

Mechanistic modelling of CAR T-cell therapy for multiple myeloma to assess multi-antigen targeting and identify factors associated with response.

Vicky Kostiou, PhD^{1*}; Eric Jurgens, MD^{2*}; Viji Chelliah, PhD¹; Piet H. van der Graaf, PharmD, PhD^{1,3,4}; Andrzej M. Kierzek, PhD¹; Ross S. Firestone, MD²; Kevin Miller, MD²; Bruno Almeida Costa, MD²; Sridevi Rajeeve, MD²; Alexander M. Lesokhin, MD²; Neha Korde, MD²; Carlyn R. Tan, MD²; Hamza Hashmi, MD²; Hani Hassoun, MD²; Kylee Maclachlan, MBBCh, PhD²; Urvi A. Shah, MD²; Malin Hultcrantz, MD, PhD²; Issam Hamadeh, PharmD²; Sergio A. Giralto, MD²; David J. Chung, MD, PhD²; Heather J. Landau, MD²; Michael Scordo, MD²; Gunjan Shah, MD²; Saad Z. Usmani, MD²; Sham Mailankody, MBBS²

¹ Certara, Sheffield, UK, affiliation 2, ² Memorial Sloan Kettering Cancer Center, New York, USA, ³ Systems Pharmacology and Pharmacy, LACDR, Leiden University, The Netherlands, ⁴ Cincinnati Children's Hospital Medical Center, USA

*equal contribution



- We developed a QSP model of CAR T-cell therapy for multiple myeloma that accounts for both BCMA and GPRC5D targeting CAR T-cell products, allowing the exploration of both mono- and combination therapies.
- Our model identified factors (high tumour proliferation, low antigen expression, and low CAR T-cell kill rate) associated with worse outcomes.
- Model predictions suggest that GPRC5D-targeted CAR T-cell therapy is more sensitive to antigen escape compared to BCMA-targeted CAR T-cell therapy.

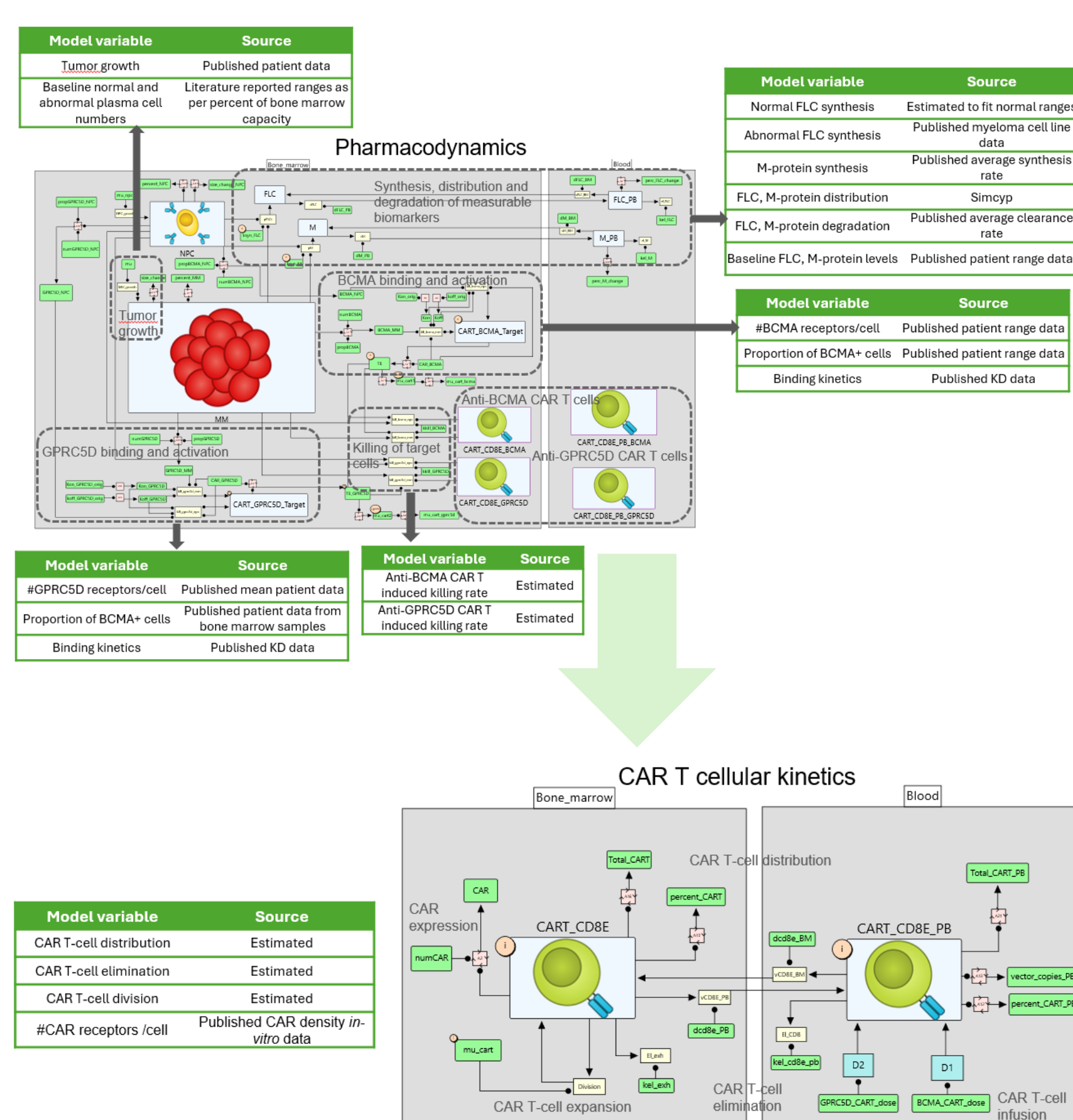


Background and Objective

Despite promising outcomes in CAR T-cell therapy for relapsed/refractory multiple myeloma (RRMM), nearly all patients eventually relapse. Resistance and relapse may be driven by CAR T-cell and tumour intrinsic factors. Several strategies are currently being investigated to improve response durability, with multi-antigen targeting being a promising area of clinical research.

Objective: A mechanistic Quantitative Systems Pharmacology (QSP) model of multiple myeloma growth and CAR T-cell therapy using measurable biomarkers was developed to evaluate anti-BCMA and anti-GPRC5D CAR T-cell therapies, to assess combination treatment approaches and identify patient-specific factors associated with response and relapse.

Figure 1: QSP model overview. Two-compartmental model, describing tumour growth and CAR T cell dynamics and activity.



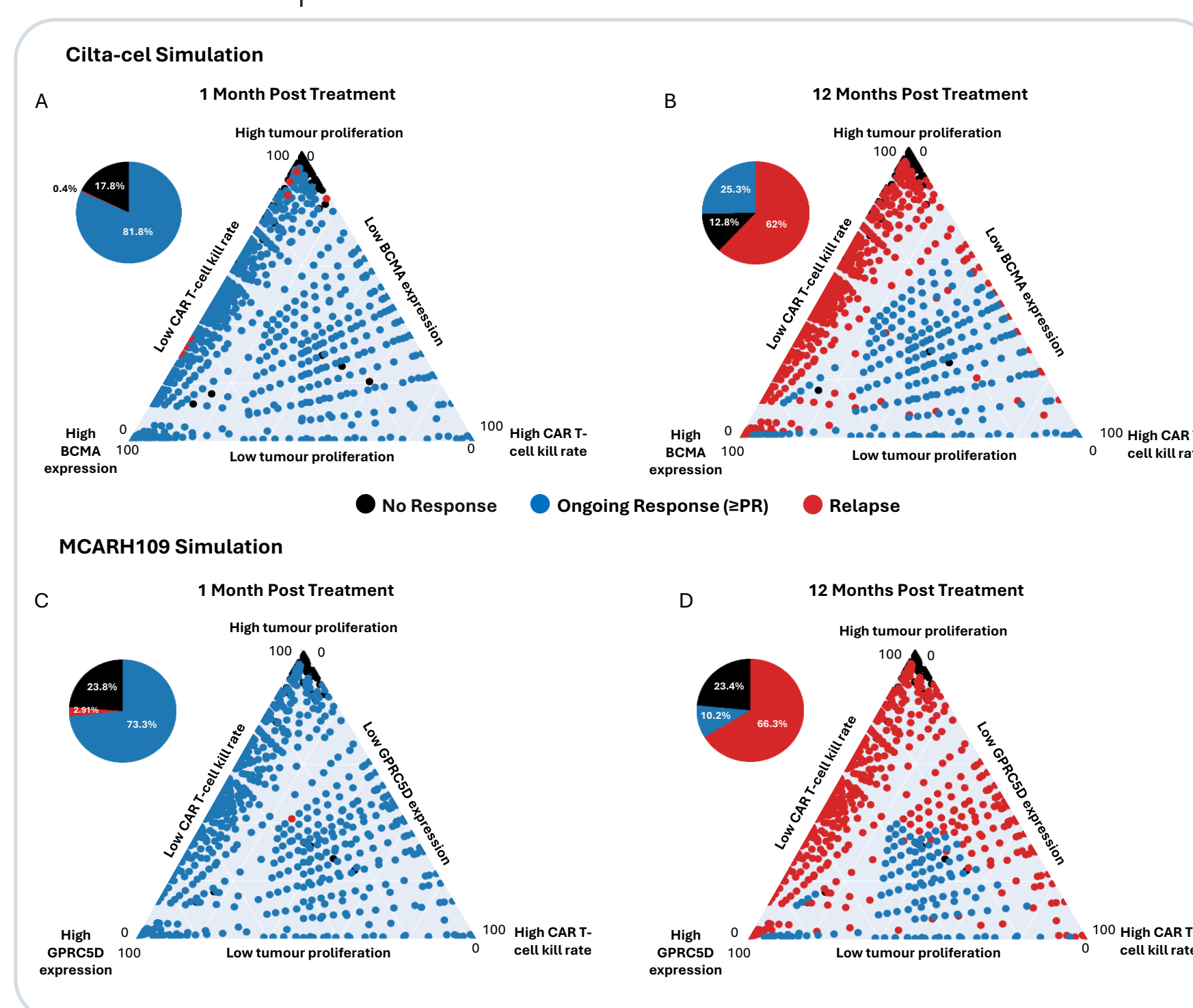
Key components and processes modelled:

- Includes essential cell-types and biomarkers needed to reproduce clinical outcomes
 - sFLC, M-protein
 - Normal and abnormal (myeloma) plasma cells
 - BCMA and GPRC5D antigen expression
- Includes CAR T cell dynamics and activity
 - CAR T cell distribution
 - CAR T- target binding and activation
 - CAR T expansion through a certain number of division cycles
 - CAR T induced tumour and normal plasma cell killing
- Includes BCMA and GPRC5D-targeted CAR T products, allowing simulation of both mono- and combination therapies

Results

- Model calibration to published patient PK and biomarker response data (see Figure 3)
 - BCMA targeted
 - Idecabtagene vicleucel (ide-cel)¹
 - Ciltacabtagene autoleucel (cilta-cel)²
 - GPRCD targeted
 - MCARH109³
- Model validation to (see Figure 4) clinical biomarker data from real world RRMM patients treated with commercial cilta-cel or ide-cel.
- Model reproduced observed pharmacokinetic and response biomarker data from publicly available ide-cel, cilta-cel, and MCARH109 CAR T-cell therapy studies.
- The calibrated model recapitulated biomarker data from 41 RRMM patients treated with commercial cilta-cel or ide-cel).
- Virtual trial simulations exploring the impact of variable baseline disease and CAR T-cell characteristics on response predicted that worse outcome is associated with rapidly proliferating tumours, low antigen expression, and low CAR T-induced killing rate (see Figure 2).
- Model predictions comparing anti-BCMA and anti-GPRC5D CAR T-cell monotherapies suggested that GPRC5D-targeted treatment is more sensitive to GPRC5D antigen downregulation.

Figure 2: Response prediction parameters. Ternary plots illustrating clinical response variability across different normalized tumour proliferation rates. CAR T-cell kill rates and proportion of antigen expressing cells for simulated patients (represented by individual dots) treated with (A, B) cilta-cel and (C, D) MCARH109 at 1 month and 12 months post treatment.



Discussion

- Our QSP model of CAR T-cell therapy for RRMM identified key factors associated with poor outcomes, including high tumour proliferation, low antigen expression, and a low CAR T-cell kill rate.
- The model predicted that GPRC5D-targeted CAR T-cell therapy is more sensitive to antigen escape to BCMA-targeted therapy.
- This modelling framework can be used to investigate mechanisms of response and relapse, as well as to explore strategies for multi-agent targeting.

Additional figures

Figure 3: QSP Model calibration outputs to publicly available clinical datasets. Model calibrated to published patient responses (black bars) after treatment with ide-cel as reflected by change in (A) serum free light chains and (B) M protein from pre-treatment baseline. Simulated virtual patient cohort (VPop) with response rates similar to response rates published for (C) cilta-cel and (D) MCARH109. Model calibrated to CAR T-cell expansion after treatment with (E) ide-cel, (F) cilta-cel, and (G) MCARH109.

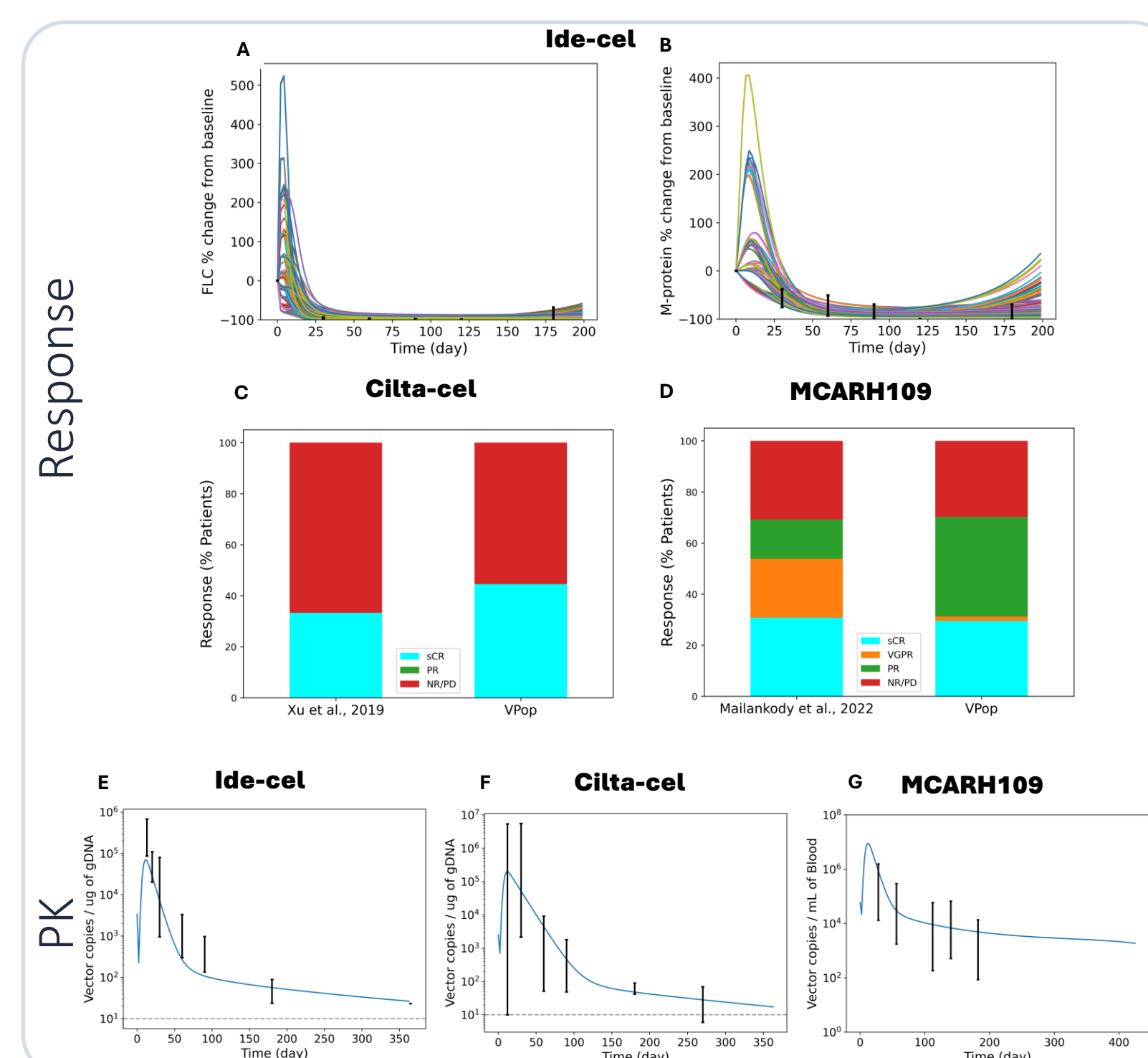
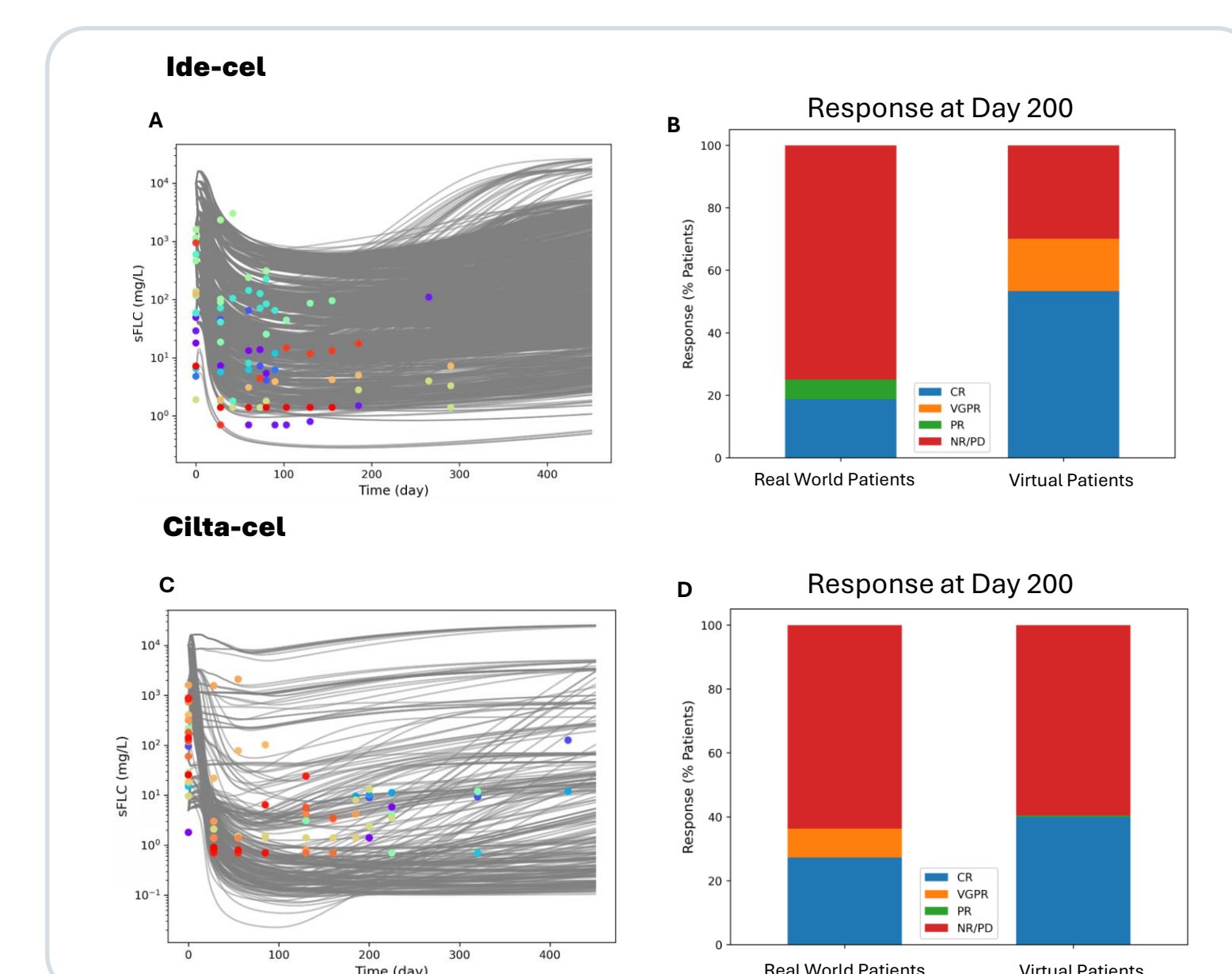


Figure 4: Clinical Validation of QSP Model in Real World Patients. Serum FLCs from real world patients (represented by coloured dots) treated with (A) ide-cel (n=19) and (C) cilta-cel (n=22) overlaid on virtual patient simulations with different input parameters (i.e. baseline FLC, M spike, tumour burden, CAR T-cell expansion). Real world response rates at Day 200 for (B) ide-cel and (D) cilta-cel compared to virtual patient response rates simulated with input parameters from real world patients.



References

1. Rajeev N et al. New England journal of medicine. 2019 May 2;380(18):1726-1737.
2. Xu J et al. Proceedings of the National Academy of Sciences of the United States of America. 2019 May 7;116(19):9543-9551.
3. Mailankody S et al. New England journal of medicine. 2022 Sep 29;387(13):1196-206.



Want to learn more?
 << Scan Here