

EP02.02: Tumour intrinsic inflammasome mutations significantly impact the development of lung adenocarcinoma



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IASLC 2026 World
Conference on Lung Cancer

SEPTEMBER 12 - 15, 2026
SEOUL, REPUBLIC OF KOREA

INTRODUCTION

Lung adenocarcinoma (LUAD) is the most common form of lung cancer and the leading cause of cancer related death. In 2017, immune checkpoint inhibitors (ICIs) were approved as part of the front-line LUAD treatment regime. However, only about 20% of non-stratified LUAD patients respond to ICI monotherapy, and predicting the response of individual patients remains challenging. The innate immune system is critical and necessary for maturation and activity of the adaptive immune system and offers opportunities to enhance the response to ICIs. Indeed, innate immune agonists like influenza vaccination improve the survival of cancer patients undergoing ICI treatment. Additionally, the importance of the innate immune cytokine, IL-1 β , in the development of LUAD was revealed by the phase III CANTOS trial which recorded a staggering 67% and 77% reduction in lung cancer incidence and mortality respectively. However, IL-1 β neutralisation in patients with existing LUAD failed to meet primary efficacy endpoints. Together this highlights the potential of harnessing the innate immune system in the treatment of LUAD but to do so requires a deep understanding of the inflammatory environment throughout the development of LUAD.

METHODS

Design:

Genomic sequencing data from public and prospective sample collections were analysed for mutations in inflammasome genes and the correlation with patient outcomes determined. The importance of tumour intrinsic *NLRP3* activity was confirmed using autochthonous mouse models of *KRAS*-driven LUAD. Spatial transcriptomics of tissue sections and single cell RNA-Seq on organoid models defined the transcriptional landscape controlled by the inflammasome.

DISCUSSION AND CONCLUSION

- Activating, tumour intrinsic *NLRP3* mutations are observed in 17% of LUAD patients
- Deletion of *Nlrp3* doubles the lifespan of a LUAD mouse model.
- Nlrp3* mutation alters AT2 transdifferentiation.

- The inflammasome will undergo natural cycles of activation and inactivation in the lung. If NLPR3 activation is sustained due to environmental insult or genetic injury, it alters the immune balance of the lung microenvironment contributing to LUAD development.**

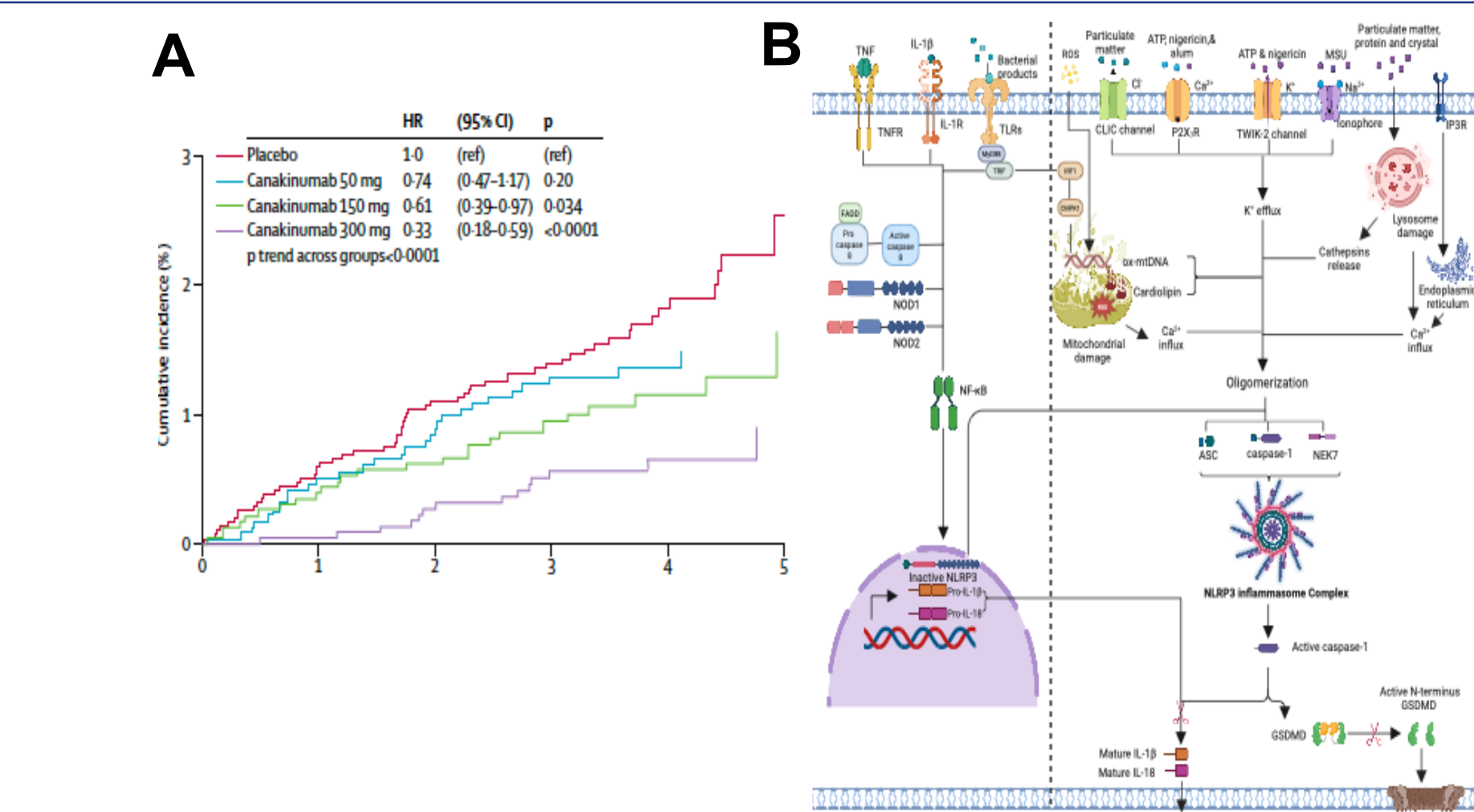


Figure 1: NLRP3 drives IL1 β production. (A) Outcomes from the CANTOS trial showing prophylactic IL1 β neutralisation reduces LUAD (1). (B) Schematic overview of IL1 β production following NLRP3-inflammasome activation

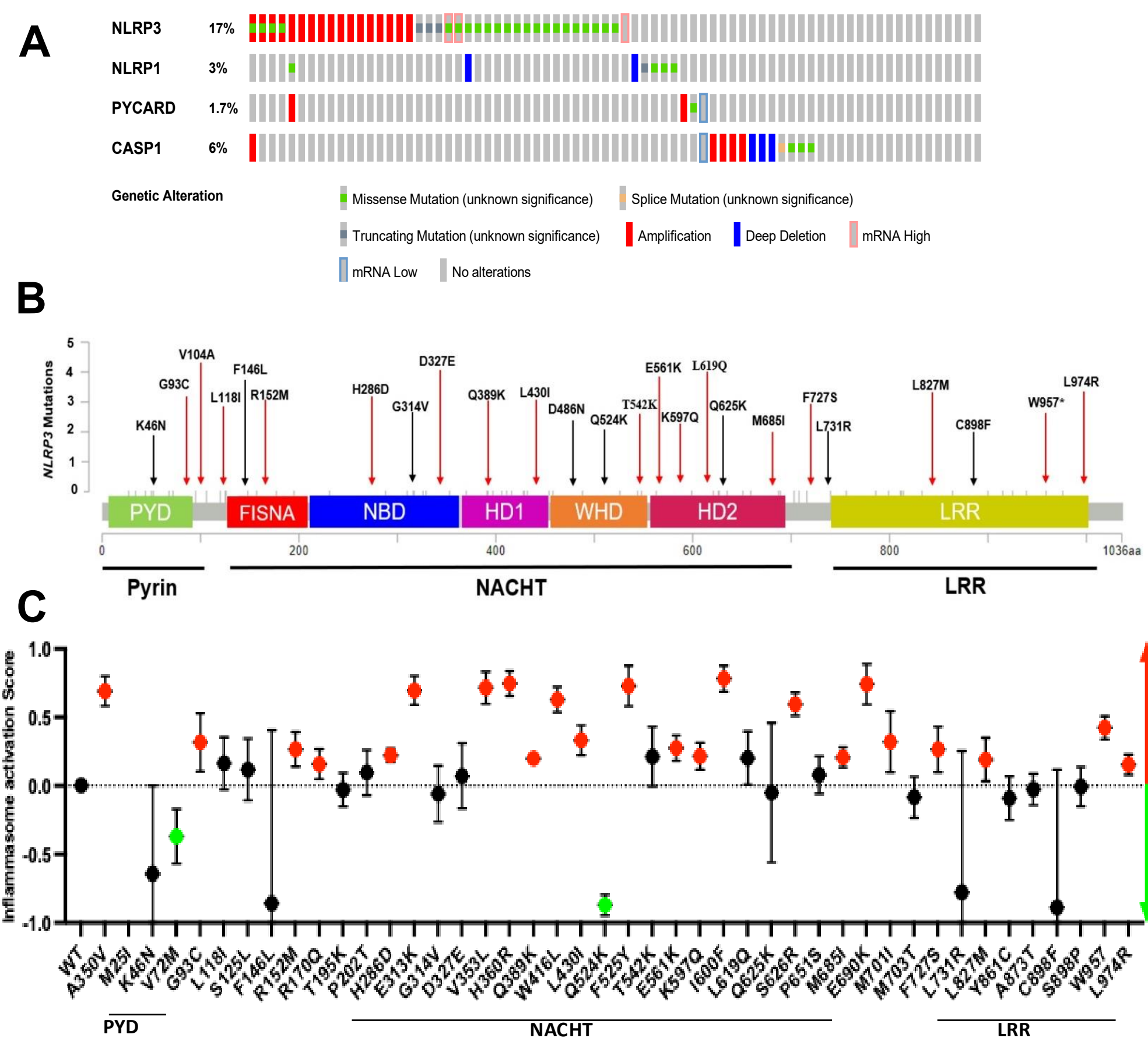


Figure 2: Activating *NLRP3* mutations are prevalent in LUAD. (A) Oncoplot showing the frequency of *NLRP3* mutation in the TCGA LUAD cohort and (B) the location of these mutations on the *NLRP3* structural domains. (C) LUAD associated *NLRP3* mutants were cloned and tested for their activity relative to wildtype (WT) and a known activating *NLRP3* mutant (A350V) according to (2).

REFERENCES & ACKNOWLEDGEMENTS

References

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Funding

National Health and Medical Research Council (APP2037135)
Peninsula and South-East Oncology Cancer Research Fellowship

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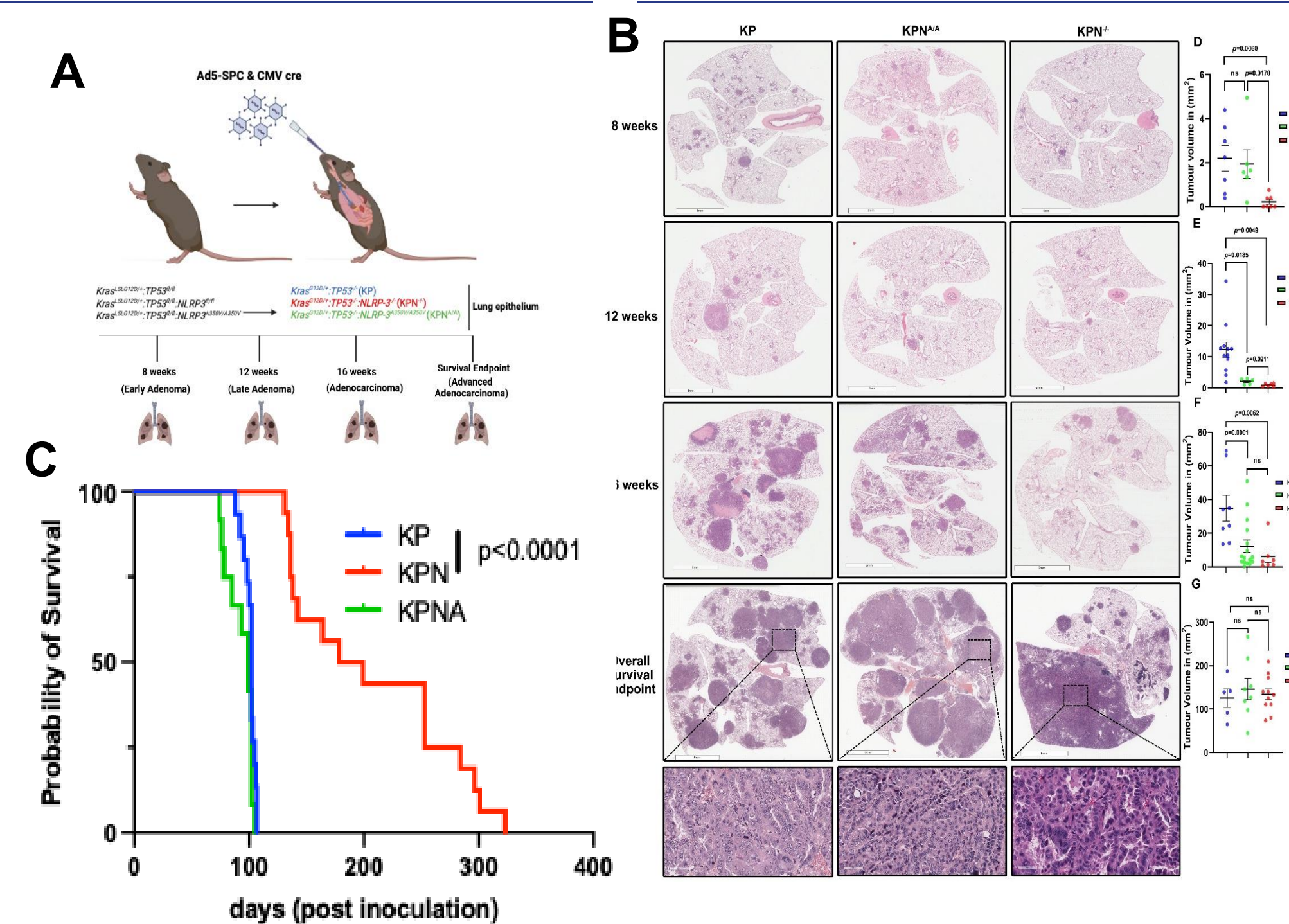


Figure 3: *NLRP3*-deletion delays *Kras*-driven LUAD in vivo. (A) Schematic overview of experiment. Adenoviral-Cre was delivered intranasally into three strains of genetically engineered mice. This resulted in the following genetic changes specifically in AT2 cells: *KRas*^{G12D}:*trp53*^{-/-} (KP), *KRas*^{G12D}:*trp53*^{-/-}*Nlrp3*^{-/-} (KPN) or *KRas*^{G12D}:*trp53*^{-/-}*NLRP3*^{A350V} (KPNA). KP express endogenous NLRP3, KPN mice do not express NLRP3 and KPNA mice express active NLRP3 specifically in tumours. (B) Lungs were harvested, fixed and H&E stained at indicated timepoints to monitor tumour growth and histology in each strain. Tumour volume was calculated using QuPath and significance determined by t-test. (C) Kaplan-Meier curve showing that *Nlrp3*-deletion significantly delays LUAD development.

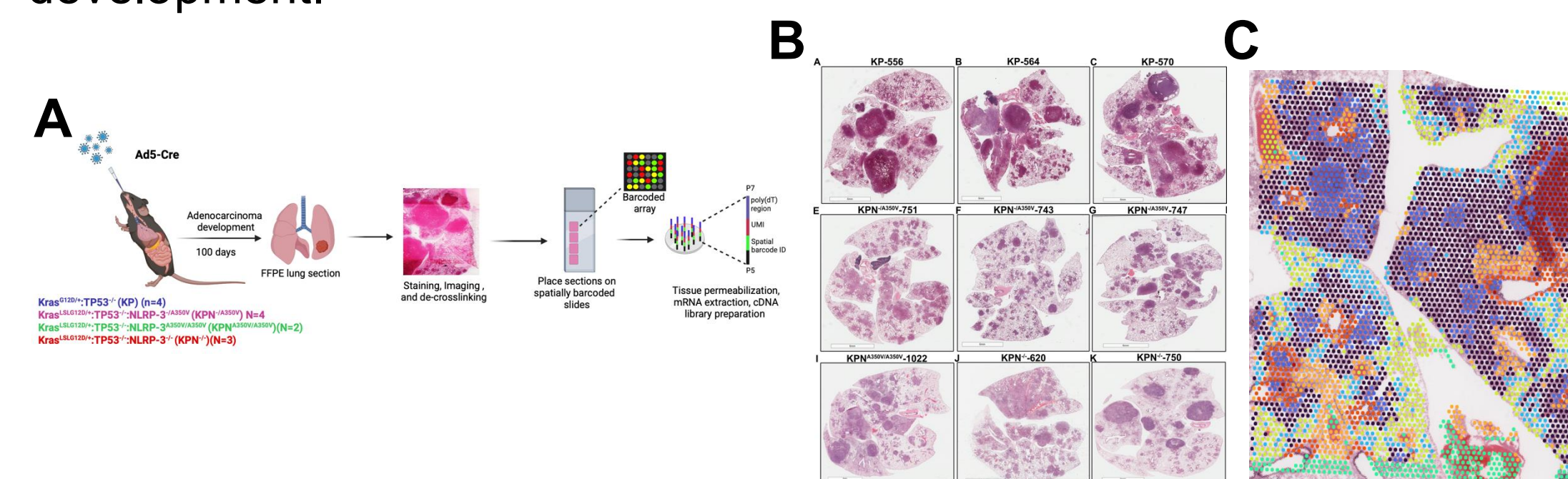


Figure 4: Spatial transcriptomic analysis of *Nlrp3*-driven changes to the tumour-microenvironment. (A) Schematic overview of spatial transcriptomic workflow. (B) H&E images of sections adjacent to those used for analysis. (C) Representative image of spatial transcriptomic resolution. A mean of 3,500 transcripts were detected per (50 μ M) spot. Colours represent clustering based on transcriptomic similarity

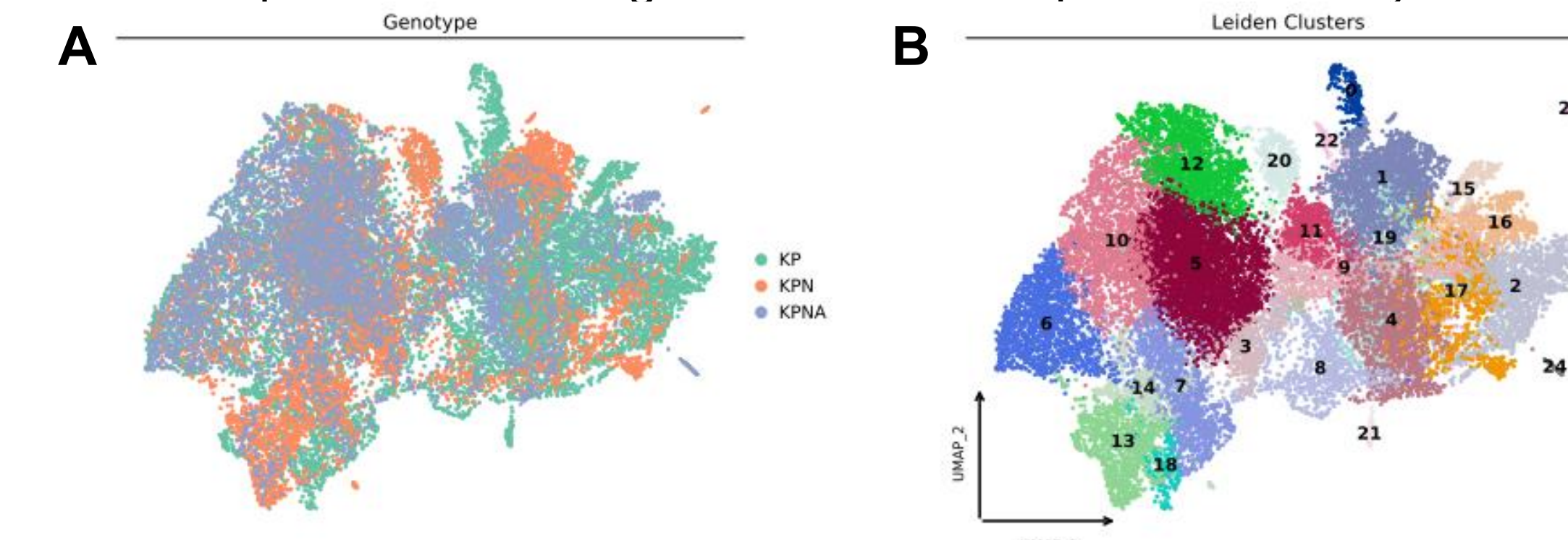


Figure 5: *Nlrp3* drives transcriptomic heterogeneity in the tumour microenvironment. (A) Replicate samples merged and batch corrected using the scVI tool. Data from each mouse genotype are represented in indicated colours showing *Nlrp3*-driven transcriptional changes. (B) Leiden clustering of transcriptional similarities across all replicates and genotypes.

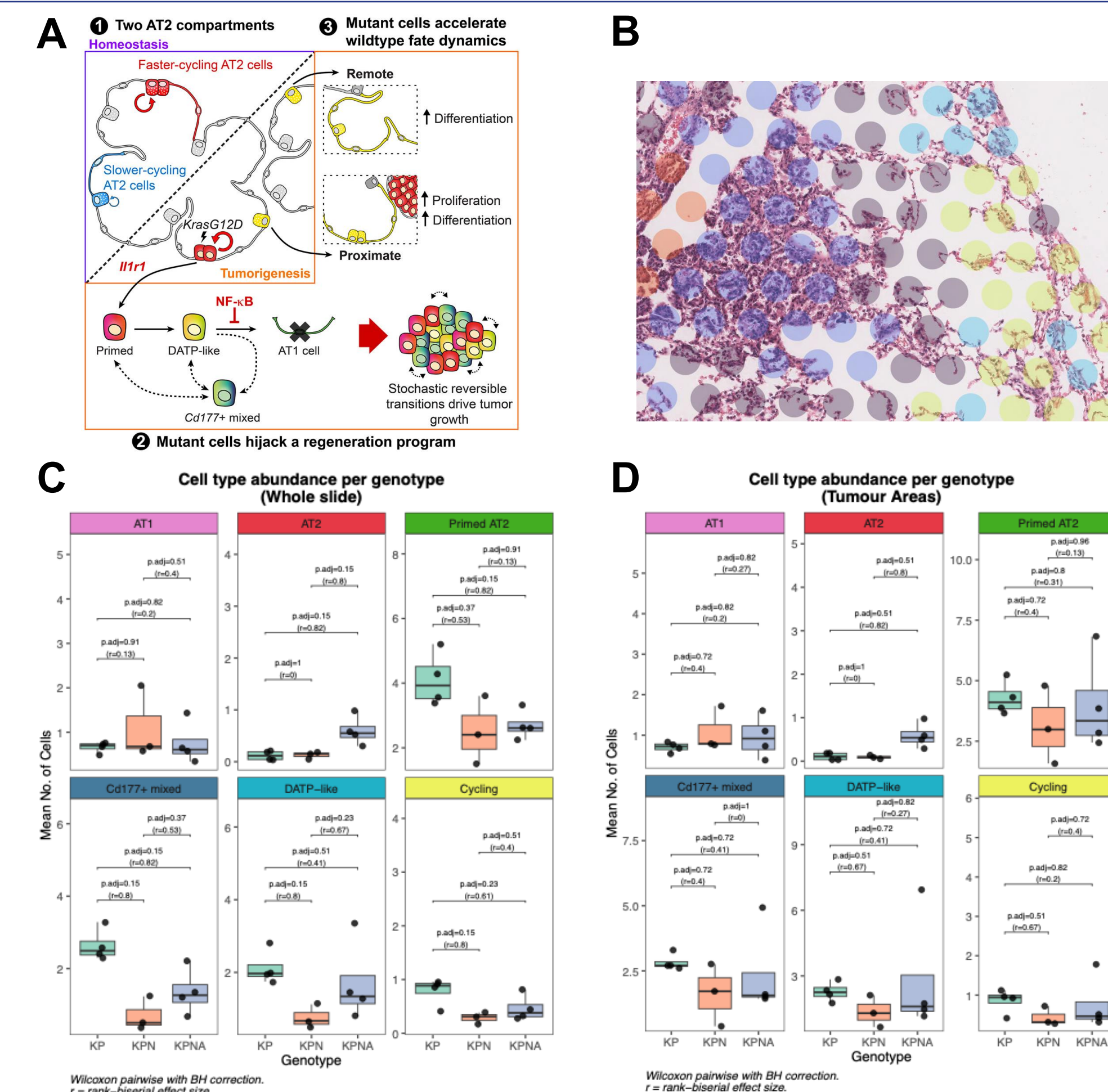


Figure 6: *Nlrp3*-dependent transdifferentiation of AT2 cells. (A) Schematic representation of IL1 β -driven AT2 transdifferentiation. Figure from (3). (B) The resolution of ST is 50 μ M which covers 5-10 cells which requires deconvolution of the proportion cell lineages under each spot. (C) Jitter plots showing that *Nlrp3*-dependent loss of Damage Associated Transient Progenitor (DATP) and CD177⁺ transitional cells across whole tissue or (D) exclusively in tumour regions (r =effect size, 0-0.2 = no effect, 0.2-0.5 modest effect, >0.5 large effect)

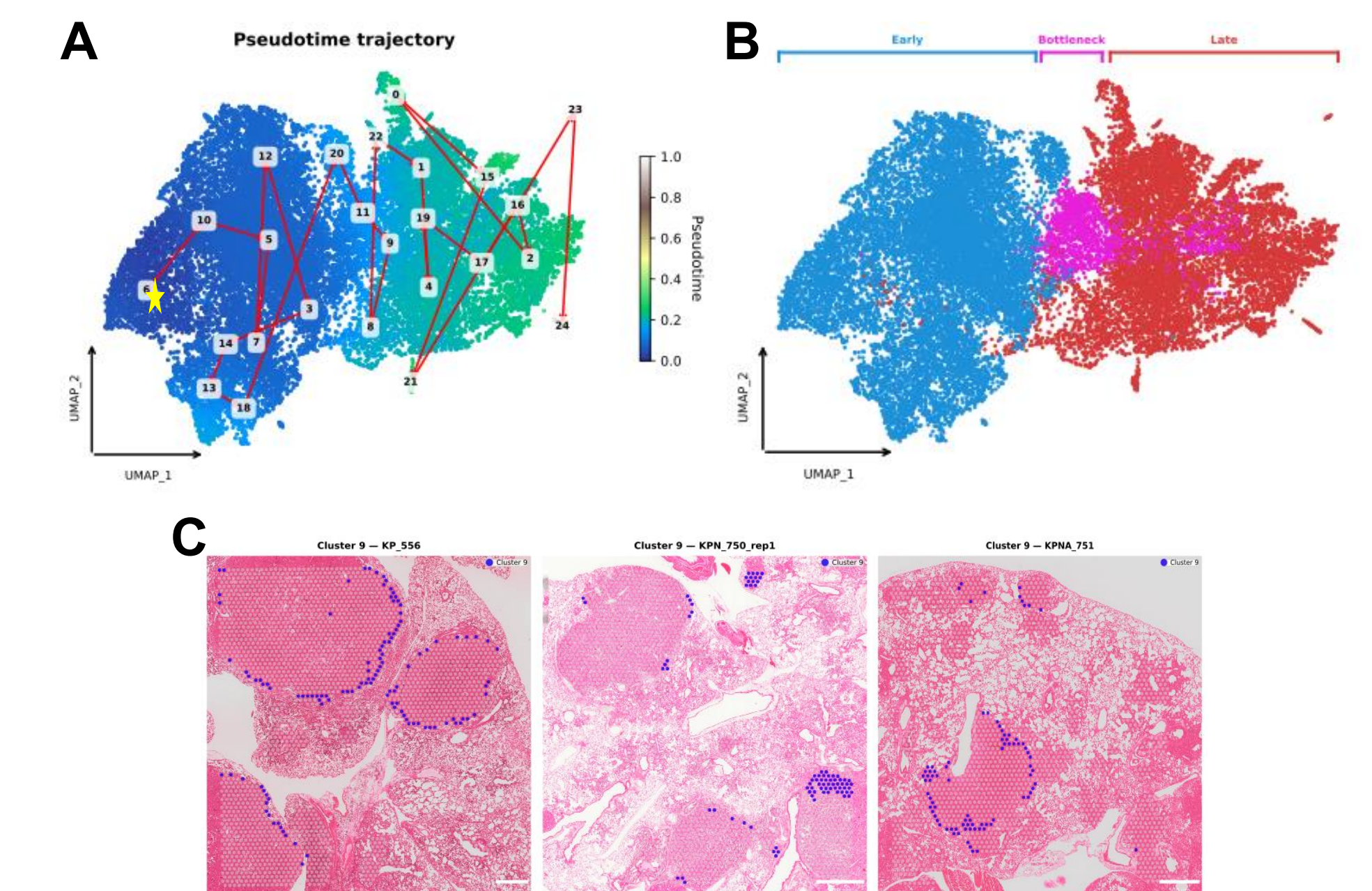


Figure 7: AT2-cell transdifferentiation trajectory is altered in the absence of *Nlrp3*. (A) AT2 cells predominately reside in cluster 6 (star). This was used as the start point for trajectory mapping. Arrows show the differentiation map of AT2 cells across all genotypes. (B) Trajectory time shows early differentiation states on the left, late differentiation states on the right separated by bottleneck populations. (C) Projection of bottleneck populations onto tissue images show discrete localisation at the invasive tumour-lung interface in *Nlrp3*-proficient tumours that is lost in *Nlrp3*-deficient tumours.