A novel mathematical framework to predict in vivo bispecific GTX-B001 binding in skin, and translation to humans

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Mechanistic quantitative pharmacology informs FIH study design for a novel bispecific antibody for chronic urticaria.

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Background and Objective

GTX-B001 is a humanized **bispecific antibody** designed to selectively **target and inhibit mast cells** by binding to **c-Kit** and **CD203c**. GTX-B001 is expected to be best-in-class for the treatment of **Chronic Urticaria** (CU).

Our novel modeling and simulation framework is based on the **integration of in vitro and in vivo data**.

Objectives:

i. to develop a quantitative framework that integrates in vitro binding dynamic data with in vivo pharmacokinetic (PK) data in Non-Human Primates (NHP) and enables to **predict GTX-B001:c-Kit:CD203c formation in skin** (target organ in CU);
ii. To aid the interpretation of GTX-B001 pharmacological activity by **identifying optimal GTX-B001 skin concentration range** to maximize skin trimer formation (driver of efficacy),
iii. to **support FIH study** design via translation to humans.

Methods

GTX-B001 in vitro binding dynamic model (SFig 1A) was based on the work by Sengers *et al.* [1] and relied on experimentally measurable parameters (N=10) and assumptions from literature [1] (N=8), **18 parameters** in total.

GTX-B001 in vivo minimal physiologically based pharmacokinetic (**mPBPK**) model (SFig 2A) was based on the work by Cao and Zhao [2, 3]. **System-specific parameters** (N=9) were informed using **literature-retrieved** values [2, 3]. **Drug-specific parameters** (N=6) were **estimated** from two NHP studies (*N=10; GTX-B001 1, 10, and 50 mg/kg administered as single and repeated dose administration; SD, RD*).

Model fitting was performed in R with the nlmixr2 package using the SAEM algorithm [4].

The GTX-B001 **in vitro model was then integrated** with the GTX-B001 **in vivo mPBPK** model assuming that: (i) GTX-B001 **binding** to its targets **occurs in the skin** compartment (tight tissue) of the mPBPK model, (ii) only **cis-binding** is happening, (iii) the two targets are uniformly mixed and exposed to the antibodies, (iv) **binding dynamics** might **not directly modify** GTX-B001 **PK**. Assumption (iv) was supported by the absence of clear target-mediated drug disposition features in the observed concentration–time profiles that could support their identifiability.

Lastly, **translation to humans** was based on **species-specific physiology** [2, 3] and **allometry** [5, 6]. Clinical regimens (*0.11, 0.33, 1, 3, 9, 27 mg/kg, administered as SD via IV infusion of 30 minutes*) were simulated to inform FIH study.

Results - GTX-B001 in vitro model

It characterized GTX-B001 binding dynamics and showed that the profile of **trimer concentrations versus GTX-B001 concentrations** follows a **bell-shaped curve**, typical for bispecific antibodies (SFig 1B). At low GTX-B001 concentrations (10^{-2}-10^{-1} nM), cell binding is dominated by cross-linked antibody, whereas monovalent binding increases at higher concentrations (10^{4}-10^{5} nM), when cross-linking is complete. **Ternary complexes** are favored at **intermediate antibody concentrations** (**1-10^{3} nM**), which are model predicted GTX-B001 **concentration** for **efficacy**.

References

[1] Sengers et al., MABS, 2016, VOL. 8, NO. 5, 905–915
[2] Cao et al., 2013, J Pharmacokinet Pharmacodyn, 40, 597–607
[3] Zhao et al., 2015, Pharm Res., 32(10), 3269–3281
[4] Fidler M., nlmixr2: Nonlinear Mixed Effects Models in Population PK/PD. R package version 5.0.0, https://nlmixr2.org/.
[5] Milo et al. Nucl. Acids Res. (2010) 38 (suppl 1): D750-D753.
[6] Germovsek et al., 2021, mAbs, 13:1, 1964935

Results – GTX-B001 mPBPK model in NHP

The model, using GTX-B001 **plasma concentrations** as **input**, **predicted concentrations** in **skin**, from which direct observations were not available (SFig 2B). Consistent with antibody distribution, **skin concentrations** resulted several folds **lower** than in **plasma**. GTX-B001 plasma clearance (CLp) was 5.9E-4 L/h (RSE%25) with IIV of 52%; plasma volume of distribution (Vp) was 1.2E-1 L (RSE%4) with IIV of 6%; vascular reflection coefficient for tight and leaky tissues (σ_1, σ_2) were 8.43E-01 (RSE%7) and 8.58E-01 (RSE%5), respectively. The model also included a non-linear CL from plasma compartment (Vmax=3.13E-04 umole/h, Km = 5.29E-01 uM), which helped to better reproduce GTX-B001 PK profiles associated with the 1 mg/kg dose administration.

Results – GTX-B001 in vitro – in vivo model

It **bridged** the **in vitro system** with the **in vivo system** and **predicted trimer concentrations** (Fig 1) and fraction occupancy in **NHP**, which are key to interpret GTX-B001 pharmacology activity. In terms of trimer formation and fraction occupancy, **1 and 10 mg/kg** resulted the **best regimens**, 50 mg/kg RD regimen resulted sub-optimal. Trimer concentrations tended to decrease after RD administration.

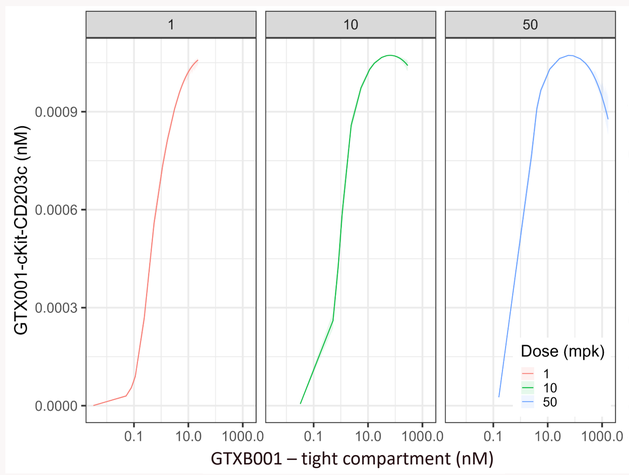


Figure 1 NHP: Predicted trimer concentration in skin versus predicted GTX-B001 concentration in skin after RD administration (see figure SFig 2B).

Results – GTX-B001 human model

3 and 9 mg/kg (administered as SD via IV infusion of 30 minutes) resulted as **best regimens** in terms of **trimer formation** and likely efficacy (Fig 2). **Doses ≥ of 3 mg/kg** achieved skin concentrations which remained **above GTX-B001 in vitro IC50 threshold** (**5.2 nM**) for the simulated period of 4 weeks. 1 and 0.33 mg/kg resulted in some trimer formation, but exposure was equal or below the in vitro IC50 threshold (even at Cmax), so they were not considered therapeutic.

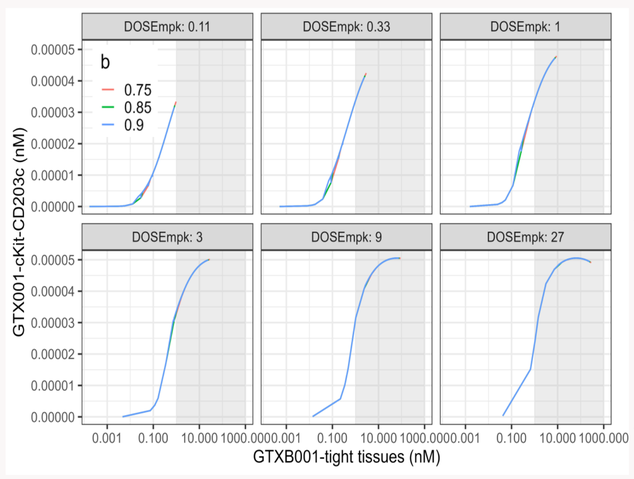


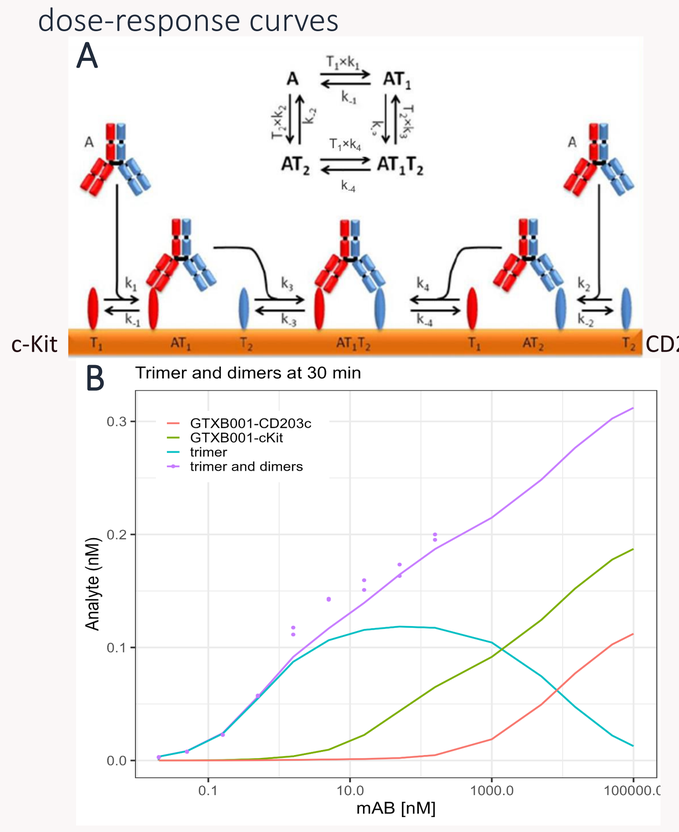
Figure 2 Simulated trimer concentrations vs GTX-B001 concentration in tight tissues. Shaded area indicates the optimal range of GTX-B001 for trimer formation.

Conclusions

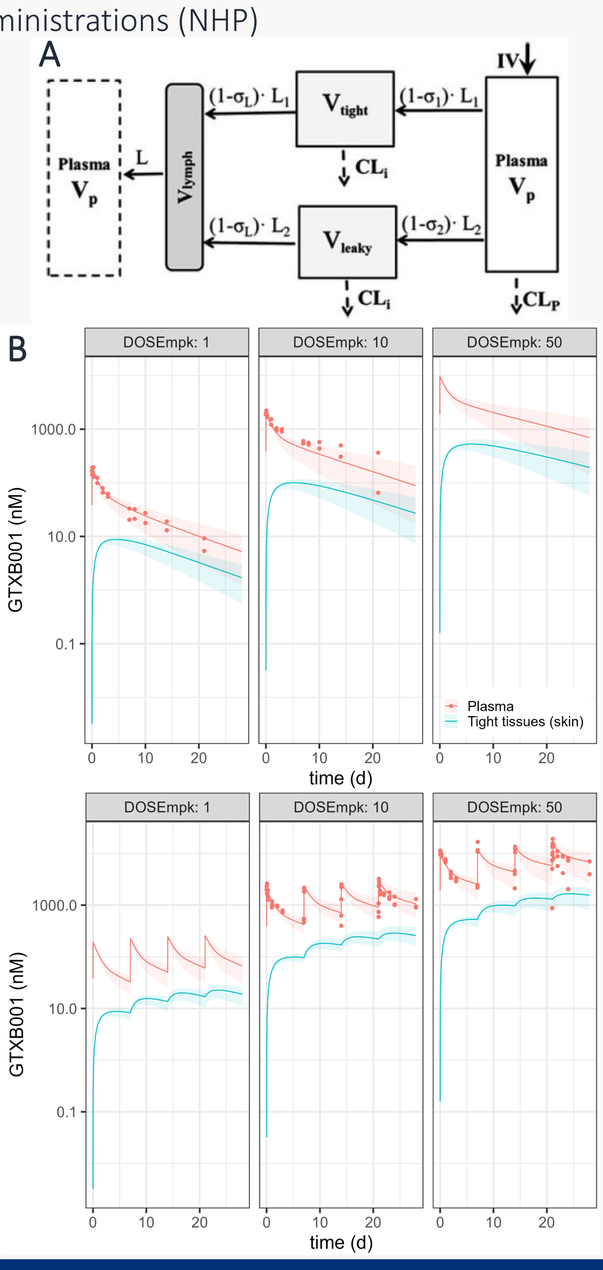
We developed a **novel mathematical framework** which **integrates in vitro data** of GTX-B001 **cellular binding with** GTX-B001 **PK data** in **NHP** and is key to **interpret pharmacological activity**. The model provides **in vivo** and **clinical predictions** of **GTX-B001:c-Kit:CD203c formation** dynamics in **skin**.

Additional Figures

Sup Figure 1 - A: In vitro binding of GTX-B001 to c-Kit and CD203c on KU812$ cell membrane. **B**: GTX-B001In vitro cell binding dose-response curves



Sup Figure 2 - A: GTX-B001 mPBPK model. **B**: Simulated GTX-B001 PK profiles in plasma and tight tissue after single and repeated dose administrations (NHP)



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