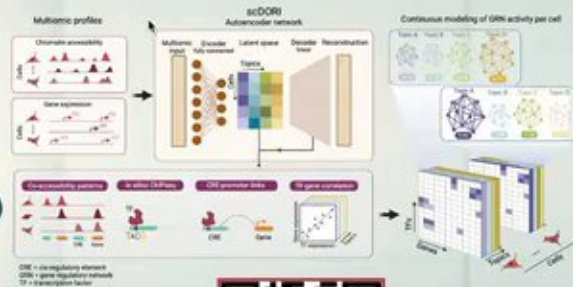


Decoding Cellular Plasticity using Deep Learning of Single Cell Gene Regulatory Networks

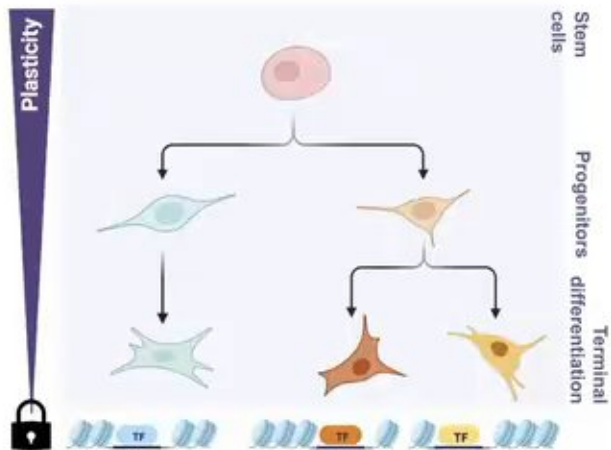


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Postdoctoral researcher

 @manusaraswat10

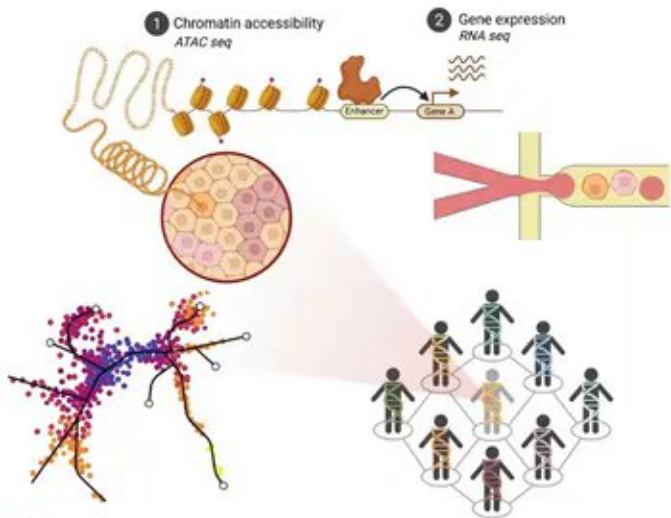


Control of cellular plasticity is required for proper development and function



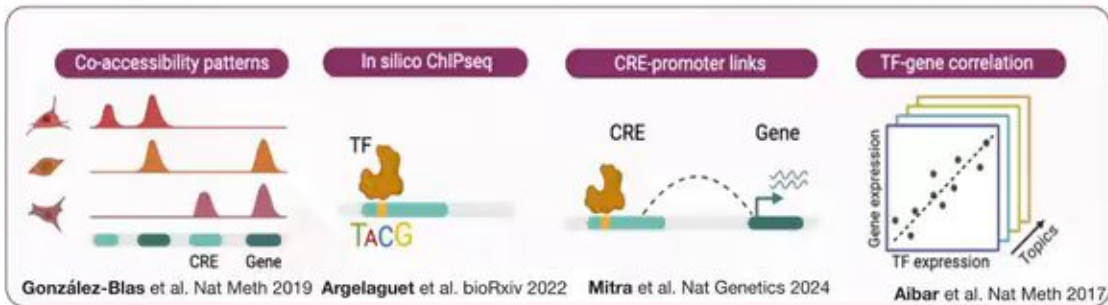
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Single cell multi-omics enables study of *continuous* cell state changes



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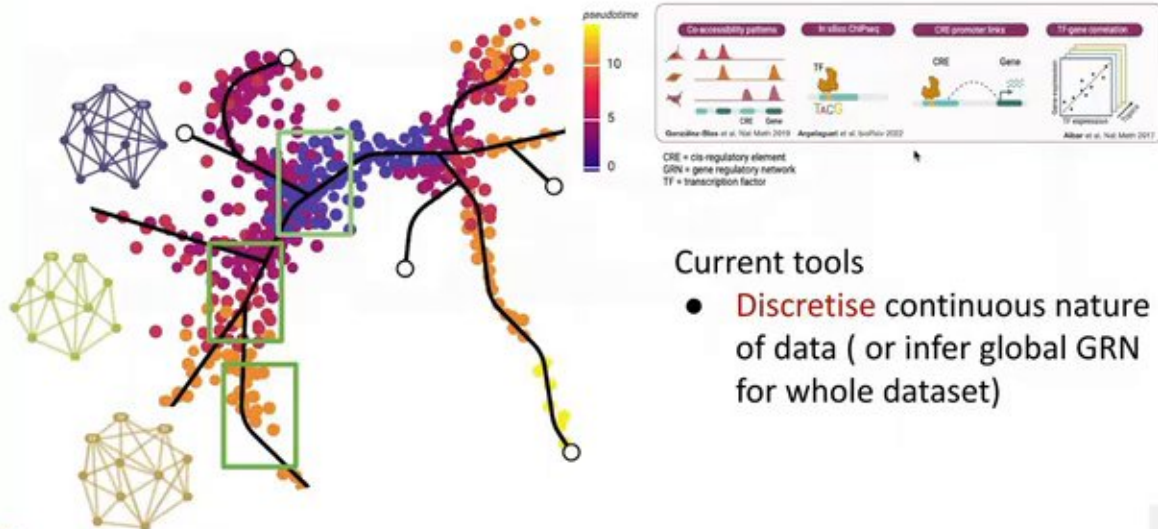
Multi-omic signatures of Gene Regulatory Networks (GRNs) inference



CRE = cis-regulatory element
GRN = gene regulatory network
TF = transcription factor



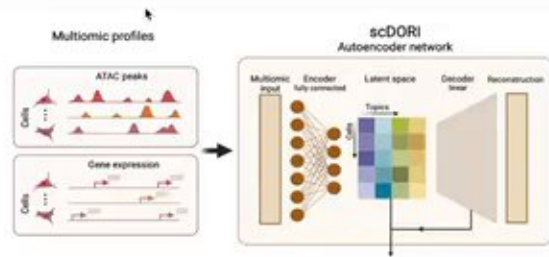
Limitations of existing tools for inference of Gene Regulatory Networks (GRNs)



Current tools

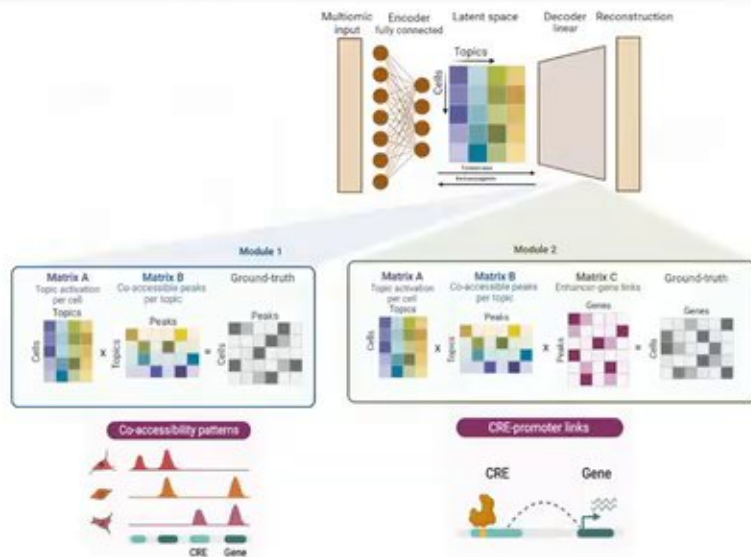
- **Discretise** continuous nature of data (or infer global GRN for whole dataset)

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scDORI: Scalable and continuous inference of gene regulatory networks

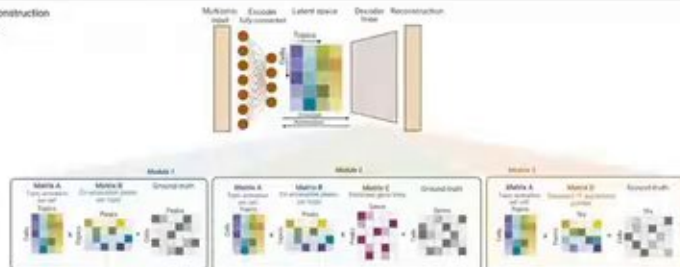
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scDORI: opening the black-box



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Stage 1: Topic construction
End-to-end learning

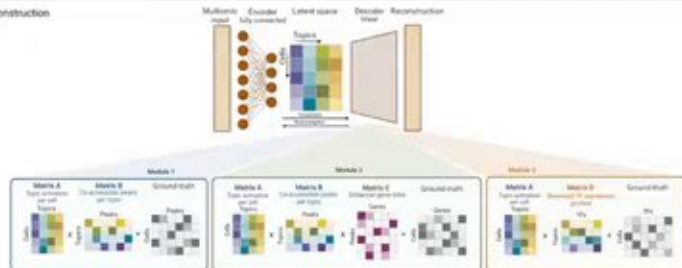


Stage 2: Refinement of topic-specific TF activity prediction
Fine-tuning matrix A, B, C, D hyper

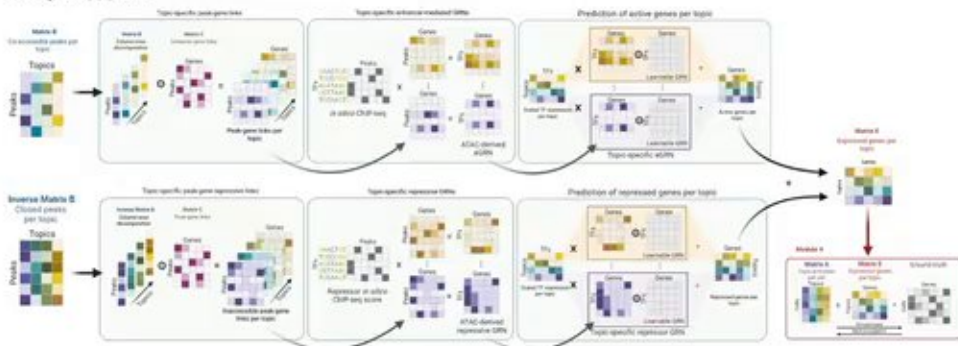


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Stage 1: Topic construction
End-to-end learning

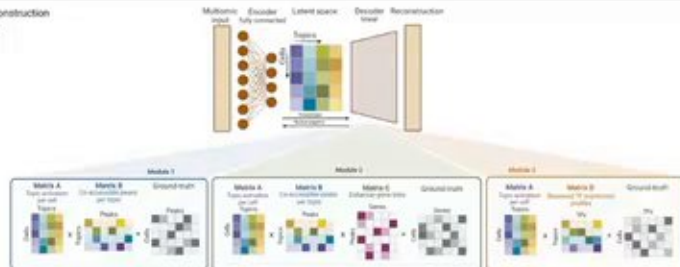


Stage 2: Refinement of topic-specific TF activity prediction
Fine-tuning matrix A, B, C, D from



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Stage 1: Topic construction
End-to-end learning

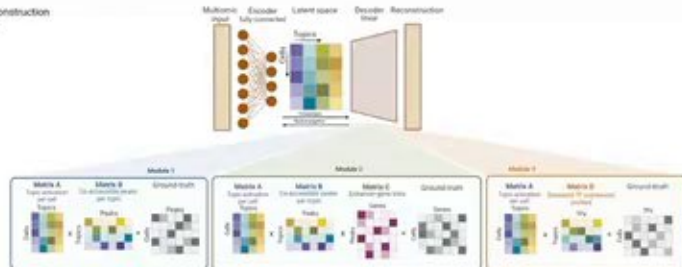


Stage 2: Refinement of topic-specific TF activity prediction
Fine-tuning matrix A, B, C, D from

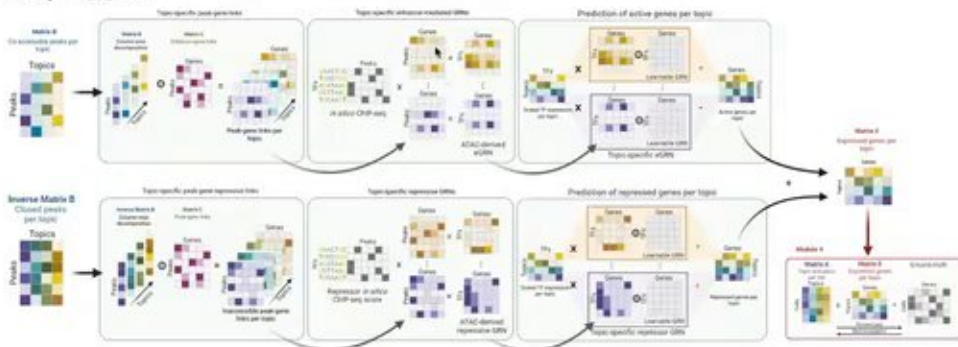


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Stage 1: Topic construction
End-to-end learning

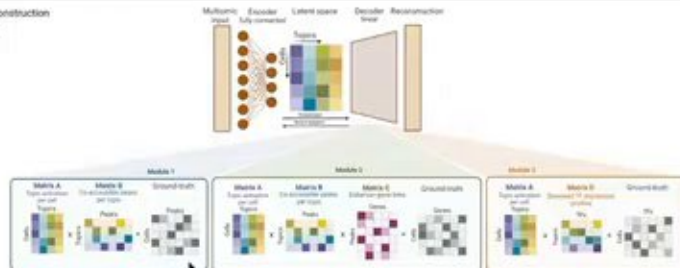


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Philippe Martin

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End-to-end learning

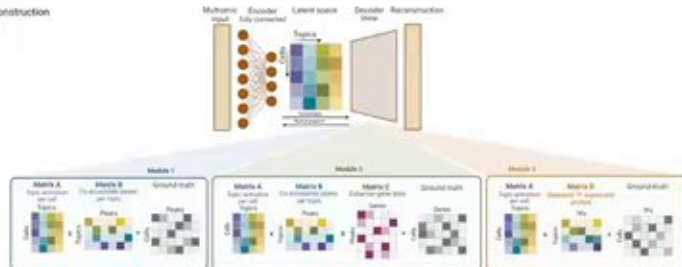


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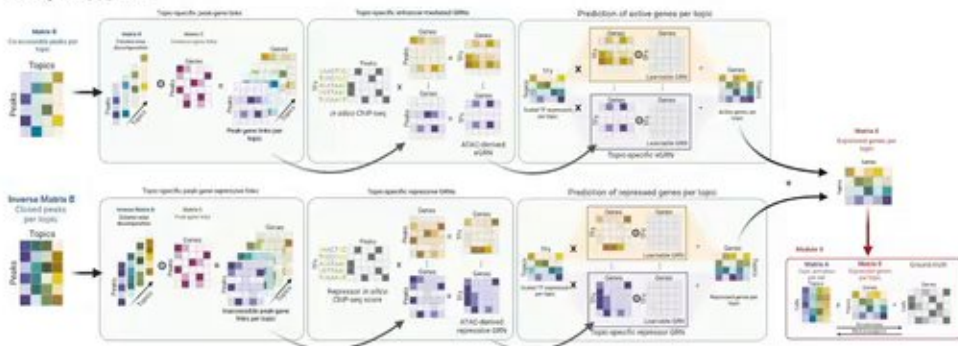


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Stage 1: Topic construction
End-to-end learning

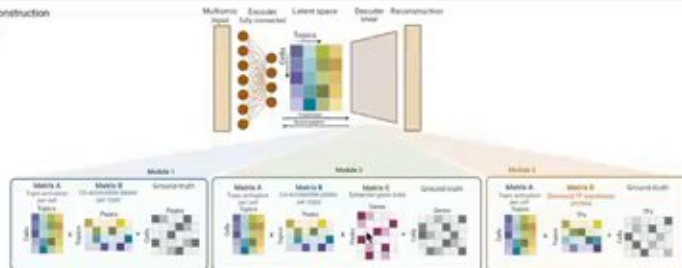


Stage 2: Refinement of topic-specific TF activity prediction
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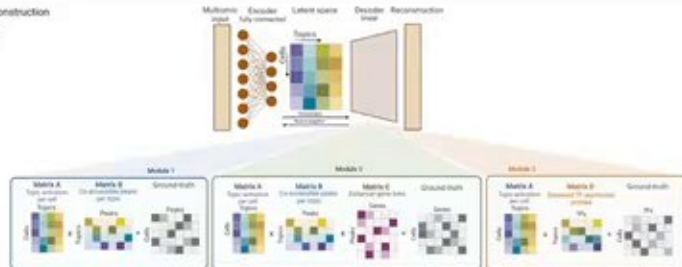


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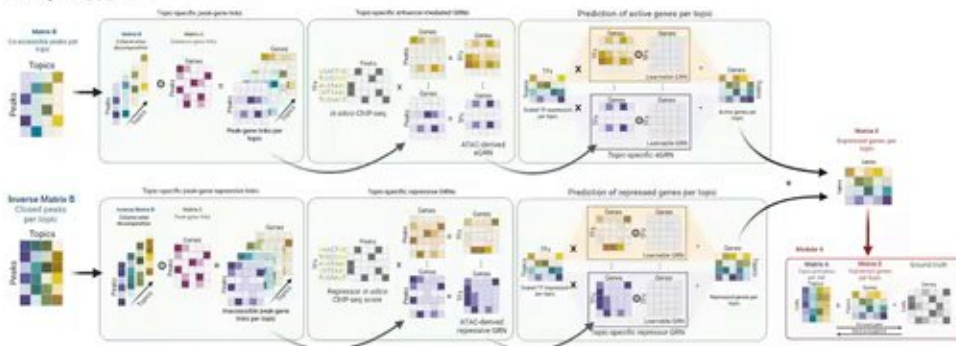


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End-to-end learning

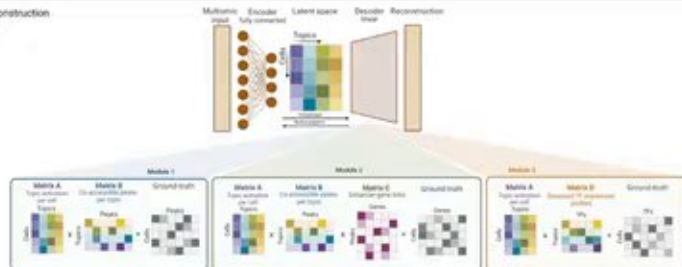


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Stage 1: Topic construction
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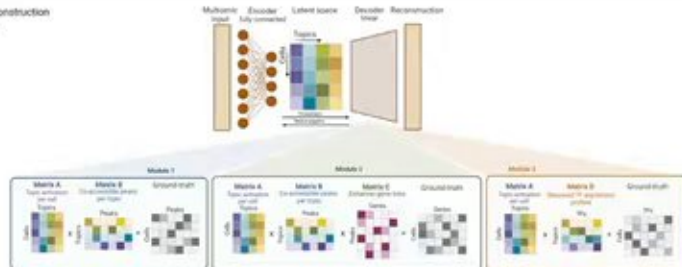


Stage 2: Refinement of topic-specific TF activity prediction
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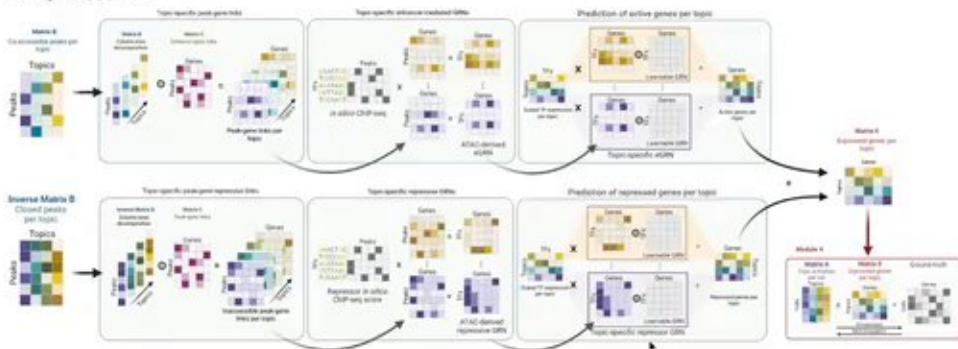


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Stage 1: Topic construction
End-to-end learning

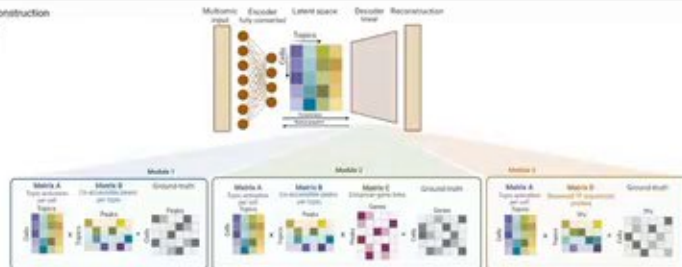


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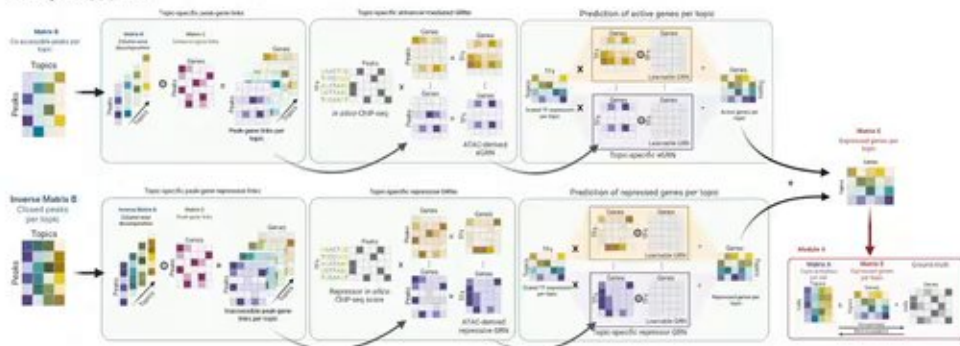


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Stage 1: Topic construction
End-to-end learning



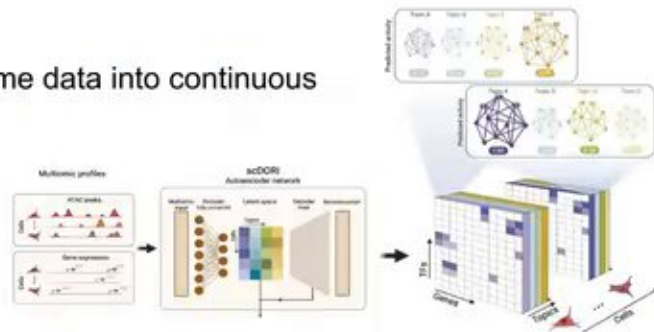
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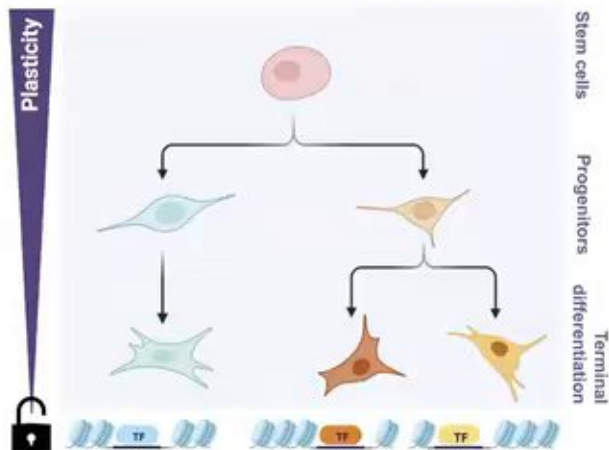
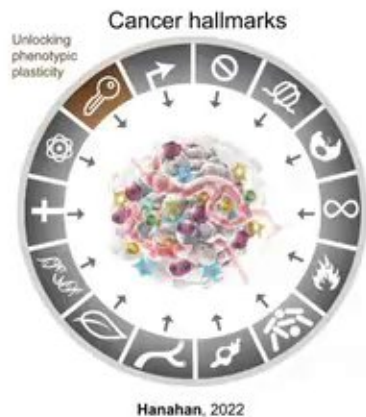
Key messages

- 1 scDoRI decomposes sc multi-ome data into continuous modules of GRNs



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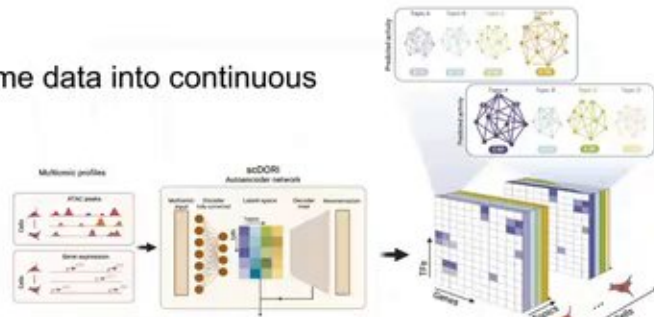
Unlocked plasticity is a hallmark of cancer



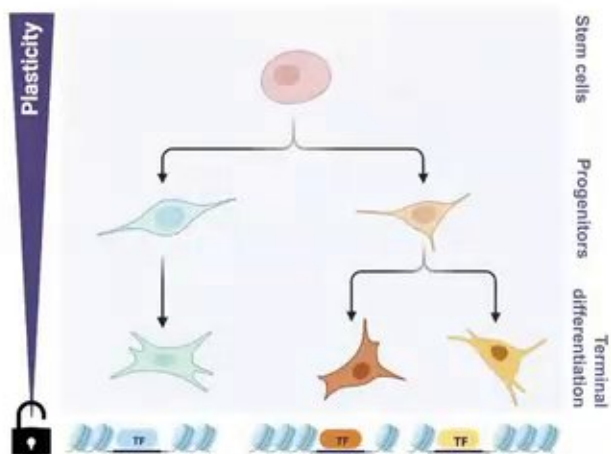
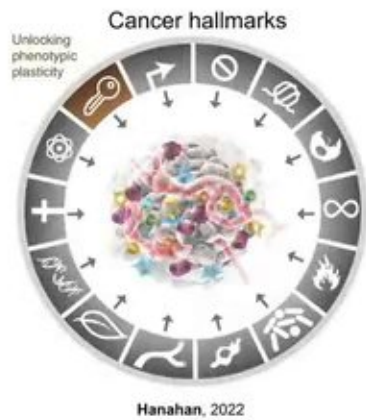
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Key messages

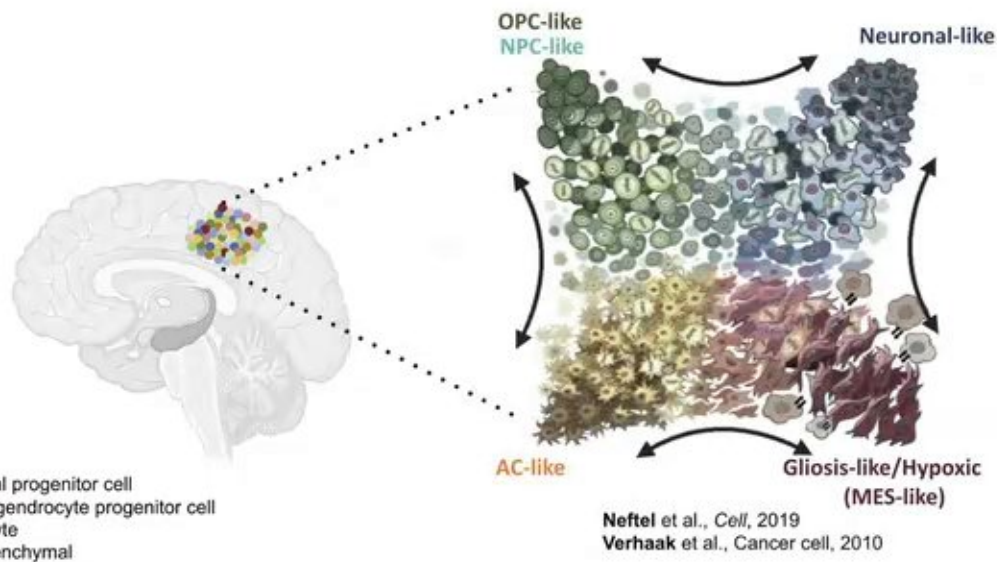
- 1 scDoRI decomposes sc multi-ome data into continuous modules of GRNs



Unlocked plasticity is a hallmark of cancer



GBM cells exhibit diverse and highly plastic states



Largest glioblastoma single-cell multiome atlas

Omer Bayraktar Lab
Wellcome Sanger Institute



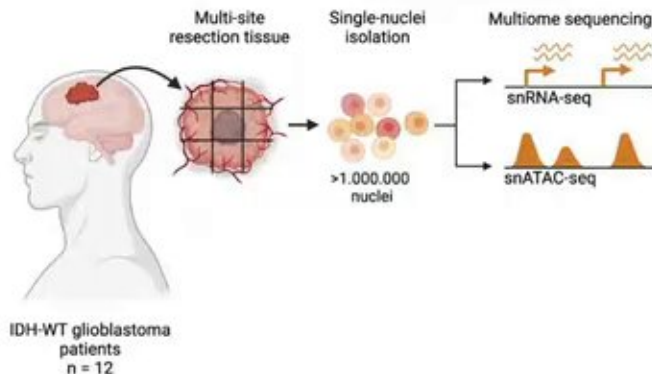
Grant De Jong



Fani Momi

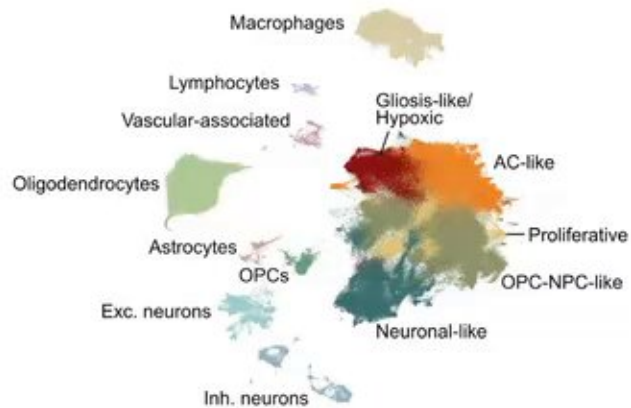


Tannia Garcia



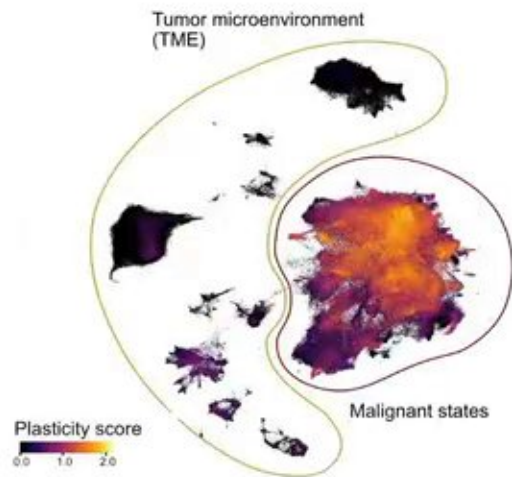
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Largest glioblastoma single-cell multiome atlas

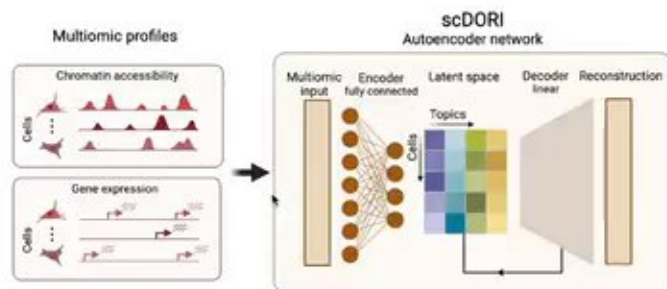


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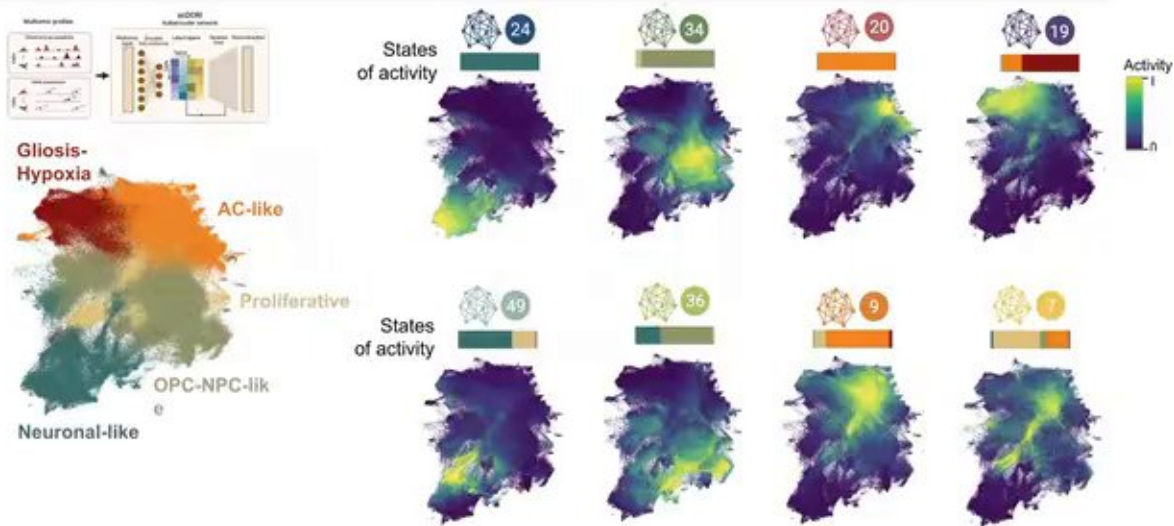
Gene accessibility and expression discrepancies reflect epigenetic plasticity



scDoRI to identify gene regulatory networks in heterogeneous populations



Distinct gene regulatory networks underlie Glioblastoma heterogeneity

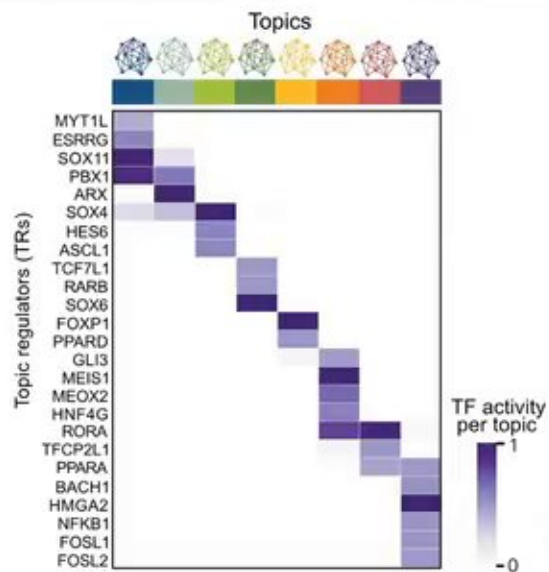


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Reconstructed GRNs enable identification of “Topic Regulators”

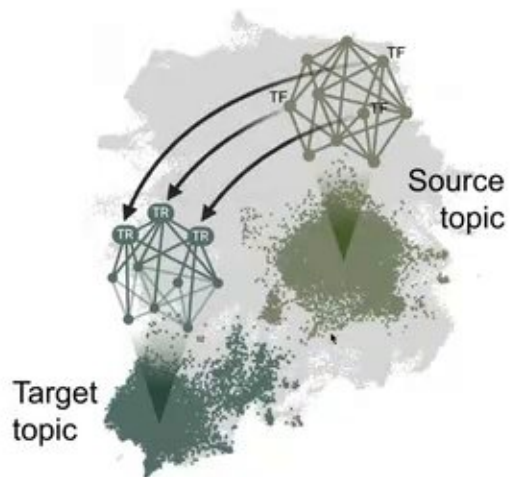


TFs with high downstream influence



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Mapping the regulatory drivers of glioblastoma state transitions



Reconstructed GRNs enable the identification of key regulators of GB topics and upstream TFs in alternate topics

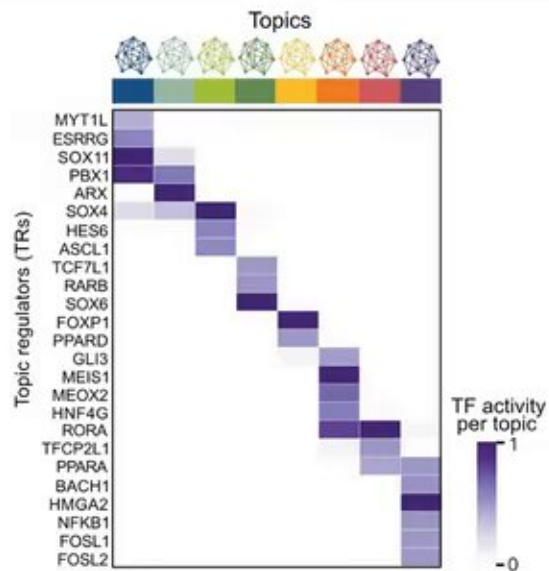
TR: Topic regulator, TF: Transcription factor



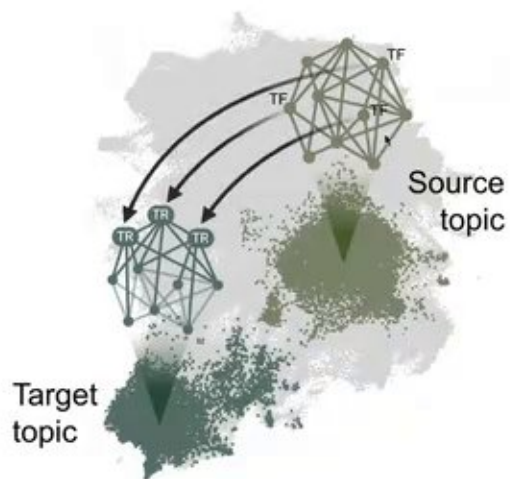
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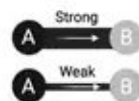


Mapping the regulatory drivers of glioblastoma state transitions

Neuronal-like topics

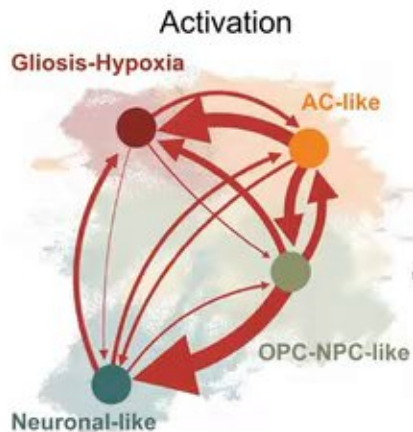


Weak activation of
alternate state topics



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Activation and repression jointly shape glioblastoma state transitions

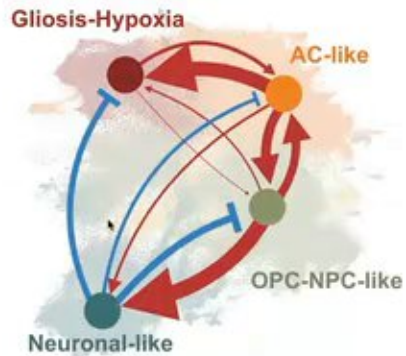


Topic inter-regulation reveals state-specific differences in transition potential

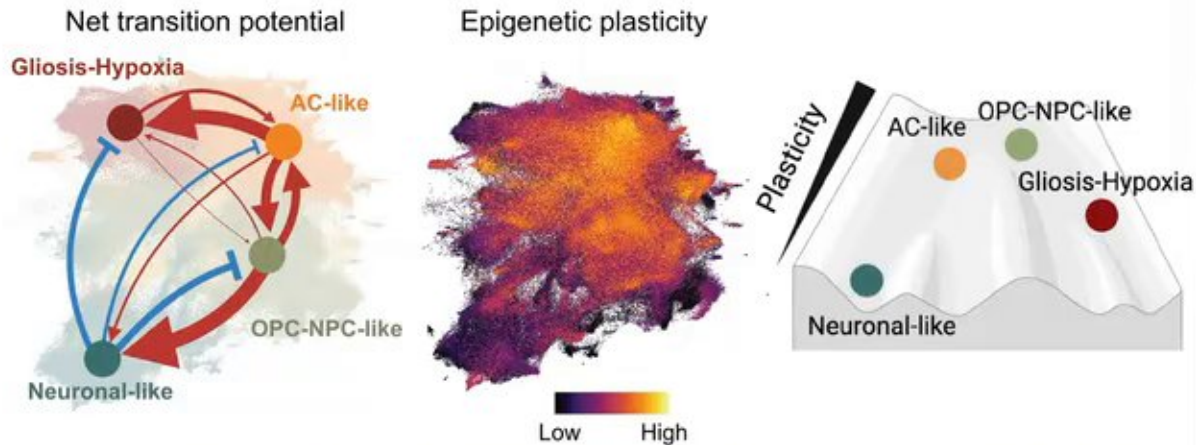


Activation and repression jointly shape glioblastoma state transitions

Net transition potential



Activation and repression jointly shape glioblastoma state transitions

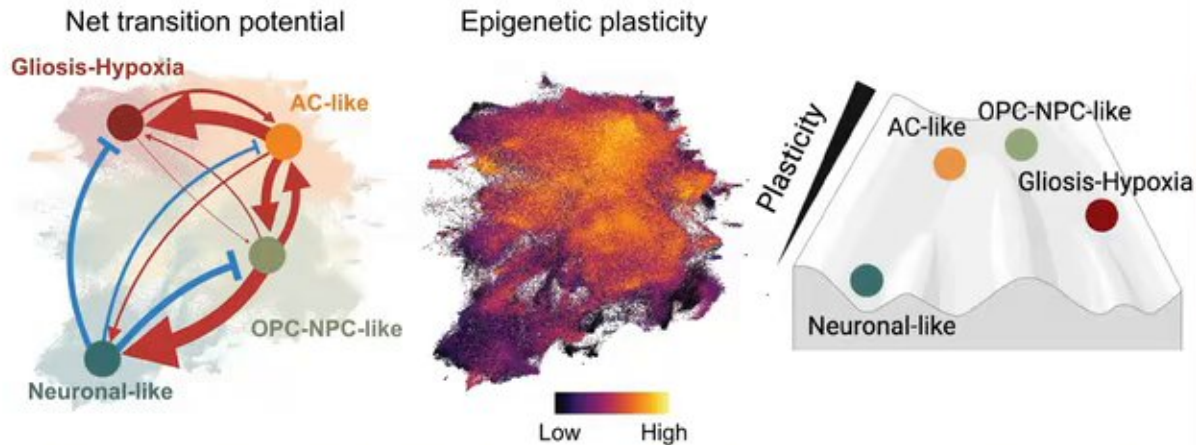


The reconstructed state transition hierarchy explains differences in epigenetic plasticity

Myriam Lizotte



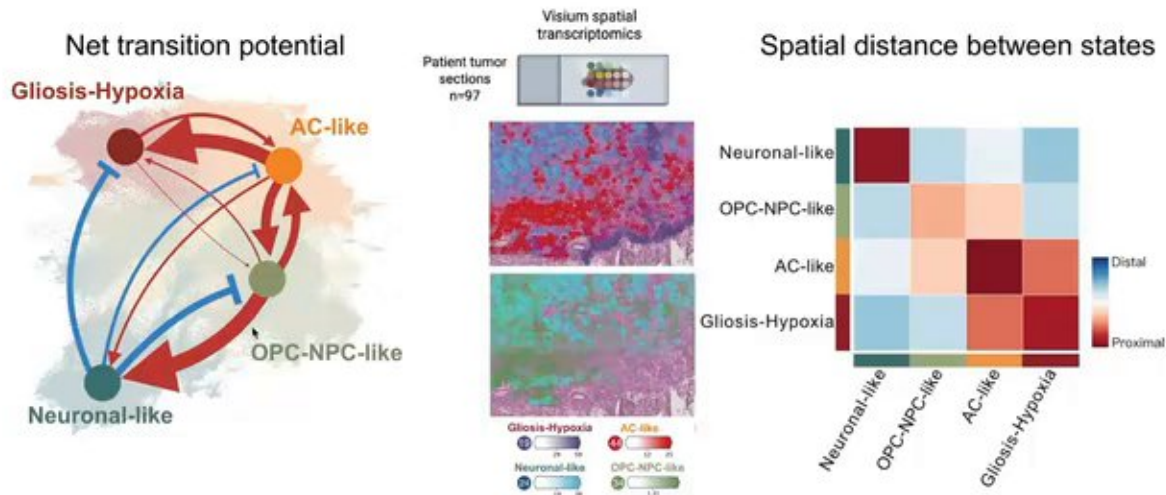
Activation and repression jointly shape glioblastoma state transitions



The reconstructed state transition hierarchy explains differences in epigenetic plasticity



Resolved state transitions align with spatial patterns of glioblastoma progression

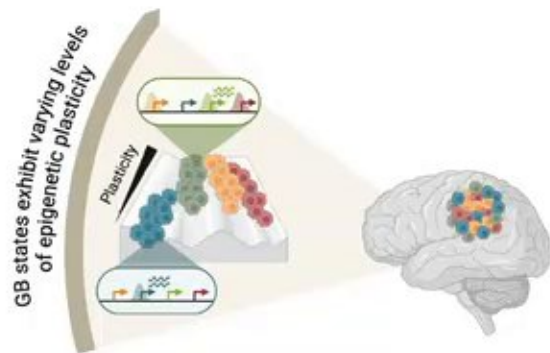


Spatial proximity between glioblastoma states correlates with higher transition potential



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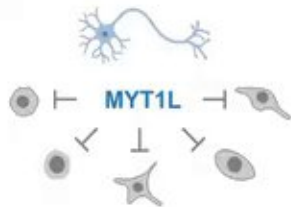
Take home messages



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The neuronal regulator MYT1L in GBM

MYT1L safeguards neuronal identity
by **repressing** *non-neuronal identities*

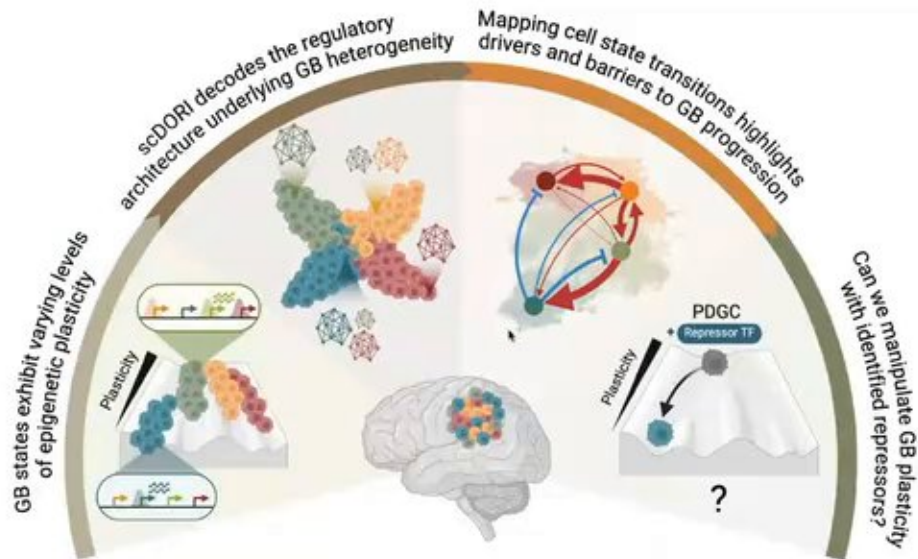


Mall et al. *Nature* (2017)



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The neuronal regulator MYT1L in GBM

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Mall et al. *Nature* (2017)



The neuronal regulator MYT1L in GBM

MYT1L safeguards neuronal identity
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Mall et al. Nature (2017)

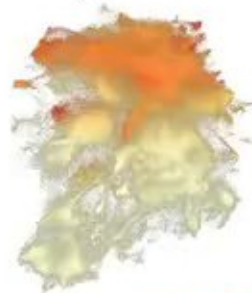
MYT1L expression



Neuronal-like

Low High

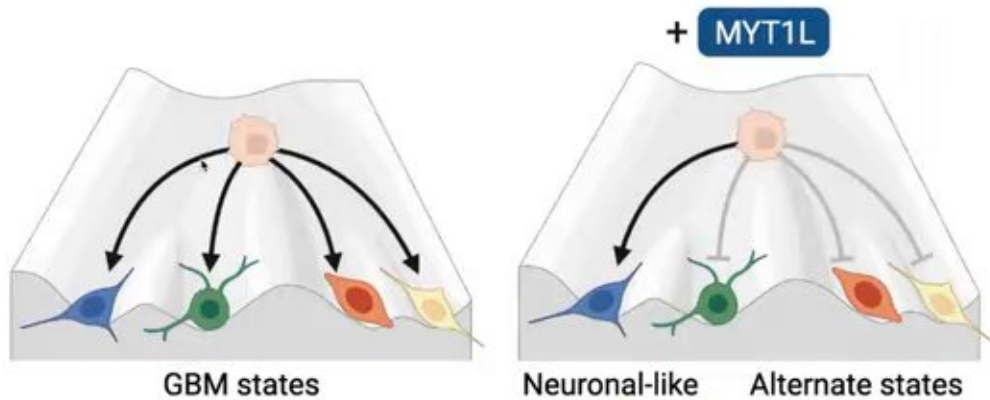
Expression of genes
predicted to be **repressed**
by MYT1L



Low High

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Manipulating GBM identity through “brakes” on plasticity



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Epigenetic changes upon MYT1L overexpression in patient-derived GBM cells



Moritz Mall



Elisa Henzelmann



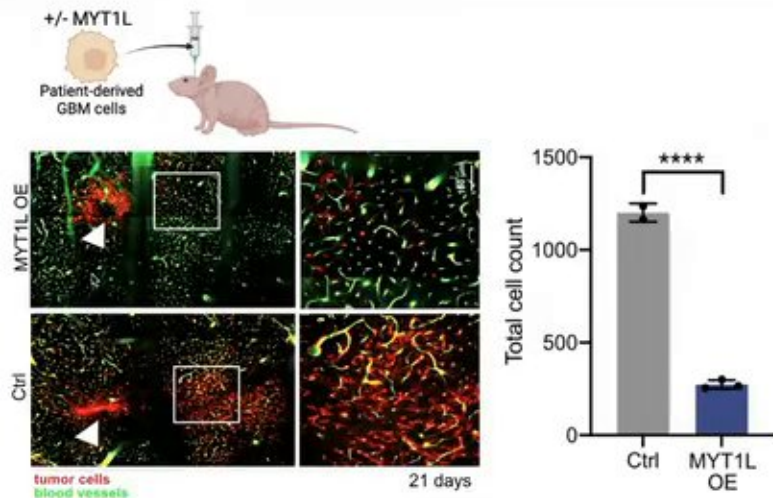
Laura Rueda Gensini



Effects of plasticity restriction on tumor progression in vivo



Effects of plasticity restriction on tumor progression in vivo



With Elisa Heinzemann, Eric Jung



Acknowledgements

Mall lab

Laura Rueda

Elisa Heinzemann

Jannes Straub

Bettina Weigel

Bryce Lim

Cedar Schloo

Tim Kindinger

Stegle lab

Martin Rohbeck

Katharina Mikulik

Olga Lazareva

Alexander Aivazidis

Collaborators

Omer Bayraktar

Grant De Jong

Tannia Gracia

Fani Memi

Oliver Gould

Frank Winkler &

Wolfgang Wick

Eric Jung

Dirk Hoffman

Sophie Weil



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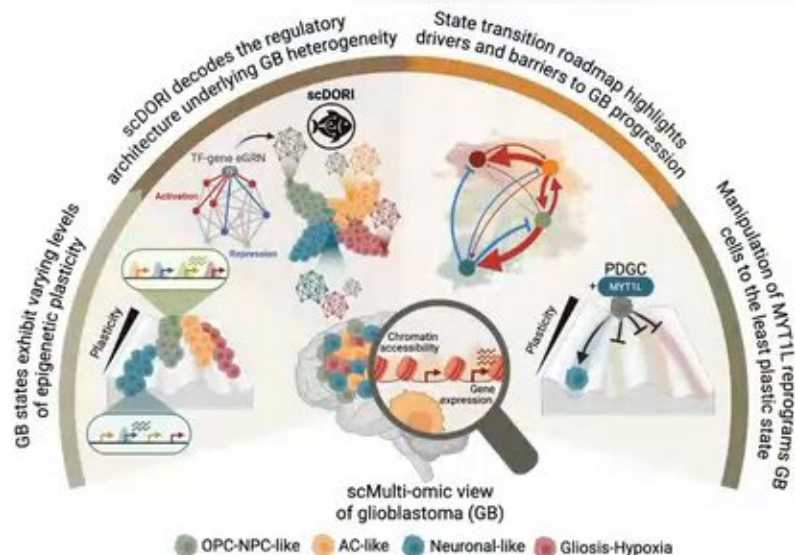


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scDBR decodes the regulatory architecture underlying GB heterogeneity

State transition roadmap highlights drivers and barriers to GB progression

GB states exhibit varying levels of epigenetic plasticity

Manipulation of MYT1L reprograms GB cells to the least plastic state

Observation Accessibility

Gene expression

scMulti-omic view of glioblastoma (GB)

OPC-NPC-like AC-like Neuronal-like Gliosis-Hypoxia

bioRxiv

make gms bigger
include multiome



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Background Layout Theme Transition

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scGB decodes the regulatory architecture underlying GB heterogeneity

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Philippe Martin





















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