# Mathematical modeling can help to successfully translate preclinical findings in mice models of asthma into first-in-human trials

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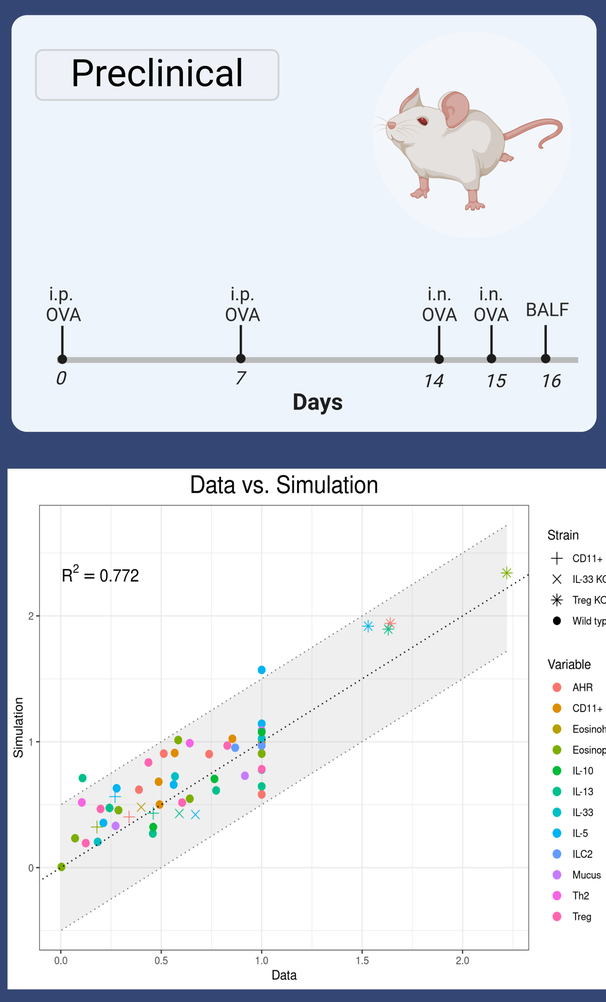
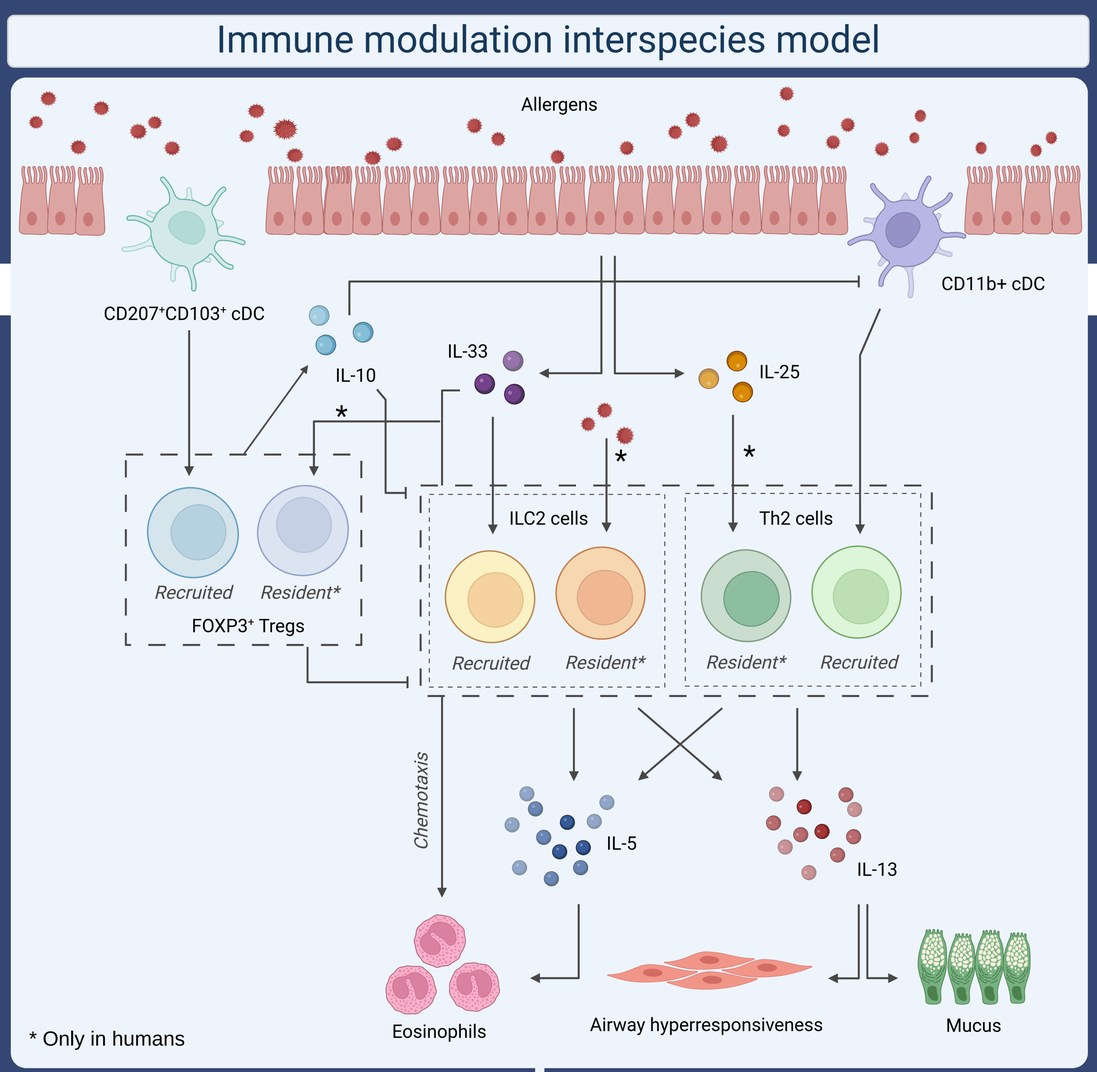
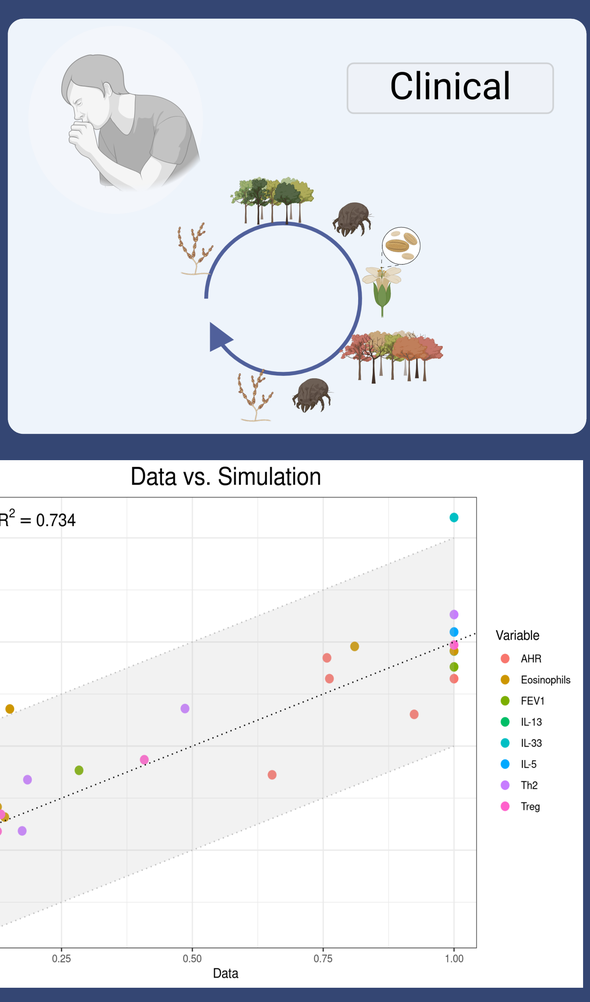
## BACKGROUND

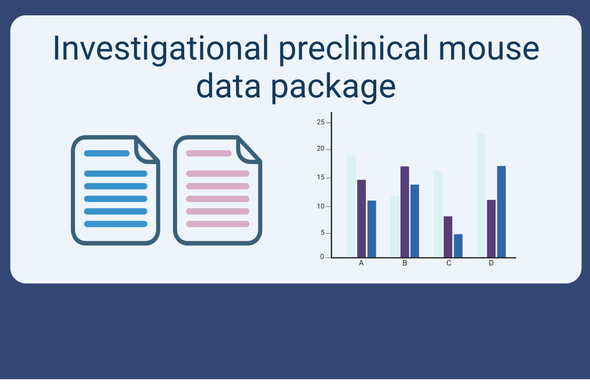
Experimental mouse models of asthma are instrumental for investigating immunological pathways and candidate drugs. But they have limitations, which has led to resources being spent on drug candidates that show promise in preclinical settings, but often fail in clinical trials. Detecting such false-positive candidates would improve the efficiency of drug development pipelines. Mathematical models could bridge preclinical results with the clinical context by incorporating species-specific characteristics and can be informed with previous treatment investigations. Here we report the development of a translational quantitative systems pharmacology (QSP) model of asthma which captures the dynamics of key immune markers following an allergen challenge, both in mice and humans.

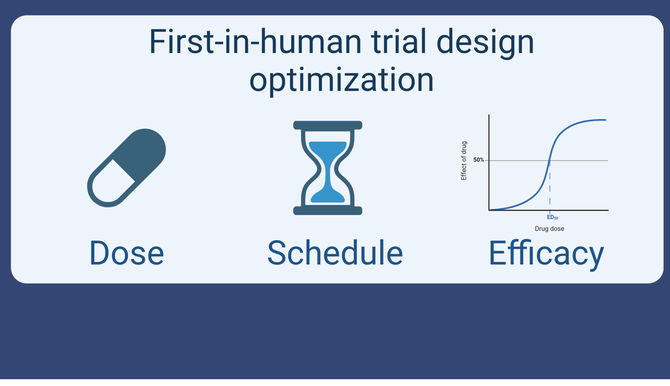
# **QSP model of asthma** can help **translate preclinical** findings in mice models of asthma into **first-in-human trials**




## METHODS

- A system of ordinary differential equations describes the kinetics of 12 biomarkers including different cell types (CD103+ and CD11+ DCs, Tregs, ILC2s, Th2, eosinophils), cytokines (IL-5,-10,-13,-33), mucus overproduction and airway hyperresponsiveness.
- The model was parametrized using a large dataset from heterogeneous sources composed of time dynamics of these markers following an allergen challenge in mice and humans, as well as their fold-change in knock-out mice strains.
- We parameterized the model to reproduce the mouse dataset and then applied allometric scaling for the translation to humans.
- We added three cell populations specific to the human model: tissue-resident memory Th2 and Treg cells, and memory-like ILC2 cells. This follows the hypothesis that the tissue-resident memory compartment in humans is highly activated compared to mice due to years of repeated allergen exposure.

## RESULTS

- Our translational model can replicate the kinetics of 12 key immune markers in response to an allergen challenge in humans, wild-type mice, and in knock-out mice with CD11+ DCs, IL-33 or Tregs depletion.
- The effect of an investigational treatment on experiments *in vitro* or with *in vivo* mouse models can then be added to the translational model. This would allow to simulate first-in-human trials for the investigational treatment, with the possibility of exploring *in silico* how humans might react to different doses, schedules, and what is the expected efficacy.
- Simulations with the model can also help to the early identification of investigational treatments that generate false positive responses in mice.

## CONCLUSION

- We developed a translational model of the late asthmatic response to an allergen challenge that can be broadly used in the drug development pipeline for new asthma treatments.
- In early stages, the model could help generate new hypotheses and guide preclinical experiments design.
- The model could also explore how candidate drugs with strong preclinical support could perform in first-in-human trials, while in later stages of drug development it could give insights for clinical trial design.

## REFERENCES

[1] Holmes et al., Animal models of asthma: value, limitations and opportunities for alternative approaches. Drug Discovery Today (2011), DOI: 10.1016/j.drudis.2011.05.014
Diagram created in BioRender.com