

P3.348 Molecular Characterization of Mechanisms Underlying Plasticity in 3D *in vitro* Lung Cancer Models

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INTRODUCTION

- SCLC is highly aggressive neuroendocrine lung carcinoma with poor prognosis (5-year-survival rate of 9%)
- first-line treatment followed by rapid relapse and acquired resistance

→ Better understanding of cellular complexity & resistance mechanisms is required

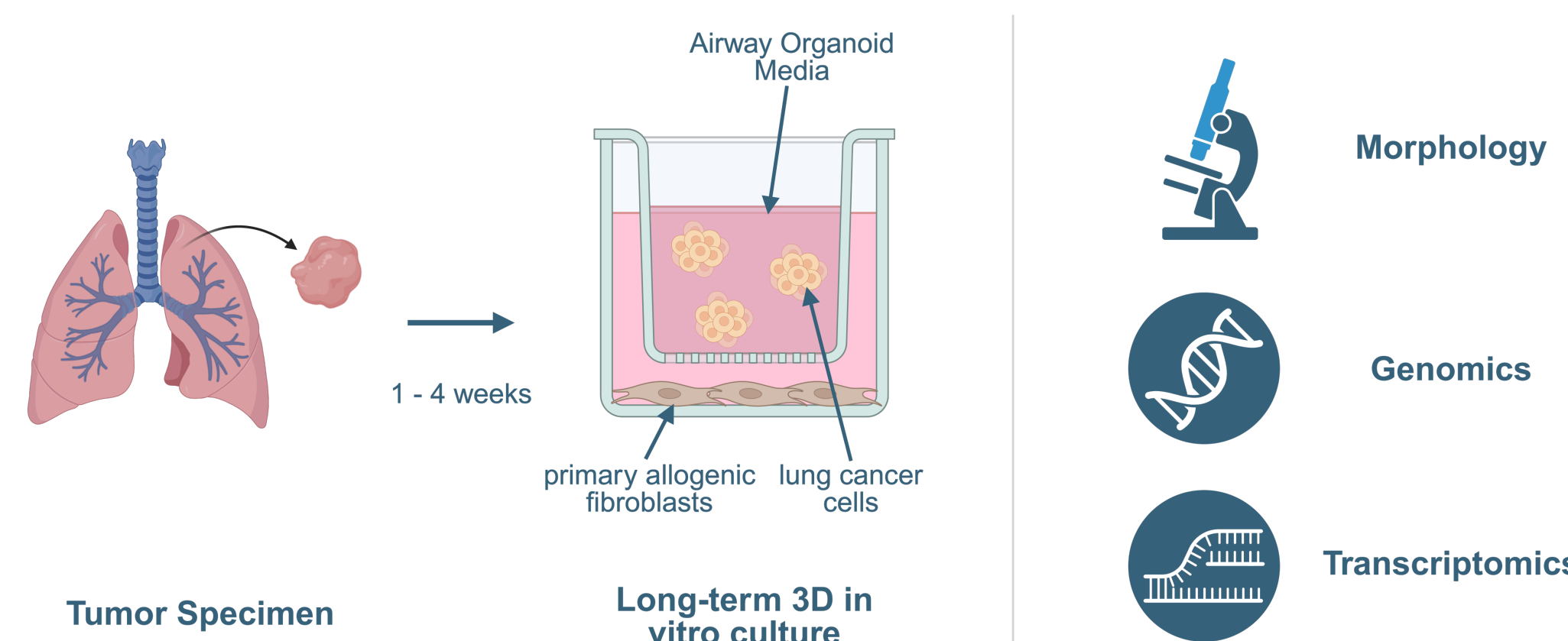
- SCLC tumors show distinct initial transcriptional profiles, therapeutic vulnerability & intratumoral heterogeneity (ITH)
- Plasticity as one of the main sources of transcriptional ITH

Aim: Untangle mechanisms underlying phenotypic plasticity and resistance in SCLC with 3D *in vitro* lung cancer models

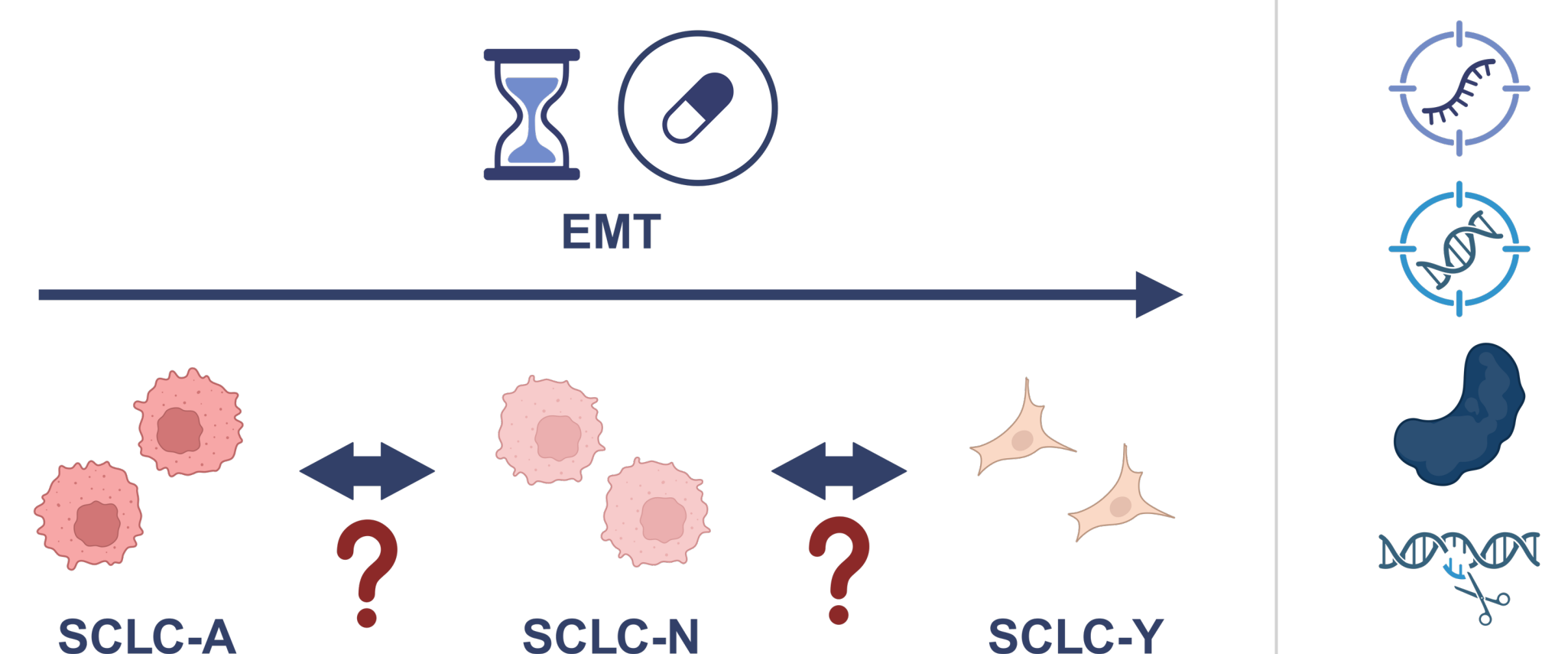
METHODS

Experimental strategy:

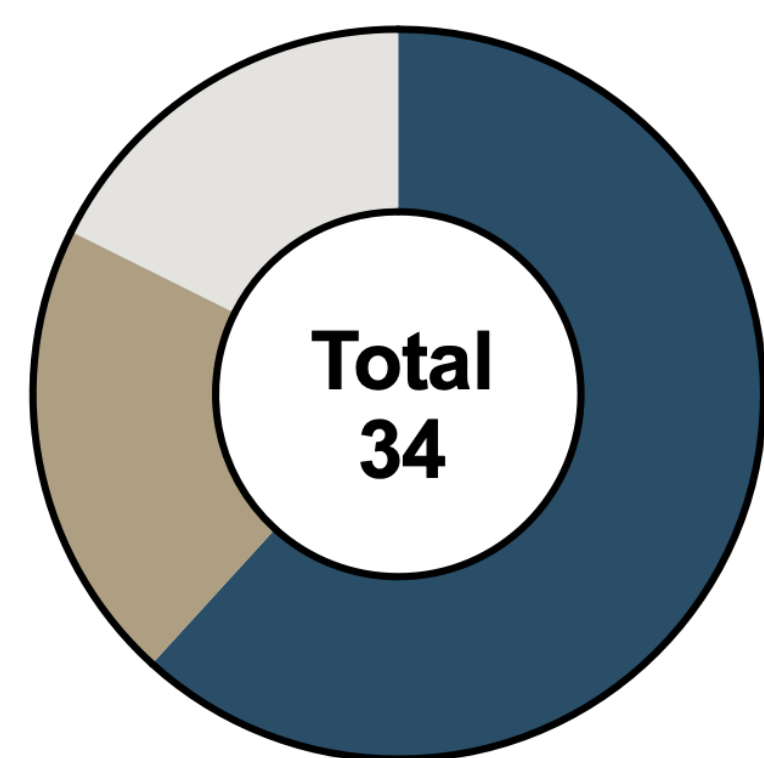
Establishment & validation of 3D *in vitro* lung cancer models



Therapeutic vulnerabilities & state transitions upon drug treatment

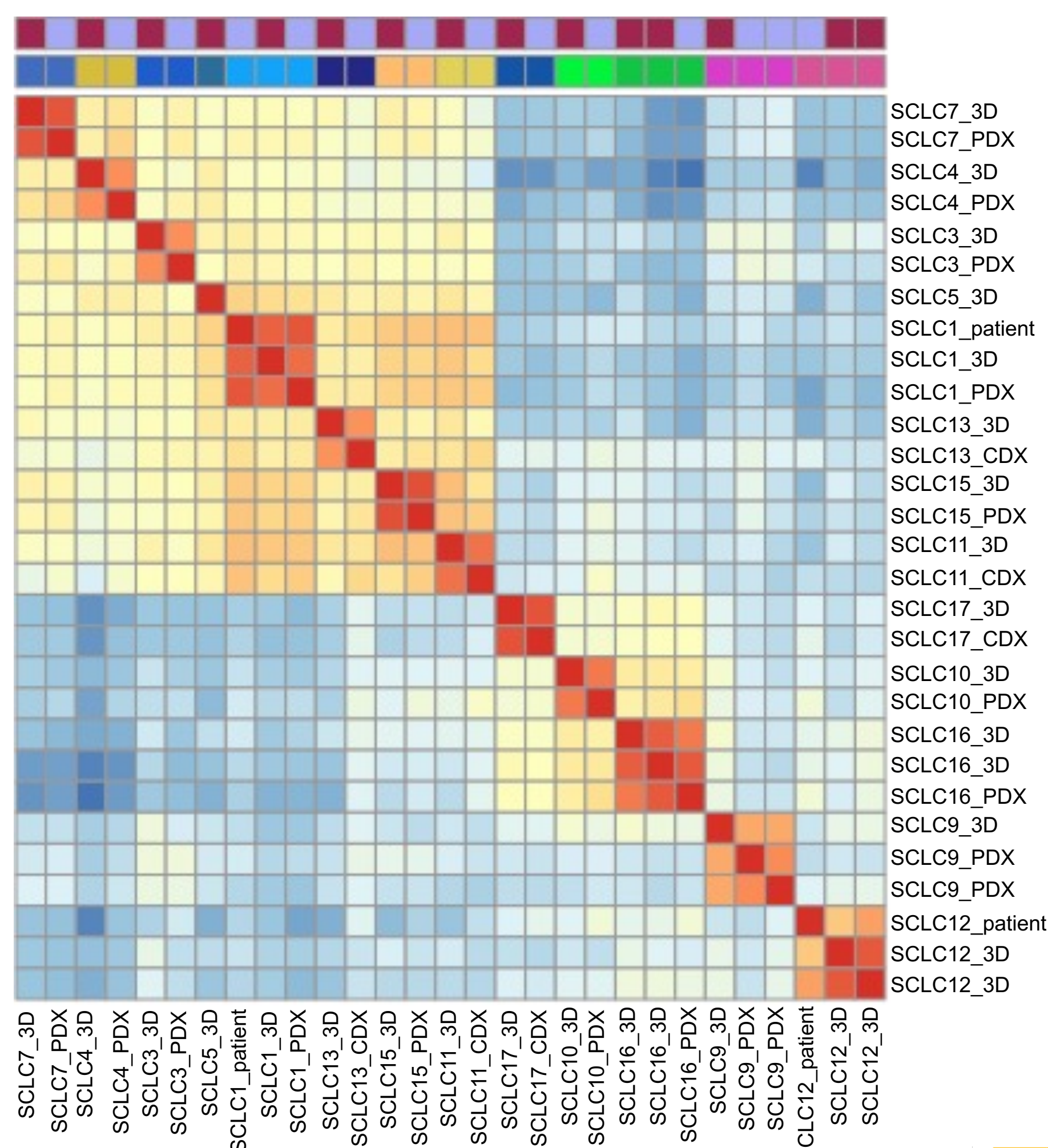


RESULTS



Successful establishment of 41 long-term 3D *in vitro* cultures from 34 patients

- cultured for >10 passages
- RNA, DNA & FFPE-Blocks available for validation as lung cancer models

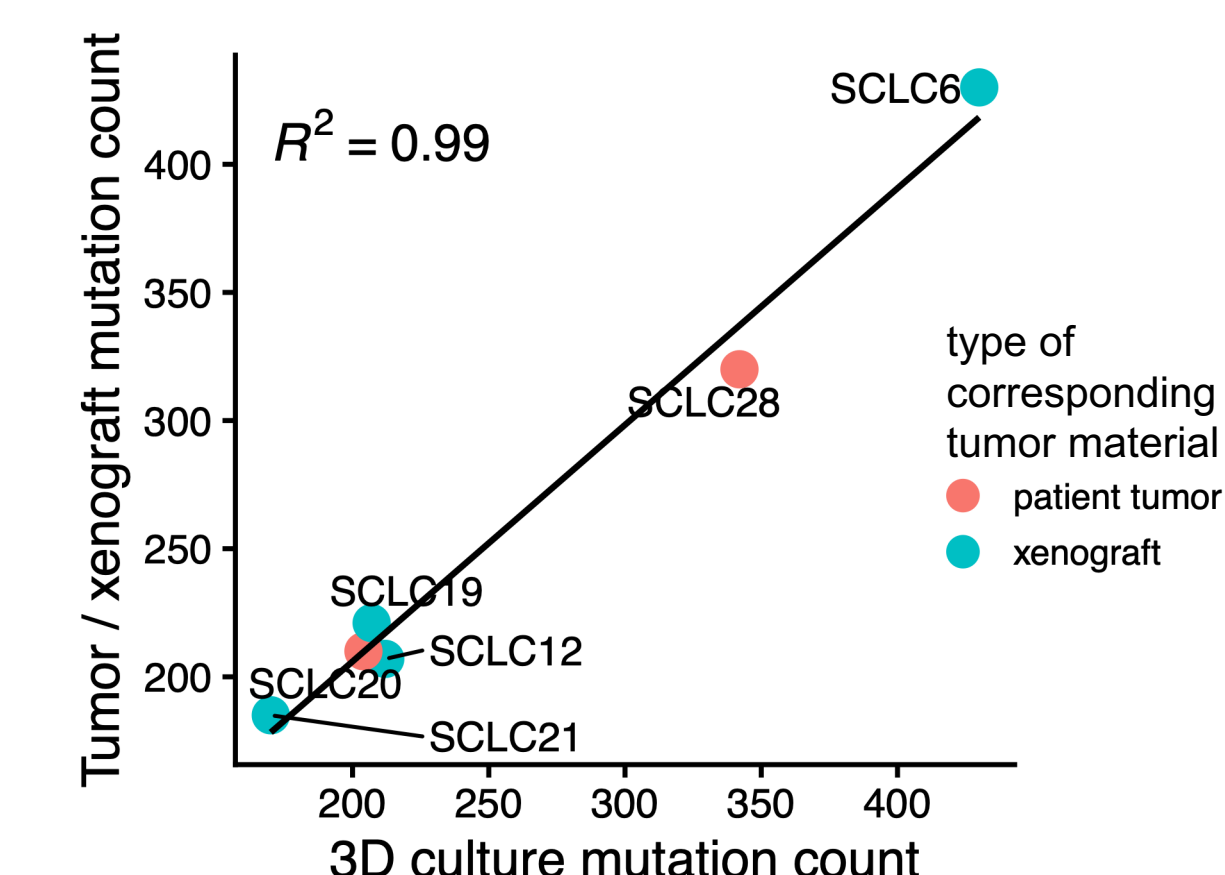


3D cultures & corresponding tumor material show similar transcriptional profile

- 29 models from 13 patients
- Models derived from different patients can be grouped based on shared expression patterns

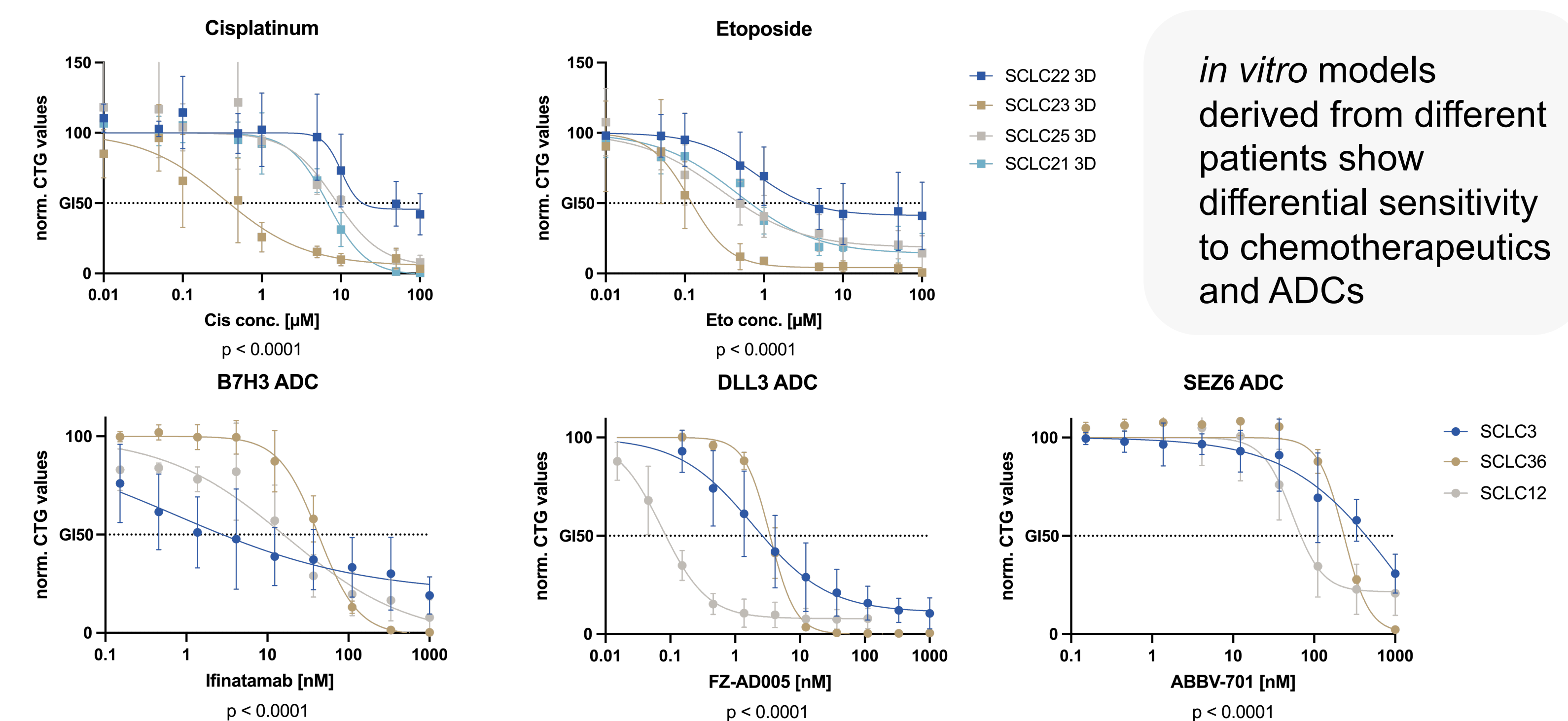
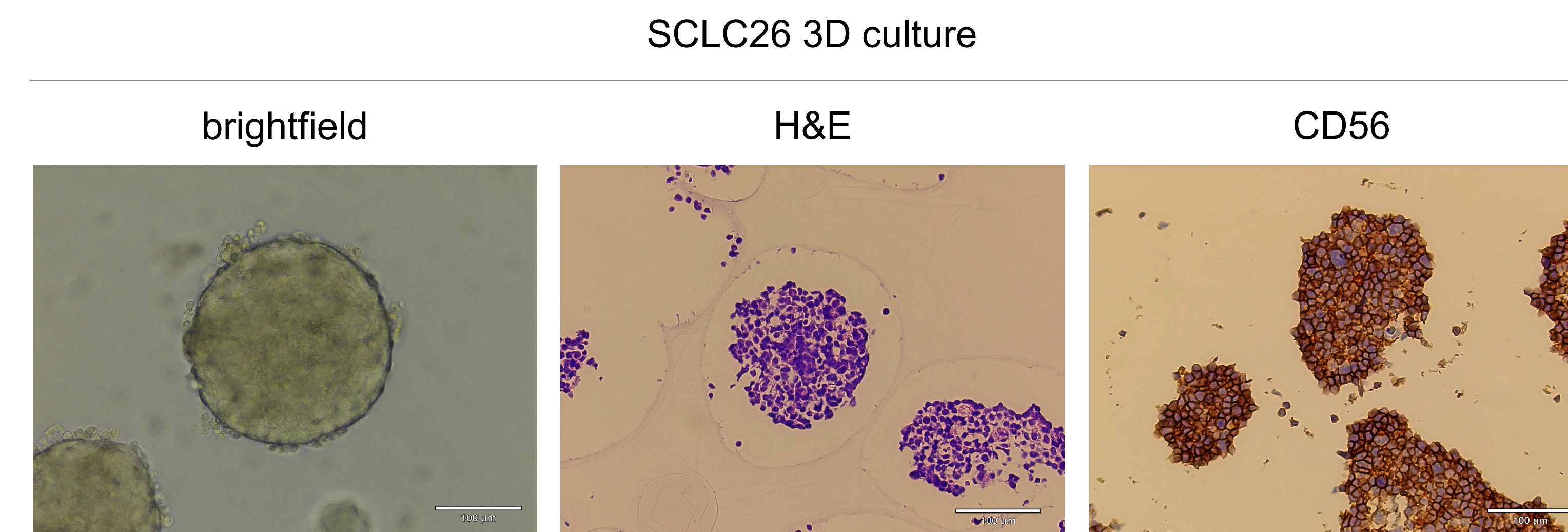
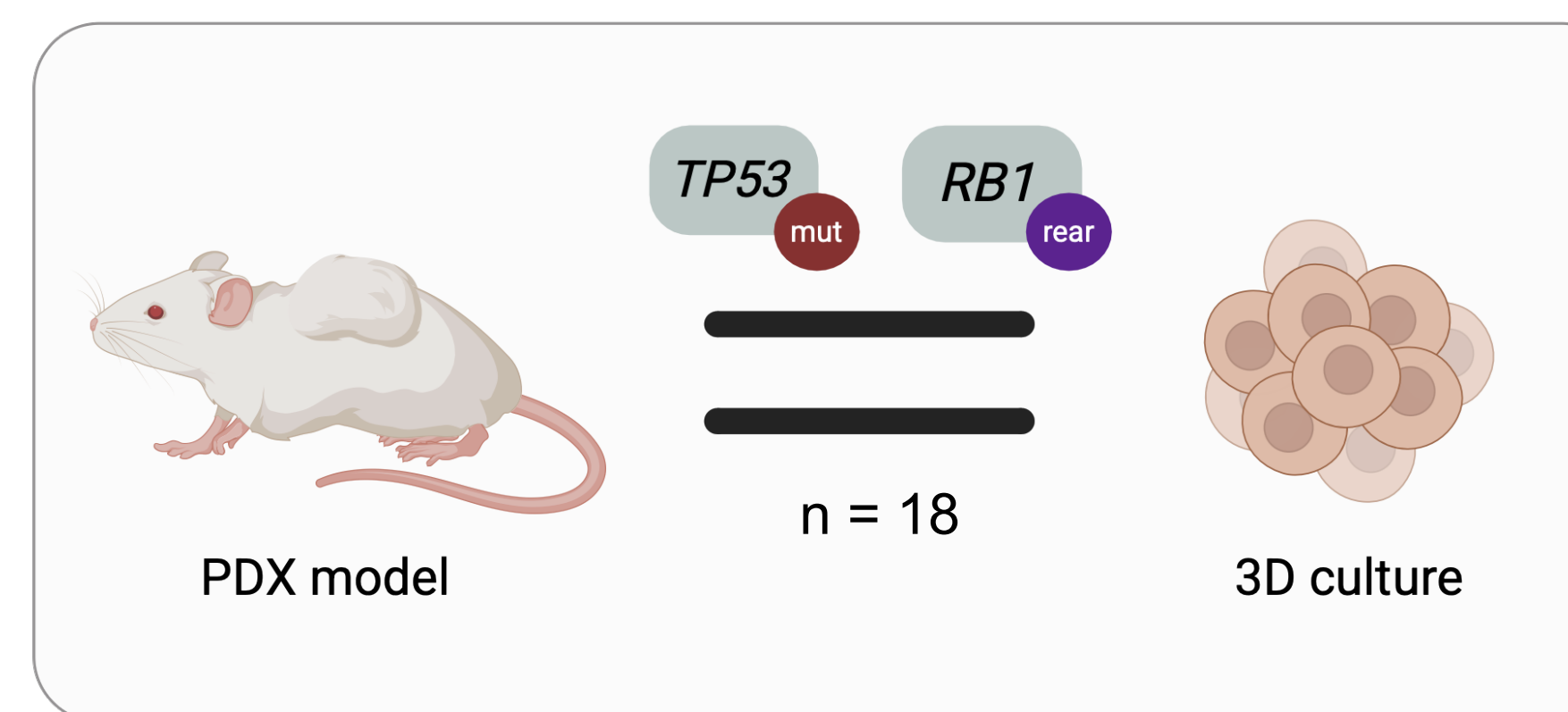
Groups of 3D *in vitro* & *in vivo* models sharing similar transcriptional profiles show differential expression of SCLC subtype markers.

- G1: higher ASCL1 expression
- G2: higher NEUROD1 expression



→ 3D cultures share the same mutations in *TP53* & *RB1* as the corresponding tumor material (xenografts or patient tumor)

→ Pearson correlation shows that number of mutations in 3D cultures and corresponding tumor material is similar.



in vitro models derived from different patients show differential sensitivity to chemotherapeutics and ADCs

SUMMARY

- Establishment of 41 long-term 3D *in vitro* cultures derived from patient biopsies or xenograft models with a new culture method
- recapitulate transcriptional profile of corresponding tumor material & can be assigned to transcriptomic subtypes of SCLC
- share mutations in *TP53* & *RB1* and show similar mutation counts as corresponding tumor material
- Established models are usable for drug treatment assays to investigate therapeutic vulnerabilities & plastic state transitions

REFERENCES & ACKNOWLEDGEMENTS



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