Characterization of oncolytic adenovirus ICVB-1042

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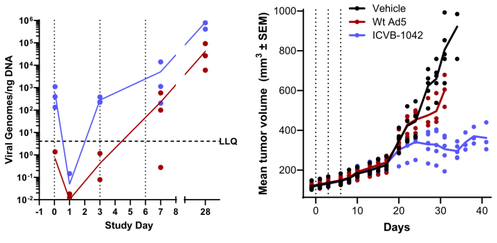
Background

- Oncolytic adenoviruses are promising cancer therapies because they can selectively infect and destroy tumor cells.
- Unfortunately, systemic delivery of the virus often leads to poor efficacy, so researchers have started to modify viruses to enhance their replication in cancer cells.
- We developed a model of tumor growth to compare viral treatment dynamics of a modified oncolytic adenovirus ICVB-1042 and a wild-type adenovirus type 5 (Wt Ad5).
- We found differences in the viral production rates and the clearance rates between the two viruses.

Experimental Data

We use data from an experiment using the two adenoviruses to treat human breast cancer (MDA-MB- 231) in mice. Virus was injected intravenously on days 0, 3, and 6. Measurements of viral load within the tumor and tumor volume were taken at various times after initiation of treatment.



Taken from Kato et al. (2024) Comm. Biol.

Mathematical Model

$$\frac{dT}{dt} = \lambda T - \beta TV - \gamma IT + \rho R$$
$$\frac{dR}{dt} = \gamma IT - \rho R$$
$$\frac{dI}{dt} = \beta TV - \delta I$$
$$\frac{dV}{dt} = pI - cV.$$

Here, uninfected tumor cells, T, replicate exponentially with growth rate λ. These cells can be infected by virus, V , at infection rate β. The cells then become infectious, I, and produce virus at production rate p. The infected cells die at rate δ and the virus is cleared at rate c. The presence of virus leads to the production of interferon (IFN), which causes cells to become resistant to infection, R, at rate γ. Resistance wanes at rate ρ.

Fitting the Model to Data

The Vehicle curve gives us the tumor growth equation:

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

where T_0 is the initial tumor volume.
After finding the tumor growth rate, we find the remaining model parameters by simulataneously viral titer, and treated tumor simultaneously for each viral strain by minimizing the Sum of Squared Residuals (SSR):

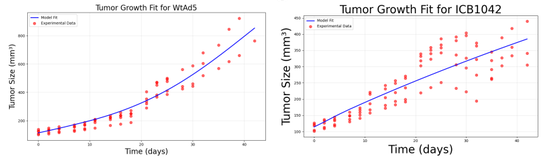
$$\mathrm{SSR} = \sum_{i=1}^{n} (y_i - f(t_i;\, \theta))^2$$

where y_i are the experimental data points, $f(t_i; \theta)$ are the model predictions, and θ is the set of parameters to estimate. Total tumor size is $T + I + R$.
Parameter uncertainty is estimated via bootstrapping, giving a distribution of values for each parameter and each viral strain.

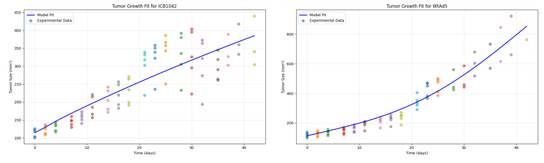
Best Model Fits

The model fits both the viral load and tumor data for both viral strains.

Tumor growth



Viral load

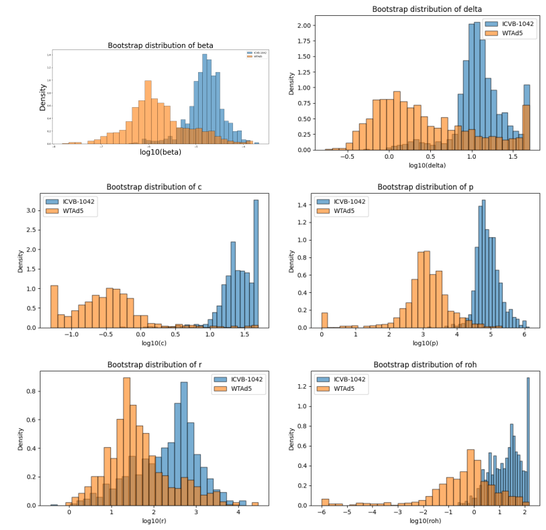


Best Fit Parameters

	Wt-AD5	ICVB-1042
β (/d)	7.95 (1.24–601)$\times 10^{-7}$	9.99 (0.0138–1.52)$\times 10^{-6}$
δ (/d)	3.01 (0.0173–50.0)	5.00 (0.170–29.53)
p (/d)	1.90 (1.02–5300)$\times 10^{3}$	8.89 (0.745–78.4)$\times 10^{4}$
c (/d)	0.160 (0.0554–50.0)	19.8 (0.0502–32.8)
γ (/d)	25.0 (0.197–645)	559 (0.147–10.1)
ρ (/d)	0.451 (1.00$\times 10^{-6}$–36.0)	82.1 (1.06$\times 10^{-6}$–17.1)

Comparing the viruses

We compare parameter values for the two viruses using the parameter distributions generated through bootstrapping.



Parameter distributions for c (viral clearance rate) and p (viral production rate) show the least amount of overlap.

Statistical tests for each parameter

- To compare the viral dynamics parameters between the two viruses, we used the Mann-Whitney U test, a non-parametric statistical test that compares two groups without assuming a normal distribution.
- For each parameter (β, δ, p, c, γ, ρ), we repeatedly drew random samples of 10 values from each virus's 1000 bootstrap runs and ran the test 100 times, averaging the resulting p-values.
- A mean p-value below 0.01 indicates a statistically significant difference between the two viruses for that parameter.

Parameter	p-value
β	0.0194
δ	0.0513
p	**0.0003**
c	**0.0004**
r	0.2079
ρ	0.0116

Conclusions

- The mathematical model successfully captured the tumor growth dynamics for both viral strains, as indicated by the close fit to experimental data.
- Because our p-values for p and c are less than 0.01, we can conclude that there is a statistically significant difference between the two viruses for those parameters.
- The higher production rate for ICVB-1042 is consistent with a virus that is more effective when delivered systemically.
- The parameters β, δ, and ρ had only a small overlap and a p value less than 0.05, suggesting possible differences in these two values between strains.
- The parameter γ did not show a statistically significant difference between the two viral strains, suggesting similar IFM-induced cellular resistance to infection.

Future directions

- Future work could incorporate more immune response dynamics into the mathematical model, as the interaction between the immune system and oncolytic viruses may play a significant role in tumor inhibition and could provide a more complete picture of treatment efficacy.
- Building on the parameter differences identified between the two viruses, future studies could use these findings to guide engineering of improved viral strains with optimized tumor growth inhibition properties.
- The model can be used to simulate different treatment regimens to optimize delivery of the virus.

SciCom Let's Talk Science

This project studies two viruses designed to fight cancer by infecting and killing tumor cells. Using data from mice with breast cancer, we compared a virus modified to improve effectiveness when delivered intravenously, ICVB-1042, to a standard adenovirus. We built a mathematical model to track how tumors grow and how each virus spreads, replicates, and is cleared by the body. By fitting the model to experimental data and running statistical tests, we found that the two viruses differ in several key behaviors, including how quickly they produce new virus and how fast they are removed. These differences may help guide the design of more effective cancer-fighting viruses.