Leveraging *in vitro* data from novel drug candidates to prioritize antibody combinations in autoimmune disease using a QSP model of IBD

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Introduction

- Treatment responses in autoimmune disease have reached a ceiling effect and so novel combination treatment approaches have been proposed [1]
- Quantitative systems pharmacology (QSP) modelling can help identify and prioritise potential combinations
- A method for using *in vitro* data from novel combinations to predict efficacy is demonstrated using a QSP model of inflammatory bowel disease (IBD)

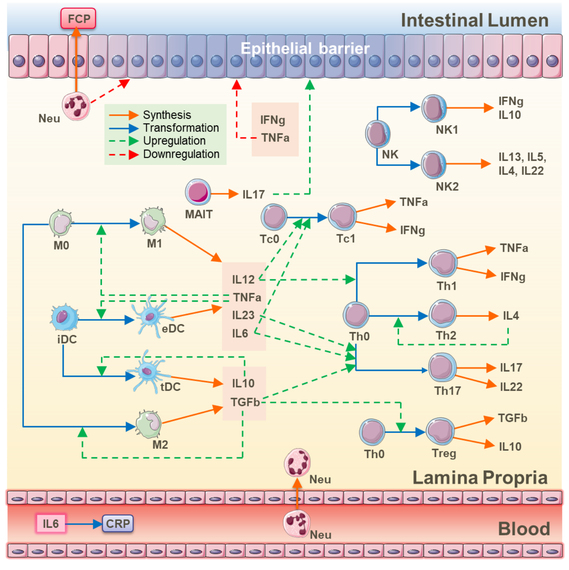


Figure 1: Overview of the IBD QSP model

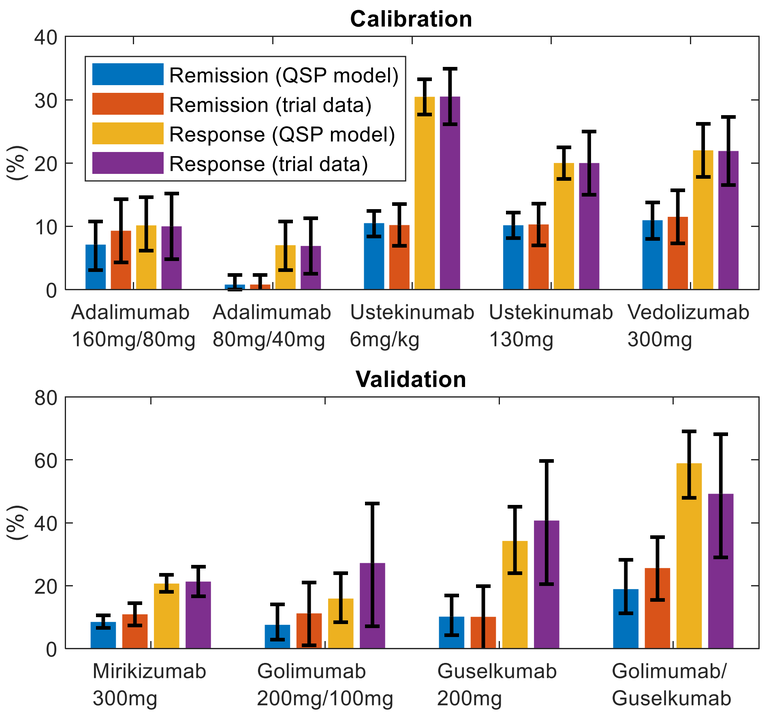
Methods

We adapted a published QSP model of IBD [2] with the following additions:

- Novel target biology and pathways to represent the mechanism of action of drug candidates for the prediction of induction therapy (Figure 1)
- An empirical representation of the full Mayo score for ulcerative colitis (UC) which assumed a correlation with cellular markers of inflammation

A virtual population (VPop) was generated with baseline patient characteristics and % clinical remission/response consistent with multiple therapies (Figure 2):

- Calibration: adalimumab (aTNFα), ustekinumab (aIL12/23), vedolizumab (aα4β7) [3-6]
- Validation: mirikizumab (aIL23) and the recent VEGA trial [1] – a published combination trial of guselkumab (aIL23) and golimumab (aTNFα) for UC



VEGA trial validation

	QSP	Data [1]
Guselkumab monotherapy remission	10.2% [4.2-16.9]	10.1% [0.0-19.9]
Guselkumab monotherapy response	34.2% [23.9-45.1]	40.7% [20.6-59.7]
Golimumab monotherapy remission	7.6% [2.8-14.1]	11.2% [1.1-21.0]
Golimumab monotherapy response	15.9% [8.5-24.0]	27.2% [7.1-46.2]
Combination therapy remission	18.9% [11.3-28.2]	25.6% [15.5-35.4]
Combination therapy response	58.9% [47.9-69.0]	49.2% [29.0-68.2]

%remission/response based on full Mayo score

Figure 2: QSP model VPop calibration & validation (mean and 95% CIs shown).

- *In vitro* data were leveraged which captured cytokine levels in healthy PBMCs in response to different doses of a novel antibody and existing anti-TNFα (aTNFα) therapy
- A scaling factor was determined by matching the *in vitro* and clinical (adalimumab) reduction observed in TNFα in response to aTNFα therapy
- This scaling factor was then applied to *in vitro* data to estimate the clinical reduction in cytokine levels for novel therapies (examples in Figure 3)

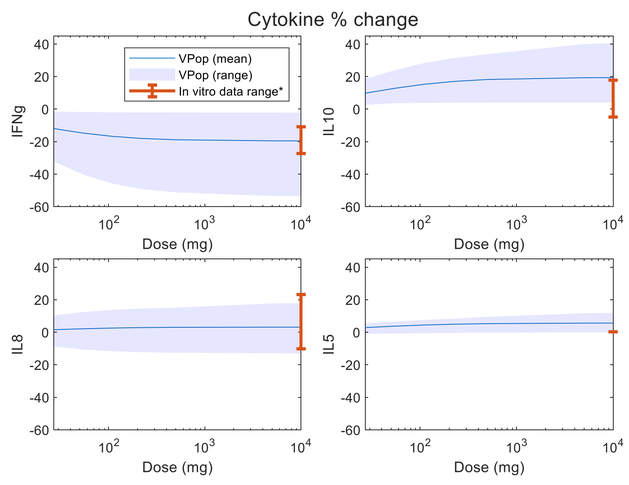


Figure 3: Comparison of VPop and *in vitro* cytokine % change. *Data scaled using factor described in text.

Results

For 2 novel antibody (mAb1 and mAb2) combinations with TNFα, our VPop predicted the following based on full Mayo score at week 12 for 150mg, Q4W:

- mAb1 induced almost no remission on its own, but combined with TNFα remission was predicted to be ~10%, slightly exceeding that of aTNFα alone
- mAb2 induced a small (~5%) rate of clinical remission on its own and >15% when combined with TNFα, greatly exceeding TNFα monotherapy (Figure 4)

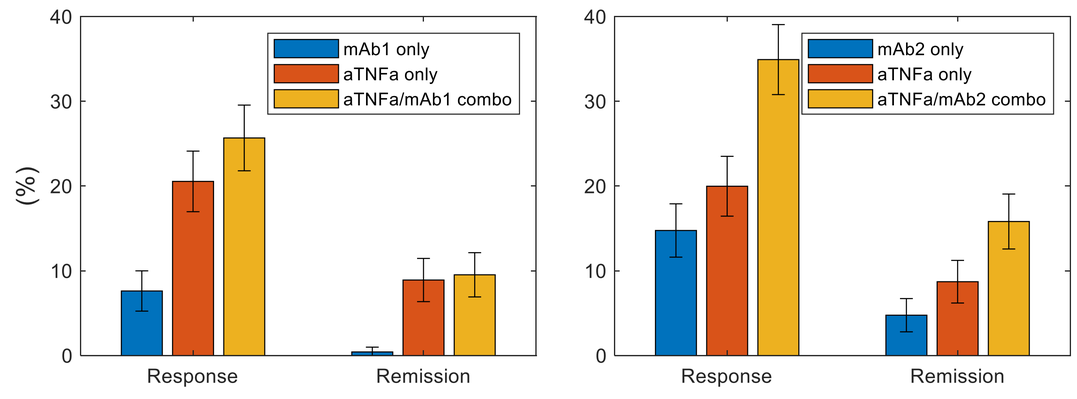


Figure 4: Bar charts showing remission/response (mean ± SD) at 150mg dose.

At doses >600mg the VPop predicted clinical remission for the aTNFα/mAb1 combination to exceed that of the aTNFα/mAb2 combination (Figure 5).

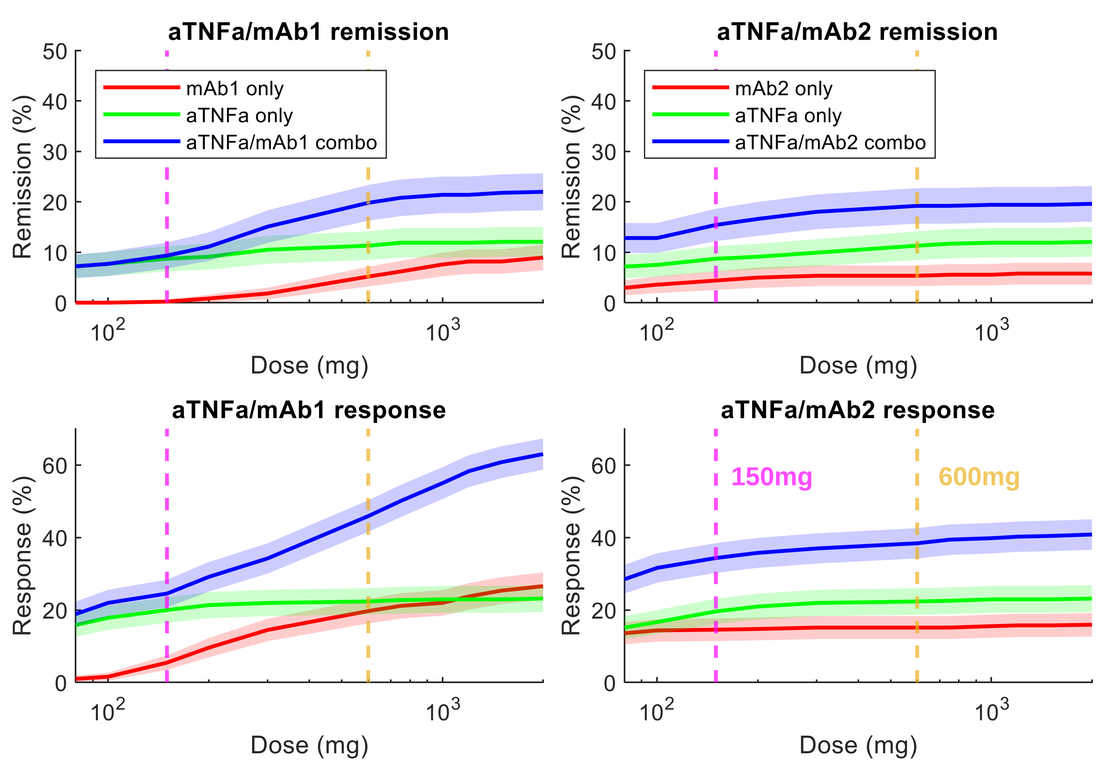


Figure 5: Dose-remission/response plots for novel antibodies as monotherapy or combination with TNFα. Solid lines/shaded regions show VPop mean ± SD.

Conclusions

- A publicly available model of IBD [2] was extended to represent novel target biology and the full Mayo score in UC for the prediction of induction therapy
- The QSP model VPop was calibrated and validated against several biologics of interest [3-6] – including the VEGA combination trial [1]
- An innovative approach was used to derive a scaling factor from available *in vitro* data for novel drug candidates which allowed us to predict and compare clinical efficacy of two novel antibody combinations with the QSP model and make recommendations to clinical teams
- The approach can be used for other drugs in development to support predictions of efficacy when clinical data are not yet available

Acknowledgements

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References

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Ahead Together