

A quantitative systems pharmacology platform for one immune cascade calibrated to four biologics

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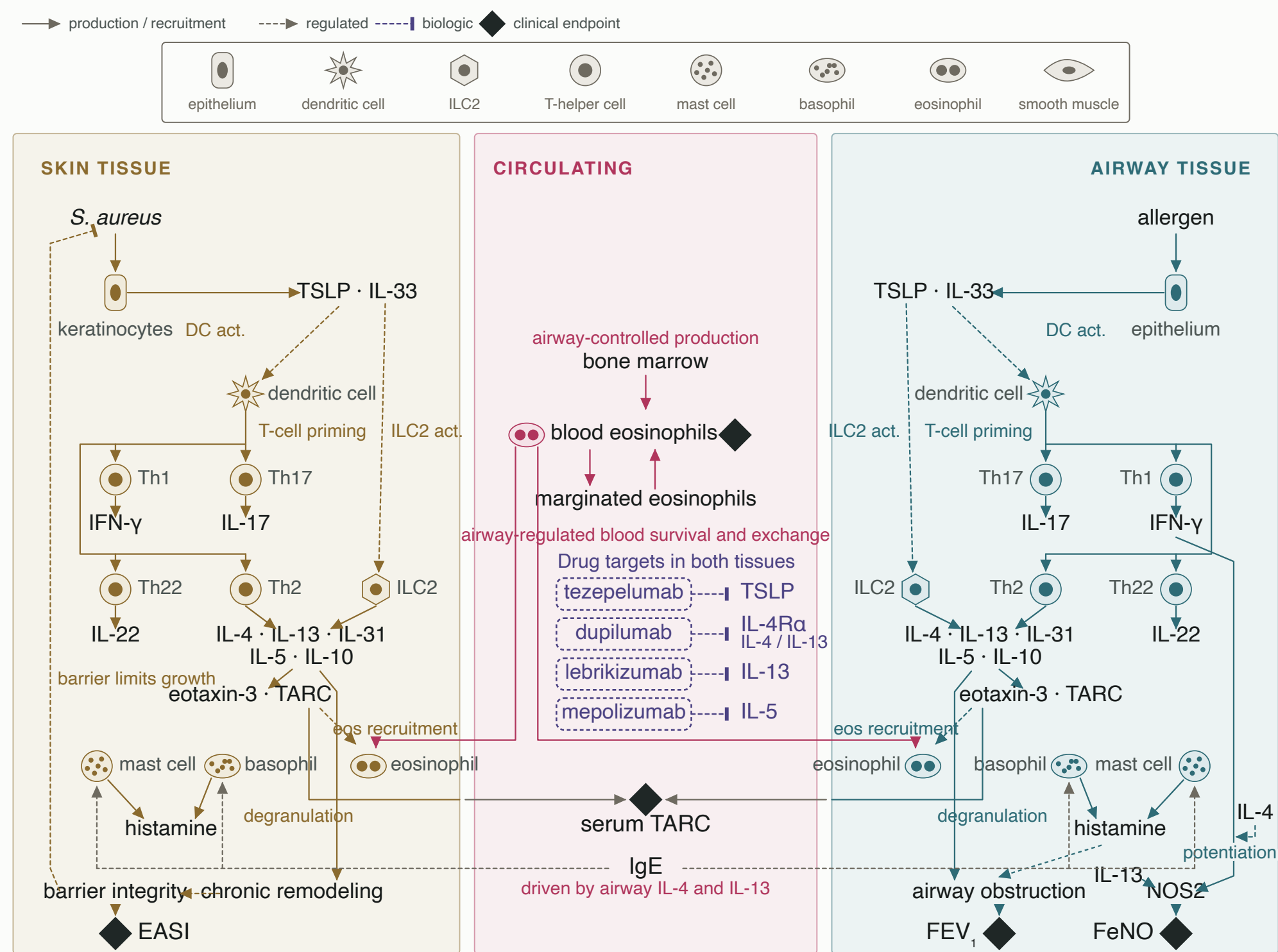
Background and Objectives

Background: Atopic dermatitis (AD) and asthma share a type-2 immune axis and the same biologics: dupilumab (anti-IL-4R α), lebrikizumab (anti-IL-13) and tezepelumab (anti-TSLP), with mepolizumab (anti-IL-5) in asthma. Published QSP models describe each disease on its own [1,2].

Objectives:

- Build one reaction network in which the same immune cascade, placed in skin or airway, gives AD or asthma, and calibrate it to biologic responses in both.
- Use it to compare a combination across indications and asthma phenotypes, and to rank untested targets.

Model Structure



- One local immune cascade, placed in skin or airway, linked by circulating IgE and blood eosinophils. Catalyst (Julia), 57 states, 226 biological/PK parameters (155 from the literature [1,2]) and 14 virtual inhibition controls.
- *S. aureus* burden in skin gives AD; persistent airway allergen gives asthma.
- Eczema Area and Severity Index (EASI) follows pathogen burden and barrier loss.
- Forced expiratory volume in 1 s (FEV₁) combines phenotype-specific fixed obstruction with reversible IL-13, IL-4, histamine and TSLP terms, amplified by baseline smooth-muscle mass.
- Fractional exhaled nitric oxide (FeNO) follows epithelial nitric oxide; serum thymus and activation-regulated chemokine (TARC) sums both tissues.

Methods

Phenotypes. Eight asthma parameter sets reproduced the baselines in Table 1 through three conditioned quantities: type-2 activation, marrow eosinophil capacity and fixed airway obstruction. AD arms started from one enrollment state (EASI 29.3 [2]) and relaxed toward the chronic state, which produced the placebo response.

Study population or subgroup	Blood eos ($\times 10^9$ /L)	FeNO (ppb)	FEV ₁ (% predicted)
Wenzel 2016, eosinophils <300	0.172	29.7	61.9
Lebrikizumab, eosinophil-low	0.18	20	62
QUEST, median baseline	0.25	25	58.4
QUEST, mean baseline	0.351	34.2	58.4
PATHWAY	0.367	33.5	58.9
Lebrikizumab, eosinophil-high	0.44	32	60
Wenzel 2013	0.55	37.5	72
Wenzel 2016, eosinophils ≥ 300	0.59	51.7	59.2

Table 1. Clinical baselines used to condition the asthma phenotypes [1,4-7,10-12]. QUEST mean and median are two summaries of the same cohort.
Eos: eosinophils.

Drugs. Each biologic had two-compartment PK [3] and acted through tissue concentration (Table 2).

Biologic	Target	Mechanism	Potency
Mepolizumab	IL-5	$E_{\max}$ 0.885	IC ₅₀ 0.85 nM
Lebrikizumab	IL-13	$E_{\max}$ 0.99	IC ₅₀ 4 nM
Tezepelumab	TSLP	$E_{\max}$ 0.99	IC ₅₀ 5.38 nM (fitted)
Dupilumab	IL-4R α	competitive shift	K 15 nM

Table 2. Drug mechanisms and potencies. Neutralization as an $E_{\max}$ function of tissue concentration; dupilumab shifts the half-maximal constants of IL-4R α -dependent responses.

Calibration. Twenty-five parameters were fitted (BOBYQA, 323 weighted terms) to biologic time courses, day-400 endpoints and serum TARC in asthma [1,4–10] (TARC not shown) and to placebo-corrected EASI, lesional markers, serum TARC and total IgE in AD [2,11]. Each arm was a single trajectory.

References

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Results: Calibration to Four Biologics

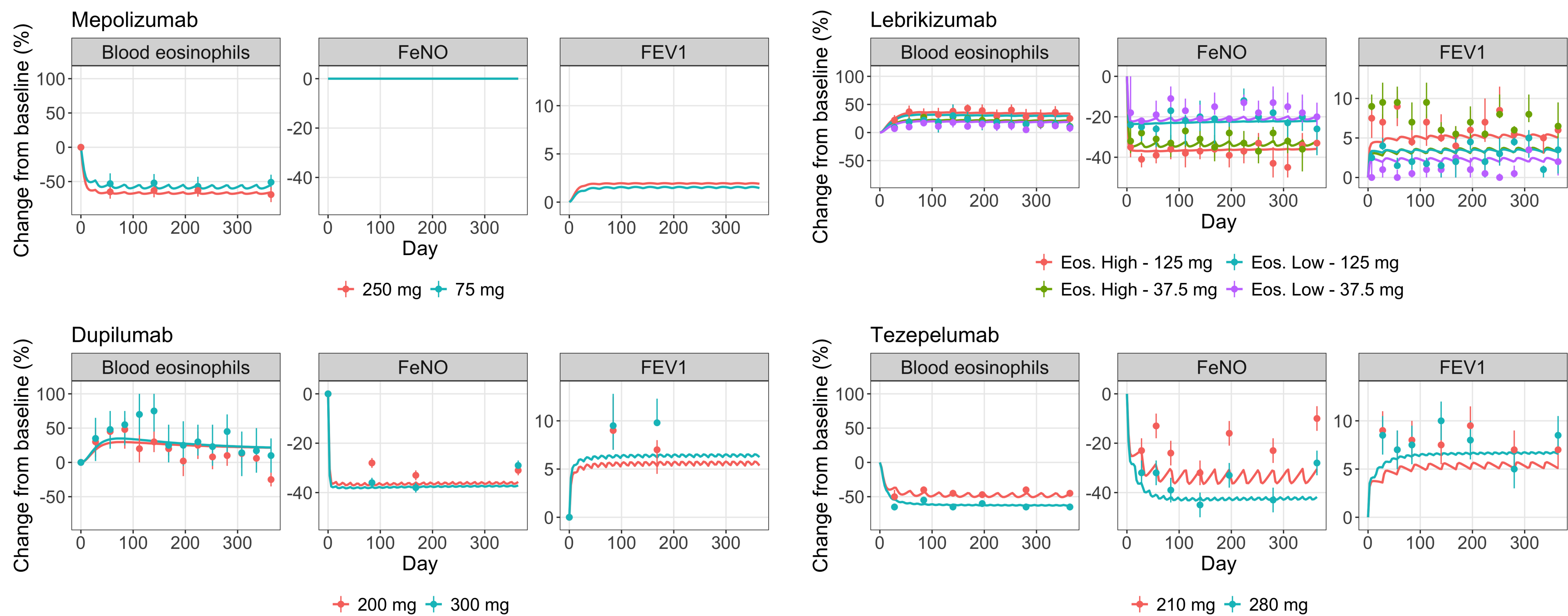


Figure 1. Biomarker time courses under the four biologics. Points are digitized trial means $[1] \pm \text{SEM}$; lines are the model. Phenotypes: Wenzel 2016 eosinophils ≥ 300 (mepolizumab, DREAM intravenous doses), eosinophil-high and -low (lembikizumab), QUEST median (dupilumab), PATHWAY (tezepelumab). Dupilumab and tezepelumab FeNo series were not fitted.

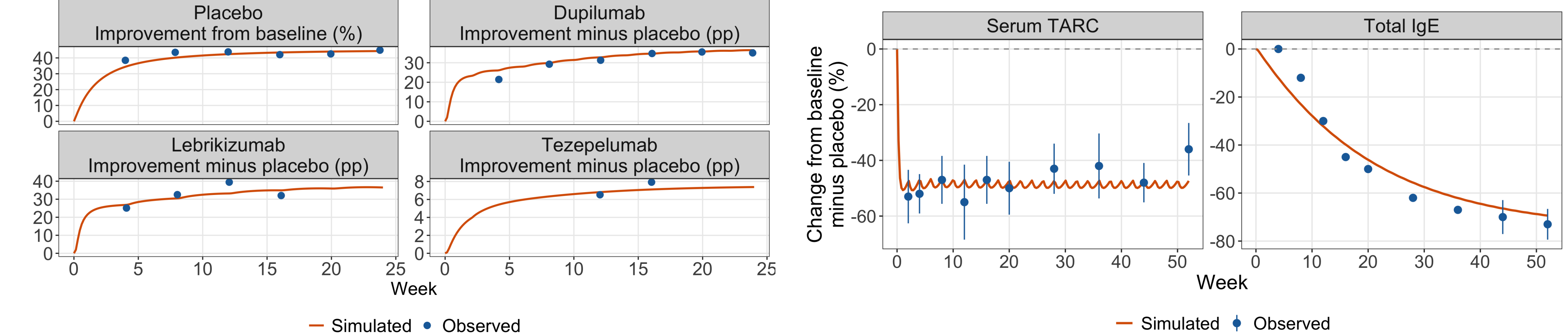


Figure 2. EASI in AD under placebo and three biologics, from one enrollment state. Points are the Miyano et al. data [2]; lines are the model. Placebo is improvement from enrollment; active arms are shown minus placebo.

Prospective Simulations

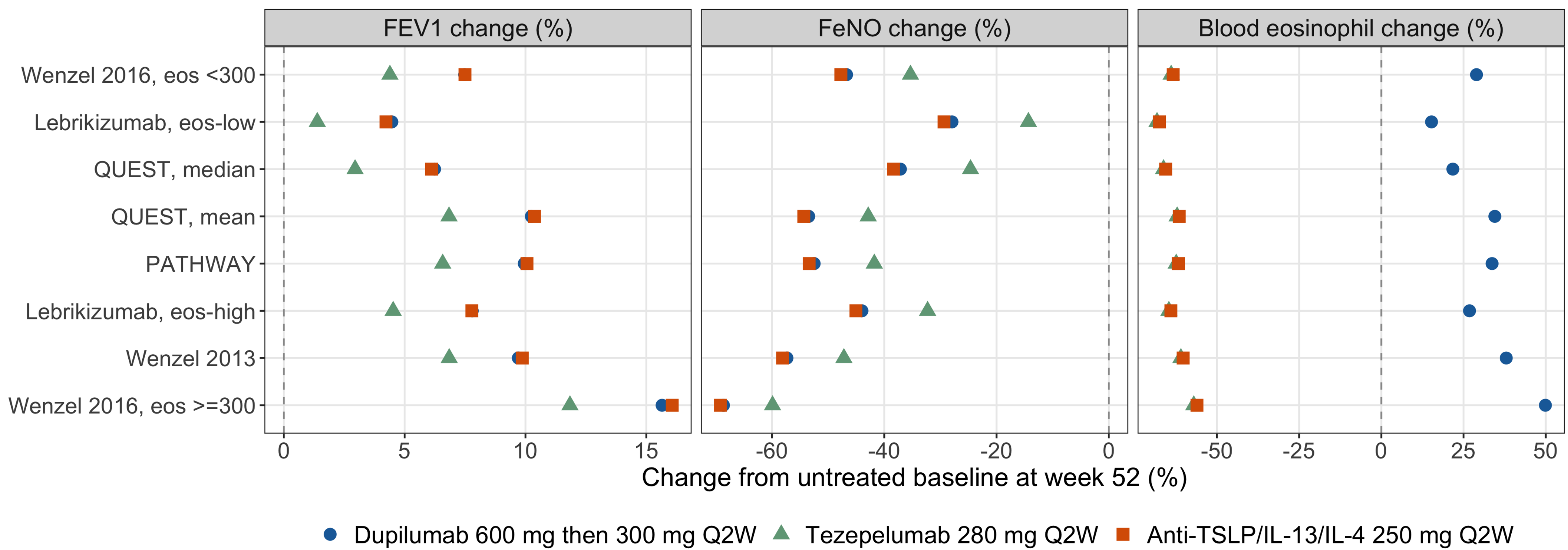


Figure 4. A hypothetical anti-TSLP/IL-13/IL-4 antibody tracks dupilumab on FEV₁ and FeNO and tezepelumab on blood eosinophils in every asthma phenotype. 250 mg SC Q2W with dupilumab-like PK, no refitting; change from each phenotype's untreated baseline at week 52; phenotypes in Table 1 order.

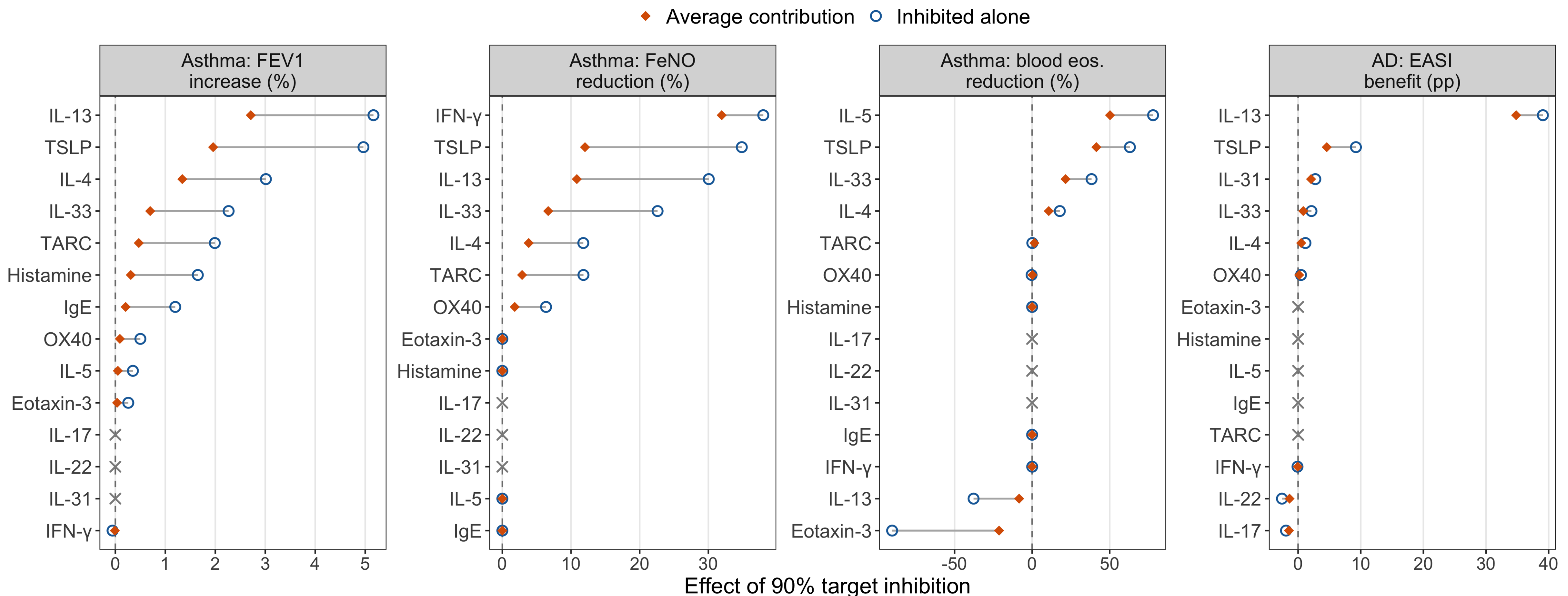


Figure 5. Target importance depends on the endpoint and the other pathways inhibited. Blue circles: inhibition alone. Orange diamonds: each target's average added effect across combination of other inhibited targets (Shapley value); targets are ordered by this value. Grey crosses: inactive pathways. All interventions inhibit 90% of total bioavailable target. Asthma: week-52 changes versus the uninhibited reference (percent of pretreatment baseline; reference FeNO 25 ppb, blood eosinophils 250 cells/ μ L). AD: additional EASI improvement at week 16 versus the uninhibited simulation (percentage points). Negative values indicate the opposite endpoint change.

Conclusions

Shared model. Shared immune kinetics described AD and asthma calibration data. Three conditioned quantities defined the asthma configurations.

Combination effects. Simulated anti-TSLP/IL-13/IL-4 combined dupilumab-like FEV₁/FeNO responses with tezepelumab-like eosinophil responses.

Consistent priorities across phenotypes. IL-13, TSLP and IL-4 ranked highest for FEV₁ improvement across all eight asthma configurations; IL-5, TSLP and IL-33 led eosinophil reduction.

Endpoint-specific rankings. Clinical priorities require validation. AD rankings remain sensitive to inherited scaling and weakly constrained pathways.