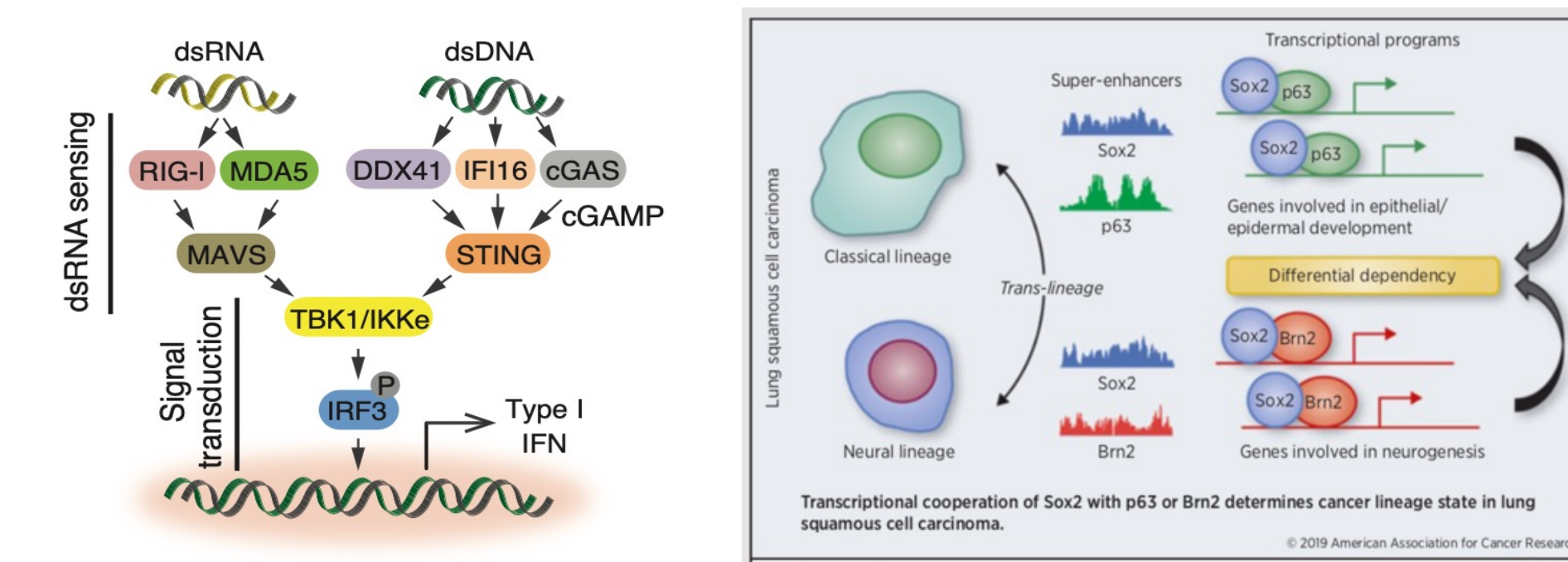


P3.073 : The cGAS–STING pathway in lung squamous cell carcinoma: lineage-associated suppression of innate immune signaling

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Introduction

- The cGAS–STING pathway plays a central role in innate immune sensing and type I interferon–mediated antitumor immunity.
- Although lung squamous cell carcinoma (LUSC) typically exhibits a high tumor mutational burden, responses to immune checkpoint inhibitors (ICI) are generally less favorable and more heterogeneous in LUSC than in lung adenocarcinoma. The mechanisms underlying this discrepancy remain unclear.
- Two distinct LUSC subtypes have been reported based on epigenomic profiling: the classical type characterized by SOX2–p63 cooperation and the neural type characterized by SOX2–BRN2 cooperation.
- We investigated the regulation and clinical significance of STING signaling in LUSC.



Methods

- Clinical LUSC specimens were analyzed for STING expression and immune cell infiltration using immunohistochemistry (IHC) and multiplex IHC.
- Publicly available LUSC cell line datasets were analyzed to assess STING pathway activity. Representative cell lines were further evaluated by qRT-PCR, Western blotting, and functional STING activation assays.
- Syngeneic SOX2–p63 and SOX2–BRN2 mouse models were used to evaluate tumor growth and response to anti-PD-1 therapy in vivo.

References & Acknowledgements

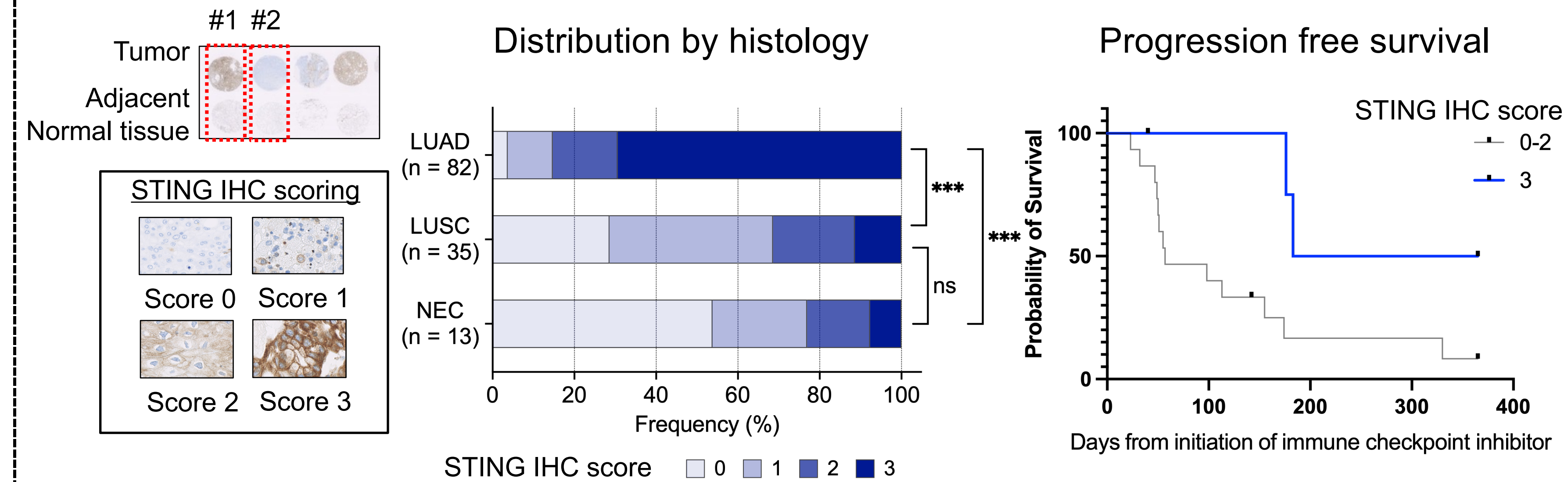
- References :
 1. Kitajima et al, Cancer Discovery . 2019.
 2. Sato, et al. Cancer Res. 2019.

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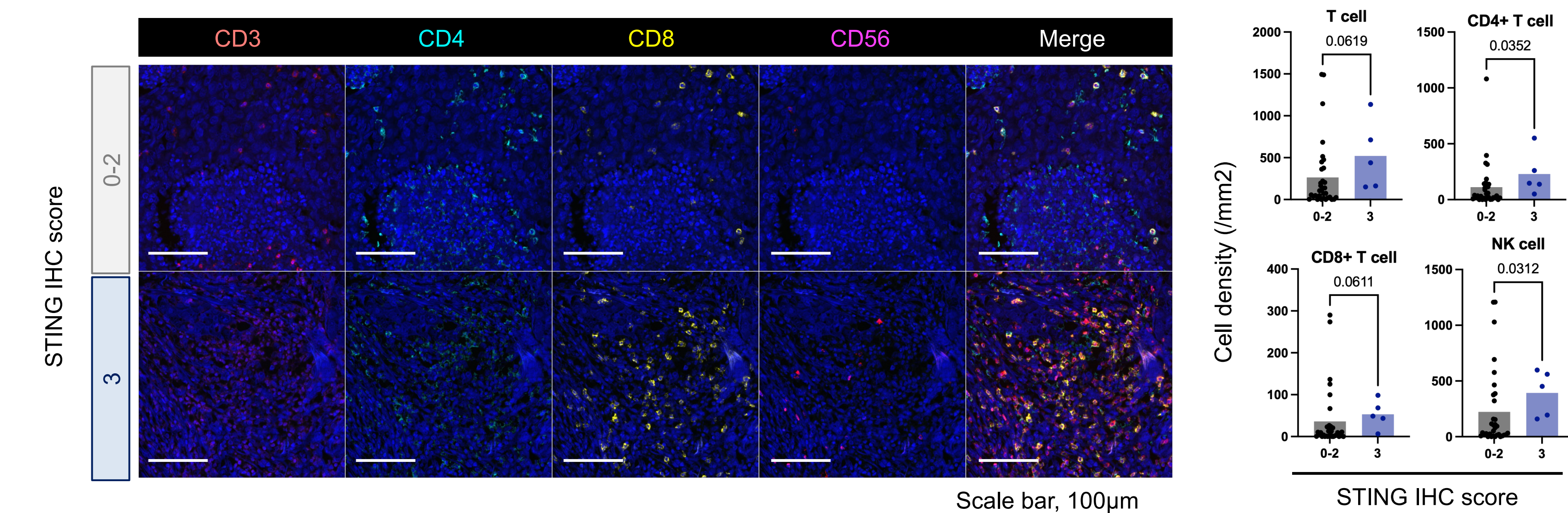
Result 1 : Clinical cohort analysis stratified by STING IHC score

- STING expression was lower in LUSC than in LUAD, and high STING expression was associated with longer progression-free survival following immune checkpoint inhibitor therapy in LUSC.



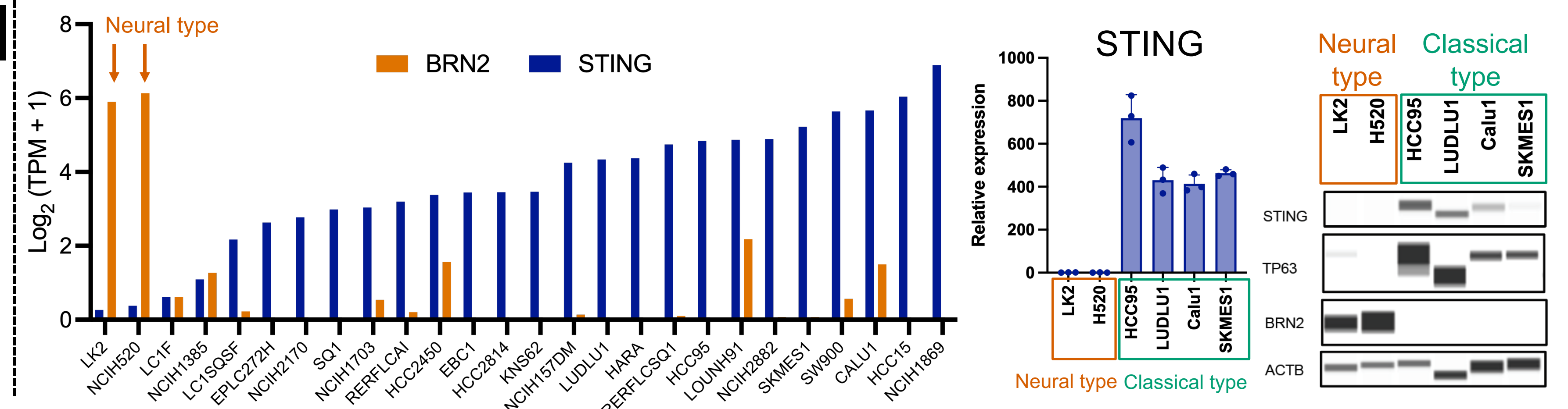
Result 2: Immune cell infiltration in LUSC according to STING IHC score

- Multiplex immunohistochemistry revealed significantly higher infiltration of CD4⁺ T cells and NK cells in STING-high tumors, with trends toward increased total T-cell and CD8⁺ T-cell infiltration.



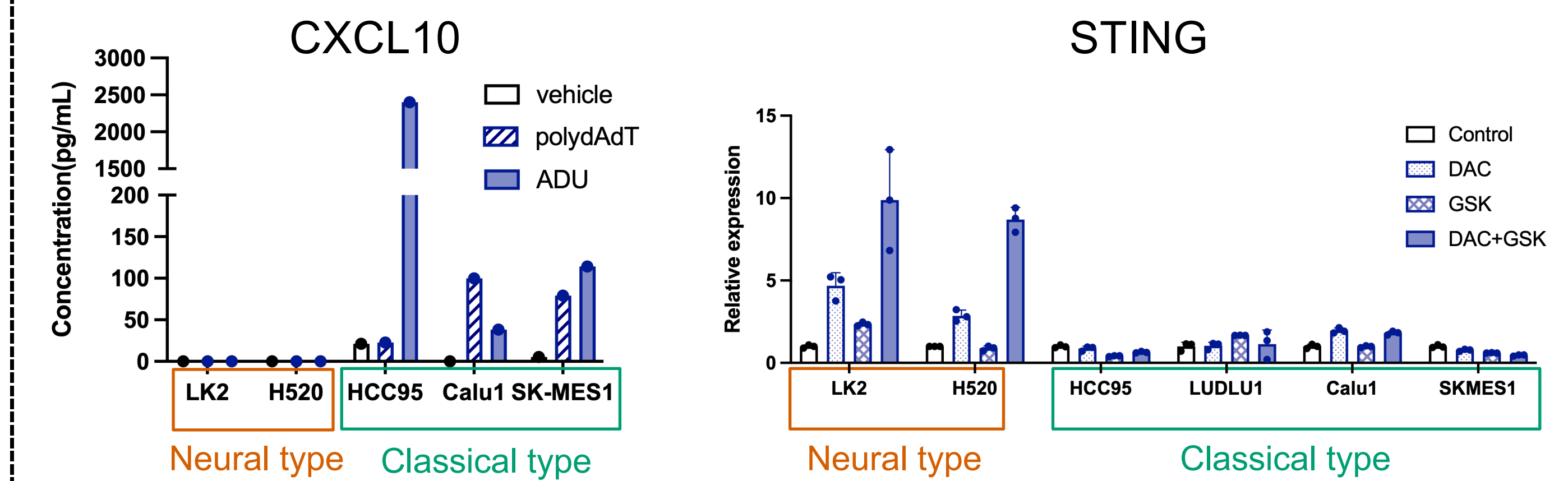
Result 3 : Validation of low STING expression in neural-type LUSC cell lines

- CCLE analysis showed that neural-type (BRN2-high) cell lines tended to have lower STING expression.
- Consistent with the CCLE data, neural-type LUSC cell lines showed low STING expression at both the mRNA and protein levels.

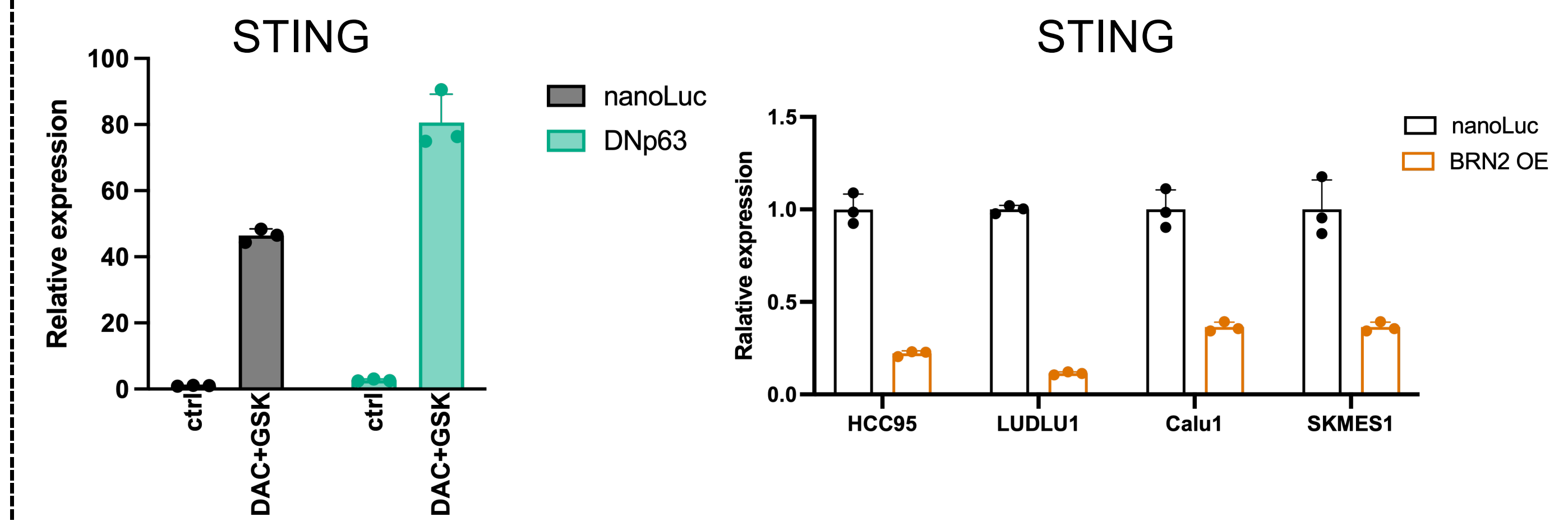


Result 4 : Suppression and restoration of STING signaling in neural-type LUSC

- STING agonist treatment induced robust CXCL10 secretion in classical-type cells, whereas neural-type cells showed minimal responses.
- Combined DAC and GSK treatment restored STING expression preferentially in neural-type cells.

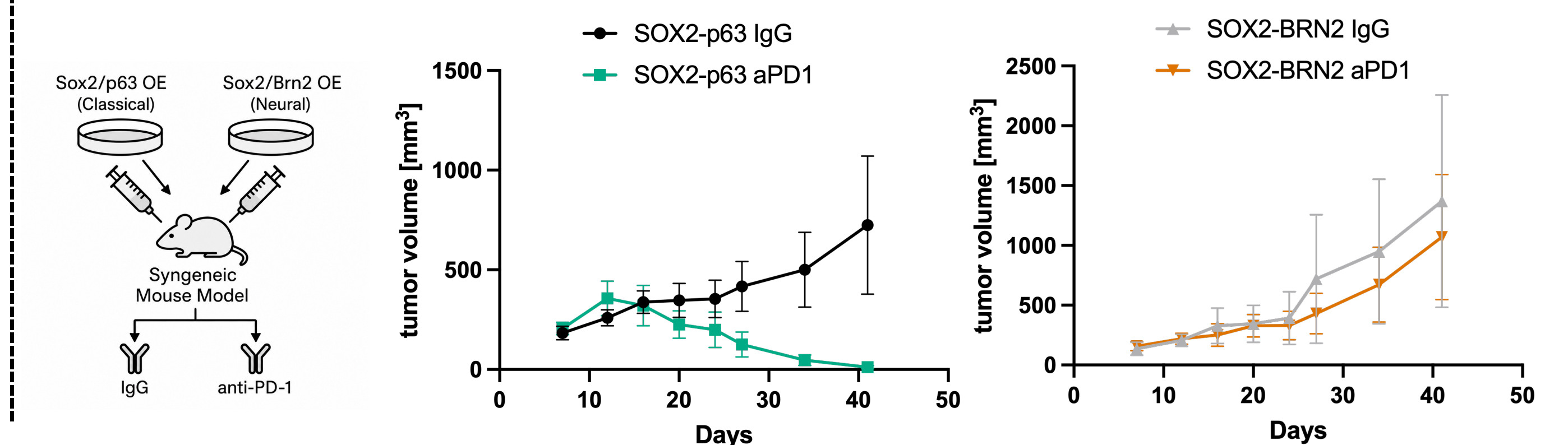


- The combination of p40 expression and DAC/GSK treatment further enhanced STING expression.
- BRN2 overexpression reduced STING expression, suggesting that BRN2 contributes to STING suppression.



Result 5 : BRN2-associated neural programs confer resistance to anti-PD-1 therapy in vivo

- SOX2–p63 tumors responded to anti-PD-1 treatment, whereas SOX2–BRN2 tumors showed limited responses, suggesting that the BRN2-associated neural program promotes resistance to anti-PD-1 therapy.



Conclusion

- LUSC frequently exhibits reduced STING expression compared with lung adenocarcinoma, which may contribute to heterogeneous responses to immunotherapy. Our findings suggest that lineage-associated transcriptional programs regulate STING signaling and tumor immune responsiveness in LUSC.
- These results provide a potential mechanistic link between tumor lineage states and innate immune signaling, supporting therapeutic STING-targeted therapy in LUSC.