Dual-Antigen CAR T-Cell Therapy

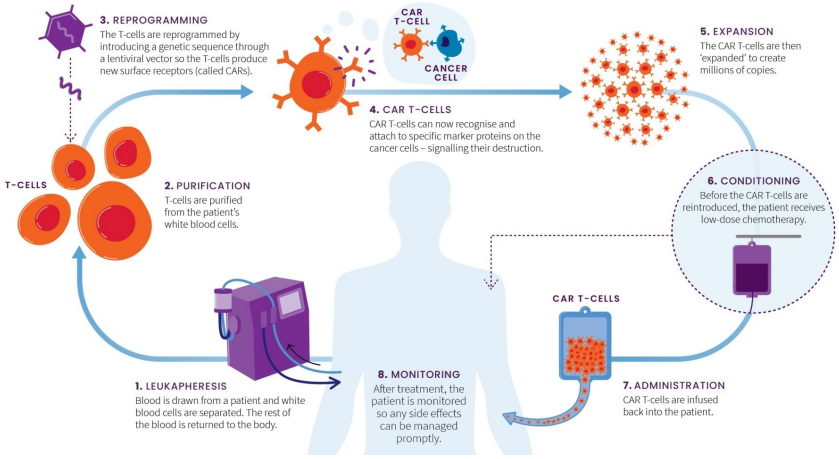
Selecting a manufacturing strategy that maximises tumour clearance under patient, tumour, and product variability

BACKGROUND

CAR T-cell therapy is modelled as two interacting cell populations. *Effector* cells are patient T cells modified ex vivo to express a chimeric antigen receptor (CAR), a surface protein that binds a designated target antigen. *Target* cells are tumour cells that express that antigen at varying levels. After infusion, contact between an effector and a target via CAR–antigen binding triggers killing of the target with some probability and may stimulate the effector to divide. The two populations evolve concurrently: effectors expand, accumulate exhaustion, and apoptose (die); targets deplete via successful kills. The population of CAR-T cells begins with heterogeneous characteristics, but as cells apoptose we see cell diversity diminish with characteristics inherited parent-to-daughter through division.

Approved single-antigen CAR T-cell products treat certain lymphomas, B-cell leukaemias, and myeloma (Majzner and Mackall 2019). The next generation of CAR T-cell products aims to broaden therapeutic reach by targeting multiple tumour antigens at once. Three manufacturing strategies for delivering dual coverage are described in the modelling and clinical literature (Bodnar et al. 2025; Li et al. 2026): two separate single-CAR products co-infused (`2s`), a single dual-CAR transgene expressed by every infused cell (`dCAR`), and a two-vector mixed product containing single-CAR and dual-CAR cells in tandem (`2v`). Each route is a different design decision that propagates through manufacturing complexity, expansion kinetics, and the in vivo behaviour of the infused population.

Comparing the three strategies experimentally would require expensive and time-consuming laboratory or clinical trials. Virtual-patient simulations allow comparisons across a distribution of patient, tumour, and product variability before manufacturing investment is committed. Determining which strategy is most effective will directly support the Malaghan CAR T-cell research programme's goals of improving the safety and effectiveness of CAR T-cell therapy.

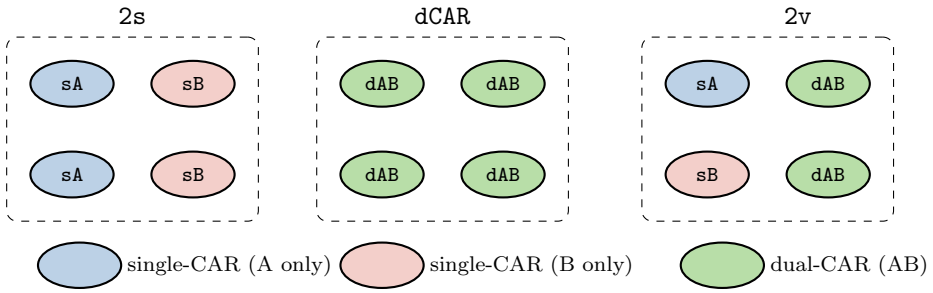


CAR T-cell manufacture and treatment workflow, from leukapheresis through ex vivo reprogramming, expansion, and reinfusion (Malaghan Institute).

OBJECTIVES

We aim to develop a stochastic agent-based model, embedded in a Monte Carlo virtual-patient framework, that allows the three dual-antigen manufacturing strategies to be compared on equal footing across a realistic distribution of patient, tumour, and product variability.

- Which manufacturing strategy maximises the probability of complete tumour clearance across realistic patient variability?
- How do antigen heterogeneity, infusion dose, and effector-pool composition interact to determine outcome?
- Is there a regime in which a mixed two-vector product (`2v`) outperforms both pure strategies, or is it strictly dominated?



The three competing manufacturing strategies and the resulting effector cell compositions infused into a virtual patient. `sA` and `sB` denote single-CAR cells targeting antigen A or B respectively; `dAB` denotes a dual-CAR cell carrying both receptors.

DATA

Calibration draws on published clinical and laboratory data:

- CAR-T expansion kinetics (fold-expansion, time-to-peak) from reported clinical studies.
- Antigen expression density distributions from tumour (flow-cytometry) data.
- Single-antigen efficacy data from approved-product trial reports.
- Tumour-burden distributions at therapy onset across reported trial cohorts.

REFERENCES

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