

Model-based Comparison Of Tfr-mediated Transcytosis & FcRn-mediated Half-life Extension To Optimize Cns Antibody Dosing

Jean-Philippe Courade^{1*}, Oleg Demin Jr², Dmitry Shchelokov², Galina Saynukova², Jean-François Gherzi-Egea³

¹discoveric bio alpha Ltd., Pfäffikon, Schwyz, Switzerland; ²InSysBio, Paphos, Cyprus, ³BIP facility, Lyon Neurosciences Research Center, INSERM U1028, CNRS UMR5292, UCBL1, Bron France.

Background

Therapeutic antibodies for central nervous system (CNS) disorders, require high systemic doses (≥ 10 mg/kg) to achieve adequate brain exposure. Strategies to reduce systemic dose include:

(1) enhancing receptor mediated blood-brain barrier transcytosis. e.g., trontinemab targeting transferrin receptor (TfR)

(2) extending systemic half-life via Fc engineering to increase neonatal Fc receptor (FcRn) recycling. e.g., YTE mutations in motavizumab-YTE.

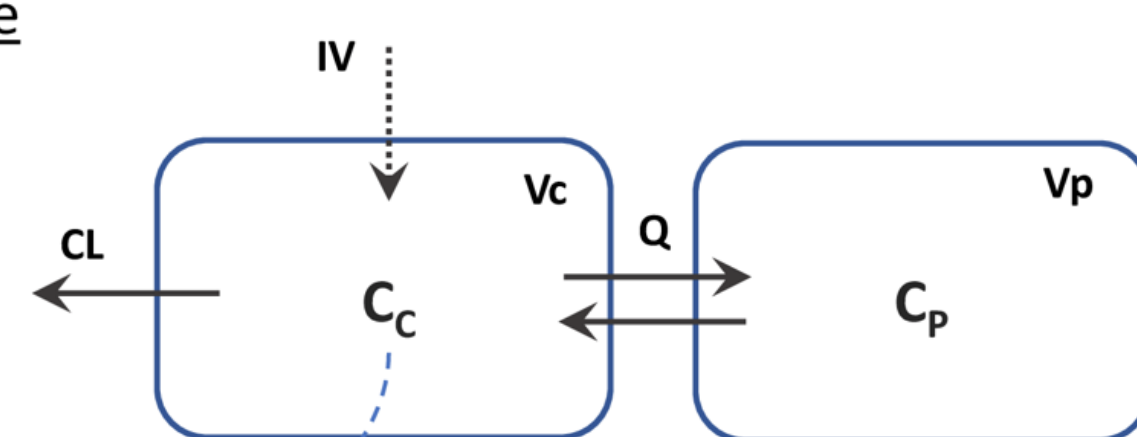
We compared quantitatively these approaches by developing a compartmental pharmacokinetic (PK) model based on published human plasma and cerebrospinal fluid (CSF) data. We applied the model to **single** and **repeated (12xQ4W)** dosing scenarios for **standard IgG (WT)**, **TfR-targeted bispecific trontinemab (TfR-targeted Ab)**, and the **half-life-extended motavizumab (YTE Ab)**.

Method

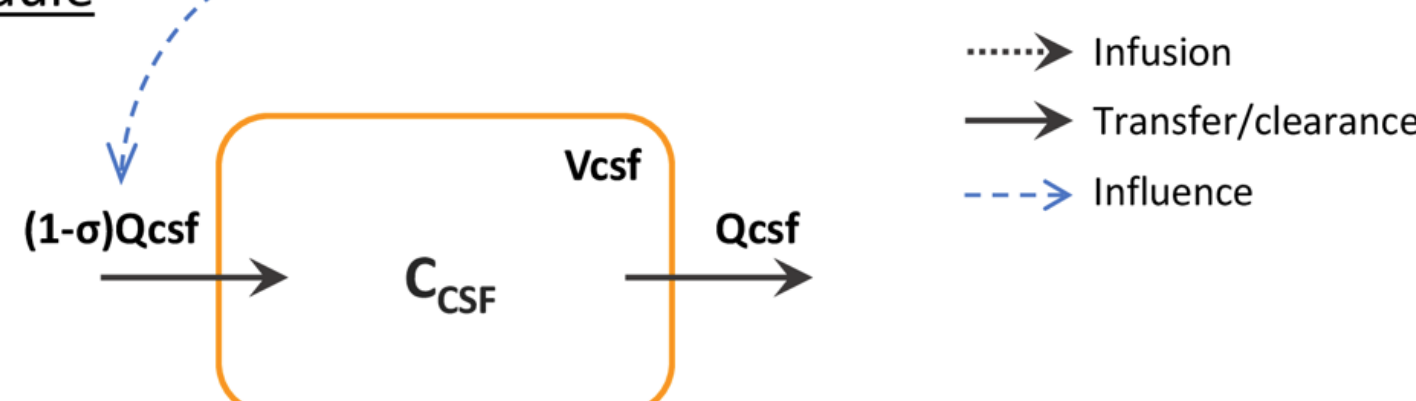
Pharmacokinetic model:

- ✓ **Implemented with i)** Published blood PK data¹ and modelled CSF concentrations for motavizumab-YTE, ii) publicly available data for modelling typical IgG1 antibodies², iii) published blood and CSF trontinemab data^{3,4}.
- ✓ **Qualified using** clinical plasma PK profile of motavizumab-YTE and trontinemab,
- ✓ **Validated using** CSF data for trontinemab^{4,5}.

PK module



CSF module



.....> Infusion
—> Transfer/clearance
- - -> Influence

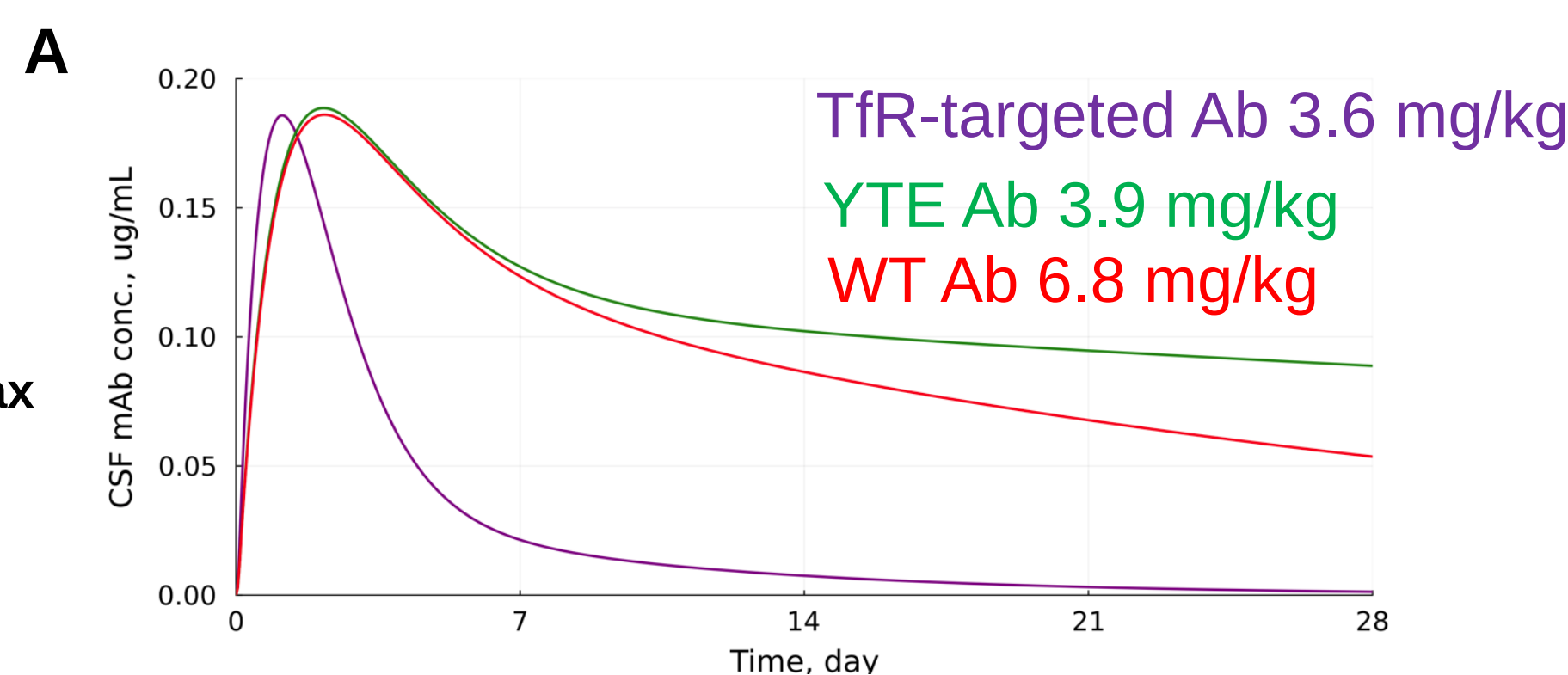
Cc: concentration of antibody in central compartment
Cp: concentration of antibody in peripheral compartment
Vc: volume of distribution in central compartment
Vp: volume of distribution in peripheral compartment
CL: clearance from central compartment
Q: inter-compartmental clearance.
Ccsf: antibody concentration in the CSF compartment
Vcsf: CSF compartment volume
Qcsf: CSF flow rate,
 σ : reflection coefficient representing the permeability of blood-brain interfaces toward the antibody

Results

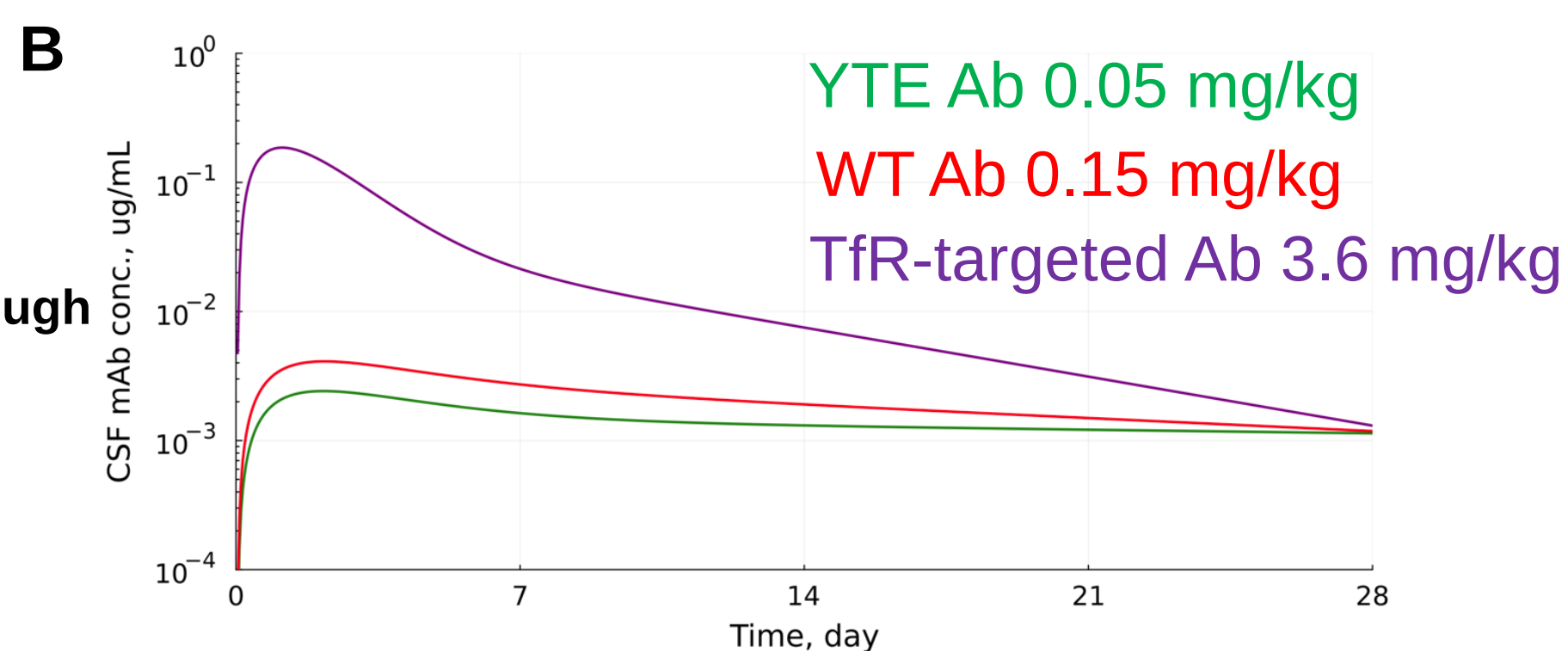
Single dose

Dose of TfR-targeted Ab < doses of WT and YTE Abs to achieve an equivalent CSF $C_{\max}$ (A). Dose of YTE Ab < doses of TfR-targeted and WT Abs to achieve comparable CSF C_{trough} (B) and total CSF exposure (AUC) (C).

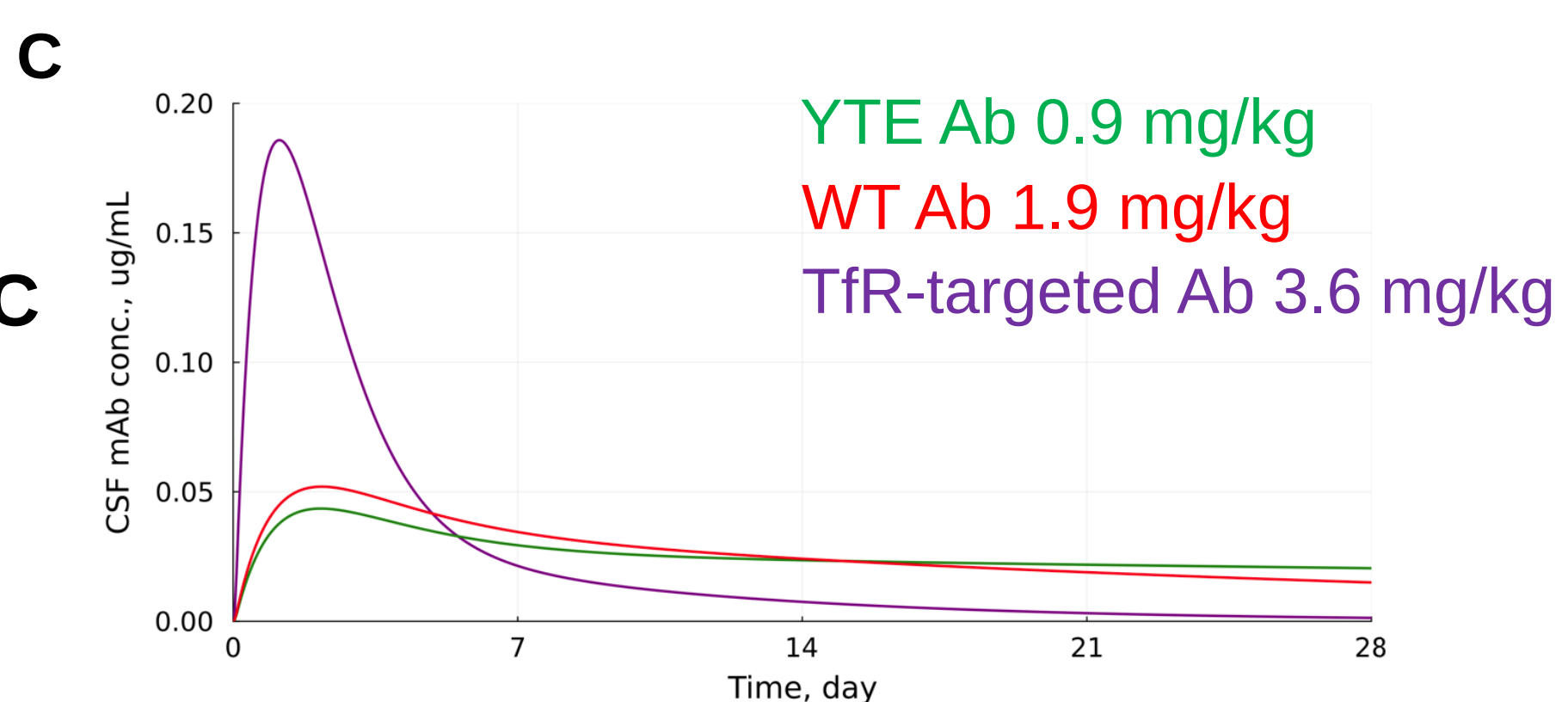
Same CSF $C_{\max}$



Same CSF C_{trough}

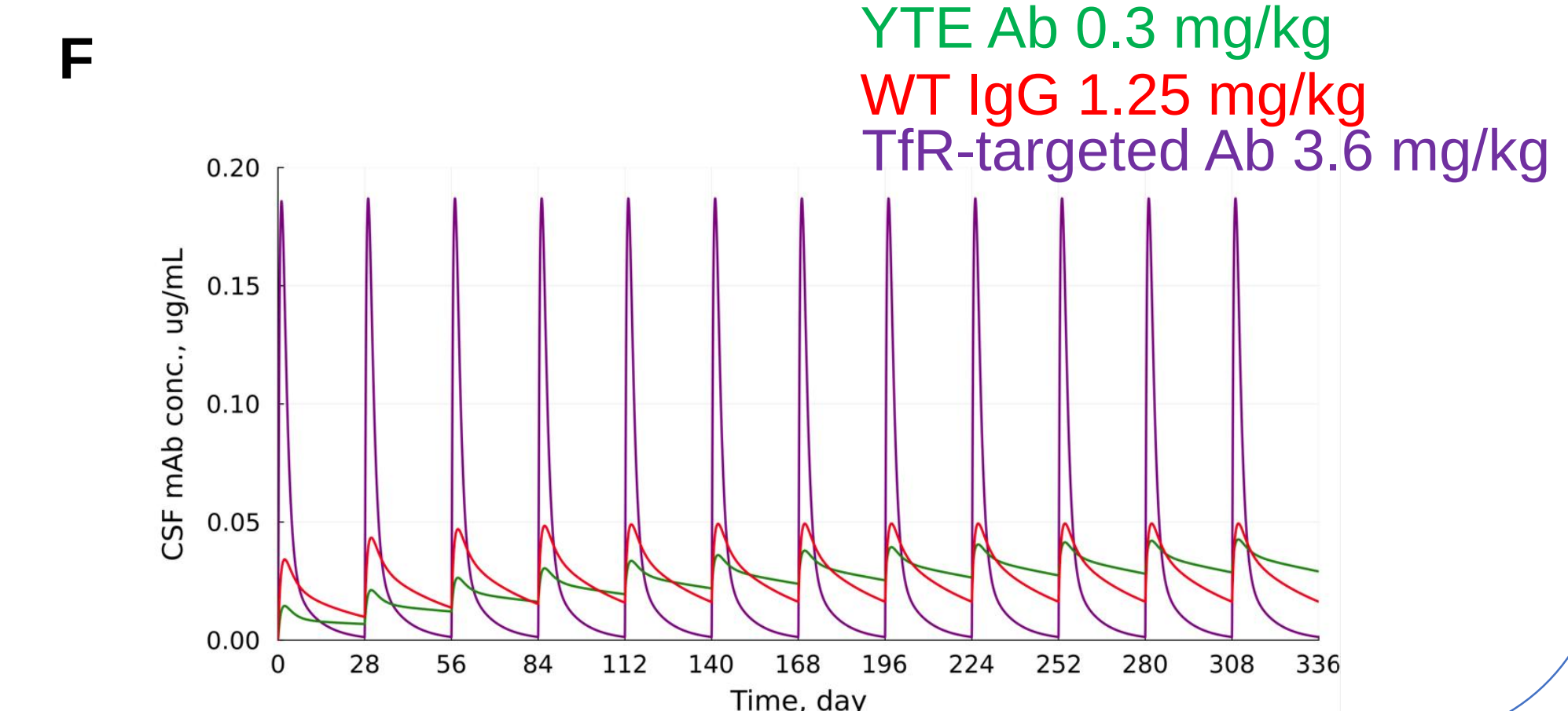
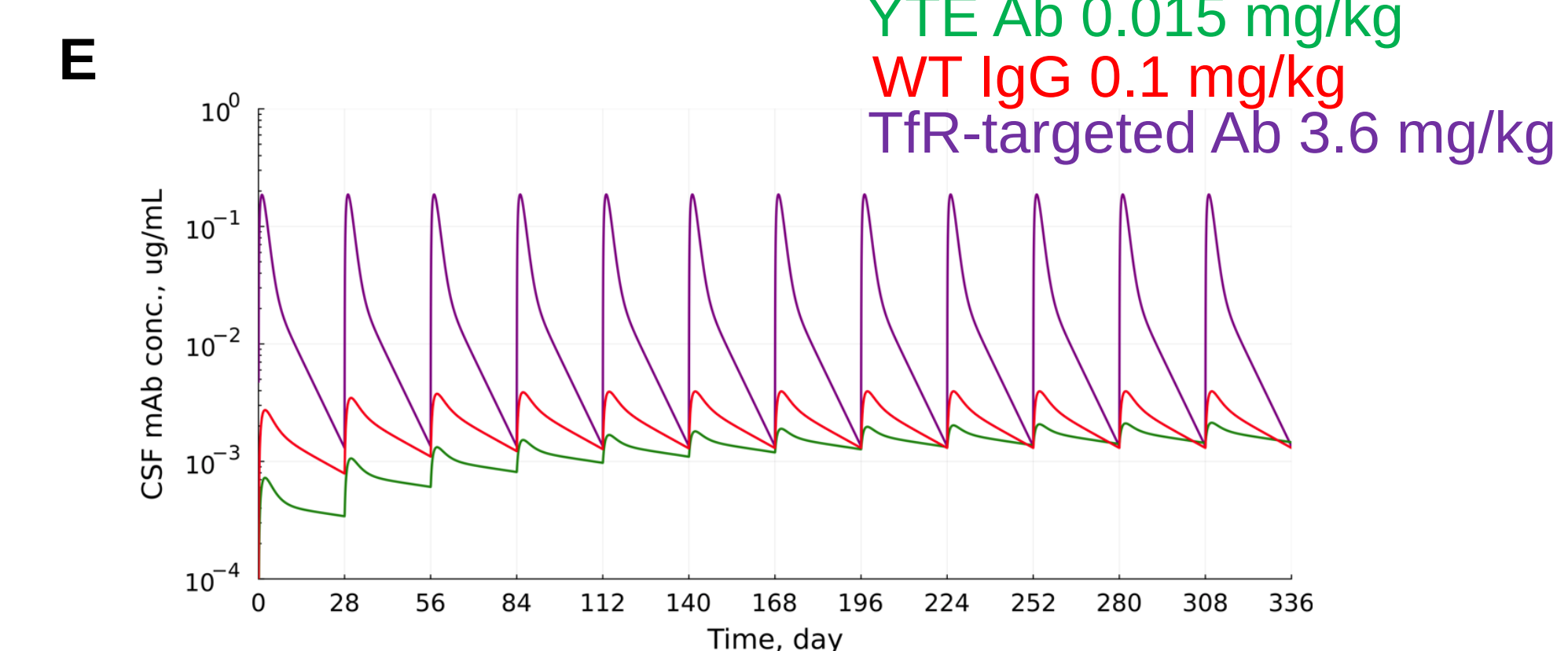
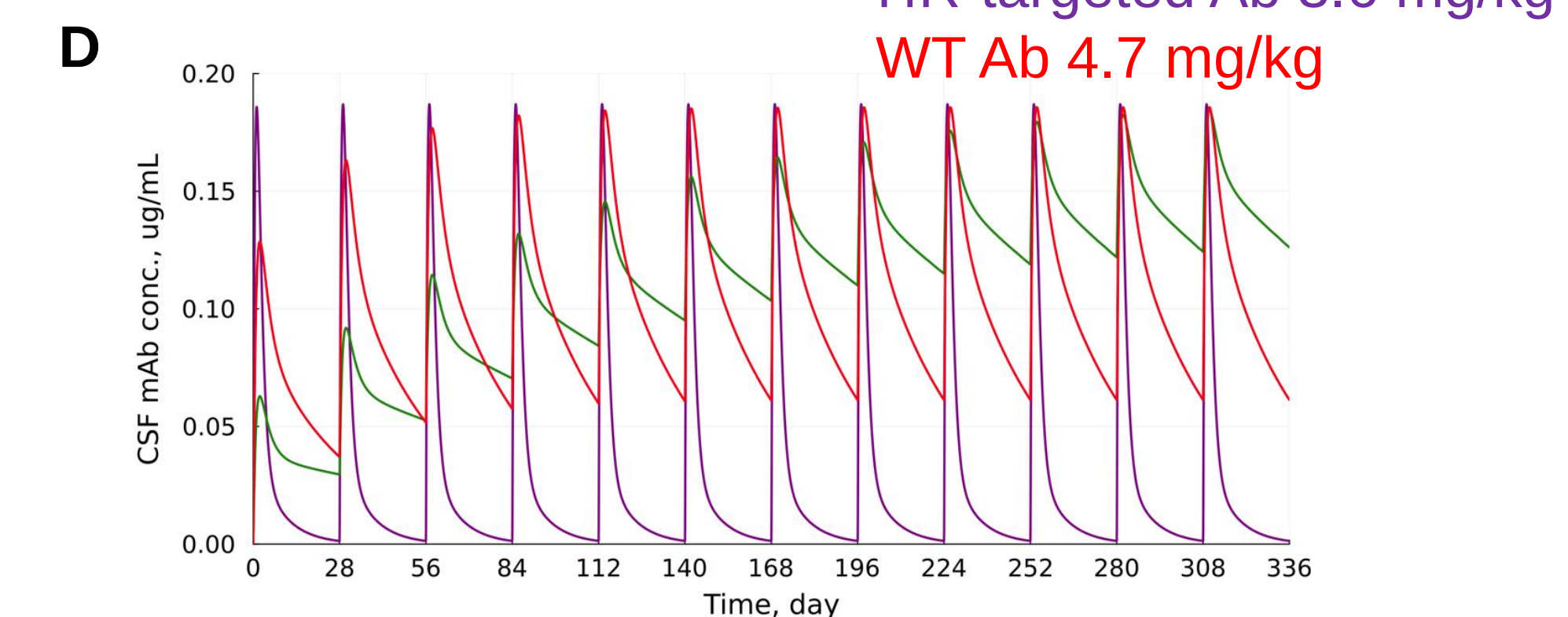


Same CSF AUC



Chronic dosing (12xQ4W)

Dose of YTE Ab < doses of TfR-targeted and WT Abs to achieve equivalent CSF $C_{\max}$ (D), CSF C_{trough} (E), and CSF AUC (F).



Conclusions

❖ Optimal antibody format for CNS indications is dictated by the pathophysiological mechanism targeted :

TfR-mediated shuttle technology: Superior efficiency for $C_{\max}$ driven mechanisms, such as rapid clearance of established amyloid-beta plaques through a high concentration pulse of antibody in the CNS.

FcRn-mediated half-life extension: Effective dose-sparing strategy for C_{trough} -driven mechanisms, such as continuous, steady-state neutralization of extracellular Tau or alpha-synuclein seeds to prevent trans-synaptic spread.

❖ This comparative framework enables the rational selection of antibody engineering strategies based on the specific pharmacodynamic requirements of the targets selected for the treatment of neurodegenerative disorders.

1 - Haraya and Tachibana. BioDrugs. 2023;37(1):99-108

2 - Van den Berg *et al.*, MAbs. 2025;17(1):2512217

3 - Grimm *et al.* MAbs. 2023;15(1):2261509

4 - Abrantes *et al.* Abstract. 29th Population Access Group Europe (PAGE) meeting; 2021

5 - <https://clinicaltrials.gov/study/NCT04023994?tab=results>.