Simulation of Rituximab and Natalizumab biomarker efficacy using simplified QSP model of B- and T-lymphocyte dynamics in Multiple Sclerosis

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INTRODUCTION

Immune-mediated disease affecting the CNS, multiple sclerosis (MS), is the leading cause of neurological disability among people aged from 20 to 50. The etiology and pathogenesis of MS have been being addressed for more than 70 years, nevertheless, a consensus has not yet been reached. Intriguingly, recent observations of the high efficiency of anti-CD20 and anti-VLA-4 therapies (Rituximab and Natalizumab, respectively) have revealed an important B cells' role, independent of antibody production, in MS development. Moreover, the latter-day study provided robust evidence that the interaction of B and T cells subsequently leads to T cells activation and expansion, being an important driver of autoimmune response in MS [1]. The goal of this work was to utilize the latest findings on the interaction between B and T cells for development of a quantitative systems pharmacology (QSP) model that describes key processes contributing to lymphocyte dynamics in MS and targeted by currently investigated therapies.

MODEL DESCRIPTION

Fig. 1. Model scheme

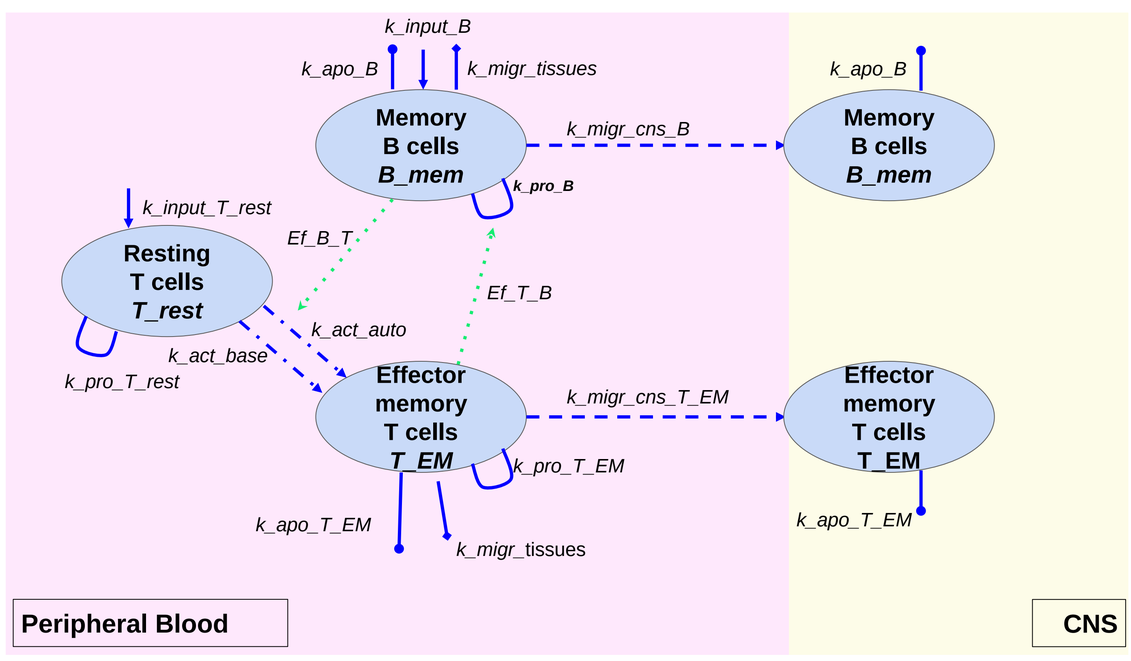


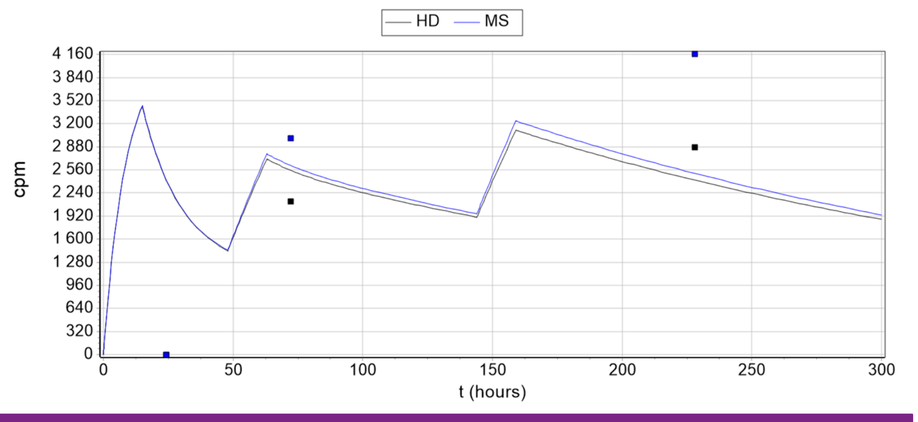
Fig. 2. Workflow of QSP model generation

- Retrieval of parameters for cell processes form IRT database
- Calibration of parameters of T- and B-cell interaction on in vitro data
- Calibration of the model on baseline data and translation from mouse data
- Calibration and validation on PD data

AUTOPROLIFERATION PARAMETERS CALIBRATION

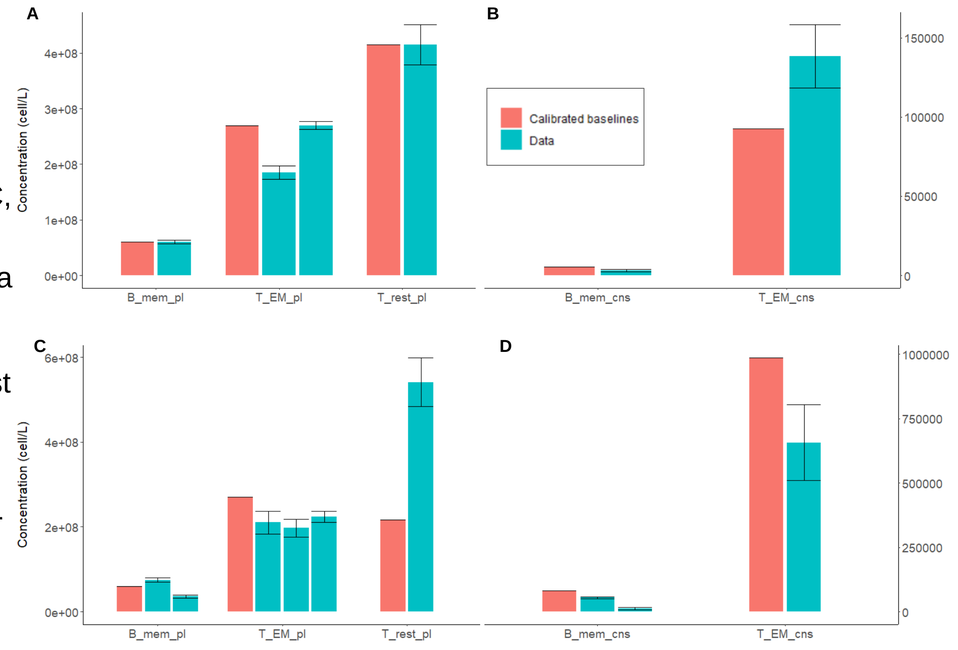
Fig. 3. Calibration of autoproliferation parameters on in vitro data [1-2].

- Calibration on in vitro auto-proliferation assay data results in k_act_auto_MS approximately 10 times more than k_act_auto_HD



IN VIVO PARAMETERS CALIBRATION

Fig. 5. Model calibration of cell counts for different cellular subtypes for HD (A, B) and MS (C, D) data sets [*].



- Cell counts data allowed to calibrate rates of B and T _rest cells input and migration. k_migr_cns is 10 times higher in MS than in HD. for both B_mem and T_EM cells.
- The limitation of our model is the fixed k_input of T_rest as in HD, thus leading to this pool underestimation in MS where the activation rate is higher

A SIMULATIONS OF NATALIZUMAB AND RITUXIMAB PHARMACODYNAMICS

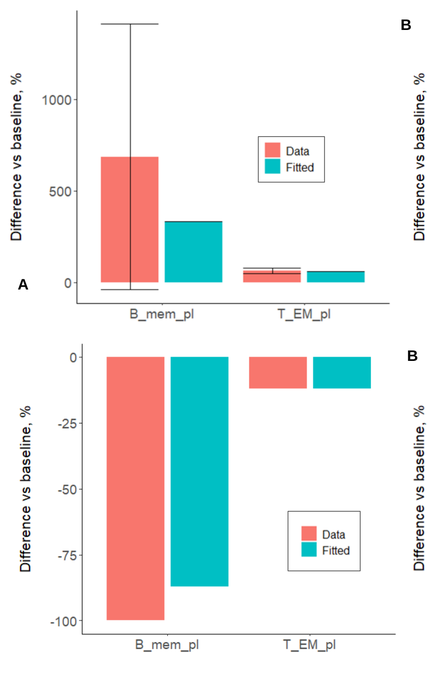


Fig. 6. Calibration of pharmacodynamic parameter (alpha*) on plasma data and **validation** on the CSF data for **Natalizumab** treatment [3-5]. *PD effect on migration to periphery relative to effect on migration to CNS.

Fig. 7. Calibration of pharmacodynamic parameter (Emax) on plasma data and **validation** on CSF data for **Rituximab** treatment [6].

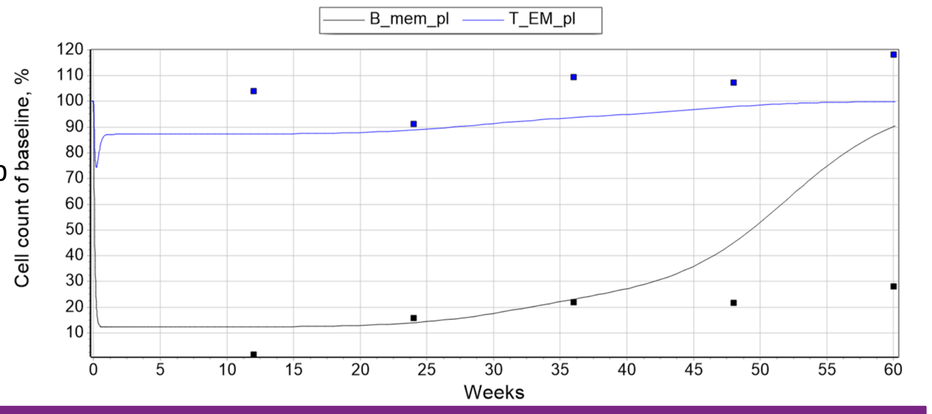


Fig. 8. Validation on PD data for B and T cell plasma pools for Rituximab treatment (single injection at t=0, dose=828 mg ± 589) [7].

CONCLUSIONS

- The current QSP model of MS describes the difference between CNS T cell accumulation in healthy and MS subjects.
- It recapitulates the major effects on lymphocyte pools in blood and CSF observed in clinical trials of Natalizumab and Rituximab based on calibration on plasma data. Simulation of B cell depletion in the plasma leads to subsequent reduction in T cells abundance in both CNS and plasma compartments.
- Model without T-cell activation in CNS underestimates T_EM depletion in CNS, so additional explanation of T-cell reduction by rituximab in CNS should be investigated.

CONTACTS

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* More than 10 sources were used to collect cellular data for calibration