Neurodegeneration quantitative systems pharmacology modelling for analysis of multiple sclerosis therapy

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BACKGROUND

The major determinant of neurological impairment during multiple sclerosis (MS) is axonal degeneration, represented as MS lesions and brain atrophy. One of commonly used biomarkers of axonal degeneration is neurofilament light protein (Nfl) elevation in cerebrospinal fluid (CSF) and plasma. Modulation of lymphocyte dynamics demonstrated efficacy on several biomarkers.

The goal of this study was to create a Quantitative Systems Pharmacology (QSP) that

(1) includes toxic effects of inflammation on neuronal cytoskeleton;
(2) describes neurofilament L dynamics in cerebrospinal fluid(CSF) during MS compared with healthy controls. That model would allow for MS therapy optimization.

MODEL DESCRIPTION

Fig. 1. Lymphocyte model scheme *
*https://www.page-meeting.org/default.asp?abstract=10154

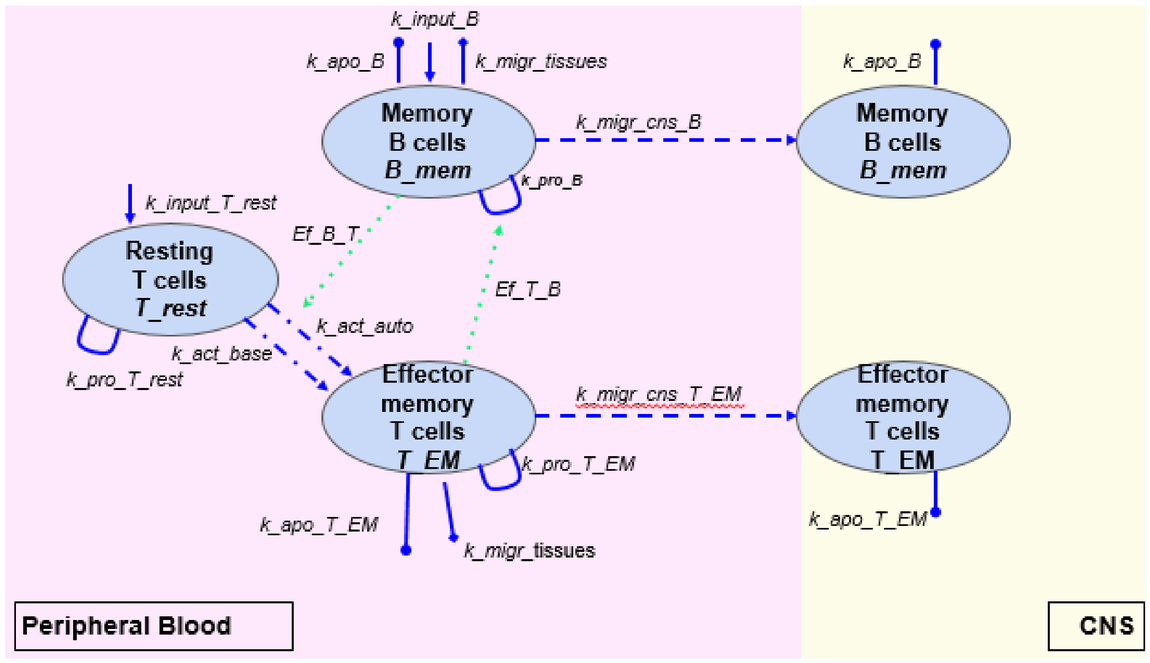
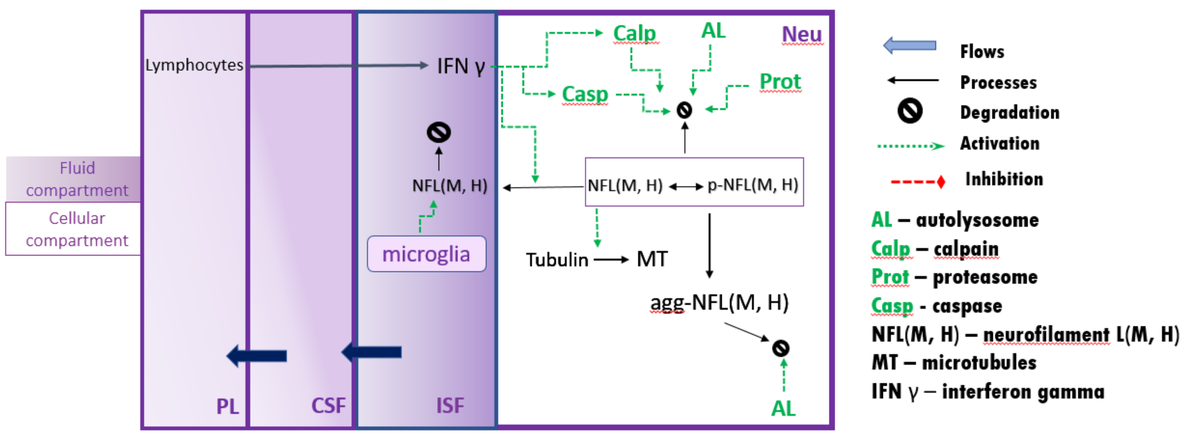


Fig. 2. Neurodegeneration model scheme **
ACoP12 (2021) QSP-218 [www.go-acop.org/?abstract=218] Quantitative Systems Pharmacology



Additionally, atrophy rate was assumed to depend on lymphocytes

Fig. 3. 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 for cell counts

Estimation of inflammatory agents influence on neurodegeneration

Integration of lymphocytes and neurodegeneration model and validation on PD data for Nfl

*** IRT (Immune Response Template) database *https://irt.insysbio.com/*

For more information, please visit our web site at **www.insysbio.ru**.
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IN VIVO PARAMETERS CALIBRATION

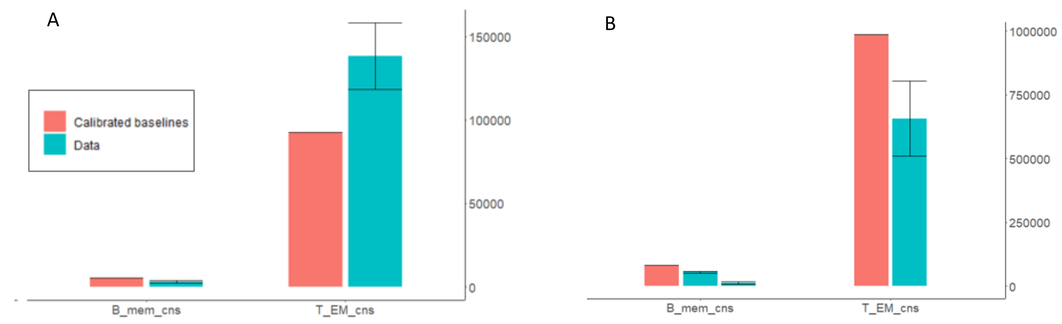

Fig. 4. Model calibration of cell counts for different cellular subtypes for HD (A) and MS (B) data sets (* More than 10 sources were used to collect cellular data for calibration).

- 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.

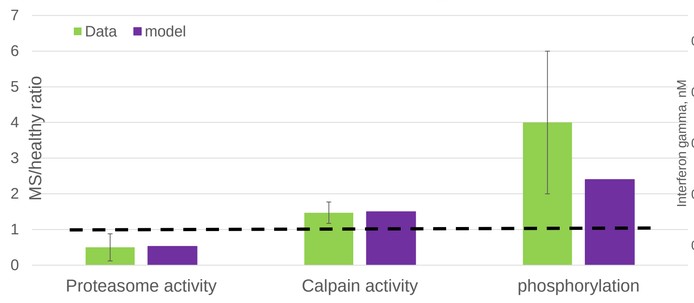

Fig. 5. Changes in proteasome, calpain activity and phosphorylation in MS patients compared with healthy controls. Data are taken from PMID21235577, PMID18619438.

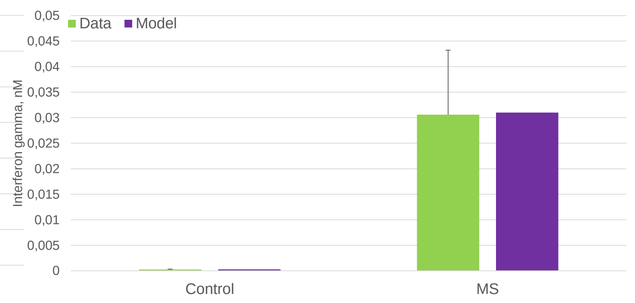

Fig. 6. Interferon gamma change in MS patients compared to control, nM. Data are taken from PMID33162830 .

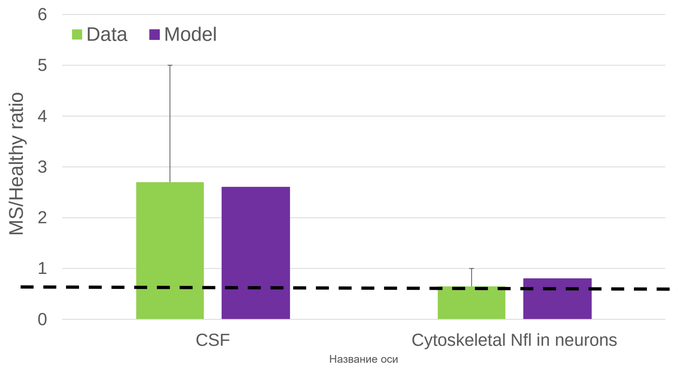

Fig. 7. The model predicts elevation of neurofilament light in CSF and reduction of cytoskeletal NFL in neurons compared to healthy controls (PMID: 31123141, PMID16007681).

SIMULATIONS OF THERAPY PHARMACODYNAMICS

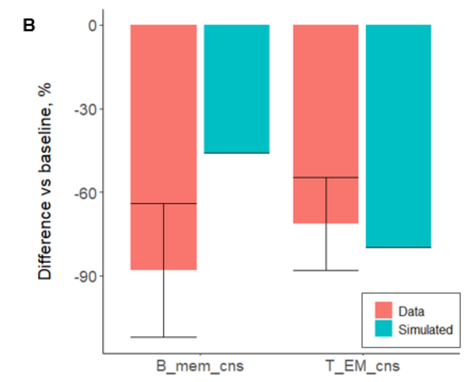

Fig. 8. Validation of pharmacodynamic parameter (alpha*) on the CSF data for **Natalizumab** treatment (PMID23226199, PMID33984651, PMID25135296). *PD effect on migration to periphery relative to effect on migration to CNS.

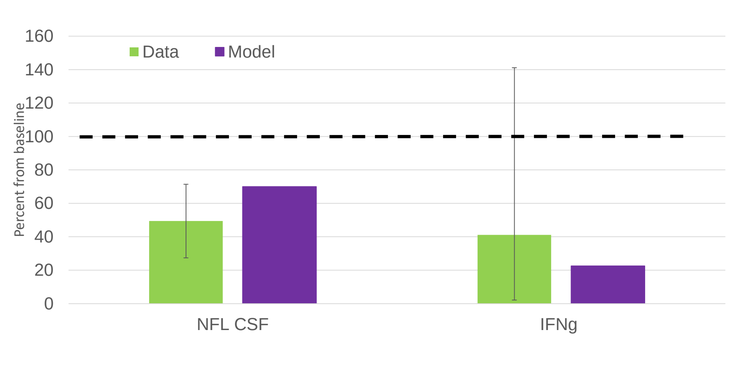

Fig. 9. Percent of NFL CSF and IFN gamma CSF from baseline after **Natalizumab** treatment (1 year from the start). Mean disease duration before treatment - 6.5 years. Data are taken from PMID23763388, PMID19220425.

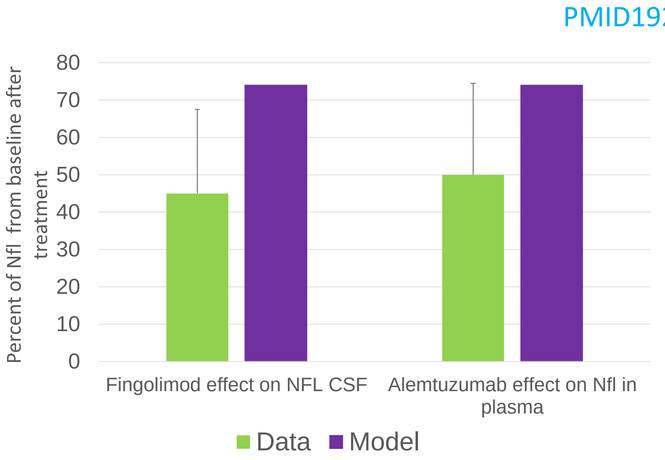

Fig. 10. Percent of NFL from baseline after **Fingolimod** and **Alemtuzumab** treatment (1 year from the start). Mean disease duration before treatment - 9 and 5 years respectively. Data are taken from PMID25809304 and PMID34378446. Lymphocyte reduction is described according to data PMID23950550 PMID17506867.

CONCLUSIONS

- The current QSP model of MS describes the difference between CNS T cell accumulation in healthy and MS subjects.
- Introduction of the inflammatory effects on intracellular processes and secretion allows for description of Nfl in CSF
- Atrophy of brain volume contributes significantly to Nfl appearance in CSF, and description of therapy efficacy on Nfl was achieved only by introducing dependence of atrophy rate on lymphocytes
- The model predicts the decrease of Nfl in CSF and plasma after Natalizumab, Fingolimod and Alemtuzumab treatment, however, Fingolimod effect is underestimated.