

A quantitative systems pharmacology model for evaluating potential drugs for treatment of asthma

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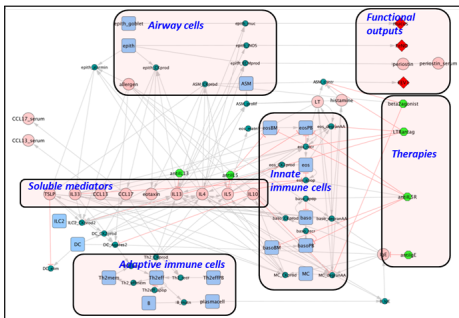
PURPOSE

- Asthma is a chronic inflammatory disease of the airways involving numerous underlying immunological and stromal pathways.
- Various treatments in development target activities or proteins in these pathways, and show differential impact on clinical outcomes and pathway biomarkers.
- To support evaluation of new asthma targets and compounds, we have developed a mechanism-based systems model representing different cellular and molecular contributors to disease.
- Here we demonstrate the ability of the model for predicting changes in biomarker endpoints for novel therapeutic interventions and obtaining a better understanding of the mechanistic drivers of that change

MODEL SCOPE & DIAGRAM

Biological Scope of Model

- Innate immune cells:** eosinophils, basophils, dendritic cells, ILC2s, mast cells.
- Adaptive immune cells:** Th2, B, & plasma cells.
- Airway resident cells:** epithelial, goblet, & ASM cells
- Soluble mediators:** IL4, IL5, IL13, IL10, IL33, eotaxin, TSLP, CCL17, CCL13, histamine, leukotrienes, IgE, and allergen, periostin.
- Clinical measurements:** FEV1, FeNO.
 - ΔFEV1 modeled via altered ASM biology.
- Interventions:** fluticasone (inhaled corticosteroid), mepolizumab (anti-IL-5), lebrikizumab (anti-IL-13), omalizumab (anti-IgE), montelukast (leukotriene antagonist), anti-ST2



Data & Patient Types

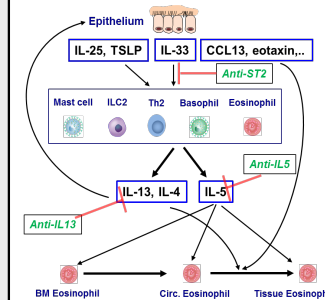
- Mechanistic connections** and initial parameter estimates were derived from published and internal non-clinical (*in vitro*) studies.
- Published clinical data** were concatenated in a large data repository (observational and clinical trials)
 - cell and mediator measurements from Phase II/III clinical trials.
 - functional measures of FEV1 and FeNO from published clinical studies.
 - bronchoscopy tissue derived cell densities from smaller observational studies.
- 4 patient phenotypes** (one healthy & three asthmatics with mild, moderate, and severe disease) developed by optimizing parameters (scatter search) against corresponding clinical data
- Variability in the underlying biology and clinical responses were explored by developing a virtual population of patients

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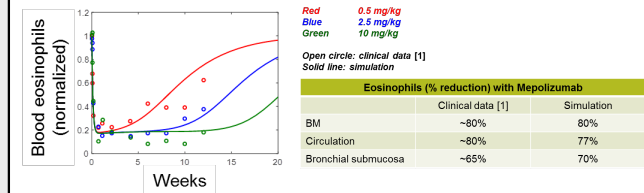
MODEL BASED RESEARCH

Exploring blood eosinophil as biomarker of response

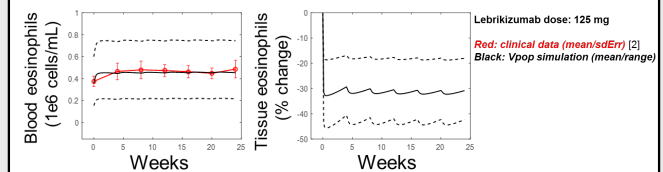


- IL-33 produced by activated epithelial cells
- IL-33, TSLP, IL-25 activate mast cells, ILC2, Th2, basophils, eosinophils and these cells produce IL-4, IL-5, IL-13
- Eosinophil maturation & apoptosis is regulated by IL-5
- Eosinophil recruitment into the tissue is regulated by:
 - IL-4 & IL-13 by regulation of expression of P-selectin & VCAM-1
 - Chemo-attractants such as CCL13, eotaxin
- Th2 cytokines regulate epithelial cell activation partially

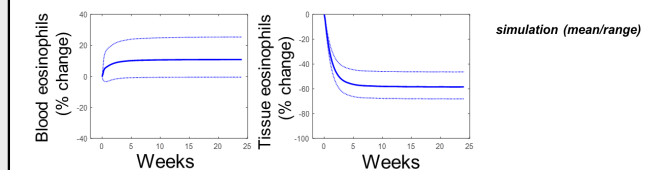
- Model captures eosinophil drop in blood and tissue with mepolizumab



- Blood eosinophils increase with lebrikizumab but tissue eosinophils predicted to drop by ~30%



- Th2 cytokines predicted to drop by ~60% with anti-ST2
- Blood eosinophils are predicted to have minimum change (opposing effects changes in IL-13 & IL-5 levels); tissue eosinophil levels predicted to drop by ~60%



SUMMARY

- We have developed a QSP model of asthma disease and tested its ability to capture critical data on patient types and treatment responses. *The ability of the model to simultaneously capture these clinical measurements increases confidence in the representations and methodologies.*
- The model has been utilized to support clinical and biomarker development strategies for novel interventions
 - For the anti-ST2 intervention the model predicts that blood eosinophil levels may not be a good indicator of expected reduction in tissue eosinophils
- The QSP Asthma platform model will continue to be utilized to support the drug development pipeline at Genentech

REFERENCES

- Smith DA, Minthorn EA, Beerah M. Pharmacokinetics and pharmacodynamics of mepolizumab, an anti-interleukin-5 monoclonal antibody. *Clin Pharmacokinet.* 2011 Apr;50(4):215-27
- Corren J et al. Lebrikizumab treatment in adults with asthma. *N Engl J Med.* 2011 Sep 22;365(12):1088-98