

A semi-mechanistic model of preclinical VSV-GP(-Luc) viral dynamics in blood and tumour

Mohammed AA Saleh (1), Katja Fiedler (1), Andreas Ackermann (1), Richard Dambra (2, 3), Joseph Ashour (2), Philippe Slos (1), Eva Germovsek (1)*

(1) Boehringer Ingelheim Pharma GmbH Co. KG., Germany, (2) Boehringer Ingelheim Pharmaceuticals, Inc., USA, (3) Drexel University, USA, *eva.germovsek@boehringer-Ingelheim.com

Introduction

Despite recent advancements in cancer treatment, cancer remains a leading cause of death globally [1,2]. Oncolytic viruses offer a promising alternative with their unique mode of action. Namely, they primarily replicate in tumour cells and induce antitumour immune responses, causing tumour cell death [3]. One such oncolytic virus is VSV-GP, an RNA virus, based on the vesicular stomatitis virus. VSV-GP was encoded with the gene for luciferase (VSV-GP-Luc), which produces replication-driven bioluminescence, to characterise longitudinal tumour viral dynamics [4].

Methods

Preclinical data

- Immunocompetent BALB/c mice, healthy or implanted with the CT26.CL25-IFNAR1 KO tumour cell line (n=256 vehicle, n=804 treated mice)
- VSV-GP(-Luc) dose: 10^5 - 10^9 TCID₅₀
- Administration routes: IV (n=660 mice), IT (n=35), IVIT (n=365)
- Observations*: tumour volume (n=6737), bioluminescence signal (n=1141), viral load in blood and tumour as genome copies (n=589) and TCID₅₀ (n=108) concentrations

Model development + evaluation

- NONMEM® 7.5.1 (SAEM) was used
- Previous viral dynamics model [5] extended to include blood (central and peripheral) compartments and additional compartments for the inactive virus.
- Different parameterisations [6,7,8] of the model were (re)tested.
- Model evaluation and comparison: visual diagnostics, parameter precision, etc.

Figure 1. Methodology

TCID₅₀ is median tissue culture infectious dose, IV is intravenous, IT is intratumoural, IVIT is combination of IV and IT, SAEM is Markov Chain Monte Carlo stochastic approximation expectation maximisation method. R 4.3.1 was used for data preparation, visual exploration and reviewing of NONMEM® outputs; PsN 5.3.1 was used to execute NONMEM® runs and produce the visual predictive checks (VPCs). *BLG measurements were excluded (6% of post-administration observations).

Aims/Objectives

- To increase our understanding of the underlying pharmacology of VSV-GP, thereby facilitating the drug development.
- To describe the preclinical viral dynamics of VSV-GP(-Luc) in blood and tumour (following different administration routes), and its effects on tumour growth by extending our previous work [5].

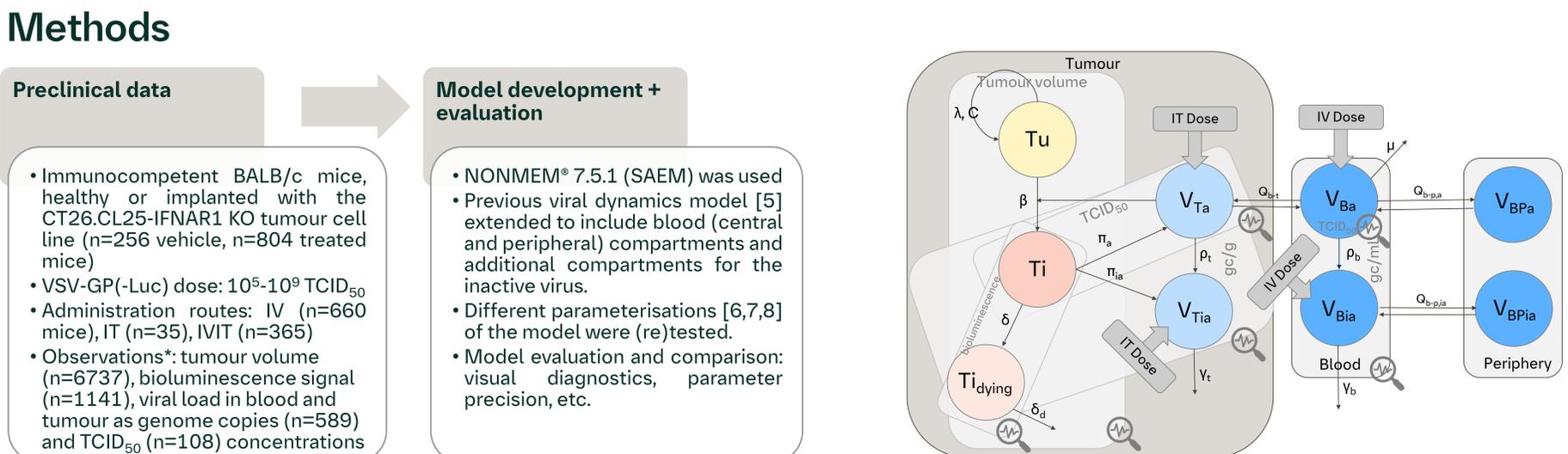


Figure 2. Semi-mechanistic viral dynamics model

T are tumour cells (u uninfected, i infected), V are viral particles, a is active virus, ia is inactive virus in either blood (B(i)a), tumour (T(i)a) or periphery (BP(i)a). For other explanations, see the rest of the poster.

Conclusions

A viral dynamics model was developed that allowed for a simultaneous analysis of the relationship between VSV-GP(-Luc) dose, viral replication / distribution dynamics and its effects on the tumour growth. Additionally, different markers of viral dynamics (such as, bioluminescence, TCID₅₀ and genome copies concentrations) were linked together in the model.

Although the model described the data adequately, some misspecifications remained.

The model could be further improved by, for example, including the role of the immune system and incorporating more IT data.

The developed model is a step towards the quantitative description of the complex behaviour of oncolytic viruses and may (once the translation from preclinical species to human has been accounted for) increase efficiency in future trial designs to maximise the benefit for cancer patients.

Results

- The viral dynamics model structure that provided the best fit was a combination of models [6,7], with one additional compartment for the dying infected tumour cells. Blood distribution was best described with one peripheral compartment (Figure 2).
- Rate constants from blood to tumour and reverse, and from periphery to blood were calibrated (reduced by 10^4) to better describe the difference between IV and IT administration types.
- Interindividual variability was included on 18 out of 25 model parameters. A combined proportional and additive residual error was estimated for all observation types, except tumour gc/g and tumour TCID₅₀/g (additive error).
- Viral clearance in blood was higher than in tumour (mean (RSE%) 9.4 mL/day (12.1%) and 2.5 nL/day (5.7%), respectively).
- The conversion factor between infected tumour cells (Ti) and bioluminescence signal was estimated as 877 (ph/s/sr)/cell (1.2%), and between Ti and TCID₅₀ amount it was fixed to 1732 TCID₅₀/cell.

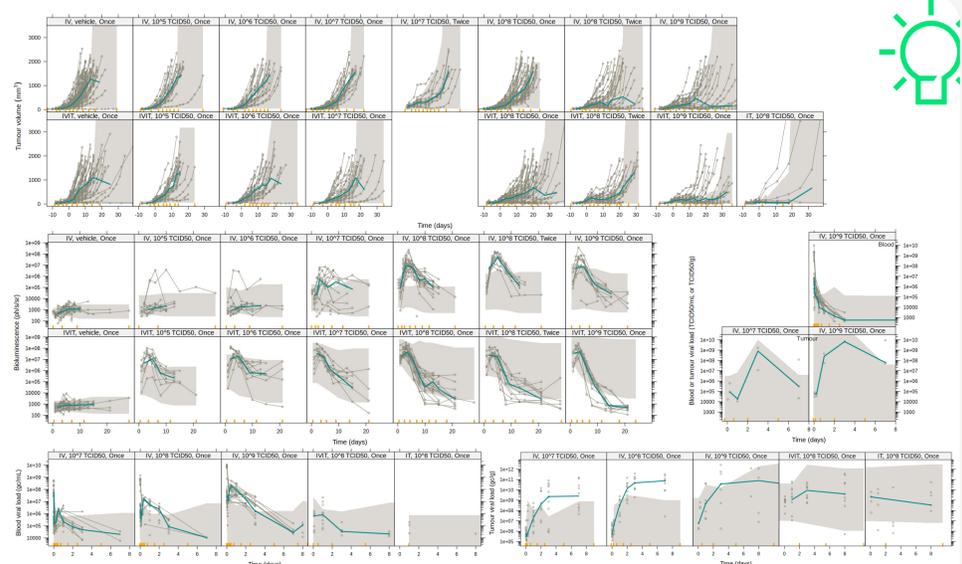


Figure 3. Visual predictive checks

Grey dots and lines are the observed data, green lines represent the median percentile of the observed data, and the areas are the corresponding 90% confidence intervals from 1,000 simulations using the final model estimates. Yellow ticks indicate bins. Time axis for tumour volume was limited to 39 days (0.2% of data omitted) and for blood viral load (TCID₅₀/mL) to 8 days (4.6% data omitted) for a clearer visual representation of the more relevant data.

References
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