

Use of a TMDD model in the translational development of a BDNF-neutralizing monoclonal antibody.

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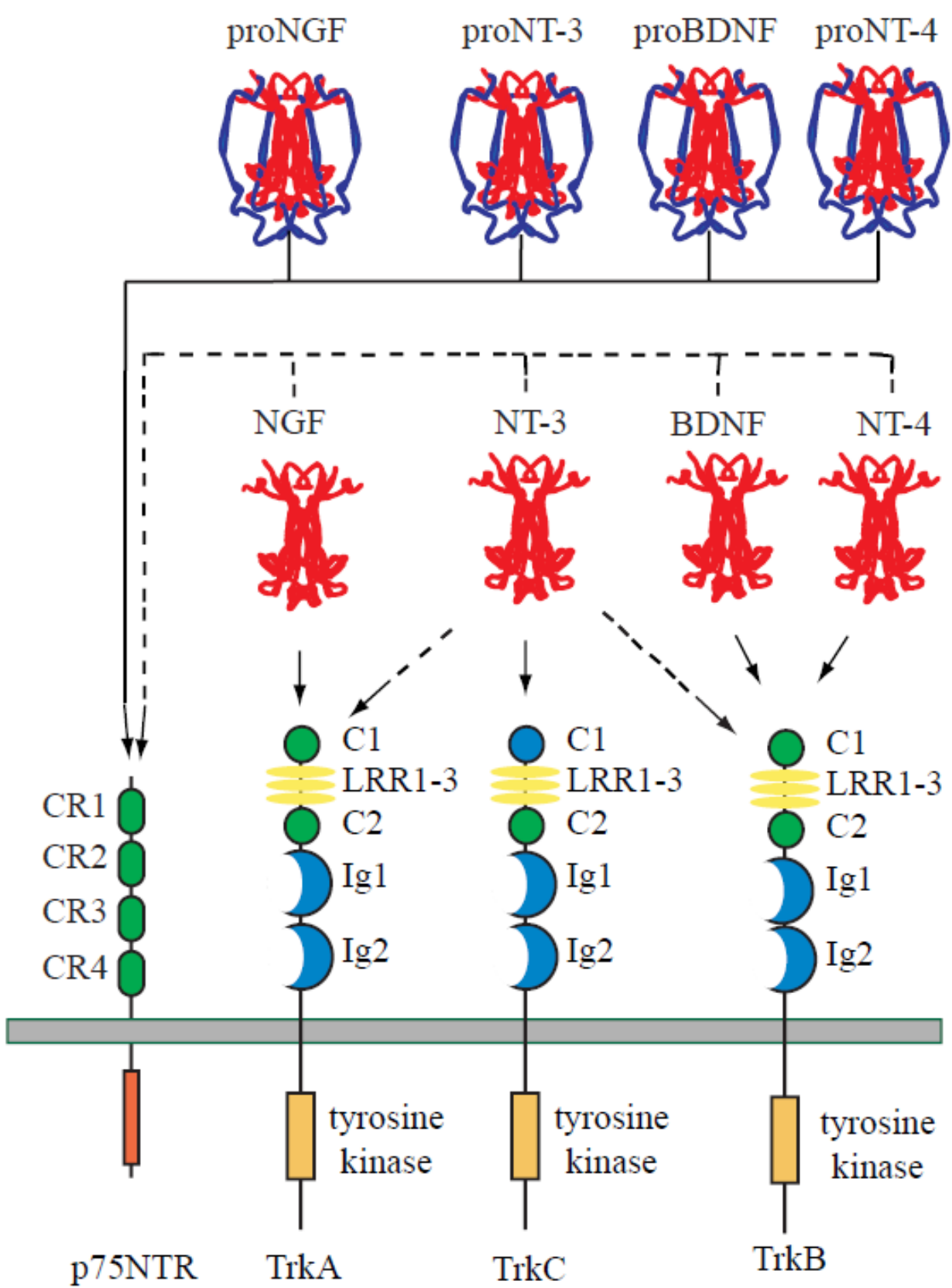
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AIM

- To build a mechanistic target-mediated drug disposition (TMDD) model describing the pharmacokinetics of monoclonal antibody (mAb) X and its ability to neutralize the Brain-Derived Neurotrophic Factor (BDNF).
- To use the model to influence the design of pre-clinical and clinical studies by predicting the relationship between mAb dose and BDNF suppression across species.

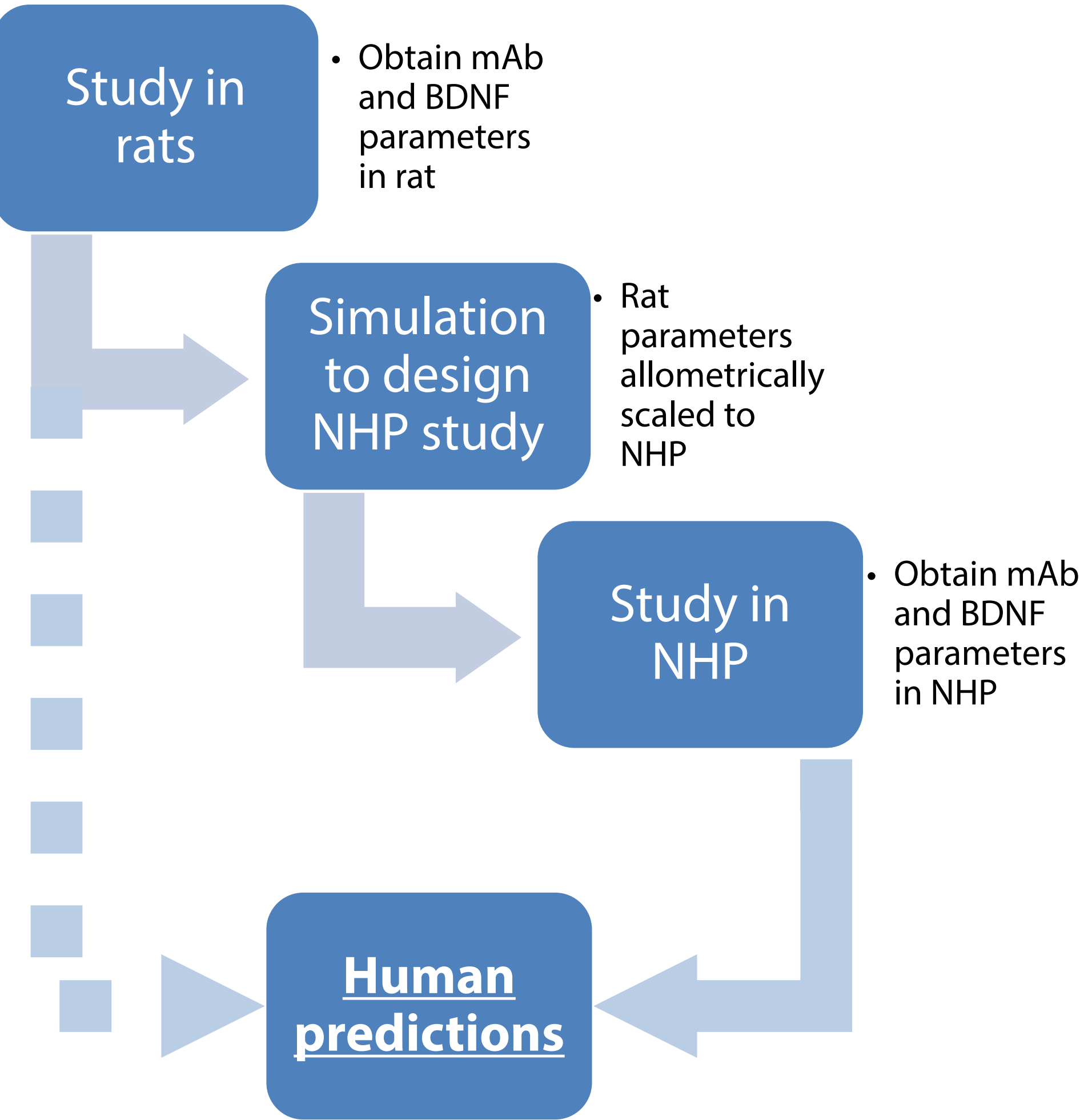
INTRODUCTION

Brain-derived neurotrophic factor (BDNF) is a small soluble protein (27 kDa) belonging to the neurotrophin family of growth factors. In sensory neurons, application of BDNF causes acute sensitization of peripheral nociceptors, leading to enhanced neuronal excitability and pain sensitivity. BDNF also promotes chronic pain processing via mechanisms involving gene transcription and alterations in the innervation pattern of sensory neurons. The pro-nociceptive actions of BDNF are mediated by both the high affinity tyrosine receptor kinase B (TrkB) and the low-affinity nerve growth factor receptor (p75NTR). Sequestration of BDNF may represent a potential therapeutic opportunity for the treatment of chronic pain states.



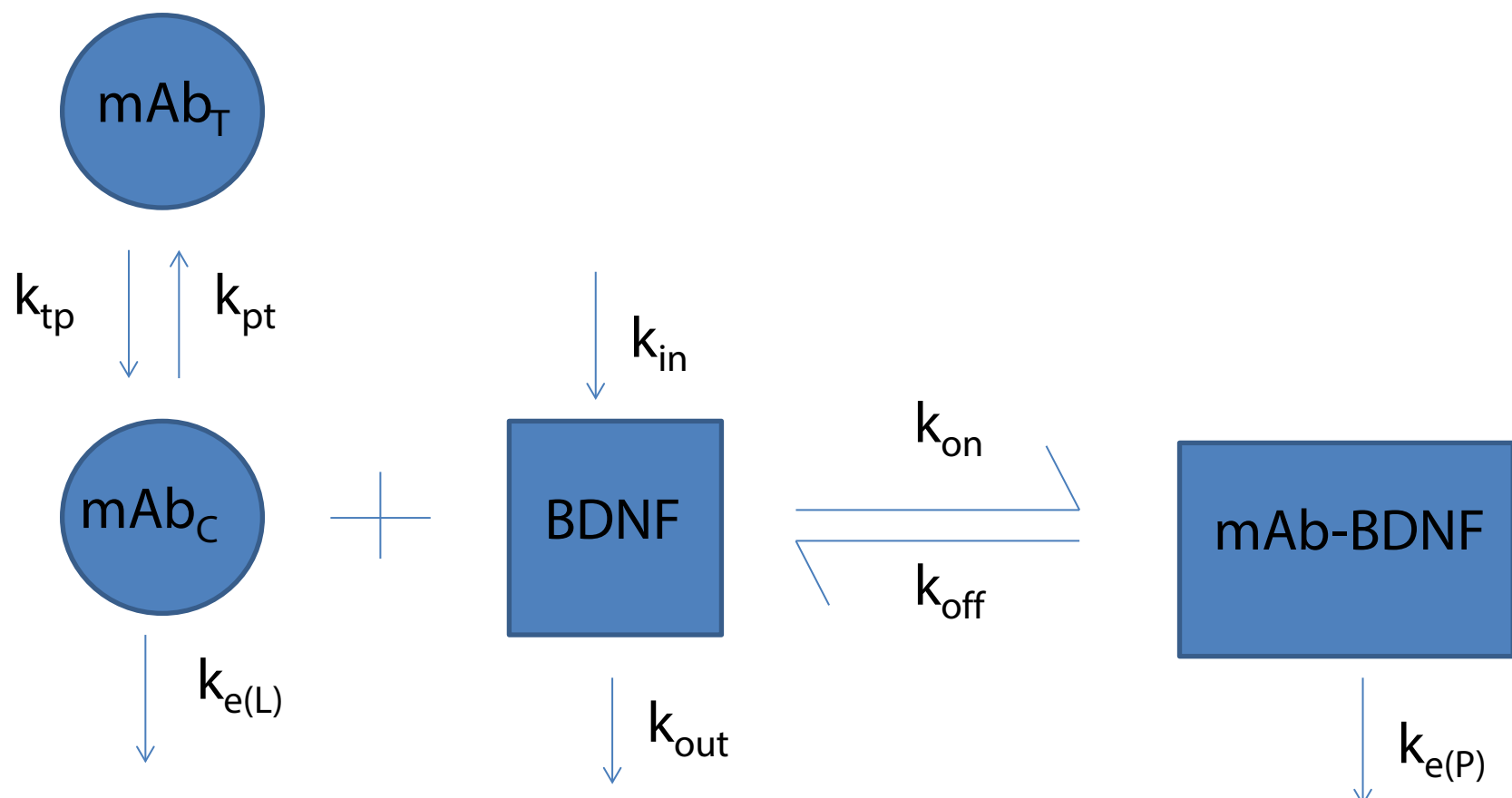
Drug X is a humanized IgG1 monoclonal antibody that is able to neutralize BDNF by inhibiting interaction with its receptors. In rat models of peripheral nerve injury, the molecule has been shown to reverse key mechanisms underlying neuronal hyperexcitability associated with peripheral nerve injury.

DEVELOPMENT STRATEGY



ANALYSIS OF RAT DATA

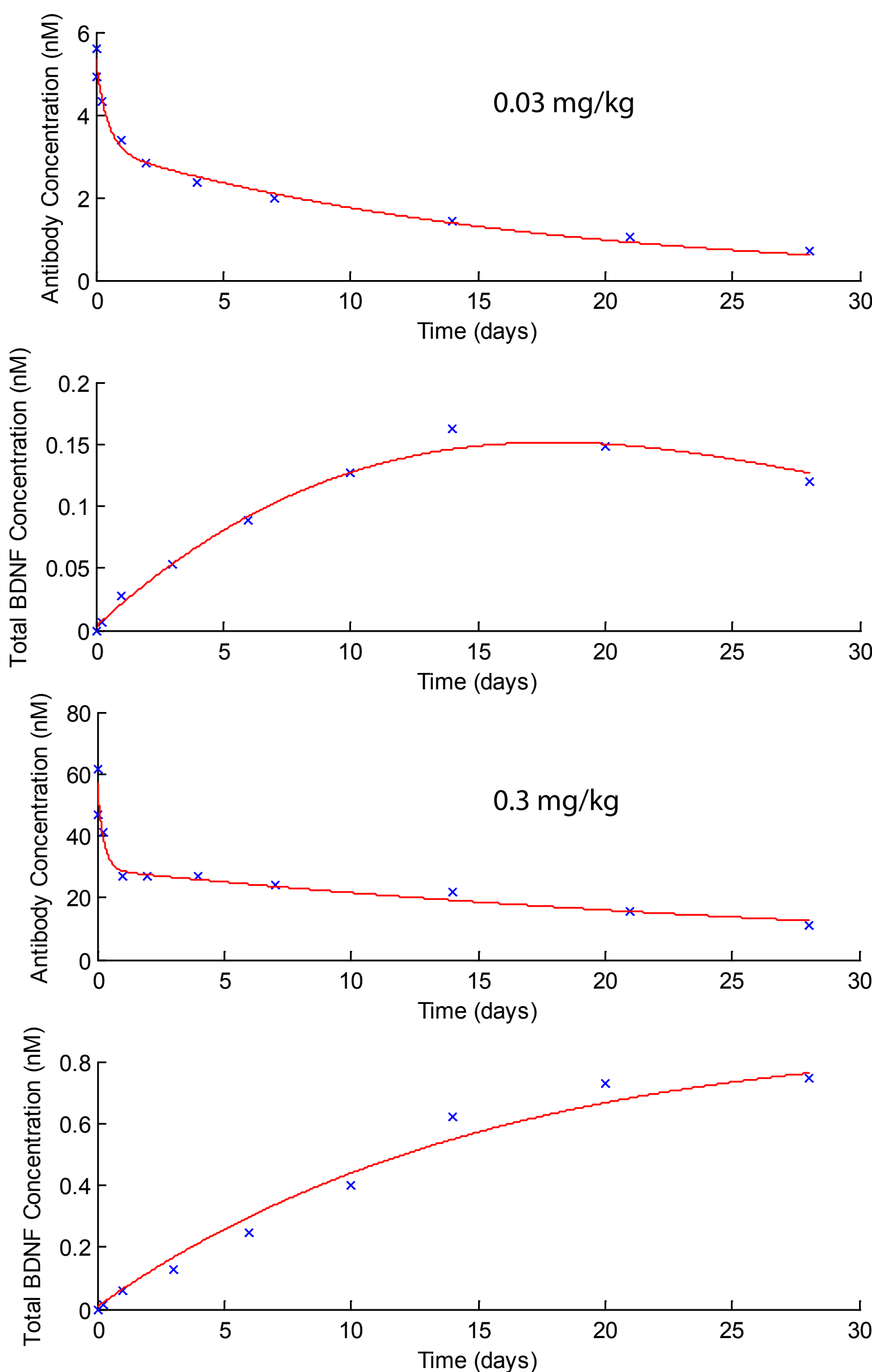
Plasma levels of mAb and total BDNF were measured after intravenous administration of drug X (0.1 and 1 mg/kg) in 4 rats for each dose level. The low dose data were removed from the final dataset because 3 rats out of 4 had suspected ADA. Mean concentrations were fitted with a TMDD model using Matlab R2012b software. Although no evidence of target-mediated drug disposition was observed in the range of tested doses, a TMDD approach was chosen because the translational biomarker of efficacy (free BDNF) is not directly measurable and must be derived through dissociation constant (Kd) from measured total BDNF.



TMDD parameters obtained in rats were used to predict the free BDNF suppression. They were allometrically scaled and used to predict the TMDD properties of drug X in *cynomolgus monkey*, so to design the following PK study in non-human primates (NHP). An early prediction of BDNF suppression in humans was also produced.

ANALYSIS OF NHP DATA

A similar approach was followed in NHP. Two dose levels (0.03 and 0.3 mg/kg) with 3 animals each were included in the analysis.

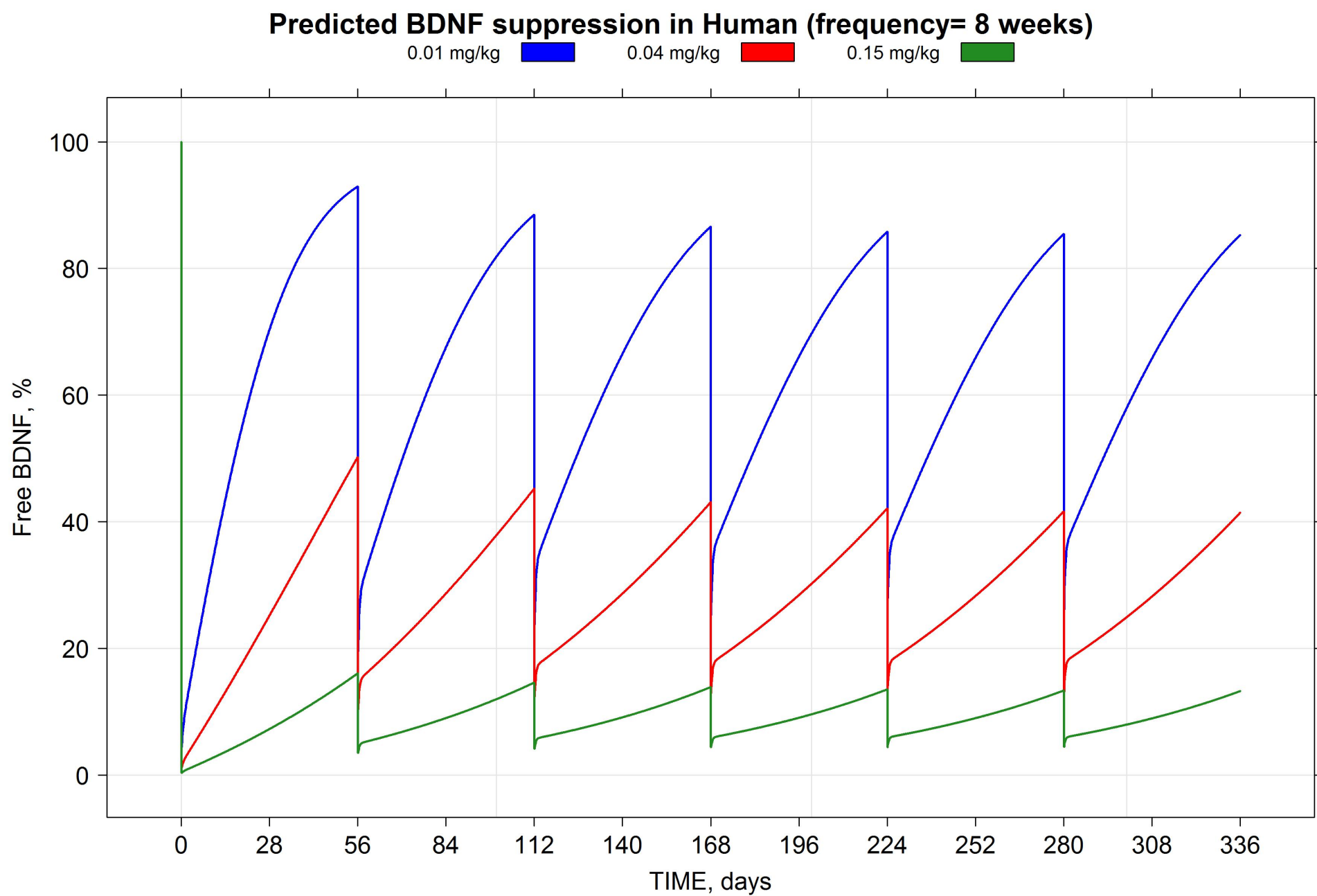


Parameter	Rats	NHP	Humans*
ke(L) (day ⁻¹)	0.064	0.073	0.025
kout (day ⁻¹)	44.586	9.762	3.374
ke(P) (day ⁻¹)	0.148	0.053	0.018
kon (nM ⁻¹ day ⁻¹)	59.053	59.558	59.558
koff (day ⁻¹)	0.625	0.505	0.505
KD (pM)	10.600	8.485	8.485
ktp (day ⁻¹)	1.387	1.677	1.677
kpt (day ⁻¹)	0.347	1.366	1.366
Half life antibody (days)	10.83	9.46	27.3
Half life BDNF (minutes)	22.4	102	296
Half life complex (days)	4.7	13.1	38.5

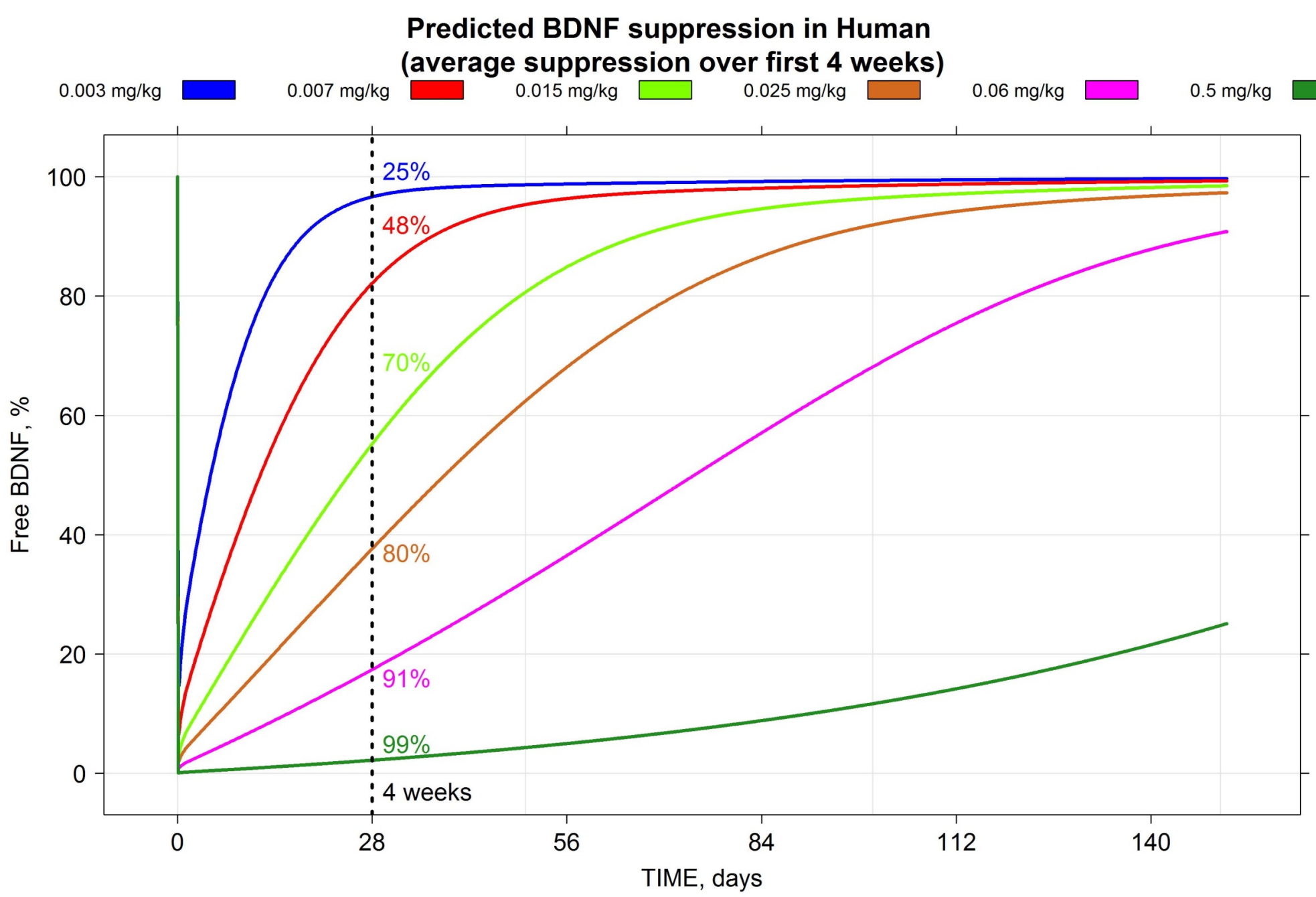
* Human TMDD parameters were allometrically scaled from NHP parameters

HUMAN PREDICTIONS

The TMDD model developed in NHP was used to predict drug X pharmacokinetics and BDNF suppression in humans. Different doses and dosing frequencies were simulated to understand the time course of the BDNF suppression and to help design future studies in man. All simulations were performed using Berkeley Madonna 8.3.18 software.



Simulations were particularly helpful in determining that, irrespective of the dose, the initial BDNF suppression following administration of potentially therapeutic doses is always >90%: this might have safety implications that need consideration when designing the first-in-human study.



Linking BDNF suppression to actual antinociceptive effect is challenging: such relationship has not been fully defined yet. In rats, the minimum dose that resulted in measurable efficacy 5 days post-dose was 0.03 mg/kg, which according to model simulations was predicted to cause an average free BDNF suppression of 37%. In humans, doses predicted to produce a range of free BDNF suppressions were identified (e.g. average 30, 70 and 90% over the considered interval).

Mean BDNF suppression in man	Time period	Dose required
30%	4 weeks	0.0035 mg/kg
70%	4 weeks	0.015 mg/kg
90%	4 weeks	0.06 mg/kg
30%	8 weeks	0.008 mg/kg
70%	8 weeks	0.03 mg/kg
90%	8 weeks	0.125 mg/kg

CONCLUSION

A TMDD model adequately described drug X pharmacokinetics and pharmacodynamics (defined as free BDNF concentration in central compartment). This analysis provides an example in which TMDD models were used to predict PKPD properties of a mAb across species, helping the design of preclinical studies and the mechanistic extrapolation of results to humans.