CAR-T PERSISTENCE MODELLING: BRIDGING BIOLOGY AND DATA

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Introduction

CAR-T kinetic models increasingly incorporate biologically structured components representing **differentiation, functional changes, and tissue distribution**. However, clinical datasets remain **sparse** and mostly limited to **peripheral readouts**, with limited characterisation of long-term persistence and phenotypic evolution.

Objectives

- Review biological determinants proposed to drive CAR T persistence
- Evaluate their implementation in published models
- Assess robustness of parameter estimation using typical adult clinical datasets

Materials & methods

Literature review of CAR T–specific and broader T cell biology to identify **determinants of CAR T persistence**. Published CAR T model-based analyses were reviewed to evaluate, for each determinant, **its structural implementation** and **the clinical data supporting its estimation**. Clinical data considered included qPCR/transgene, flow cytometry, immunophenotyping, cytokines, and tissue/bone marrow assessments.

Model complexity was then compared with available **data richness and resolution** to identify potential **non-identifiability**.

Results

Eleven candidate biological determinants were identified (Figure 1), of which six were implemented in published models (Table 1). Peripheral blood **qPCR/transgene data** consistently supported expansion–contraction dynamics and proliferation-related parameters.

Tumour burden, prior treatment lines, and CD4/CD8 composition were included as **covariates** but did not resolve internal cellular heterogeneity.

More complex biological mechanisms included:

- differentiation cascades (TSCM, TCM, TEM, TEFF)
- exhaustion states
- cytokine-mediated survival
- manufacturing-related effects

These models introduced latent compartments and subset-specific kinetic parameters. However, **longitudinal immunophenotyping and cytokine data** were often **sparse** or missing, limiting parameter identifiability from peripheral blood alone.

Anatomical extensions (e.g. bone marrow antigen source) further increased model complexity, often relying on **paediatric datasets**, **summary-level** parameters, and **non-verifiable structural assumptions**.

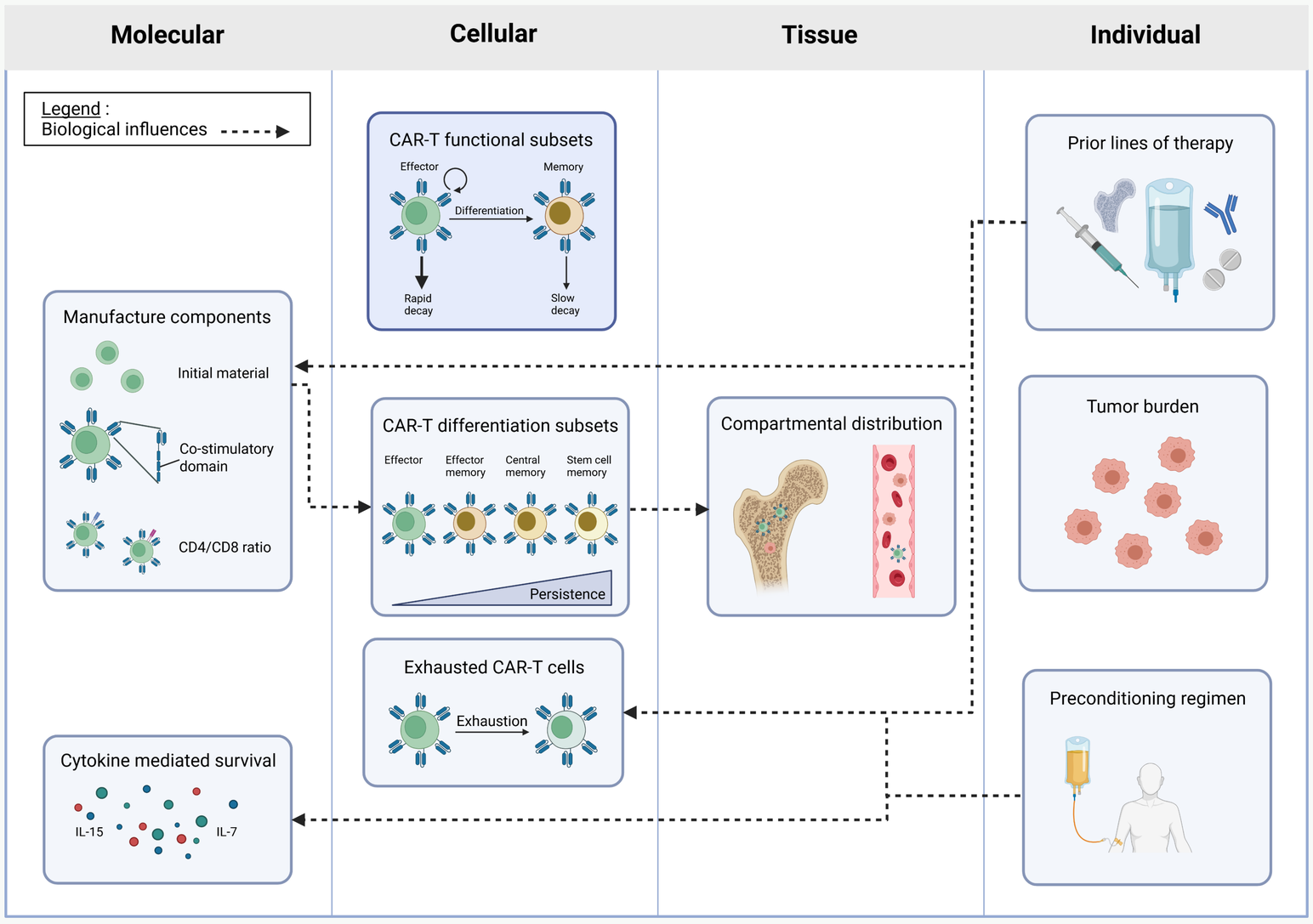

Figure 1 : Biological determinants of CAR-T cell persistence across biological levels

Biological determinant	Models	Data support	Modeling strategy
CAR-T functional subsets	13	Mostly global CAR-T qPCR/kinetic profiles; limited direct immunophenotypic measurements from flow cytometry	Effector–memory state structure
Tumor burden	7	Mixed clinical, imaging, and experimental tumor data; some inferred/system-level representations	Dynamic tumor burden; tumor-dependent CAR-T activation
CAR-T differentiation subsets	2	Flow cytometry-derived immunophenotypes; limited pediatric longitudinal data	TSCM-to-TEFF differentiation rates
CAR-T exhaustion	2	Primarily inferred; indirect validation	Effector exhaustion dynamics; tumor-driven exhaustion switch
Compartmental distribution	2	PB-to-BM transformed clinical data; pediatric literature-informed assumptions	BM-equivalent disease scaling; mechanistic marrow compartment
CD4/CD8 ratio	2	Flow cytometry-derived subset proportions; Data available for one product only	CD4/CD8 expansion covariate; subset-specific expansion kinetics

Table 1 : Current integration of biological determinants in CAR-T persistence models

Conclusion

Current adult datasets mainly support **simple CAR T persistence models** directly informed by peripheral blood data. More complex biological structures remain prone to **non-identifiability** without sufficiently granular longitudinal measurements.

Key unmet need:

- adult immunophenotyping
- bone marrow/tissue-level assessments

→ Required to support **richer CAR T persistence models**.

Reference : Barros et al. 2021. doi:10.3390/cancers13122941 ; Hardiansyah et al. 2019. doi:10.1002/psp4.12407 ; Kirouac et al. 2023. doi:10.1038/s41587-023-01687-x ; Liu et al. 2021. doi:10.1002/cpt.2040 ; Martínez-Rubio et al. 2021. doi:10.3390/ijms22126371 ; Mueller-Schoell et al. 2021. doi:10.3390/cancers13112782 ; Ogasawara et al. 2021. doi:10.1007/s40262-021-01039-5 ; Paixão et al. 2022. doi:10.3390/cancers14225576 ; Salem et al. 2023. doi:10.1002/psp4.13009 ; Singh et al. 2019. doi:10.1080/19420862.2019.1688616 ; Singh et al. 2021. doi:10.1002/psp4.12598 ; Stein et al. 2019. doi:10.1002/psp4.12388 ; Wu et al. 2022. doi:10.1111/cts.13421

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