

## 2026 World Conference on Lung Cancer

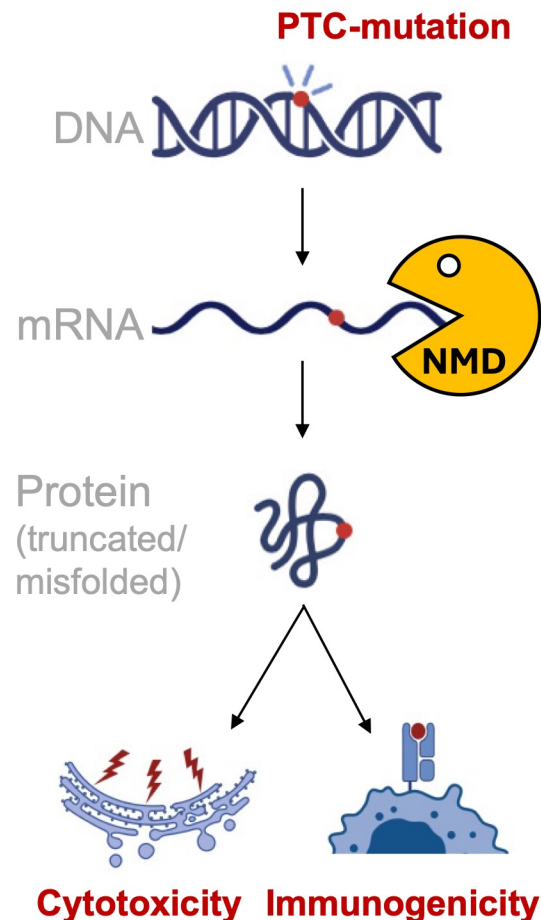
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**TMB creates a targetable dependency on nonsense-mediated decay (NMD) to escape proteotoxic stress and immune recognition in SCLC**

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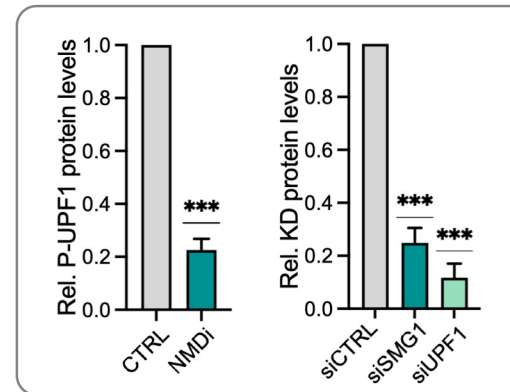
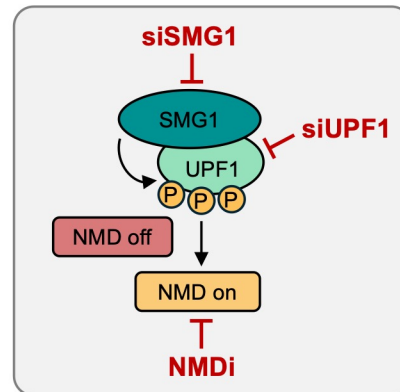
# TMB creates a targetable dependency on nonsense-mediated decay (NMD) to escape proteotoxic stress and immune recognition in SCLC

## Introduction

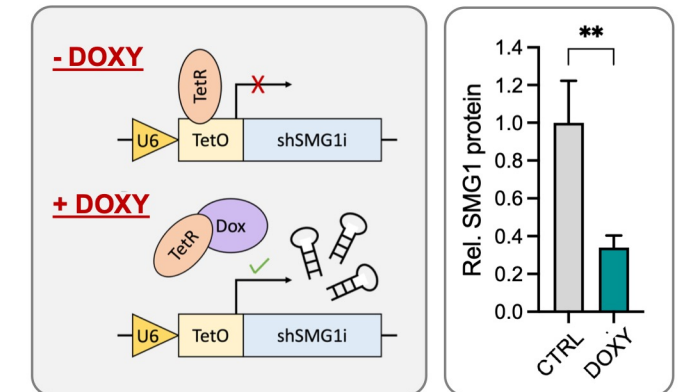


## NMD inhibition

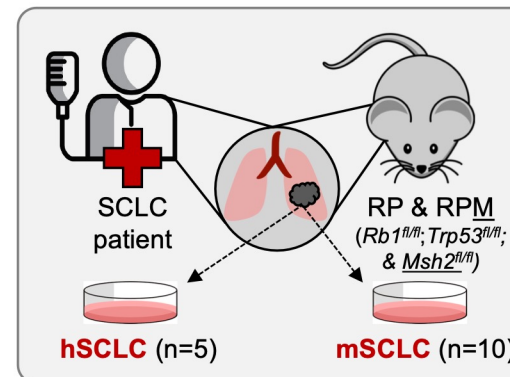
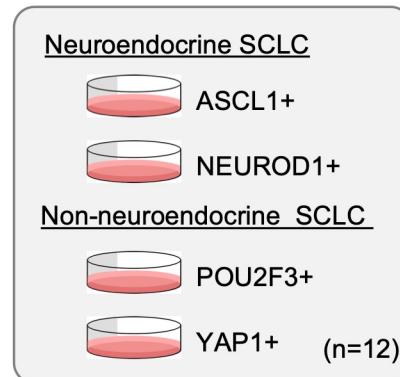
- Small molecule inhibitors & siRNA-mediated NMD knockdown



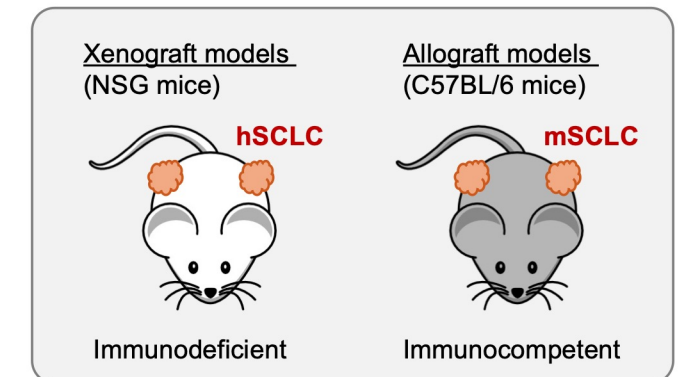
- Doxycycline-inducible NMD knockdown



- NMD inhibition *in vitro* in cell lines and primary cell cultures

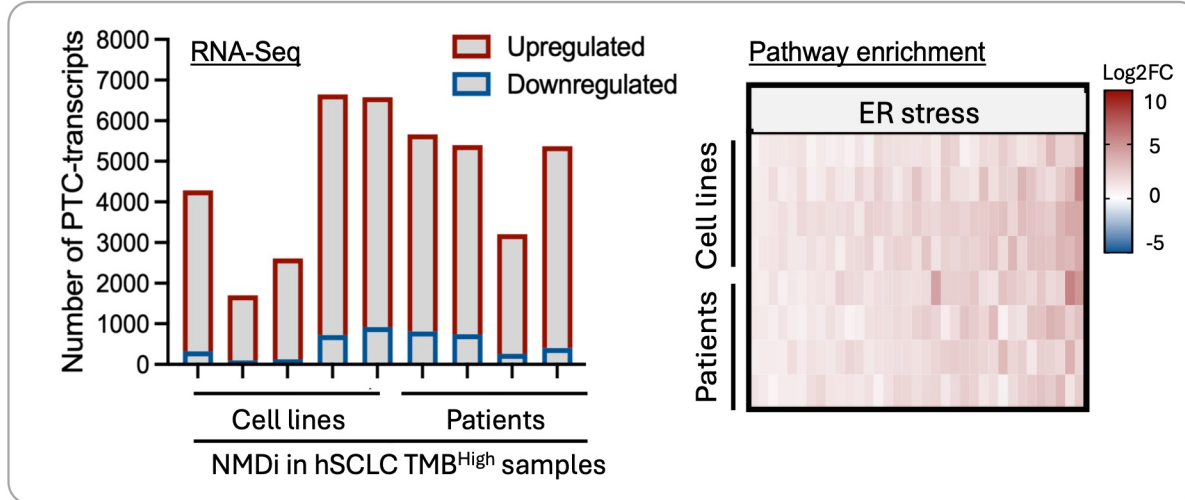


- Mouse models for NMD inhibition *in vivo*

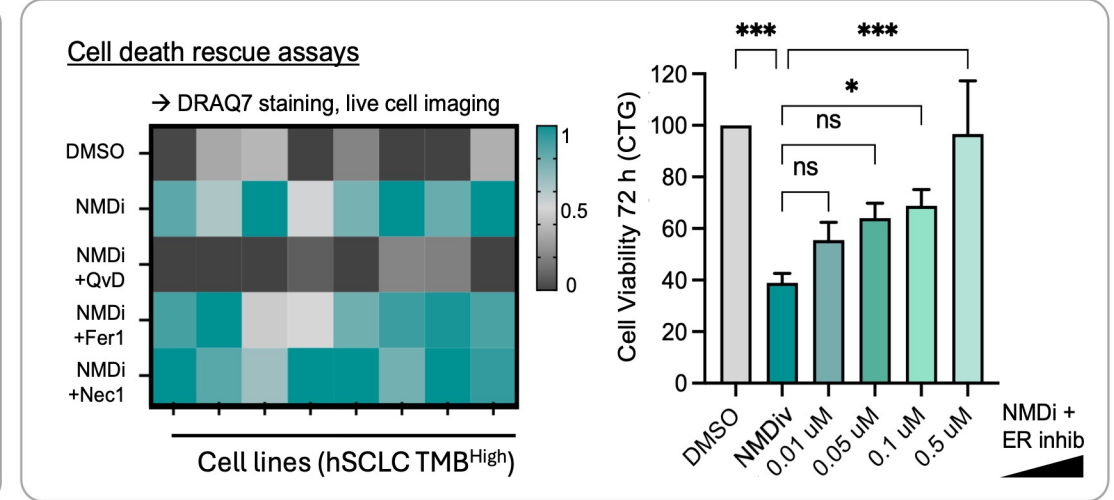


# TMB-dependent cell-intrinsic vulnerability to NMD inhibition *in vitro*

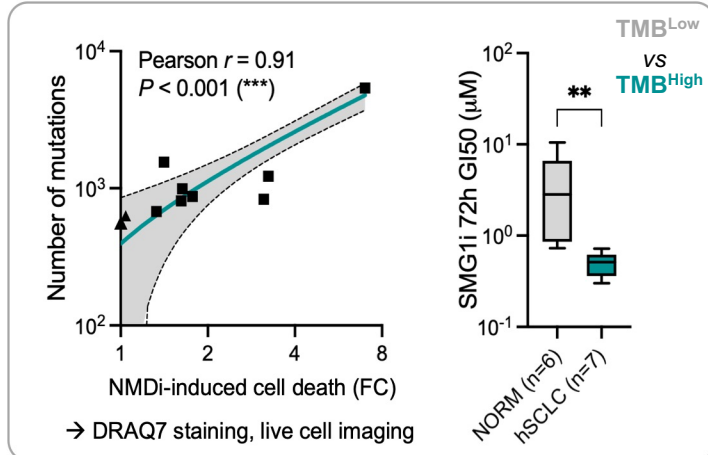
- Accumulation of misfolded proteins from PTC-transcripts generates ER stress



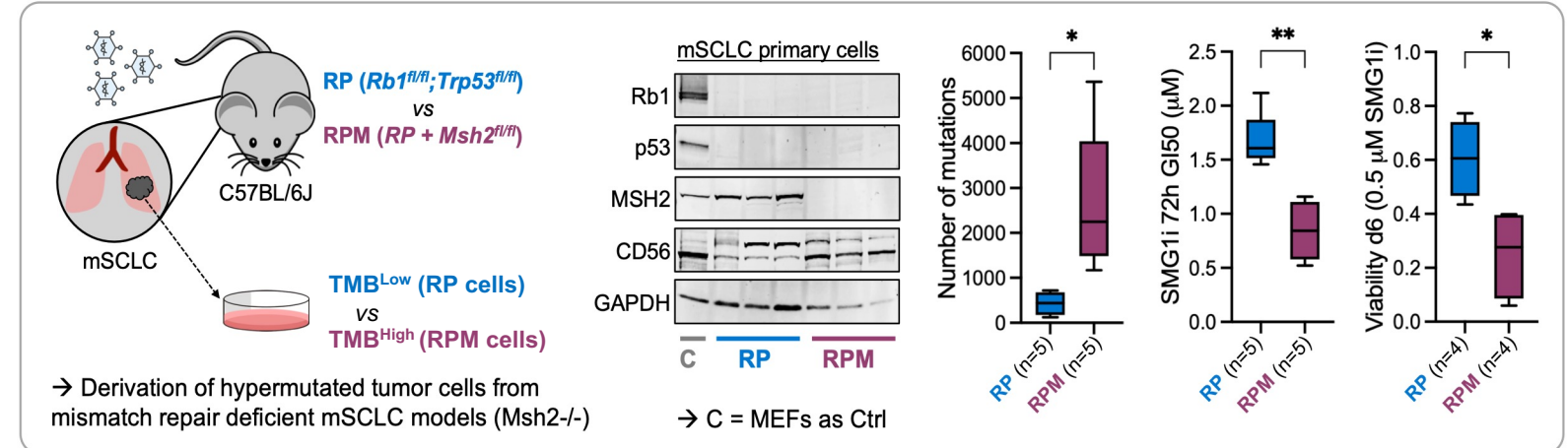
- Unresolved ER stress in a TMB<sup>High</sup> context results in apoptotic cell death



- TMB-correlated vulnerability to NMD inhibition

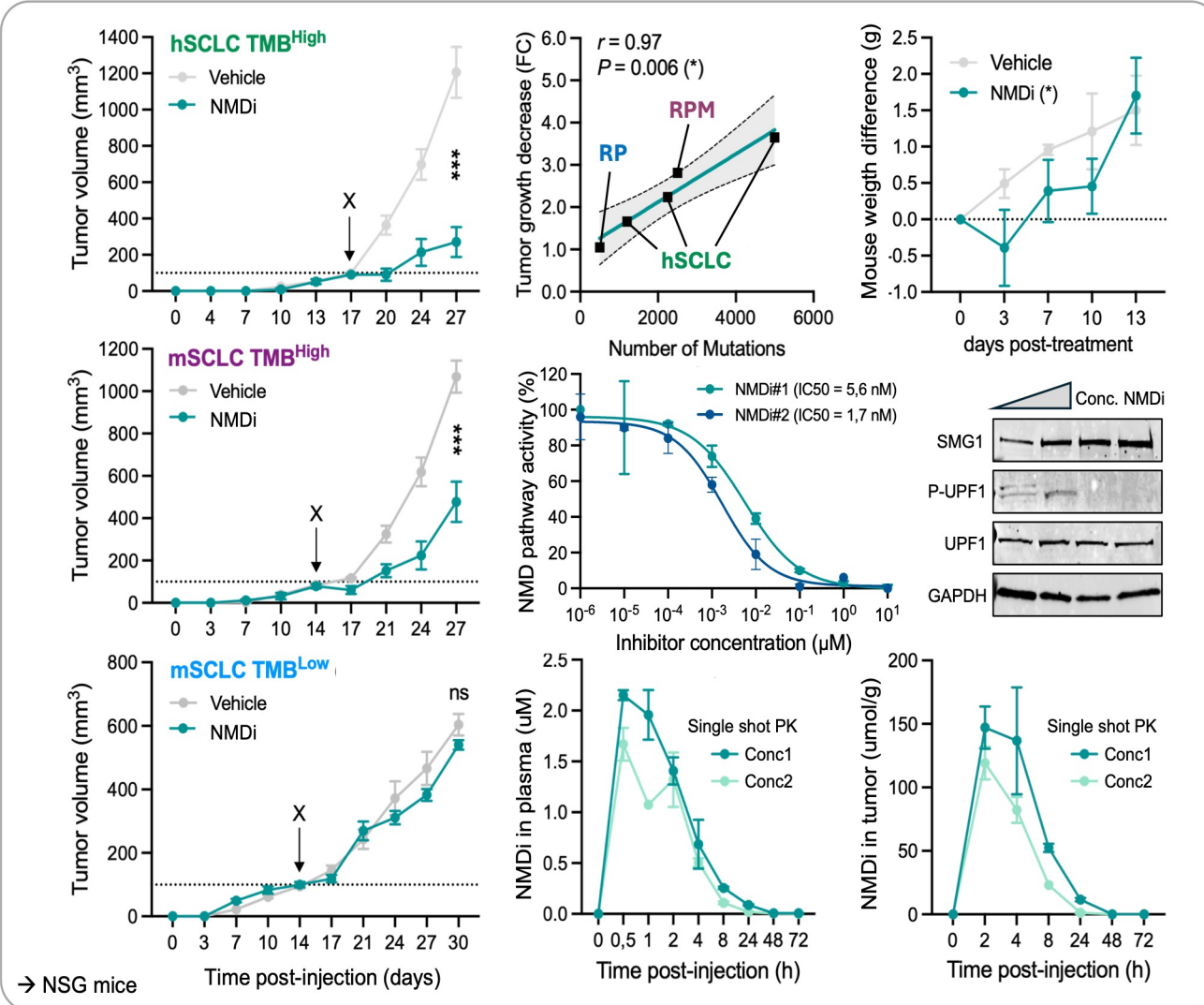


- TMB-dependent vulnerability to NMD inhibition: somatic hypermutation increases sensitivity to NMD inhibition

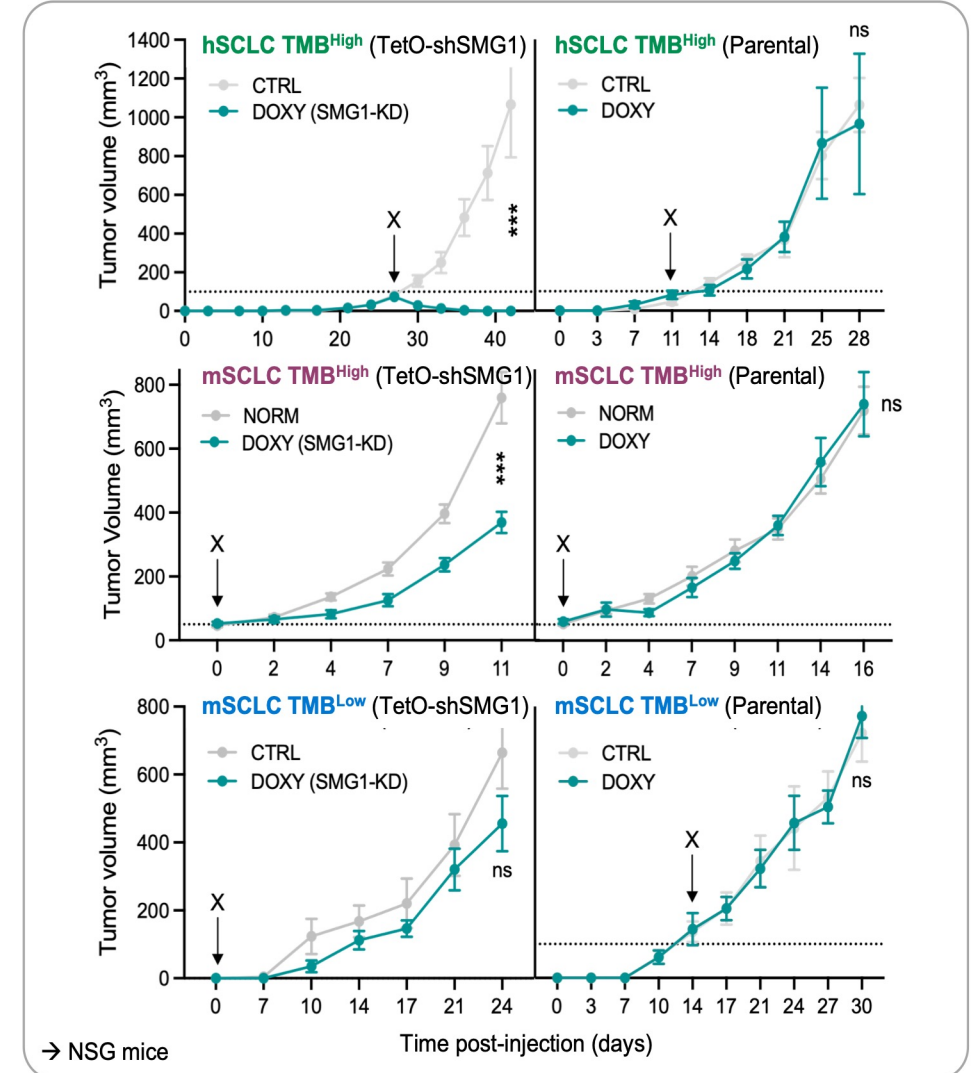


# TMB-dependent cell-intrinsic vulnerability to NMD inhibition *in vivo*

- Pharmacological NMD inhibition *in vivo* decreases tumor growth without overt toxicity

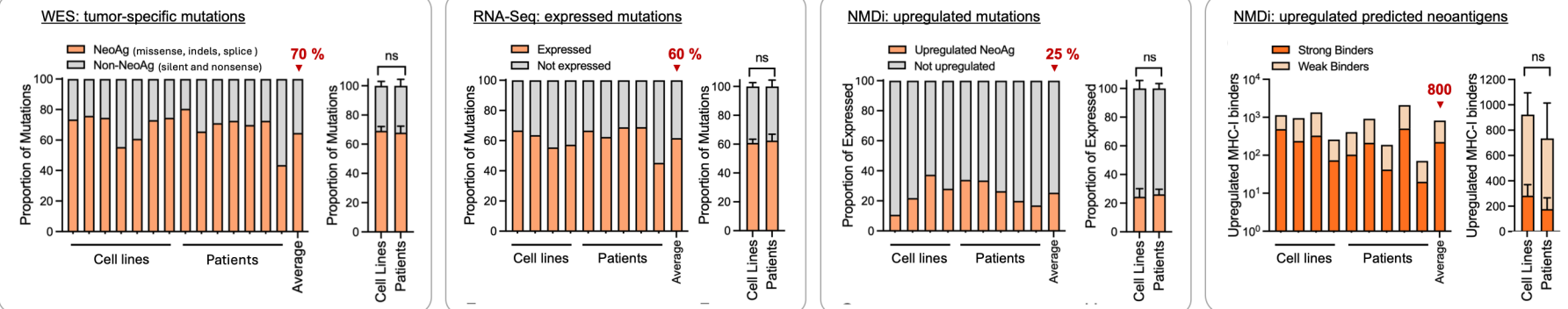


- Tumor-targeted NMD inhibition *in vivo* decreases tumor growth

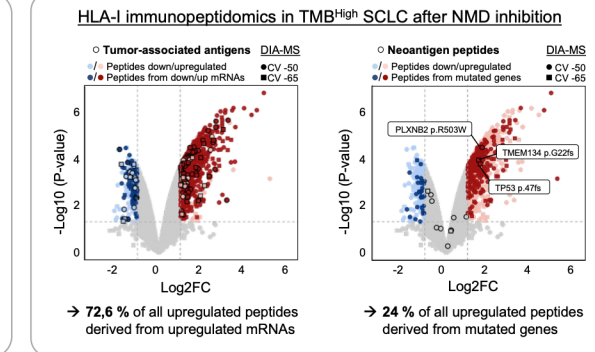


# Increased neoantigen diversity and enhanced tumor immunogenicity upon NMD inhibition

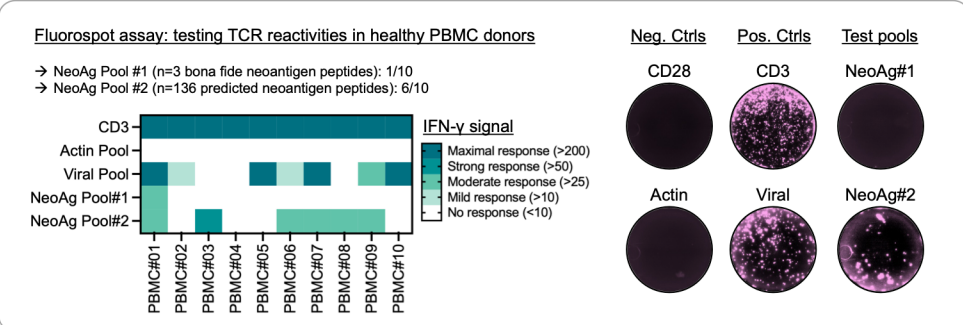
- Integration of SCLC genomic and expression data with HLA-I binding modeling shows a massive upregulation of predicted neoantigens (i.e. predicted HLA-I binders) after NMD inhibition



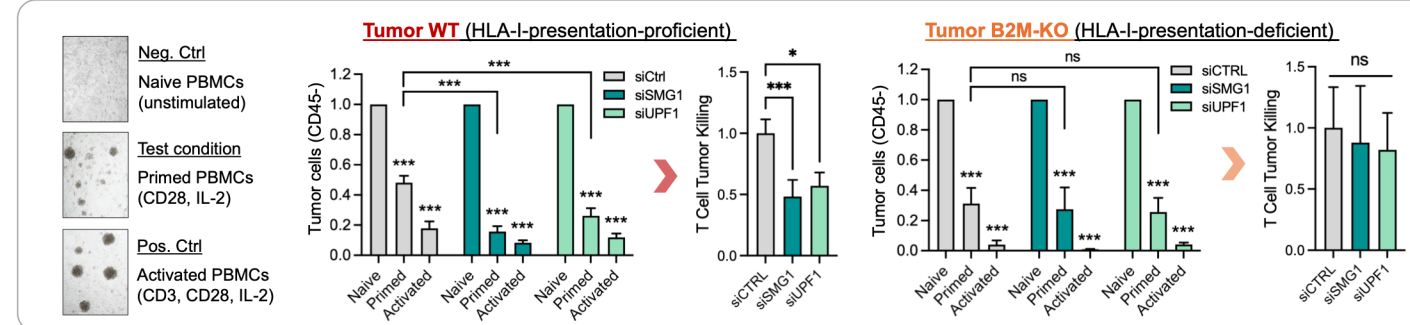
- Inhibition of NMD globally reshapes the immunopeptidome



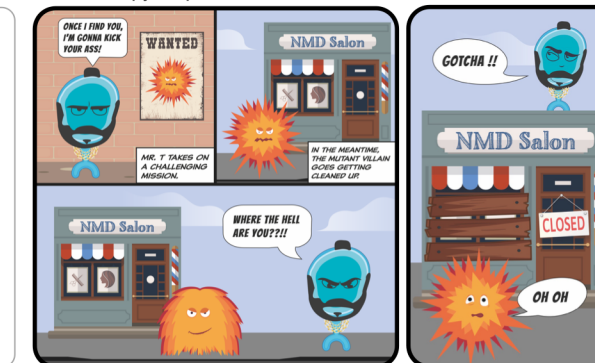
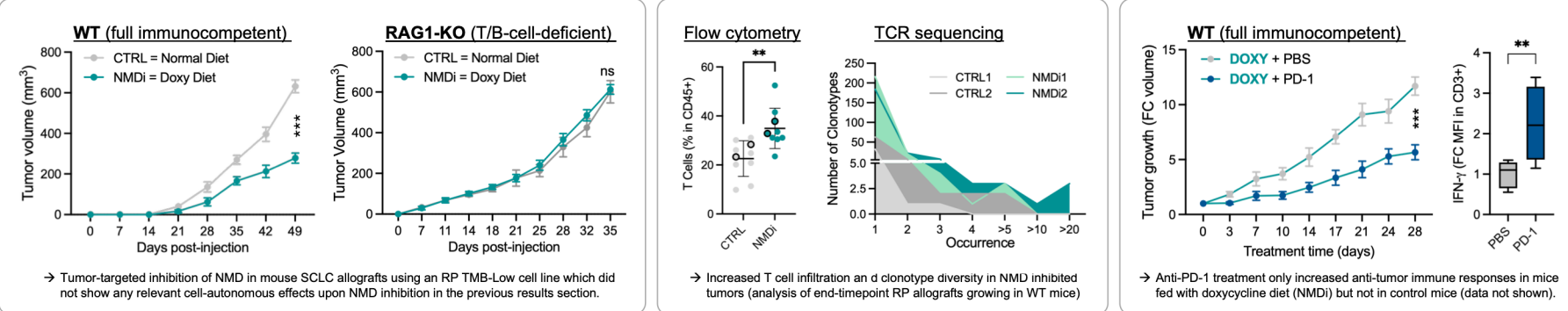
- NMD regulates the expression of remarkably immunogenic neoantigen peptides



- In vitro* co-cultures of TMB<sup>High</sup> tumor cells with T cell-enriched PBMCs show enhanced HLA-I-dependent T cell-mediated tumor killing upon NMD inhibition

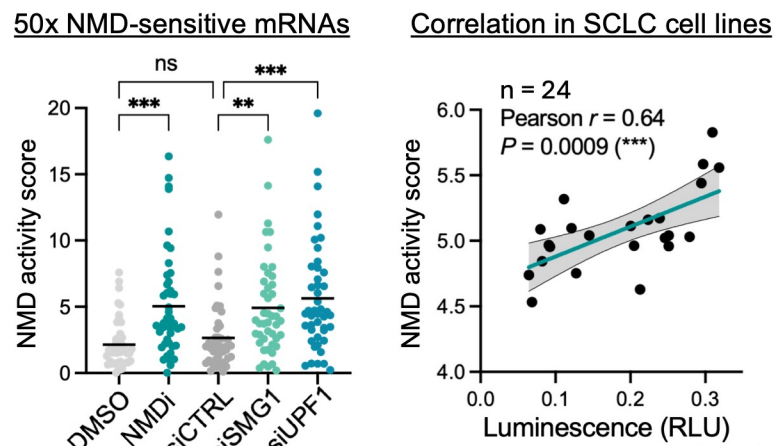


- NMD inhibition enhances T cell recognition through neoantigen diversification: increased T cell-dependent control of tumor growth, increased T cell infiltration and TCR clonotype diversity, and improved immunotherapy response were observed in NMD inhibited tumors

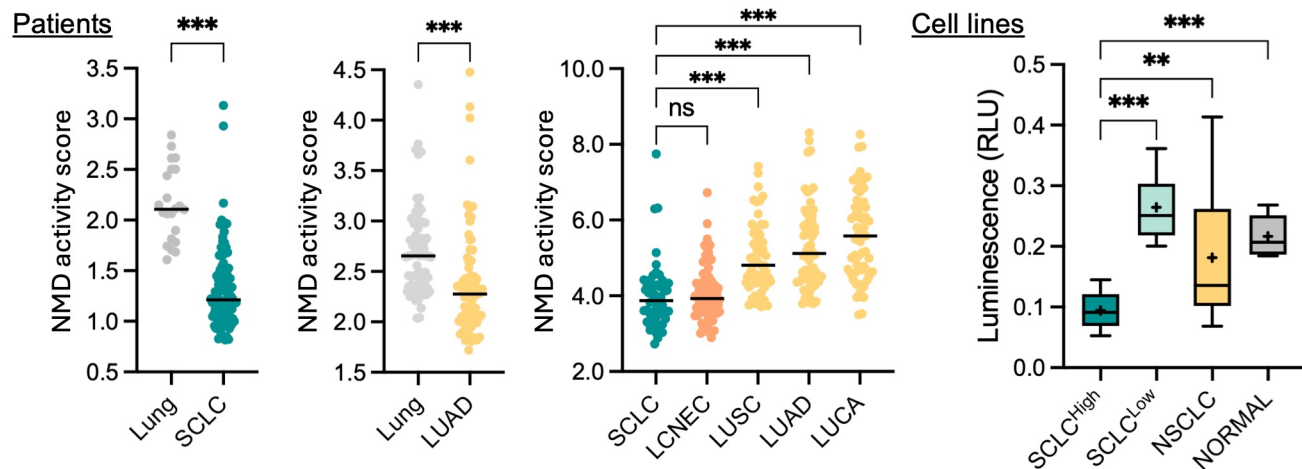


# NMD pathway hyperactivity in TMB-High cancers

## Transcriptome-based NMD activity score

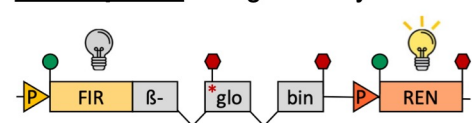


## Hyperactive NMD pathway in SCLC vs normal lung & NSCLC

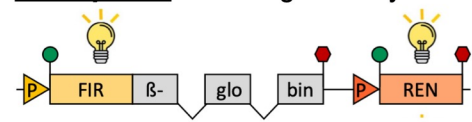


## Luciferase-based NMD activity

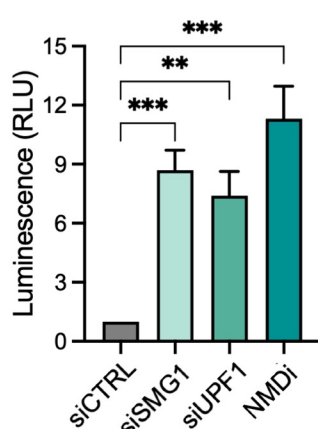
**PTC reporter** = degraded by NMD



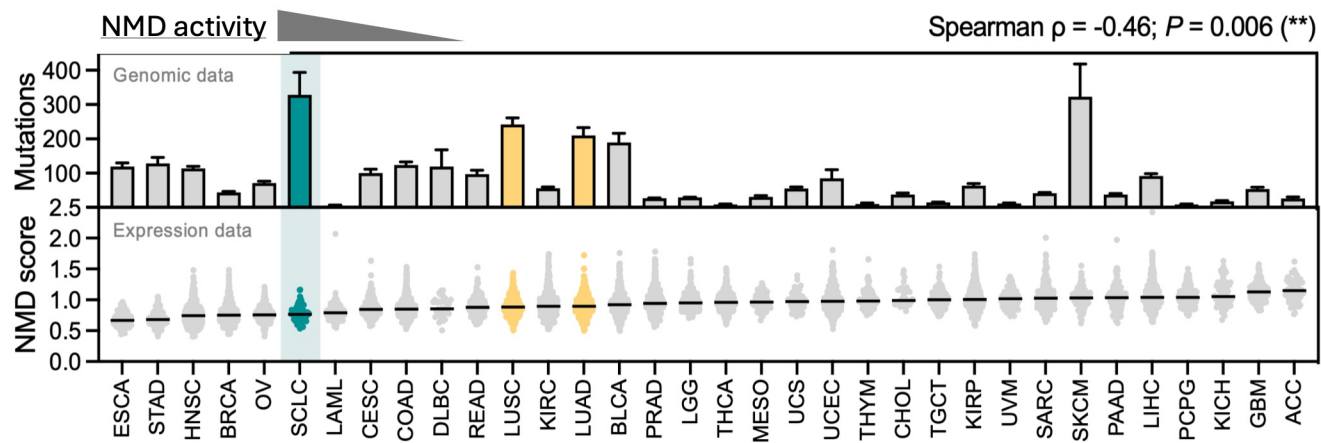
**WT reporter** = not degraded by NMD

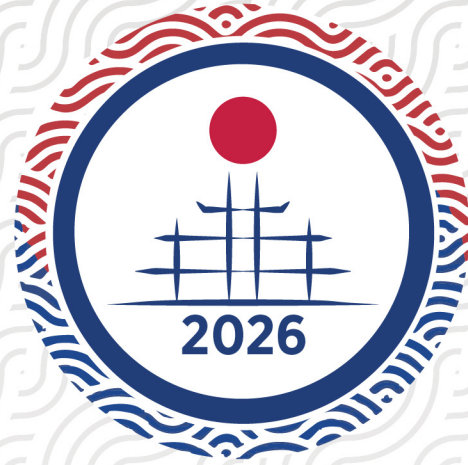


$(FIR/REN)_{PTC} / (FIR/REN)_{WT}$



## Hyperactive NMD pathway in TMB-High cancers (TCGA database)





# Thank You.