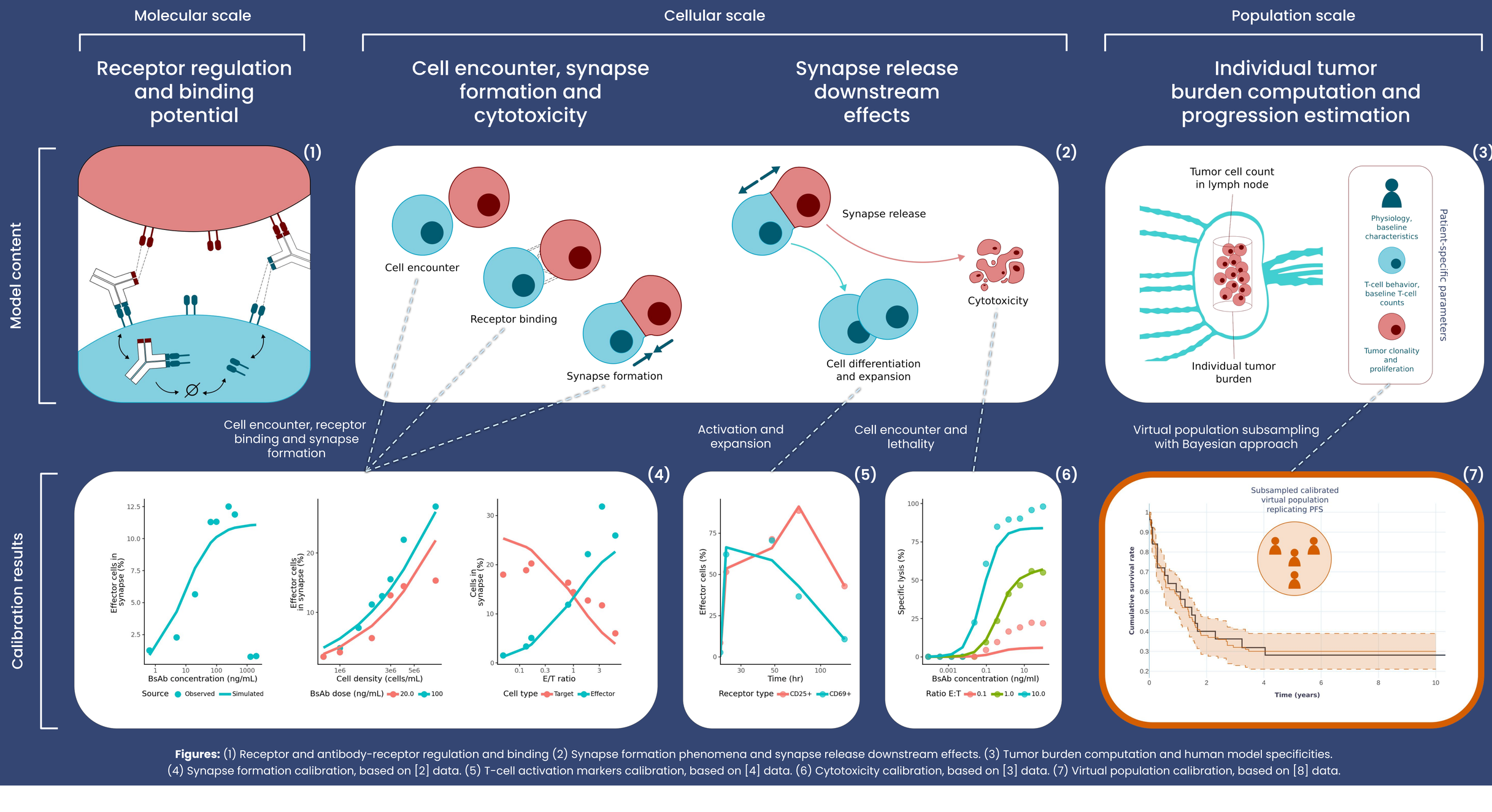
QSP platform of bispecific T-cell engager for multi-scale modeling: Blinatumomab study case

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Mechanistic and translational description of immunological **synapse formation** combined with **Bayesian virtual patient sampling** allows the **reproduction of clinical PFS**



Figures: (1) Receptor and antibody-receptor regulation and binding (2) Synapse formation phenomena and synapse release downstream effects. (3) Tumor burden computation and human model specificities. (4) Synapse formation calibration, based on [2] data. (5) T-cell activation markers calibration, based on [4] data. (6) Cytotoxicity calibration, based on [3] data. (7) Virtual population calibration, based on [8] data.

BACKGROUND

Due to (i) their tumor cells accessible to immune effectors, (ii) favorable targets with restricted antigens, and (iii) clear unmet needs, hematological malignancies represent a promising context for immuno-therapies, in particular for bispecific antibodies. This has translated into multiple approvals, high response rates in refractory settings, and a very active pipeline. **One of the main challenges for bispecific antibody dose selection for first-in-human studies is the translation of in vitro cytotoxicity data to human efficacy.** In this context, quantitative systems pharmacology (QSP) modeling appears as a powerful tool to investigate translation hypotheses and predict in-human dose-response curves, while leveraging data from all stages of the clinical development pipeline.

METHODS

Here, we propose a mechanistic multiscale QSP model of T-cell engager mechanism of action and apply it to the in vitro to in vivo translation of Blinatumomab (CD3xCD19 bispecific antibody) efficacy. This model falls within a long-term collaboration between Nova In Silico and Genmab, building an oncology QSP platform in order to accelerate drug development [1][2].

This model integrates phenomena across multiple scales, from molecular events like receptor binding and regulation to cellular dynamics (see Fig. 1, 2). A central feature is the **computation of immune synapse formation**, which serves as the crucial link between scales [3], derived from the combined effects of cross-linking and cell encounter. This comprehensive representation allows for the capture of downstream effects, including effector cell differentiation and proliferation, as well as target cell lysis (see Fig. 3). The T-cell engager model is combined with a lymphoma model, as well as a minimal PBPK model imported from [4]. All model solving and calibration steps were performed using Nova's modeling platform **Jinkō (jinko.ai)**. The final combined model for T-cell engager predictions in human B-NHL patients amounts to approximately 250 parameters, 50 variables, and 70 reactions.

The model has been calibrated on *in vitro* data and PK measurements using the CMAES algorithm in Jinkō. The virtual population reproducing the survival target was subsampled using **a Bayesian subsampling method**, also available in Jinkō. Based on the simulated annealing algorithm, this allows to optimally select a subpopulation replicating targets of interest among an initial virtual population with high inter-patient variability.

RESULTS

In vitro synapse formation and cytotoxicity are captured

The model captures synapse formation data as reported by [5], as a function of antibody concentration, E-T ratio, time and cell densities (see Fig. 4). The model also captures in vitro effector cell activation data from [6] (see Fig. 5) and cytotoxicity data from [7] (see Fig. 6) at various E:T ratios.

Human PK is calibrated and virtual population reproduces FL patients PFS

The model is also calibrated to capture the PK of Blinatumomab in DLBCL patients [8-10]. Finally, the translation to human is performed in the context of B-cell non-Hodgkin lymphoma (B-NHL), and a virtual population is calibrated to match stratified progression-free survival (PFS) endpoints as reported by [11] (see Fig. 7). The parameters calibrated on in vitro data were directly re-used and scaled to the human context, showcasing the translation power of such a model.

CONCLUSION

The multi-scale structure allows to integrate multi-source data and thus to inform the model in a complete and robust manner. A key insight gained from this modeling study is that the immune synapse formation is central in understanding the efficacy of T-cell engagers in human. This goes along the lines of the wide modeling study reported in [3], going further in the translation of a synapse-based QSP model into human clinical predictive model.

This work demonstrates the potential of a translational platform, enabling relevant predictions for decision makers, and aggregating data from various contexts (in vitro, human) but also from different bispecific antibodies.

REFERENCES

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