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Deciphering mechanisms driving malignant transformation in Neurofibromatosis Type I, from single-cell transcriptomics

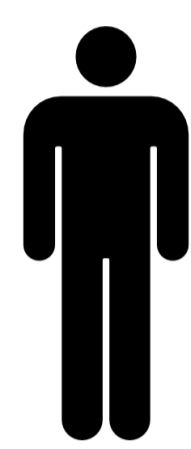
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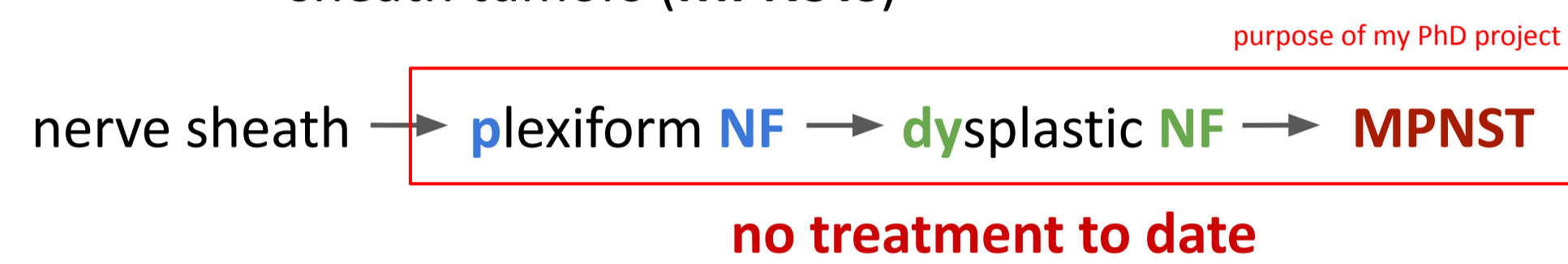
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NF1 IS A GENETIC DISEASE



- Affects 1 / 3,000 births worldwide
- Bi-allelic mutation of **NF1** in Schwann cell lineage
- Numerous symptoms, including development of benign nerve sheath tumors : **neurofibromas** (NFs), and their progression to malignant peripheral nerve sheath tumors (**MPNSTs**)



Nf1-KO MOUSE MODEL [1]

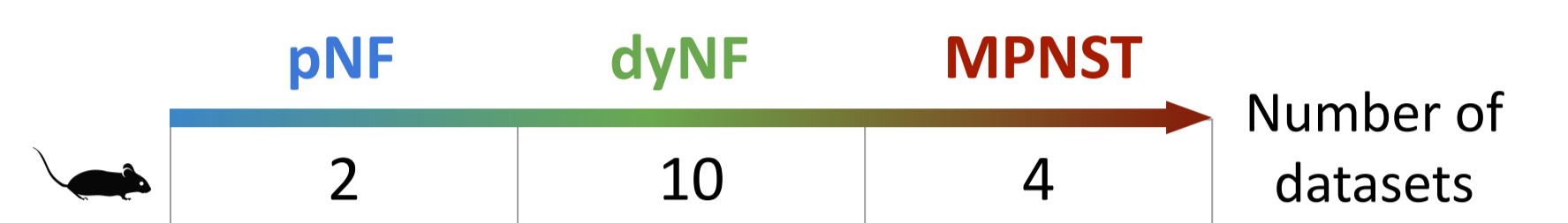


- Bi-allelic mutation of **Nf1** in Schwann cell lineage
- **Nf1** mutant cells are traced by the **Tomato** reporter
- **Nf1**-KO mice share common features with NF1 patients, including development of pNFs and their progression into MPNSTs through a dysplastic stage

What are the molecular events driving malignant transformation of pNF into MPNST, in tumor forming cell populations, in the mouse model and in NF1 patients ?

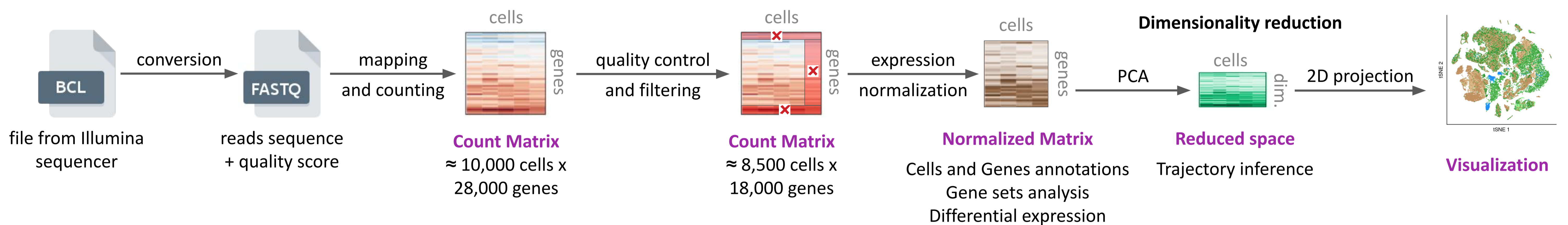
AVAILABLE DATASETS

Single-cell transcriptomic technologies enable the study of NFs and MPNSTs transcriptional landscapes considering their cellular heterogeneity.



Single-cell RNA sequencing : for each biological sample, we have a genes x cells expression matrix

METHODS



RESULTS

Peripheral Nerve Sheath Tumors atlas from Nf1-KO mice

What is the identity of each cell population ?

Figure 1 - tSNE showing 60,000 cells from 16 datasets. One dot represents one single cell. Cells are colored by sample of origin. Batch-effect has been removed using harmony [2]. Some cell populations are specific from pNF (blue) or MPNST (brown).

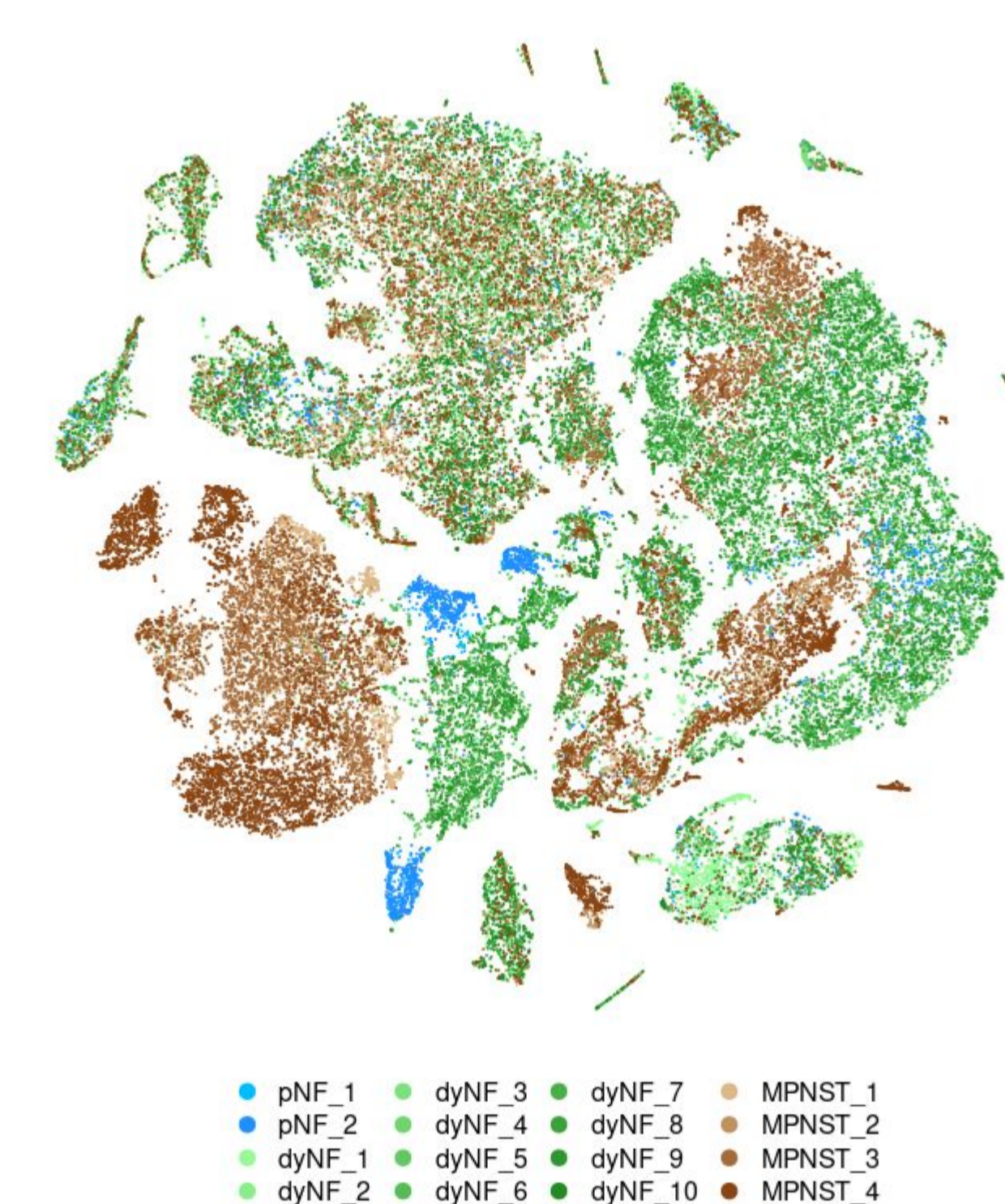
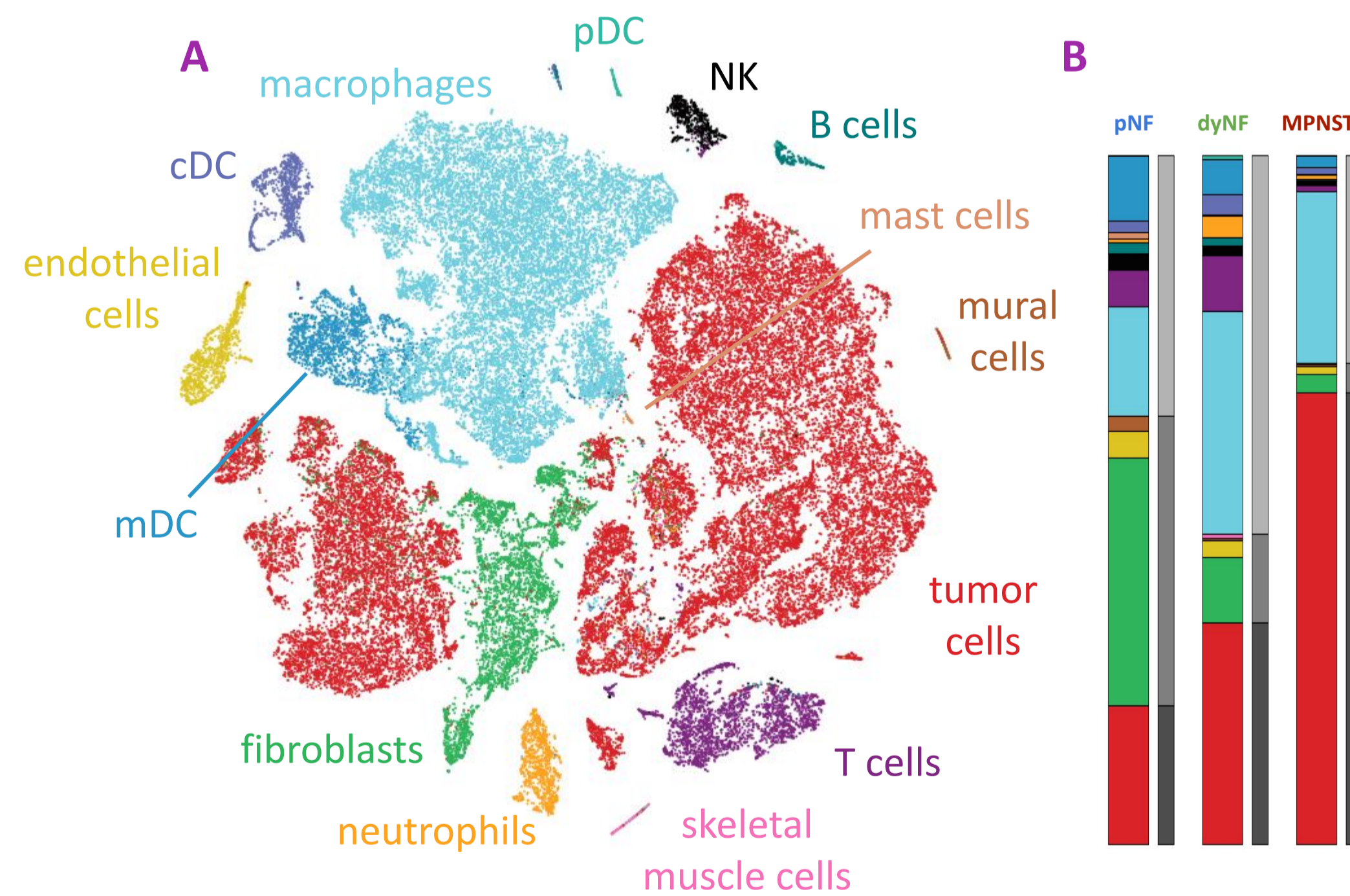


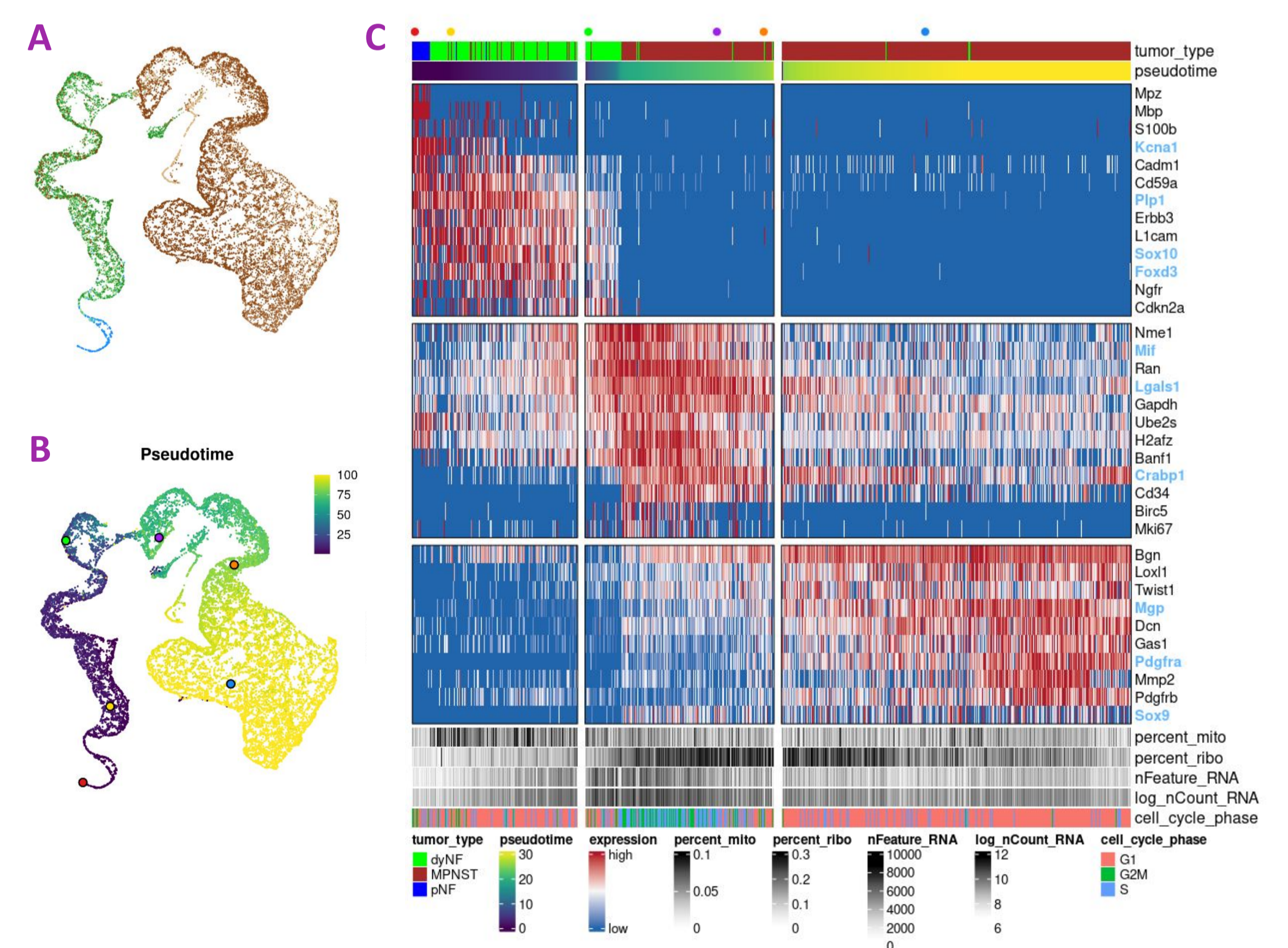
Figure 2 - (A) tSNE showing 60,000 cells from 16 datasets. We designed an automatic cell type annotation method. Annotation is validated using **Tomato** expression level, a tumor immune cell atlas [3], and known marker genes. (B) Barplot depicting tumor type specific composition. Tumor cell population (■) becomes predominant in MPNST, while stromal cells (■) decline, and immune cells (■) amount peaks in dysplastic tumors.



Tumor cell populations transcriptional landscape from pNF to MPNST

What is the transcriptomic profile of tumor cells ?

Figure 3 - (A) Representation of 20,000 tumor cells from 16 datasets. Cells are colored by sample of origin. Same legend as Fig. 1. (B) Pseudotime inference using Slingshot [4] reconstructs cell-to-cell transcriptomic changes from pNFs to MPNSTs. (C) Heatmap showing gene expression changes along pseudotime. Expression of genes in blue have been validated by immunolabeling. Tumor cells in pNF carry a glial signature (Sox10) whereas MPNST cells have a mesenchymal signature (Sox9).



CONCLUSIONS & PROSPECTS

Single-cell transcriptomics allow tumor forming populations study at a single cell level

- Tumors are formed by about 10 cell populations, whose proportions and transcriptomic activities changes during malignant progression
- Tumor cell population becomes predominant in MPNST, while stromal cells decline, and immune cells amount peaks in dysplastic tumors
- Trajectory inference shows a switch in tumor cells identity, confirmed by immunolabeling

Prospects

- Study the tumor micro-environment, and their interactions with the tumor cell populations
- Functional validation of candidate genes implicated in malignant transformation
- Integrate other types of data : mutational landscape, single-nuclei ATAC-Seq and NF1 patients scRNA-Seq

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