A Model Based Approach for Translation in Oncology - From Xenografts to RECIST
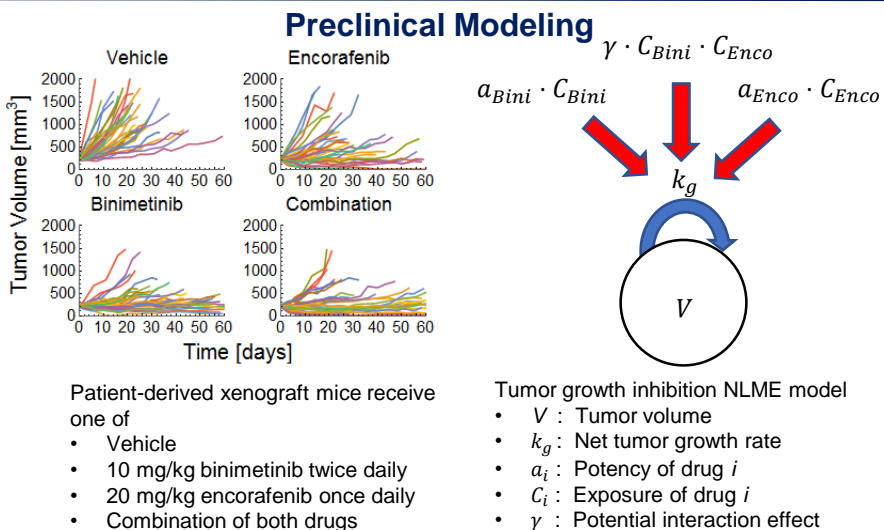
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Introduction

A major problem in drug development is translating results from preclinical studies to the clinical setting. Therefore, we evaluate the translational potential of semi-mechanistic tumor models (based on xenograft data) to predict clinical oncology results (RECIST data). Two commonly used translational methods are evaluated: (1) replacement with human PK, and (2) allometric scaling of PD parameters. We then compute optimal scaling coefficients given the observed clinical data and relate them to the standard allometric exponents in method (2). The analysis is performed for three drug combinations: binimetinib/encorafenib (shown below), binimetinib/ribociclib, and cetuximab/encorafenib.

Preclinical Modeling

Patient-derived xenograft mice receive one of
- Vehicle
- 10 mg/kg binimetinib twice daily
- 20 mg/kg encorafenib once daily
- Combination of both drugs

Tumor growth inhibition NLME model
- V : Tumor volume
- k_g : Net tumor growth rate
- a_i : Potency of drug i
- C_i : Exposure of drug i
- γ : Potential interaction effect

Translational Methods

We evaluate two translational methods by applying them to the NLME model.
θ_r denotes pharmacodynamic rate parameters (k_g, a_i, γ).

(1) Replacement of mouse with human exposure

(2) Step 1 and $\theta^i_{r,\text{Human}} = \theta^i_{r,\text{Mouse}} \left(\frac{\text{BW}_{\text{Mouse}}}{\text{BW}_{\text{Human}}}\right)^{-0.25}$

We also investigate if we can find optimal allometric exponents, ρ, by minimizing the sum of square of the model predictions and clinical data.

(3) Step 1 and $\theta^i_{r,\text{Human}} = \theta^i_{r,\text{Mouse}} \left(\frac{\text{BW}_{\text{Mouse}}}{\text{BW}_{\text{Human}}}\right)^{\rho^i}$

Clinical Predictions

Clinical predictions the made using the following bootstrap method:

- Use translated preclinical models to simulate 1000 studies of the same design as the clinical data
- Categorize the individuals in each simulated study according to the RECIST criteria
- Compute mean values and 95% CI for each RECIST category

Comparison of clinical predictions with data for Encorafenib/Binimetinib. Green/red indicates whether clinical data are inside predicted 95% CIs.

	Clinical	Method 1	Method 2	Method 3
Encorafenib				
CR/PR [3]	51 %	76 (71-82) %	36 (29-43) %	30 (23-37) %
CR/PR+SD [3]	84 %	82 (76-86) %	82 (77-88) %	84 (78-88) %
Binimetinib				
CR/PR [4]	23 %	20 (9-40) %	11 (3-26) %	11 (3-26) %
CR/PR+SD [4]	60 %	29 (14-46) %	49 (31-66) %	60 (46-83) %
Encorafenib + Binimetinib				
CR/PR [3]	63 %	96 (92-97) %	77 (71-83) %	63 (55-70) %
CR/PR+SD [3]	92 %	97 (93-99) %	96 (92-98) %	95 (92-98) %

RECIST Categories: Complete Response (CR), Partial Response (PR), Stable Disease (SD)
95% Confidence intervals in parentheses

Method 1: Predicted clinical efficacy largely overestimated

Method 2: Predictions closer to the clinical data. Combination still overestimated

Method 3: Almost all predictions are adequate compared to the clinical data

- Similar predictions were observed for binimetinib/robiciclib and cetuximab/encorafenib

- Optimal exponents using method 3 were close to but somewhat larger in general than -0.25

Conclusions

- Clinical efficacy of drug combinations overestimated using translational methods 1 and 2

- Good predictions using method 3 indicates translational potential even for simple tumor models

- The optimal exponents were in general larger (absolute value) than the standard exponent

- To propose a more generally applicable exponent, potentially drug/cancer type specific, more drug combinations have to be analyzed

Acknowledgements

References

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