Epigenetic encoding, heritability and plasticity of glioma transcriptional cell states

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Emerging Technologies in Single Cell Research 2020

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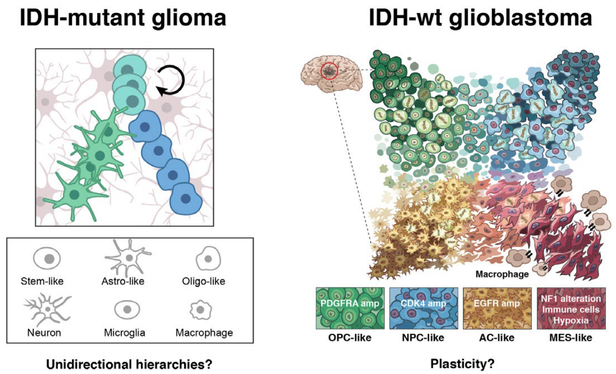
Weill Cornell Medicine

Multi-omics single-cell sequencing of primary human gliomas separates malignant vs. non-malignant cells, and enables high-resolution copy number alteration mapping



- **Epigenetic encoding of cells states?**
- **Heritability of cell states?**
- **Transition dynamics of cell states?**

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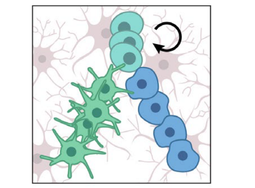
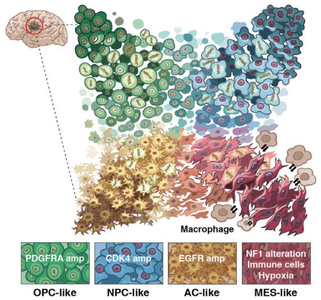
IDH-mutant glioma



Unidirectional hierarchies?

IDH-wt glioblastoma



Plasticity?

- **Epigenetic encoding of cells states?**
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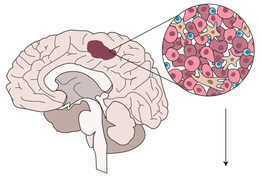
1,728 single-cell RNA + DNA methylomes + somatic mutation capture

Joint RNA and DNAme (Gaiti et al., Nature 2019)

GBM (n= 7 patient samples)
IDH-MUT (n= 4 patient samples)



Dissociate tumor into single cells

Single cell sorting

Poly(A) RNA capture by oligo(dT) magnetic beads

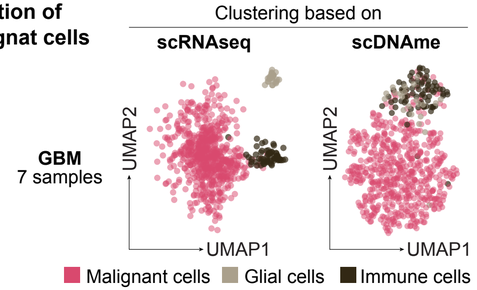
gDNA isolation

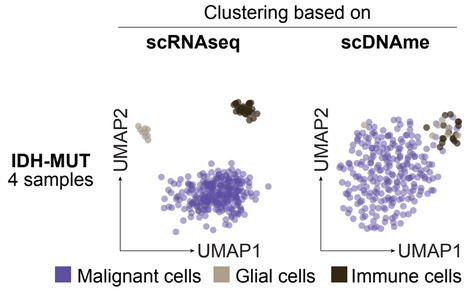
CNA inference SNVs

scDNAme (MscRRBS)

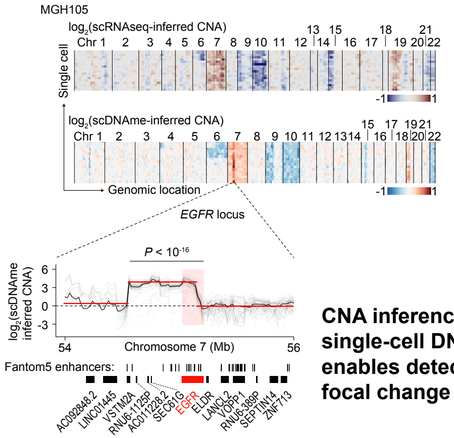
scRNAseq (SMARTseq2)

Identification of non-malignat cells



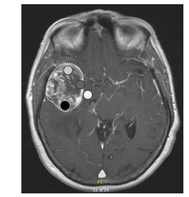


Inference of copy number aberrations (CNAs) from single-cell DNAme



CNA inference by single-cell DNAme enables detection of focal change

CNA inference by single-cell DNAme enables detection of genetic sub-clones



MGH105A MGH105C
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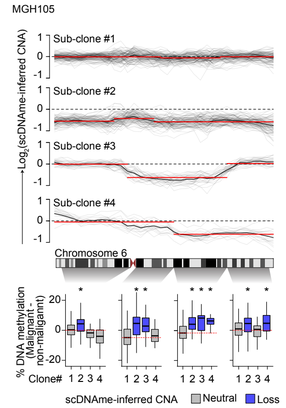

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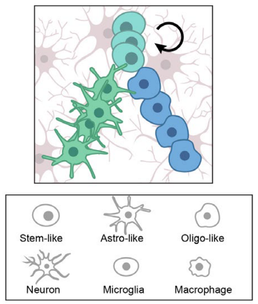

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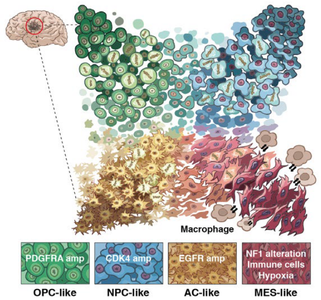

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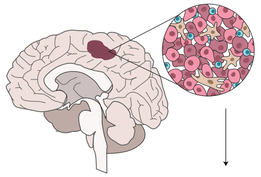

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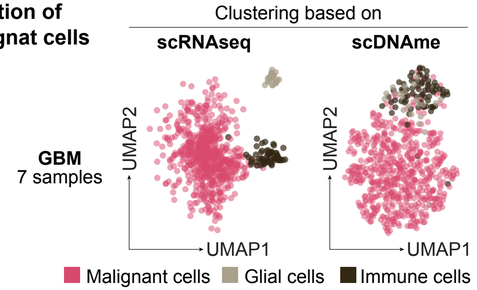

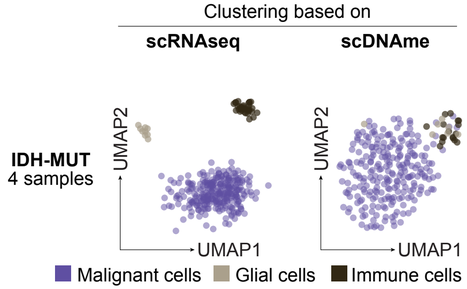

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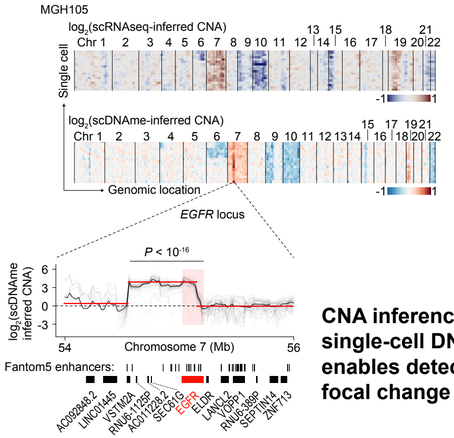

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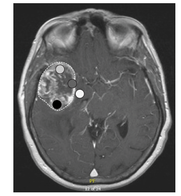

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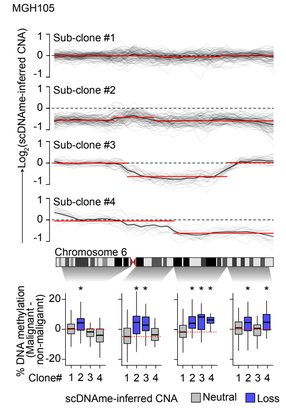
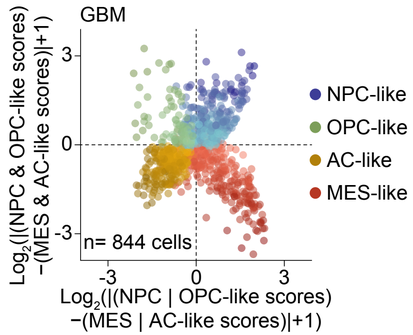
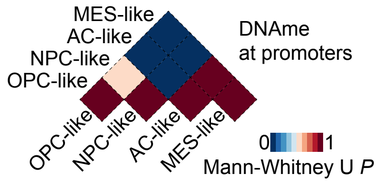


Collaboration with Mario Suva lab - MGH/Broad Institute

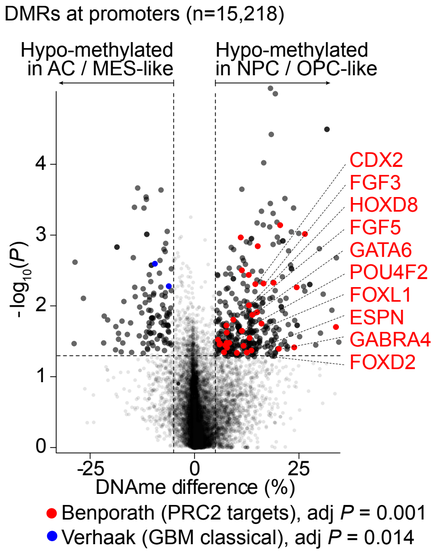
Stem-like GBM cells exhibit PRC2 targets hypomethylation compared with more differentiated cell states within the same GBM patient samples

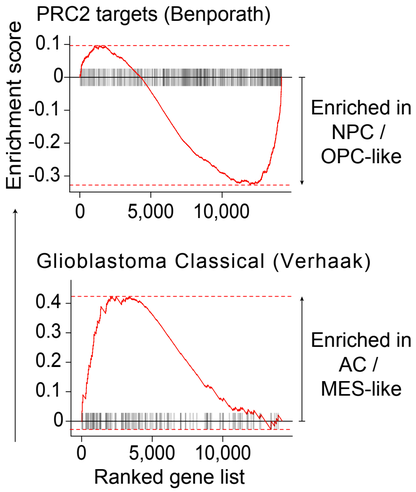
Transcriptional cell states in GBM



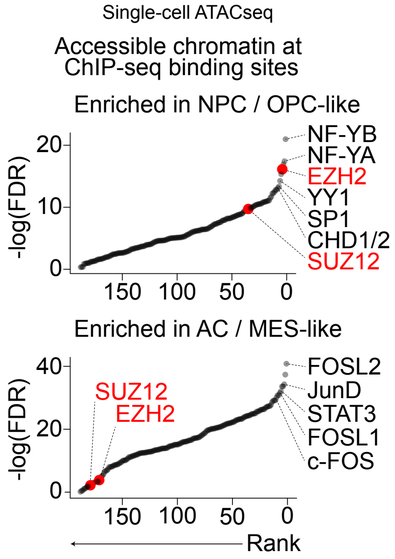


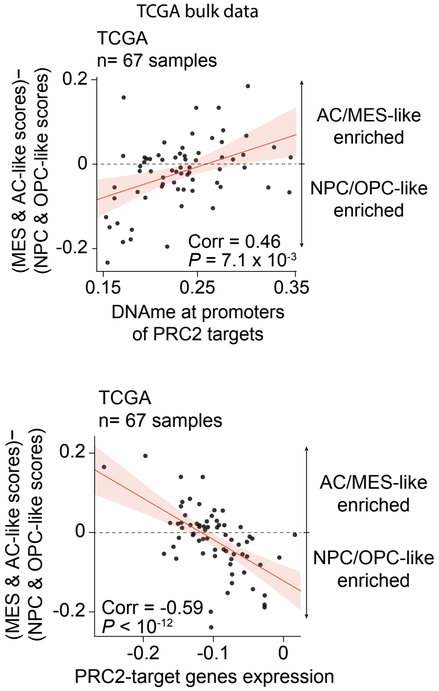
PRC2 targets are hypo-methylated in stem-like cells



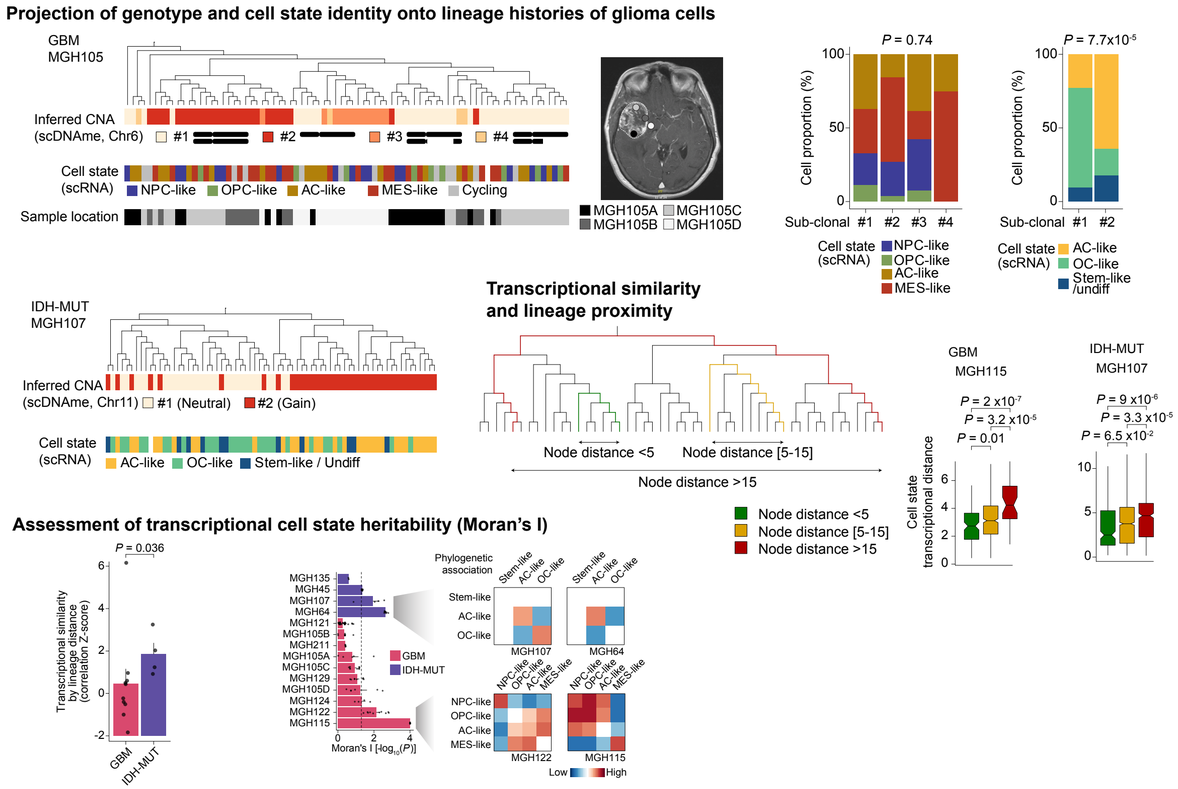


Validation of PRC2 hypo-methylation in stem-like cells





Cell state transition dynamics inference from lineage tree architectures reveal higher cellular plasticity in GBM compared to a more stable differentiation hierarchy in IDH-MUT



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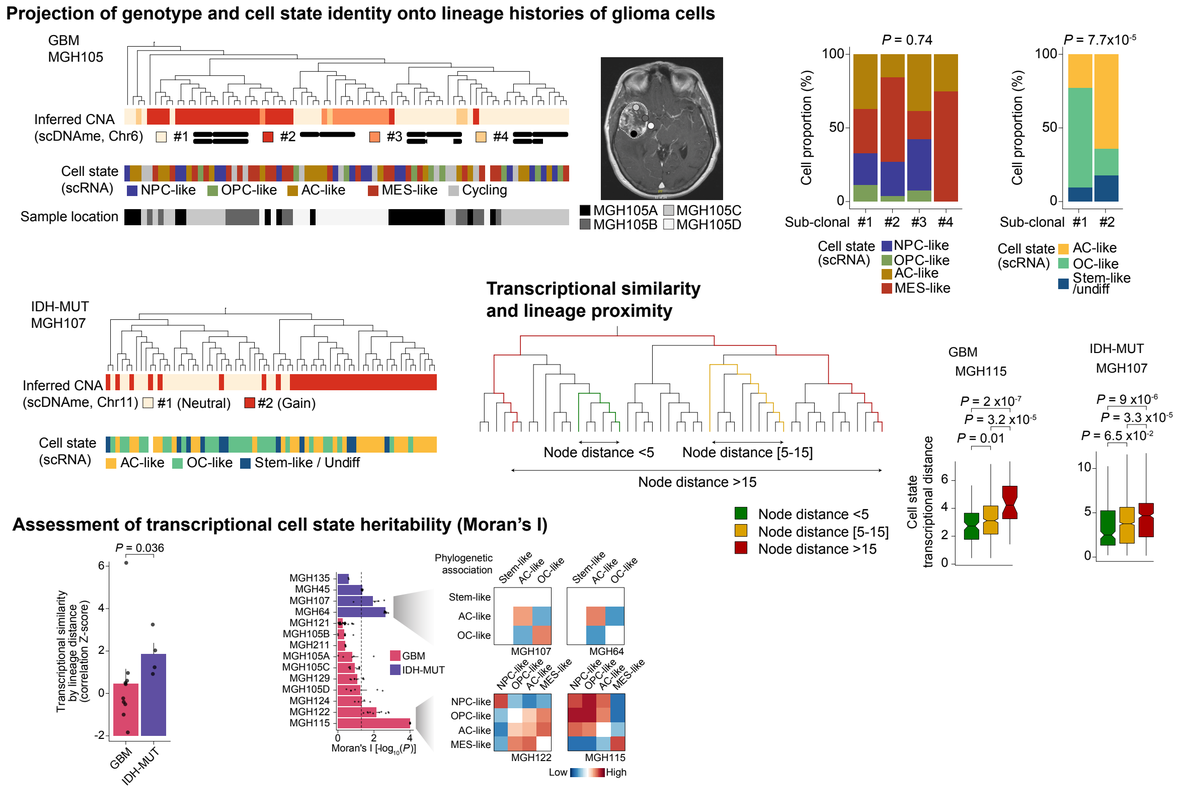
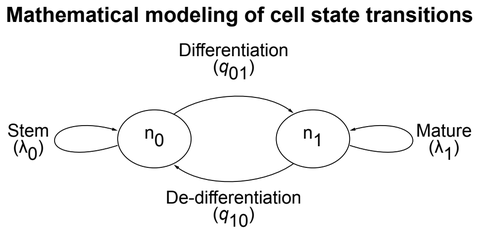
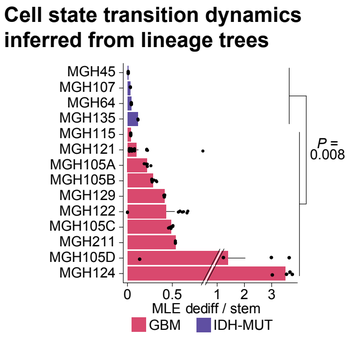
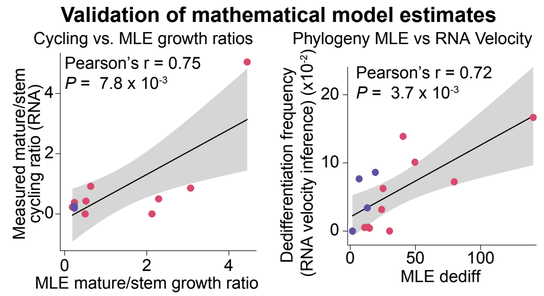
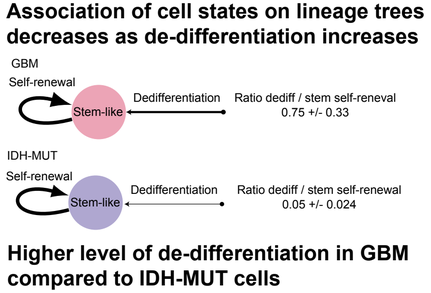
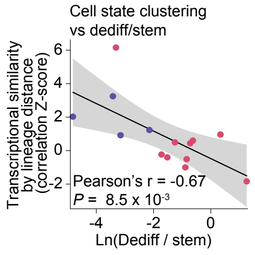






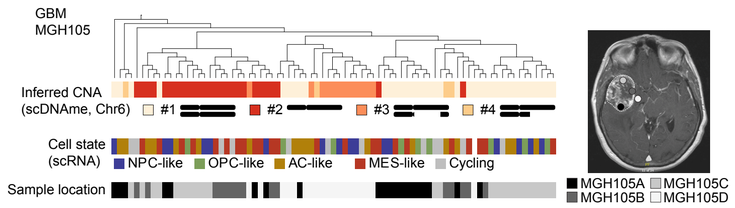


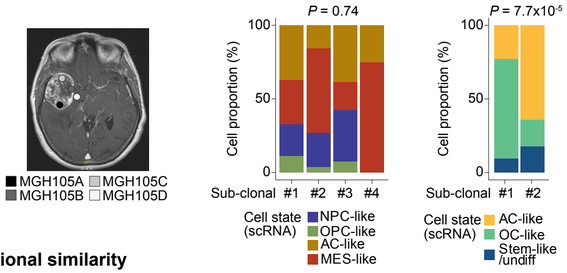


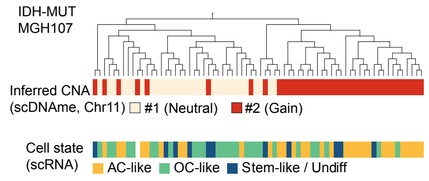


Higher level of de-differentiation in GBM compared to IDH-MUT cells

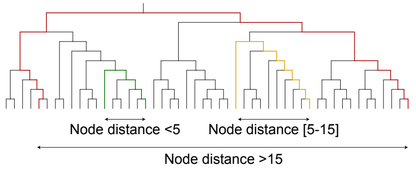
Projection of genotype and cell state identity onto lineage histories of glioma cells

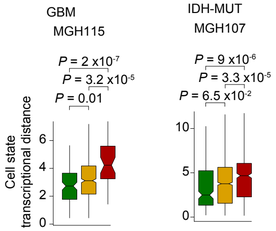




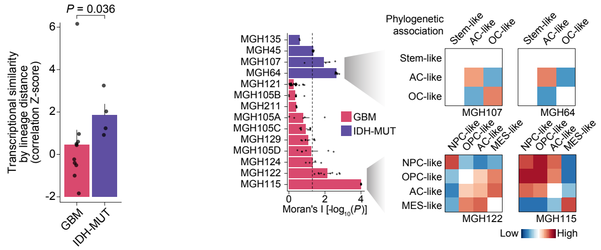


Transcriptional similarity and lineage proximity

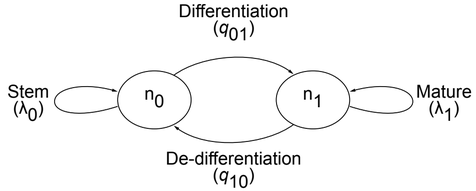




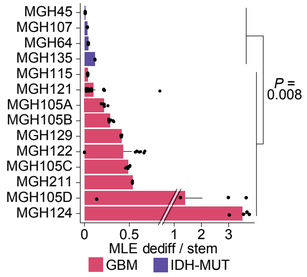
Assessment of transcriptional cell state heritability (Moran's I)



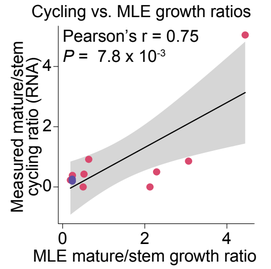
Mathematical modeling of cell state transitions

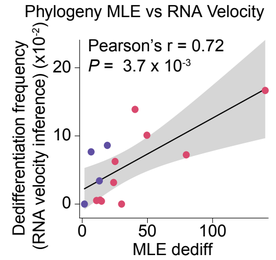


Cell state transition dynamics inferred from lineage trees

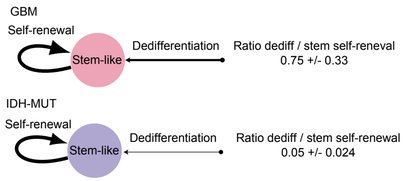


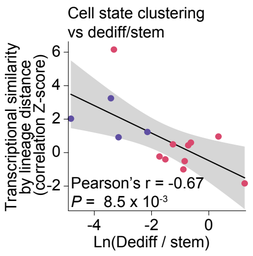
Validation of mathematical model estimates





Association of cell states on lineage trees decreases as de-differentiation increases





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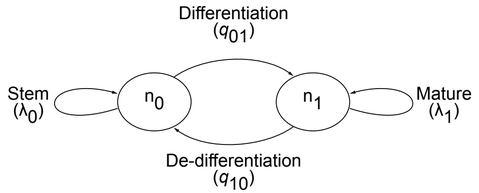

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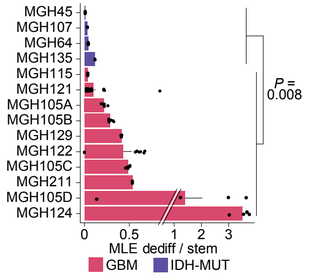

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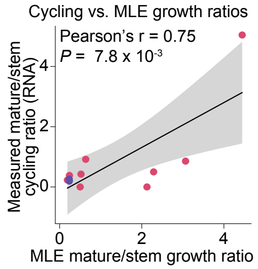

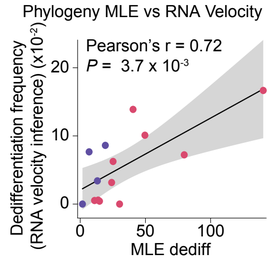

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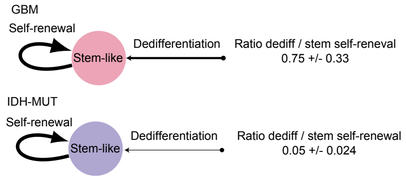

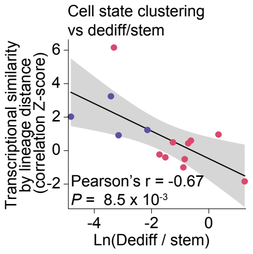

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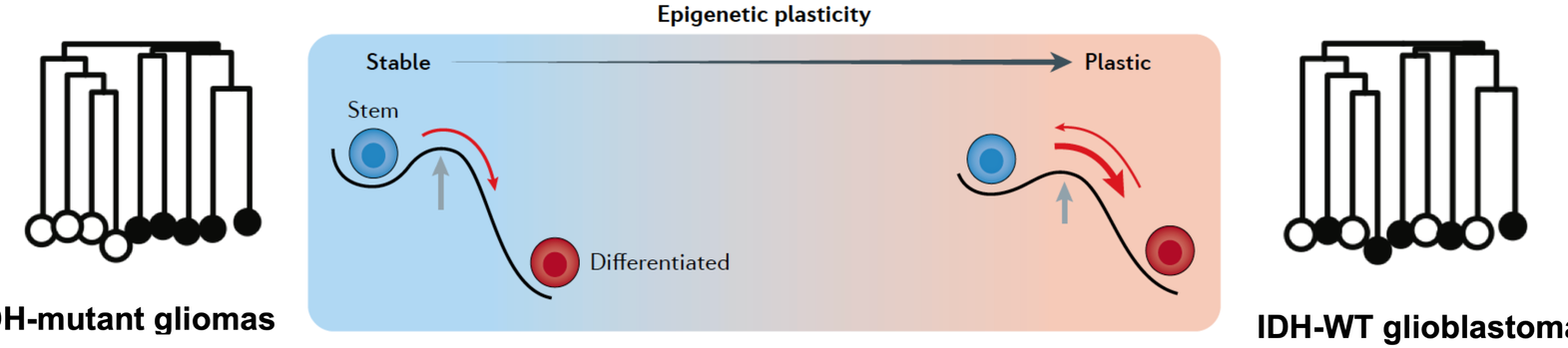
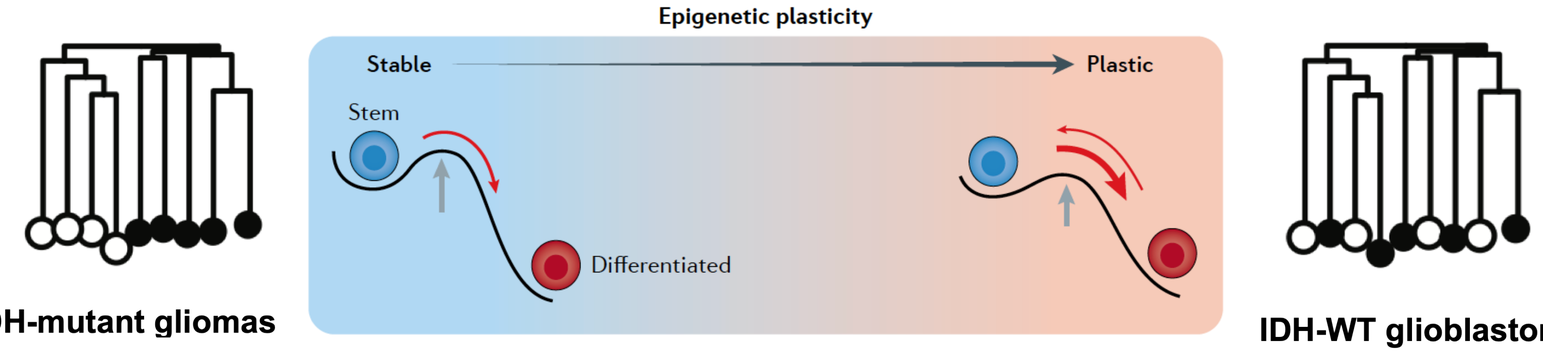


IDH-mutant gliomas

Unidirectional developmental hierarchy

IDH-WT glioblastoma

Plastic bi-directional developmental hierarchy



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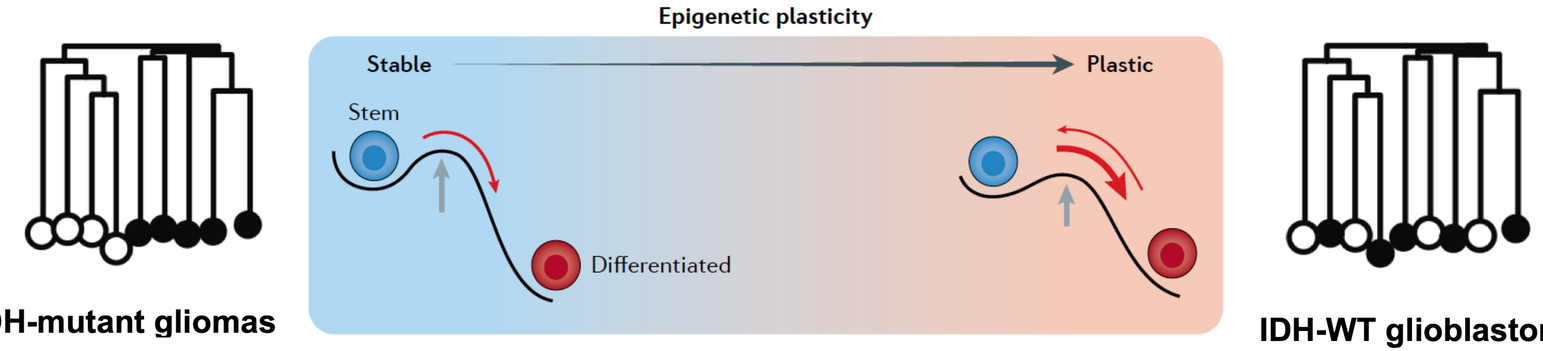

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- Challenge to glioma stem-like cell targeting paradigm?
- Cell state targeting?
- Cell transition targeting?