A semi-mechanistic model to describe preclinical tumour viral dynamics of an oncolytic virus

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Introduction

Cancer is still one of the leading causes of death worldwide [1,2]. Oncolytic viruses (OVs) may be a good new therapeutic option due to their selective mode of action, i.e. they only productively replicate in tumour cells, causing their death. One OV currently investigated is a pseudotyped variant of the vesicular stomatitis virus carrying the lymphocytic choriomeningitis virus' glycoprotein GP (VSV-GP) [3]. To obtain more information on its dynamics in the tumour, VSV-GP was encoded with the gene for enzyme luciferase (VSV-GP-Luc) due to it being capable of producing bioluminescence signal [4].

Objectives

We aimed to describe the tumour viral dynamics of VSV-GP-Luc (and consequently its effects on tumour growth) using data from preclinical studies, by:

- Reviewing the literature and identifying semi-mechanistic models describing viral dynamics
- Re-estimating and comparing the literature models using the experimental mice data

Methods

Preclinical data

- Immune-competent BALB/c mice, implanted with the CT26.CL25-IFNAR KO, CT26-RIG-I KO or CT26-IFNAR KO tumour models (n=96 vehicle, n=168 OV-treated mice)
- VSV-GP-Luc dose: 0-10^9 $TCID_{50}$
- Administration route: IV, IVIT
- Available observations: TV (n=1980) & BL (n=1022)

Literature search

- Identify semi-mechanistic ODE models describing viral dynamics

Re-fitting

- NONMEM 7.4.3
- 1 tumour mm^3 = 10^5 tumour cells [5]
- 1 $TCID_{50}$ = 1 infectious virion

Compare & evaluate models

- GOF plots, VPC
- OFV, AIC

Figure 1. Methodology

$TCID_{50}$ is median tissue culture infectious dose, IV is intravenous, IVIT is combination of IV and intratumoural (IT), TV is tumour volume, BL is bioluminescence signal, AIC is Akaike-Information Criterion, OFV is objective function value, ODE are ordinary differential equations.

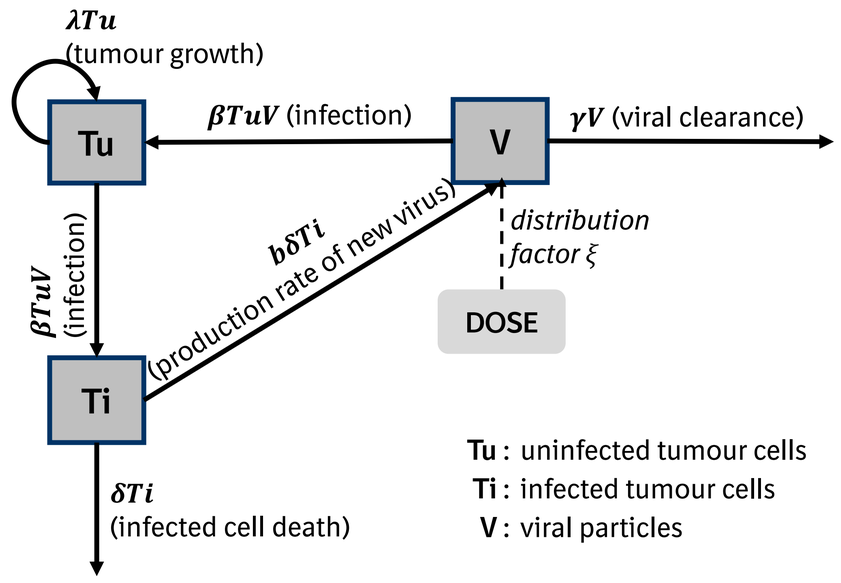

Figure 2. An example of the semi-mechanistic viral dynamics model [10]

Key findings & Conclusions

- The final model described the general trends in the VSV-GP-Luc preclinical tumour volume and bioluminescence data, however, there were still misspecifications, e.g. the OV effect on the tumour growth was overpredicted in the lower dose groups of the IV administration, and underpredicted for the highest dose of the IVIT administration.
- Collecting more informative data in the future might help addressing the misspecifications and making the model more suitable to support oncolytic virus drug development.

Results

- N=5 identified distinct literature models [6-11]
- Re-estimated semi-mechanistic models from Parra-Guillen *et al* [10] and from Phan and Tian [11], described the data best in terms of AIC. The model based on [10] was more stable and had fewer parameters → final

Table 1. Final model parameters

Model parameter	IV (mean, (RSE), [shr])	IVIT (mean, (RSE), [shr])
Baseline tumour volume: $Tu(0)$ [mm^3]	143 FIX*	143 FIX*
Infection rate: β [mm^3/day]	0.004 (56%)	0.006 (12%)
Tumour growth rate: λ [/day]	0.13 FIX*	0.13 FIX*
Infected cell death rate: δ [/day]	1.1 (17%)	1.3 (1%)
Burst size: b [$TCID_{50}$/cell]	3.0 (33%)	3.0 FIX
Viral clearance: γ [/day]	9.0 (14%)	12.3 (13%)
Unit conversion factor: Ξ	1.1 10^5 (8%)	7.3 10^4 (14%)
'Tumour bioavailability'# ξ	0.0002 FIX*	0.0002 FIX*
Background bioluminescence: Ξ_1 [ph/s/sr]	1114 FIX*	1114 FIX*
IIV on $Tu(0)$	170 (11%) [23%]	138 (6%) [4%]
Prop σ for BL data	1.2 (4%) [1%]	1.2 (5%) [0.2%]
Add σ for BL data [ph/s/sr]	10 (NA) [1%]	291 (53%) [0.2%]
Prop σ for TV data	0.4 (14%) [2%]	0.5 (3%) [1%]
Add σ for TV data [mm^3]	39 (158%) [2%]	90 (3%) [1%]

*obtained in R 3.5.3, #proportion of the IV dose reaching the tumour, BL bioluminescence, TV tumour volume, Prop is proportional, Add is additive, shr is shrinkage, IIV is interindividual variability. The IIV, σ and shrinkage are in SD units.

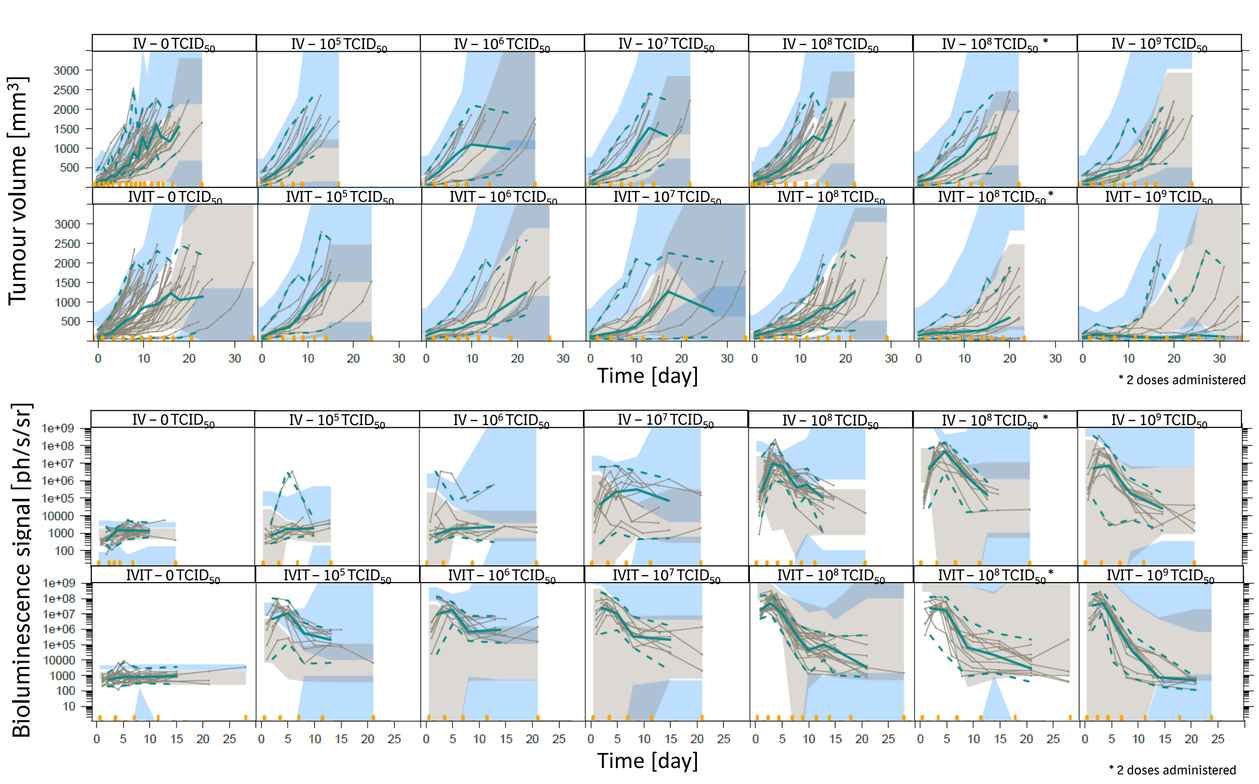

Figure 3. VPCs for tumour volume (above) and bioluminescence data (below).

Grey dots and lines are the observed data, green lines represent the 2.5th, 50th and 97.5th percentiles of the observed data and the areas are the corresponding 95% confidence intervals from 1,000 simulations using the final model estimates. Yellow ticks indicate bins.

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Presented at 31st PAGE meeting, A Coruña, Spain, June 2023

This preclinical study was funded by Boehringer Ingelheim. The authors were fully responsible for all poster content and editorial decisions and have approved the final poster version.

https://tinyurl.com/bdfkbx8n