Omics data integration for the identification of cell-type-specific gene regulatory networks and regulatory variants in Parkinson's disease

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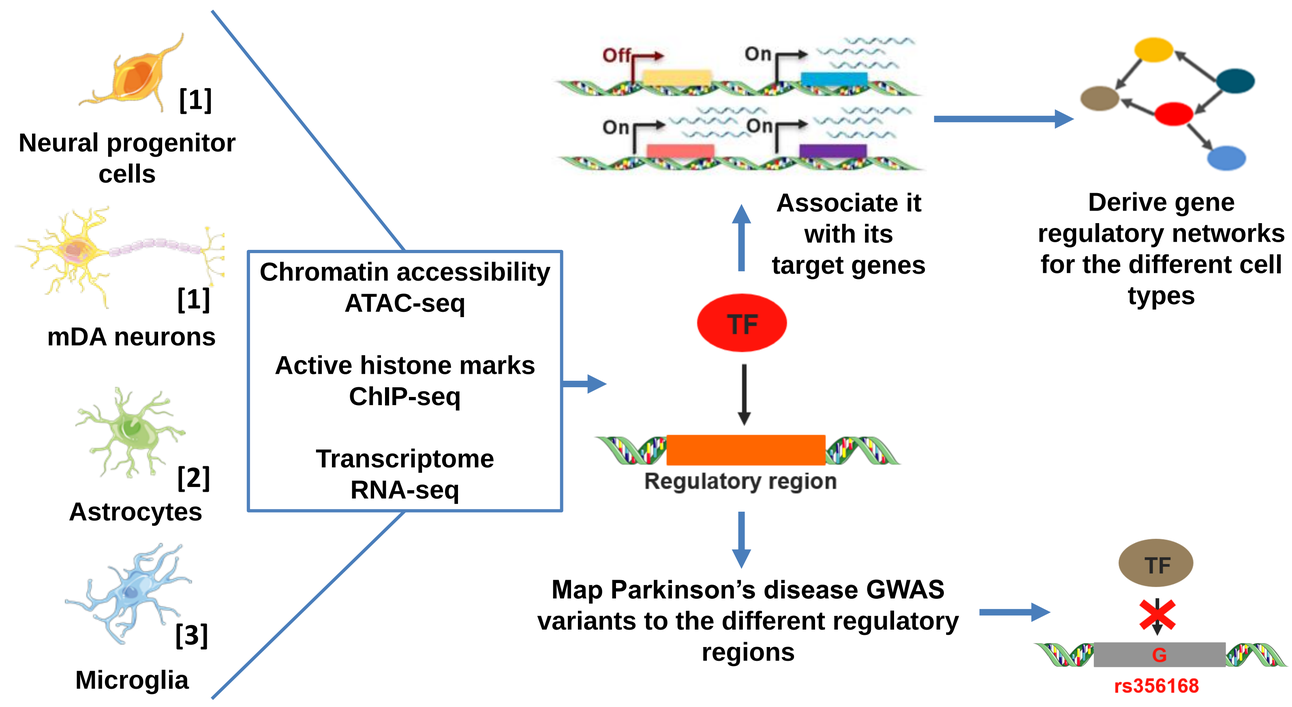
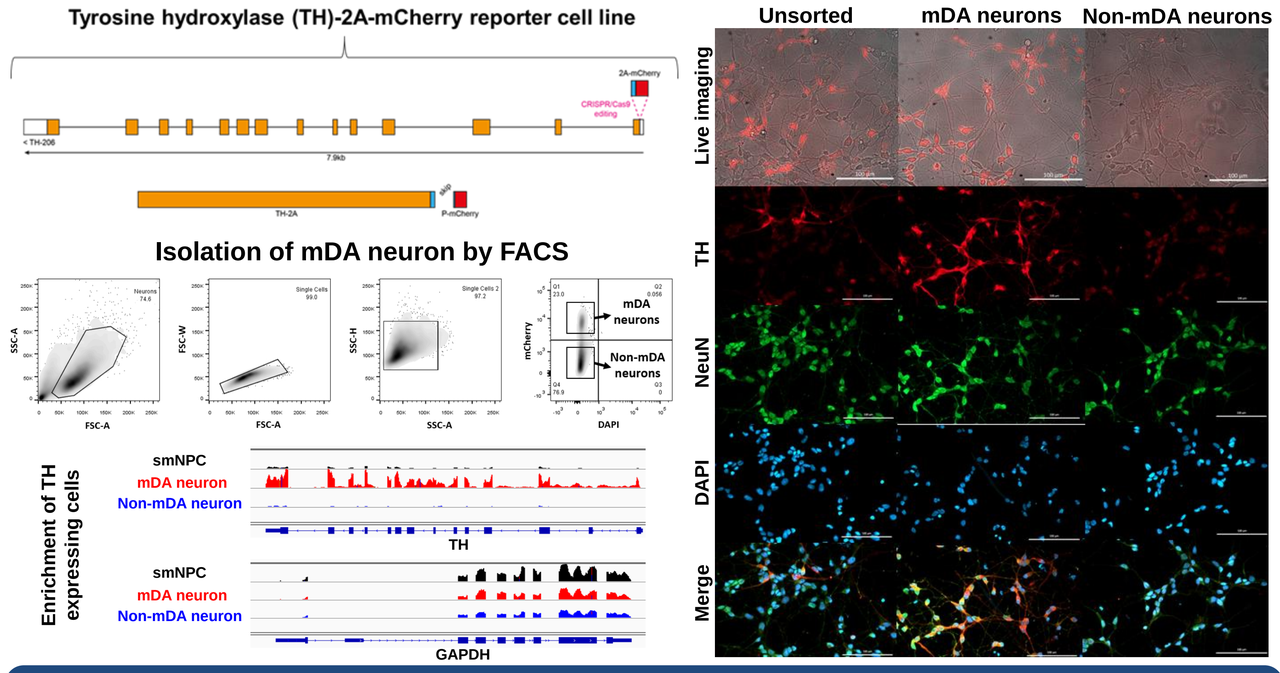
Abstract

Genome-Wide Association Studies (GWAS) have identified many variants associated with different diseases. However, it is still a challenge to make sense of this data as the majority of genetic variants are located in non-coding regions, complicating the understanding of their functionality. In the last few years, it has been found that non-coding variants concentrate in regulatory regions in the genome, which are cell type and cell-stage specific. In this project, we seek to identify functional Parkinson's disease GWAS non-coding variants that could make carriers more prone to developing PD. To do so, we are using induced pluripotent stem cell (iPSC) technology to differentiate somatic cells into midbrain dopaminergic (mDA) neurons, astrocytes and microglia. Assessing their chromatin accessibility, active chromatin regions and transcriptome, we can identify crucial regulatory regions in the genome, key transcription factors and derive the gene regulatory networks for the three different cell types. Then, we will map the non-coding variants to the different regulatory regions and predict their effect *in silico* for the subsequent validation *in vitro*. This innovative approach will also identify novel factors controlling cell fate and cell identity.

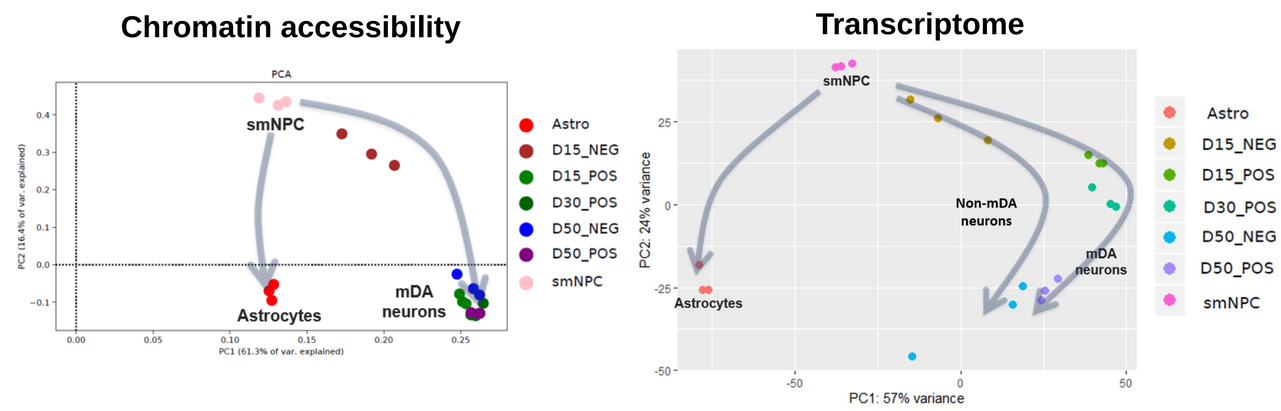
Derivation of cell-type-specific GRN and identification of regulatory variants



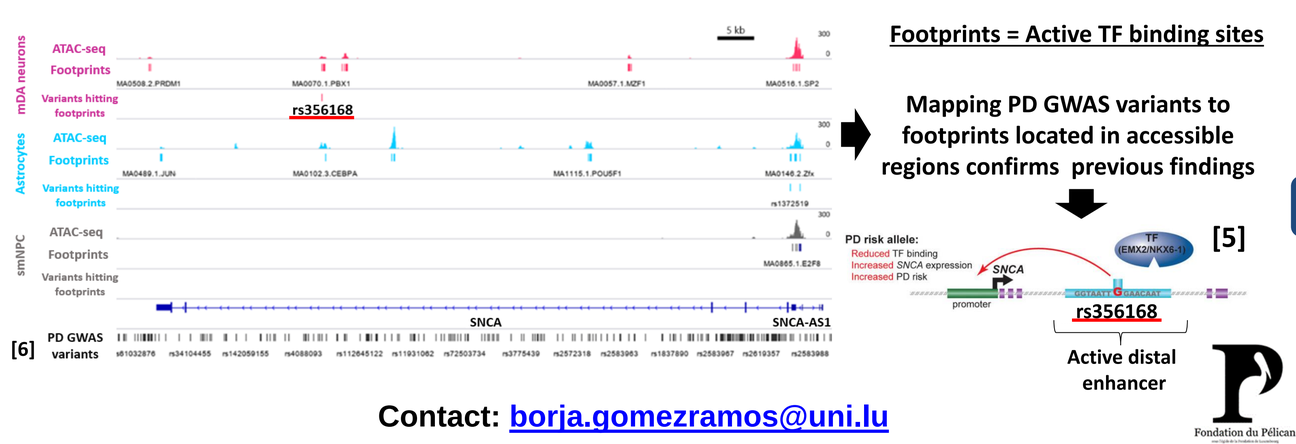
Isolation of mDA neurons for transcriptomic and epigenomic analysis



Transcriptome analysis differentiate better cellular subtypes than chromatin accessibility



Prioritization of functional non-coding PD-associated variants using footprints



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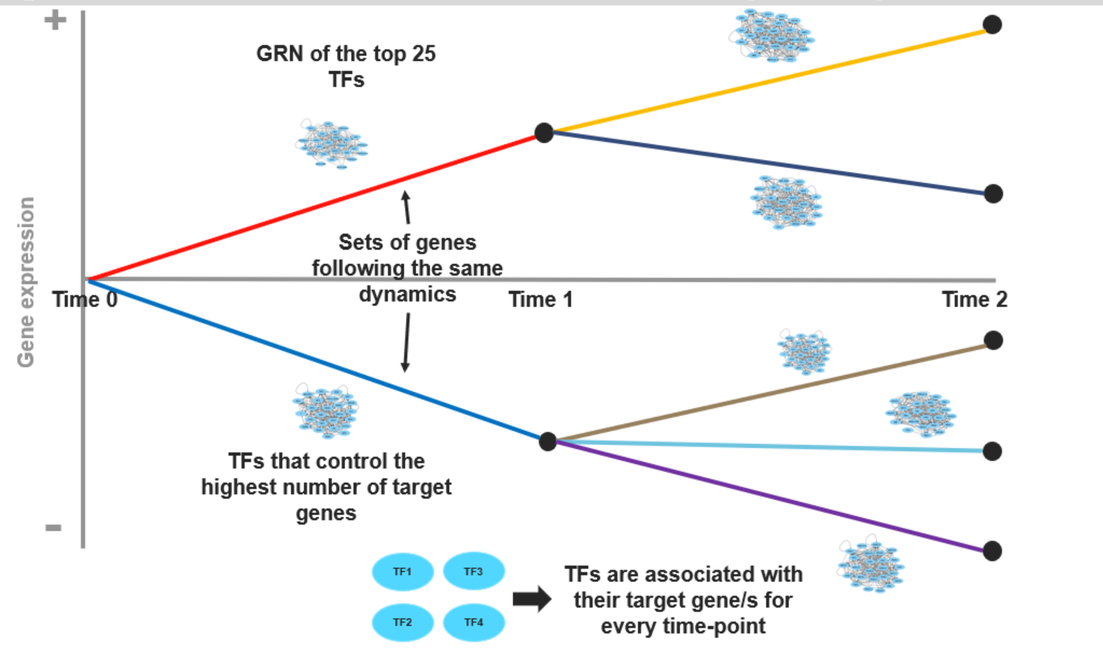
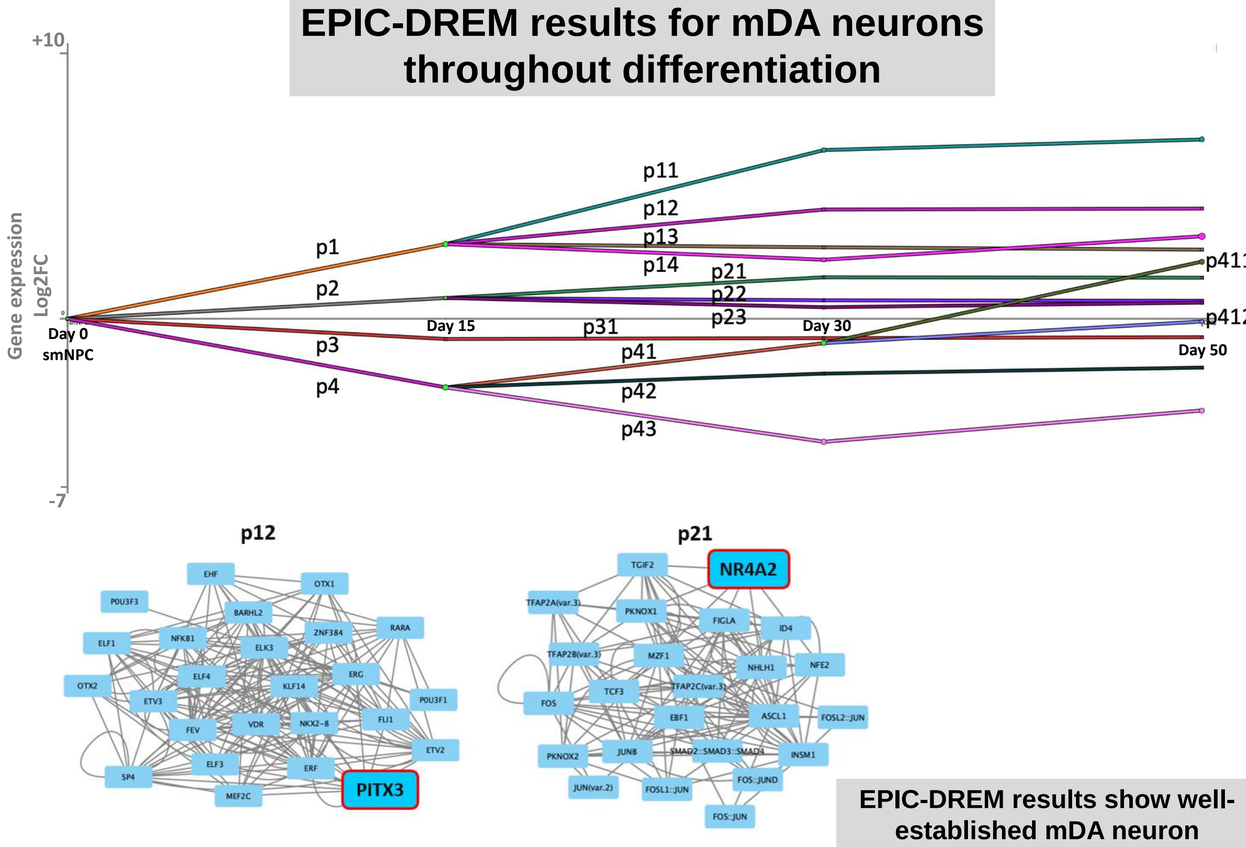
Identification of key transcription factors controlling mDA neuron differentiation using EPIC-DREM [4]

EPIC-DREM integrates time series transcriptomic and epigenomic data for the derivation of time point specific GRN

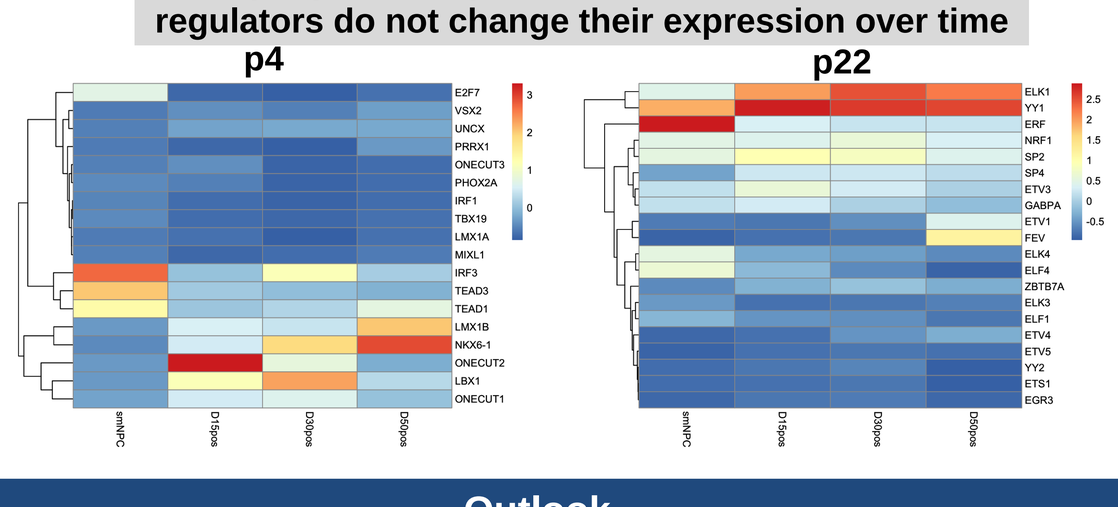


EPIC-DREM results for mDA neurons throughout differentiation



EPIC-DREM results show well-established mDA neuron transcription factors in the derived GRN

Many top transcription factors classified as main regulators do not change their expression over time



Outlook

- Use EPIC-DREM results to identify novel factors controlling mDA neuron differentiation
- Map GWAS variants to accessible regions to find hits in a cell-type-specific manner
- Identify variants affecting TF binding affinity
- Functional validation of variants using genome editing

References

[1] P. Reinhardt *et al.*, [2] T. Palm et al., [3] W. Haenseler et al., [4] D. Gérard et al., [5] F. Soldner et al., [6] M. A. Nalls et al.

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