

TUMOUR GROWTH MODELLING IN IMMUNOTHERAPY

Zinnia P Parra-Guillén⁽¹⁾, Pedro Berraondo⁽²⁾, Benjamin Ribba⁽³⁾, Iñaki F. Trocóniz⁽¹⁾

⁽¹⁾Department of Pharmacy and Pharmaceutical Technology, School of Pharmacy, University of Navarra (Spain)

⁽²⁾Division of Gene Therapy and Hepatology, Center for Applied Medical Research (CIMA), University of Navarra, Spain

⁽³⁾NUMED project-team, INRIA Grenoble-Rhône-Alpes, Montbonnot- Saint Ismier, France



Background

A vaccine vector that targets the human papillomavirus 16 E7 antigen to dendritic cells has shown potent immune response against a tumour cell lines expressing E7 antigen in a murine model of cervical carcinoma [1]. However a decrease in the response was observed as the time between tumour cell injection and vaccination increased [1].

Objective

The aim of the study is to develop a population model in mice able to describe tumour growth dynamics and the effect the vaccine on tumour size to better understand the mechanisms implied.

Animal experimentation

5x10⁵ tumour cells expressing HPV16-E7 proteins were injected into the shaved back of C57BL/6 mice in 200µL of PBS.

In two independent studies, a single dose of 50µg of vaccine or PBS (control group) was intra-peritoneally administered to mice on different days after tumour inoculation (day 4,7,11 and 25).

Tumour size, presented as the average of two perpendicular diameters (mm), was measured at regular intervals. Mice were euthanized if tumour size reached 20mm.

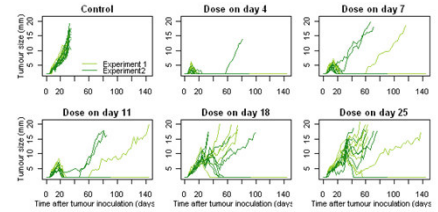


Figure 1. Raw data. Number of responder mice over the total number of mice and the percentage of cure is presented in the plot

Methodology

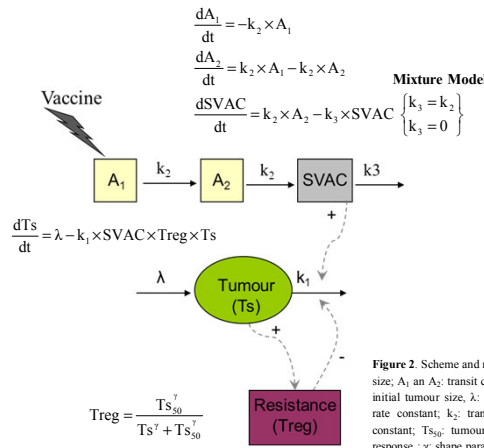
Model development

A step-wise approach was followed to develop a kinetic model considering the ensuing main aspects:

- A linear growth model successfully characterized tumour progression in control group (Base model).
- Drug effect was modelled assuming that the vaccine triggers a non-instantaneous immune response inducing cell death.
- Delayed response was described with a series of transit compartments.
- Mouse relapse was tackled considering a mixture model at the level of the vaccine elimination, assuming the not all the mice will be able to trigger a permanent immune response.
- Tolerance effect dependent upon tumour size was incorporated

M3 method [2] was used to account for the observations below the limit of quantification (LOQ), considering 2 mm as the lowest measurable value.

Berkeley-Madonna, R, NONMEM VII and PsN softwares were used to develop the model.



Model Evaluation

- Non parametric bootstrap was used to evaluate precision of parameter estimates.
- Goodness of fit plots and individual fits were represented.
- Visual Predictive Checks (VPCs) were performed by simulating 1000 individuals for each of the treatment groups included in the analysis. 5th, 50th and 95th percentiles were calculated and plotted against the observed data
- % of simulations above the LOQ were obtained and plotted against raw data, taking into account that mice were killed if tumour size reached 20 mm.
- 1000 thousand studies were simulated. The simulated probability of cure for each group was calculated and compared with the experimental one

Figure 2. Scheme and mathematical equations of the model. Ts: Tumour size; A₁ and A₂: transit compartments, SVAC: signal of the vaccine. Ts₀: initial tumour size; λ: tumour growth rate constant; k₁: vaccine killing rate constant; k₂: transit rate constant; k₃: vaccine elimination rate constant; Ts₅₀: tumour size able to inhibit the 50% of the vaccine response; γ: shape parameter.

Results

Table I: Base model parameter estimates

Parameter (units)	Estimate (5 th -95 th)
Ts ₀ (mm)	0.324 (0.117-0.550)
λ (mm/day)	0.354 (0.328-0.377)
IIV λ	10.1% (6.04%- 12.74)

Table II: Treatment model parameter estimates

Parameter (units)	Estimate (5 th -95 th)
k ₁ (au-mm/day)	0.885 (0.604 - 4.23)
k ₂ (1/day)	0.121 (0.100-0.157)
k _{3,1} (1/day)	0 FIX
k _{3,2} (1/day)	0.121 (0.100-0.157)
p(1)	0.844 FIX*
Ts ₅₀ (mm)	4.89 (1.773-5.937)
γ	3.66 (2.541-4.719)

* Parameter fit to a previous result obtained when analysing only groups of days 4,7 and 11, where no tolerance was observed.

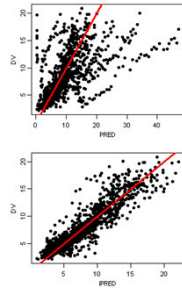


Figure 3. Observations (DV) versus population predictions (PRED) (top) or individual predictions (IPRED) (bottom) above LOQ are represented.

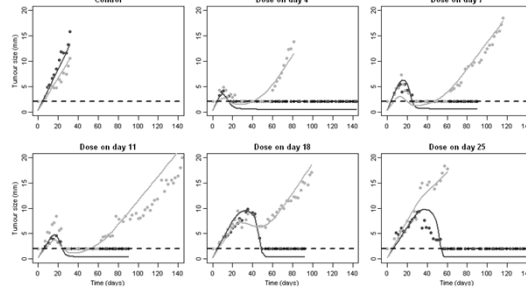


Figure 4. Individual predictions (lines) versus raw data (points) are represented for two individual for each group of treatment, one that respond (black) to the vaccine, and another one that does not (dark blue)

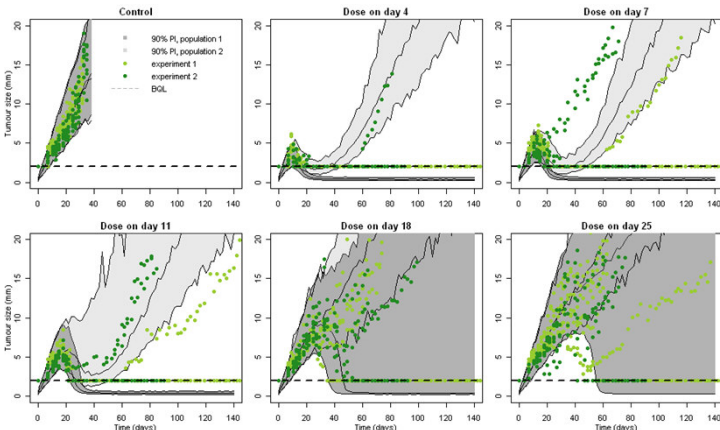


Figure 6. Visual Predictive Checks stratified by day of dose administration after tumour inoculation. Dark blue area represents the 90% prediction interval of subpopulation 1 (k₃=0) and light blue area the 90% prediction interval of subpopulation 2 (k₃=k₂). Black points represent raw data. Limit of quantification was considered to be 2 mm.

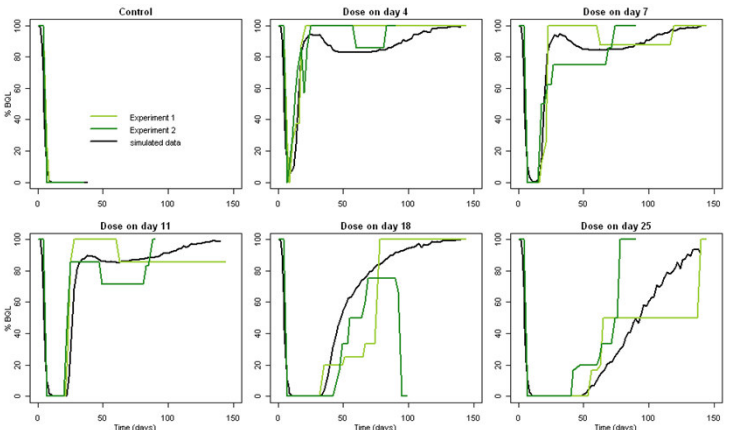


Figure 7. Percentage of data below quantification limit (BQL) stratified by day of dose administration after tumour inoculation and plotted against raw data, separated by group of experimentation.

Conclusions

A preliminary model that accounts for tumour growth, vaccine efficacy, possibility of relapse and a tolerance effect on the vaccine efficacy in two populations has been proposed to successfully describe tumour size under different vaccination protocols.

Data required of model complexities at both the typical/structural population, and the stochastic level.

Further improvements in the model are still needed to better characterize data variability.

References

- Berraondo P *et al.* Cancer Res 2007; 67: 8847-8855
- Carlsson KC. AAPS J 2009; 11: 148-154.
- Beal SL. J Pharmacokinet Pharmacodyn 2001; 28: 481-504.

Acknowledgement

This work was supported by a pre-doctoral fellowship from the Spanish Government, Ministry of Education and from Institut National de Recherche en Informatique et Automatique