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## Gene networks controlling functional cell interactions in the pig embryo revealed by omics studies

Adrien Dufour, Cyril Kurylo, Jan B Stöckl, Yoann Bailly, Patrick Manceau, Frédéric Martins, Stéphane Ferchaud, Bertrand Pain, Thomas Fröhlich, Sylvain Foissac, et al.

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➤ Gene networks controlling functional cell interactions in the pig embryo revealed by omics studies

Hervé Acloque

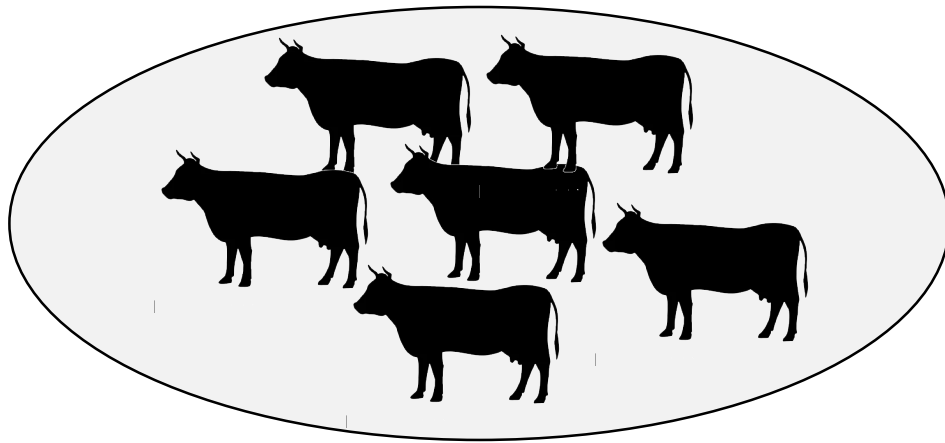
GABI Laboratory INRAE Jouy en Josas France

[herve.acloque@inrae.fr](mailto:herve.acloque@inrae.fr)

## ➤ Pluripotent stem cells in livestock: a platform for high throughput phenotyping

A challenge for animal production: phenotyping complex traits and predicting breeding values for those traits

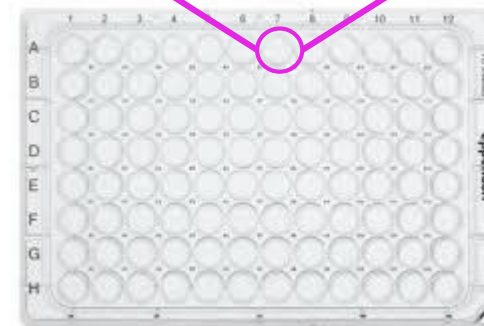
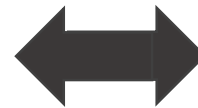
Reference population



**Phenotypes**

Genotypes

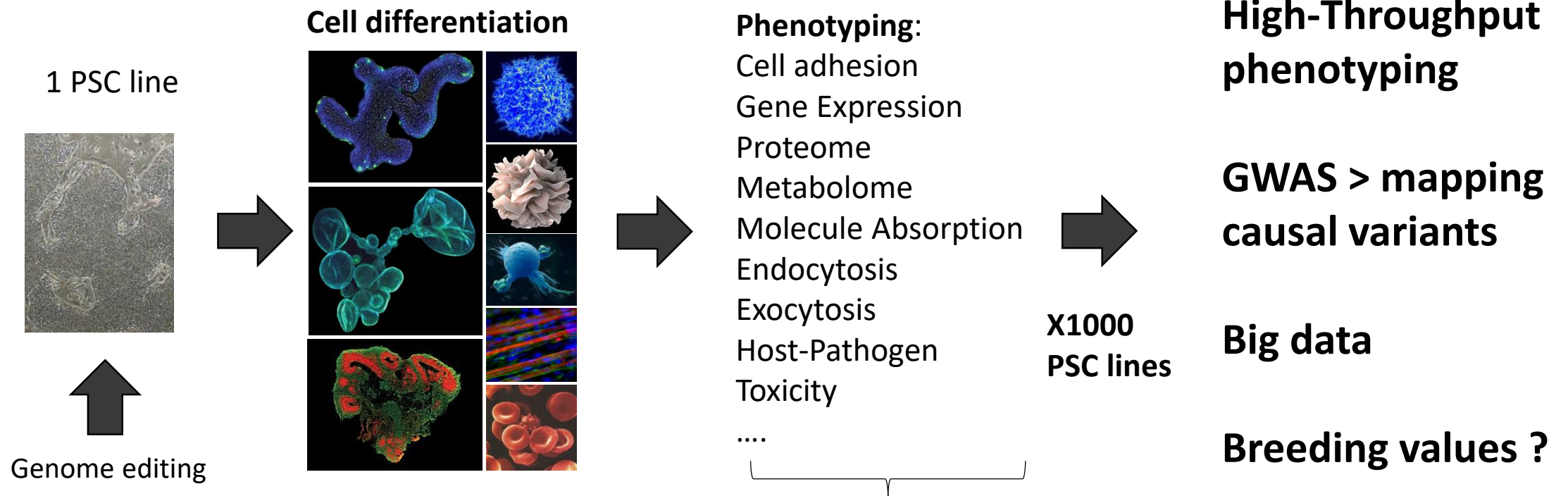
*In vitro* reference population (x1000) cell lines



Biobank of pluripotent stem cells

# ➤ Pluripotent stem cells in livestock: a platform for high throughput phenotyping

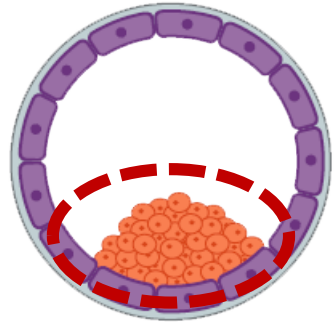
A challenge for animal production: phenotyping complex traits and predicting breeding values for those traits



Proxies or intermediate phenotypes not accessible on living animals



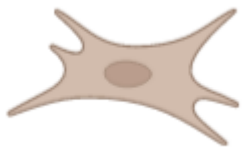
## ➤ Producing standardized true PSCs for livestock species is still challenging



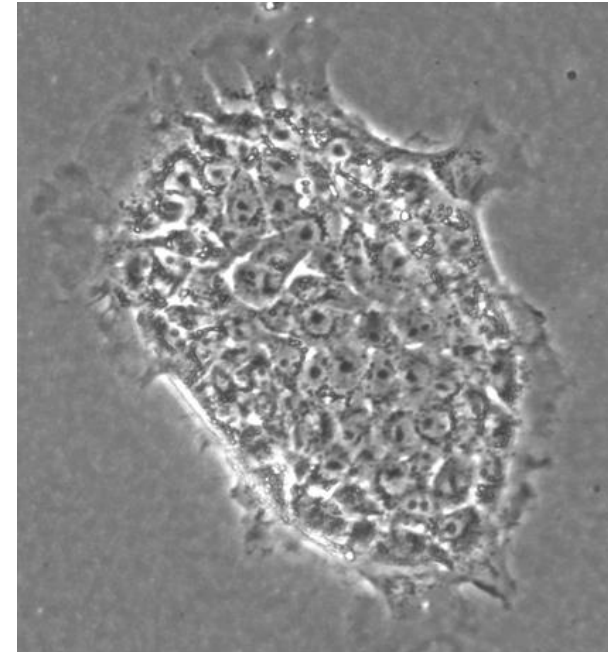
Amplification of **Epiblast cells**



**Chemically defined medium**

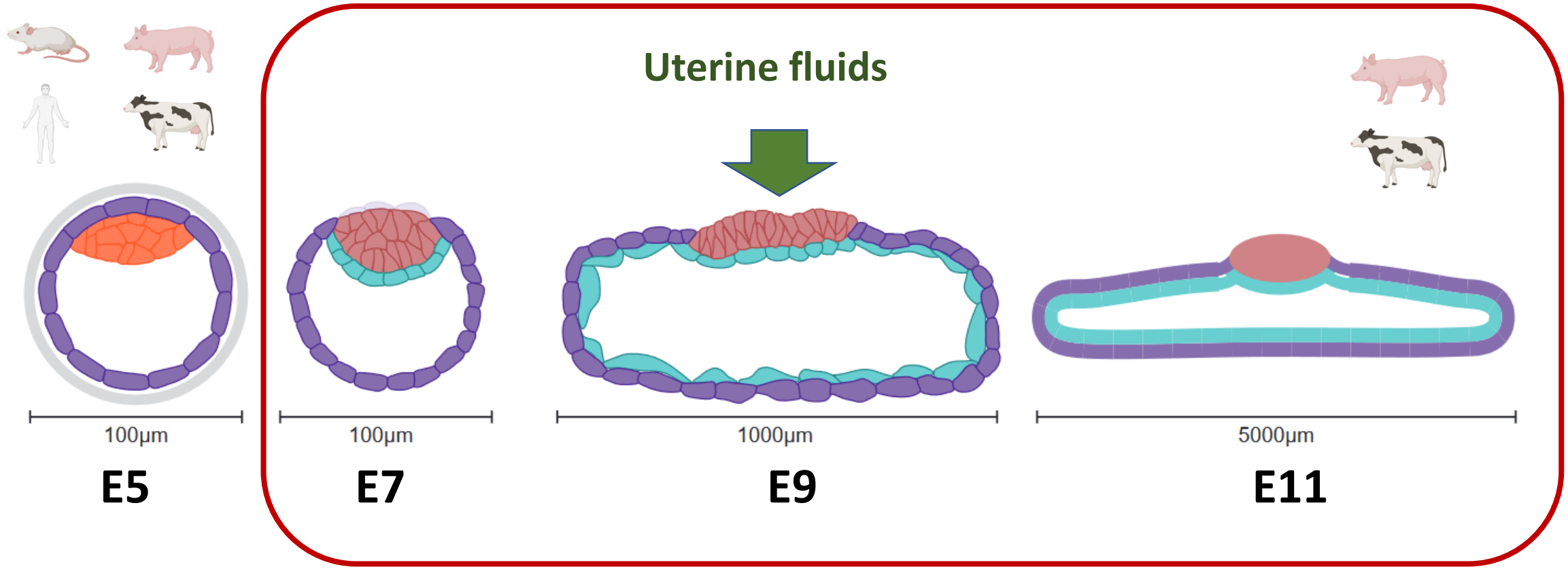


Reprogramming cocktail  
(OCT4, SOX2, KLF4, MYC)



Heterogeneity ?  
Stability overtime ?  
Differentiation potential ?

# ➤ What can we learn from the embryo ?



● Epiblast (pluripotent cells)    ■ Trophectoderm    ● Hypoblast



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Gene networks controlling functional cell interactions in the pig embryo  
29 August 2023 / EAAP meeting / Hervé Acloque

## ➤ Working hypothesis

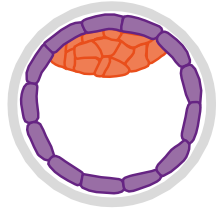


Paracrine regulations specific to pig embryonic development are not taken into consideration for the establishment of pig's pluripotent lines

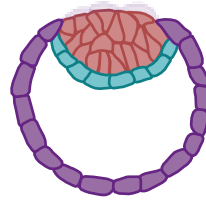


Embryonic regulatory networks are not necessarily conserved in mammals

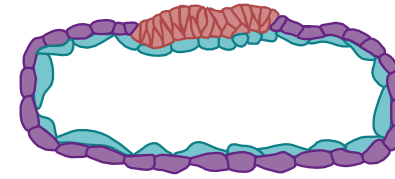
## ➤ Methods



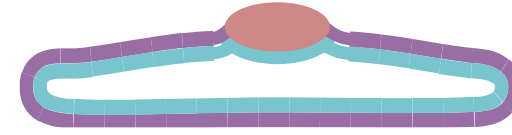
Early blastocyst **E5**



Hatched blastocyst **E7**



Spherical blastocyst **E9**



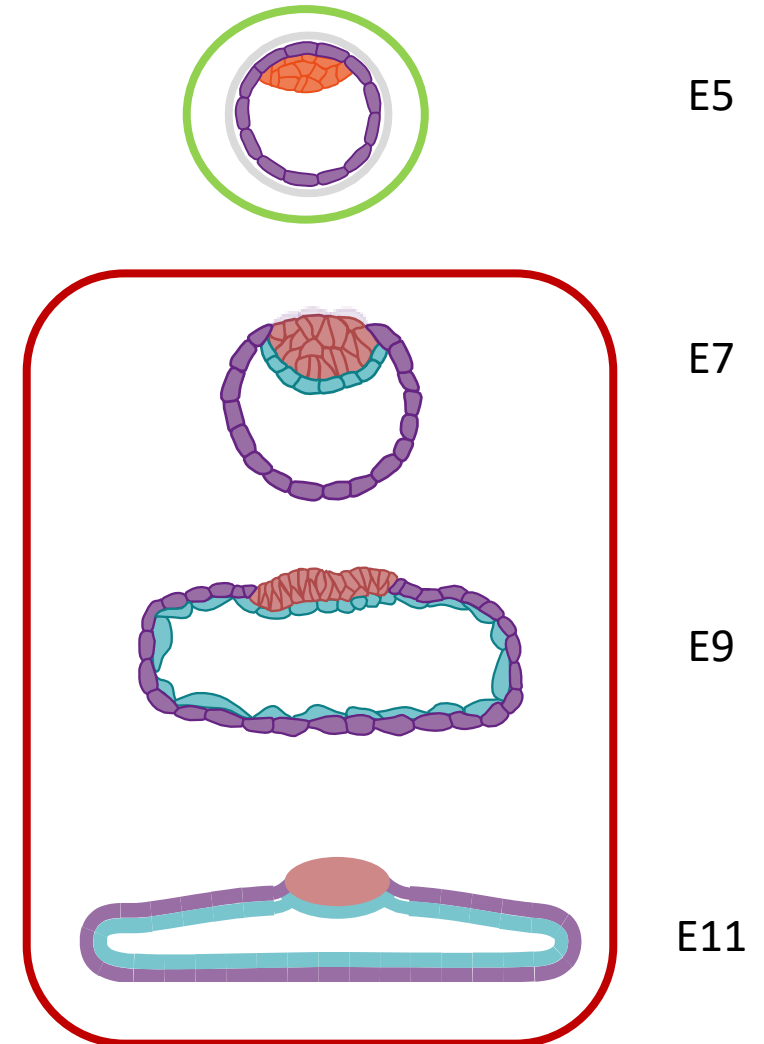
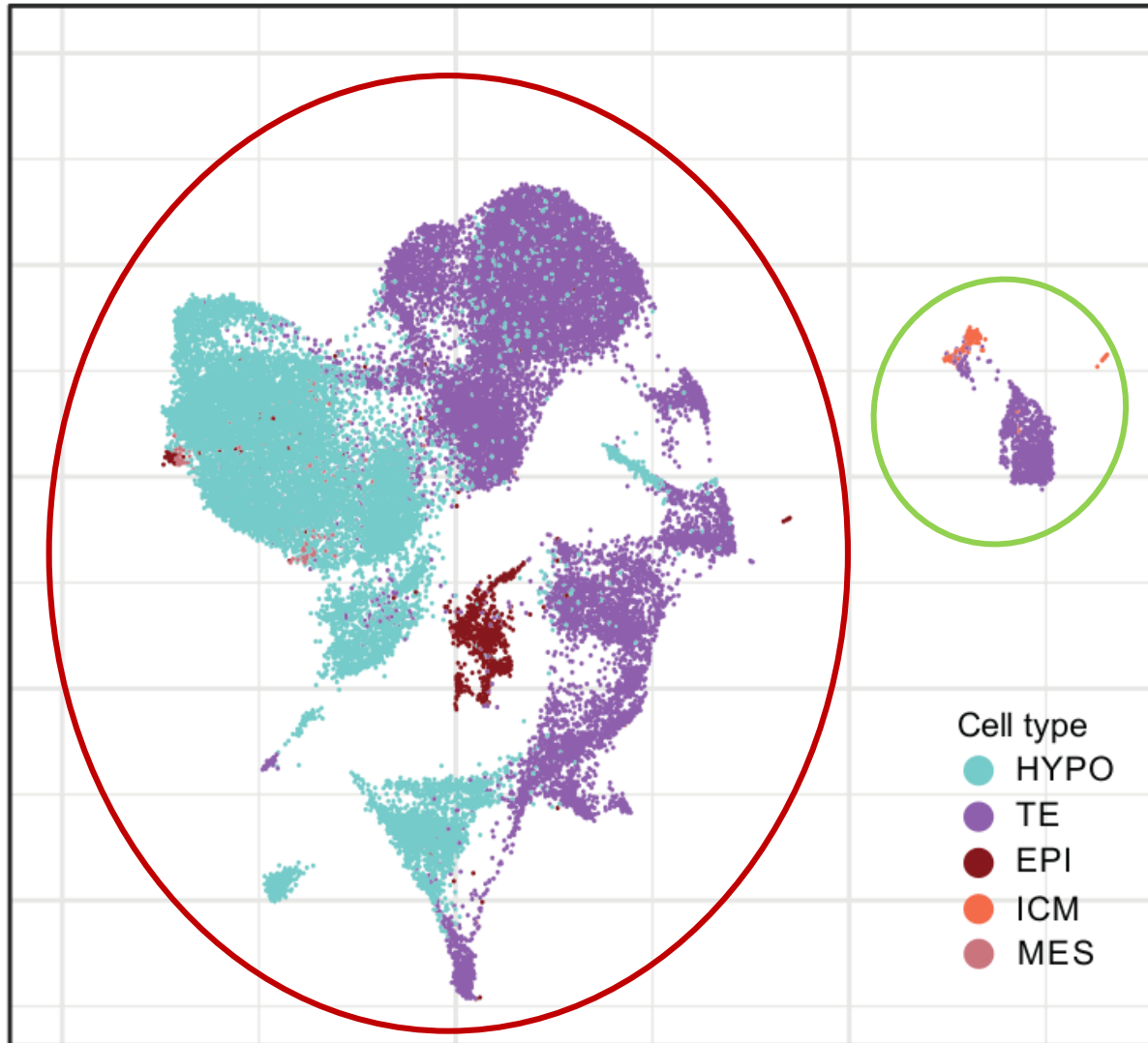
Ovoid blastocyst **E11**

Single-cell RNAseq	2 libraries (~2000 cells each)	4 libraries (~1000 cells each)	4 libraries (~3000 cells each)	2 libraries (~6000 cells each)
Uterine fluids	8 sows	4 sows	3 sows	3 sows
Single-cell multiomics (scATAC-seq + scRNA-seq)	0	1 library (~2000 cell's nucleus)	2 libraries (~4000 cell's nucleus)	4 libraries (~8000 cell's nucleus)



➤ scRNAseq allows the identification of cell populations constituting the embryo

UMAP of 34,888 cells

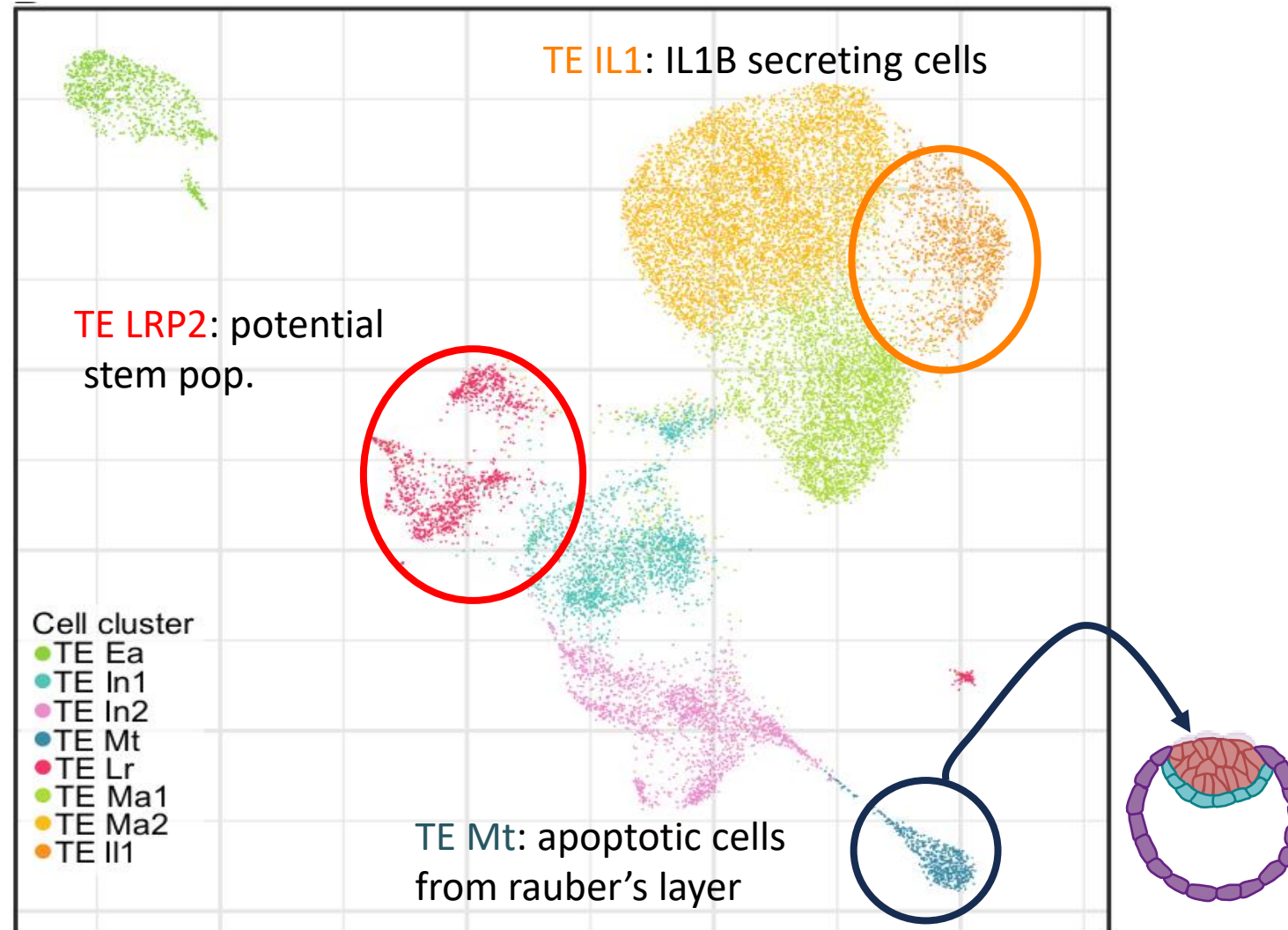


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➤ scRNAseq data provide cues to better understand the biology of the pig embryo

### Identify new subpopulations

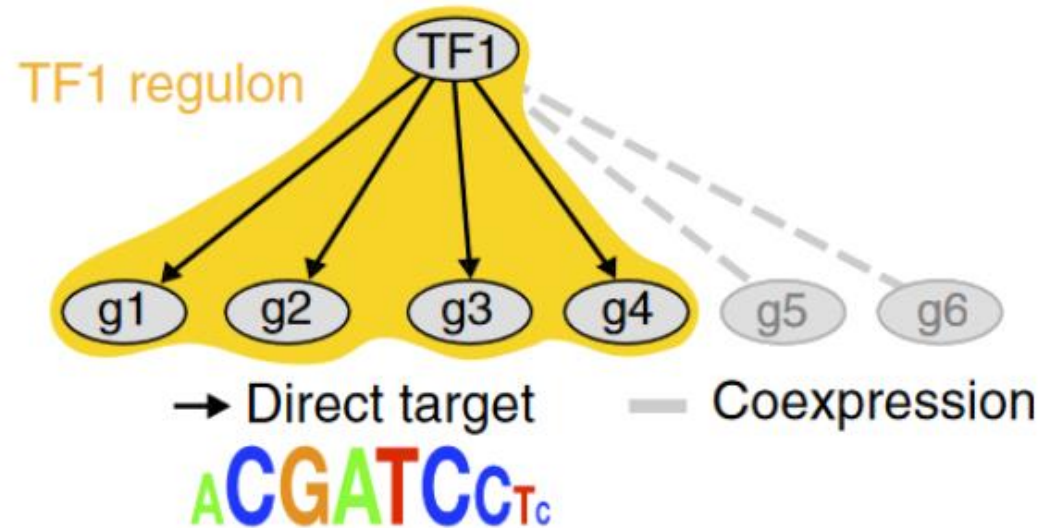
UMAP of 18,239 TE cells



- scRNAseq data provide cues to better understand the biology of the pig embryo

## Identify modules of gene regulation

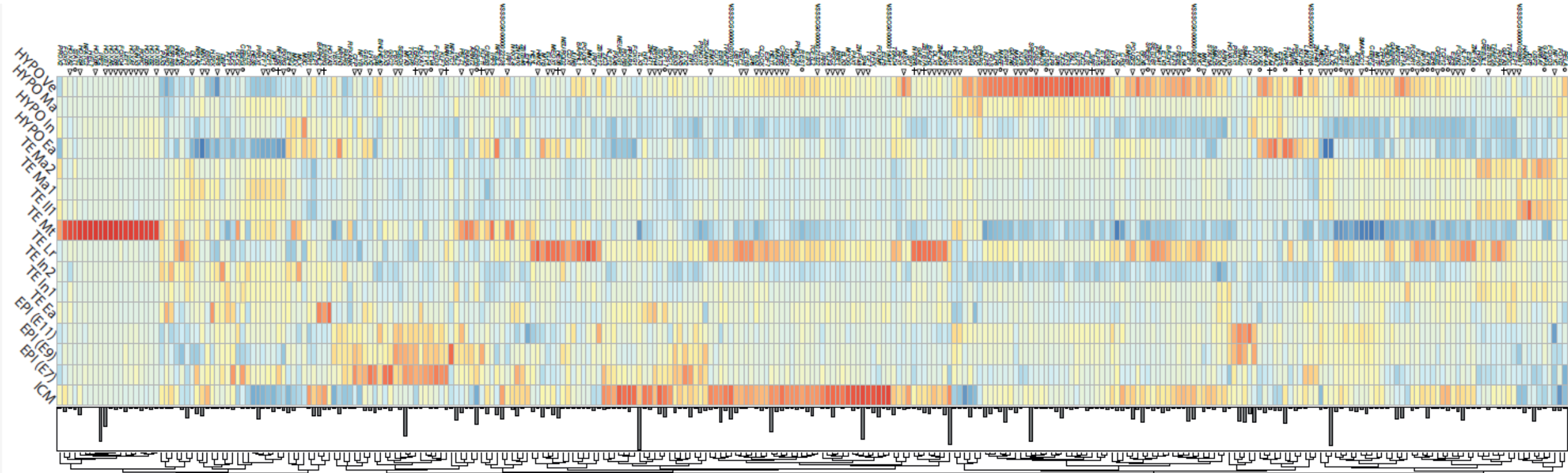
Regulons  
(gene regulatory network)



Aibar et al. 2017

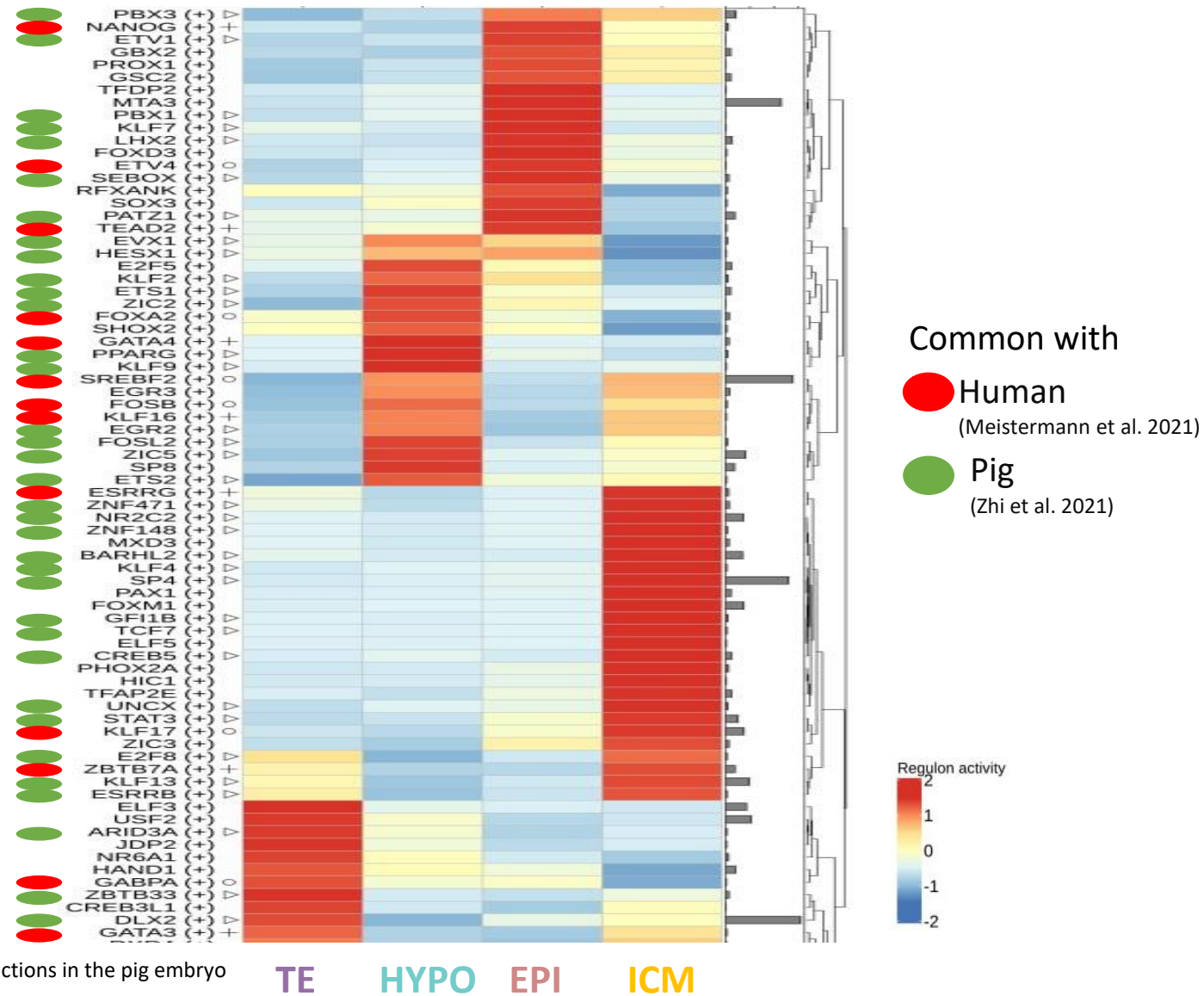
# ➤ scRNAseq data provide cues to better understand the biology of the pig embryo

## Identify modules of gene regulation

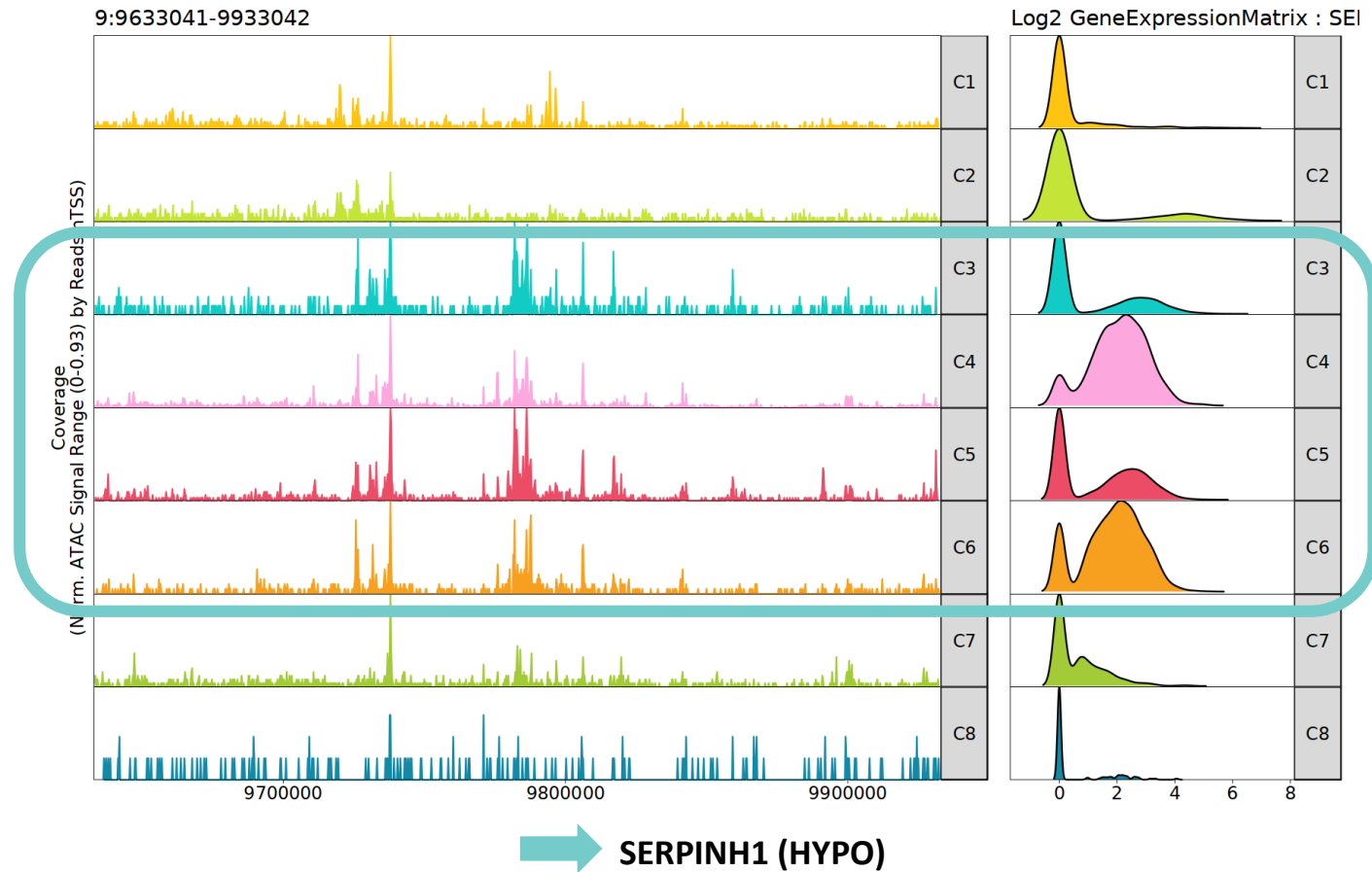
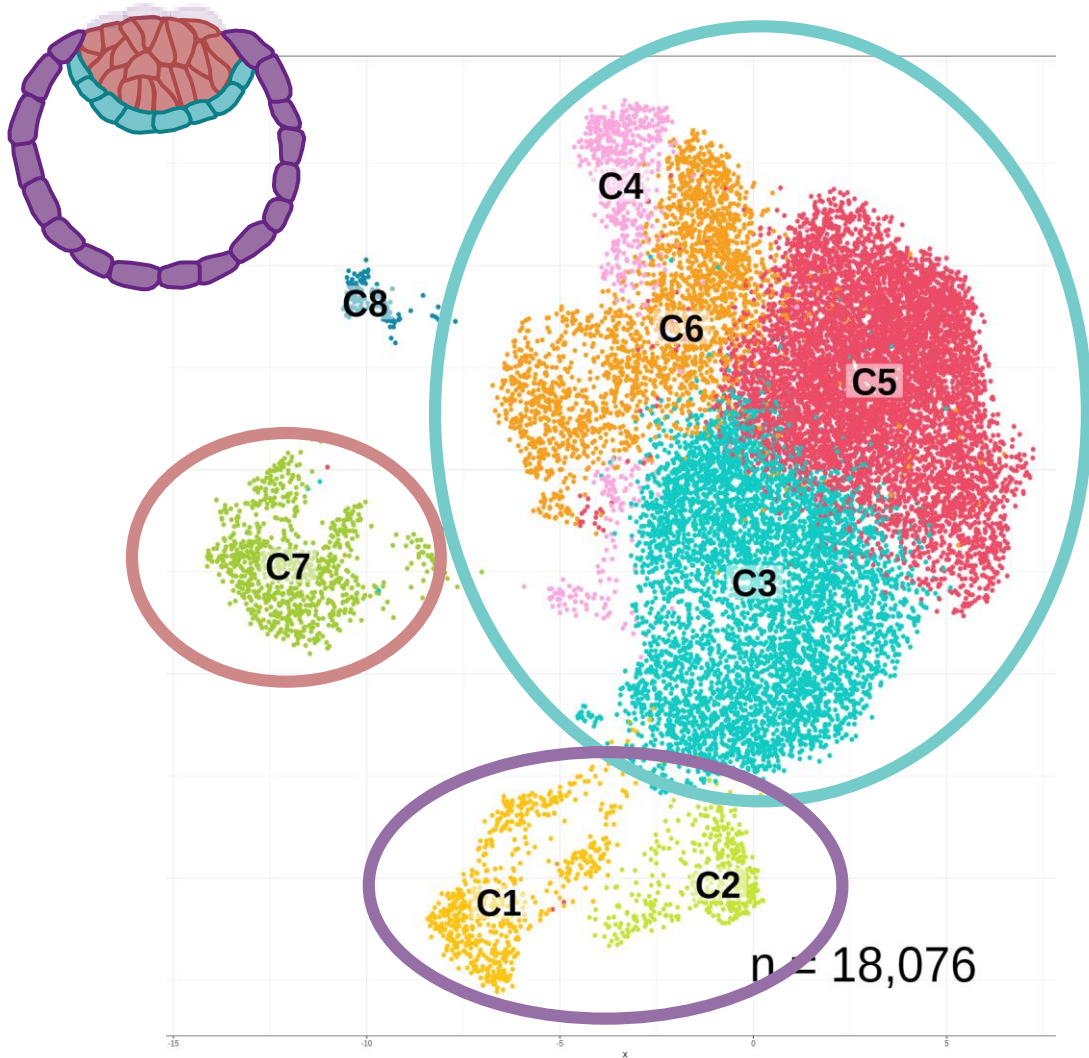


➤ scRNAseq data provide cues to better understand the biology of the pig embryo

## Identify modules of gene regulation

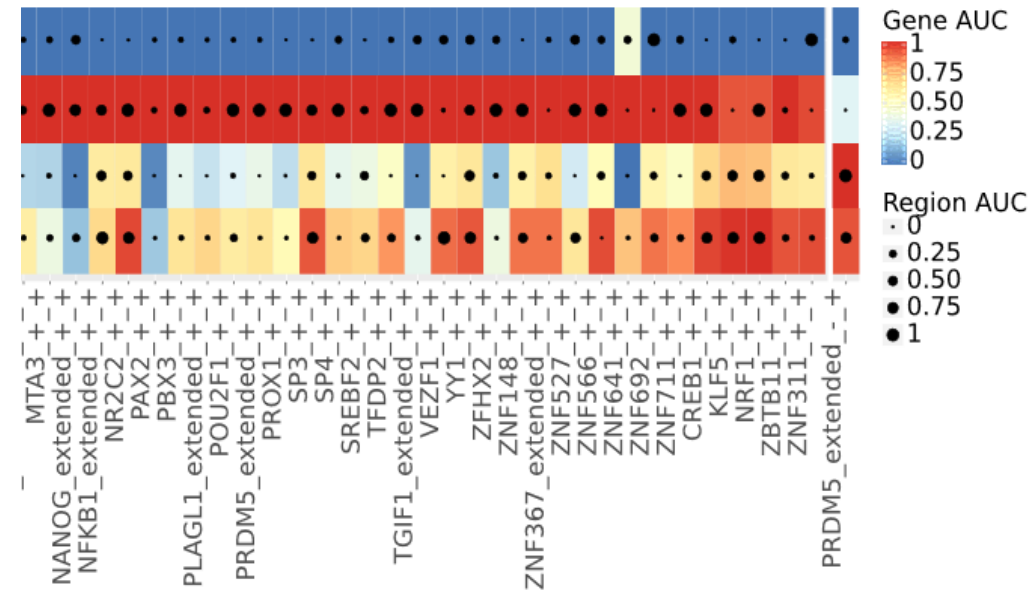
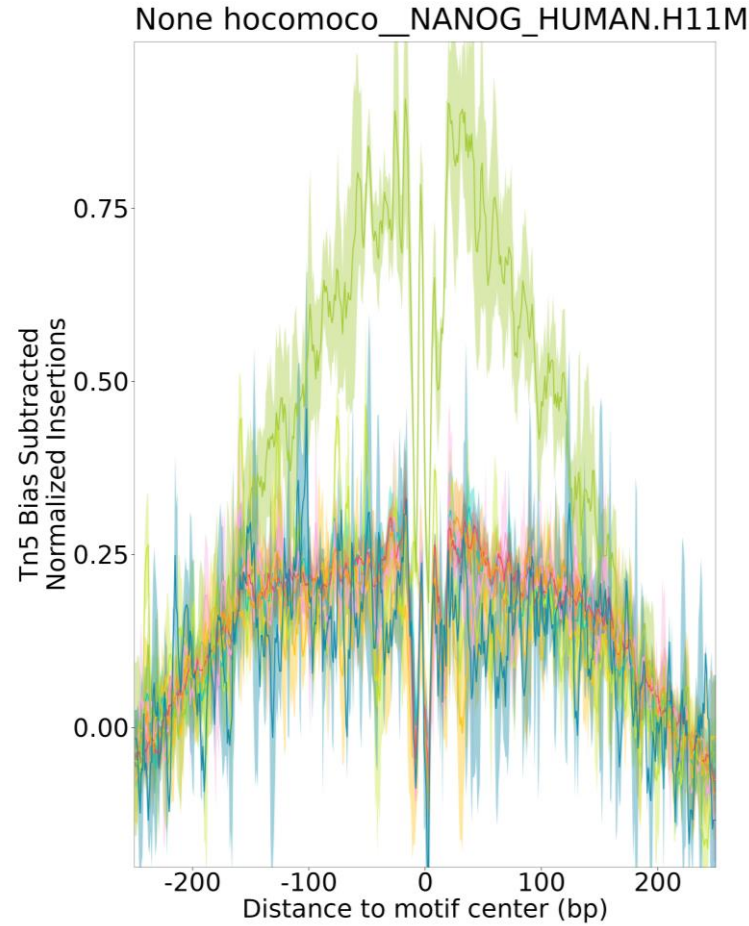
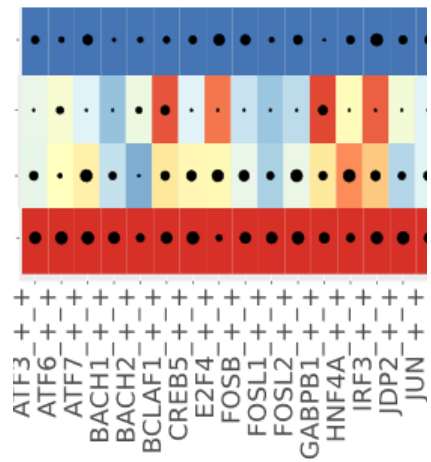
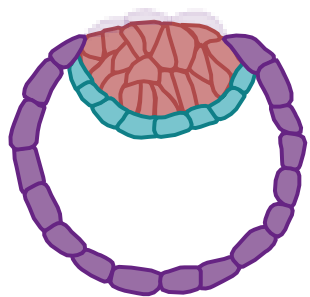


# ➤ scOMICS: adding a layer of information to refine module of gene regulation



# ➤ Added value of omics data: selection of active regulons

TE  
EPI  
HYPO (early)  
HYPO (late)

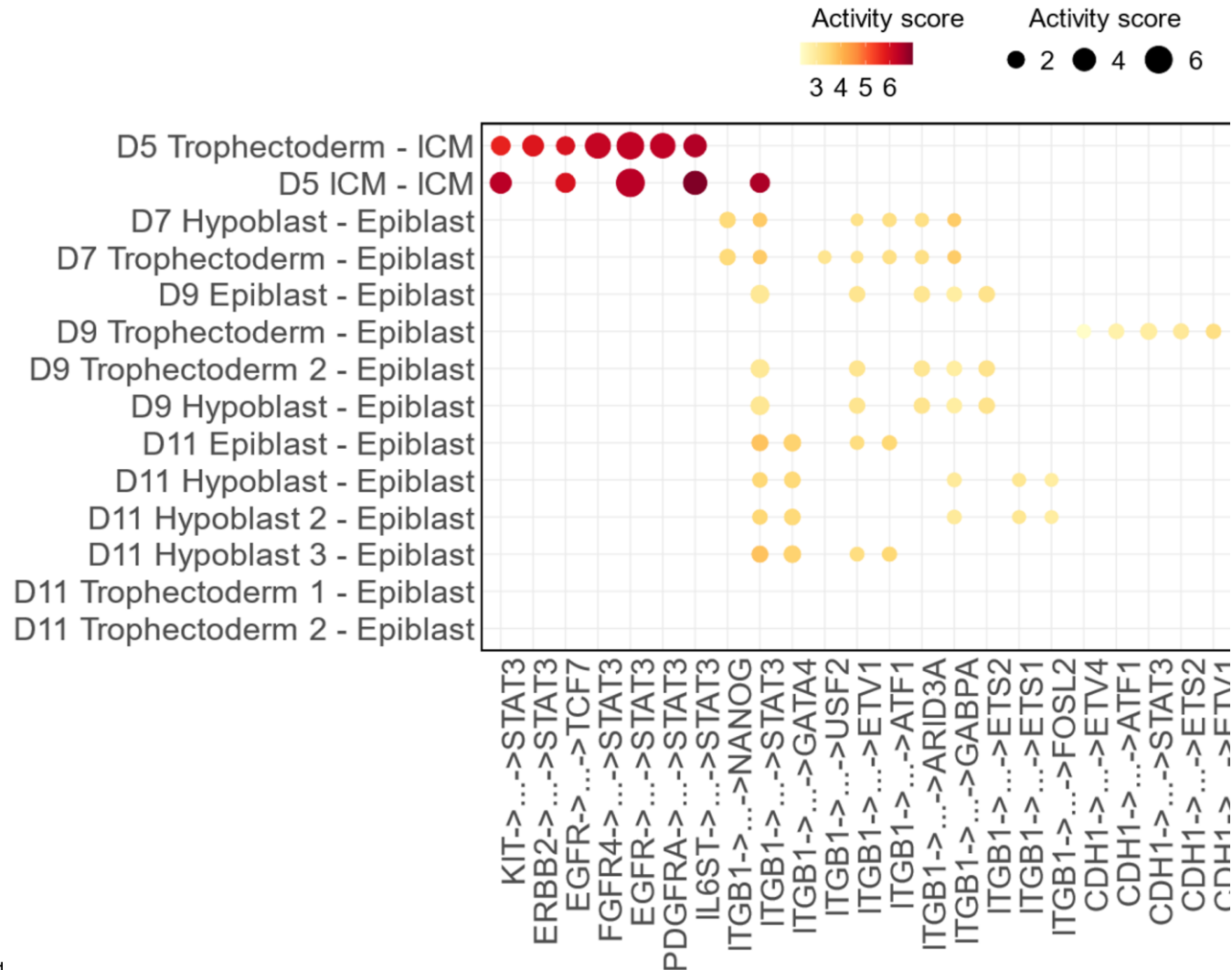


INRAE

Dufour et al. unpublished

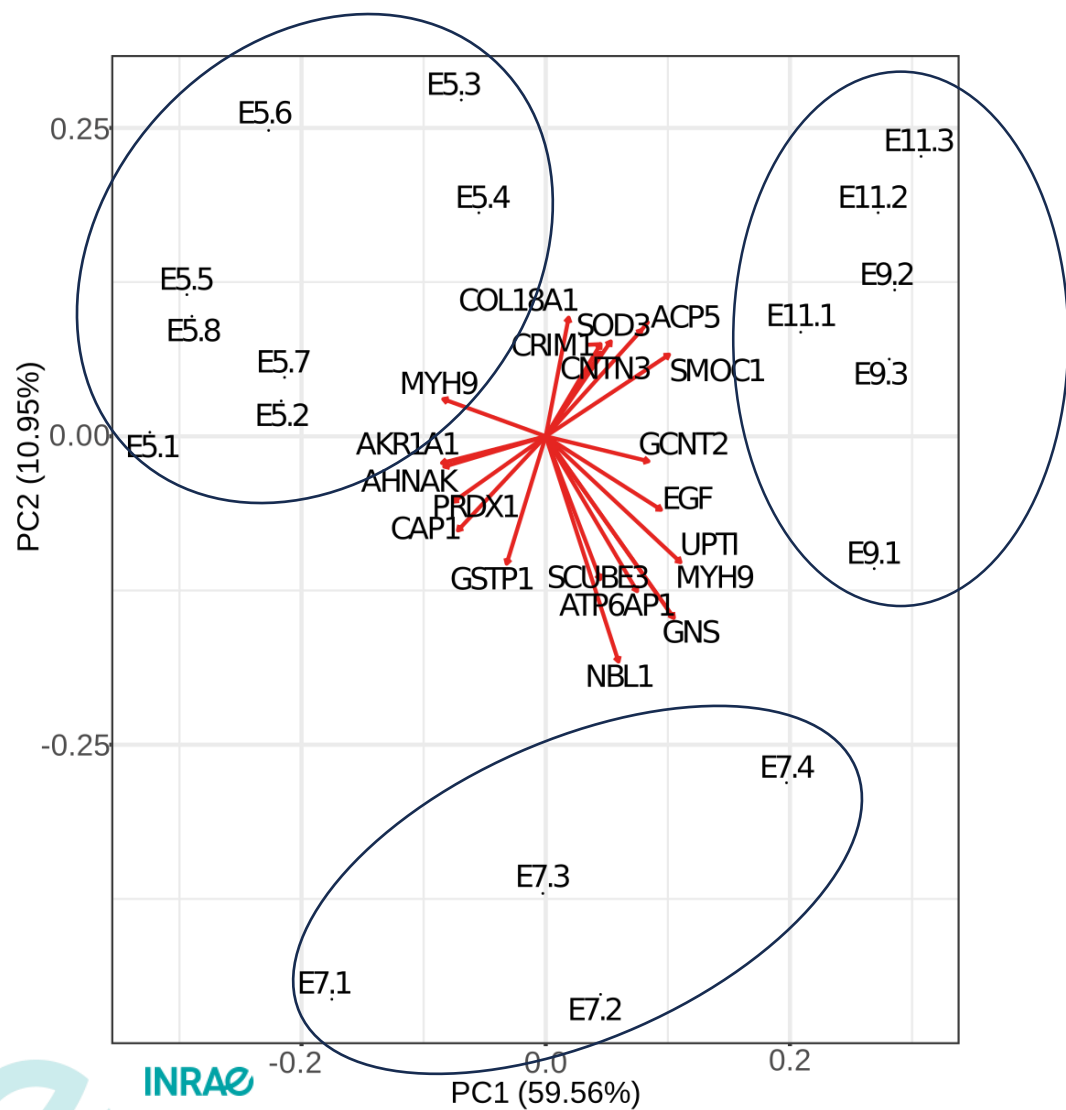
# ➤ scRNAseq data provide cues to better understand the biology of the pig embryo

## From ligand/receptor interactions to modules of gene regulation



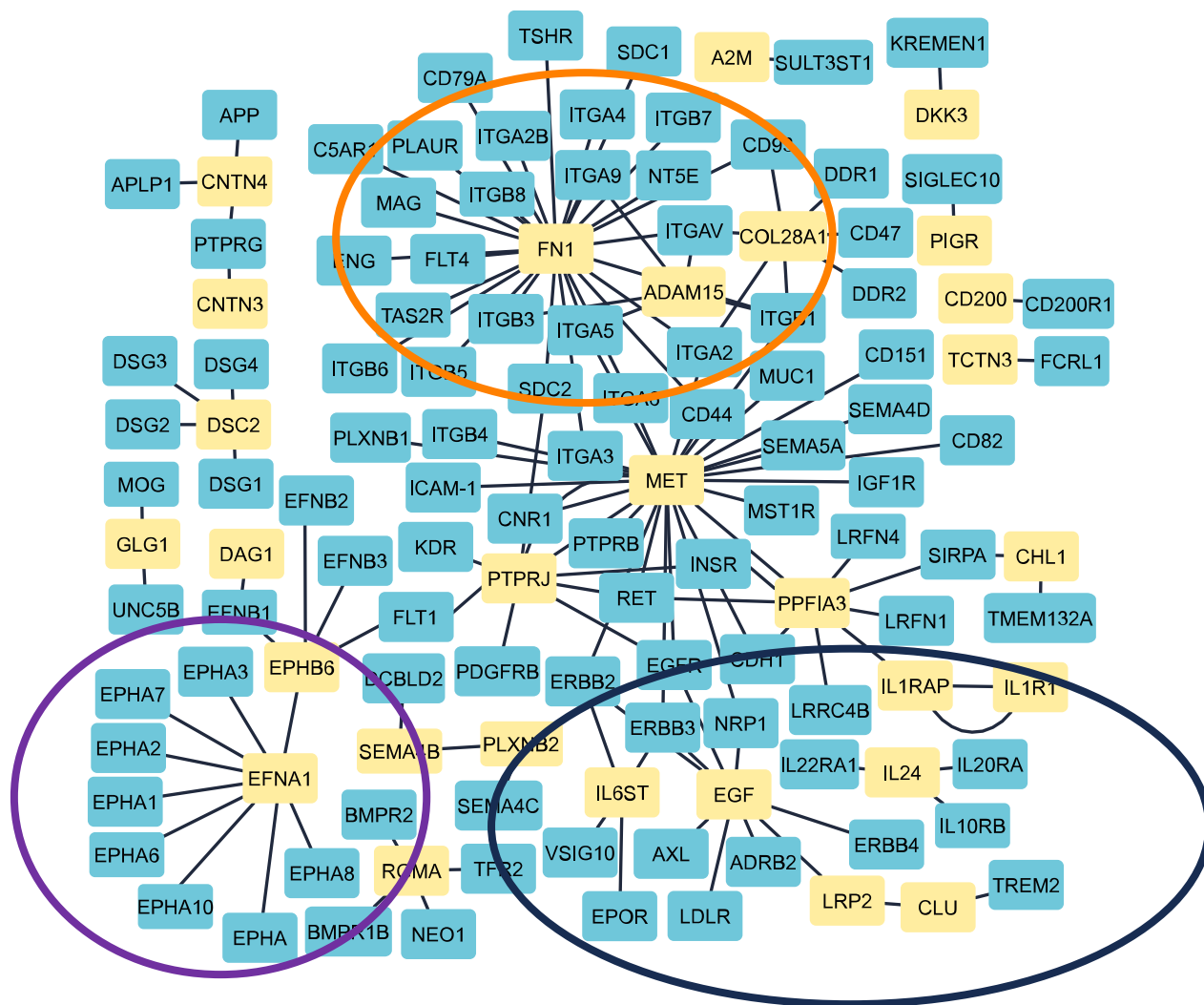


# ➤ Adding the fourth dimension: input from uterine fluids proteomics



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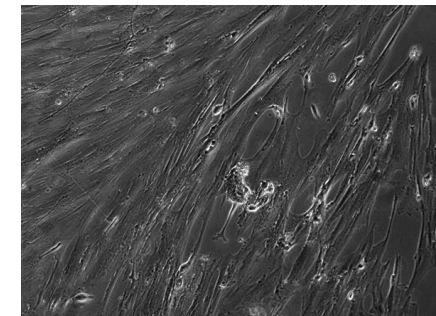
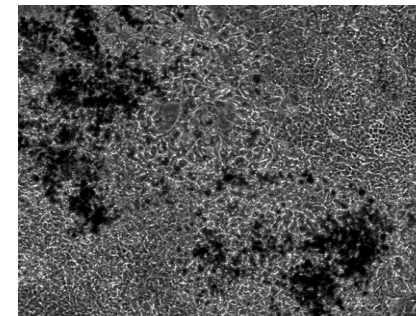
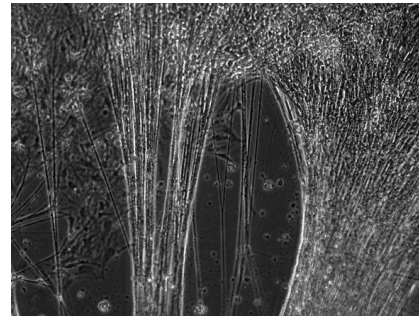
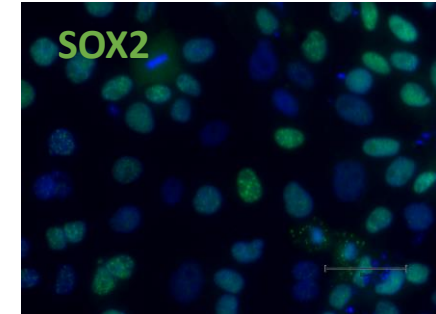
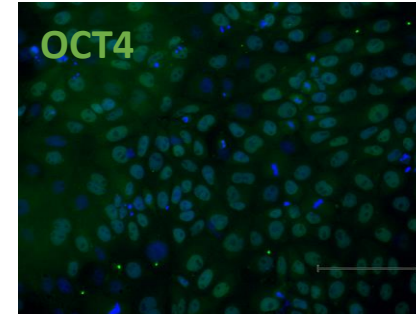
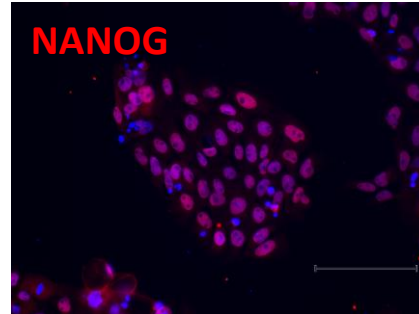
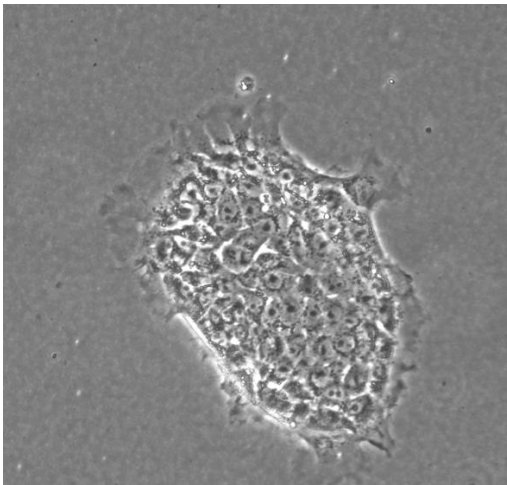
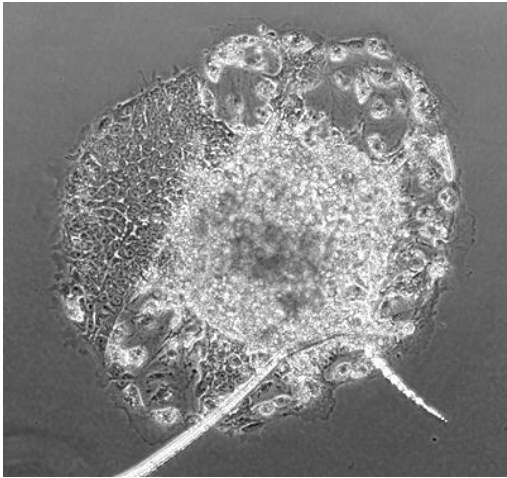
Dufour et al. submitted; <https://doi.org/10.1101/2023.05.30.542847>



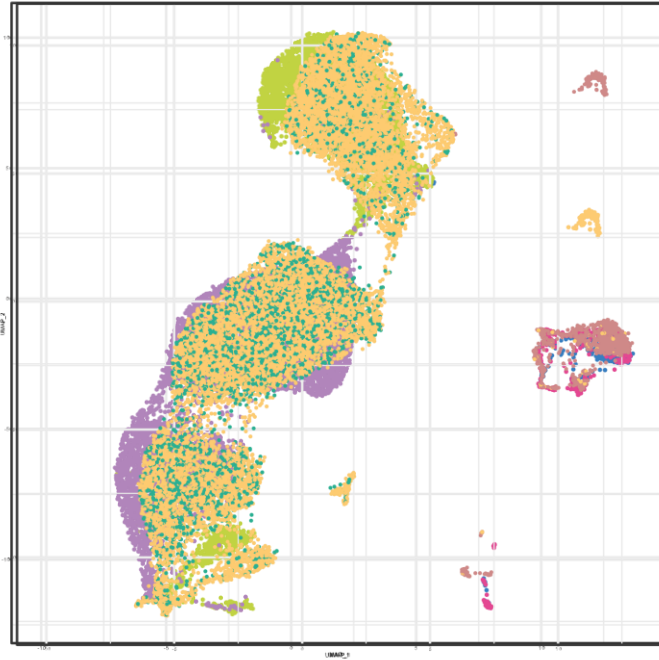
Interactions between **uterine fluid ligands** and **trophoblast receptors (E9/E11)**

# ➤ Omics plus-value: detection of poised states in pig ESCs

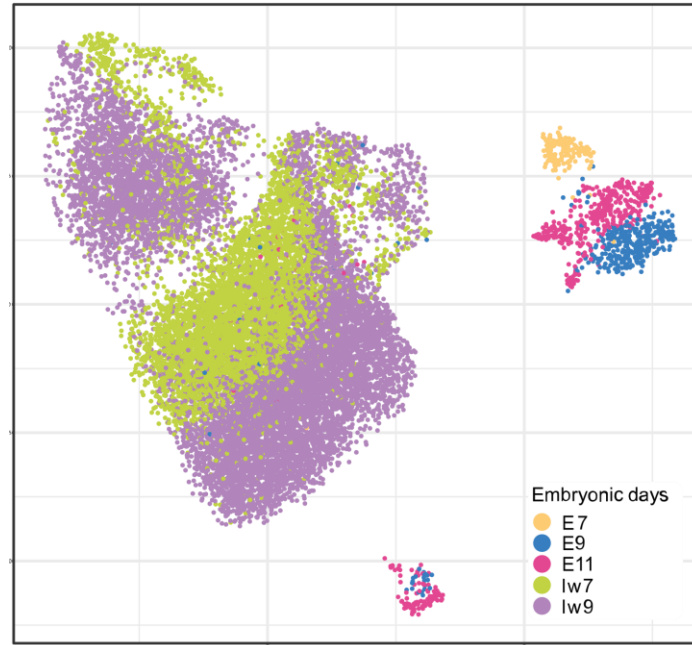
Pig ESCs



# ➤ Omics plus-value: detection of poised states in pig ESCs

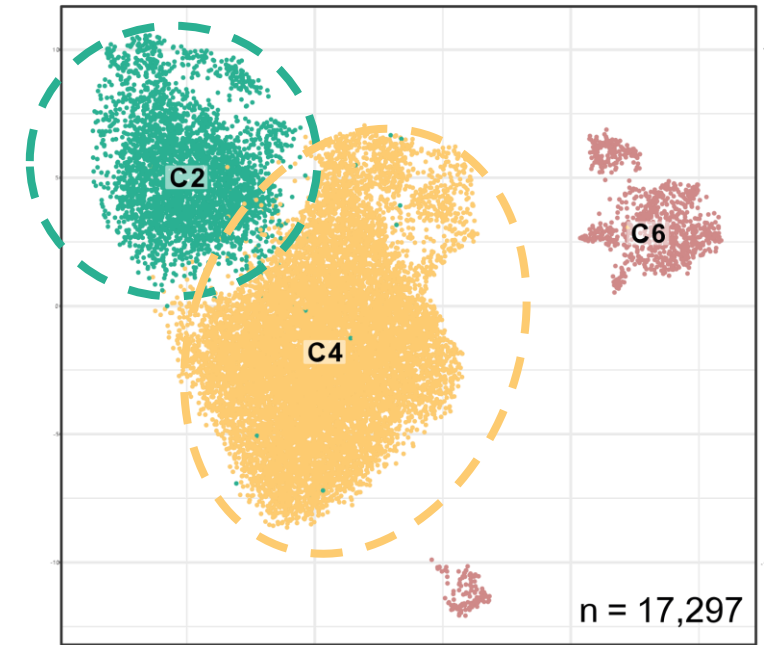


scRNAseq



scOMICS

Cells poised toward a neural fate



Cells poised toward non neural ectoderm & mesendoderm fate



## > Conclusions

### **Added values of omics vs gene expression:**

- Identification of potential molecular interactions between embryonic cells and uterine fluids
- Better characterisation of gene regulatory networks at work in embryonic cells
- Validation of candidate regulons with motif footprints
- Detection of cell states not detectable by looking at gene expression only



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