Testing the efficacy of Sindbis Viruses in the treatment of malignant gliomas

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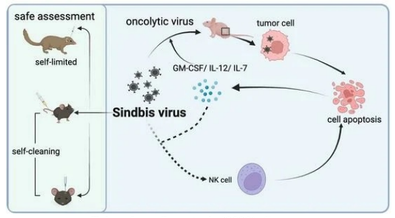
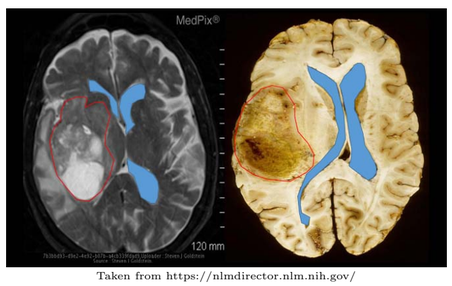
Background

- Gliomas are central nervous system tumors that have an aggressive growth pattern, making them insensitive to traditional treatment.
- Characteristics of gliomas, such as their resistance to drugs, have made patients likely to benefit from oncolytic therapy.
- Sindbis Viruses (SINVs) with a combination of cytokines are used to test oncolytic virus treatment.
- We are developing a model to quantitatively compare tumor growth patterns based on the oncolytic virus and cytokine combination injected.

Graphical Abstract



Taken from Sun et al. (2023) *Cancers*



Taken from https://nlmdirector.nlm.nih.gov/

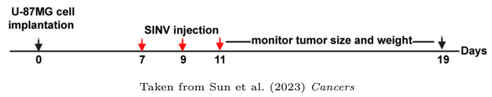
Glioblastoma

- Glioblastoma multiforme (GBM) is the most aggressive glioma currently known.
- It is difficult to treat via surgical resection
- GBM patients have a median overall survival (OS) of only 15 months
- The neurotoxicity caused by viruses during treatment is a significant obstacle for the oncolytic virus therapy of GBM

SINV Virus

- ▷ The sindbis virus (SINV) is a member of the genus Alphavirus in the family Togaviridae
- ▷ SINV is a positive single-stranded RNA virus that encodes four non-structural proteins (NSP1-4) and five structural proteins (C, E3, E2, 6K and E1)
- ▷ E2 glycoprotein is the virulence protein of the virus, and the amino acid mutation in E2 affects the neurotoxicity of the virus
- ▷ SINV is a blood-borne virus and can therefore reach most tissues of the body
- ▷ Many studies have shown that replicable SINV can effectively kill tumors like pancreatic, ovarian, and cervical cancers, but few studies focus on glioblastoma.

Experimental data



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Data Fitting process

This model evaluates SINV variants' effectiveness in controlling tumor growth and the impact of cytokine therapy.

1. We used an ordinary differential equation (ODE) model to describe the inhibition of tumor growth by oncolytic SINVs.
2. Model includes variables for uninfected and infected tumor cells, viral load, and cytokine concentration.
3. Data extracted from published tumor growth curves are used to estimate key parameters, including viral replication rate, tumor growth rate, and cytokine effects.
4. Parameter fitting is performed by minimizing the Sum of Squared Residuals (SSR) between model predictions and experimental data.
5. Error in the parameters is estimated through bootstrapping to find the best fit parameters with 95 percent confidence intervals.

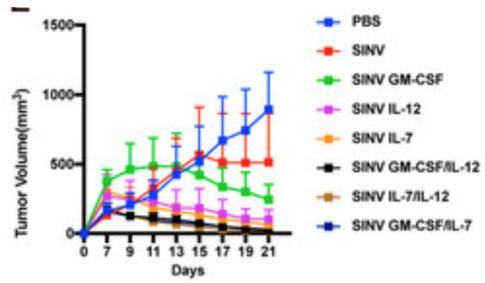
Tumor Growth Model

We fit the control (PBS) data using a tumor growth curve,

$$T(t) = T_0 e^{\lambda t},$$

to find the growth rate of the untreated tumor.

Volume-Time Plot of Tumor Growth



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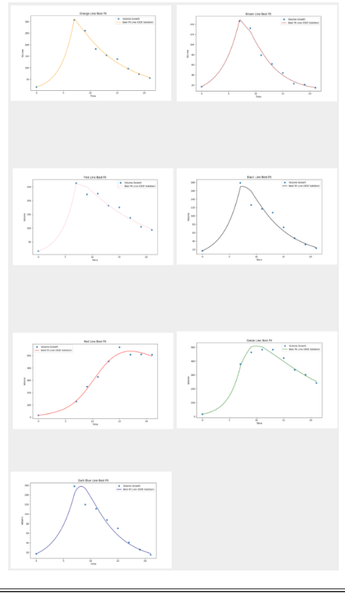
Mathematical Models

Mathematical model to characterize the effect of Sindbis virus as well as the effect of the different cytokines.

$$\begin{aligned} \frac{dT}{dt} &= \lambda T - \beta TV - kCT \\ \frac{dI}{dt} &= \beta TV - \delta I \\ \frac{dV}{dt} &= pI - cV \\ \frac{dC}{dt} &= V - \gamma C. \end{aligned} \tag{1}$$

- T represents uninfected tumor cells, that replicate at an exponential rate λ.
- The cells can be infected by virus, V , at infection rate β.
- The infected cells, I, produce the virus at rate p.
- The infected cells die at rate δ. The virus clears at rate c.
- Cytokines removes tumor cells at the rate k.
- Cytokins are cleared from the system at the rate γ.

Data Fitting



Conclusions

- This study provides a quantitative framework for evaluating the therapeutic effects of an oncolytic SINV combined with cytokines in glioma treatment.
- By providing parameter estimates for key biological processes, our model can help optimize treatment strategies and guide future experimental research in oncolytic virotherapy.