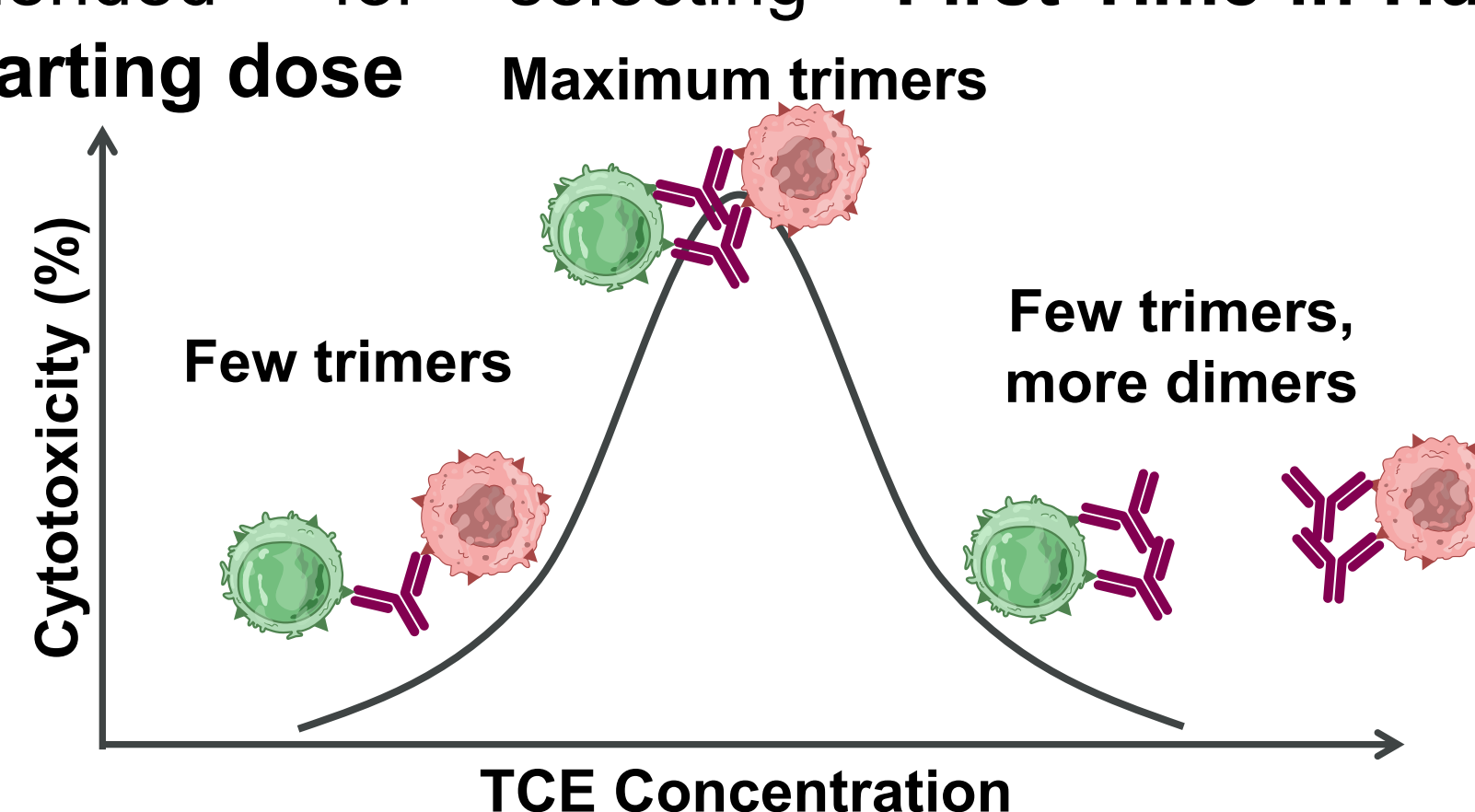
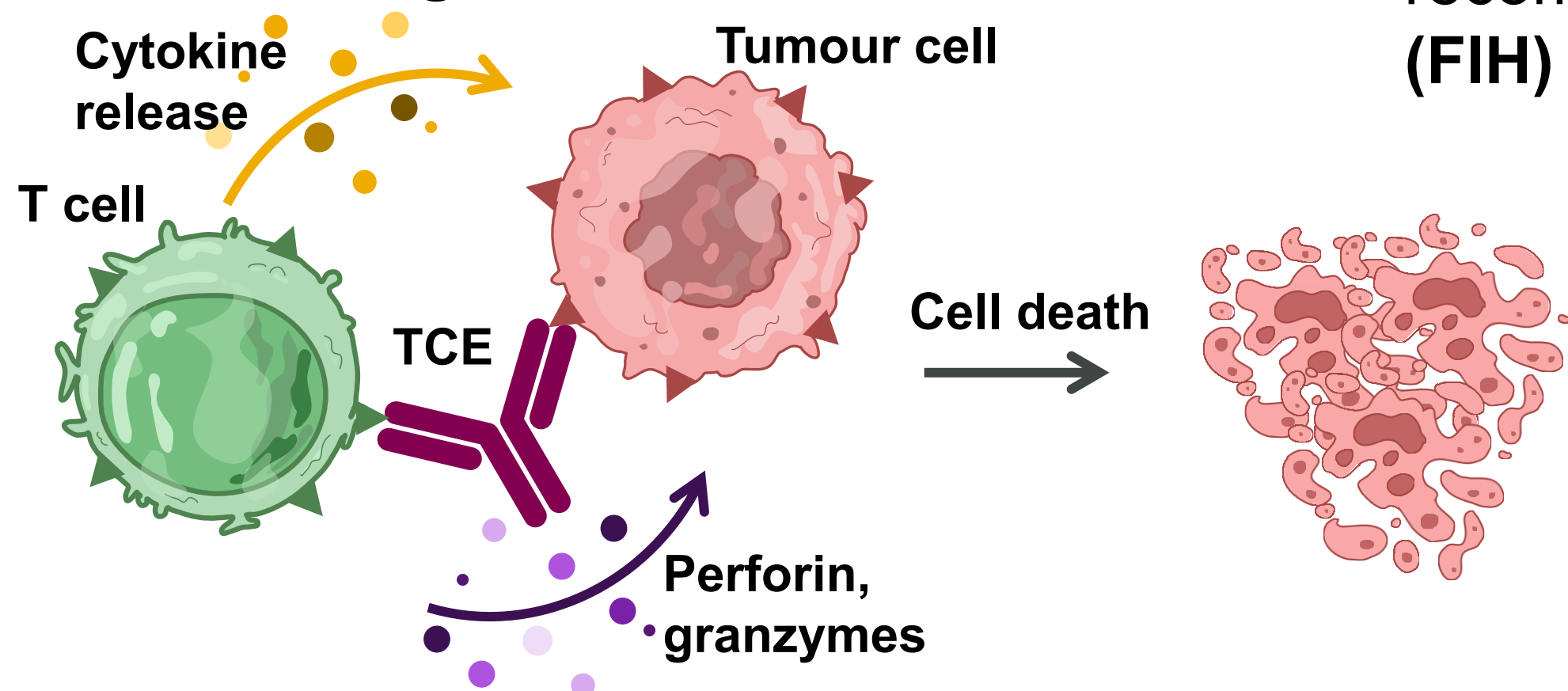


A trimer-based MABEL approach for the FIH starting dose selection of T-cell Engagers

Introduction

T-cell engagers (TCEs) are promising immunotherapeutic agents, which can redirect T cells to recognize and kill cancer cells by forming an **active trimer between drug, tumour cells and T cells**

TCEs have a narrow therapeutic window, with potential **risk of cytokine release syndrome (CRS)** at low doses and a **bell-shaped response**. A minimal anticipated biological effect level (**MABEL**) approach is recommended¹ for selecting **First-Time-in-Human (FIH) starting dose**



Objectives

Challenge:

- Estimate a **FIH starting dose** that is both **safe** and as close to the **minimally efficacious dose** as possible

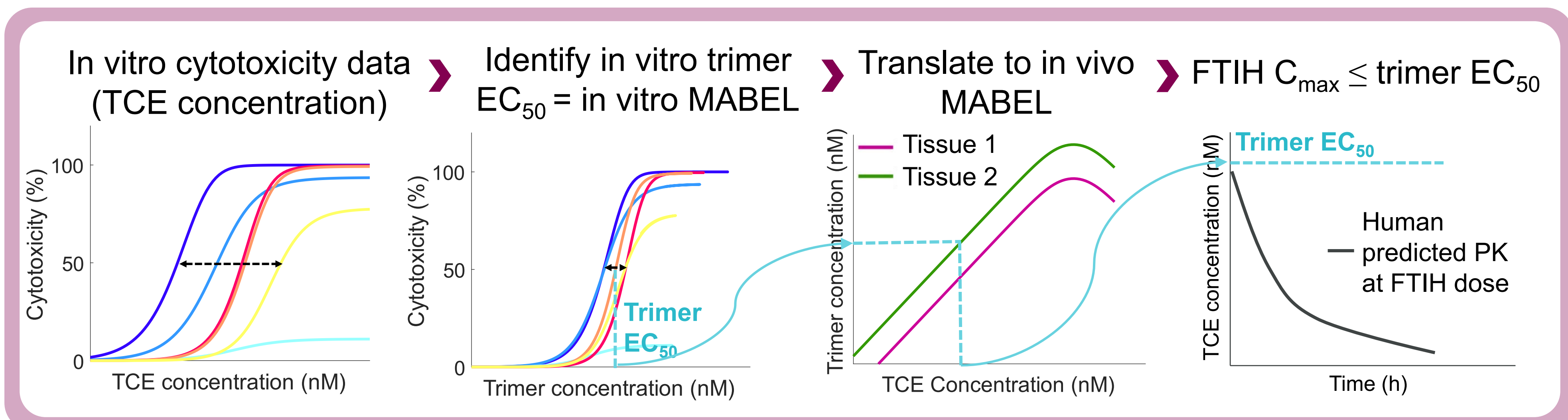
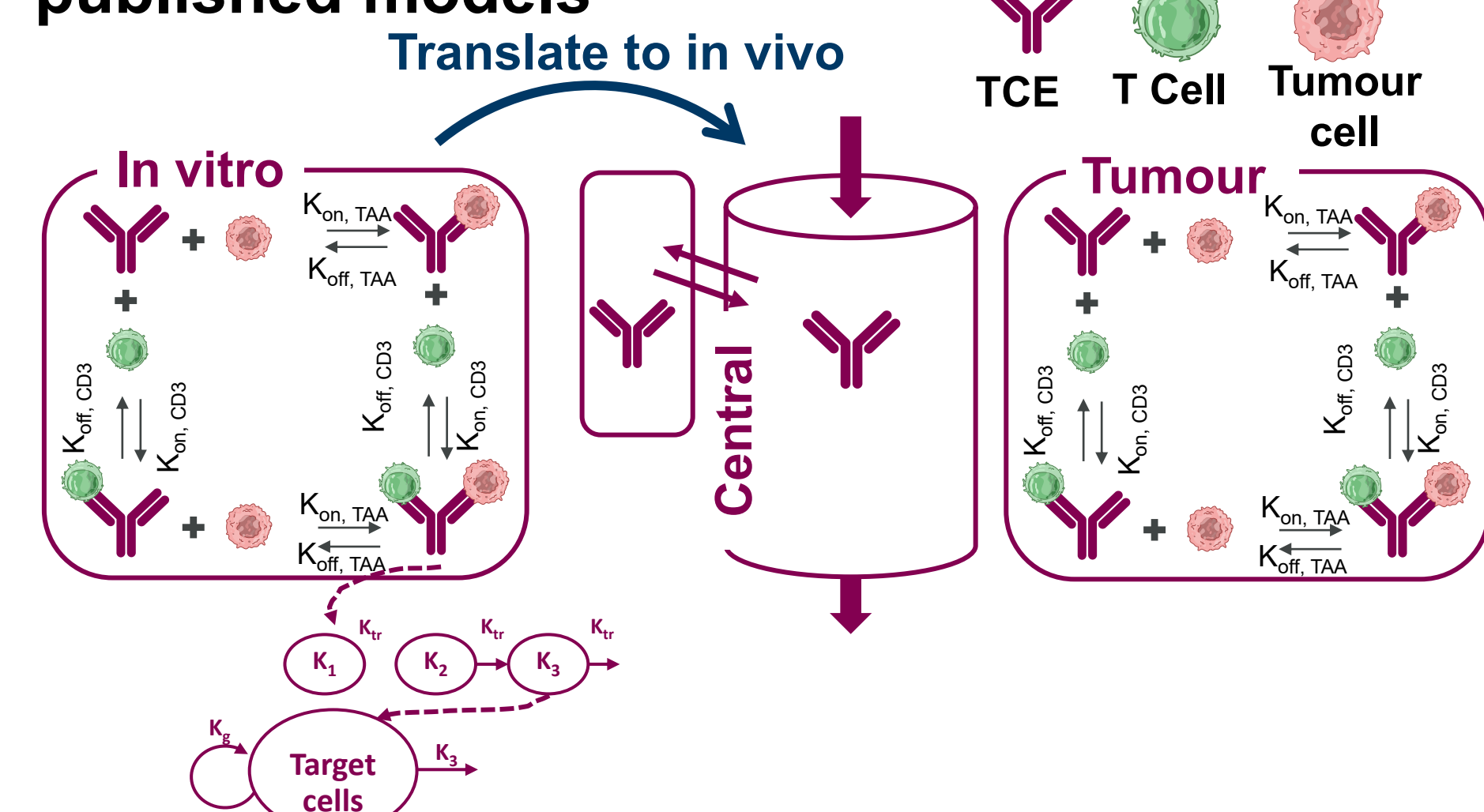
→ Could a **mechanistic trimer model** help identify a higher FIH starting dose than a standard MABEL approach, while still being safe?

→ What is the impact of **trimer normalization** on the starting dose?

→ What is the impact of using data from different **tumour tissues** on the estimated starting dose?

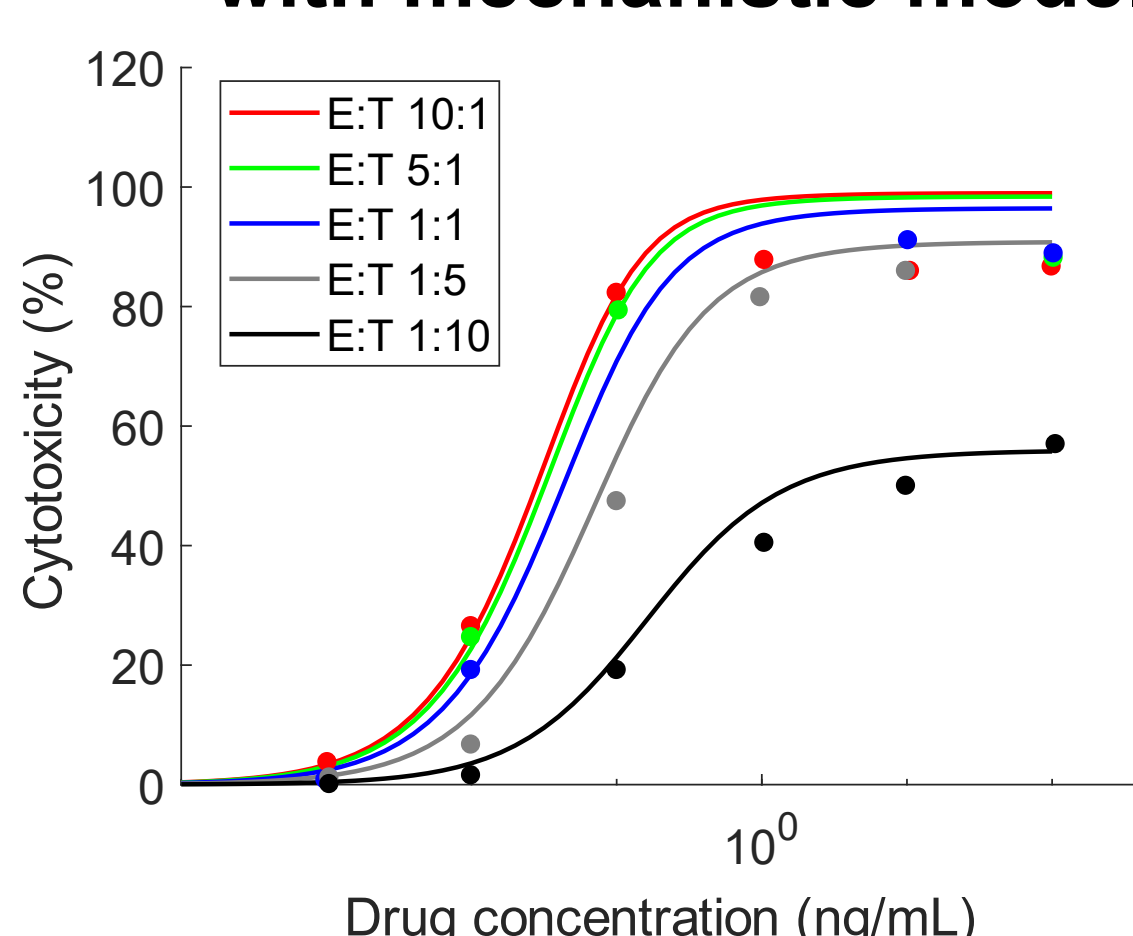
Methods

Mechanistic framework based on previously published models¹⁻³



- Trimer formation via **binding** of TCE to tumour antigen (TAA) on tumour cells and CD3 on T cells (no avidity factor)
- T cells dynamics** not included (T cells assumed to be constant in time)
- In vivo tumour **penetration factor** assumed to be 30% for bone marrow²
- E:T for blood **1.7:1**, E:T for bone marrow **0.1:1**²

In vitro blinatumomab data fit with mechanistic model²



Relevant clinical doses for blinatumomab⁵

Starting dose	Selected initial priming dose/target dose	Minimally efficacious dose	Maximum tolerated dose
0.5 µg/m ² /day (~0.9 µg/day)	5/15 µg/m ² /day (~9/28 µg/day)	5 µg/m ² /day (~9 µg/day)*	60 µg/m ² /day (~108 µg/day)

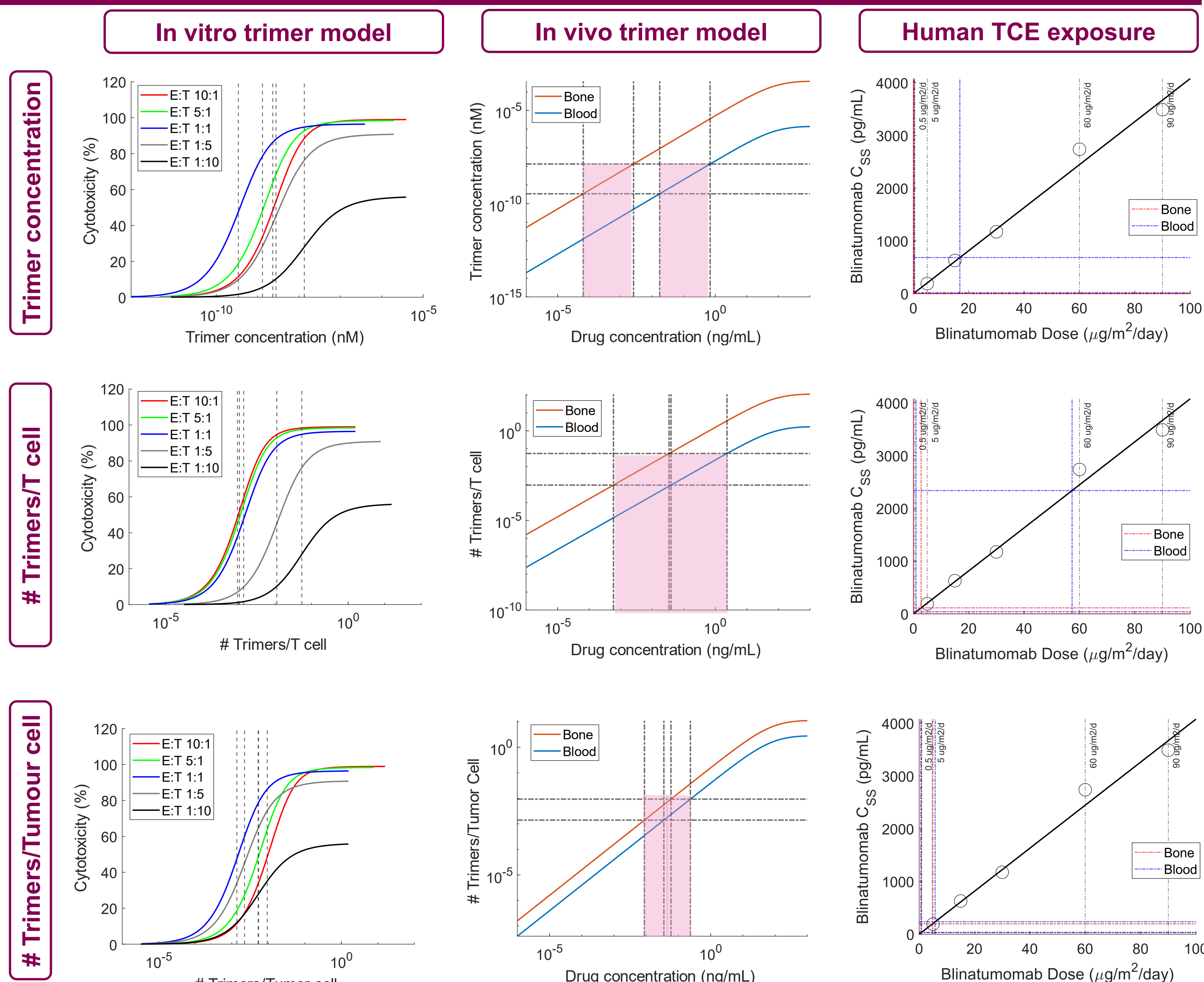
*First dose where B cell depletion was observed⁵

**Average BSA of 1.8m² assumed for dose conversions

Results

- Estimated FIH doses **range from 0.1 to 30 µg/m²/day**, depending on tissue considered and trimer normalization used
- All the combinations (apart from trimer molar concentration in the bone marrow) led to **higher starting doses than the FIH dose** of 0.5 µg/m²/day selected for blinatumomab.
- All doses are **below the maximum tolerated dose** of 60 µg/m²/day, with some above the minimally efficacious dose of 5 µg/m²/day
- Blood consistently led to higher starting doses than bone marrow**, likely due to the lower E:T ratio and cell densities in blood compared to bone
- Highest doses obtained using # trimers/T cells**, lowest doses using trimer molar concentration

	Trimer concentration		# Trimers/T cell		# Trimers/Tumour cell	
	Bone	Blood	Bone	Blood	Bone	Blood
Average Starting dose [range] (µg/m ² /day)	0.11 [0.0053-0.21]	8.6 [0.42-16.8]	1.4 [0.048-2.78]	29 [0.96-57]	2.8 [0.72-4.8]	3.3 [0.86-5.77]



Conclusions and next steps

- The obtained FTIH doses were in most cases **higher than the FIH starting dose** selected for blinatumomab, and mostly **in the range of doses tolerated** in the clinic
- A **large variability** in the estimated doses was observed when using different trimer normalizations and different tumour tissue, highlighting the impact of modelling choices on the selection of an appropriate starting dose
- Additional information might be helpful to deal with variable doses, e.g. benchmarking against competitors and back-translating clinical TCEs against same target
- The modelling framework is currently being tested on additional TCEs to confirm its appropriateness for starting dose selection

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