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Comparison of Two oHSV Vectors for the Treatment of Glioblastoma

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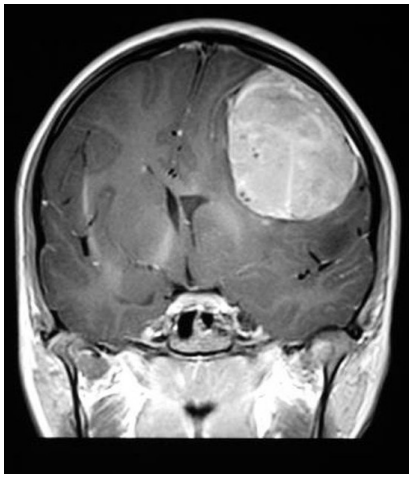
The University of Pittsburgh, Pittsburgh, PA

Disclosures

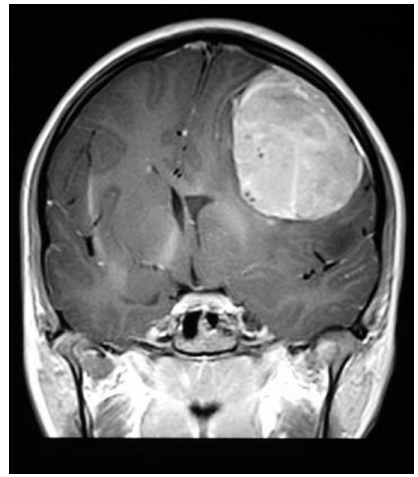
- None

Glioblastoma multiforme (GBM)



- Common and highly aggressive neoplastic malignancy
  - Incidence: 22,000 new diagnoses/year
- Characterized by rapid and invasive growth aided by the degradation of the extracellular matrix surrounding the brain parenchyma
  - Immunosuppressive tumor microenvironment
- Treatment: Tumor resection → radiotherapy and chemotherapy
  - Diffuse tumor cell infiltration of the brain→ common recurrence
- 5-year survival rate ~5%

Glioblastoma multiforme (GBM)



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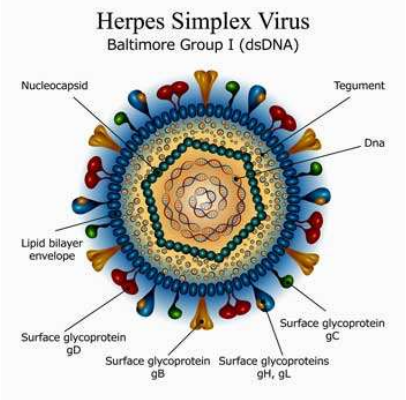

- Treatment: Tumor resection → radiotherapy and chemotherapy
  - Diffuse tumor cell infiltration of the brain→ common recurrence

- 5-year survival rate ~5%

Need a "alternative therapy" to combat GBM

oHSV Designs

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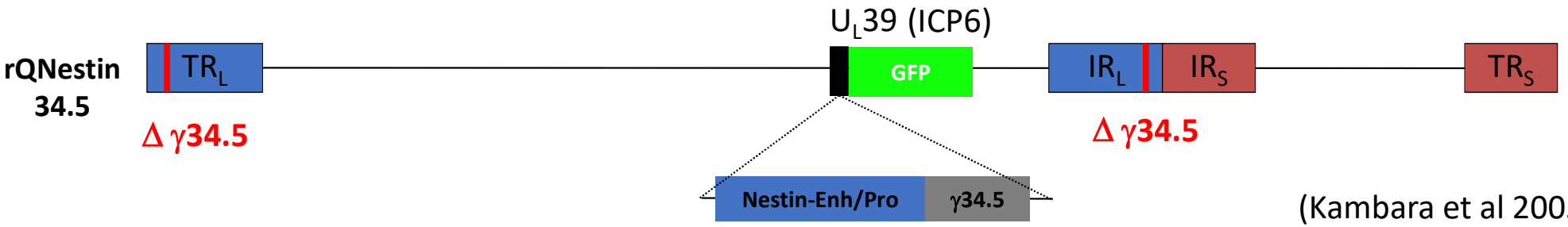
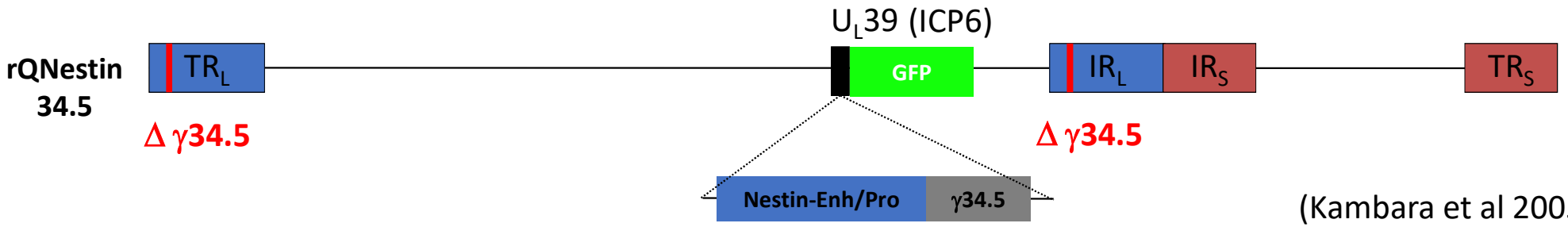


(Kambara et al 2005)

oHSV Designs



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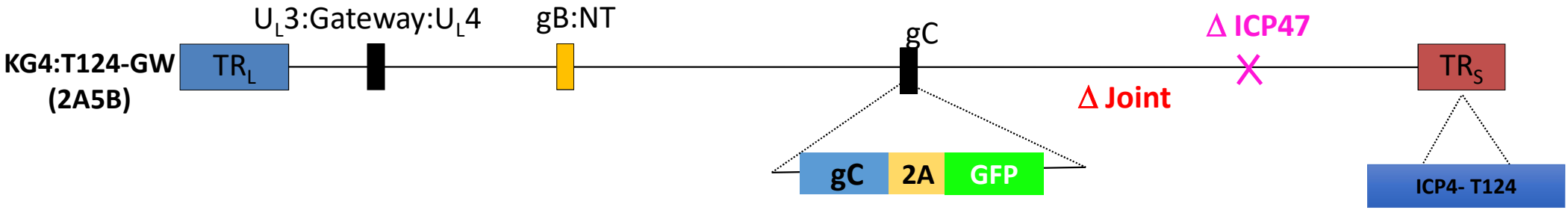
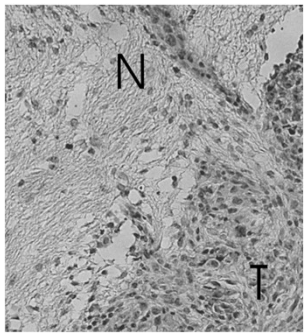


Syngeneic Models

GL261N GBM Model

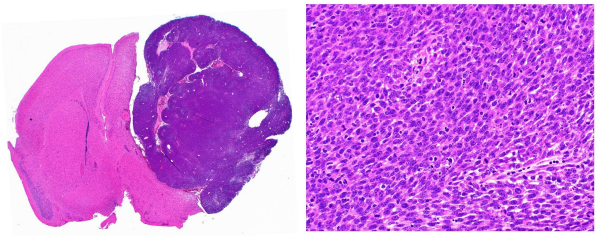


N= normal tissue

T= tumor tissue

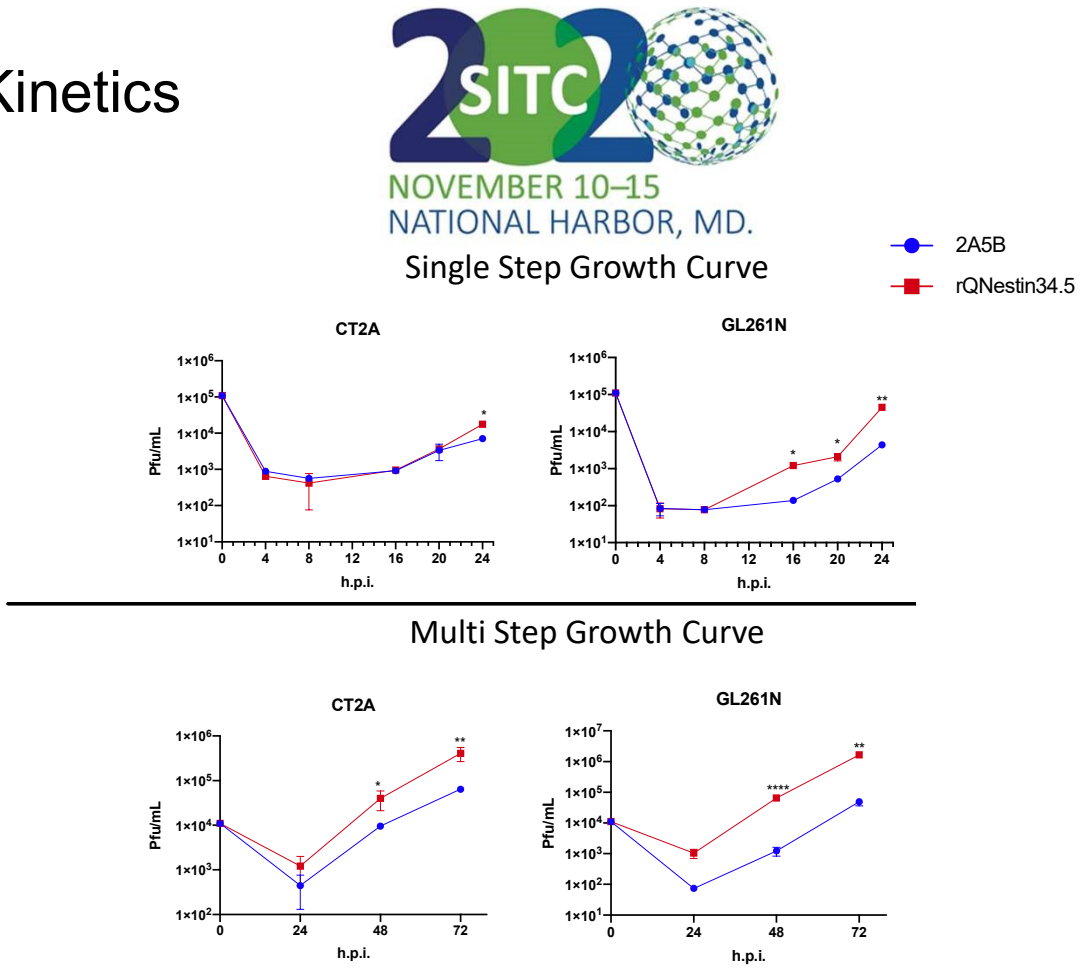
- GL261(N) cell line
- Engineered to express nectin-1
- Animal survival ~25-35 days
- Effective interventions exist
- ~2,100 expressed non-synonymous mutations

CT2A GBM Model

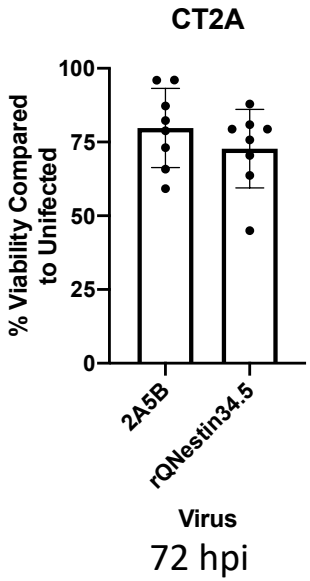


- CT2A cell line
- Animal survival ~17-20 days
- Effective interventions are exceedingly rare
- High PD-L1 and MHC-1 expression
- ~1,000 mutations

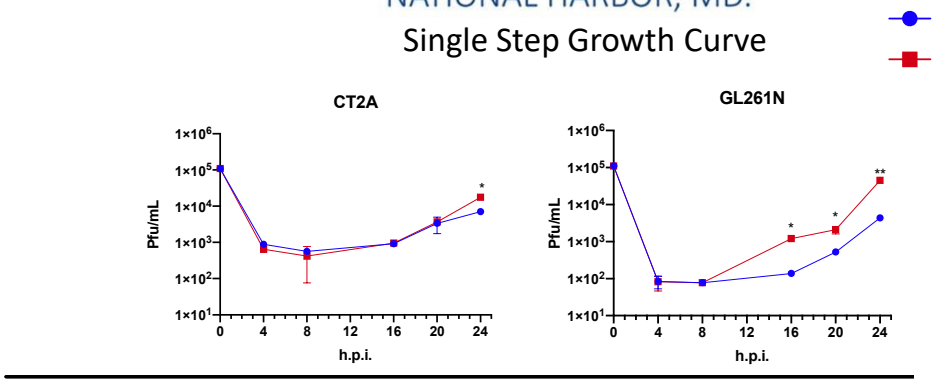
Viral Growth Kinetics



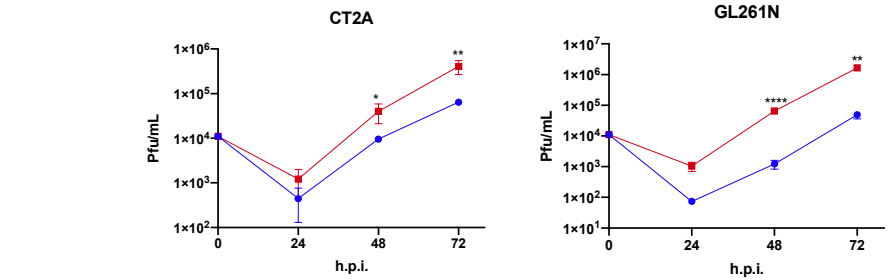
Viral Growth Kinetics

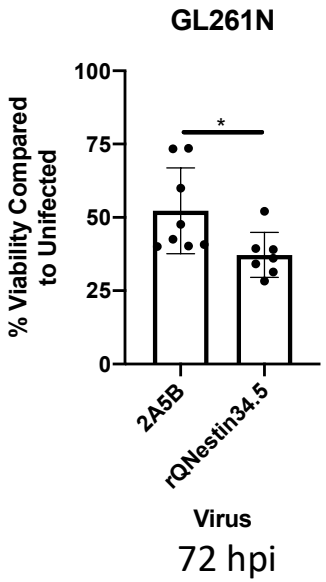


Single Step Growth Curve

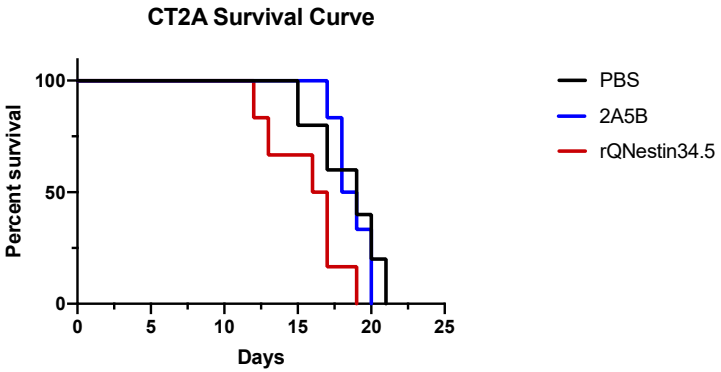


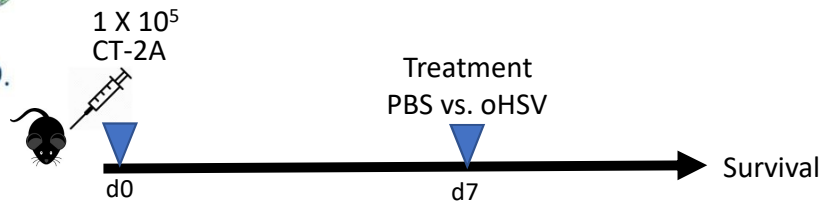
Multi Step Growth Curve





CT2A Analysis





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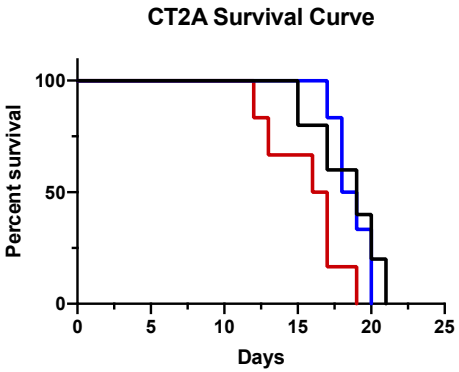
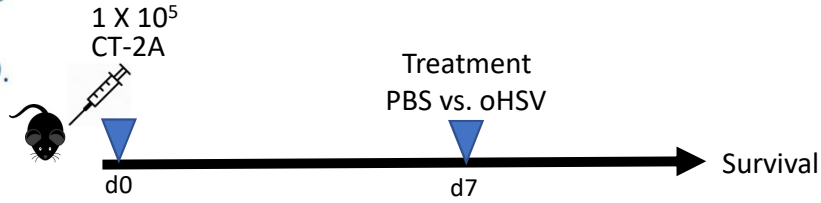
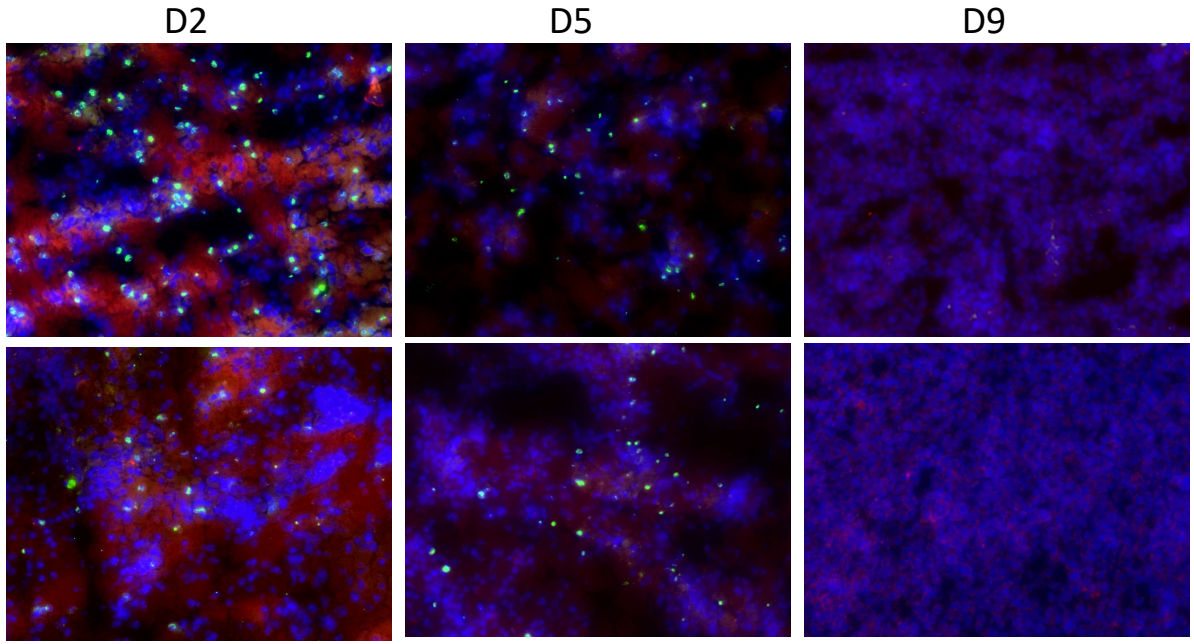


PBS
2A5B
rQNestin34.5





Green – HSV (ICP4), Red – Nestin, Blue – DAPI

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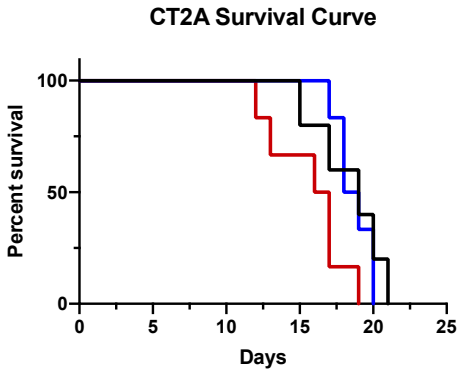

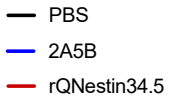

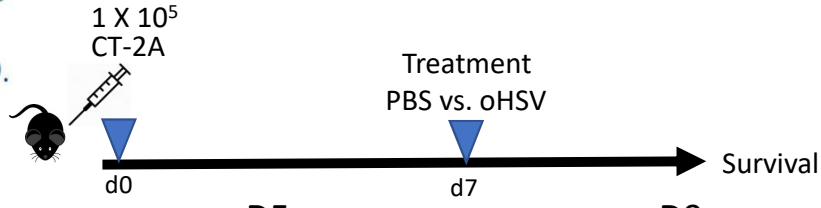

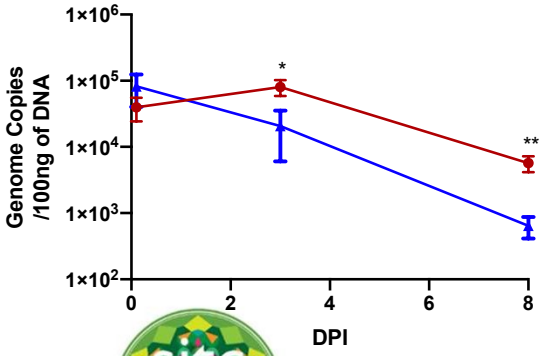

D2 D5 D9

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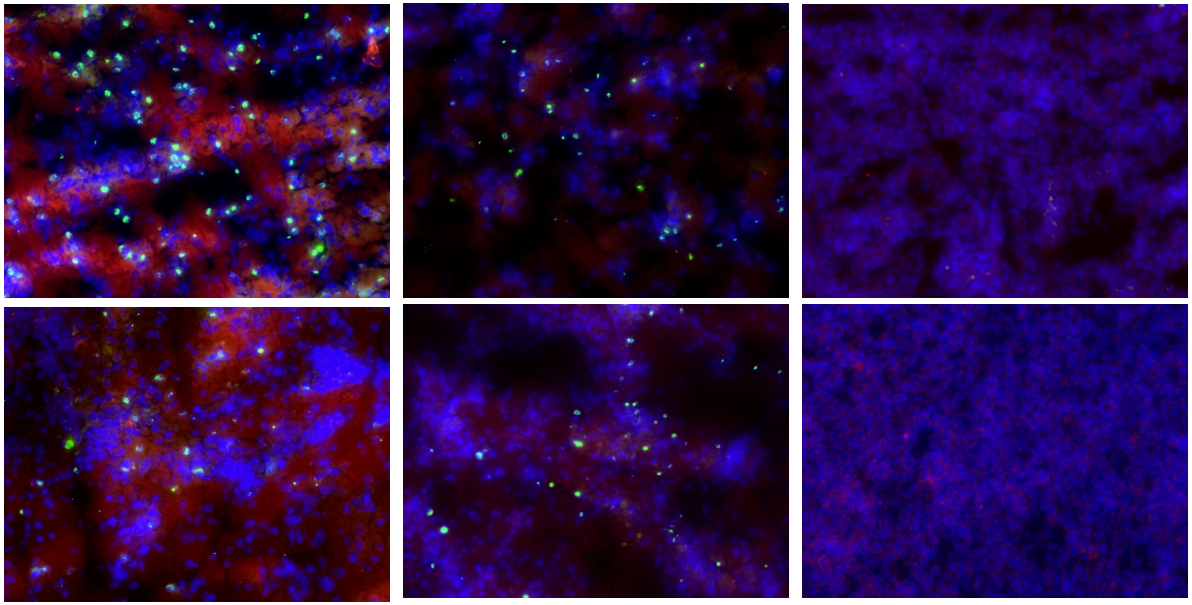
2A5B



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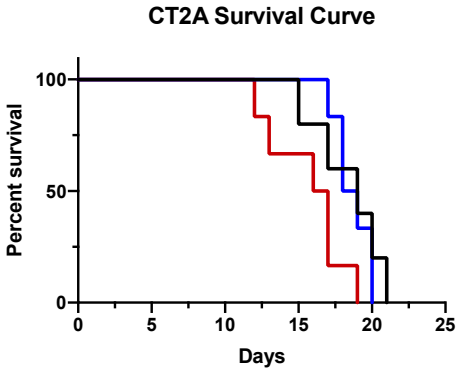

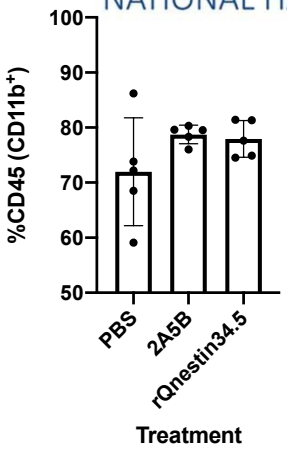

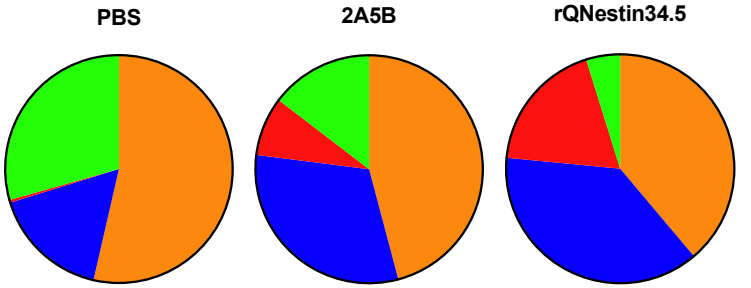

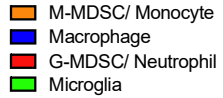

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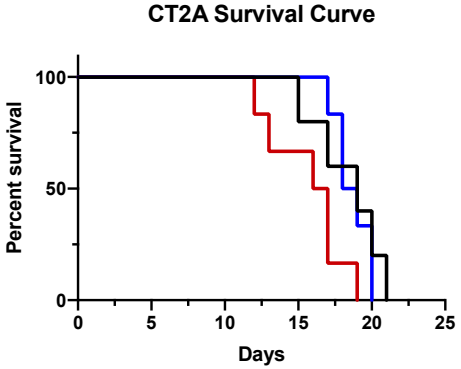

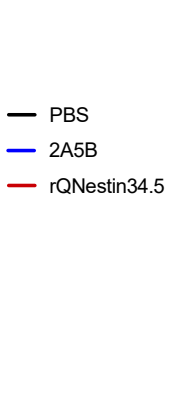

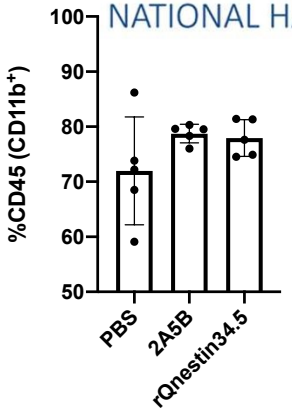

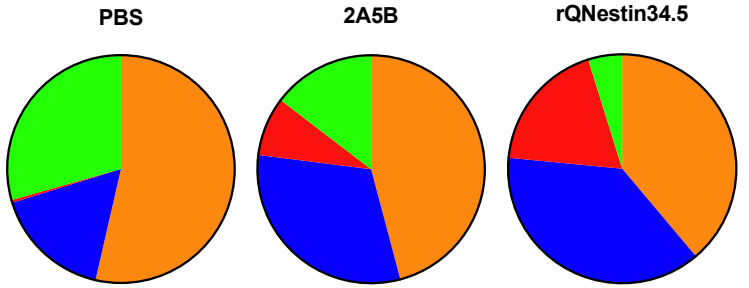

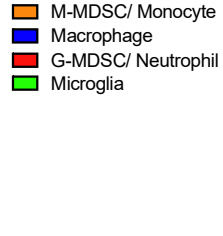

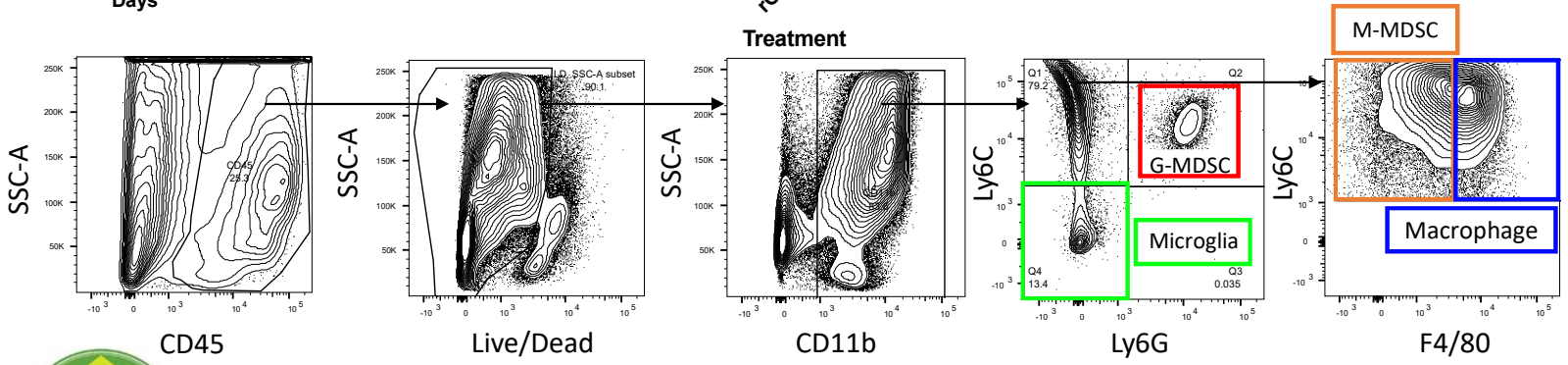

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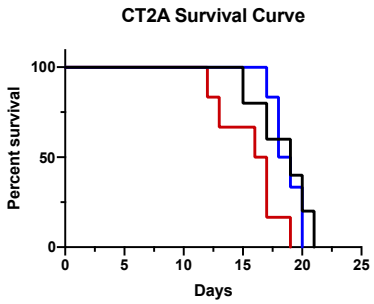

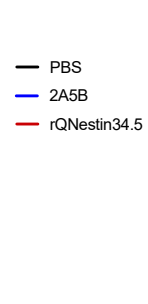

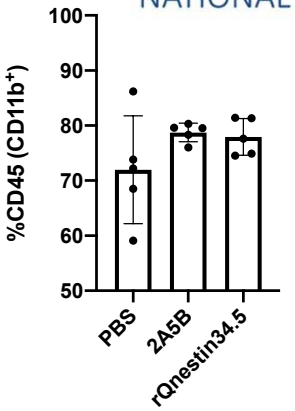

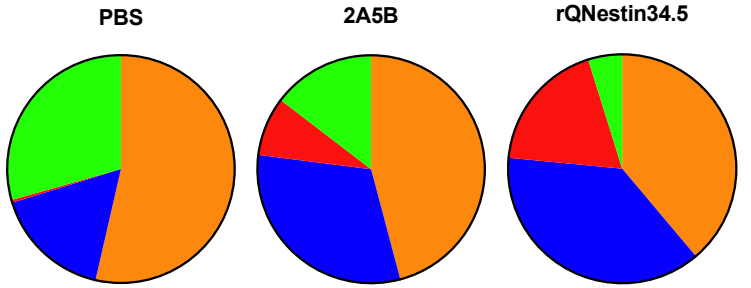

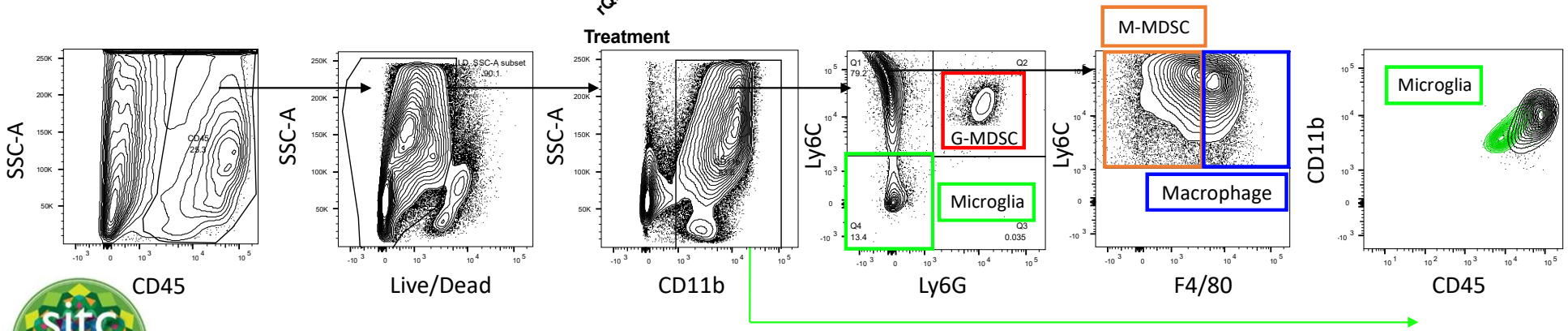

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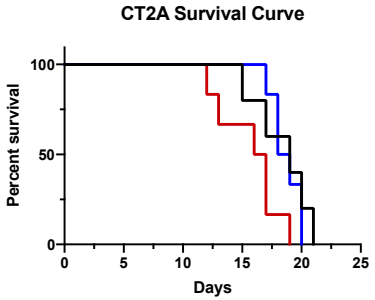
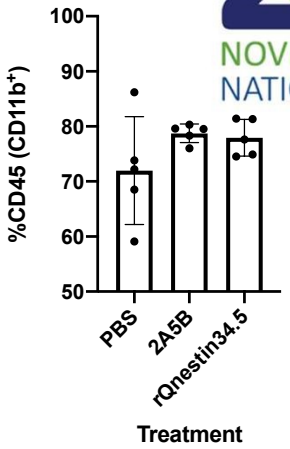
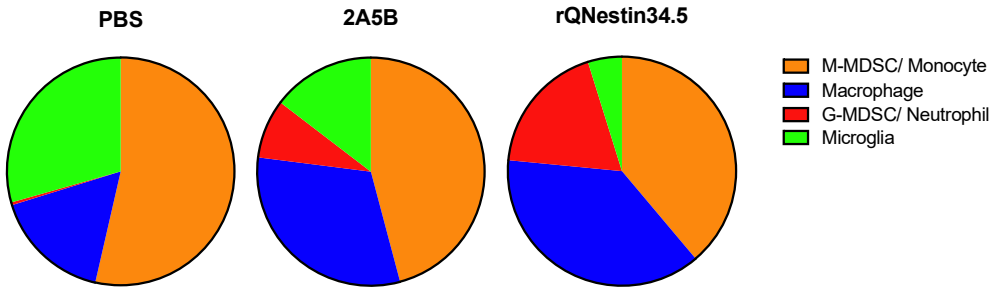
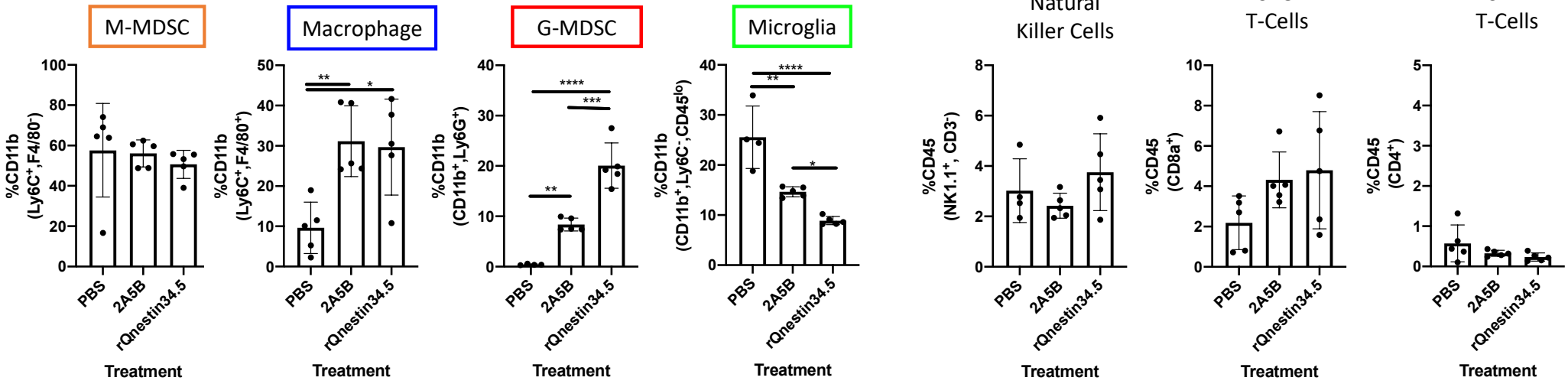




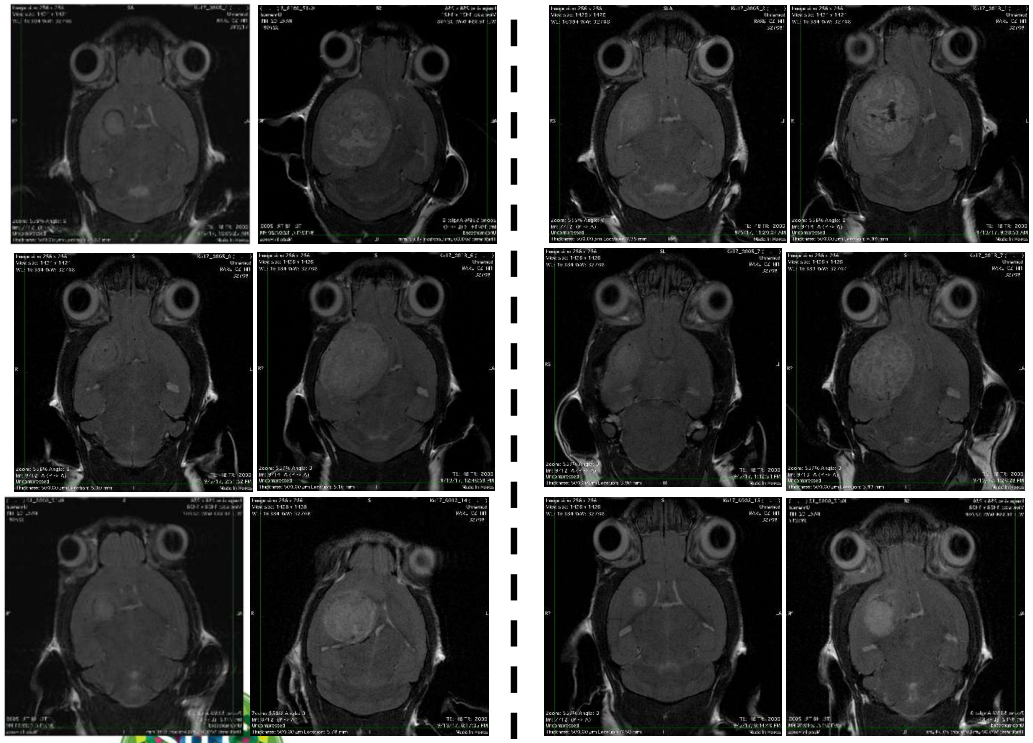




GL261N Analysis

Representative MRI images

d11 d19 d11 d19



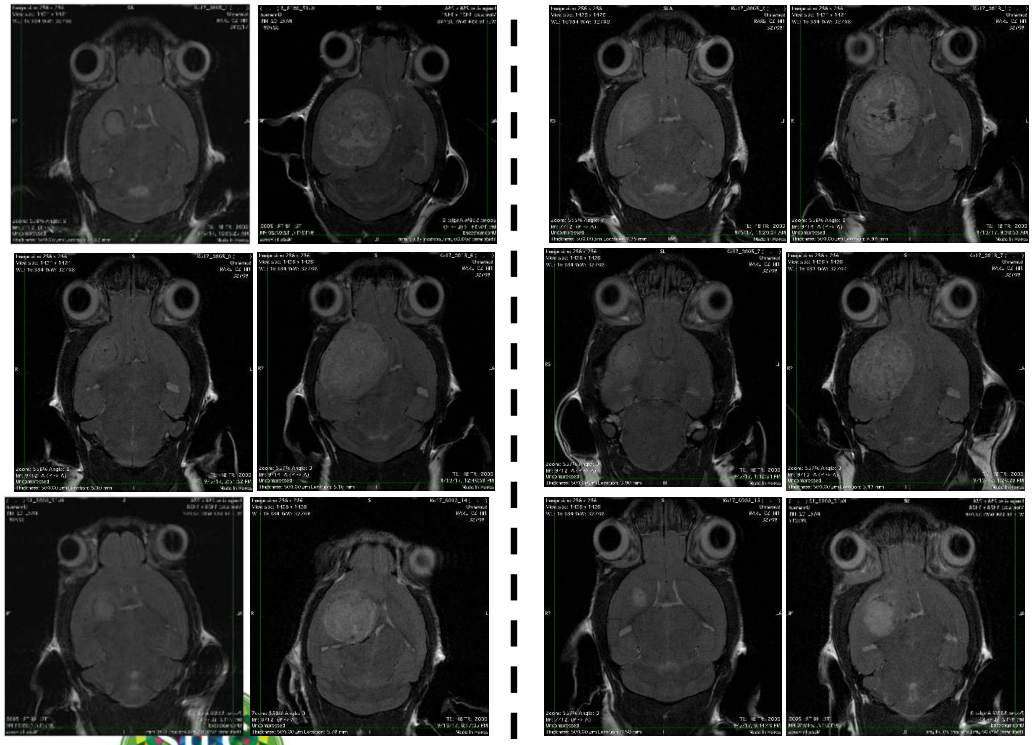
PBS

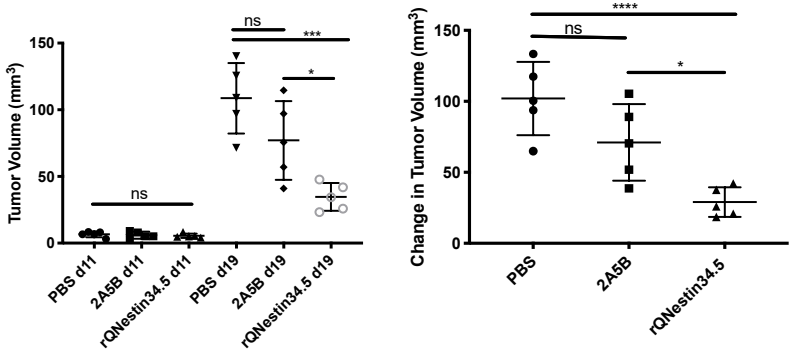
2A5B

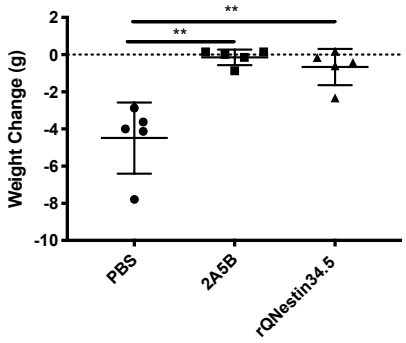
rQNestin 34.5

GL261N Analysis

Representative MRI images







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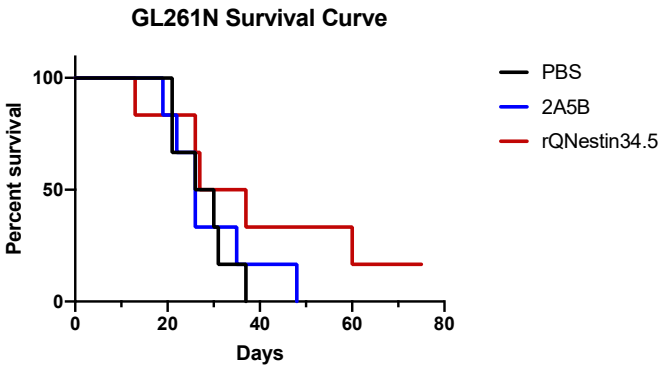

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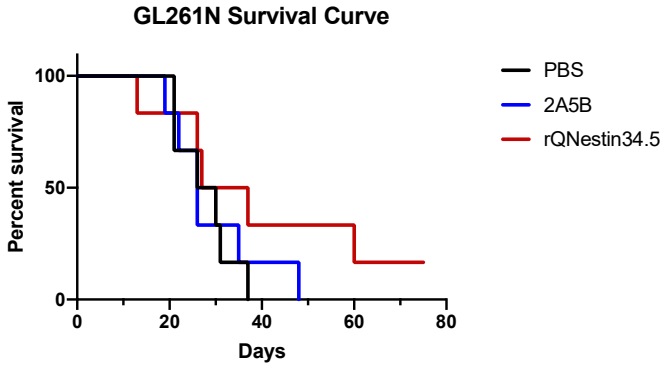

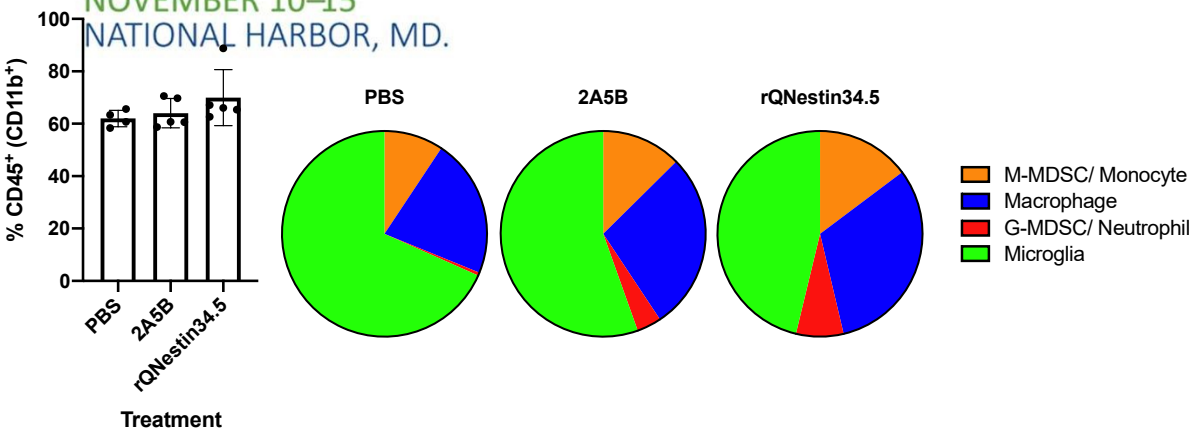

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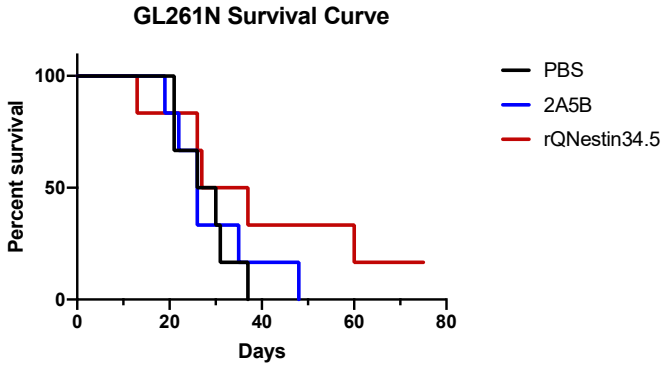
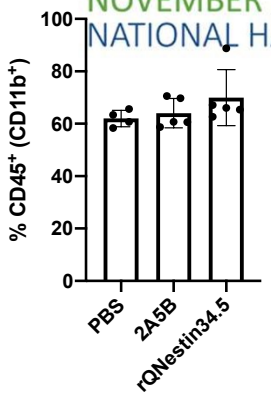
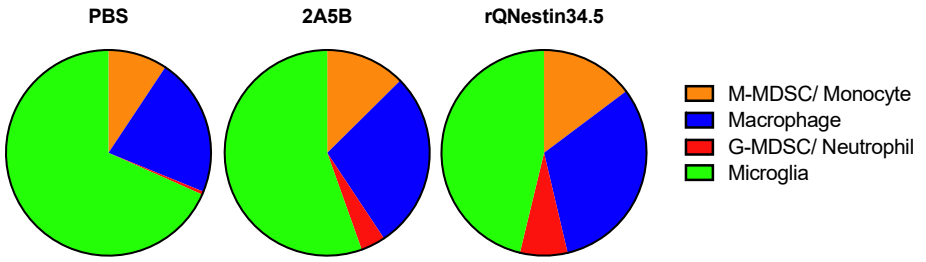
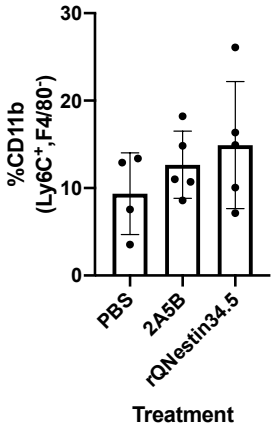


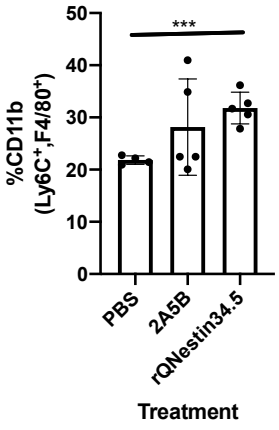




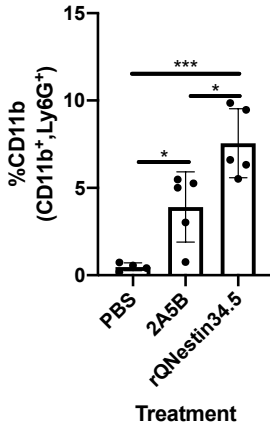
M-MDSC



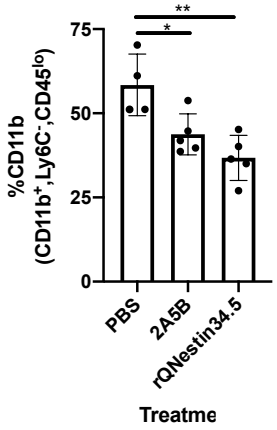
Macrophage



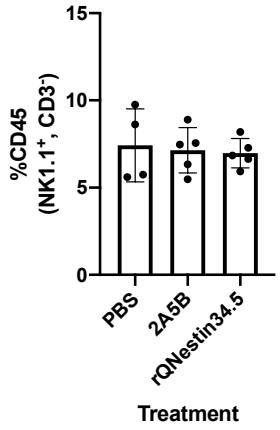
G-MDSC



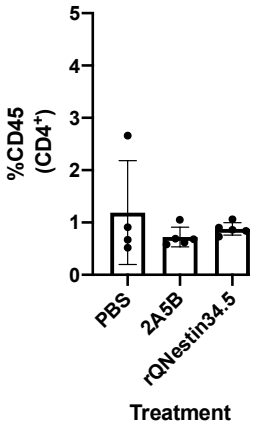
Microglia



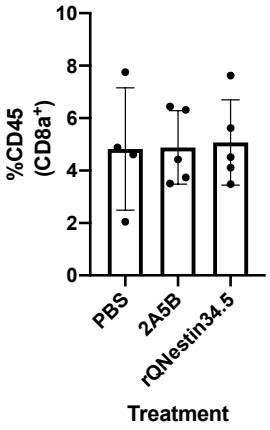
Natural Killer Cells



CD8 T-Cells

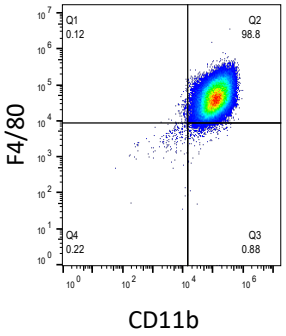


CD4 T-Cells



GL261N Analysis

Harvest Bone Marrow



Bone Marrow differentiation into Bone Marrow Derived Macrophages

Stimulated with supernatant from GL261N cells infected with:
2A5B
rQNestin34.5
uninfected

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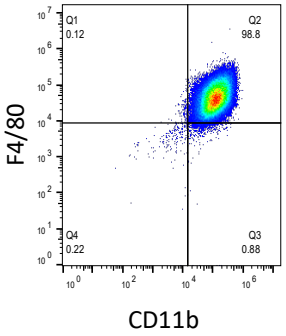

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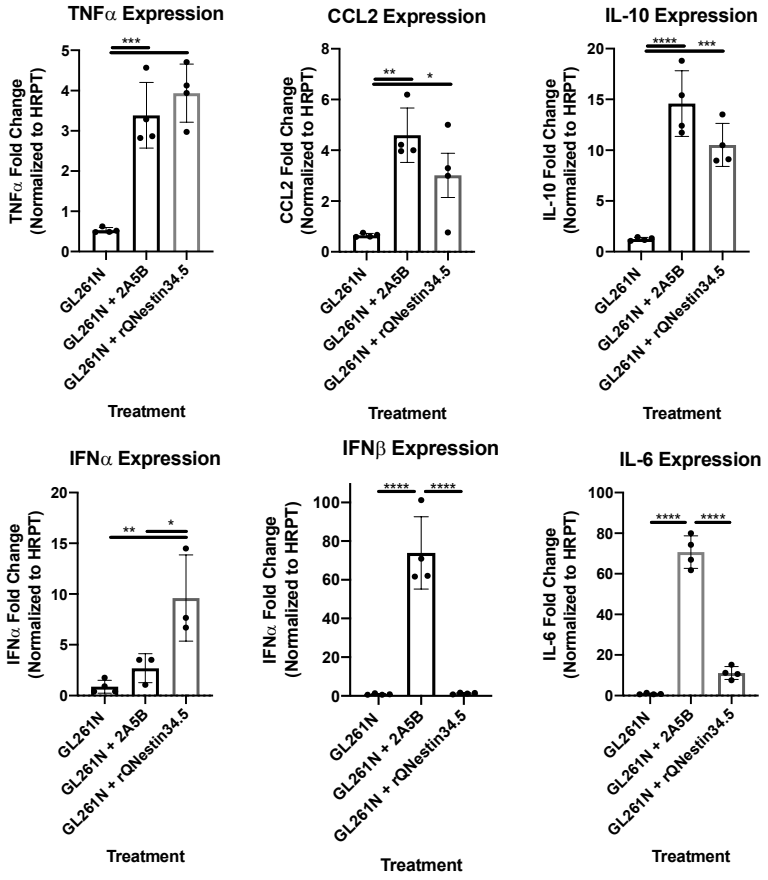
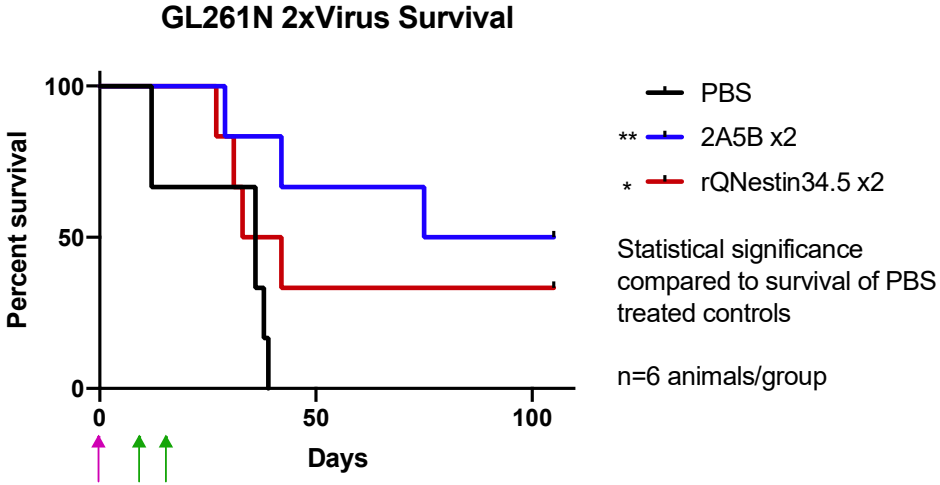
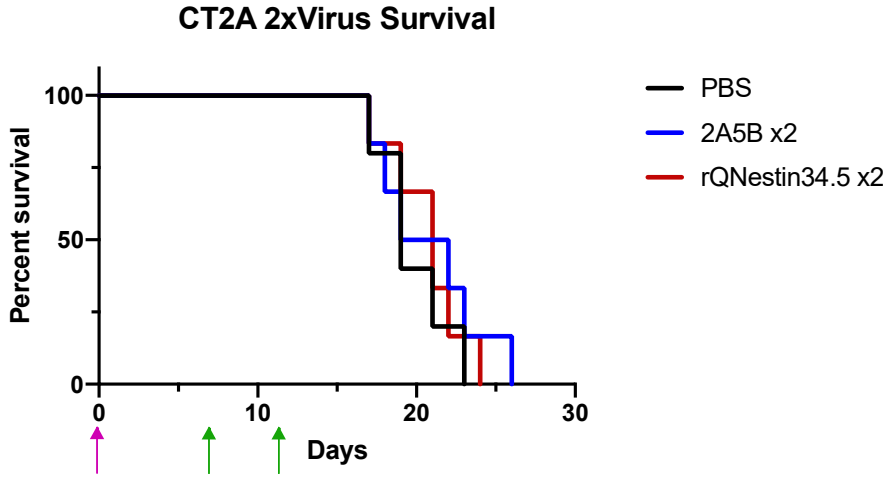


Multiple Injections



↑ = Tumor injection 10^5 GL261N cells/mouse

↑ = Virus injection $2x10^6$ PFU/mouse (D7/D11)



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Conclusions/Future Directions

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- Similar changes in the syngeneic CT2A and GL261N tumor microenvironment (TME) with a significant macrophage and neutrophil influx at 2 days post virus treatment
- rQNestin34.5: reduced GL261N tumor growth and enhanced GL261N survival, no effect on CT2A tumor survival
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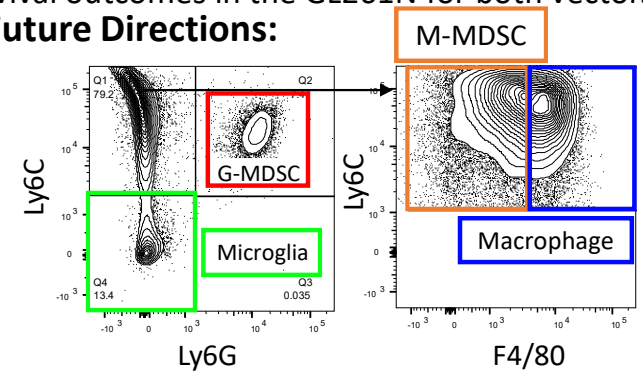

- RNA seq on sorted populations
- Later time points post virus infection for TME analysis
- Repeat *in vivo* growth curve with GL261N

Acknowledgements

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