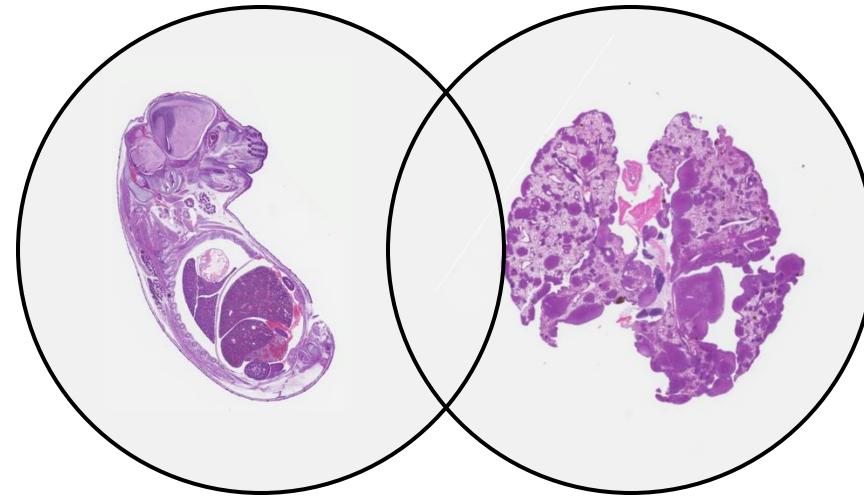


DEVELOPMENT



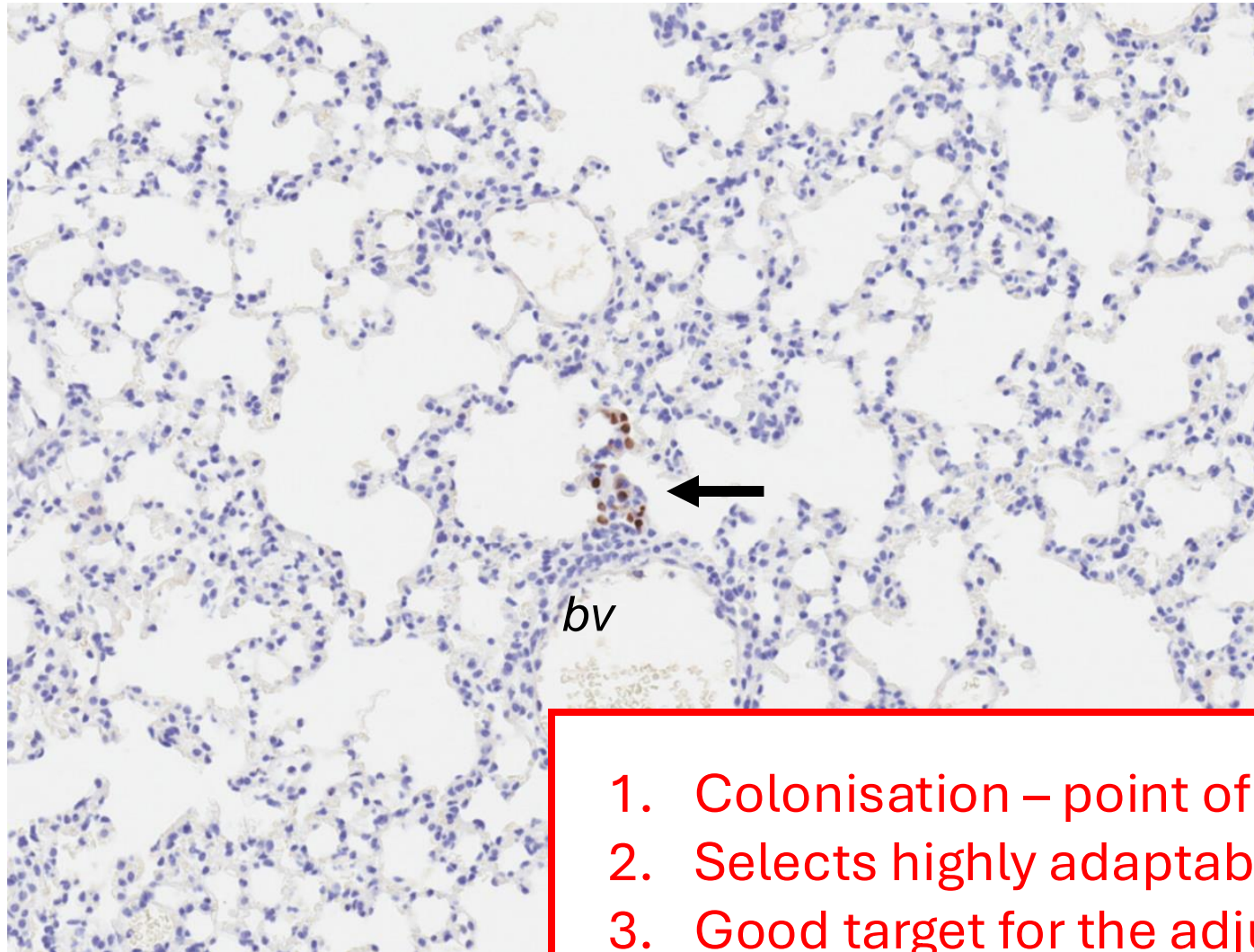
CANCER

Embryonic gene module re-expression in melanoma yields insights into a Hdac2-driven mechanism of plastic adaptation

Kerrie Marie, PhD

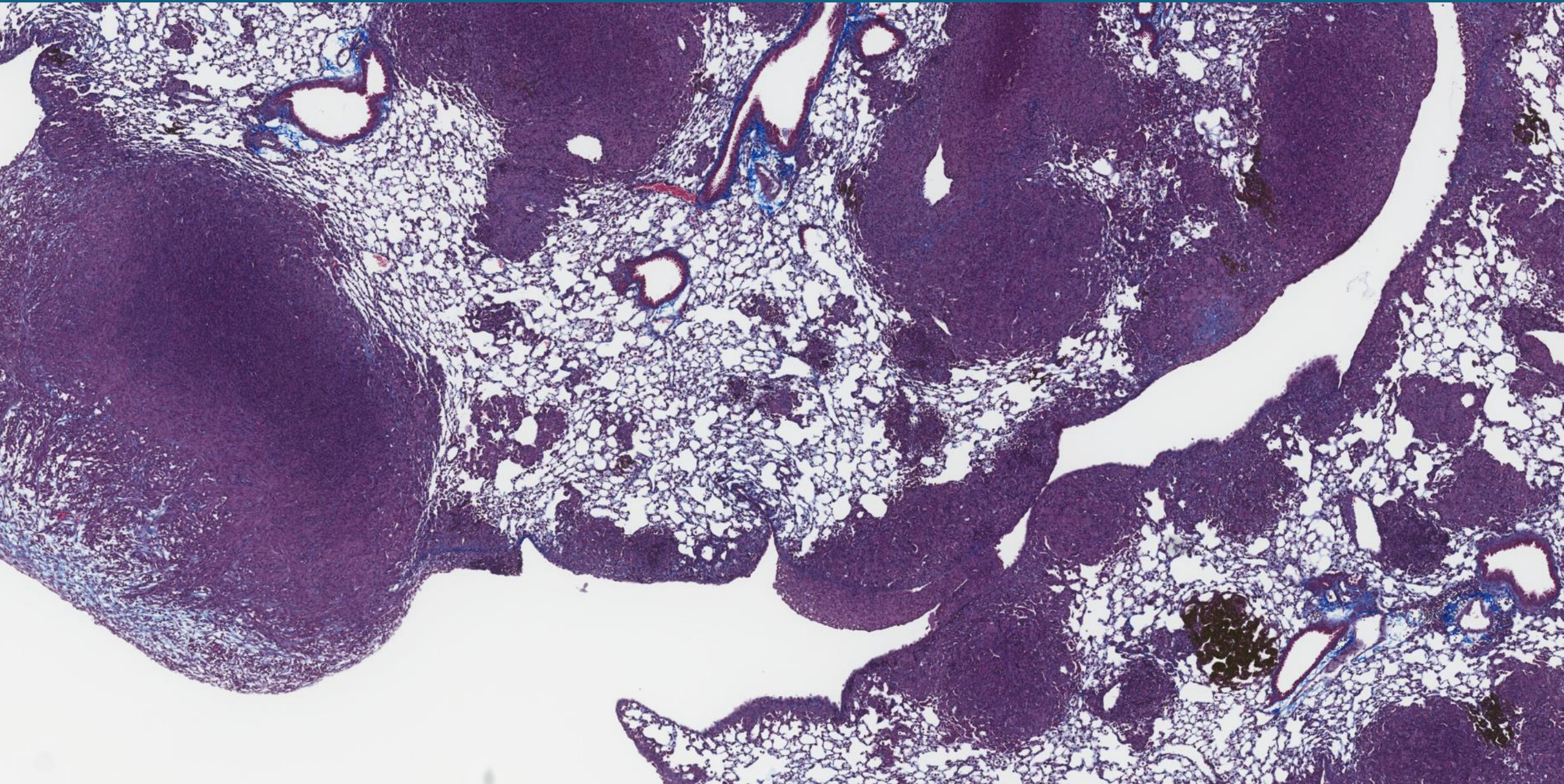
Metastatic Colonisation – a highly selective process

1 week post colonisation

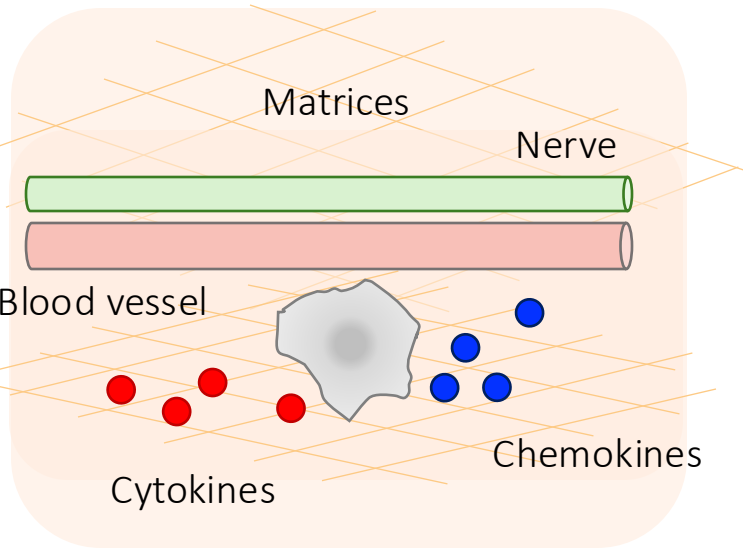
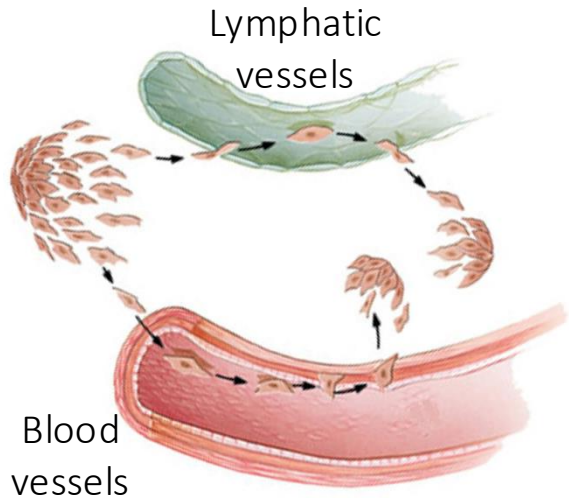


1. Colonisation – point of extreme vulnerability
2. Selects highly adaptable cells
3. Good target for the adjuvant setting

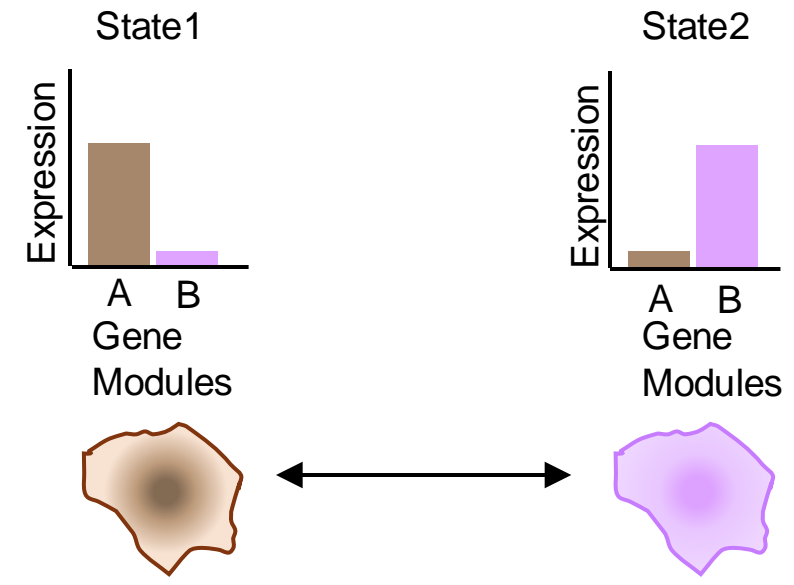
Fully involved lung – therapy resistant and heterogeneous



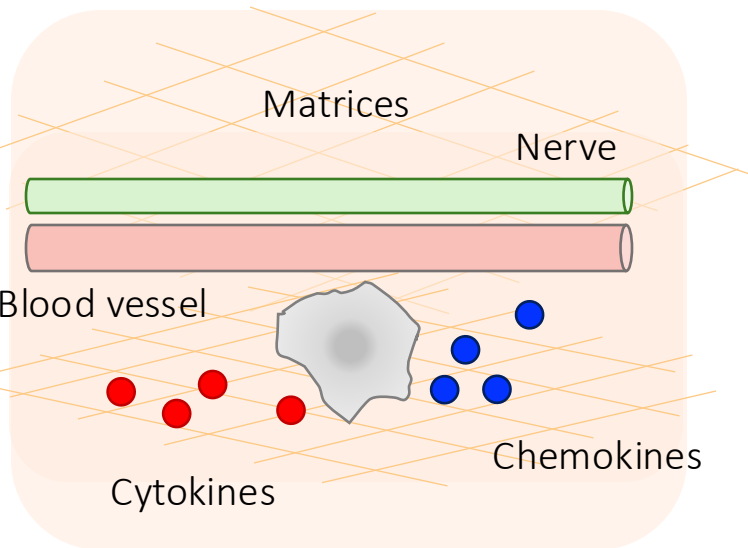
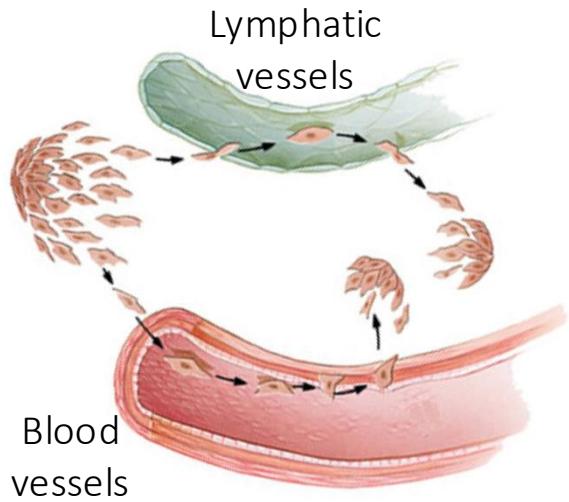
Adaptation at the cellular level



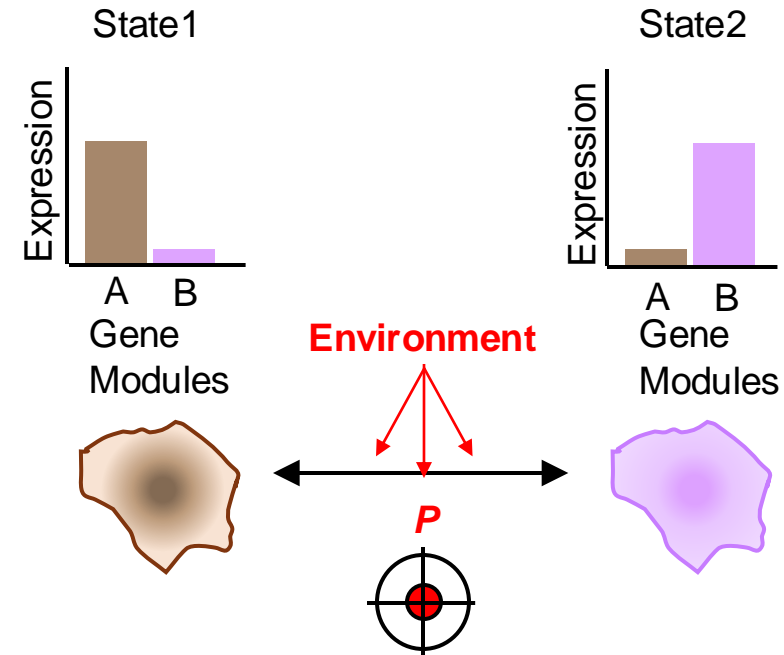
- Interact
- Heterogeneous



Hypothesis: A cell's capacity for cell-state switching determines its capacity for metastasis and therapy resistance

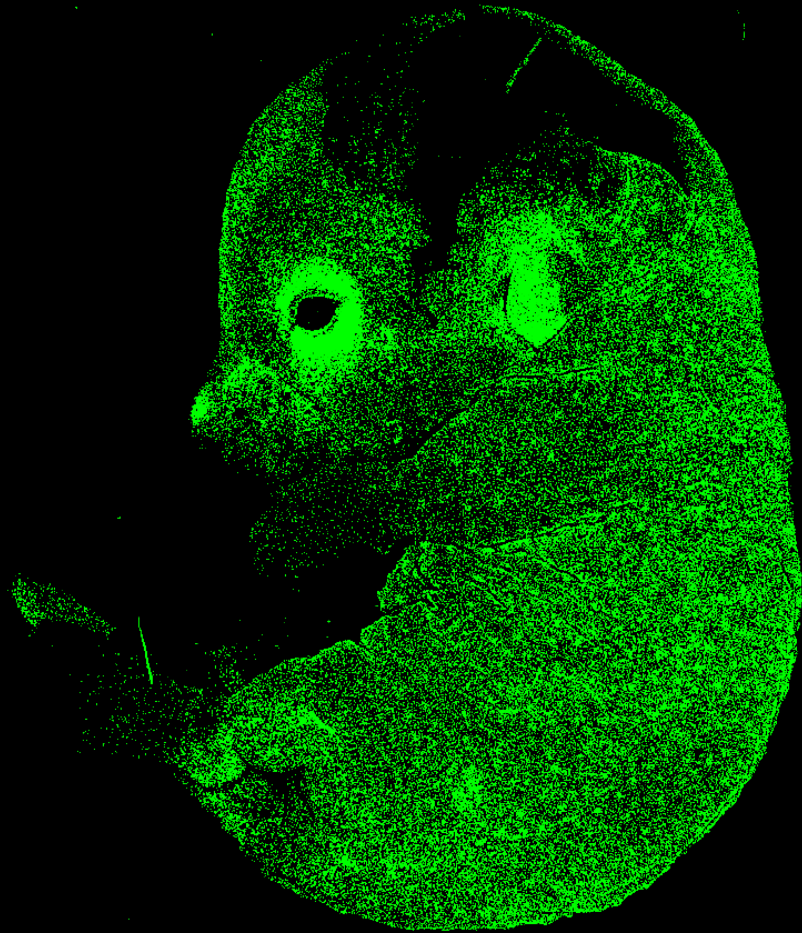


- Interact
- Heterogeneous

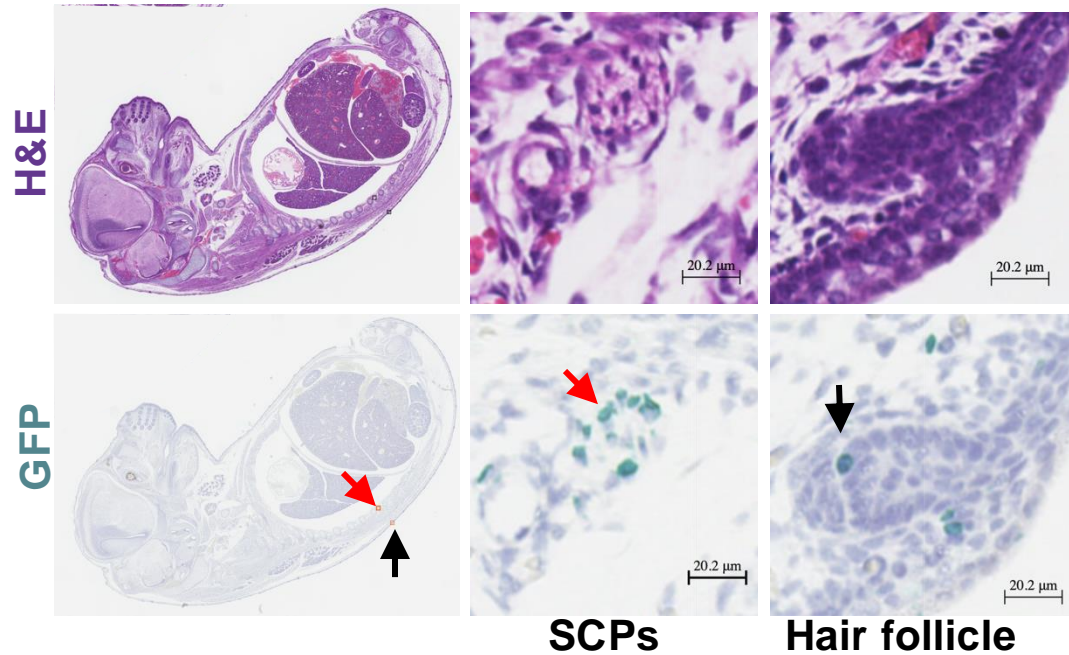


Can we learn more from single embryonic melanocytes?

E15 iDct-GFP mouse

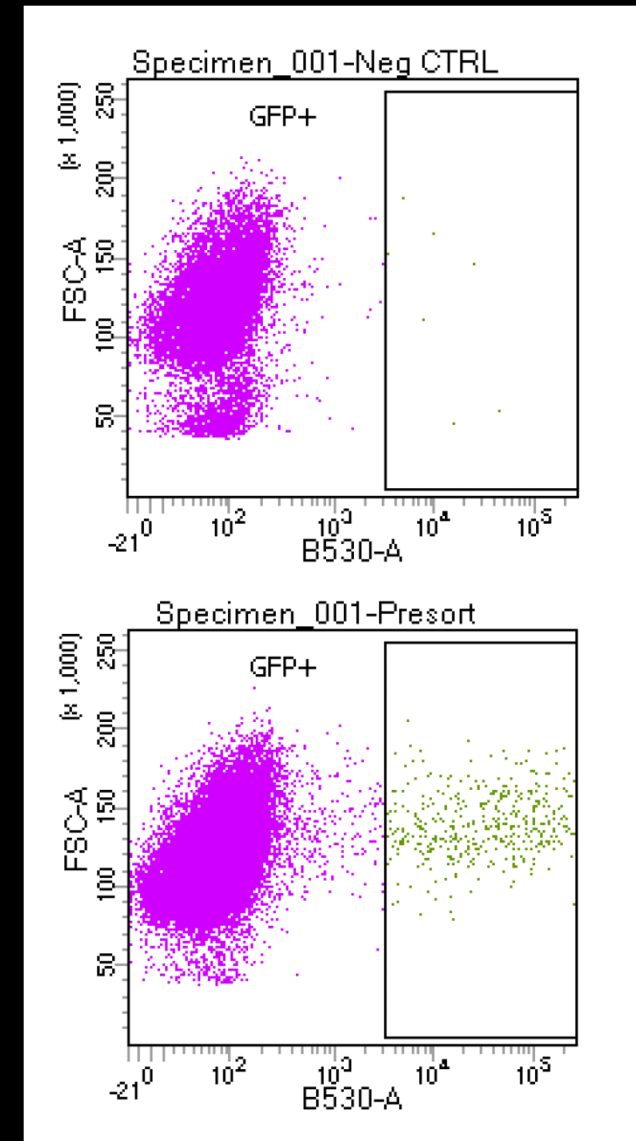
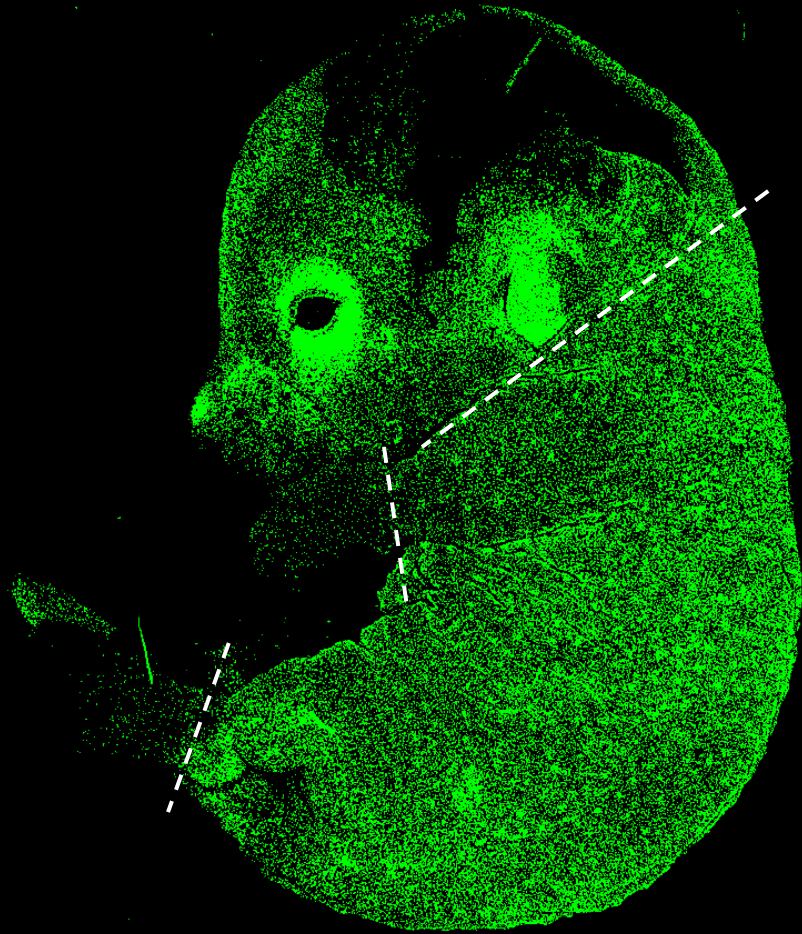


GFP+ cells at stem cell niche & hair follicles



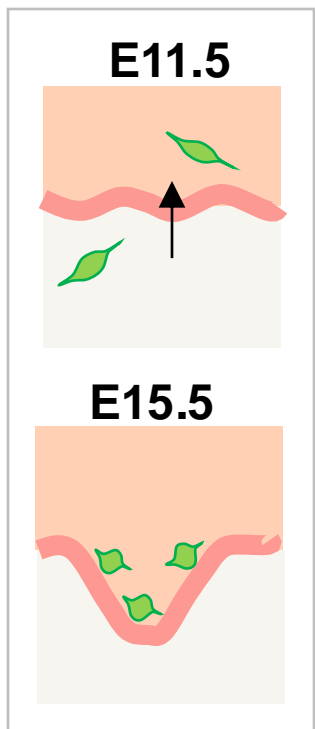
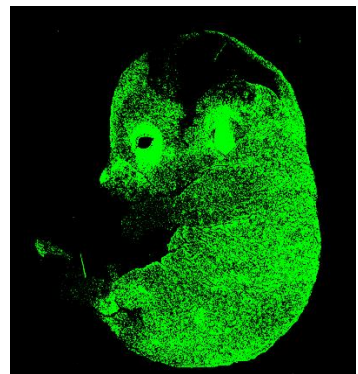
A Melanoblast reporter mouse

E15 iDct-GFP mouse

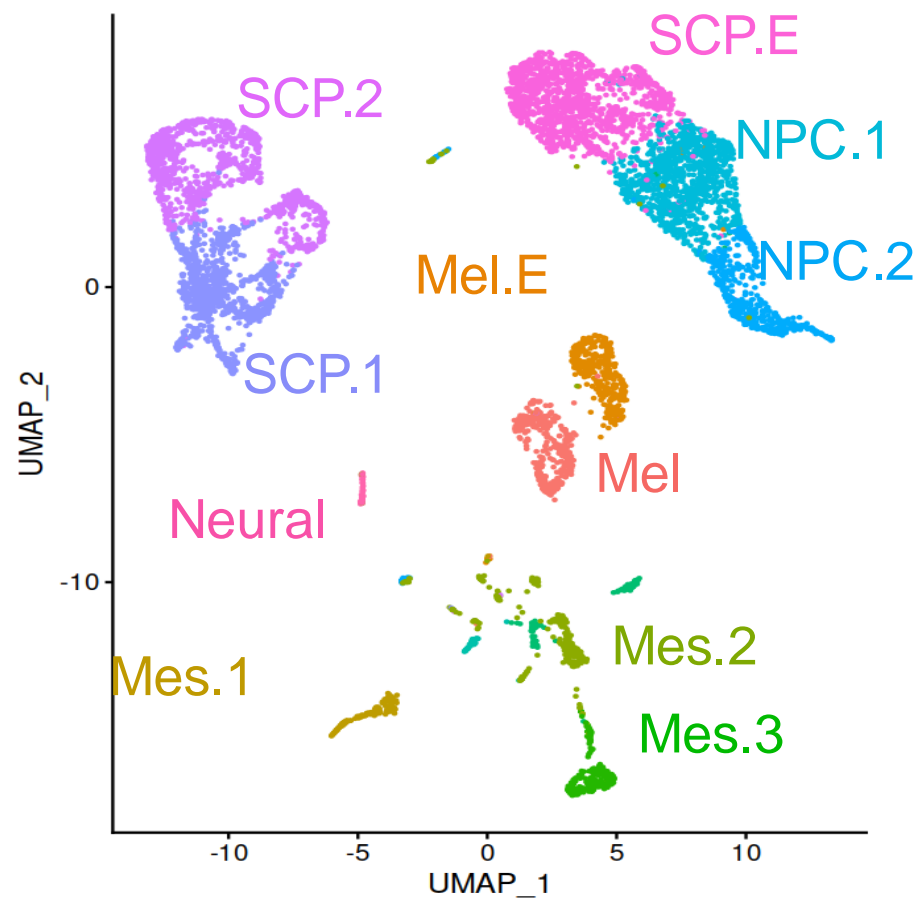


Dct-rtTA; tre-H2B-GFP
Zaidi et al., 2011

Multiple subpopulations identified

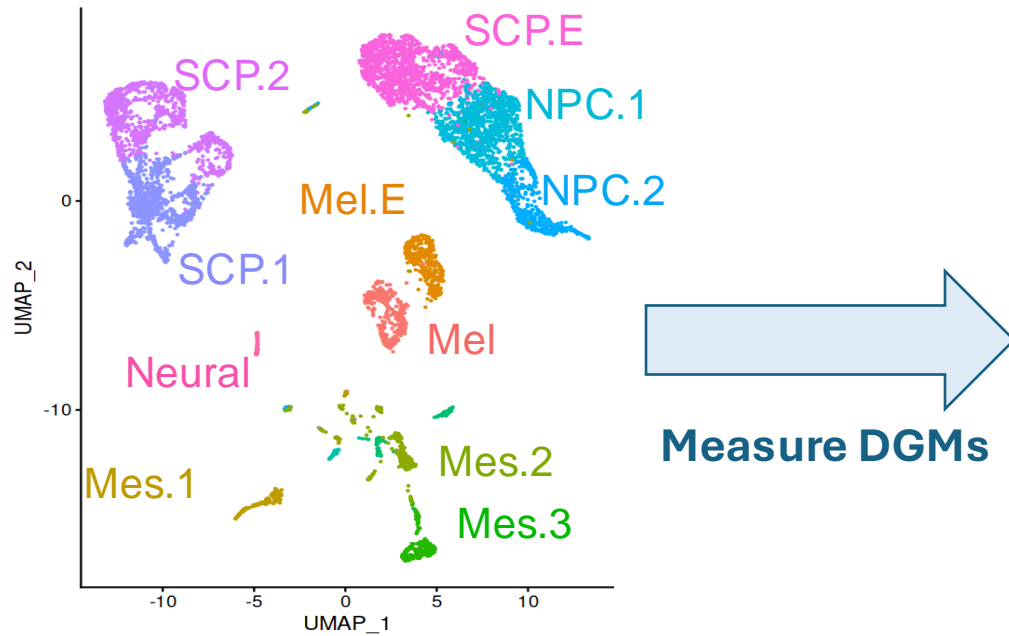


Embryonic melanocyte precursors

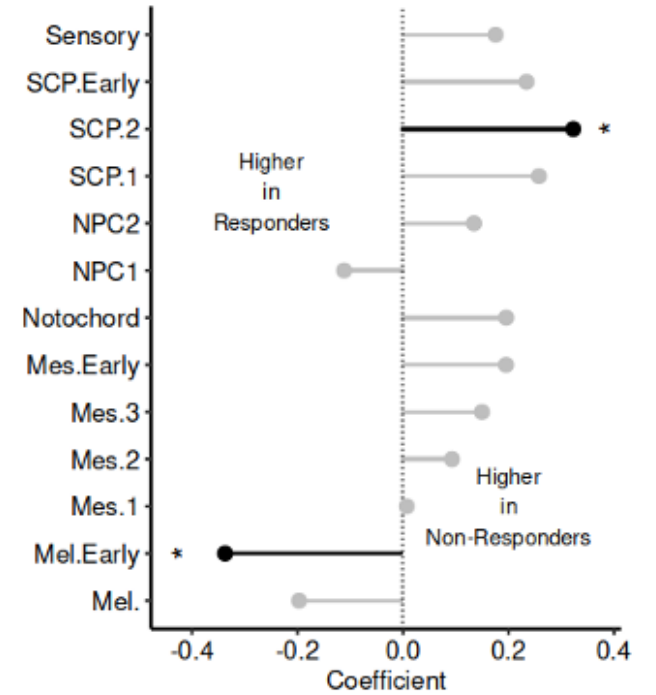
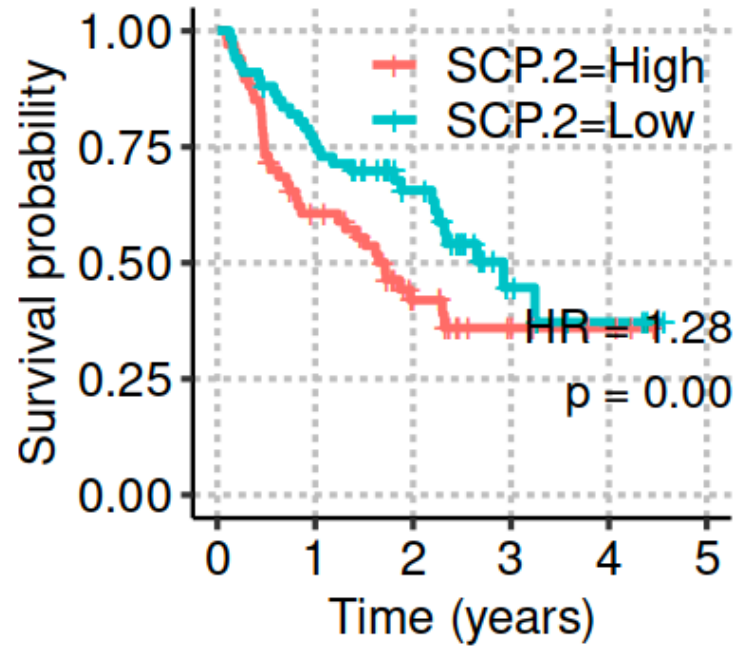


Developmental Gene Module expression in melanomas

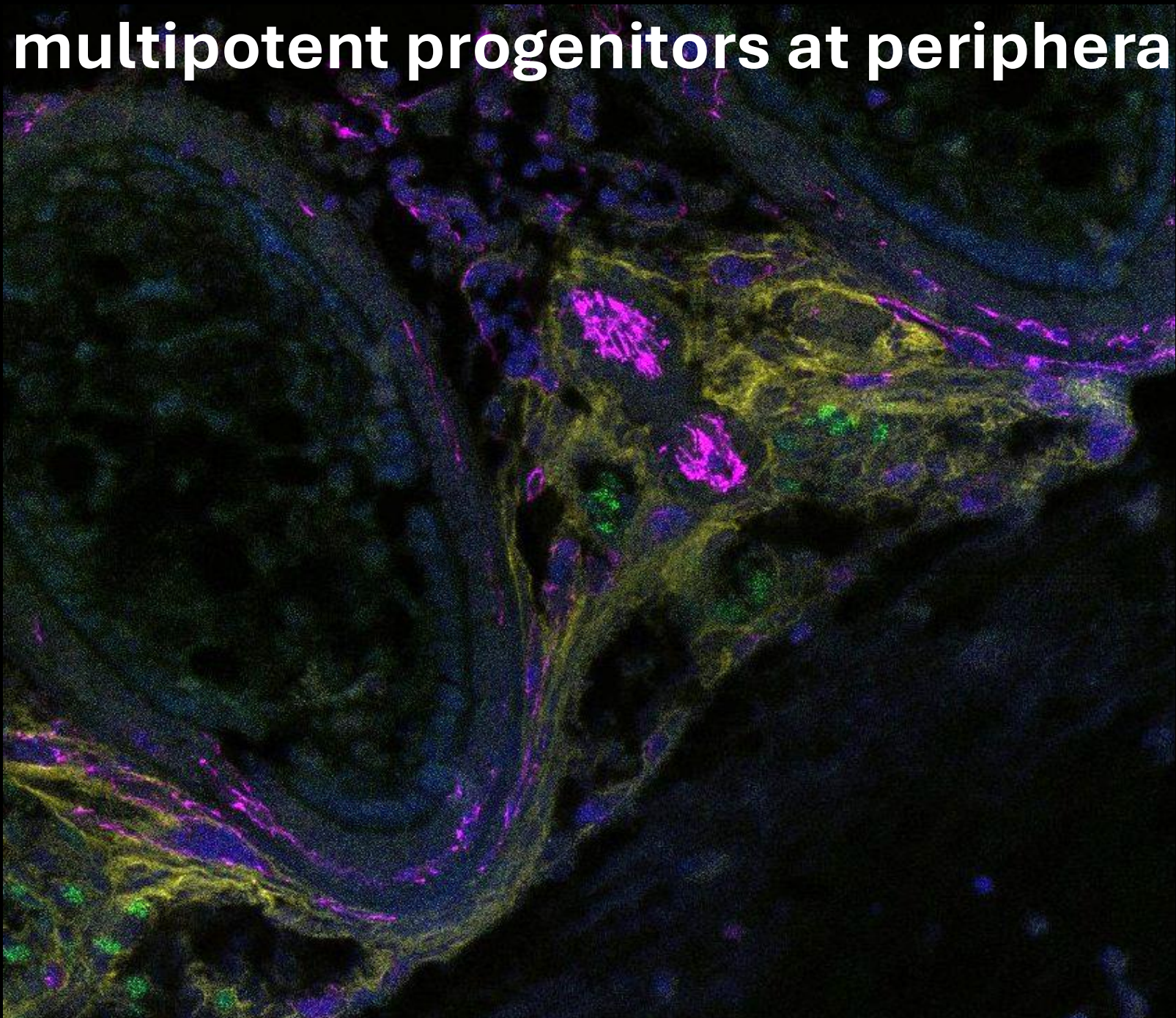
Identify cell states



Schwann Cell Precursor signature predicts worse prognosis

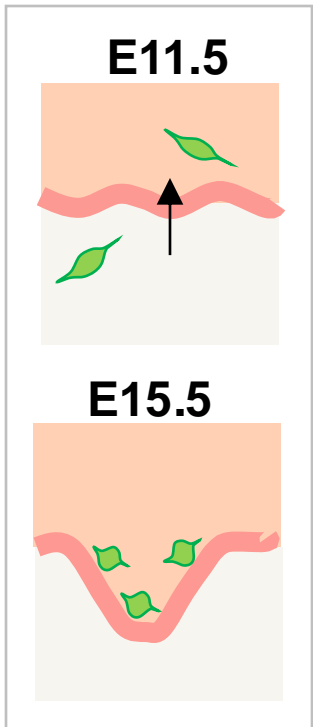
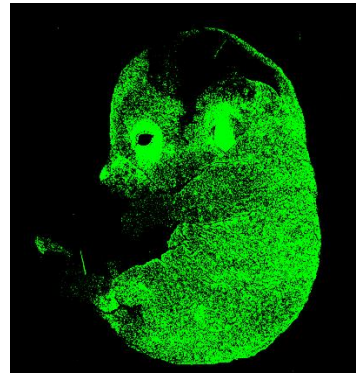


SCPs are multipotent progenitors at peripheral nerves

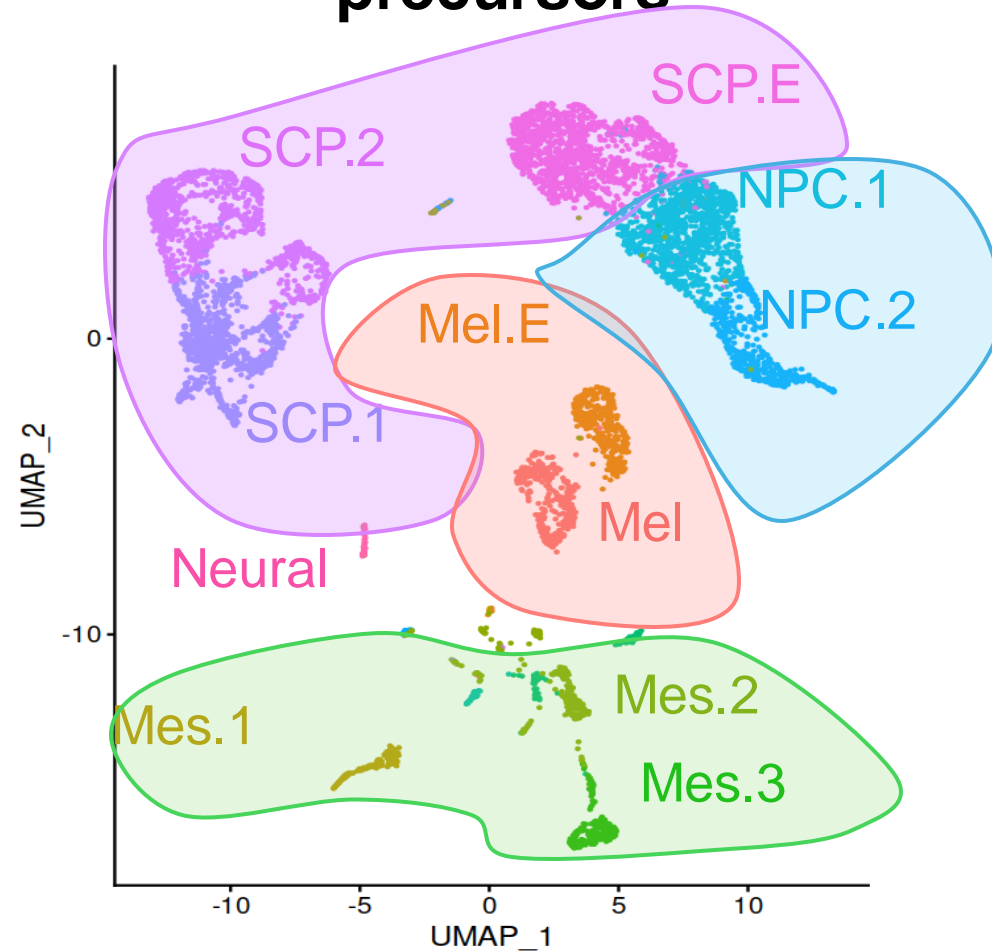


CD31-AF647
NGFR-Co555
GFP-Co488
DAPI

Four main cell identities

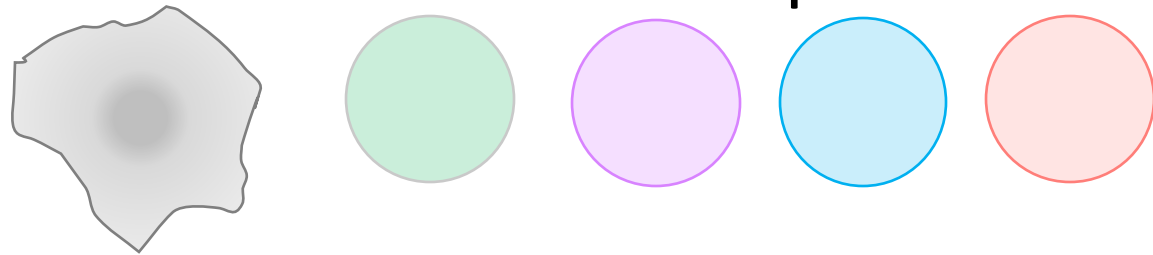


Embryonic melanocyte precursors



Hybrid states in cancer

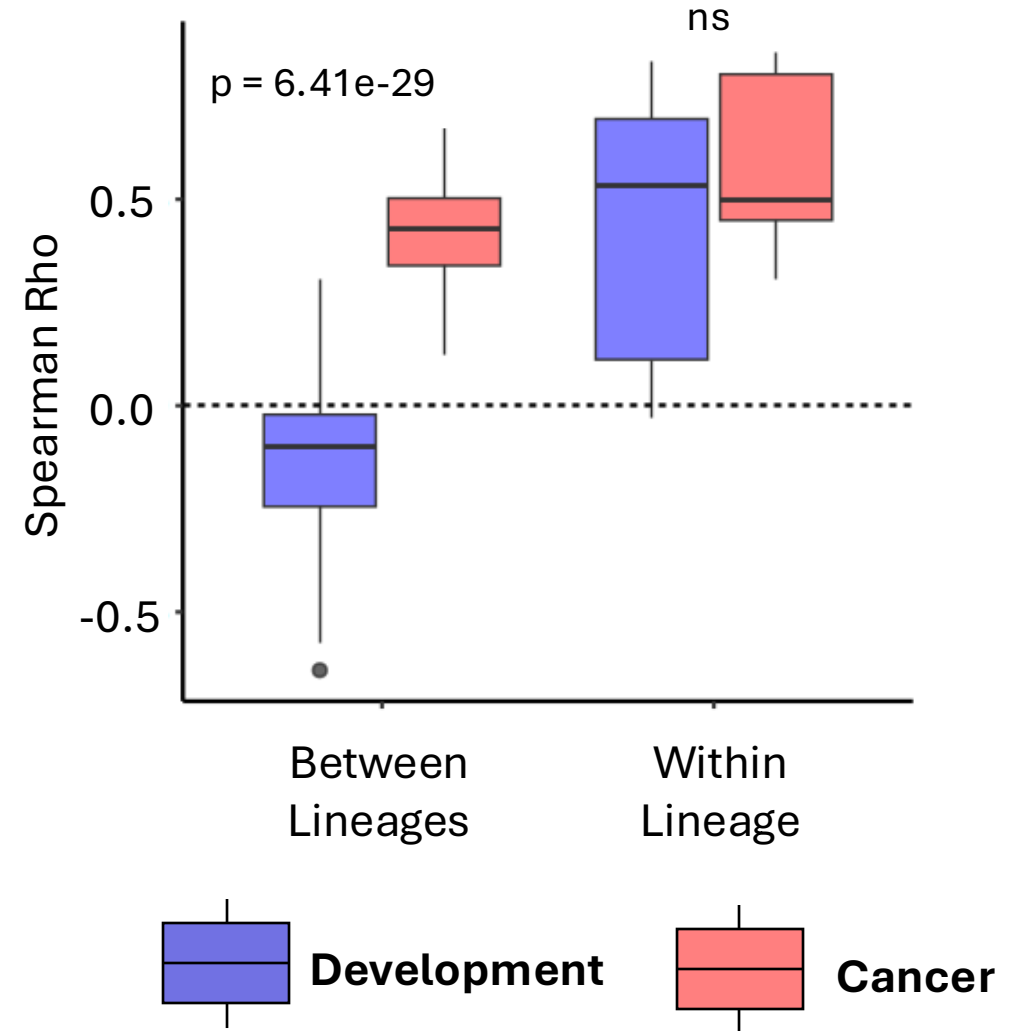
Exclusive gene expression
in development



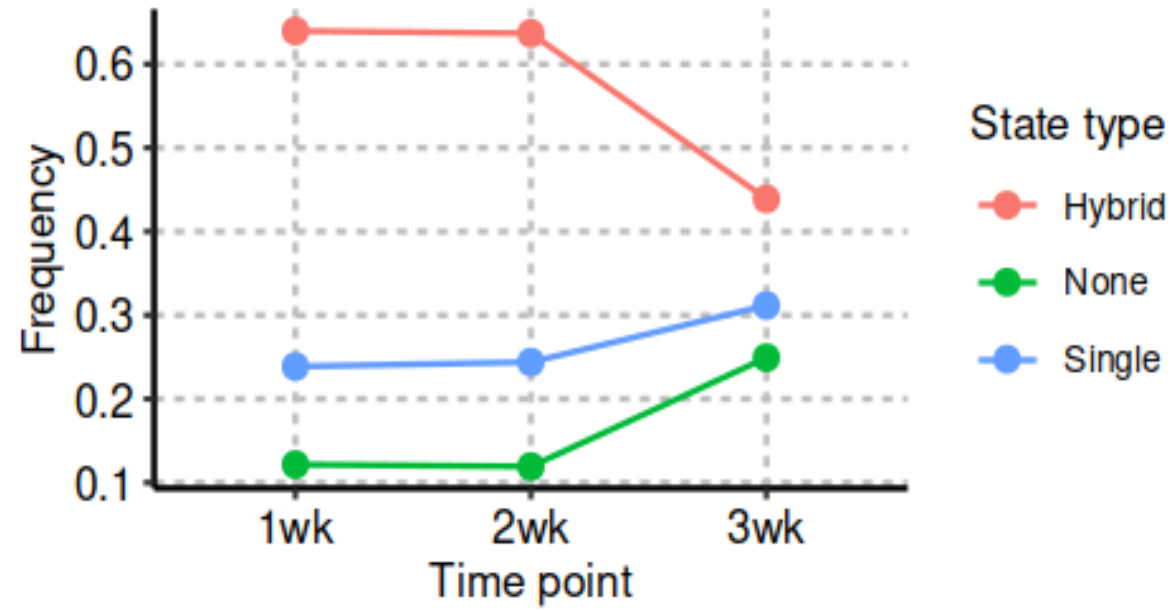
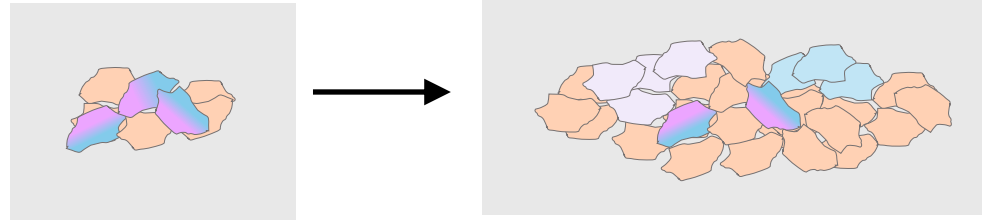
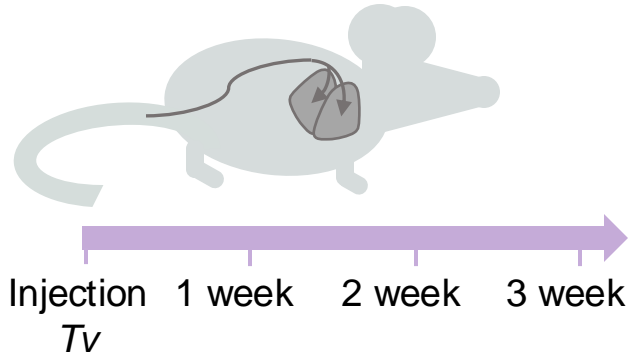
Co-expressed
genes in cancer



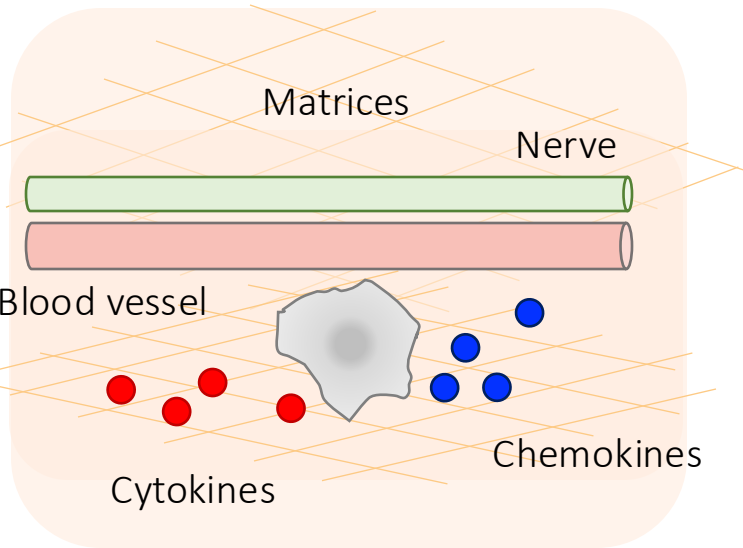
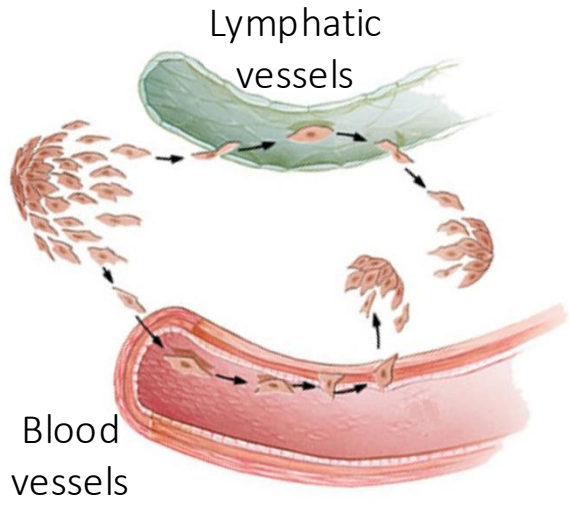
Gene expression correlation



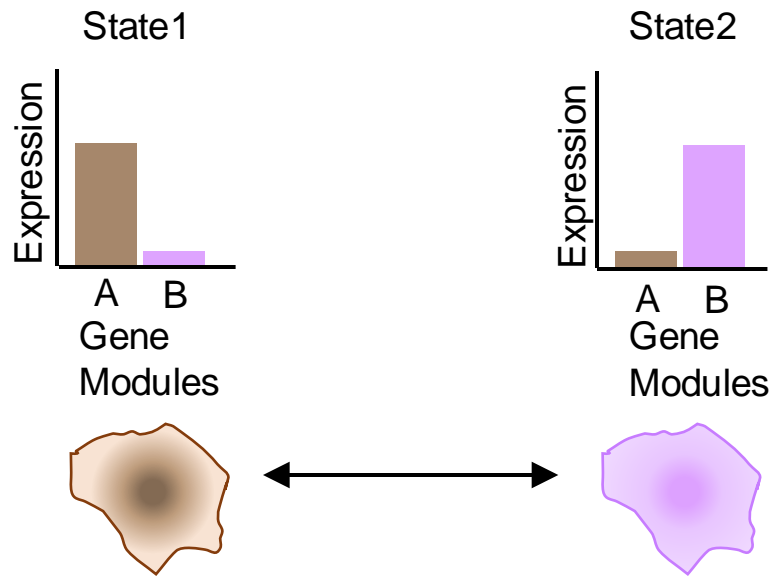
Hybrid states in metastases



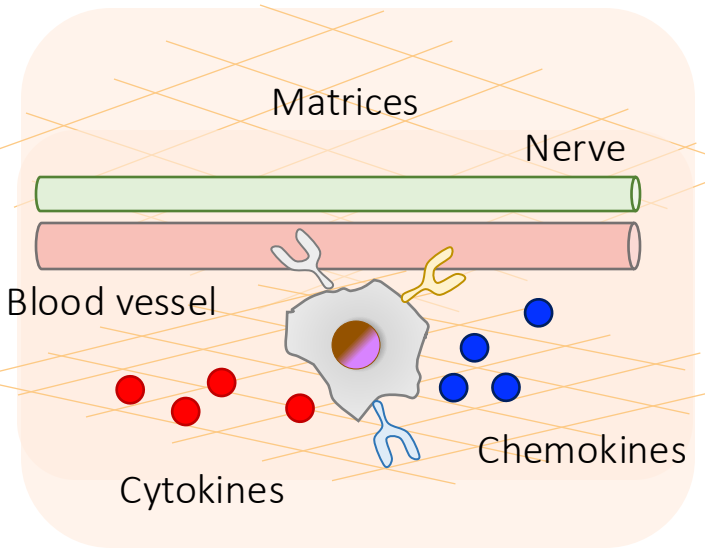
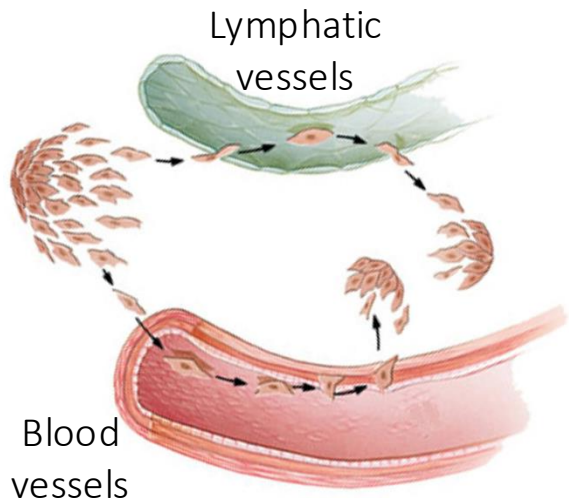
Adaptation at the cellular level



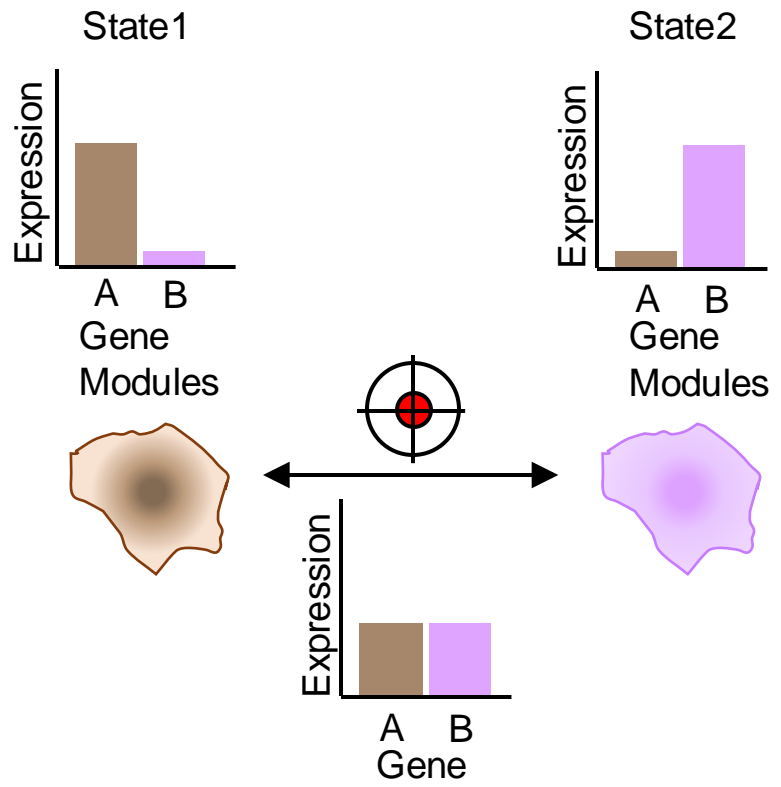
- Interact
- Heterogeneous



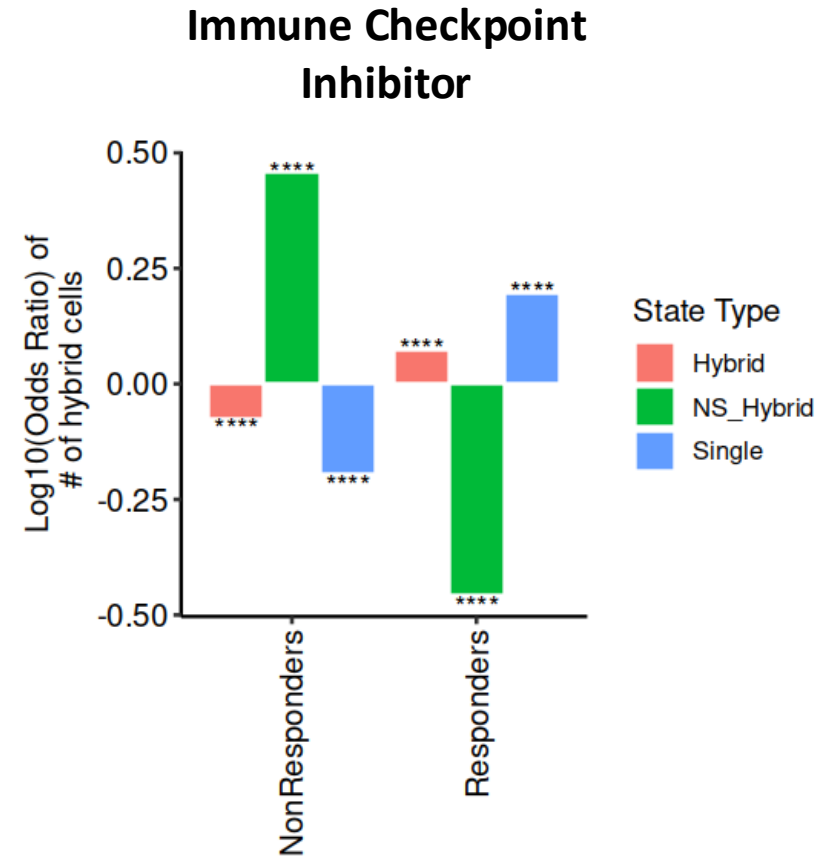
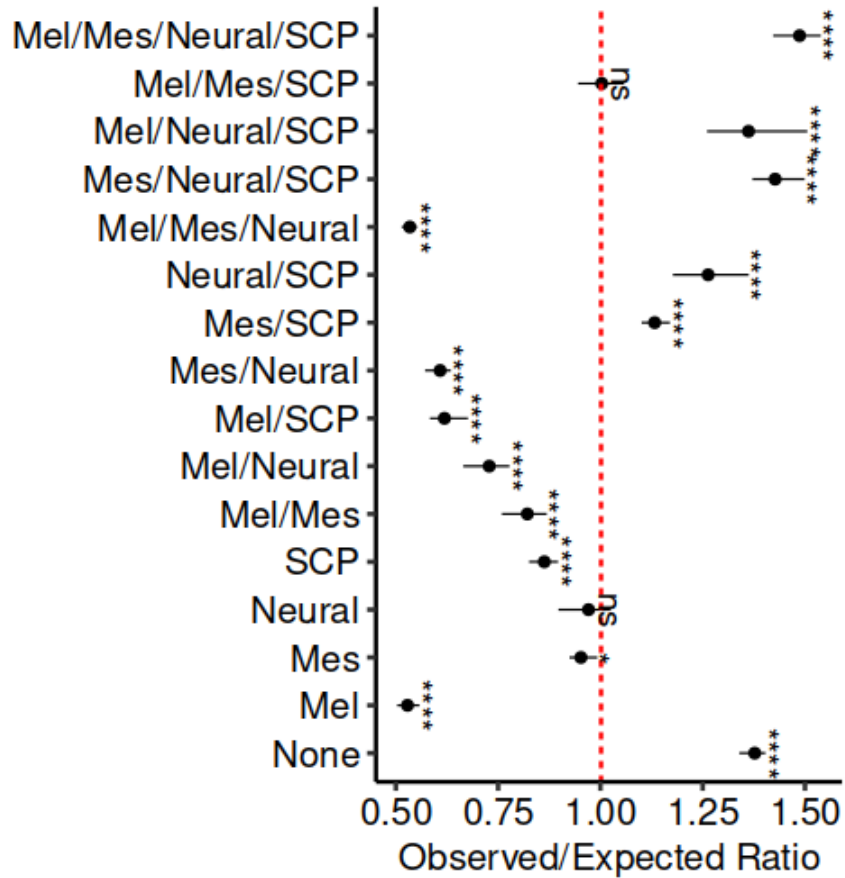
Adaptation at the cellular level



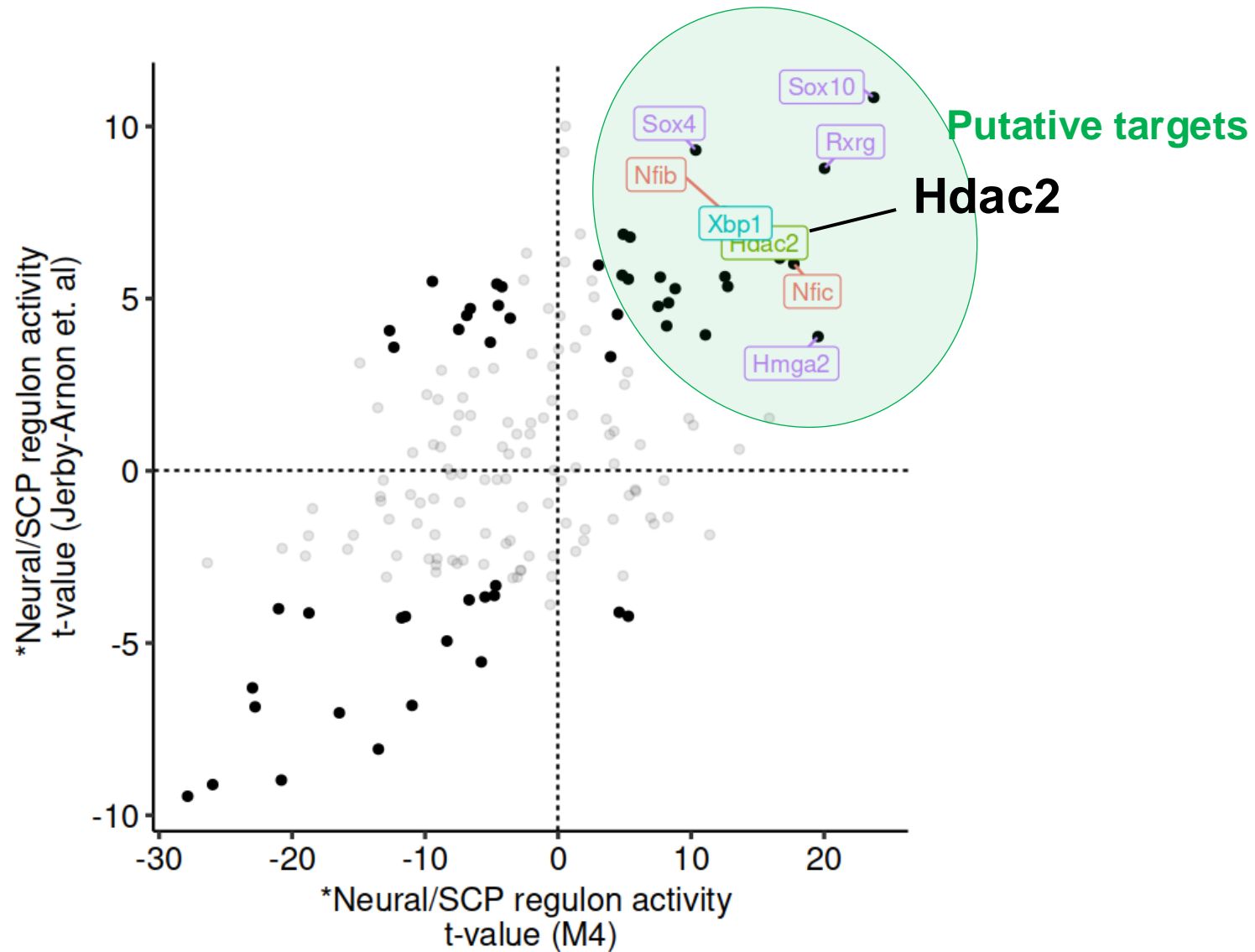
- Interact
- Heterogeneous



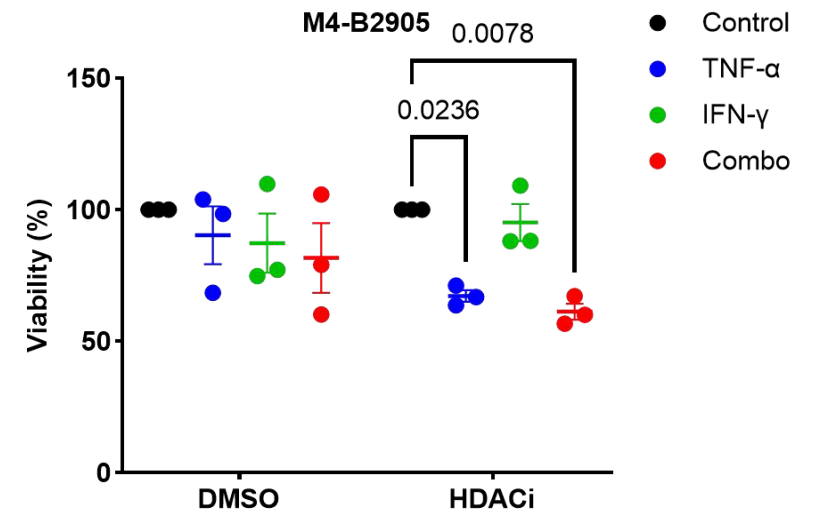
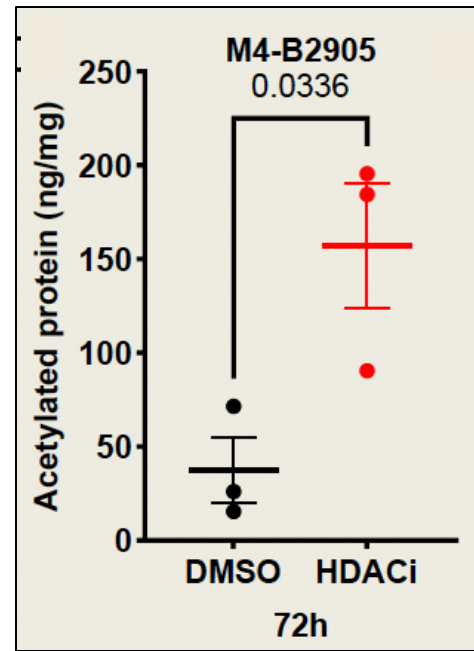
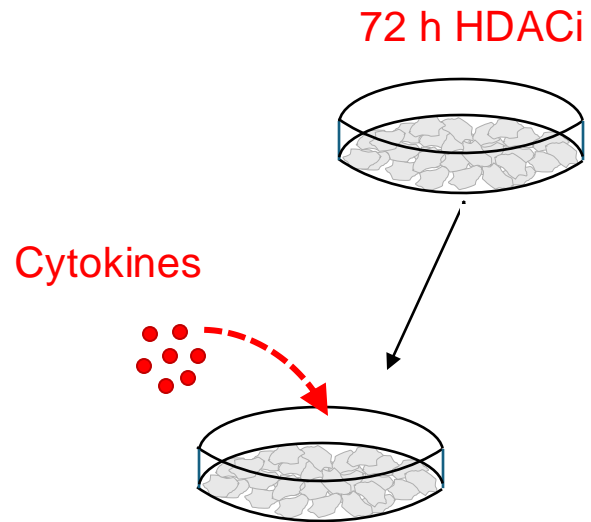
Hybrid states in treatment resistance



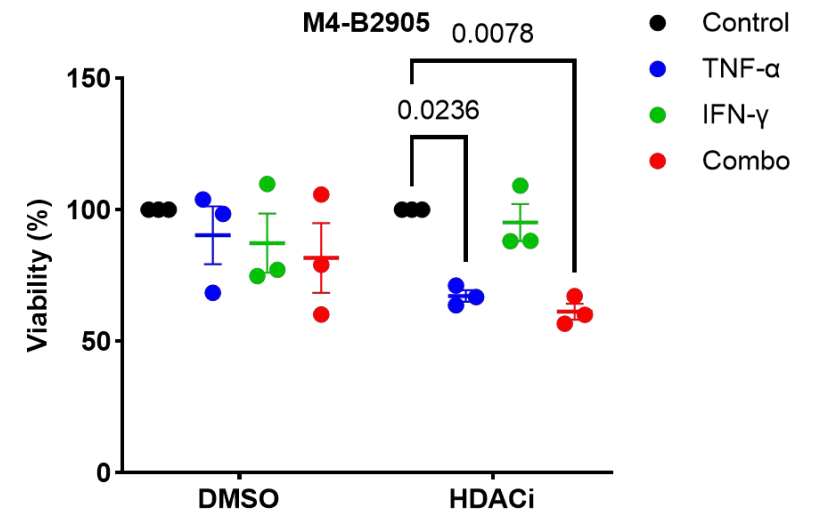
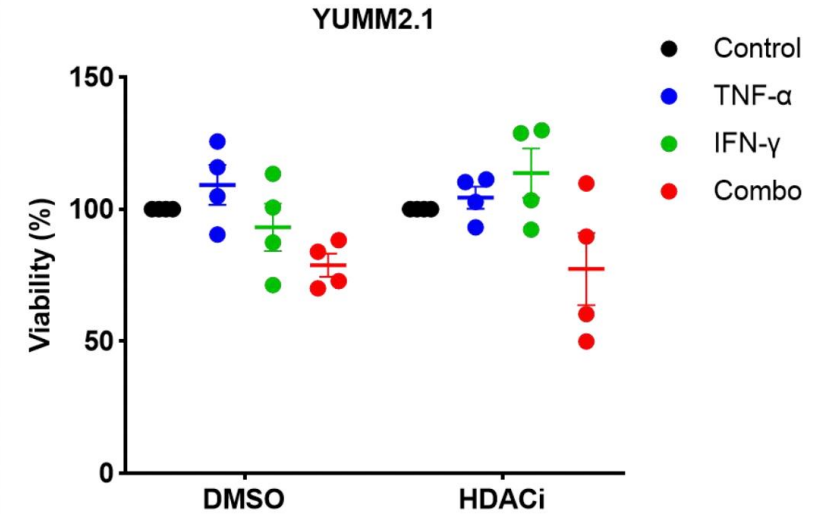
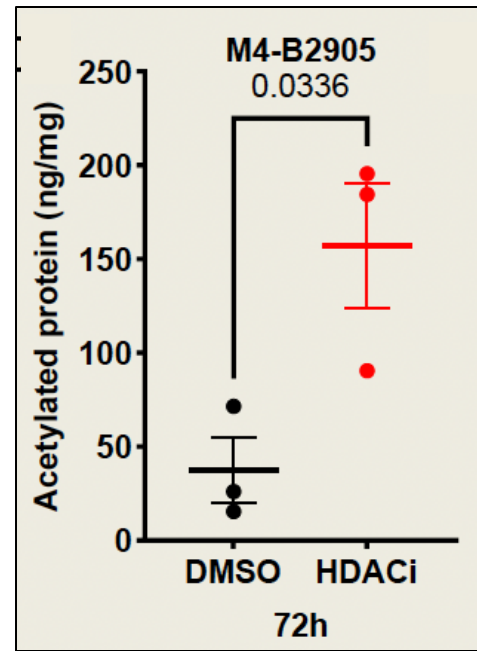
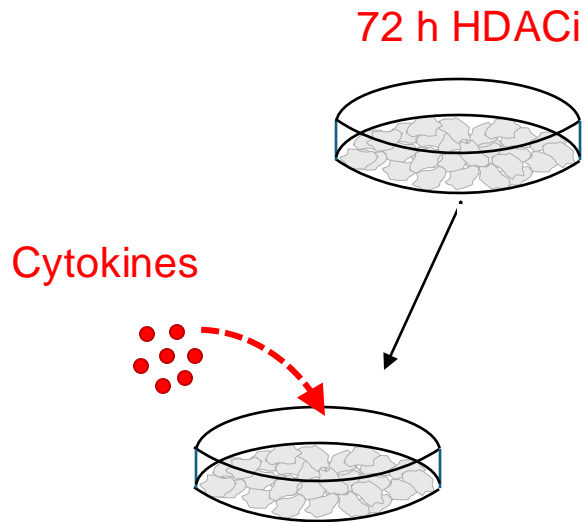
Predicting mechanisms of gene regulation



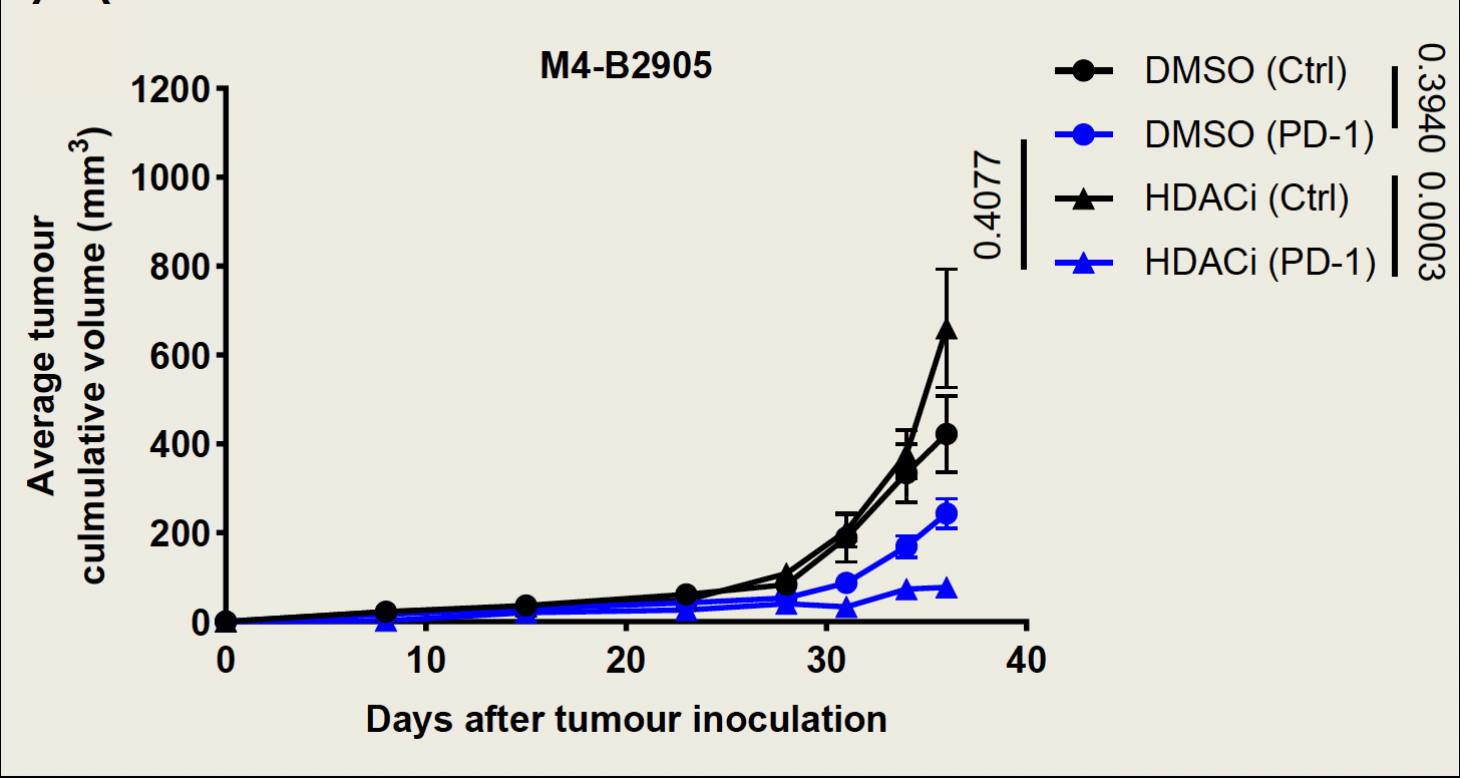
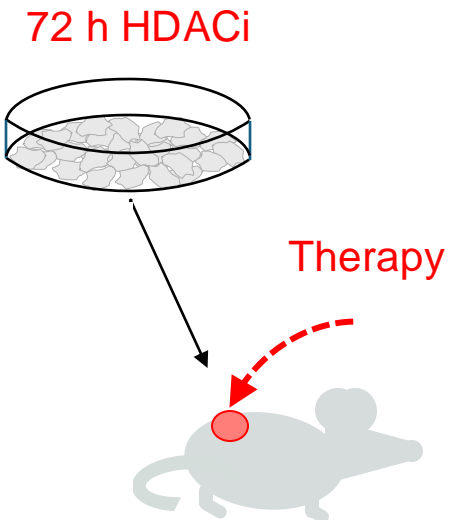
HDACi sensitises cells to TNF α



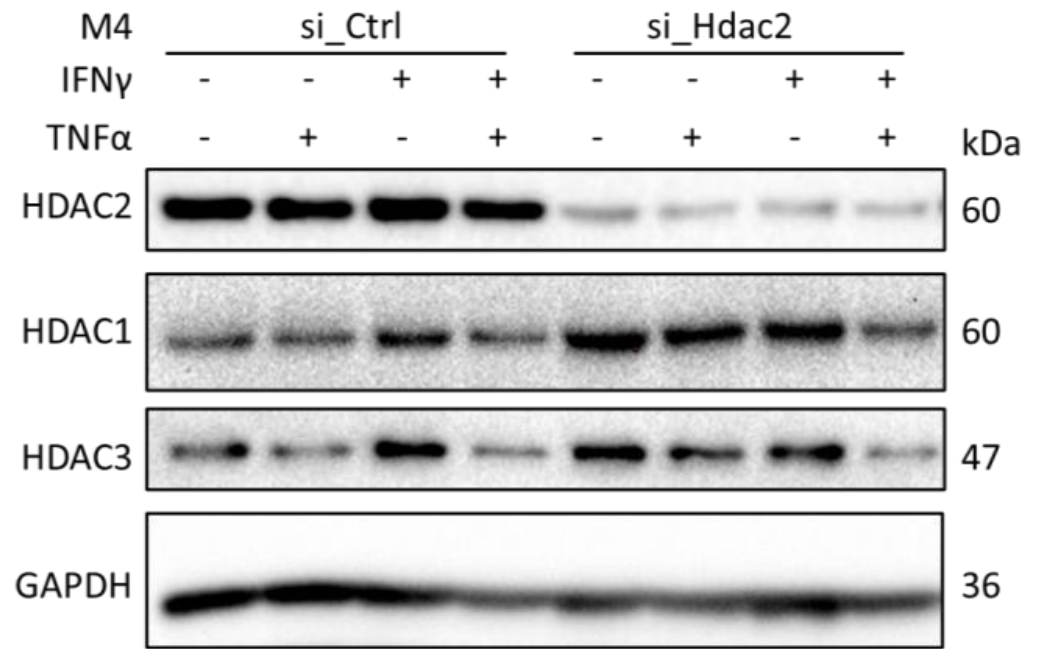
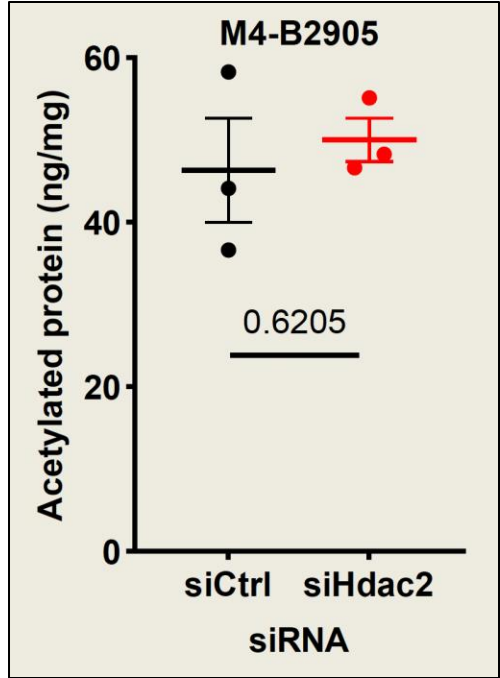
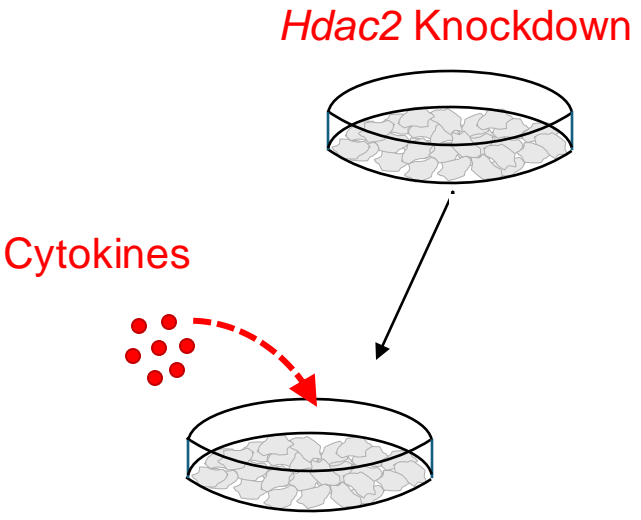
HDACi sensitises cells to TNF α



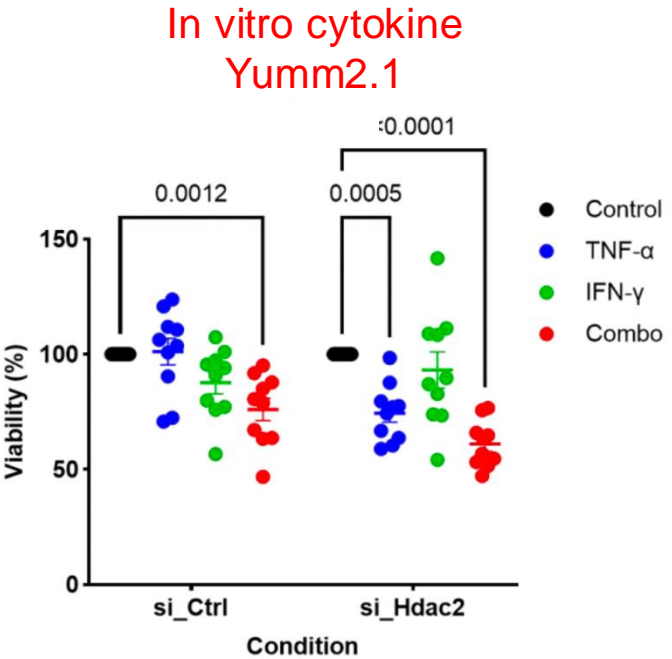
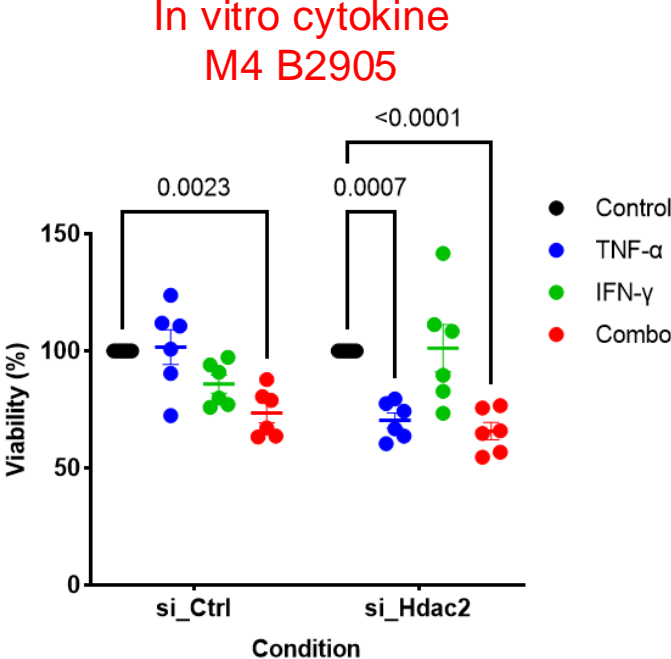
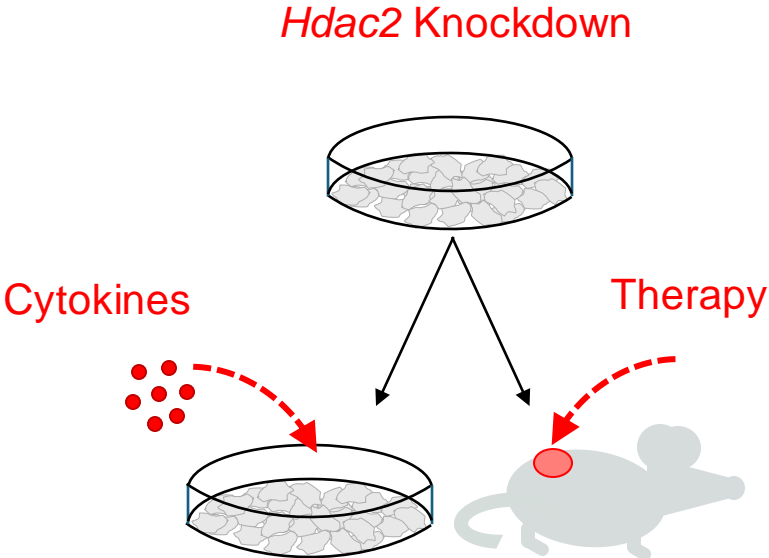
HDACi sensitises cells to anti-PD-1 therapy



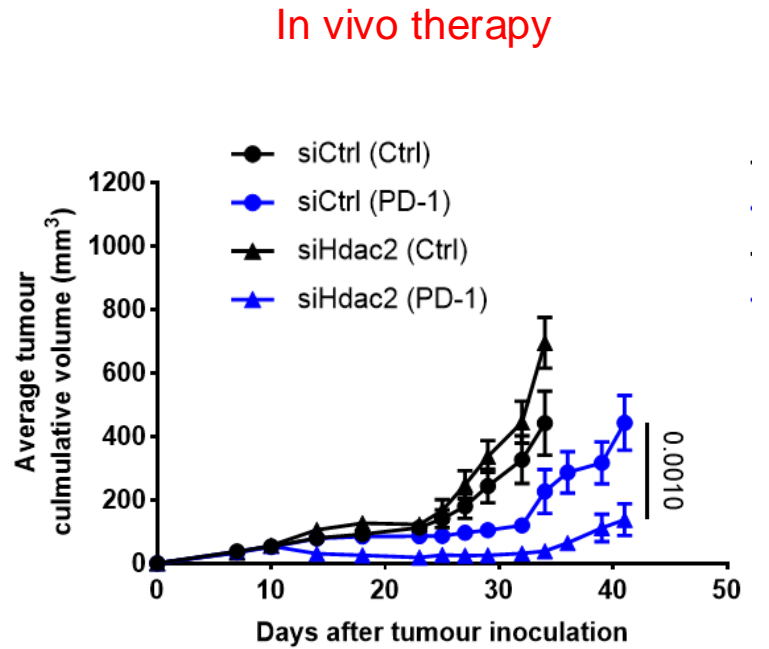
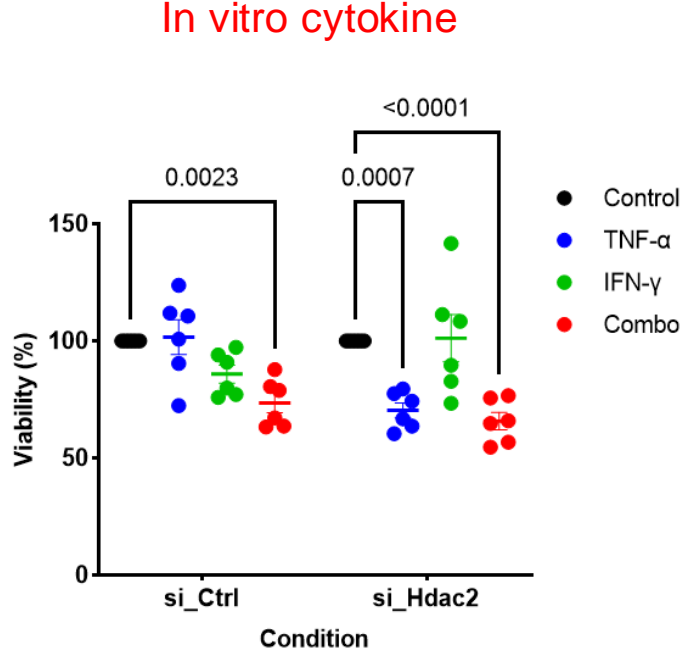
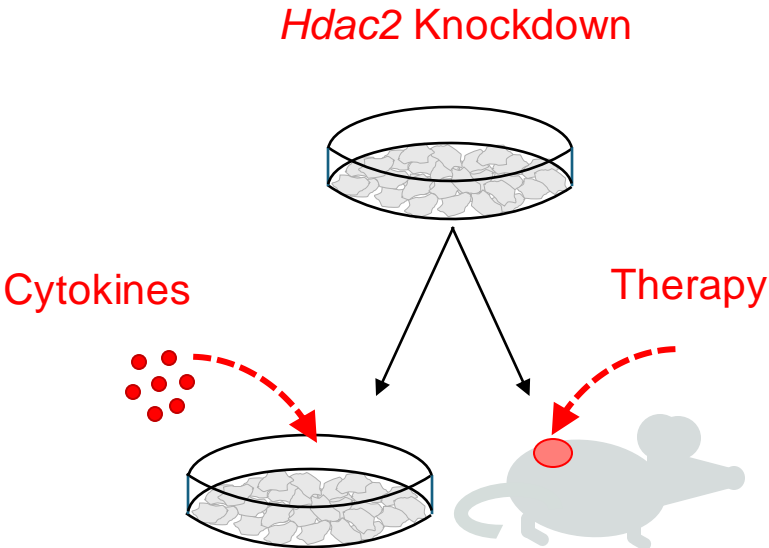
Hdac2 KD sensitises cells to TNF α and to therapy



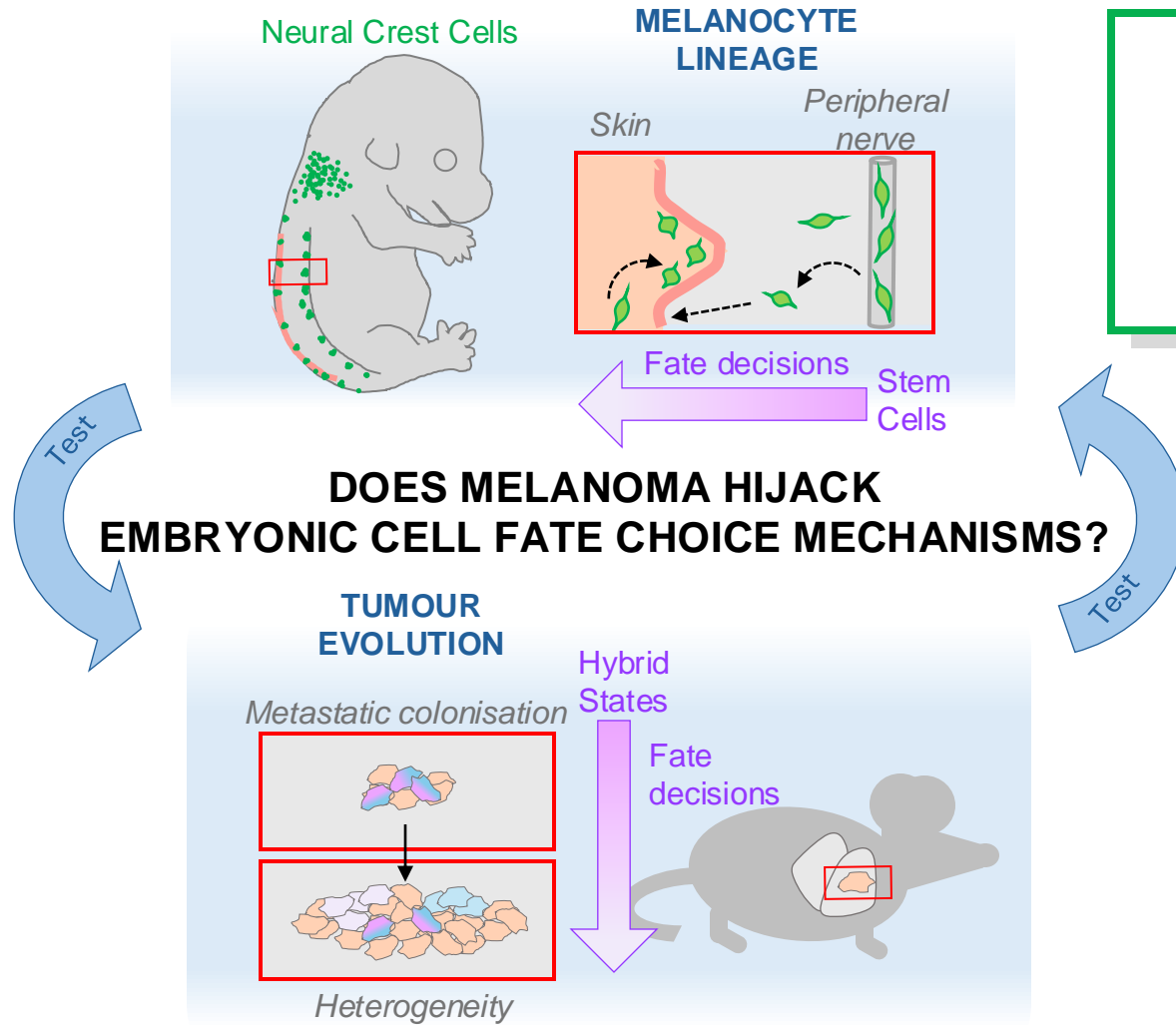
Hdac2 KD sensitises cells to TNF α and to therapy



Hdac2 KD sensitises cells to TNF α and to therapy



Summary



Targeting embryonic-specific pathways in adults may have less side effects

Summary

- Melanoma cell states are conserved from development
- DGMs can predict patient outcome with embryonic gene signatures
- **Hybrid state cells are associated with metastatic adaptation and non-response to therapy**
- **Hdac2 is critical for survival of melanoma cells following TNF α and anti-PD-1**
- Hybrid state cells could be a type of *intermediate* melanoma cells

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UoM Bioimaging Core

NCI FACS Core

NCI Single Cell Analysis Facility

Glenn Merlino

Chi-Ping Day

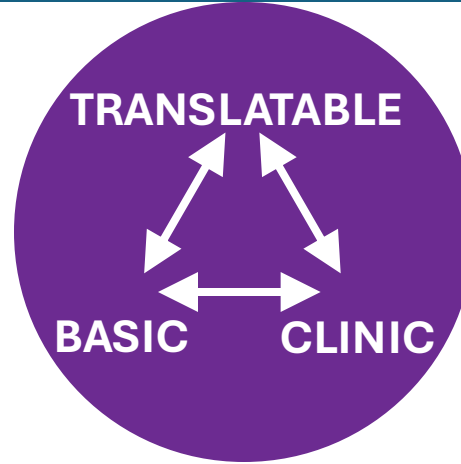
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Sung Chin

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