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Réseaux de gènes contrôlant la biologie de l'embryon de porc préimplantatoire et des cellules souches pluripotentes révélées par une approche multi-omiques à l'échelle cellule unique

Hervé Acloque

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

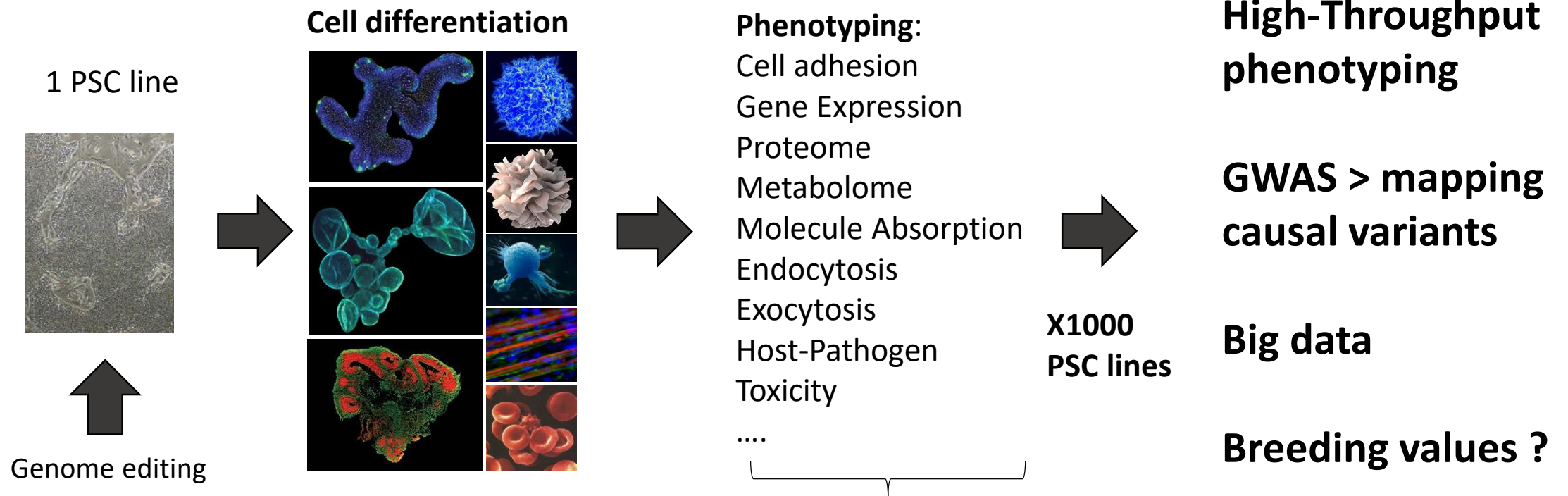
Hervé Acloque

GABI Laboratory INRAE Jouy en Josas France

herve.acloque@inrae.fr

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

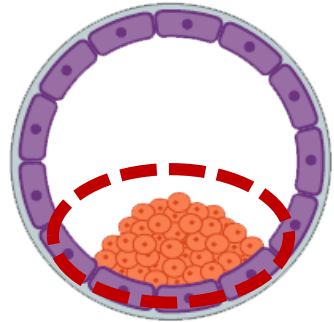
A challenge for animal production: phenotyping complex traits and predicting breeding values for those traits



Proxies or intermediate phenotypes not accessible on living animals



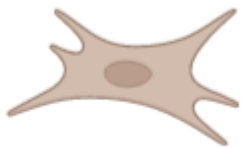
➤ Producing standardized true PSCs for livestock species is still challenging



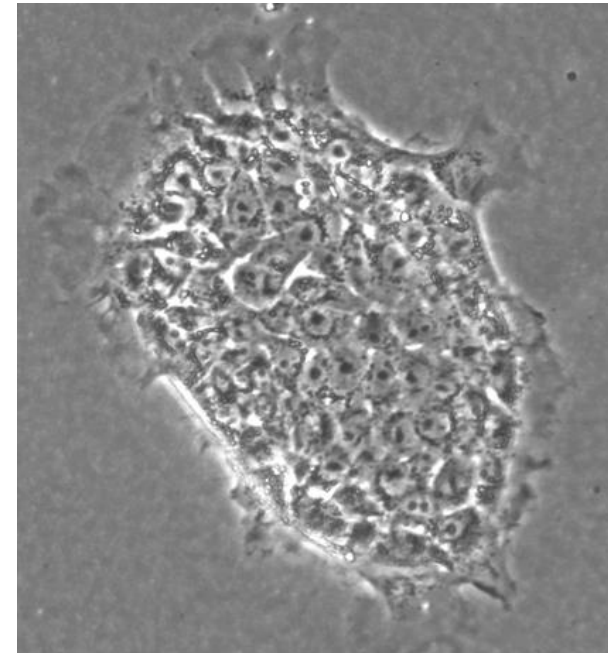
Amplification of **Epiblast cells**



Chemically defined medium

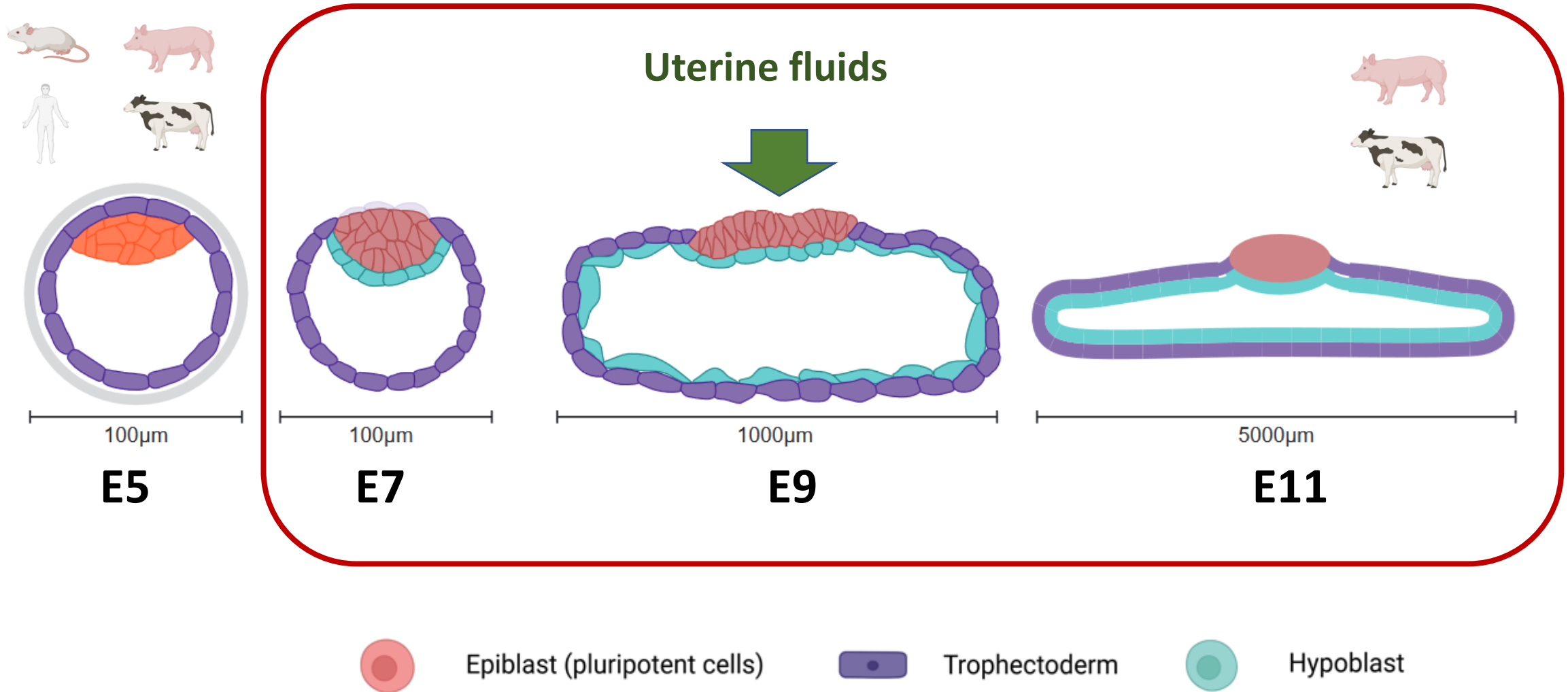


Reprogramming cocktail
(OCT4, SOX2, KLF4, MYC)



Heterogeneity ?
Stability overtime ?
Differentiation potential ?

➤ What can we learn from the embryo ?



➤ Working hypothesis

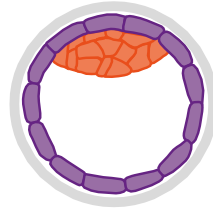


Paracrine regulations specific to pig embryonic development are not taken into consideration for the establishment of pig's pluripotent lines

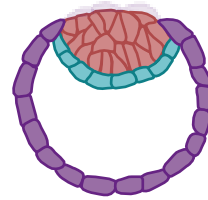


Embryonic regulatory networks are not necessarily conserved in mammals

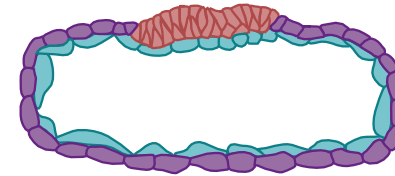
➤ Methods



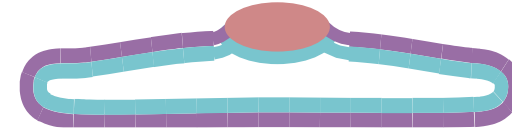
Early blastocyst **E5**



Hatched blastocyst **E7**



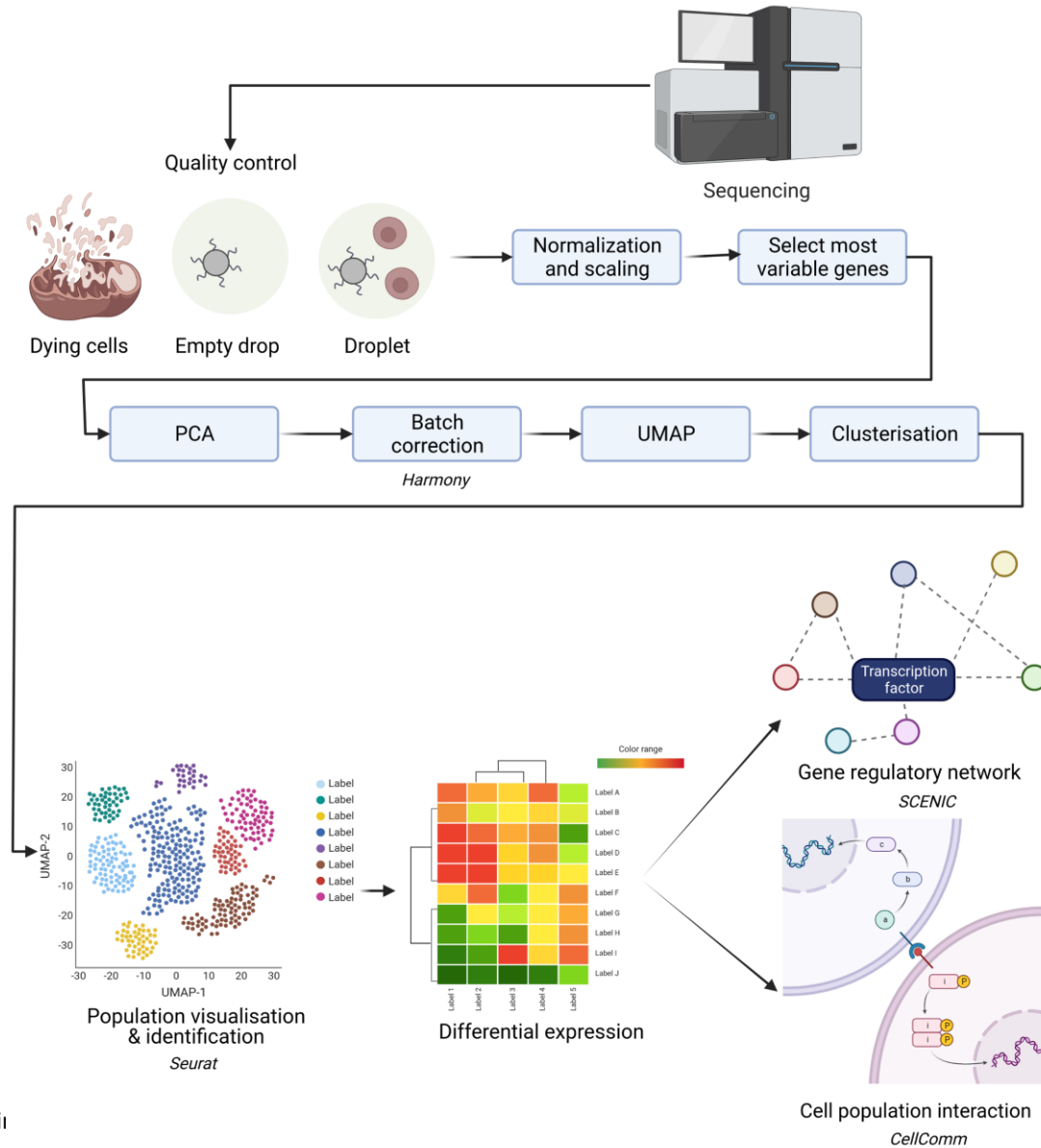
Spherical blastocyst **E9**



Ovoid blastocyst **E11**

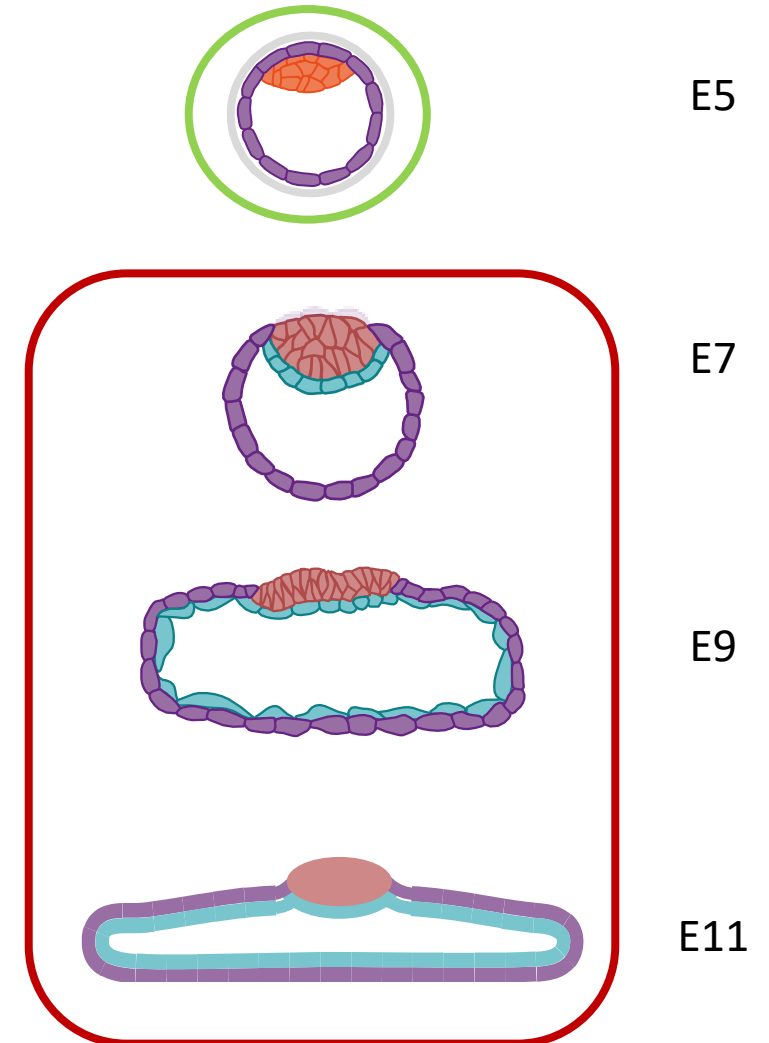
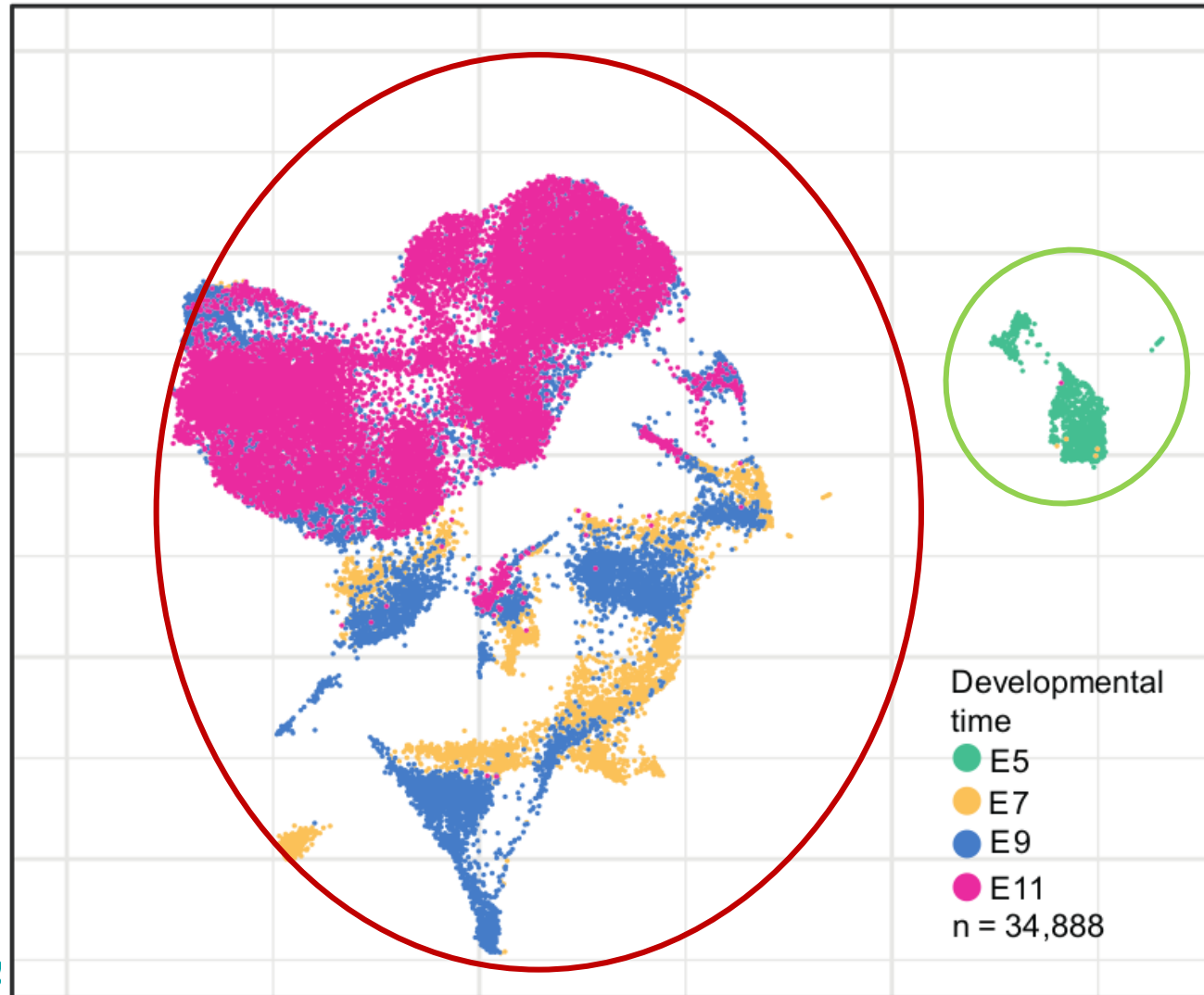
Single-cell RNAseq	2 libraries (~2000 cells each)	4 libraries (~1000 cells each)	4 libraries (~3000 cells each)	2 libraries (~6000 cells each)
Uterine fluids	8 sows	4 sows	3 sows	3 sows
Single-cell multiomics (scATAC-seq + scRNA-seq)	0	1 library (~2000 cell's nucleus)	2 libraries (~4000 cell's nucleus)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

➤ Methods

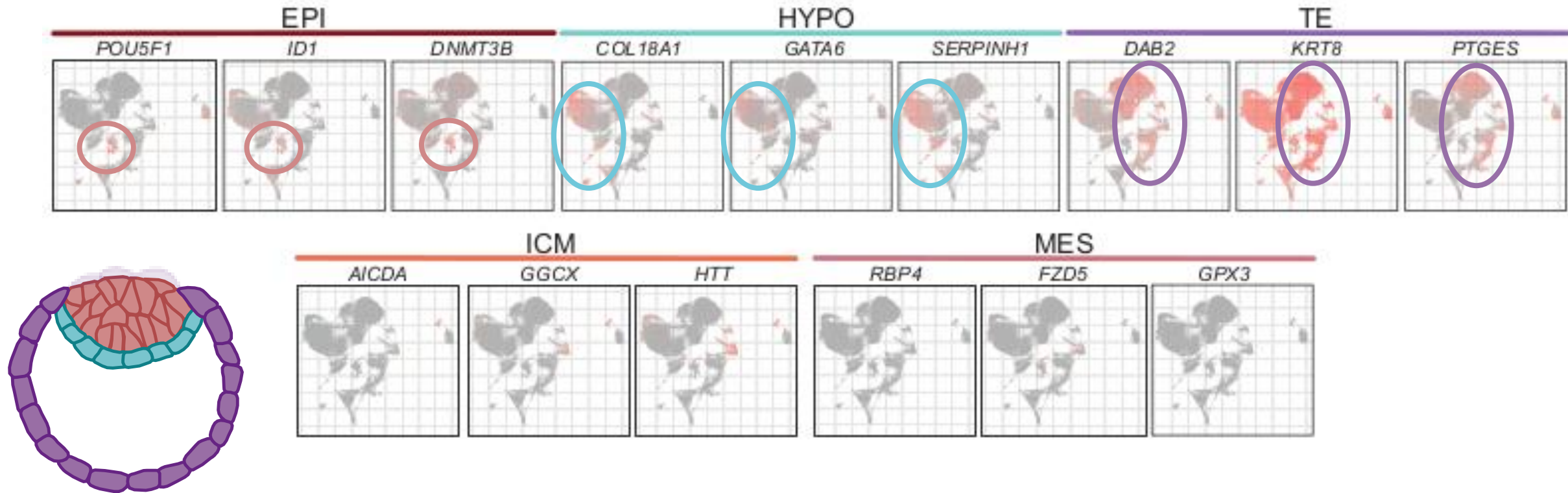


➤ scRNAseq allows the identification of cell populations constituting the embryo

UMAP
of 34,888 cells



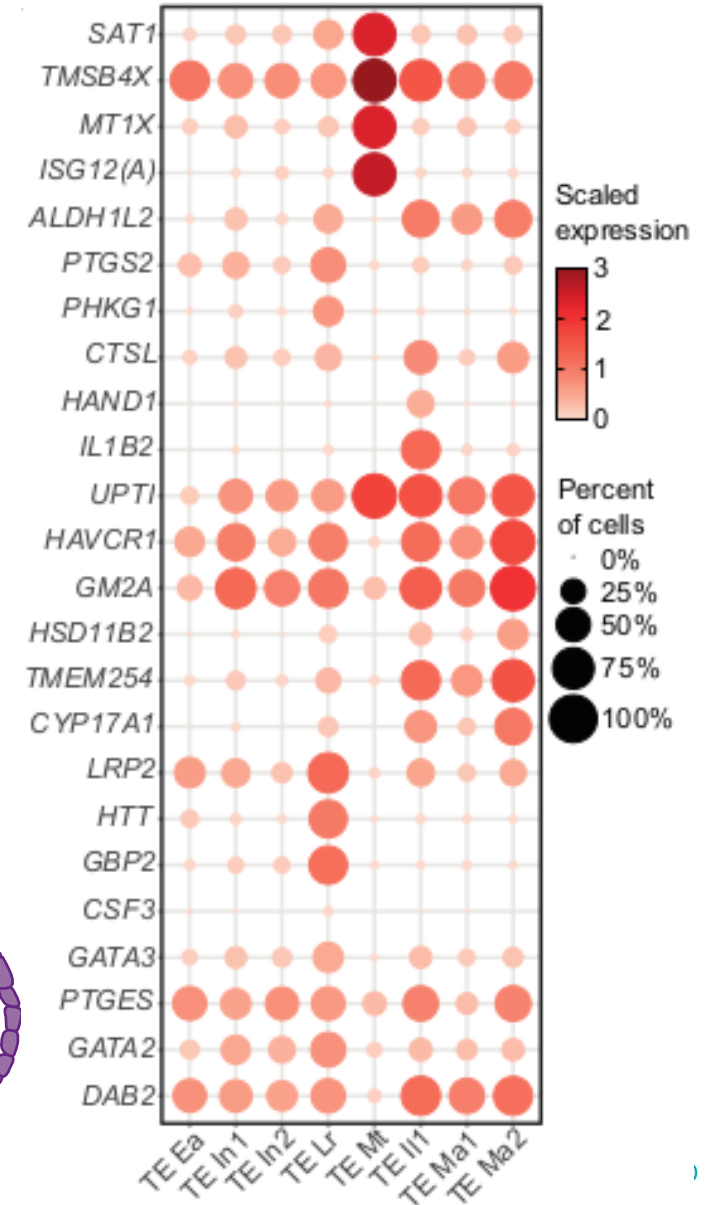
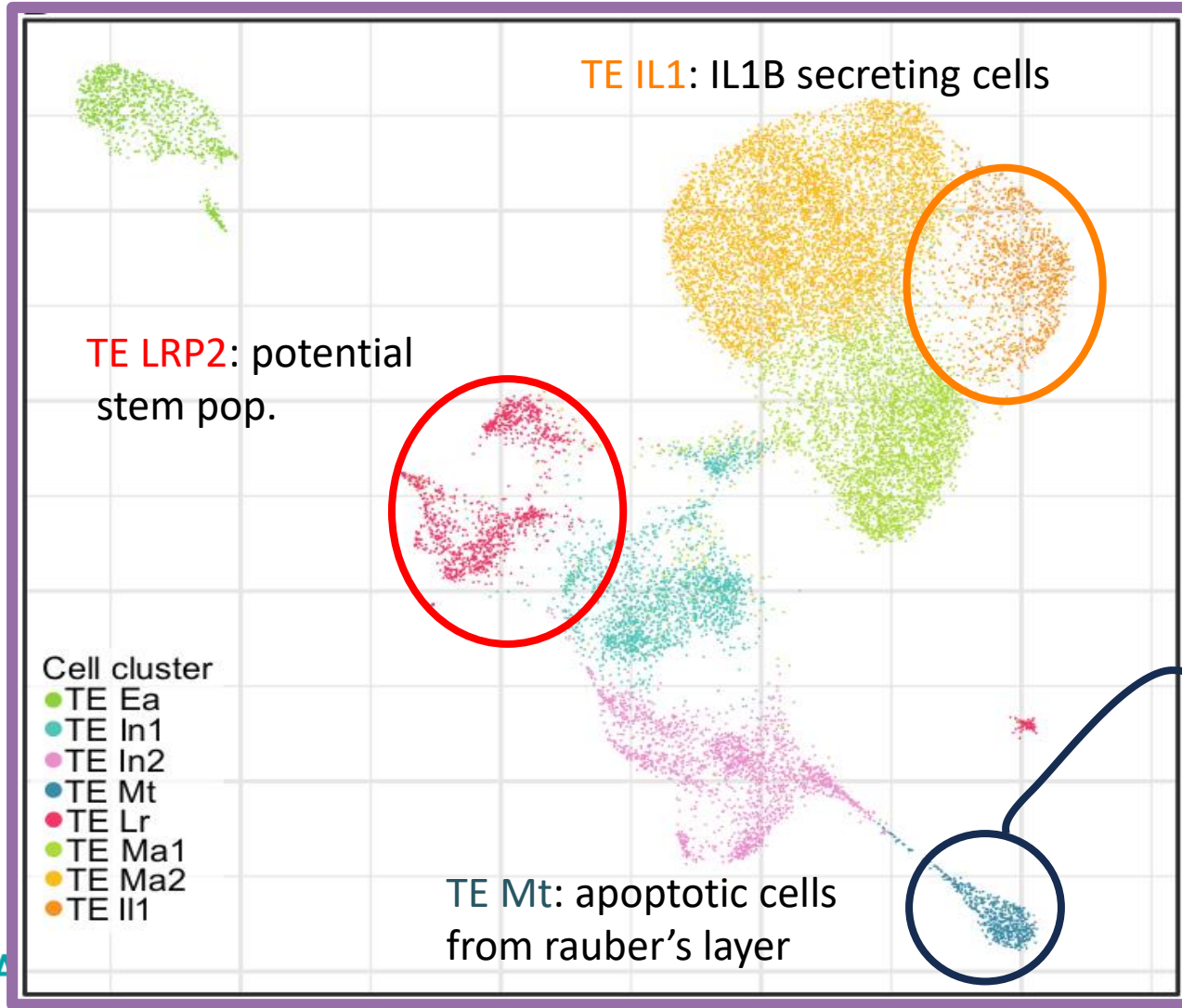
➤ scRNAseq allows the identification of cell populations constituting the embryo



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

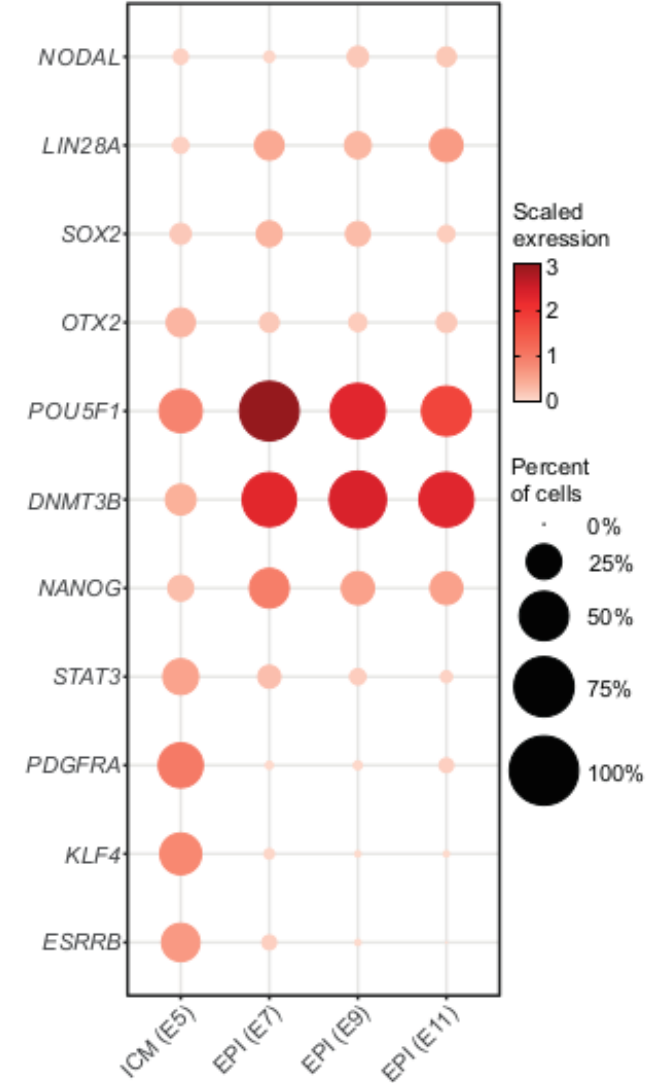
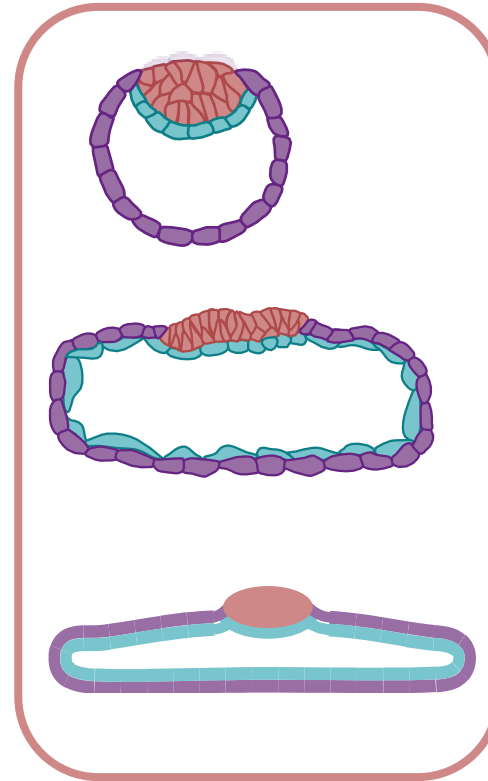
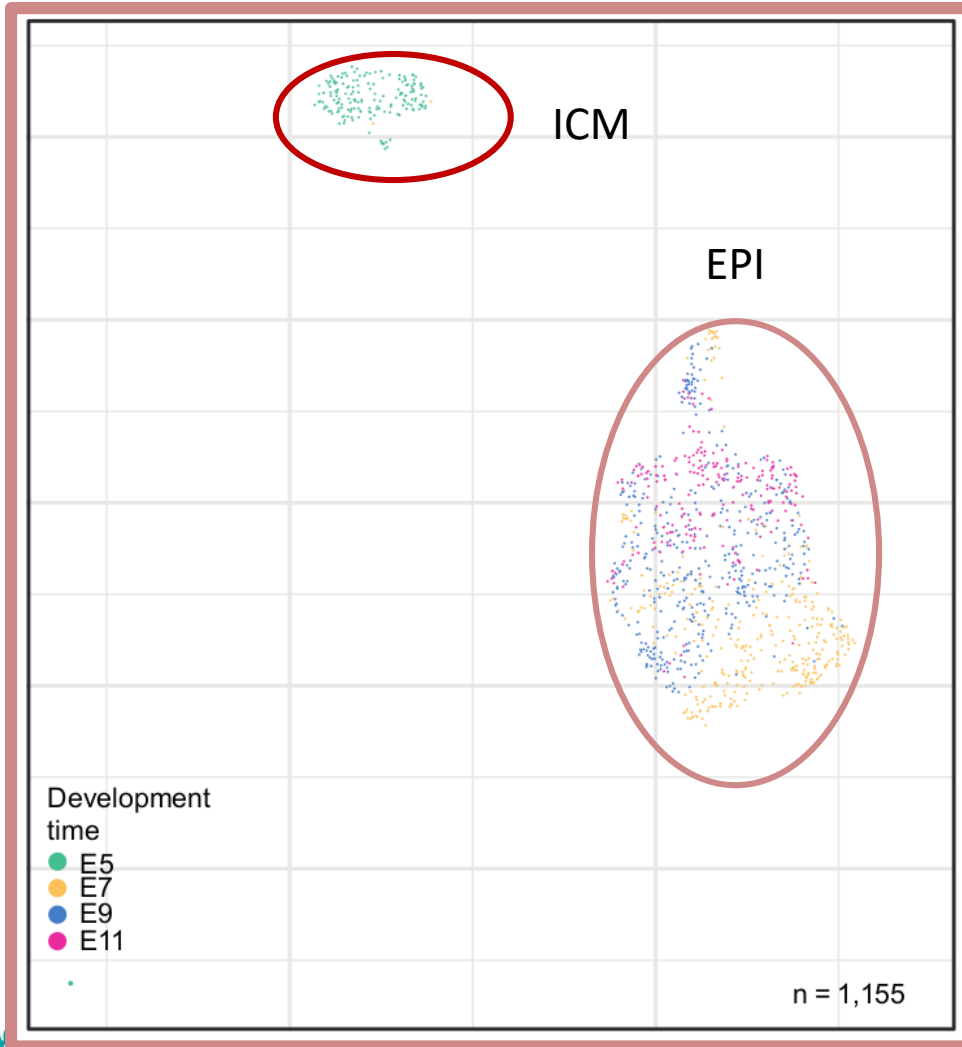
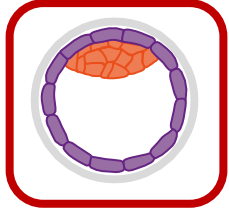
Identify new subpopulations

UMAP of 18,239 TE cells



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

Identify subpopulations



UMAP of 1'155 EPI cells

INRA

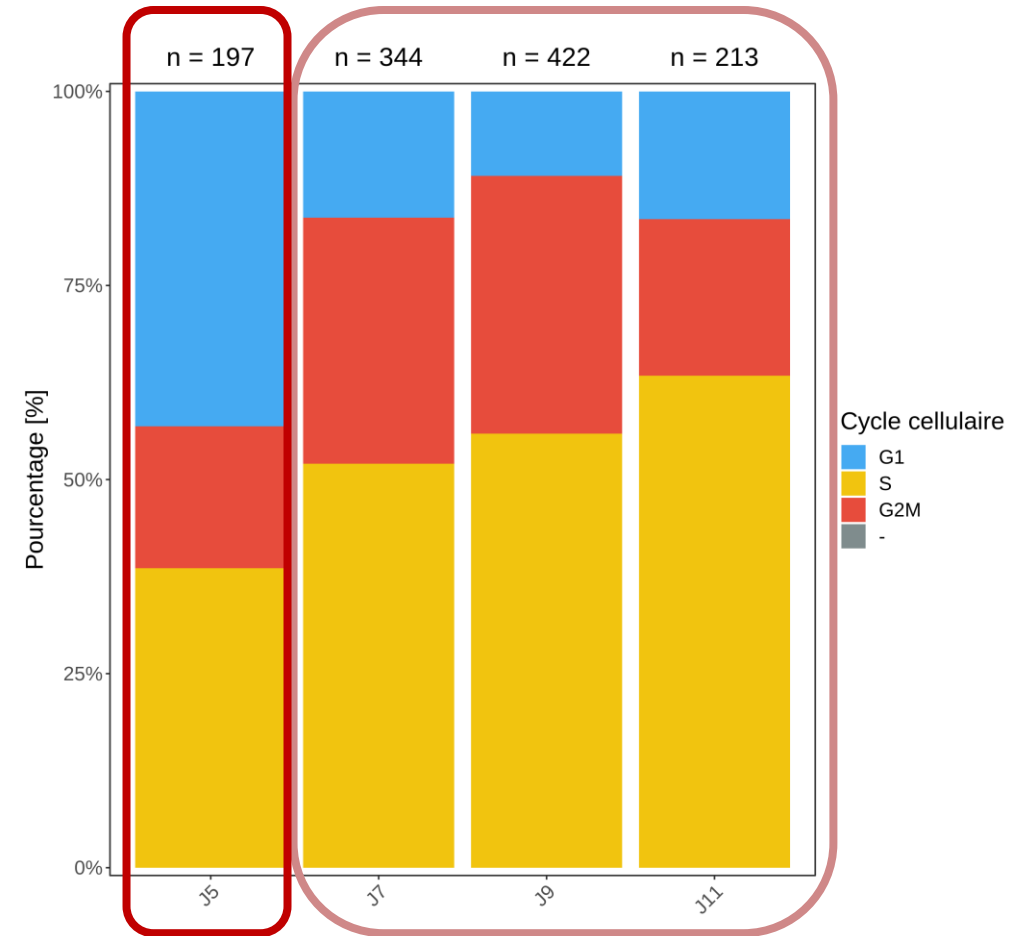
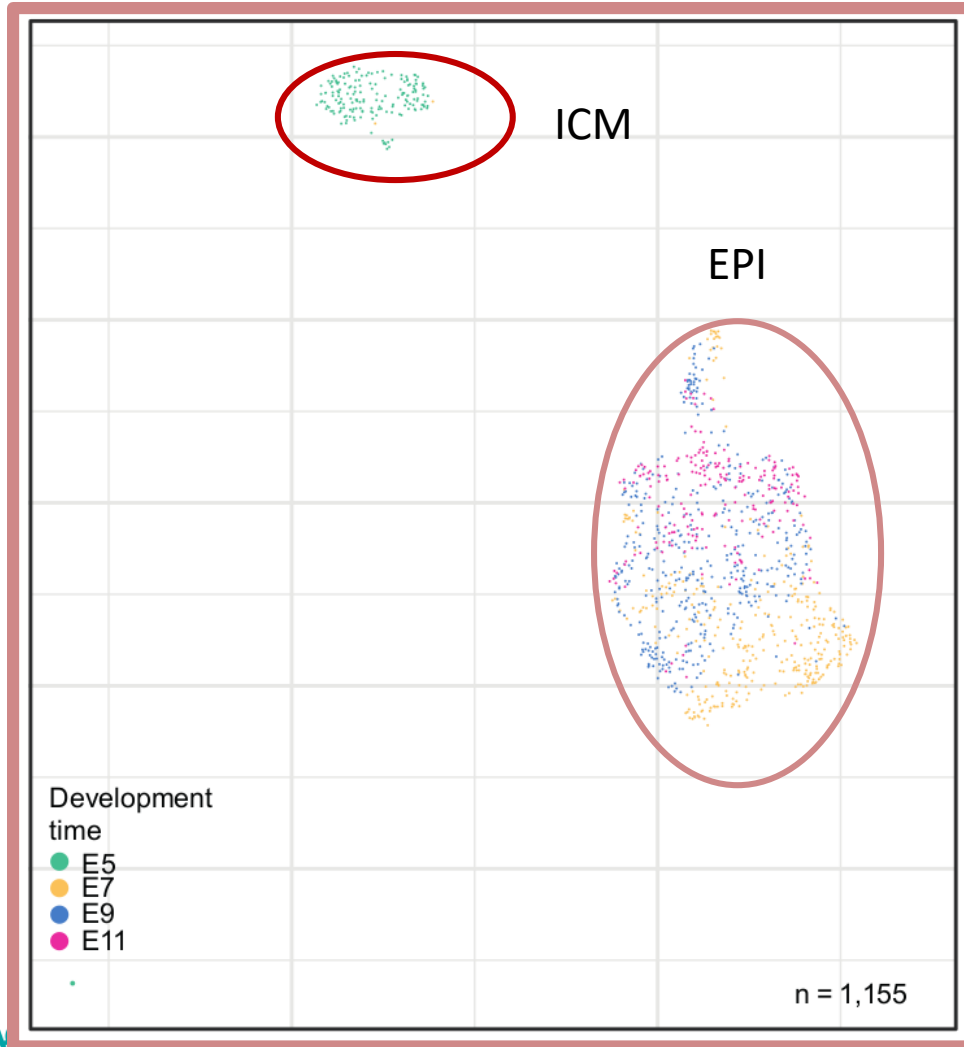
Gene networks controlling functional cell interactions in the pig embryo

16 Octobre 2023/ EPIPHASE meeting / Hervé Acloque

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

Identify subpopulations

UMAP of 1'155 EPI cells



INRA

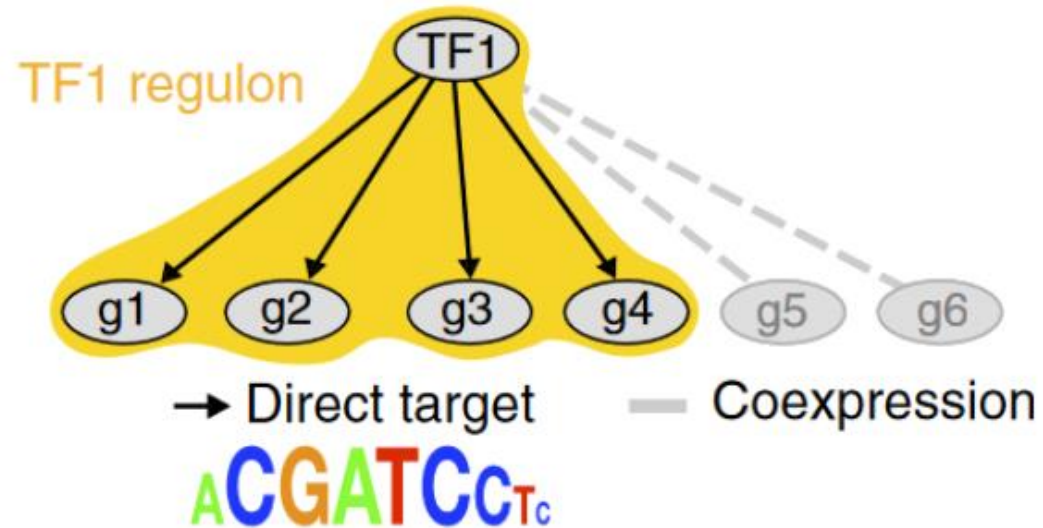
Gene networks controlling functional cell interactions in the pig embryo

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

Identify modules of gene regulation

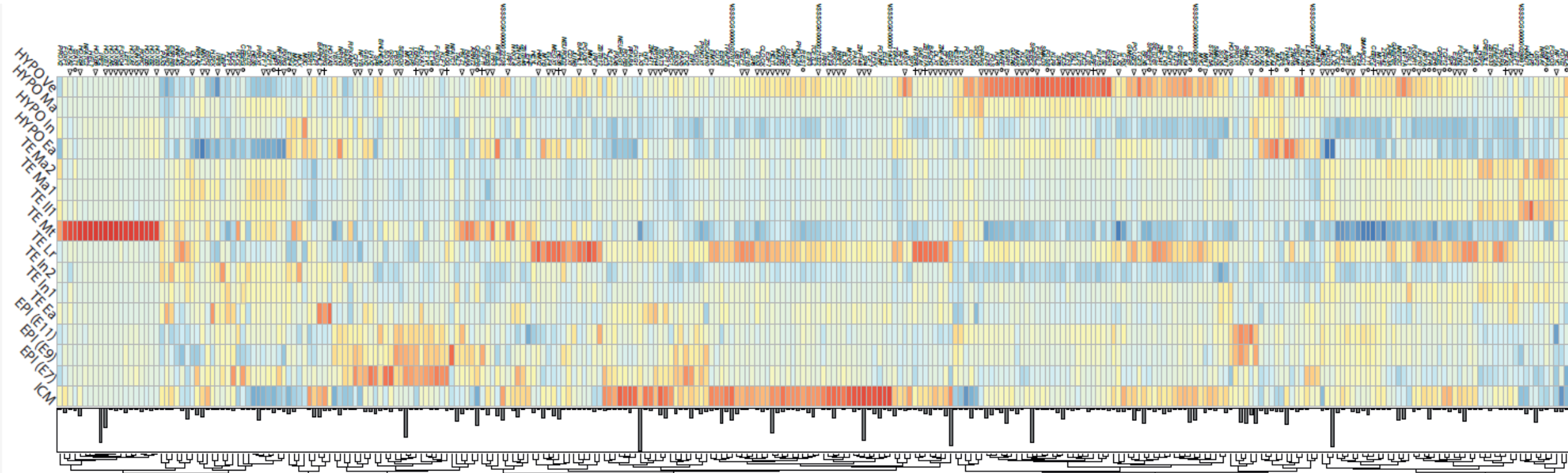
Regulons
(gene regulatory network)



Aibar et al. 2017

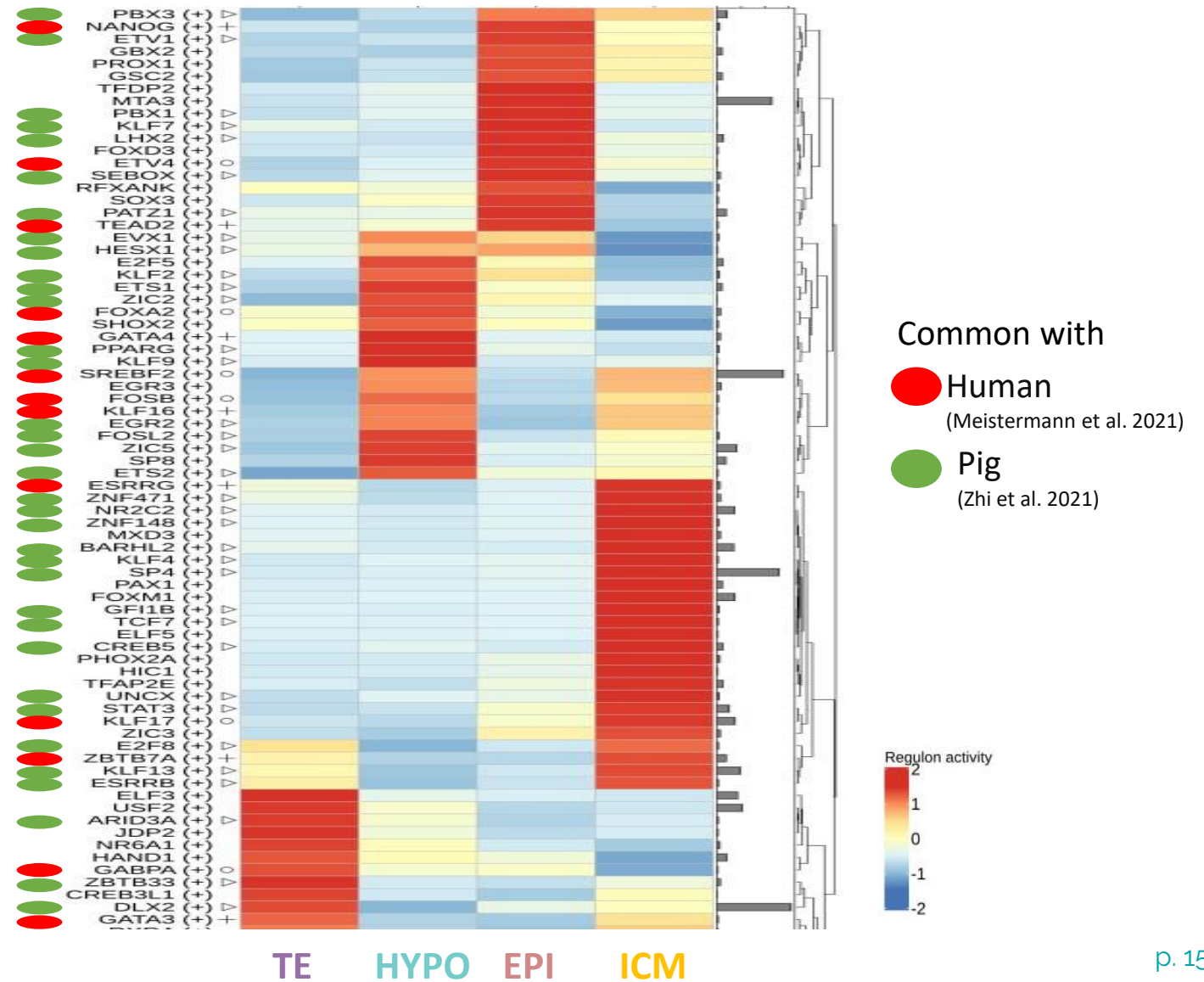
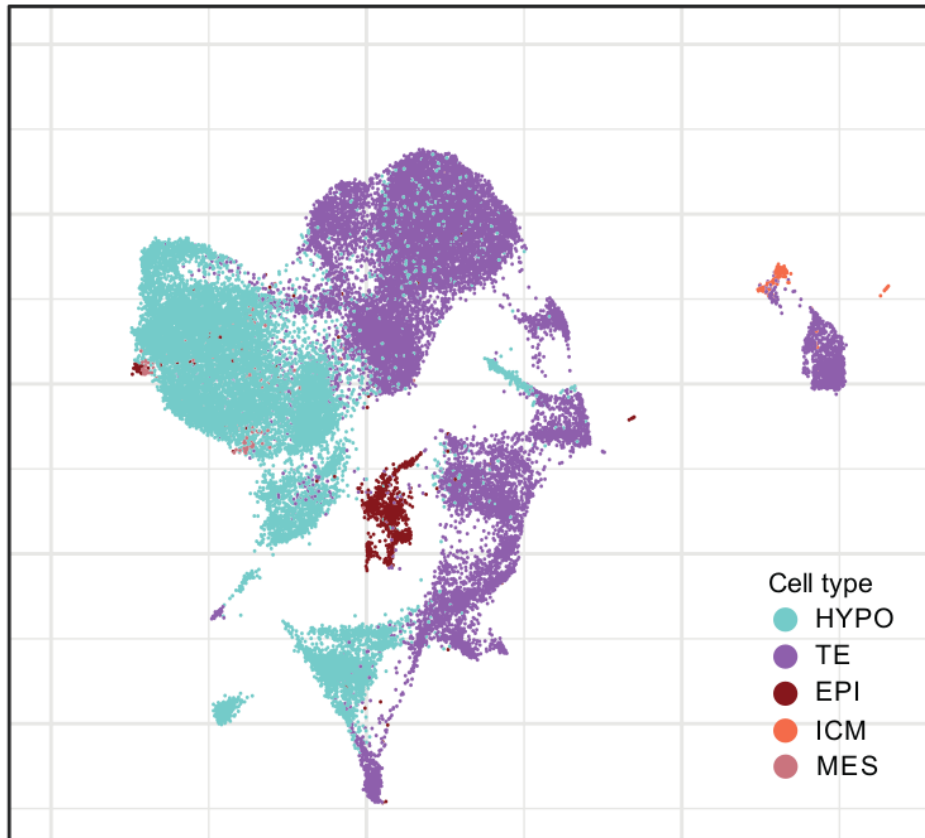
➤ scRNAseq data provide cues to better understand the biology of the pig embryo

Identify modules of gene regulation

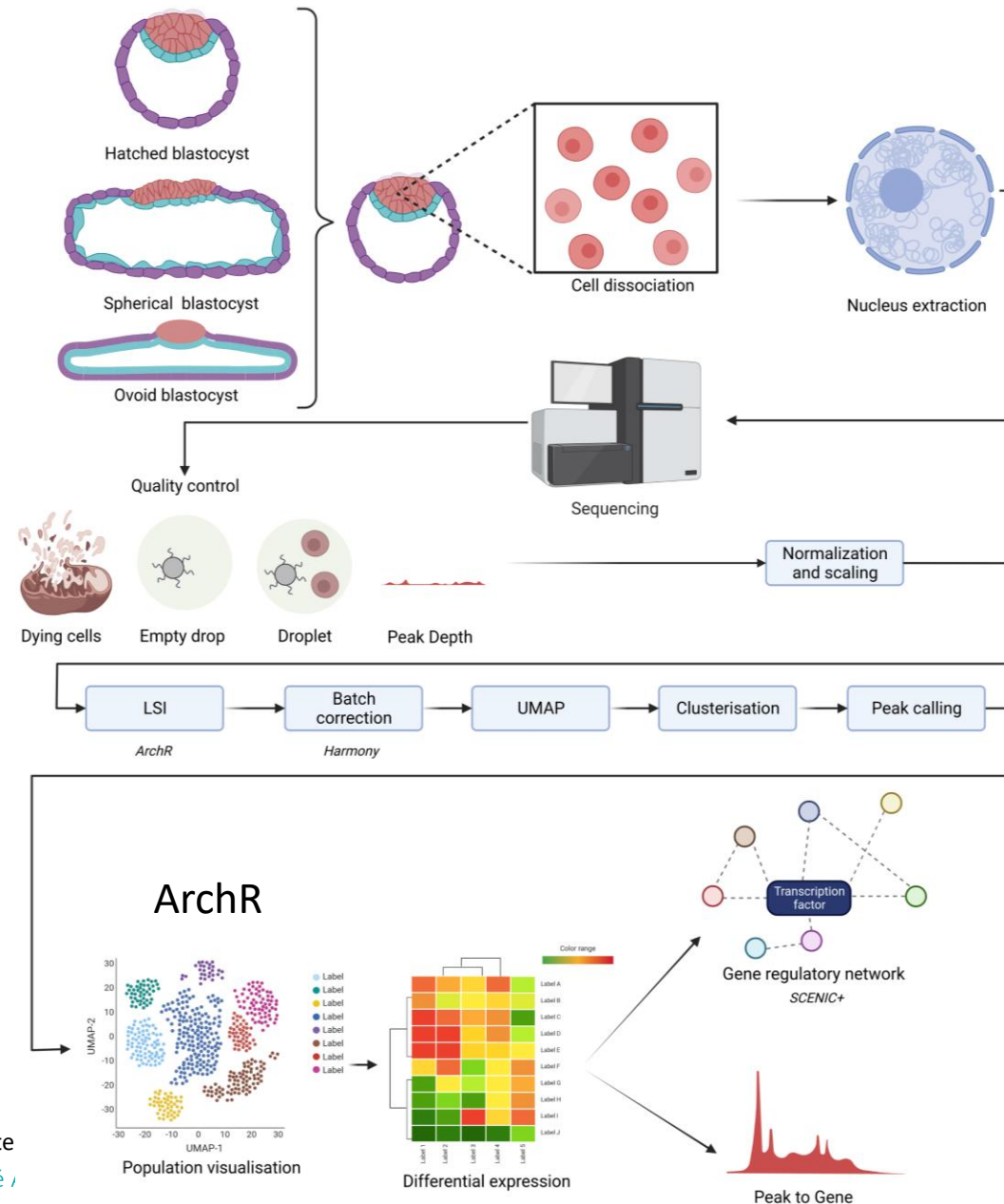


➤ scRNAseq data provide cues to better understand the biology of the pig embryo

Identify modules of gene regulation



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



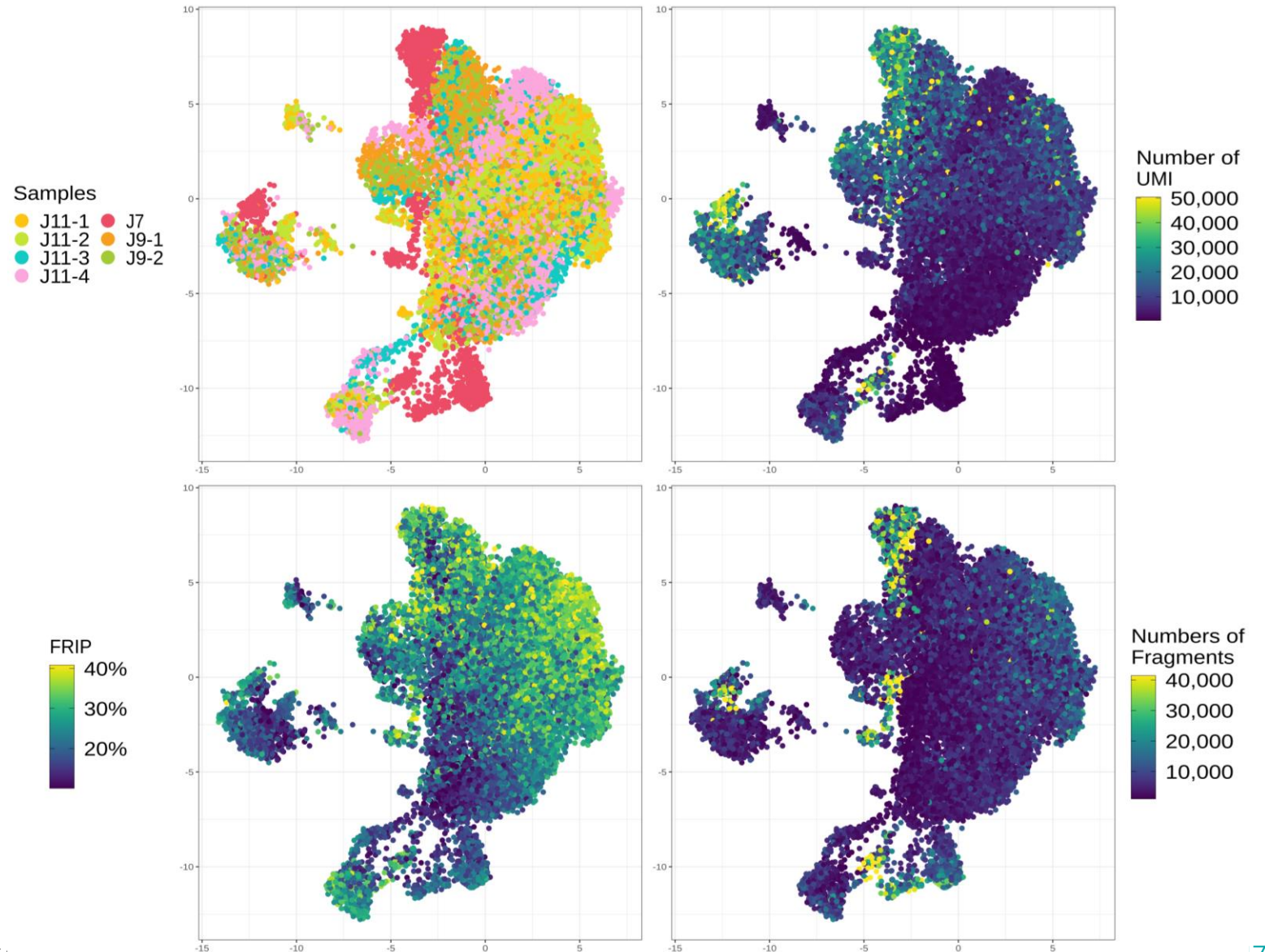
➤ scOMICS: adding a layer of information to refine module of gene regulation

Quality Control

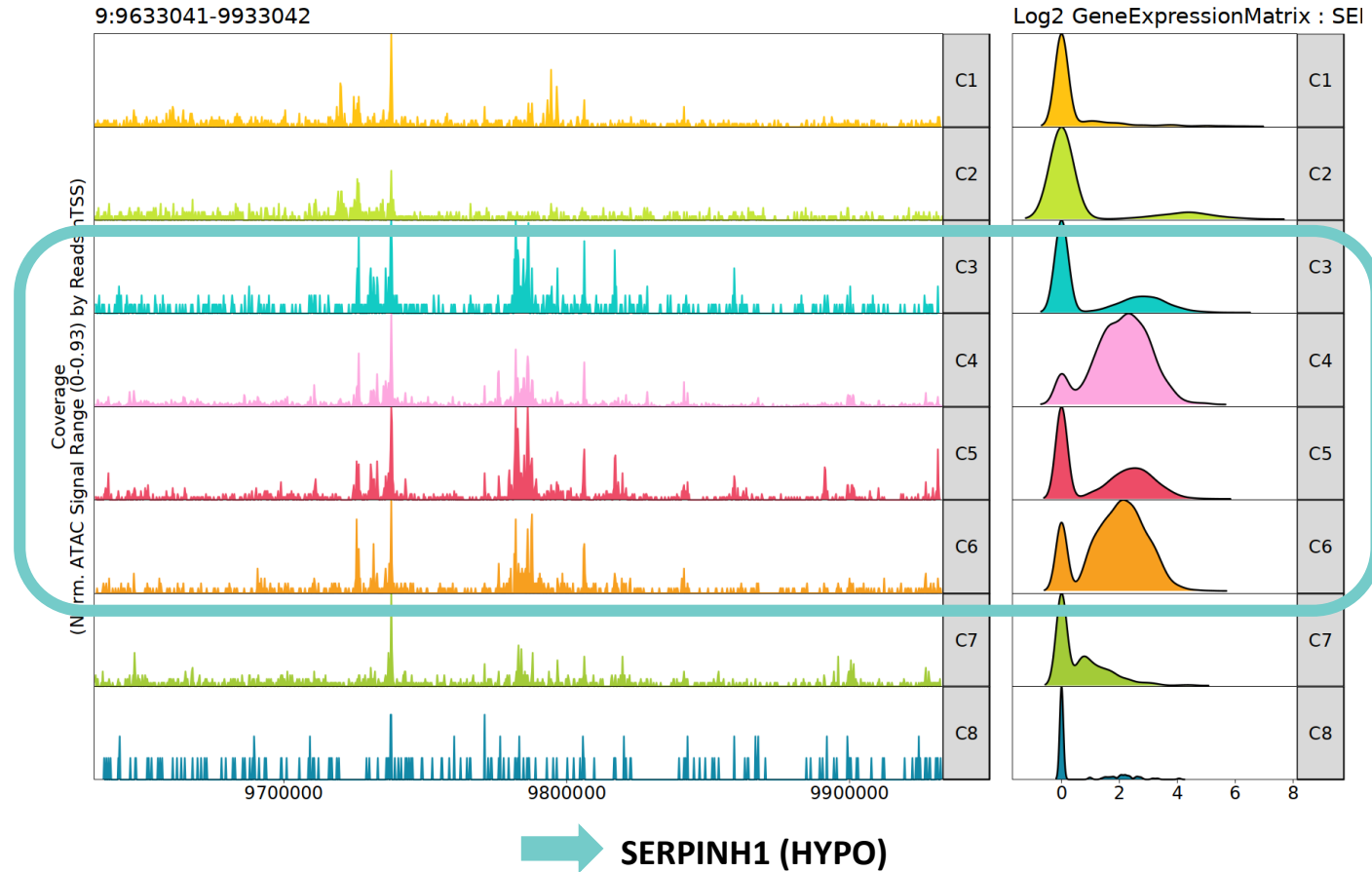
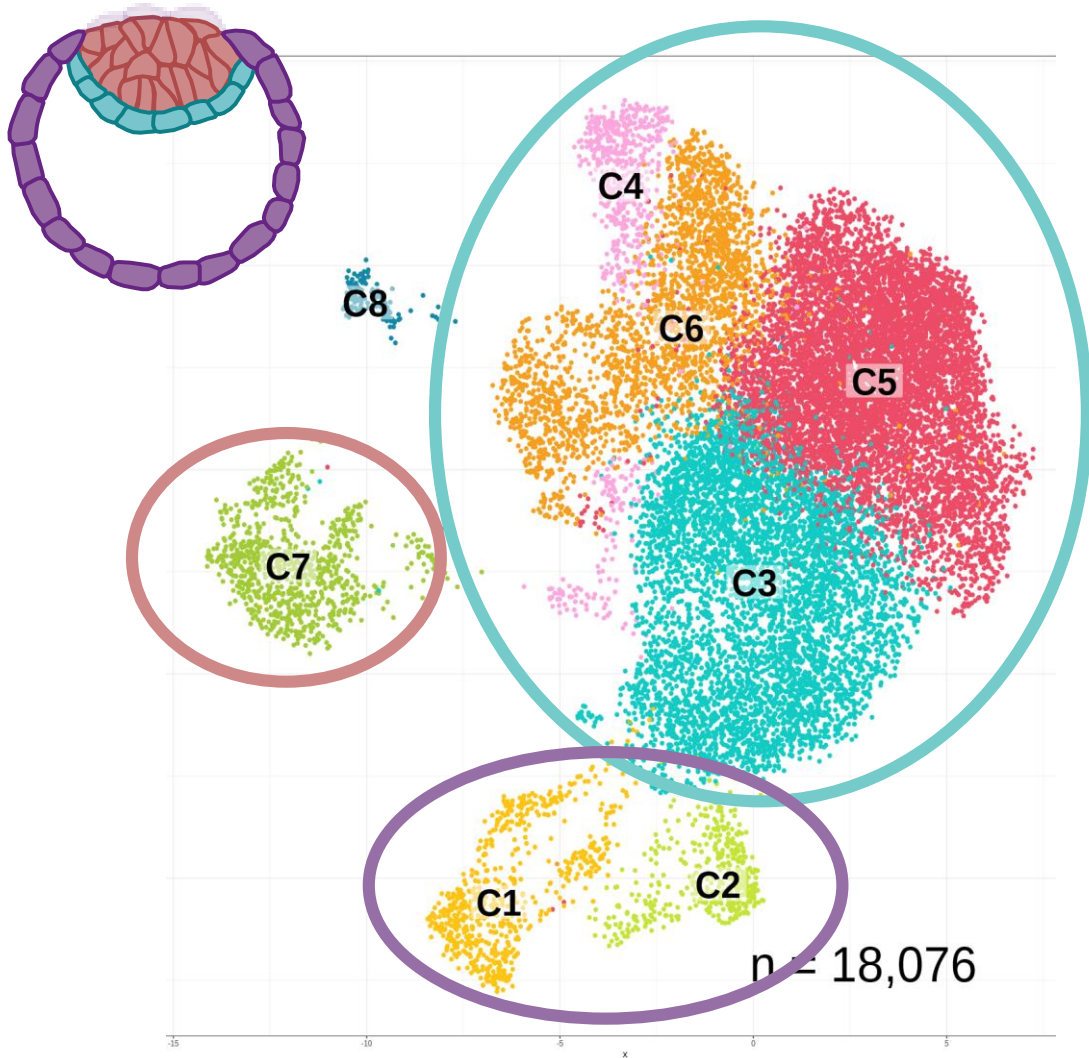
- Remove cells without both information (RNA+ATAC)
- Remove doublets (~5%)

Select cells based on:

- UMIs number
- Fragments number
- FRIP score

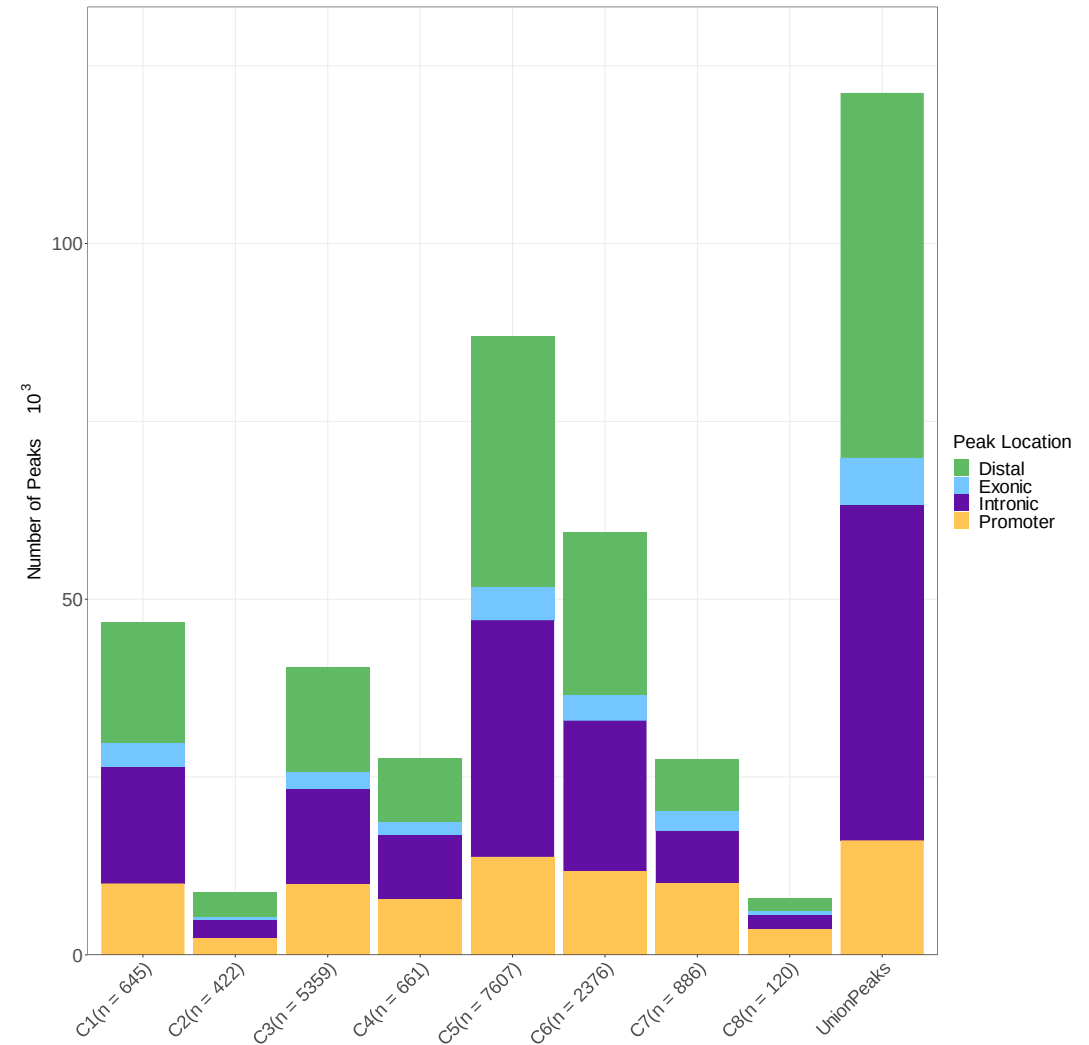


➤ scOMICS: adding a layer of information to refine module of gene regulation



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

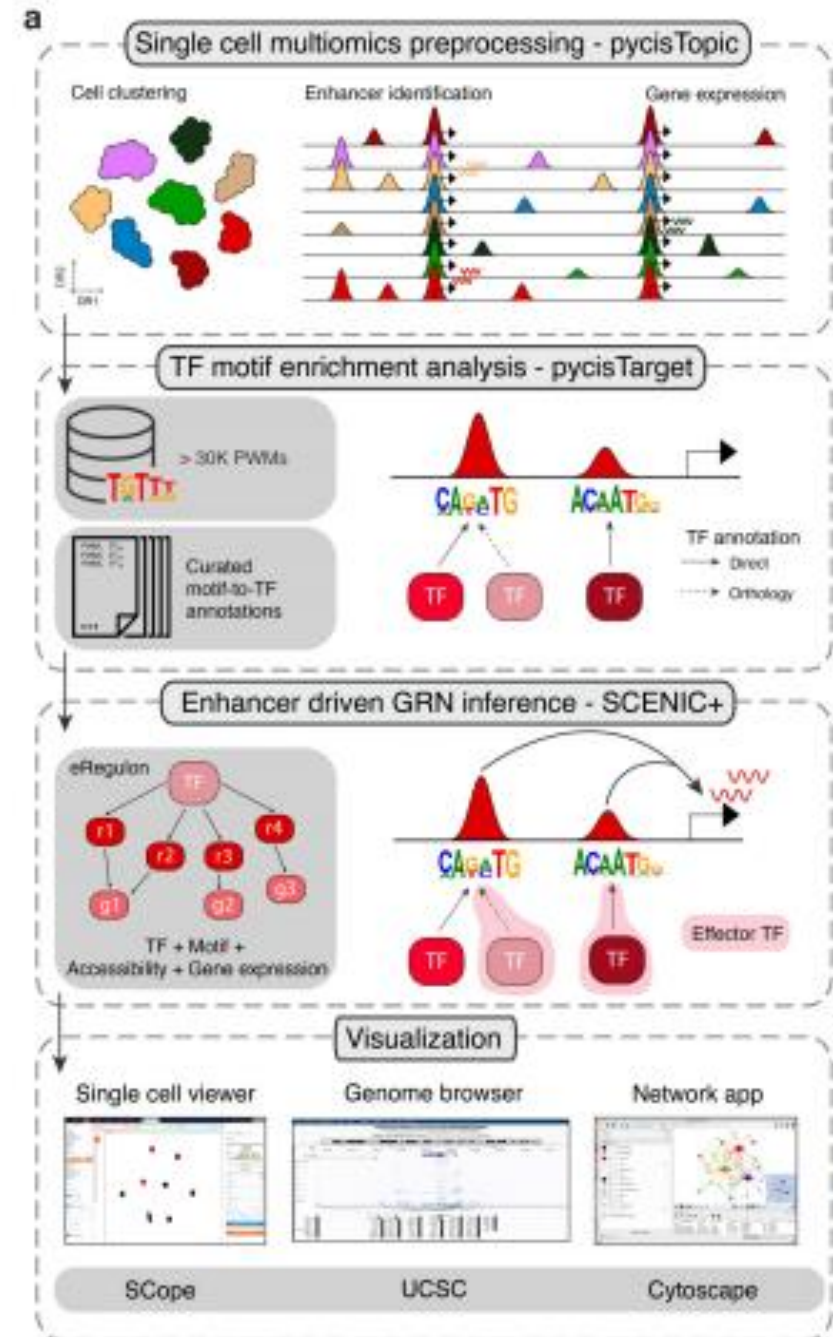
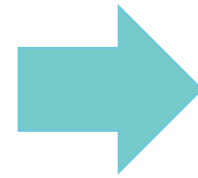
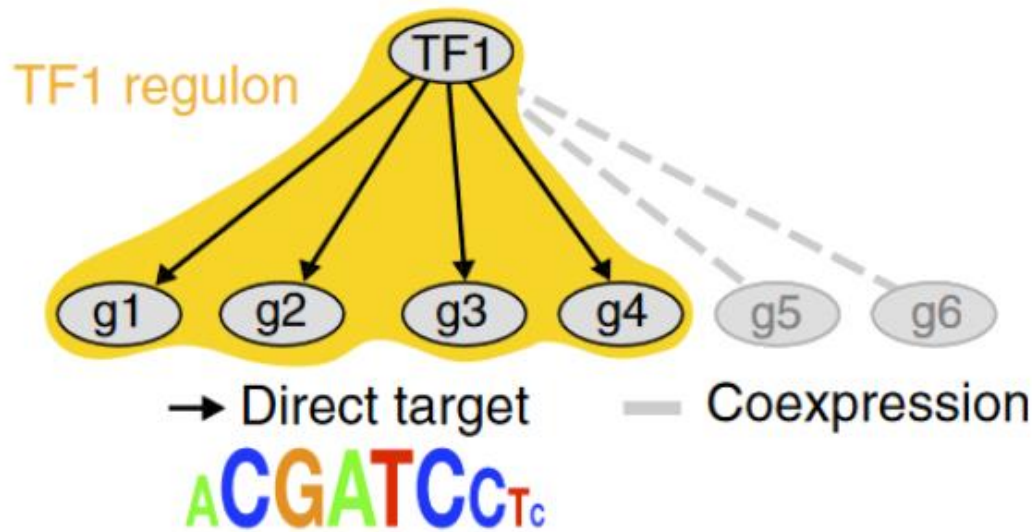
Peaks' localization



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

Identification of regulons By SCENIC+

Regulons
(gene regulatory network)

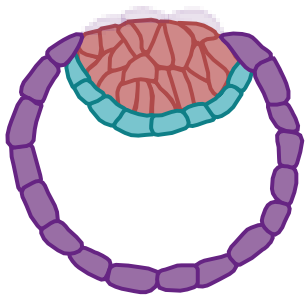
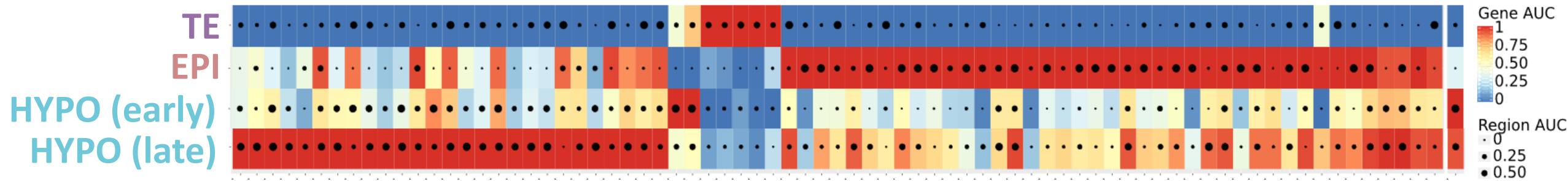


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Gene networks controlling functional cell interactions in the pig embryo

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➤ Added value of omics data: selection of active regulons

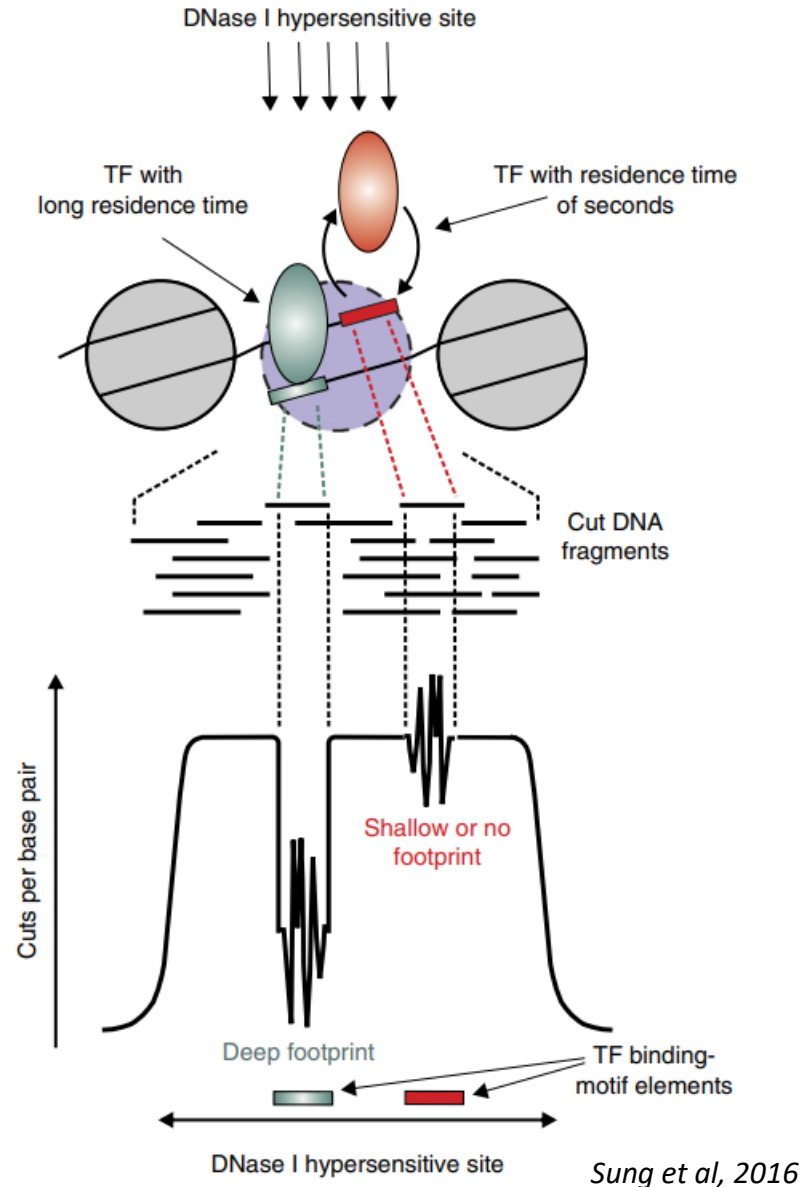


INRAE

Dufour et al. unpublished

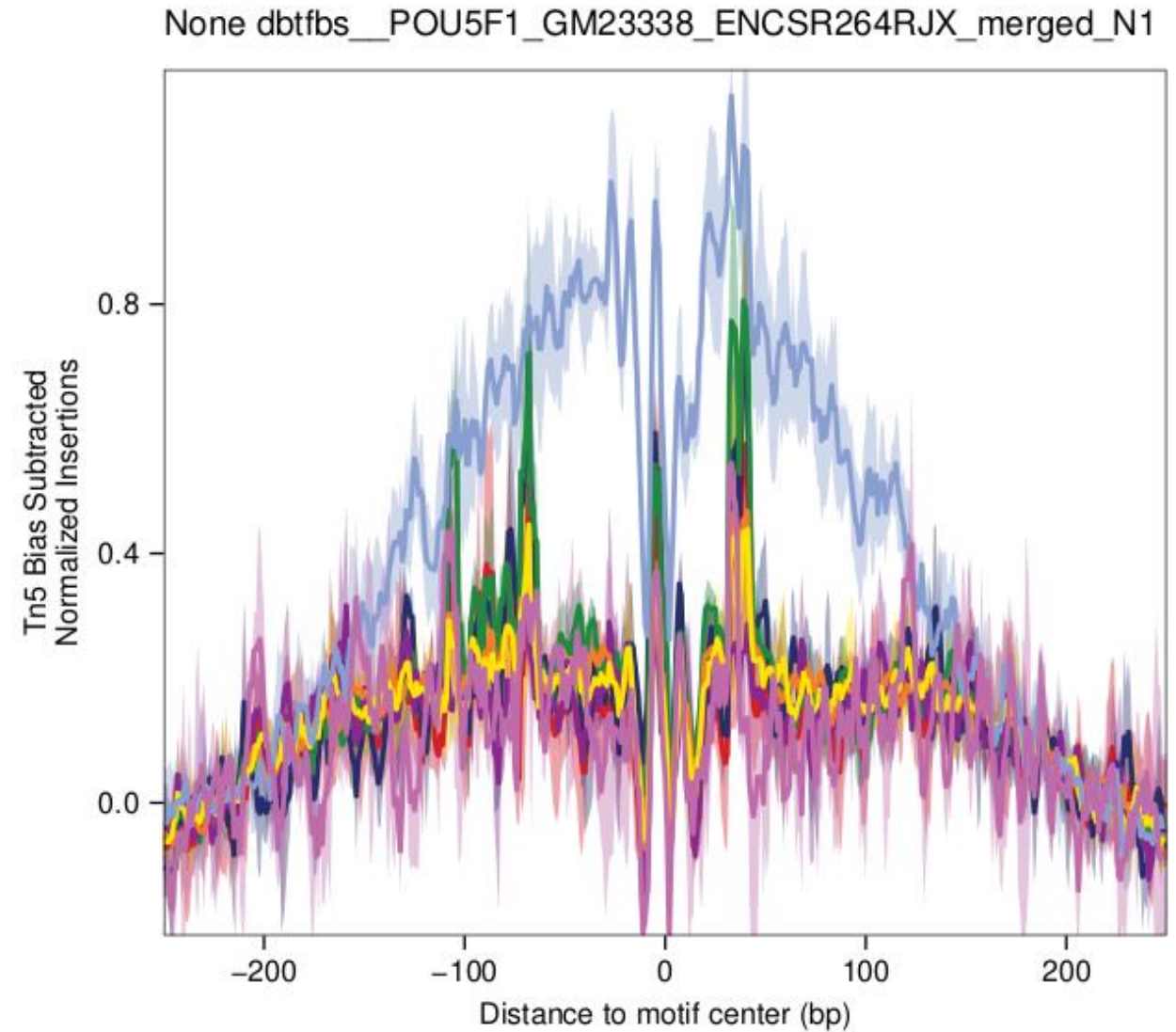
➤ Added value of omics data: selection of active regulons

Detection of TFs' footprint



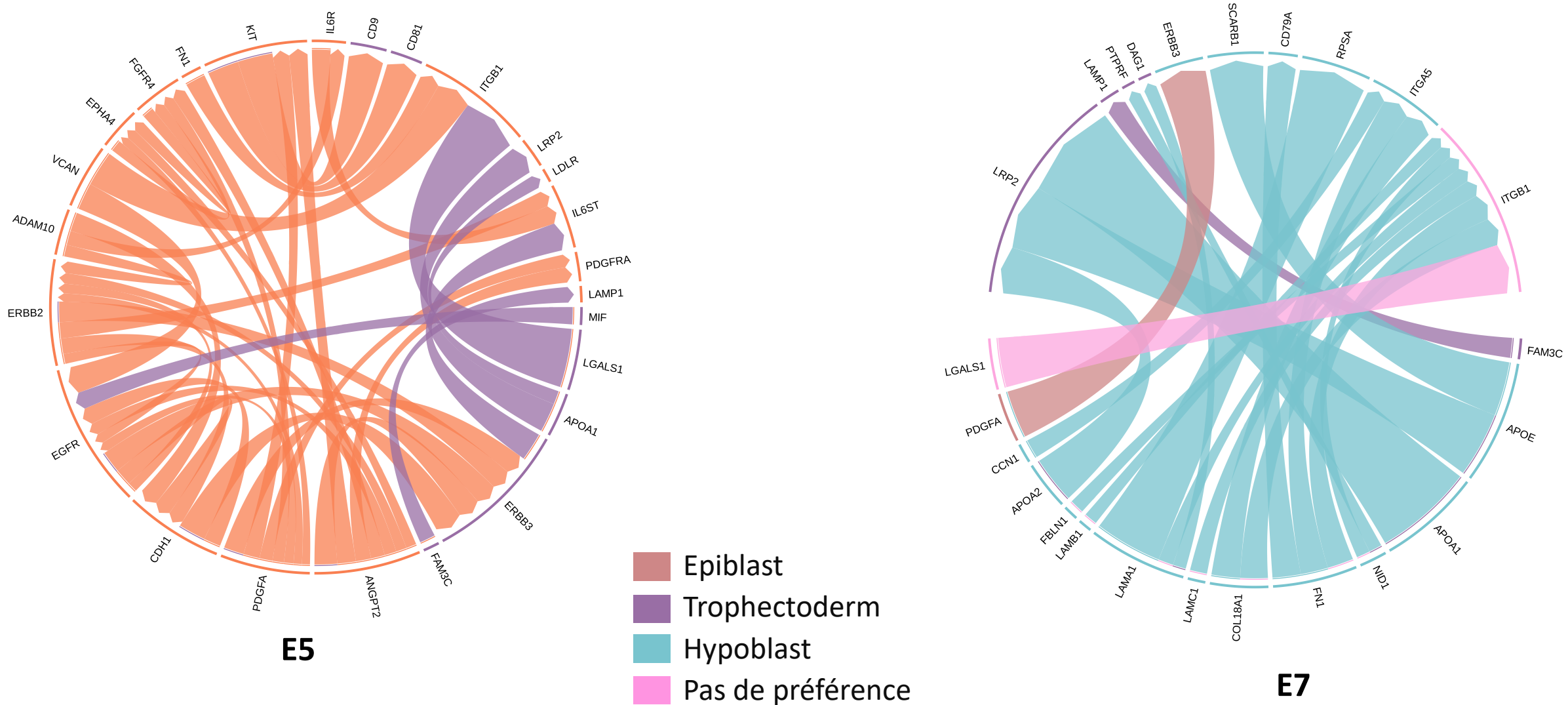
➤ Added value of omics data: selection of active regulons

Detection of TFs' footprint



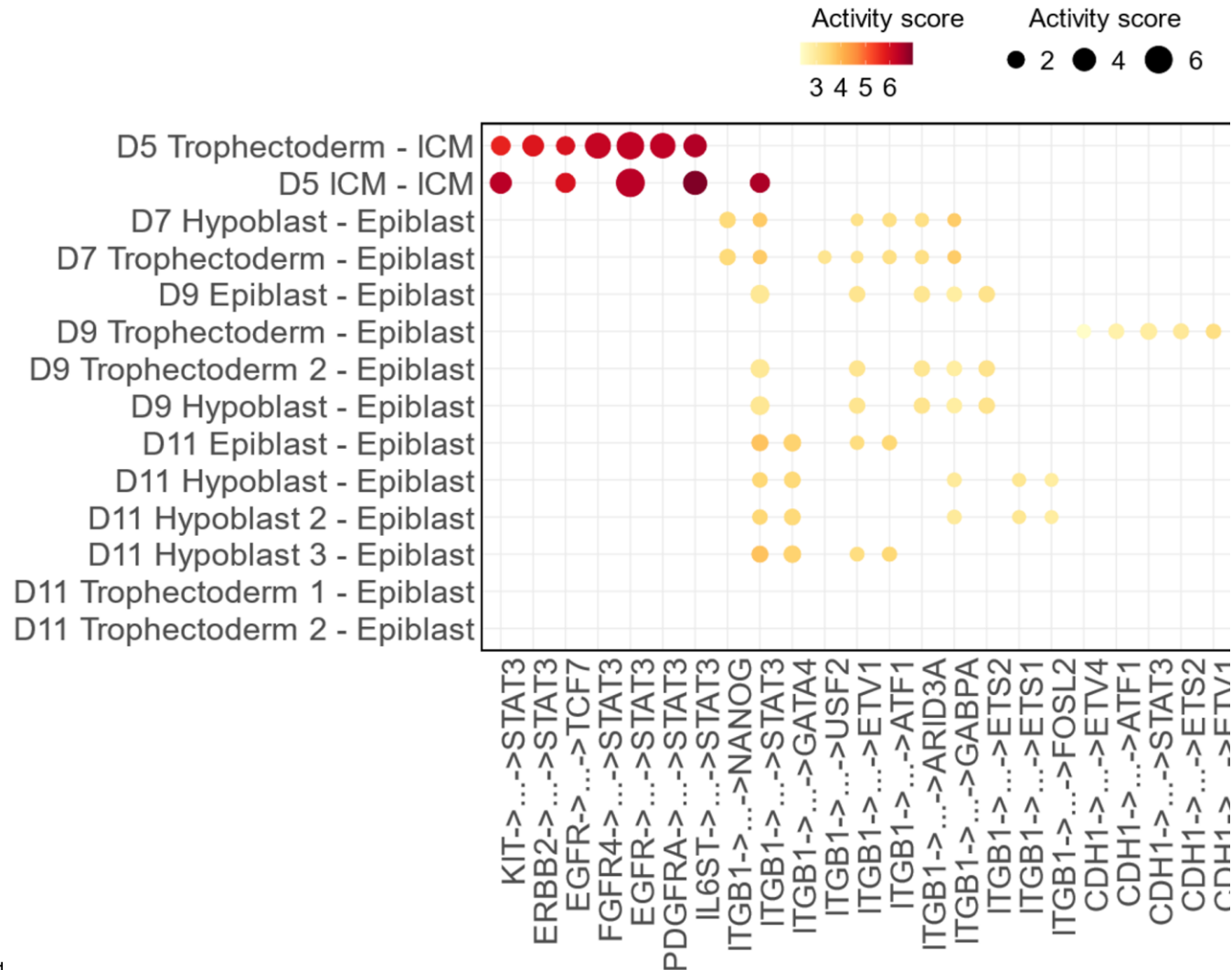
scRNAseq data provide cues to better understand the biology of the pig embryo

From ligand/receptor interactions to modules of gene regulation



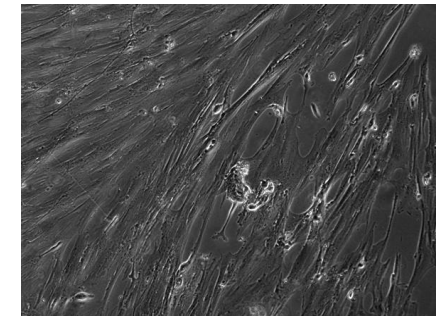
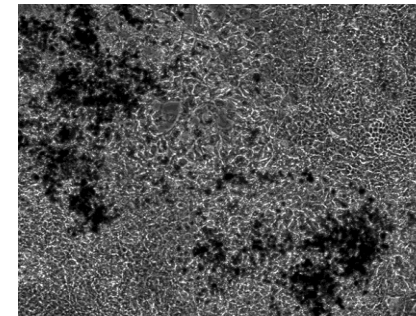
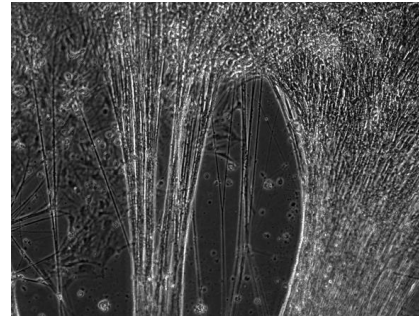
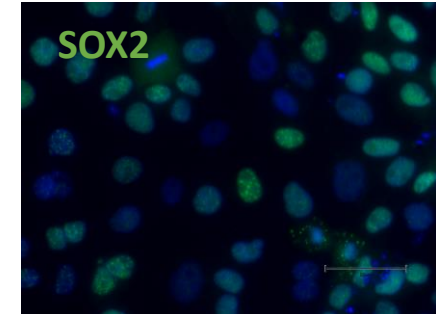
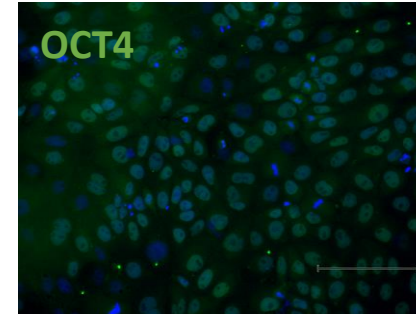
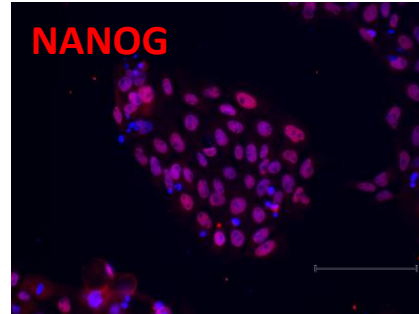
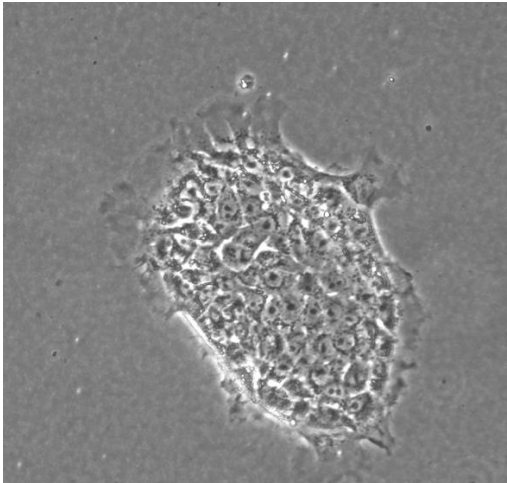
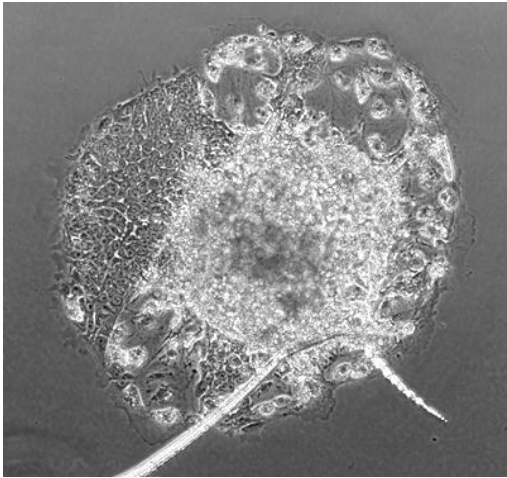
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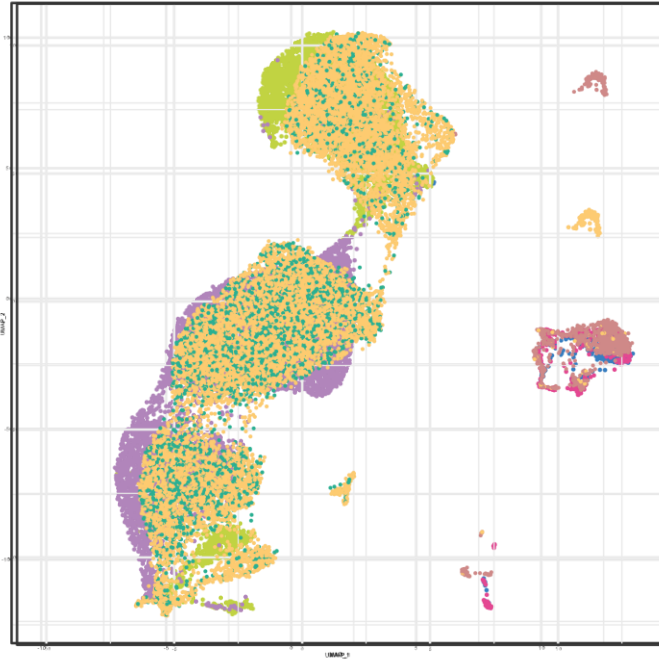


➤ Omics plus-value: detection of poised states in pig ESCs

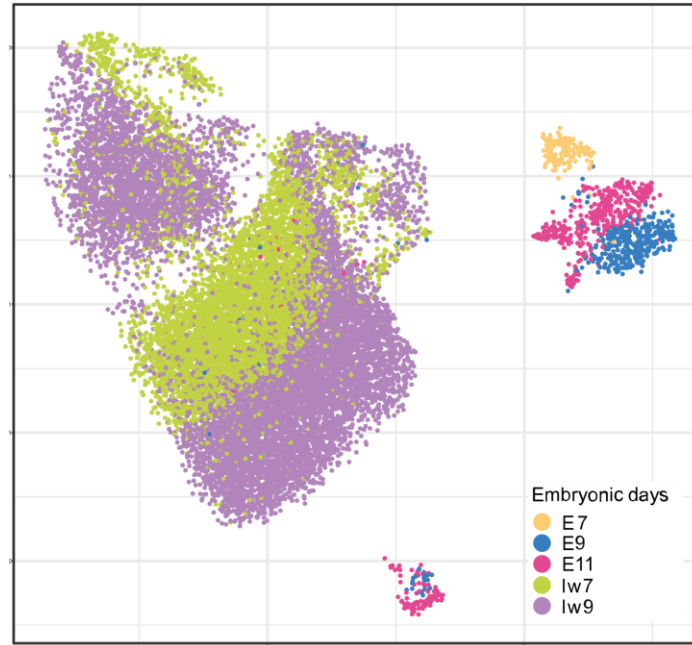
Pig ESCs



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

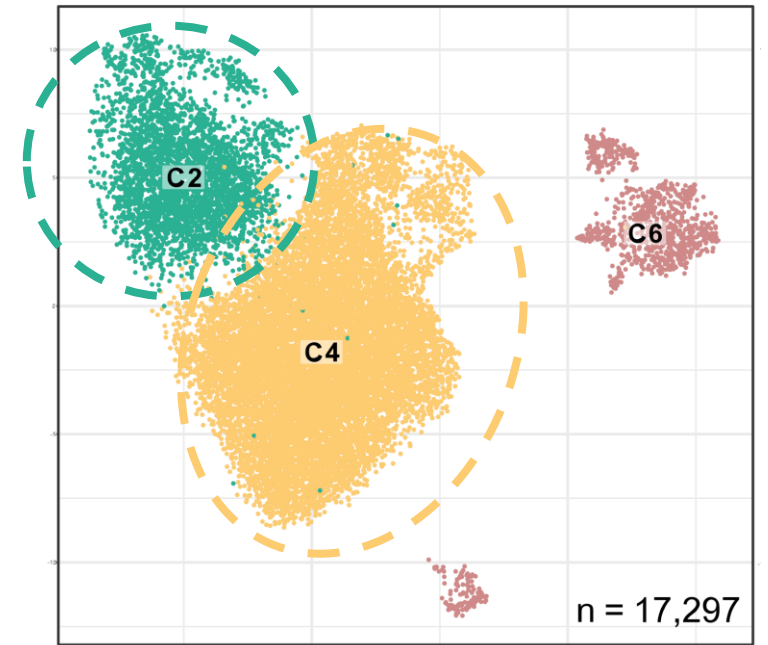


scRNAseq



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



➤ Acknowledgements

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