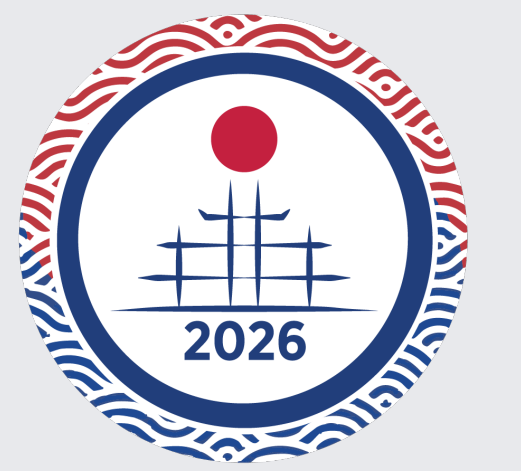


P3.324 Reconstructing the Genetic Trajectory of SCLC Development

Department of
Translational GenomicsKarina Polkovnychenko^{1*}, Julie George^{1,2} and Roman Thomas^{1,3}¹Translational Genomics Department, University Hospital Of Cologne, Cologne, Germany²Department Of Otorhinolaryngology, Head And Neck Surgery, Faculty Of Medicine And University Hospital Cologne, Cologne, Germany³Institute of Pathology, Medical Faculty, University Hospital Cologne, Cologne, GermanyIASLC 2026 World
Conference on Lung CancerSEPTEMBER 12 - 15, 2026
SEOUL, REPUBLIC OF KOREA

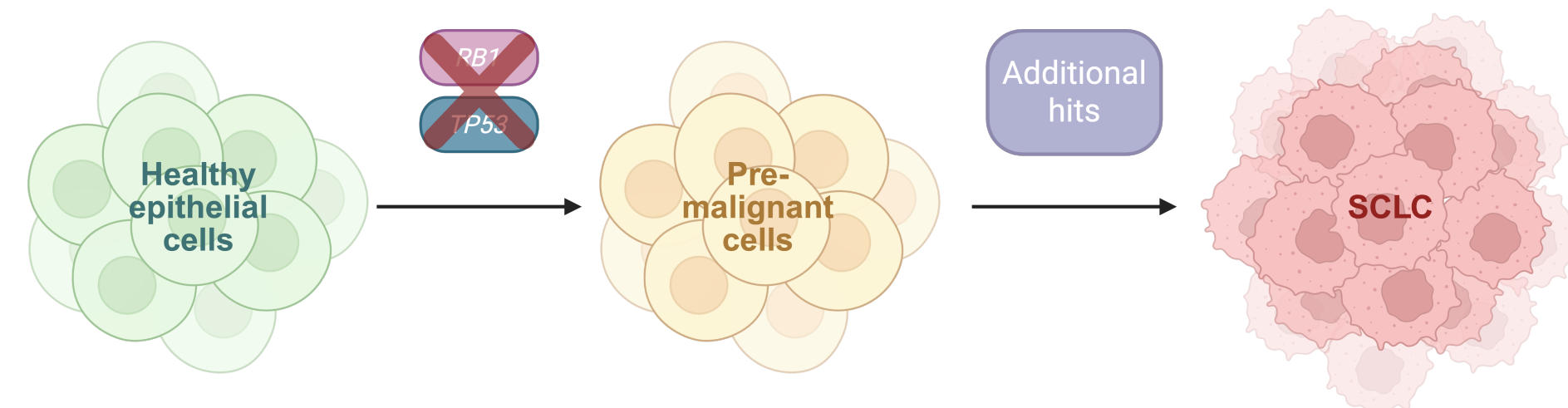
SCLC | Small Cell Lung Cancer

- 1 Most aggressive type of lung cancer
- 2 Very high mutational burden (8,62 non-synonymous mutations/MB)
- 3 Key drivers: biallelic inactivation of **TP53** and **RB1**
- 4 Significant and recurrent co-alterations in epigenetic regulators, NOTCH pathway and MYC family amplification

RATIONALE & AIM

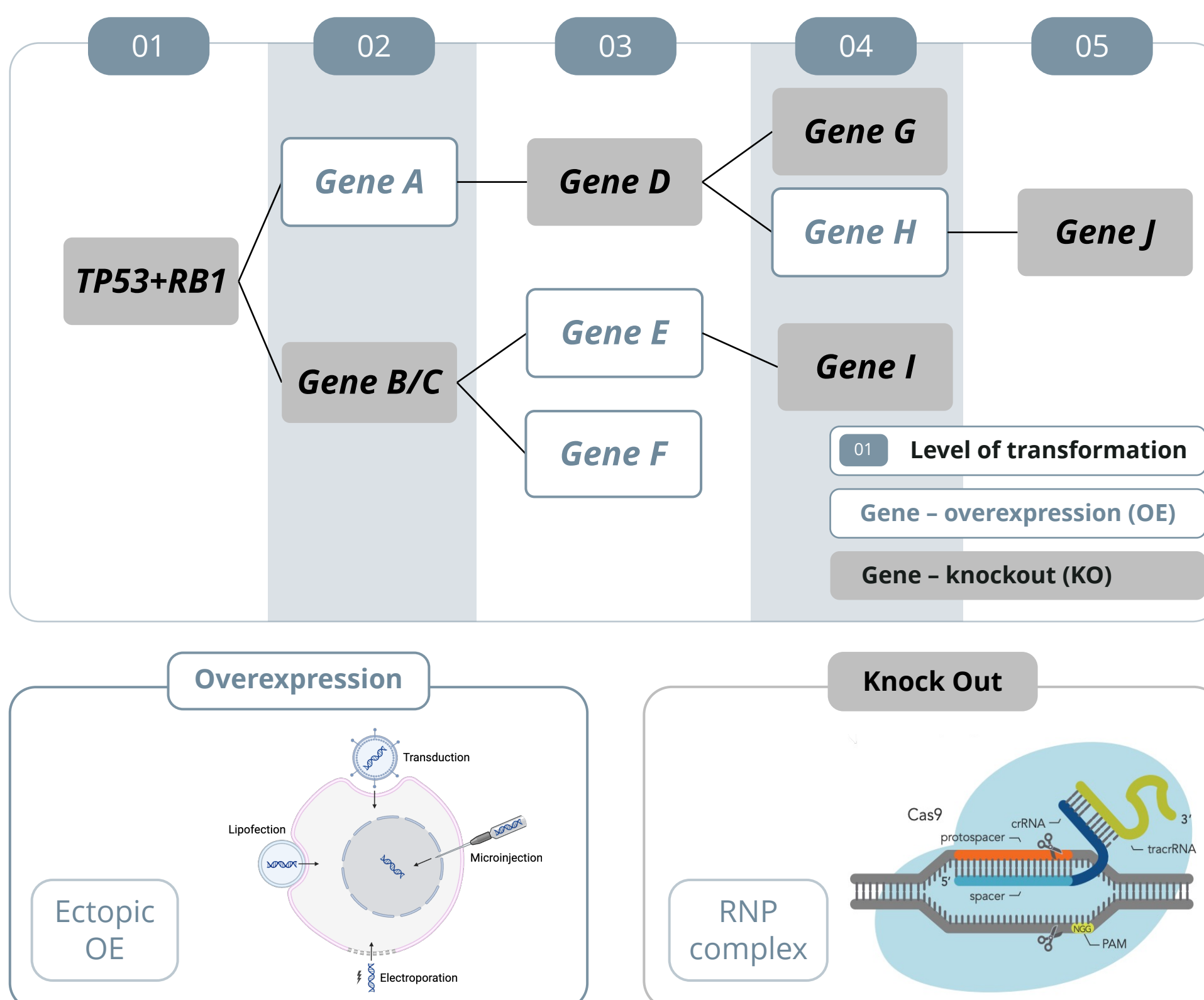
What minimal genetic changes are required for SCLC transformation?

- Loss of TP53/RB1 not sufficient for full malignant transformation (4): additional genetic alterations needed
- Transformed cells display a neuroendocrine phenotype
- Specific combinations of co-alterations driving SCLC at this point unclear



EXPERIMENTAL STRATEGY

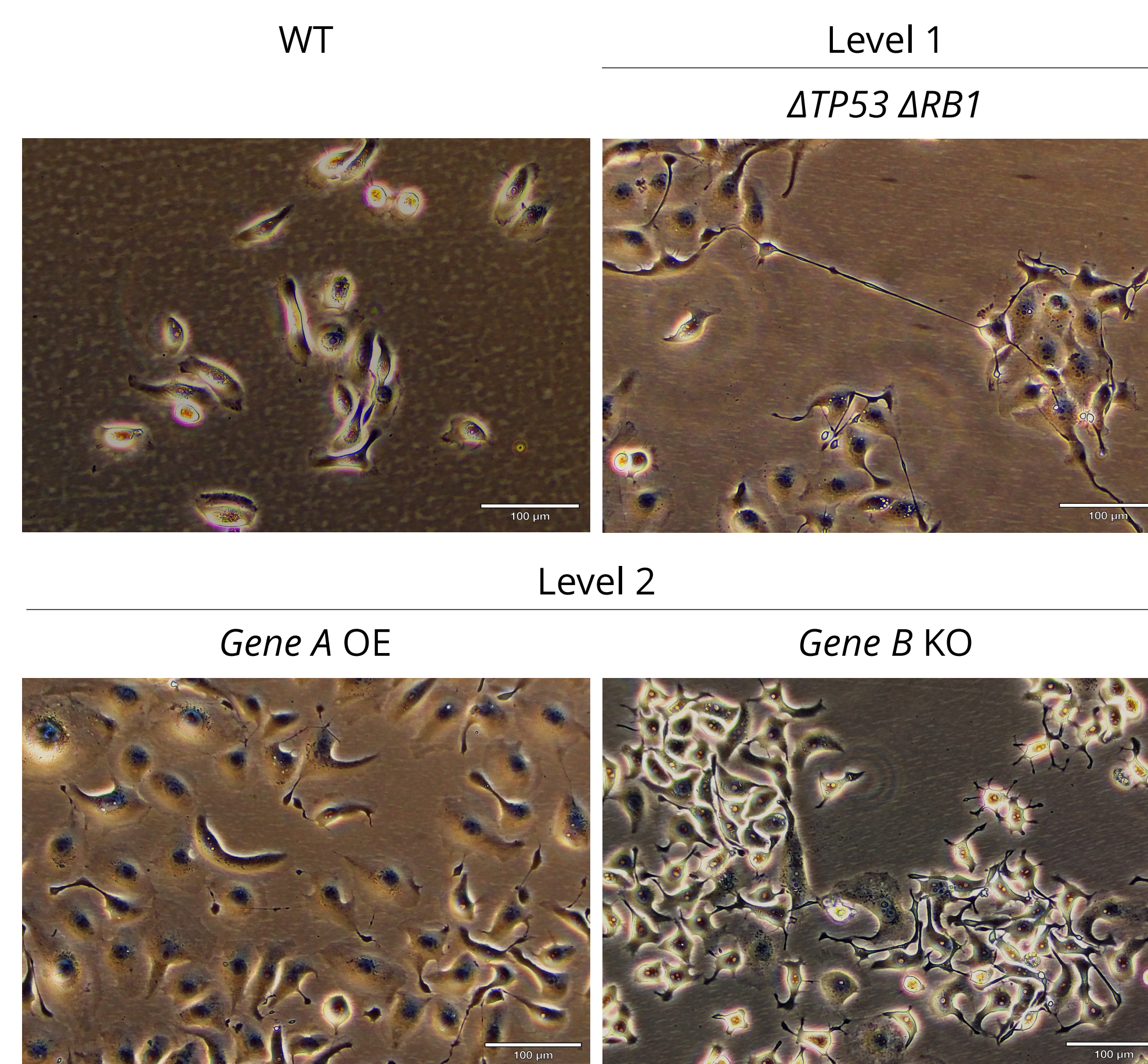
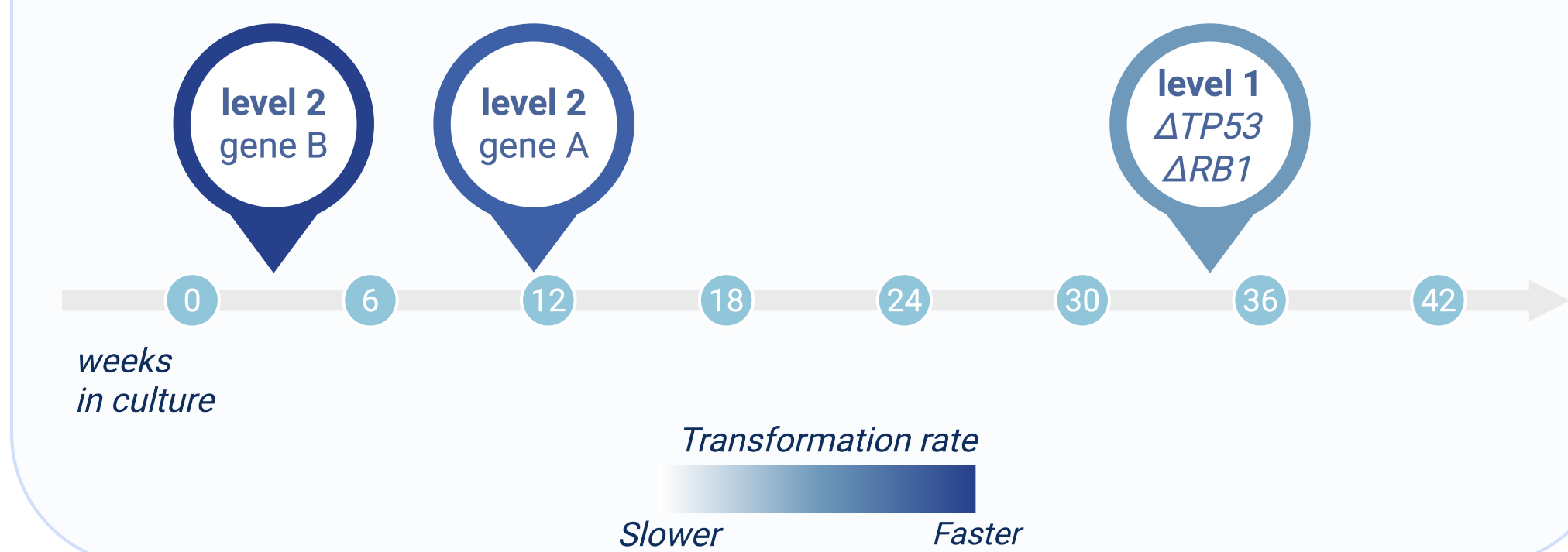
Stepwise engineering of healthy lung epithelial cells with defined mutations to model SCLC transformation



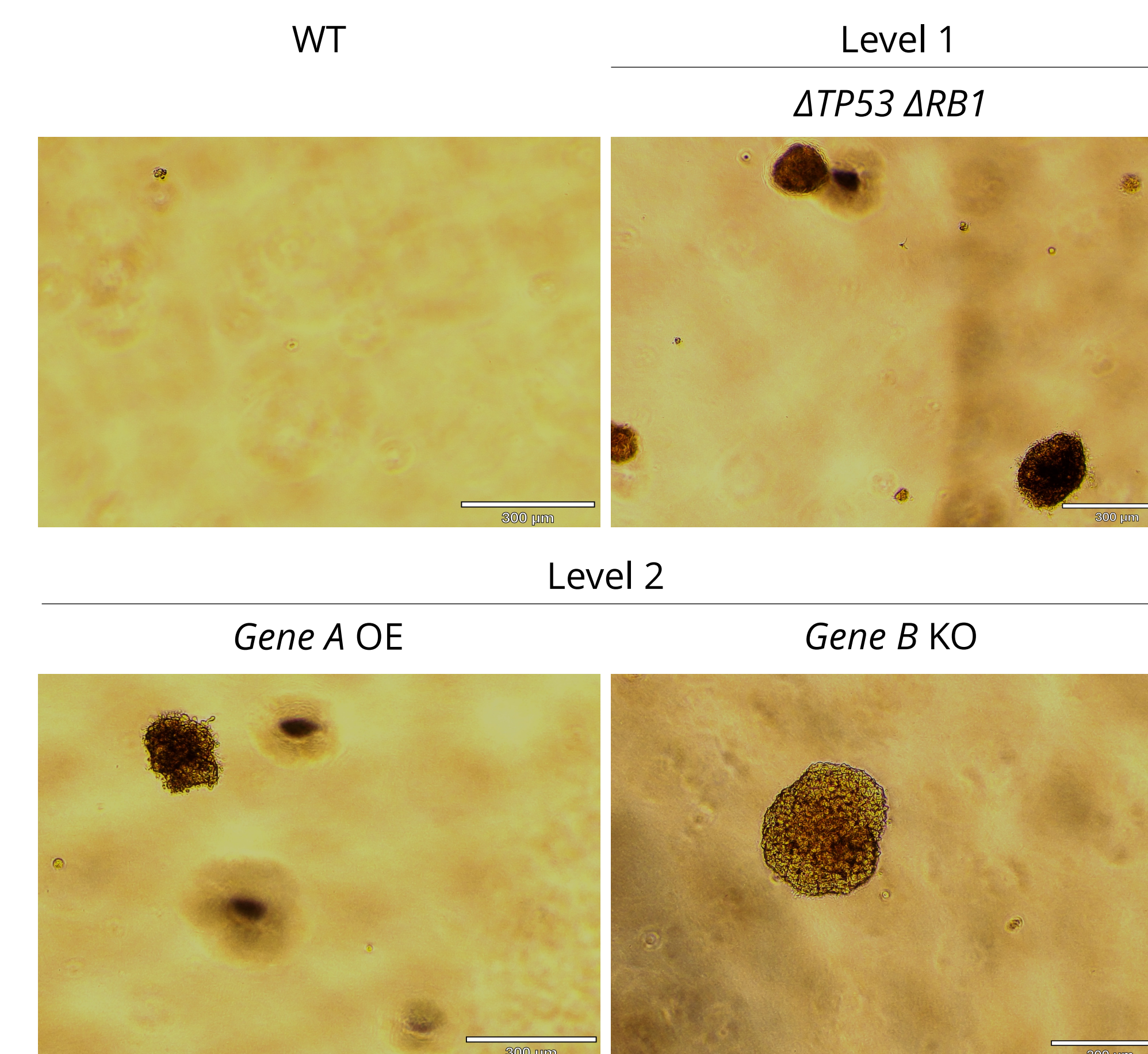
RESULTS

- Combined *TP53/RB1* KO in healthy lung epithelial cells does not induce immediate transformation (30-36 weeks)
- Key alterations accelerate cell state remodelling

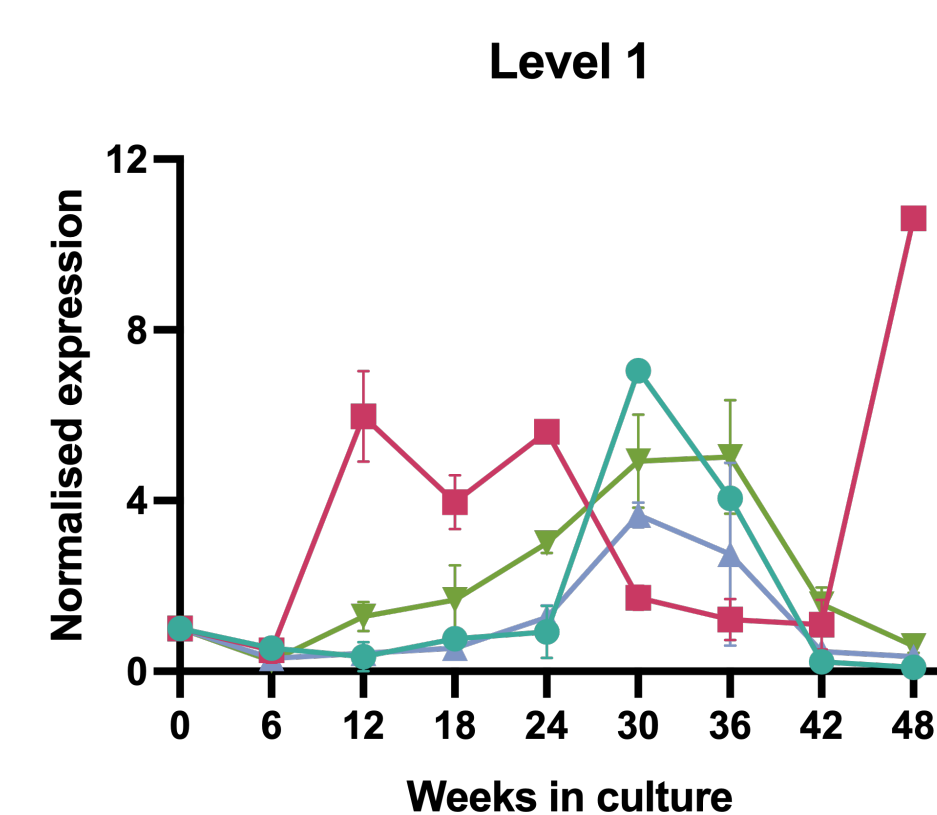
Time to *in vitro* transformation



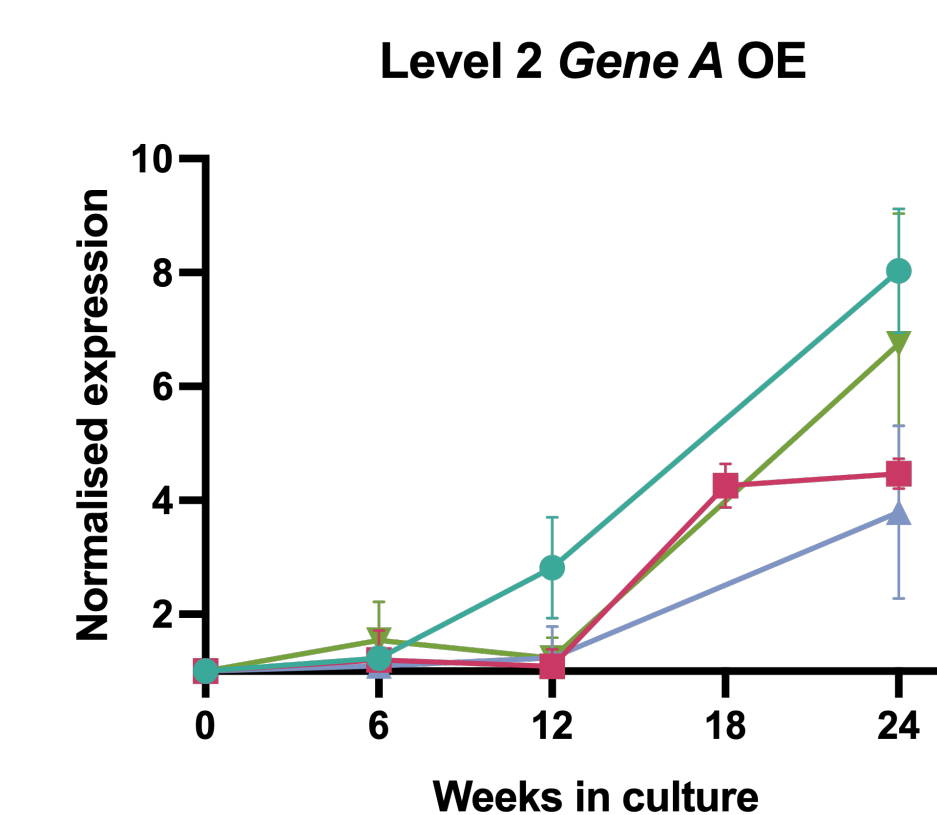
- Genetically perturbed lung epithelial cells exhibit progressive changes in morphology during prolonged culture



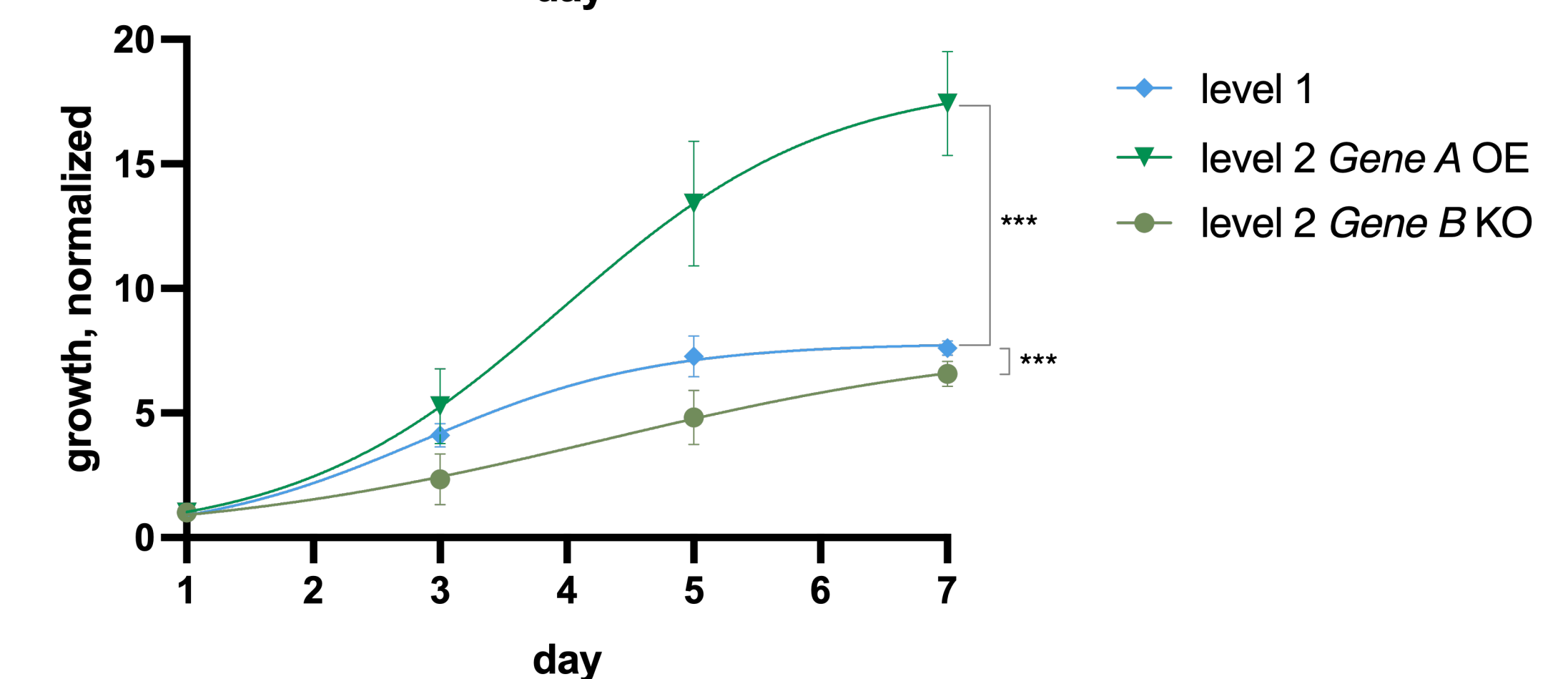
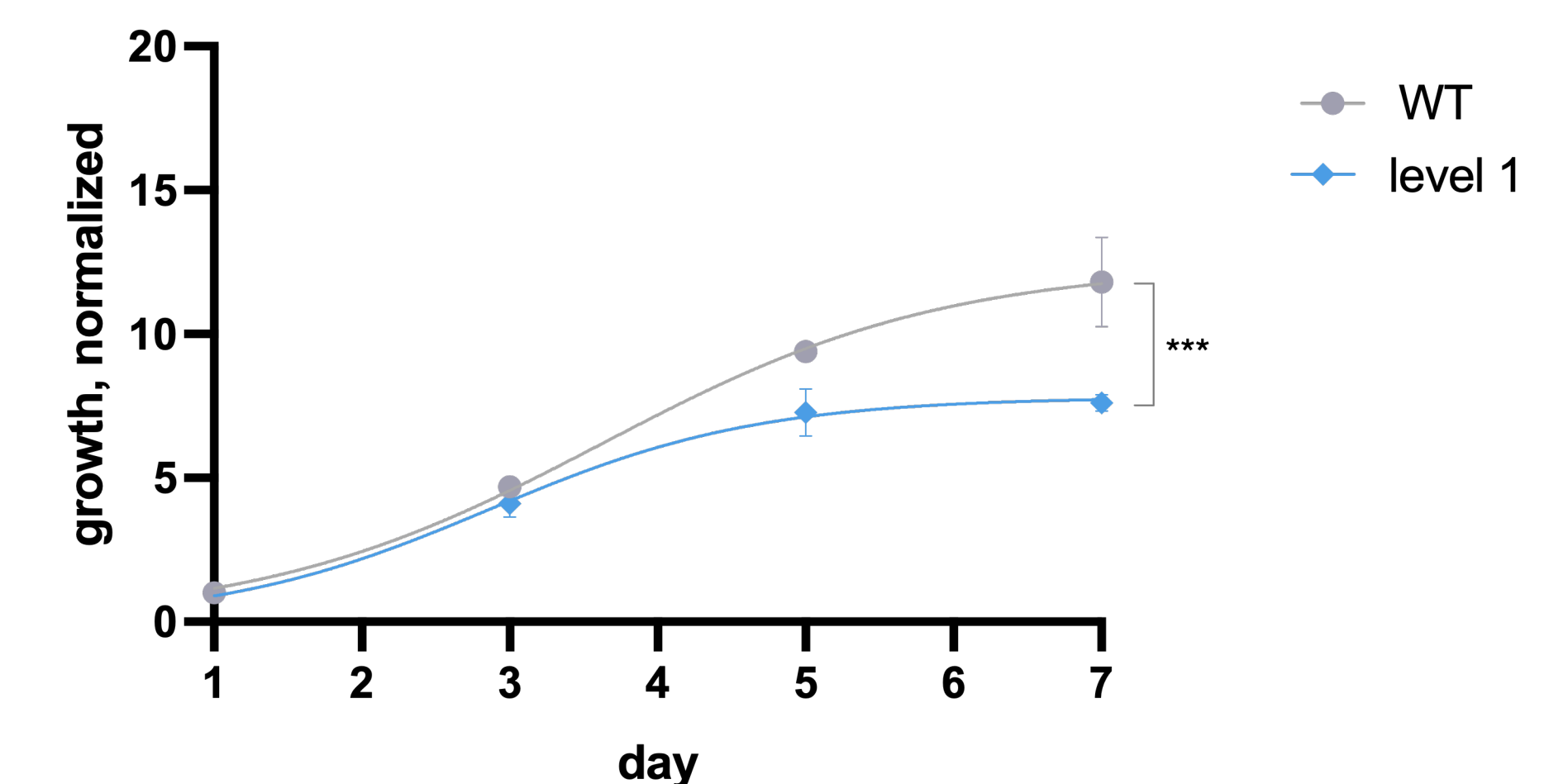
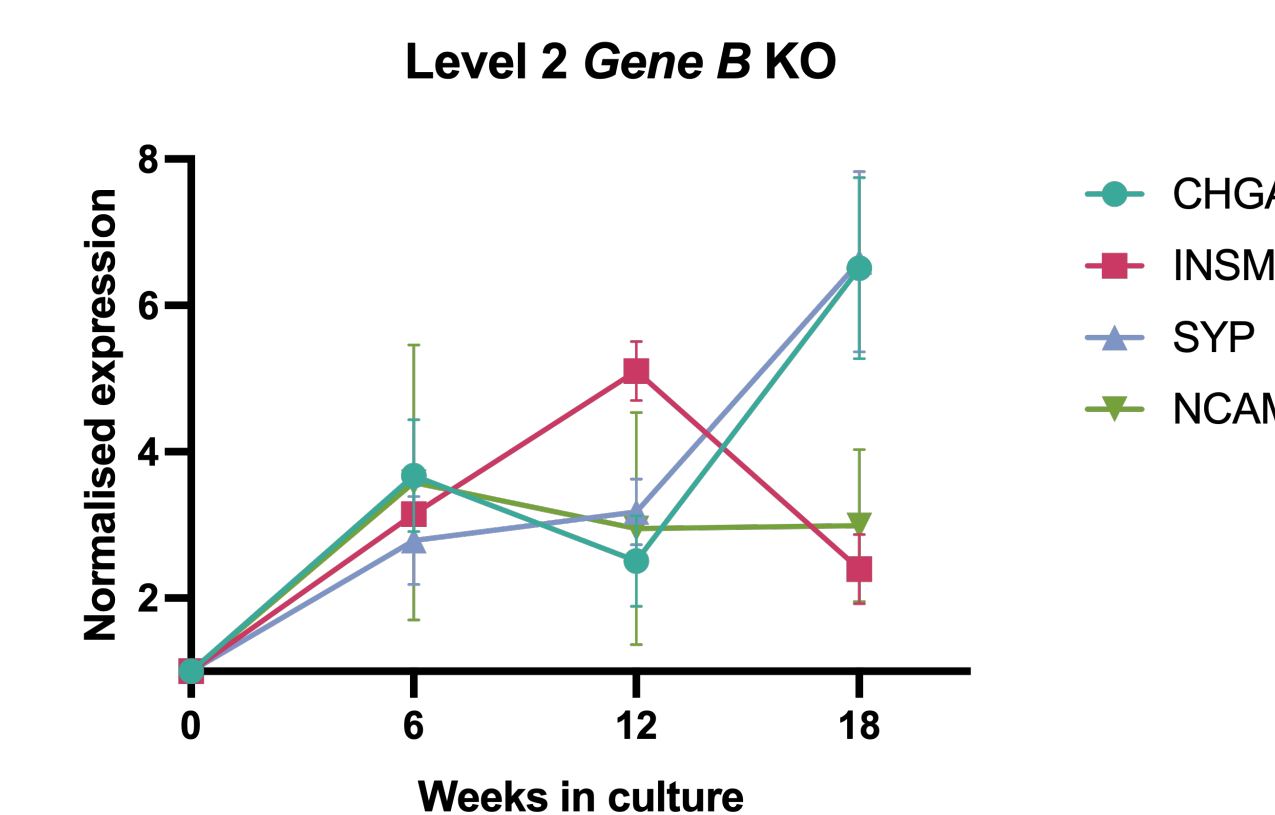
- Upon genetic perturbations and prolonged culturing, lung epithelial cells undergo partial transformation (anchorage-independent growth in soft agar)



- In Level 1 transformation, INSM1 and other neuroendocrine factors show opposing temporal expression, suggesting dynamic neuroendocrine state remodeling during transformation



- Progressive transformation is accompanied by increased expression of neuroendocrine factors, suggesting acquisition of a more neuroendocrine phenotype

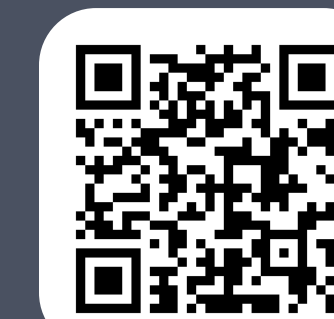


- Cells with *ΔTP53* and *ΔRB1* grow significantly slower than WT
- Additional *Gene A* overexpression accelerates growth
- *Gene B* knockout further reduces the growth rate

SUMMARY

- 1 Transformation is a time-dependent and multistep process influenced by genetic context
- 2 Further genomic and molecular characterization is ongoing to define the mechanisms underlying distinct transformation trajectories
- 3 Defining the genetic and temporal trajectories of cellular transformation provides insight into the early steps of lung cancer development

REFERENCES

Research sponsored by the German
Research Foundation (DFG) as part of the
Sonderforschungsbereich 1399 (SFB1399)

karina.polkovnychenko@uni-koeln.de