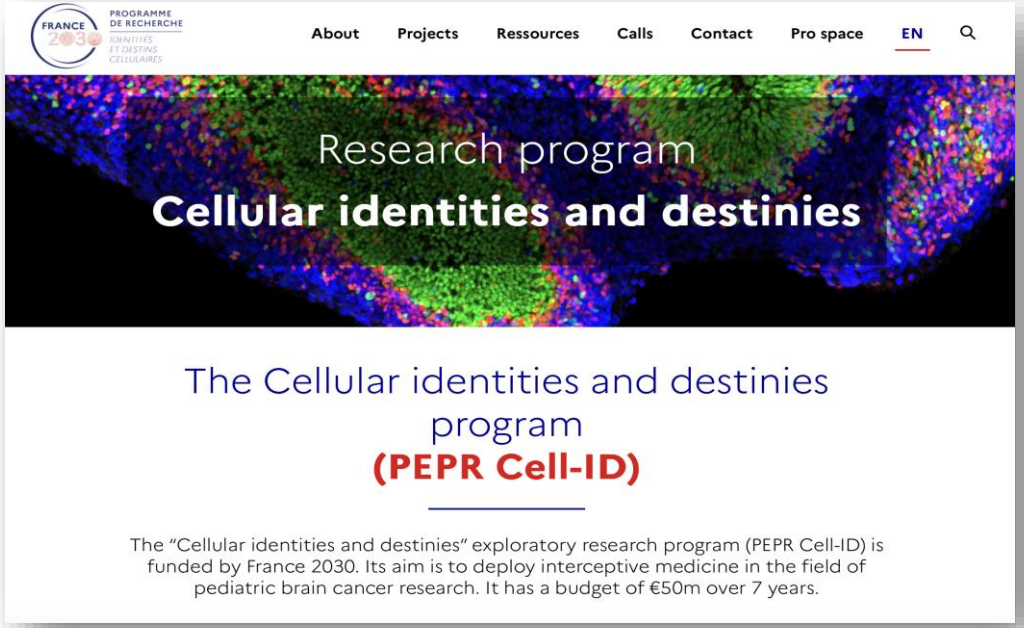
PEPR Cell-ID

CELL IDENTITIES AND DESTINIES



Website: https://www.pepr-cell-id.fr

PEPR Cell-ID - Intercepting disease by tracking Cell identities

Priority Research Programs and Equipment (PEPR)

Scientific Coordination: G. Almouzni (CNRS- Institut Curie)

Representative Leaders in scientific areas:

G. Cavalli (CNRS) M. Nollman (CNRS)	**Cell Context** Cells in space and time
S. Nedelec (Inserm) G. Legube (CNRS)	**Cell Exp** Dedicated experimental systems
T. Walter (Mines-Paris) D. Jost (CNRS)	**Data**Med Data analysis and AI
D. Castel (Inserm) L. Bally-Cuif (CNRS-Pasteur)	Data**Med** Towards disease interception
G. Almouzni (CNRS-Curie) S. Jarriault (CNRS)	**Cell Next** Training, career development & Cell-ID Innovation

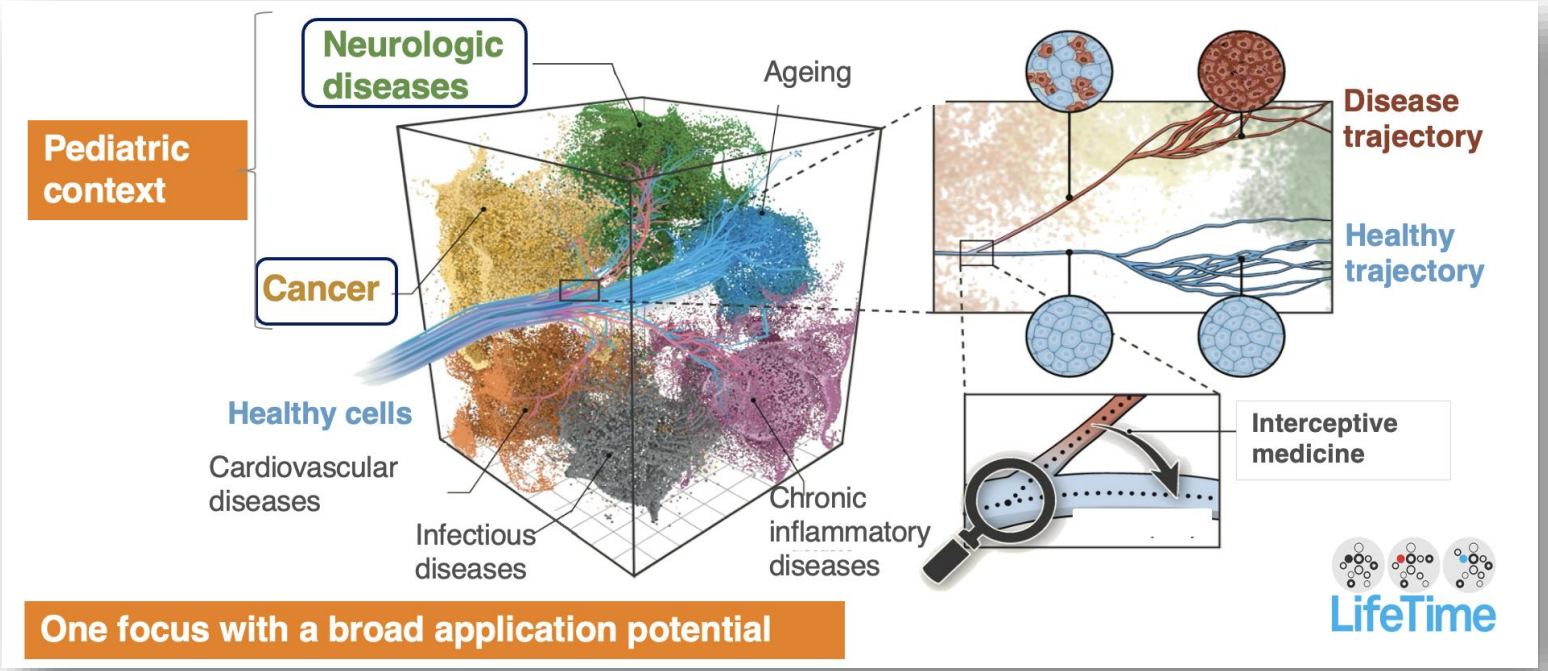
Pilot CNRS, co-pilot INSERM

Partner universities : Montpellier, Strasbourg, Paris Cité, PSL & Sorbonne, Toulouse Paul Sabatier

Partner institutions: Curie, Pasteur, CEA, Ecole des Mines, Gustave Roussy, IGBMC Strasbourg

The concept of cell-based disease interception

Rajewsky, N., Almouzni*, G. et al. LifeTime improving European healthcare through cell-based interceptive medicine. Nature (2020)

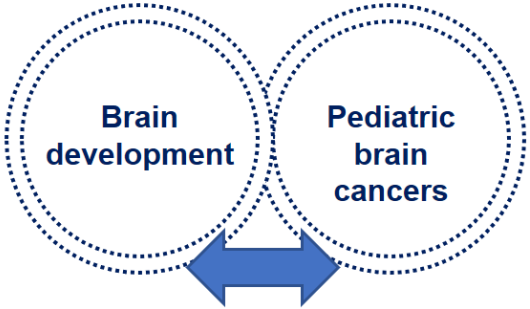


- ❑ Detect the earliest cellular and molecular signs of derailed cell fate (onset/ relapse)
- ❑ Improve diagnosis of onset, risk of progression or recurrence
- ❑ Earlier intervention

PEPR Cell-ID - Pediatric context

Brain development with a focus on pediatric brain cancers

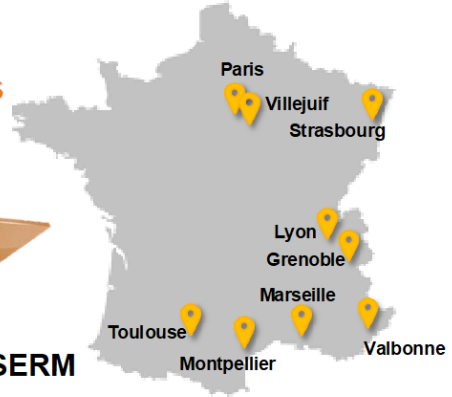
Cell-ID will jointly focus on:



- **A societal burden**
- **Emerging medical need identified* (France, EU)**
- **Disease origin in selected pediatric cancers:**
  - **Derailed cell trajectories** during development
  - **Ideal for cell-based interception of disease**

Urgent need for collaborative and interdisciplinary efforts in France

Assembling forces across France



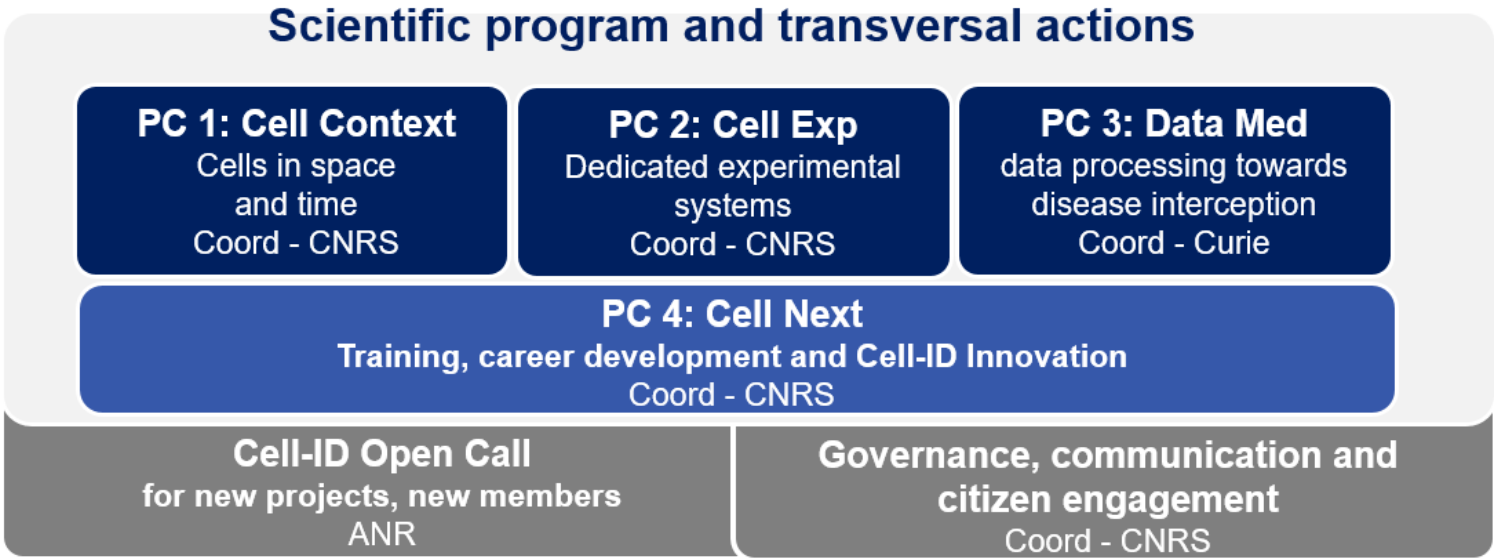
Pilot CNRS, co-pilot INSERM

Partner universities: Montpellier, Strasbourg, Paris Cité, PSL & Sorbonne, Toulouse Paul Sabatier

Partner institutes: Curie, Pasteur, CEA, Mines-PSL, Gustave Roussy, IGBMC Strasbourg

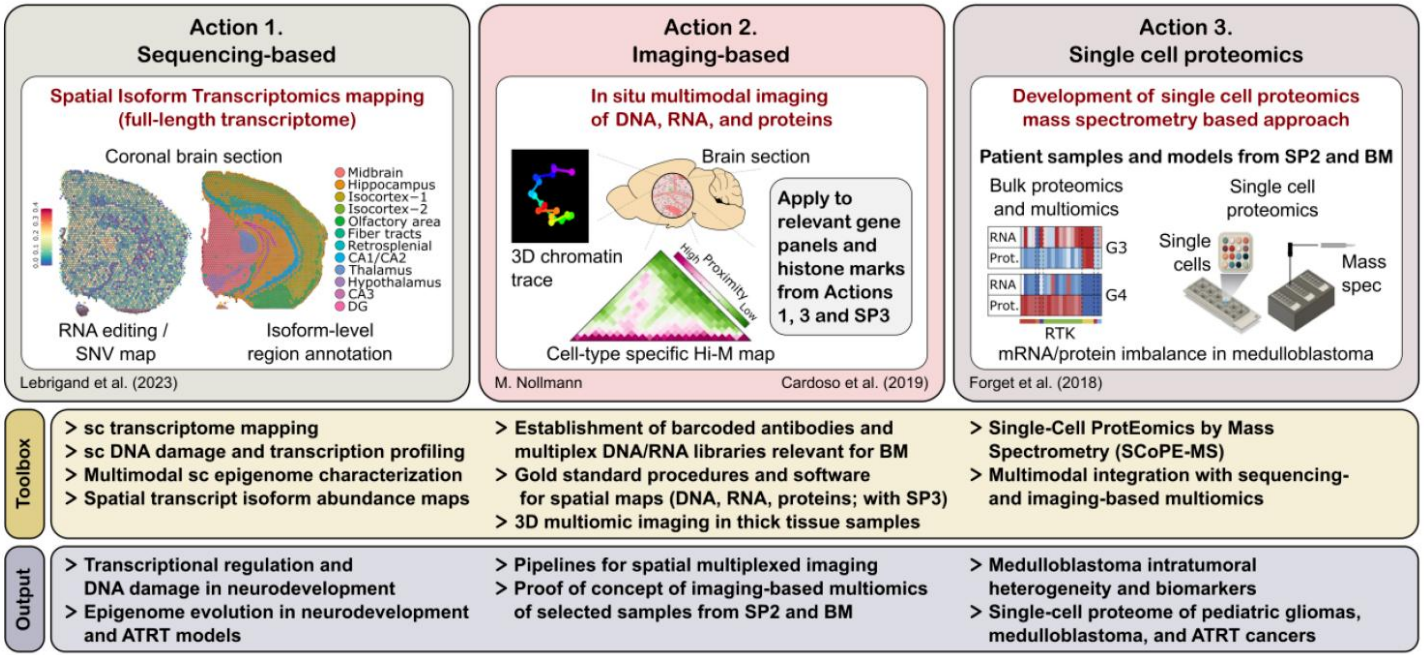
PEPR Cell-ID - Implementation and strategy

Targeted Projects (Projets Ciblés= PC), Open Calls, Governance and communication



PC1: Cell context

Methodological developments for others PC actions



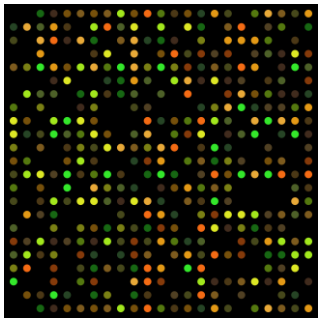
Spatial multi-omics in neurodevelopment and pediatric cancers: 1) development of sequencing-based single-cell multi-omics and spatial transcriptomic approaches with their application for multi-layer information on patient samples and models from SP2 and SP4, thanks to analysis and modeling by SP3; 2) imaging-based multi-omics to access single cell biology by simultaneously profiling chromatin architecture, gene expression, and cell history. Imaging multi-omics to focus on candidate RNAs, chromatin marks and proteins stemming from actions 1 and 3; 3) development of sc-Proteomics, a crucial missing brick to the “omics” toolset to identify changes in protein abundance/modifications and application to pediatric cancers.

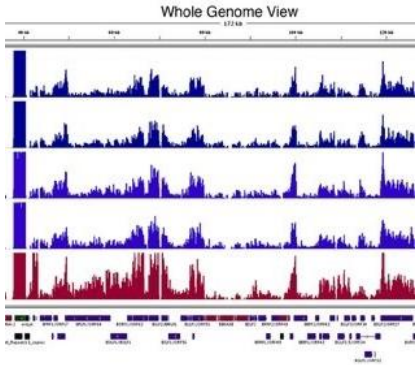
Single-cell and Spatial isoform Transcriptomics

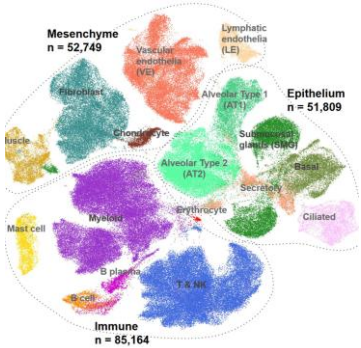
Kévin Lebrigand
Computational Biology and Omics Data Analysis
https://cobioda.github.io
IPMC, CNRS, Côte d'Azur University, France
lebrigand@ipmc.cnrs.fr
@kevinlebrigand

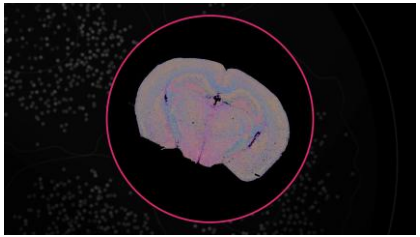
20 years of transcriptomics

Driven by microfluidics technological developments









Early 2000's: DNA microarray

- Large-scale transcriptome
- Oligonucleotide probe tilling
- Fluorochrome signal analysis
- Bulk resolution

Cost : 4k€
20 samples
25k genes
0,5M matrix

Late 2000's: RNA sequencing

- Whole transcriptome
- Next Generation Sequencing
- Full-transcript coverage
- Bulk resolution

Cost : 4k€
20 samples
50k genes
1M matrix

Mid 2010's: Single-cell

- Whole transcriptome
- Microfluidics + NGS
- 3p-end gene signal (UMI)
- Sensitivity (6%)
- Single-cell / state resolution

Cost : 4k€
5k cells
50k genes
250M matrix

2020's : Spatial

- Up to 5,000 genes
- Imaging analysis
- Multiplexing FiSH (single molecule)
- Sensitivity (30%)
- Sub-cellular resolution

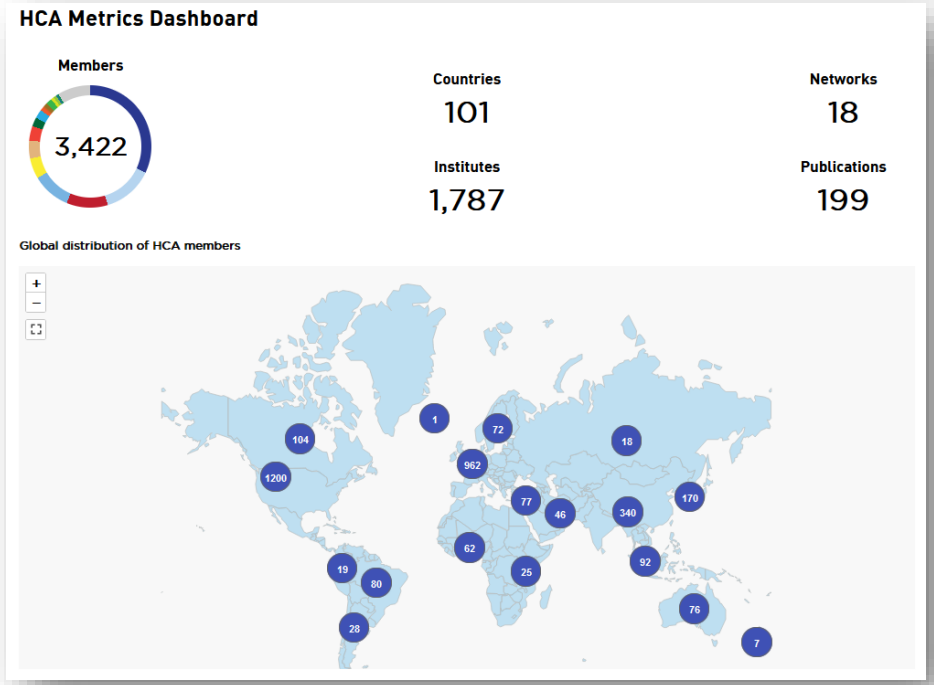
Cost : 4k€
250k cells
1k genes
250M matrix
+ Spatial dimension

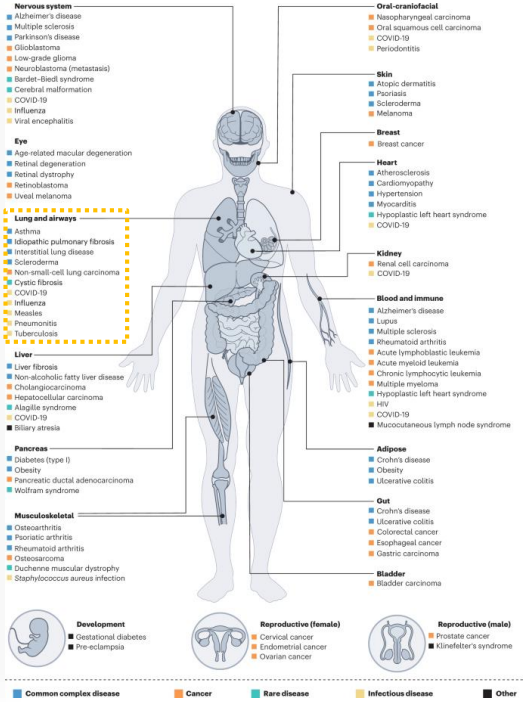
Human Cell Atlas (2016)

Pascal Barbry's lab

HUMAN CELL ATLAS

Mission to create comprehensive reference maps of all human cells, the fundamental units of life, as a basis for both understanding human health and diagnosing, monitoring, and treating disease.





Human Cell Atlas (2016)

Pascal Barbry's lab contribution

HUMAN CELL ATLAS

2019

TECHNIQUES AND RESOURCES | 23 OCTOBER 2019

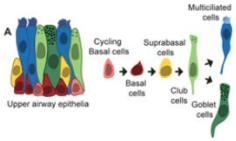
Novel dynamics of human mucociliary differentiation revealed by single-cell RNA sequencing of nasal epithelial cultures

In collection: Human development

Sandra Ruiz García, Marie Deprez, Kevin Lebrigand, Amélie Cavard, Agnès Paquet, Marie-Jeanne Arguel, Virginie Magnone, Marin Truchi, Ignacio Caballero, Sylvie Leroy, Charles-Hugo Marquette, Brice Marcet, Pascal Barbry , Laure-Emmanuelle Zaragosi

+ Author and article information

Development (2019) 146 (20): dev177428.



2019

Home > American Journal of Respiratory and Critical Care Medicine > List of Issues > Volume 202, Issue 12

A Single-Cell Atlas of the Human Healthy Airways

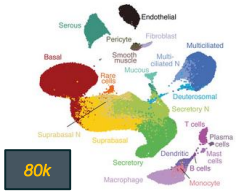
Marie Deprez, Laure-Emmanuelle Zaragosi, Marin Truchi, Christophe Becavin, Sandra Ruiz García, Marie-Jeanne Arguel, Magali Plaisant, Virginie Magnone, Kevin Lebrigand, Sophie Abelanet, Frédéric Brau, Agnès Paquet, Dana Pe'er, Charles-Hugo Marquette, Sylvie Leroy, and Pascal Barbry ... Show less

+ Author Affiliations

21125 215

https://doi.org/10.1164/rccm.201911-2199OC PubMed: 32726565

Received: November 15, 2019 Accepted: July 28, 2020



80k

2021

Analysis | Published: 02 March 2021

Single-cell meta-analysis of SARS-CoV-2 entry genes across tissues and demographics

Christoph Muus, Malte D. Luecken, Gökcen Eraslan, Lisa Sikkema, Avinash Waghray, Graham Heimberg, Yoshihiko Kobayashi, Eeshit Dhaval Vaishnav, Ayshwarya Subramanian, Christopher Smillie, Karthik A. Jagadeesh, Elizabeth Thu Duong, Evgenij Fiskin, Elena Torlai Triglia, Meshal Ansari, Peiwen Cai, Brian Lin, Justin Buchanan, Sijia Chen, Jian Shu, Adam L. Haber, Hattie Chung, Daniel T. Montoro, Taylor Adams, The NHLBI LungMap Consortium & The Human Cell Atlas Lung Biological Network

+ Show authors

Nature Medicine **27**, 546–559 (2021) | Cite this article

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2021

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Perspective | Published: 08 September 2021

A roadmap for the Human Developmental Cell Atlas

Muzlifah Haniffa, Deanne Taylor, Sten Linnarsson, Bruce J. Aronow, Gary D. Bader, Roger A. Barker, Pablo G. Camara, J. Gray Camp, Alain Chédotal, Andrew Copp, Heather C. Etchevers, Paolo Giacobini, Berthold Göttgens, Guoji Guo, Ania Hupalowska, Kylie R. James, Emily Kirby, Arnold Kriegstein, Joakim Lundeberg, John C. Marioni, Kerstin B. Meyer, Kathy K. Niakan, Mats Nilsson, Bayanne Olabi, Human Cell Atlas Developmental Biological Network

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Nature **597**, 196–205 (2021) | Cite this article

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2022

The discovAIR project: a roadmap towards the Human Lung Cell Atlas

Malte D. Luecken, Laure-Emmanuelle Zaragosi, Elo Madissoon, Lisa Sikkema, Alexandra B. Firsova, Elena De Domenico, Louis Kümmerle, Adem Saglam, Marijn Berg, Aurore C.A. Gay, Janine Schniering, Christoph H. Mayr, Xesús M. Abalo, Ludvig Larsson, Alexandros Sountoulidis, Sarah A. Teichmann, Karen van Eunen, Gerard H. Koppelman, Kourosh Saeb-Parsy, Sylvie Leroy, Pippa Powell, Ugis Sarkans, Wim Timens, Joakim Lundeberg, Maarten van den Berge, Mats Nilsson, Peter Horváth, Jessica Denning, Irene Papatheodorou, Joachim L. Schultze, Herbert B. Schiller, Pascal Barbry, Ilya Petoukhov, Alexander V. Misharin, Ian M. Adcock, Michael von Papen, Fabian J. Theis, Christos Samakovlis, Kerstin B. Meyer and Martijn C. Nawijn

500k

2023

nature medicine

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Resource | Open access | Published: 08 June 2023

An integrated cell atlas of the lung in health and disease

Lisa Sikkema, Ciro Ramírez-Suástegui, Daniel C. Strobl, Tessa E. Gillett, Luke Zappia, Elo Madissoon, Nikolay S. Markov, Laure-Emmanuelle Zaragosi, Yuge Ji, Meshal Ansari, Marie-Jeanne Arguel, Leonie Apperloo, Martin Banchero, Christophe Bécavin, Marijn Berg, Evgeny Chichelnitskiy, Mei-i Chung, Antoine Collin, Aurore C. A. Gay, Janine Gote-Schniering, Baharak Hooshiar Kashani, Kemal Inecik, Manu Jain, Theodore S. Kapellos, Lung Biological Network Consortium, ... Fabian J. Theis

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Nature Medicine **29**, 1563–1577 (2023) | Cite this article

72k Accesses | **59** Citations | **379** Altmetric | Metrics

2,4M

2020

10x GENOMICS

High throughput error corrected Nanopore single cell transcriptome sequencing

Kevin Lebrigand, Virginie Magnone, Pascal Barbry & Rainer Waldmann

Nature Communications **11**, Article number: 4025 (2020) | Cite this article

36k Accesses | **83** Citations | **67** Altmetric | Metrics

Oxford NANOPORE Technologies

2023

The spatial landscape of gene expression isoforms in tissue sections

Kevin Lebrigand, Joseph Bergenstråhle, Kim Thrane, Annelie Mollbrink, Konstantinos Meletis, Pascal Barbry , Rainer Waldmann, Joakim Lundeberg

Author Notes

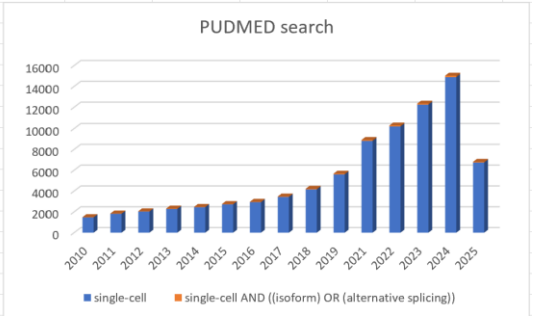
10x GENOMICS

Nucleic Acids Research, Volume 51, Issue 8, 8 May 2023, Page e47, https://doi.org/10.1093/

A single-cell gene-level era

- mRNA is the proxy to explore gene expression and real-time cell activity
- Over 90% of genes generate multiple isoforms, shaping protein diversity and function
- Isoform-specific roles are increasingly recognized in developmental and pathological processes
- But ~99% of single-cell studies still focus only on the gene level

	single-cell	single-cell AND ((isoform) OR (alternative splicing))	%age
2010	1472	23	1,56
2011	1816	27	1,49
2012	2031	28	1,38
2013	2279	38	1,67
2014	2451	27	1,10
2015	2719	34	1,25
2016	2932	37	1,26
2017	3433	47	1,37
2018	4157	65	1,56
2019	5598	75	1,34
2021	8813	95	1,08
2022	10202	97	0,95
2023	12244	104	0,85
2024	14887	144	0,97
2025	6743	65	0,96



Our work focuses on accessing isoforms to enable a more precise transcriptome characterization

Isoform-centric therapeutics

Act on gene isoforms expression balance

Review Article | Published: 04 September 2024

Protein isoform-centric therapeutics: expanding targets and increasing specificity

Peter Kjer-Hansen, Tri Giang Phan & Robert J. Weatheritt

Nature Reviews Drug Discovery **23**, 759–779 (2024) | Cite this article

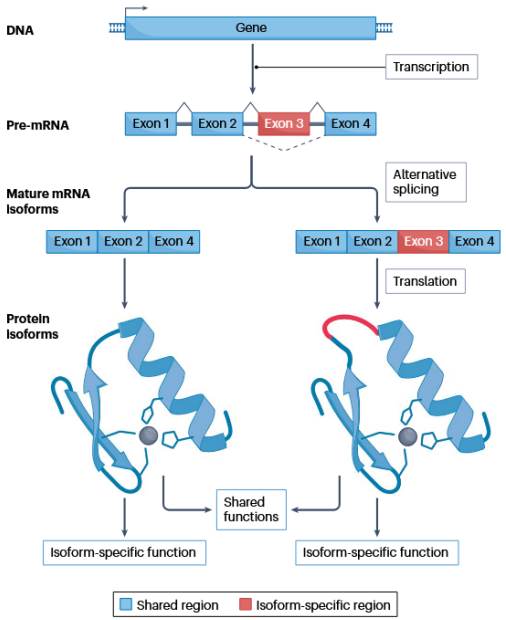


Table 1 | Examples of protein isoform switching therapies in preclinical studies

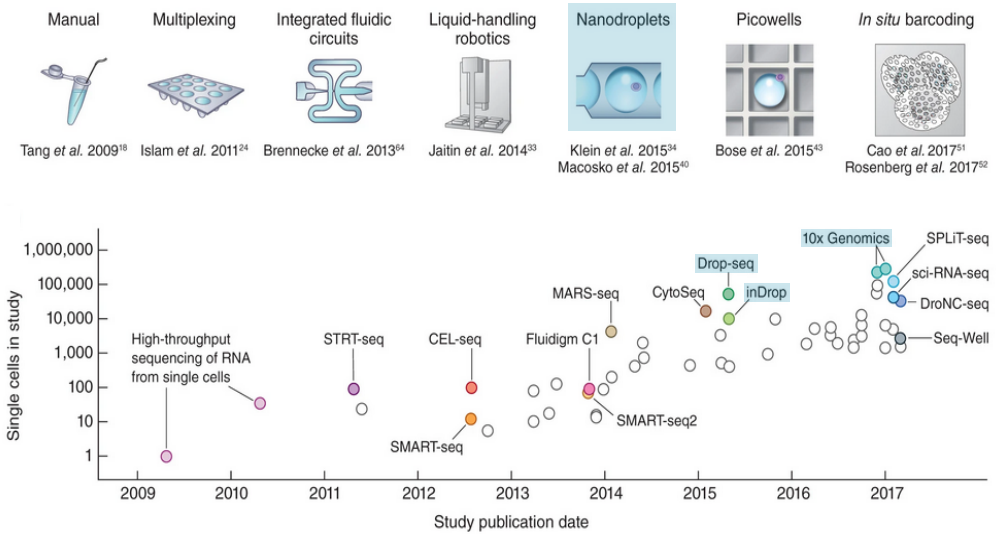
Disease	Gene	Isoform endogenous or disease specific	Treatment strategy	Aim	Refs.
Hutchinson–Gilford progeria syndrome	*LMNA*	Disease specific	ASO	Favour production of lamin C isoform over disease-causing progerin isoform	43,44, 46–48
			CRISPR–Cas9 nuclease	Remove region in *LMNA* gene that encodes a cryptic exon that gives rise to disease-causing progerin	178
			Base editing	Correct substitution in *LMNA* gene that creates cryptic splice site, resulting in disease-causing progerin	36,179
Collagen VI-related dystrophy	*COL6A1*	Disease specific	ASO	Block cryptic splice site in *COL6A1* that results in disease-causing dominant negative COL6A1 isoforms	32,180
Timothy syndrome type 1	*CACNA1C*	Endogenous	ASO	Favour usage of exon 8 over exon 8a (mutually exclusive exons) as exon 8a contains pathogenic mutations	33
Alzheimer disease	*LRRP8* (ApoER2)	Endogenous	ASO	Favour inclusion of exon 19 in ApoER2 to improve synaptic function, memory and learning	52
	APP	Artificial	ASO	Favour skipping of exon 17 in *APP*, thereby removing the γ-secretase cleavage site, to reduce formation of substrate for senile plaque formation	181
Tauopathies with 3R tau overabundance	*MAPT* (tau)	Endogenous	Trans-splicing (SMaRT)	Favour production of 4R tau isoforms	38,182,183
Tauopathies with 4R tau overabundance		Endogenous	ASO	Favour production of 3R tau by promoting exon 10 skipping	184
Neuropathic pain	*NRCAM*	Endogenous	ASO	Favour production of NRCAM isoforms without exon 10	185
Inflammation	*TNFRSF1B* (TNFR2)	Endogenous	ASO	Favour production of secreted TNFR2 to serve as a decoy receptor that alleviates inflammation*	186
	IL6ST (GP130)	Endogenous	ASO	Favour production of secreted GP130 isoforms that serve as decoy receptors to reduce pro-inflammatory IL-6 trans-signalling	34
Allergy	*MS4A2*	Endogenous	ASO	Favour skipping of exon 3 in MS4A2 to produce intracellular receptor isoform, which reduces mast cell sensitivity to IgE	35
Cancer	*BCL2L1* (BCL-X)	Endogenous	ASO	Favour production of pro-apoptotic BCL-X_S over anti-apoptotic BCL-X_L to promote tumour cell death	55–57
			Small molecule	Favour production of pro-apoptotic BCL-X_S over anti-apoptotic BCL-X_L to promote tumour cell death	37
	BCL2L11 (BIM)	Endogenous	ASO	Favour inclusion of exon 4 over exon 3 in BCL-2L11 to re-sensitize cancer cell lines to imatinib	187
	AR	Disease specific	ASO	Prevent formation of androgen receptor isoforms that contribute to anti-androgen therapy in castration-resistant prostate cancer	188
	MKNK2	Endogenous	ASO	Favour production of tumour-suppressive MNK2a over pro-oncogenic MNK2b to promote tumour cell death	53
	PKM	Endogenous	ASO	Favour production of PKM1 over PKM2 to alter kinase activity and glucose metabolism to promote tumour cell death	189
	PDCD1	Endogenous	ASO	Favour production of secreted PD1 isoform, which is suggested to enhance immune-mediated killing of tumour cells	190
	RAP1GDS1	Endogenous	ASO	Favour production of specific RAP1GDS1 isoforms to disrupt isoform ratios, thereby suppressing prenylation of small GTPases to promote tumour cell death	54
	STAT3	Endogenous	ASO	Favour production of pro-apoptotic STAT3β over STAT3α to promote tumour cell death	191
	ERBB4 (HER4)	Endogenous	ASO	Favour production of HER4 CYT2 isoforms over CYT1 to promote tumour cell death	192
	SLAMF6	Endogenous	ASO	Favour production of specific SLAMF6 isoform to promote T cell activation and antitumour activity	193
	INSR	Endogenous	ASO	Favour production of insulin receptor B over insulin receptor A to promote tumour cell death	194
	PLEC	Endogenous	ASO	Favour production of PLEC isoforms lacking exon 31 to promote tumour cell death	195
	ARHGAP17	Endogenous	ASO	Favour production of ARHGAP17 lacking poly(C) exon to promote tumour cell death	196

ASO, antisense oligonucleotide; SMaRT, spliceosome-mediated RNA trans-splicing. *It is debated whether secreted TNFR2 functions as a decoy receptor that effectively removes TNF or stabilizes TNF and thereby worsens inflammation[191].

Single-cell transcriptomics

Droplet-based approaches

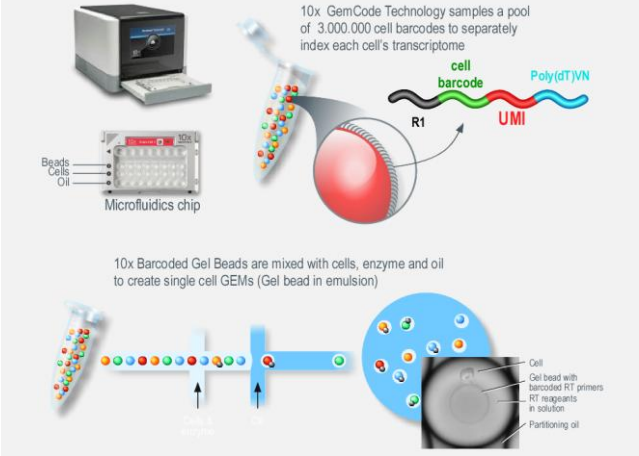
InDrop, Klein et al, 2015
Drop-seq, Macosko et al, 2015
10x Genomics, Zheng et al, 2016

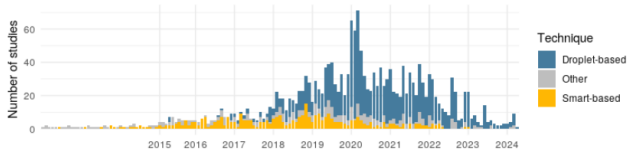


Exponential scaling of single-cell RNA-seq in the past decade
Svensson et al., *Nature Protocols*, 2018

10x Genomics Chromium single cell controller (2016)

- Easy-to-set-up and robust workflow
- Generalize UMI usage
- Shows high scalability (1,3M cells dataset)



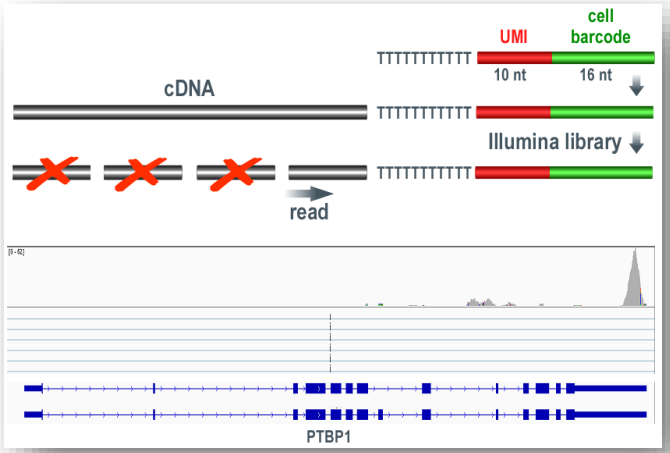


A curated database reveals trends in single cell transcriptomics, Svensson et al., Database , 2020

Long-read transcriptomics reveals diversity

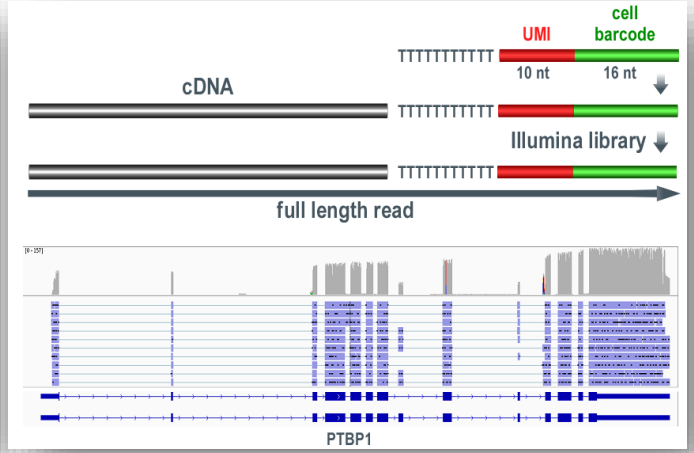
Droplets-based approach short reads vs long reads

Standard short-read sequencing



Gene-level matrix

Long-read full-length sequencing



Isoform-level matrix

Information on alternative splicing, fusion transcripts, SNV, editing, imprinting, allelic imbalance

Is lost

Remain accessible

Single-cell long-read isoform profiling

Lebrigand et al. 2020

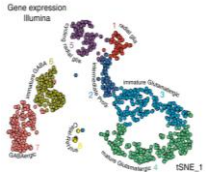
High throughput error corrected Nanopore single cell transcriptome sequencing

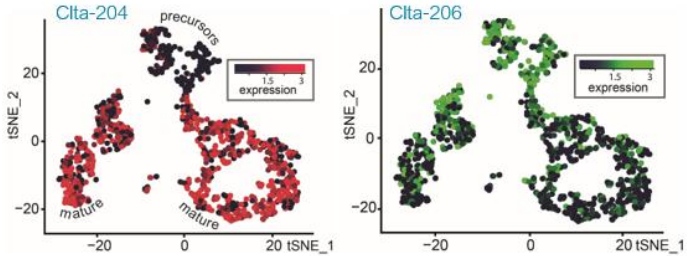
Kevin Lebrigand, Virginie Magnone, Pascal Barbry & Rainer Waldmann

Nature Communications **11**, Article number: 4025 (2020) | Cite this article

20k Accesses | **38** Citations | **58** Altmetric | Metrics

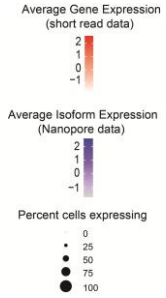
E18 Mouse brain

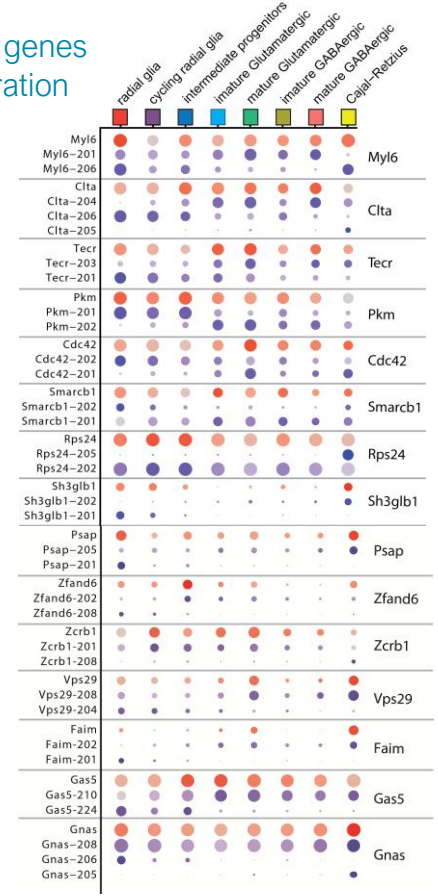




https://github.com/ucagenomix/sicelore-2.1

76 isoform-switching genes along neuronal maturation





Spatial long-read isoform profiling

Lebrigand et al. 2023

The spatial landscape of gene expression isoforms in tissue sections

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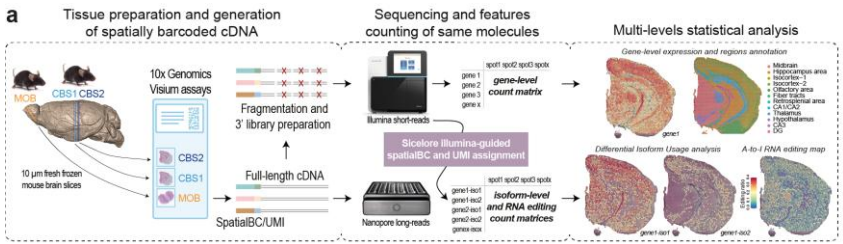
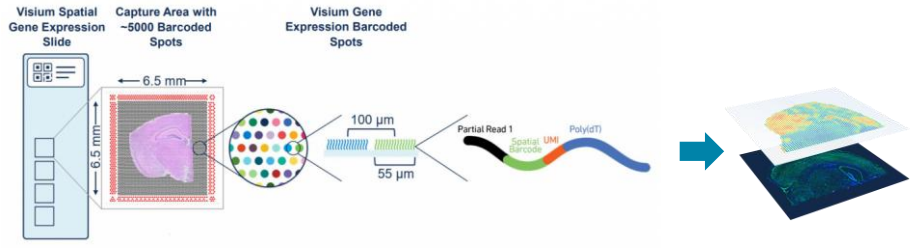
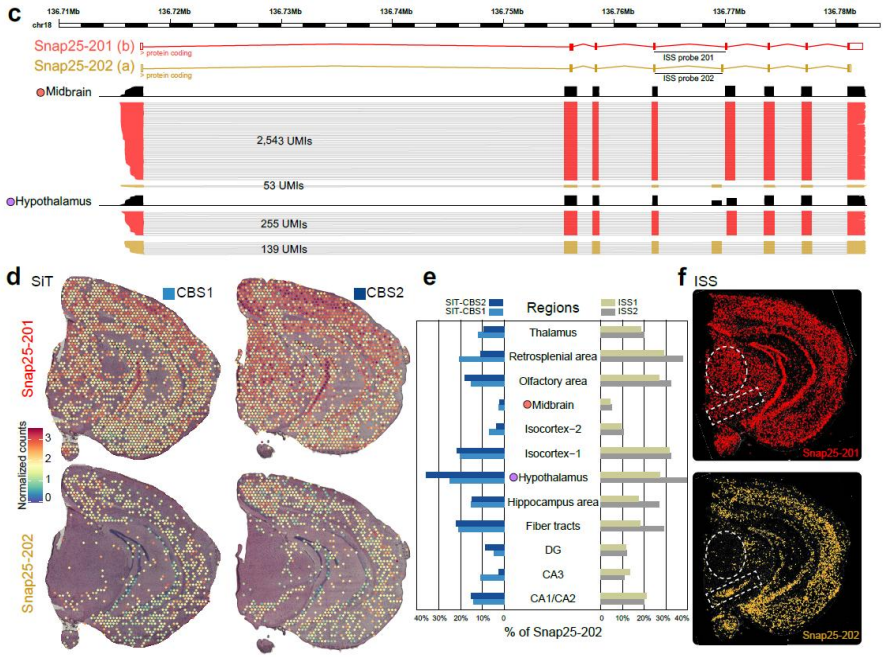




61 isoform-switching genes
across brain anatomical regions

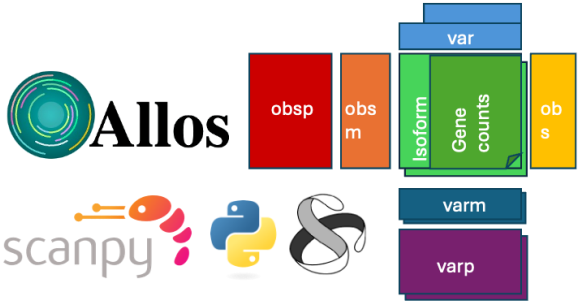


Allos

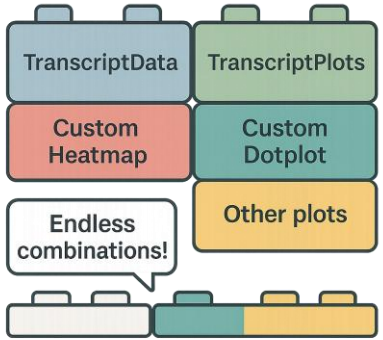
A python statistical and explorative framework for isoform-level transcriptomics

- Aim to integrate all necessary steps for a robust statistical analysis and exploratory analysis based upon scverse ecosystem
- Readers for various experiment designs
  - Bulk either short (exon-level) or long-read
  - Single-cell smartseq-based or long-read
  - Spatial in-situ capture long-read (Visium)

Isoform-level matrix



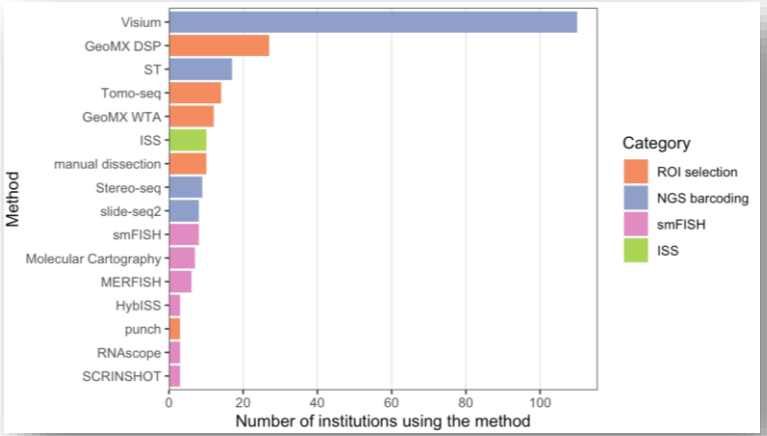
- Quality control tools
- Implementation of methods for isoform differential usage calling
- Easy-to-explore toolkit, experiment and gene-level reports
- Direct linkage to isoform functional domains
- Decipher regulators of gene isoforms expression

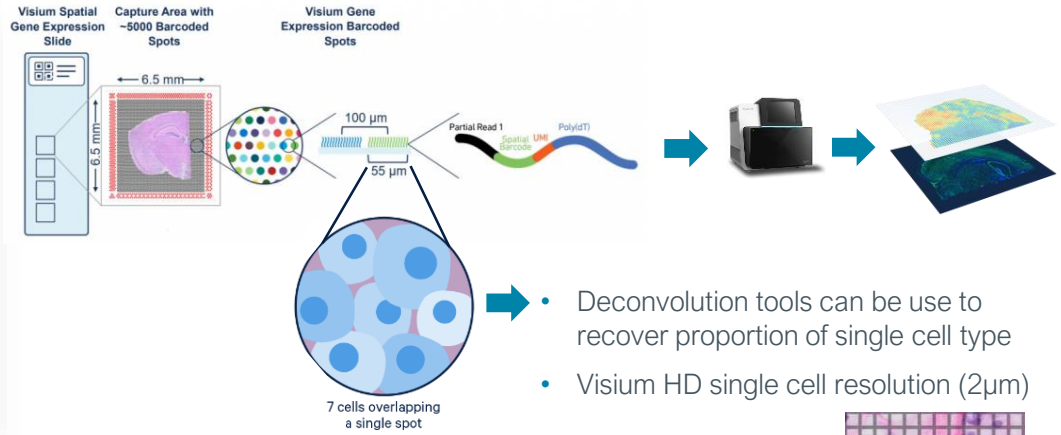



Eamon Mcandrew, Anna Diamant et al.
In preparation

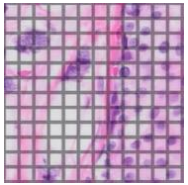
In-situ capture Spatial Transcriptomics (2017-2022)

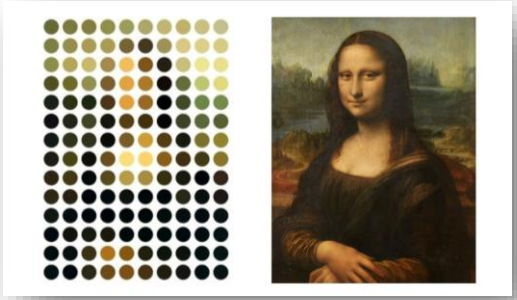
Visium is widely adopted by academics





- Deconvolution tools can be use to recover proportion of single cell type
- Visium HD single cell resolution (2µm)





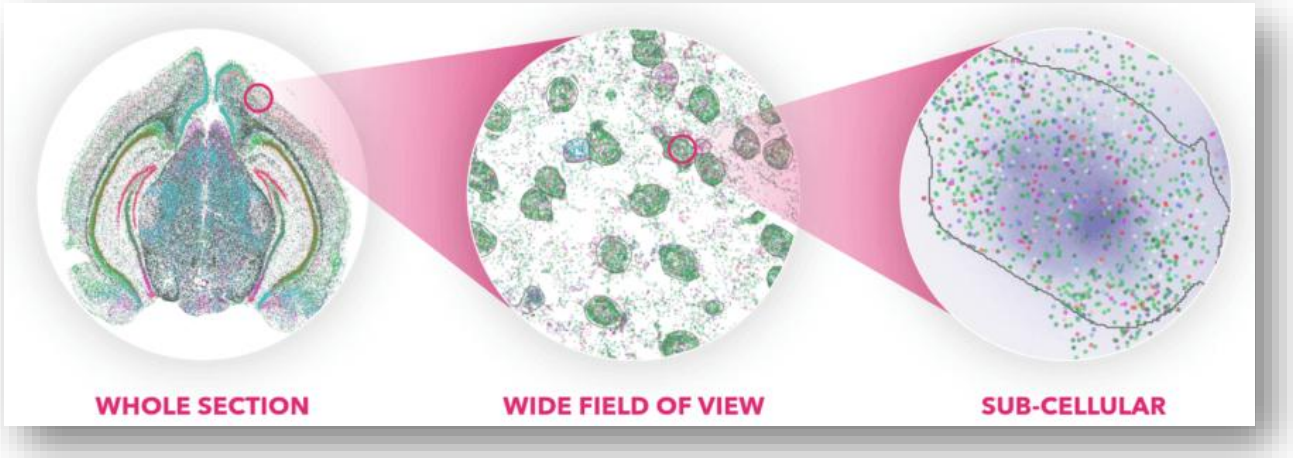
But is not the ideal readout for spatial biology

(Akoya credit rough caricature)

Imaging-based Spatial Transcriptomics (since 2022)

The next transcriptomics revolution

- Lower gene panel targets (from whole transcriptome to maximum 5,000 genes)
- Higher sensitivity (from ~6% to 30-80%)
- Larger imaging area (42 to 236 mm2)
- Higher resolution (from 55 µm to subcellular)



Imaging-based Spatial Transcriptomics (since 2022)

System's detection strategies

Nanostring CosMx

ISH-based

Vizgen Merscope

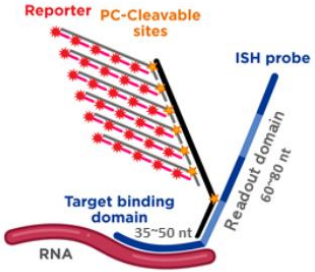
Multiplex Error-Robust FISH

Available (oct.2022)

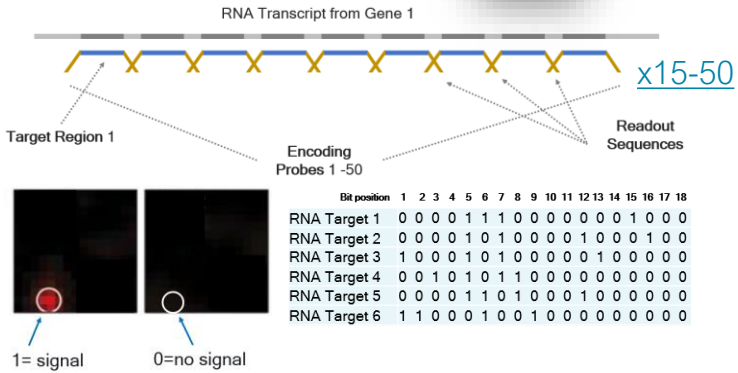
10xGenomics Xenium

Cartana ISS, padlock probes / RCA

Available (jan.2024)



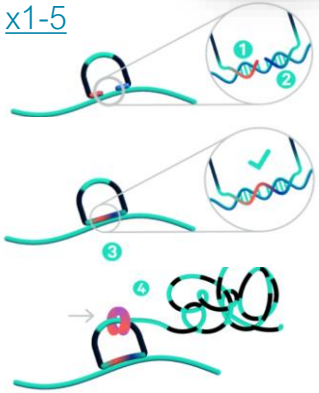
x4-8 / target gene



Bit position	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
RNA Target 1	0	0	0	0	1	1	1	0	0	0	0	0	0	0	1	0	0	0
RNA Target 2	0	0	0	0	1	0	1	0	0	0	0	1	0	0	0	1	0	0
RNA Target 3	1	0	0	0	1	0	1	0	0	0	0	0	1	0	0	0	0	0
RNA Target 4	0	0	1	0	1	0	1	1	0	0	0	0	0	0	0	0	0	0
RNA Target 5	0	0	0	0	1	1	0	1	0	0	0	1	0	0	0	0	0	0
RNA Target 6	1	1	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0

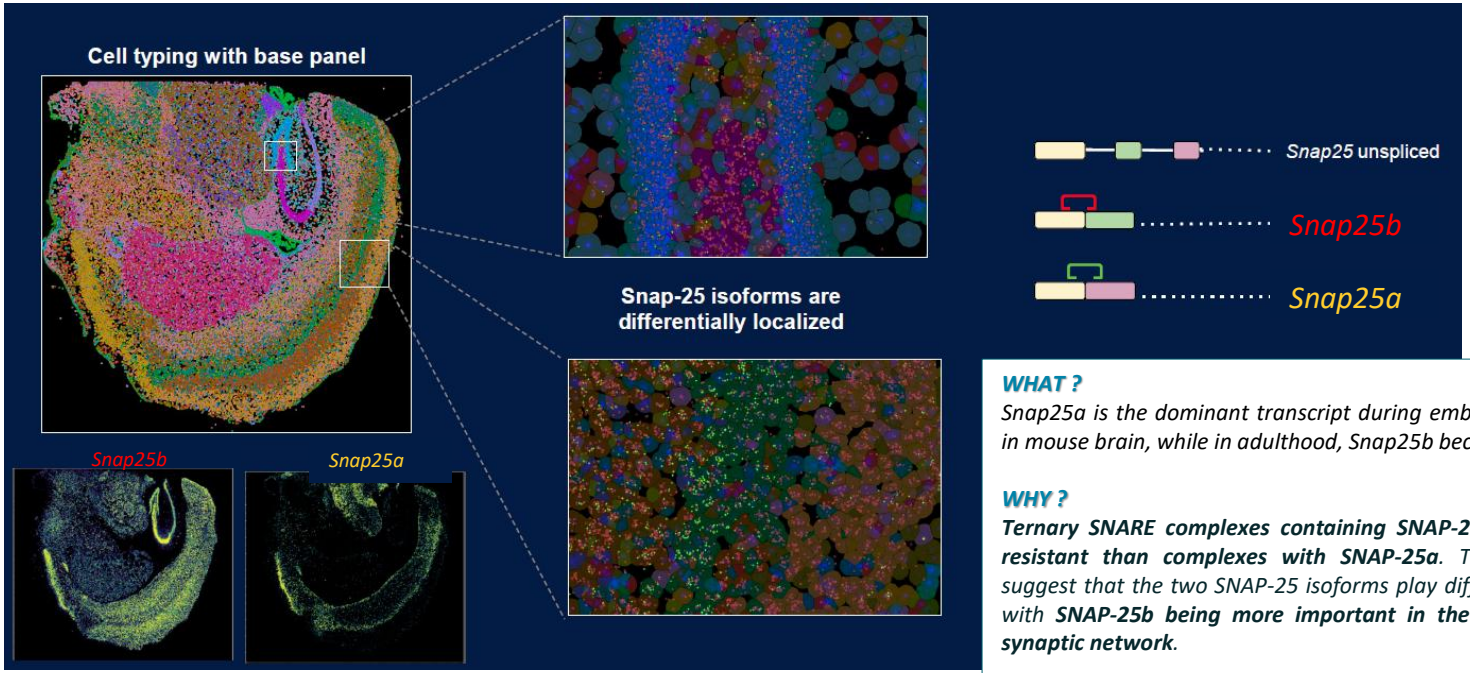
Cyclic *in situ* Hybridization Chemistries

x1-5



Xenium isoform detection (FF adult mouse coronal brain section)

Josh Talboom, 10x genomics workshop, January 2024



WHAT ?

Snap25a is the dominant transcript during embryonic and early postnatal day in mouse brain, while in adulthood, Snap25b becomes the dominant mRNA

WHY ?

***Ternary SNARE complexes containing SNAP-25b are more stable and heat resistant than complexes with SNAP-25a**. These previous findings might suggest that the two SNAP-25 isoforms play different roles in central neurons, with **SNAP-25b being more important in the consolidation of the mature synaptic network**.*

HOW ?

Isoform expression could be regulated according to **cell type**, **anatomical region** or **developmental stage**, **neurodevelopmental disorder**, etc.... Could it be correlated with splicing factor activity. Explore **regulation** and **function**.

Sub-cellular Isoform-level spatial transcriptomics

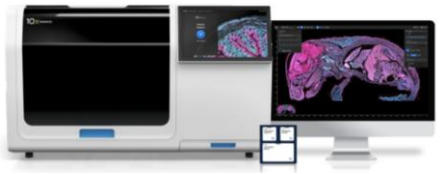
Focus on early brain development and synaptogenesis

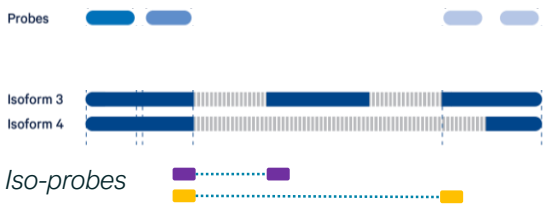
- Last 10 years : 99% academics single-cell publications relies on gene-level
- Complex outcomes of transcriptomics: **90%** of genes are subjected to alternative splicing
- We need methods to explore Isoform-level gene expression in space and time
- Develop expertise for Isoform-level Xenium add-on panel optimization
- Proof-of-concept project for method transfer to Cell-ID pathological studies

10x Genomics Xenium

Xenium Prime 5K Mouse Pan Tissue & Pathways Panel

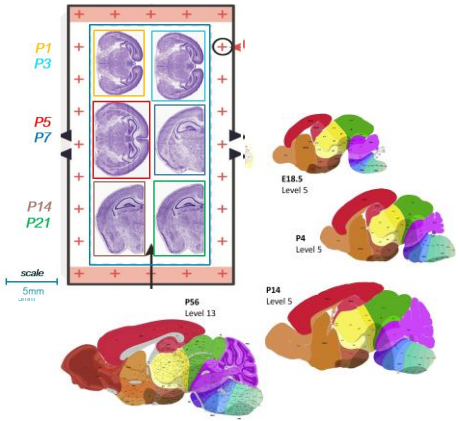
Profile murine biological pathways, receptor-ligand pairs, cell-cell interactions, biomarkers, and more.





Mouse brain development

P1-P21

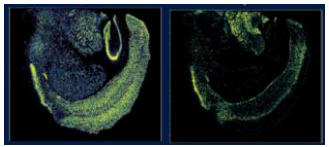


Xenium run in 2 weeks

100 Add-on Isoform-level targets panel

46 isoform switching genes in literature

Synaptogenesis Step	Function Category	Genes
1. Neuronal Differentiation & Migration	Neurodevelopmental Regulation	Pax6, Gfap, Mapt, Map1a, Fmr1, Ttbk1
2. Axon Guidance & Target Recognition	Cell Adhesion, Guidance Cues	Nrxn1, Nrxn2, Nrxn3, Nlgn1, Lrp8, Dab1, Kif1a
3. Synapse Formation (Initiation)	Synaptic Vesicle & Membrane Proteins	Snap25, Snap23, Stxbp1, Dnm1, Clta, Stau2, App, Agrn
4. Synaptic Maturation & Plasticity	Receptors & Signaling Molecules	Gria1, Gria2, Gria3, Gria4, Grin1, Bdnf, Ntrk2, Cacna1c, Dlg4
5. Synaptic Maintenance & Pruning	Regulatory RNA/Proteins & Degradation	Hnrnpa2b1, Khdrbs3, Mbnl2, Ptbp1, Ptbp2, Rbfox1, Sqstm1, Tia1
Cross-cutting	Metabolism & Modulation	Abat, Bace1, Pkm, Emc10, Bin1, Clstn1



Isoform 3 *Isoform 4*

Acknowledgments

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