

Nanomedicine and Nanoscale Delivery I

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Polymalic acid-based nanoconjugate passing blood-brain barrier and targeting extracellular matrix laminin-411 modulates brain immune system to inhibit glioblastoma growth

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INTEGRATING
Delivery Science
ACROSS DISCIPLINES

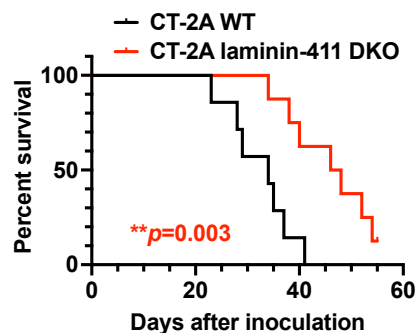


Depletion of glioblastoma microenvironment component laminin-411 in mouse gliomas by CRISPR/Cas9 knockdown or BBB-passing nanoconjugate significantly prolongs animal survival

Survival of mice with GBM after CRISPR/Cas9 laminin-411 $\alpha 4 + \beta 1$ depletion

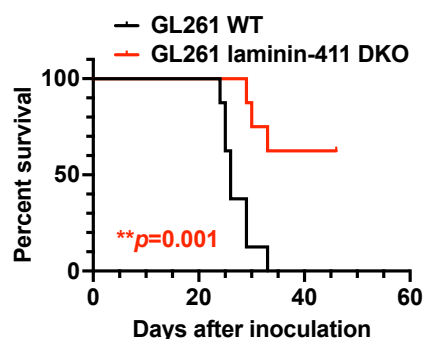
Double knockout CT-2A GBM

Median 34 vs. 47 days

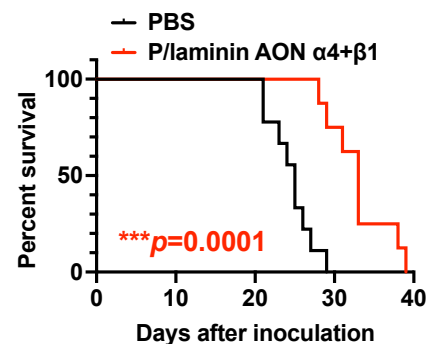


Double knockout in GL261 GBM

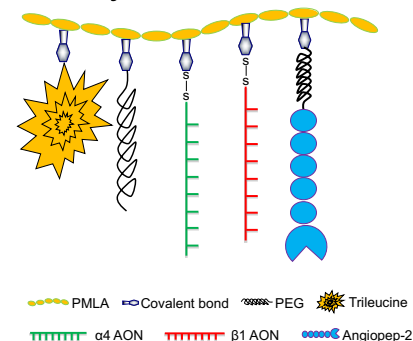
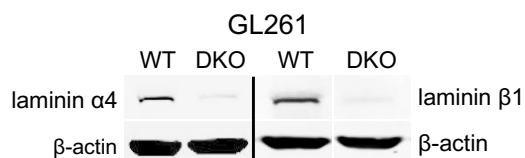
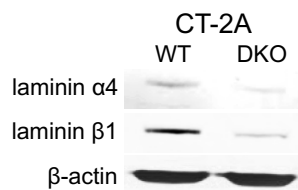
Median 26 vs. undefined



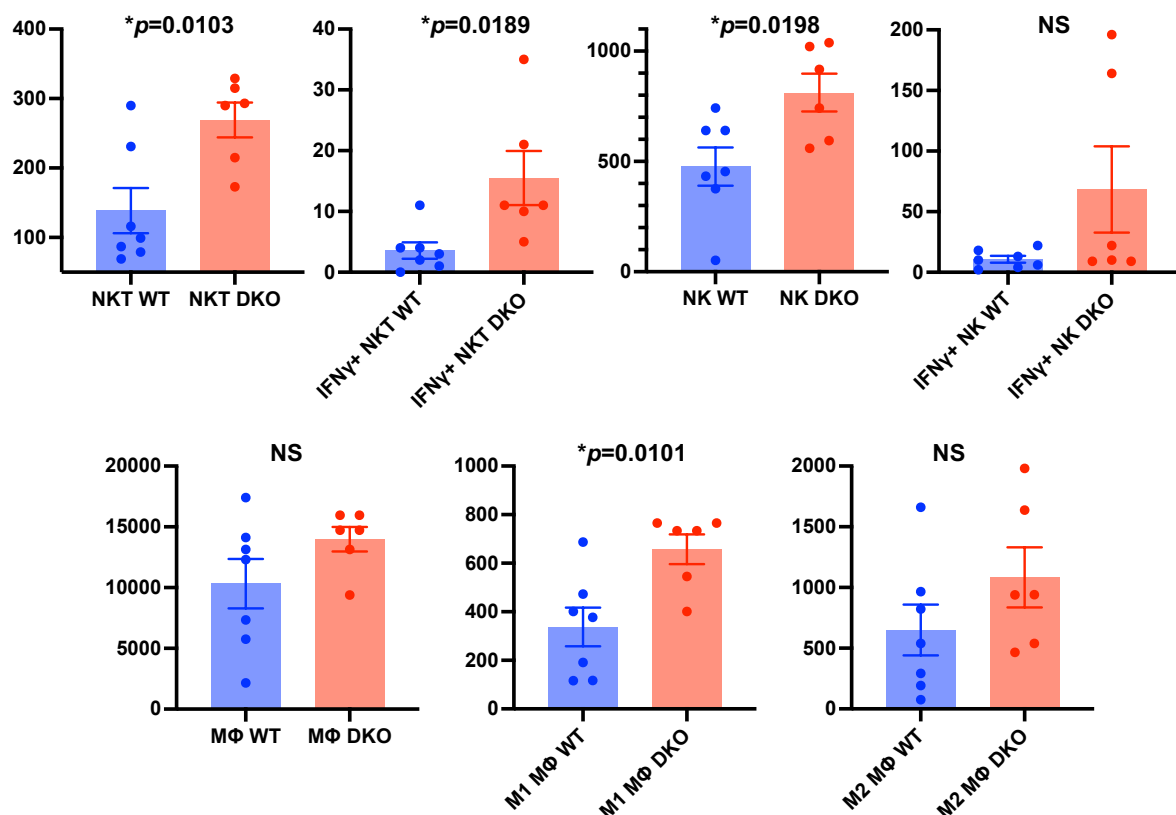
Survival of mice with wild type GL261 GBM after treatment with nanoconjugate



Validation of laminin-411 depletion by western blot



Activation of innate immune response in gliomas formed from GL261 cells with CRISPR/Cas9 double knockout of laminin-411 $\alpha 4$ and $\beta 1$ chains

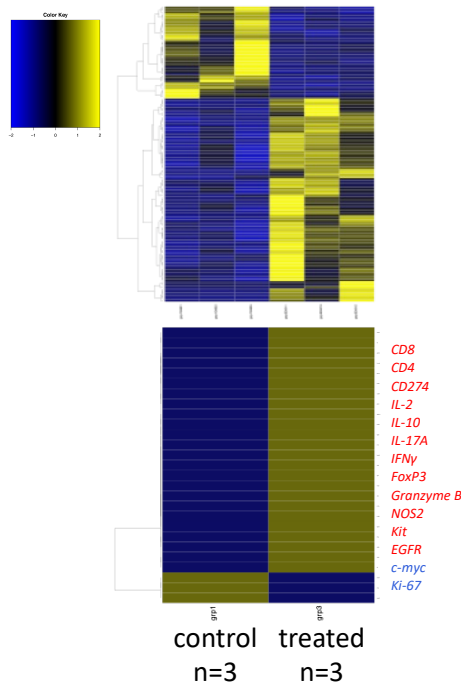


GL261 glioma flow cytometry (Sony Spectral): wild-type (WT) vs. laminin-411 $\alpha 4$ and $\beta 1$ chains double knockout (DKO). In tumors from DKO cells there is significant activation of the innate immune system including natural killer cells (NK), natural killer T cells (NKT), especially positive for interferon γ (IFN γ), and M1 anti-tumor macrophages (M Φ). Total and pro-tumor M2 M Φ were not significantly changed.

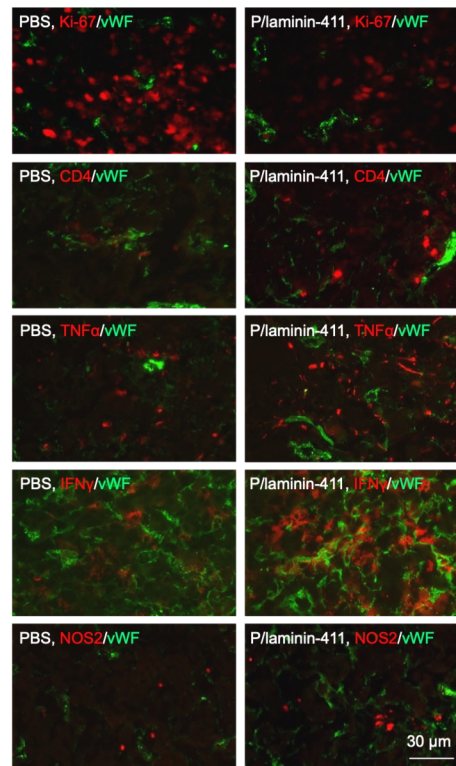
Laminin-411 inhibition in GBM is associated with suppression of cancer genes and immune system modulation. Bioinformatic/AI analysis of RNA-seq and marker validation

Heatmap of gene expression

P/Lam $\alpha 4$ + Lam $\beta 1$ AONs



RNA-seq validation: decreased KI-67 (proliferation), and increase in CD4 (T cells), TNF α , IFN γ , and NOS2 (M1 M Φ)



Ingenuity/AI pathway analysis activation of TNF and IFN γ pathways

