Supplementary Materials:

The Nasal Mucosal Late Allergic Reaction to Grass Pollen involves Type 2 Inflammation (IL-5 and IL-13), the Inflammasome (IL-1β) and Complement

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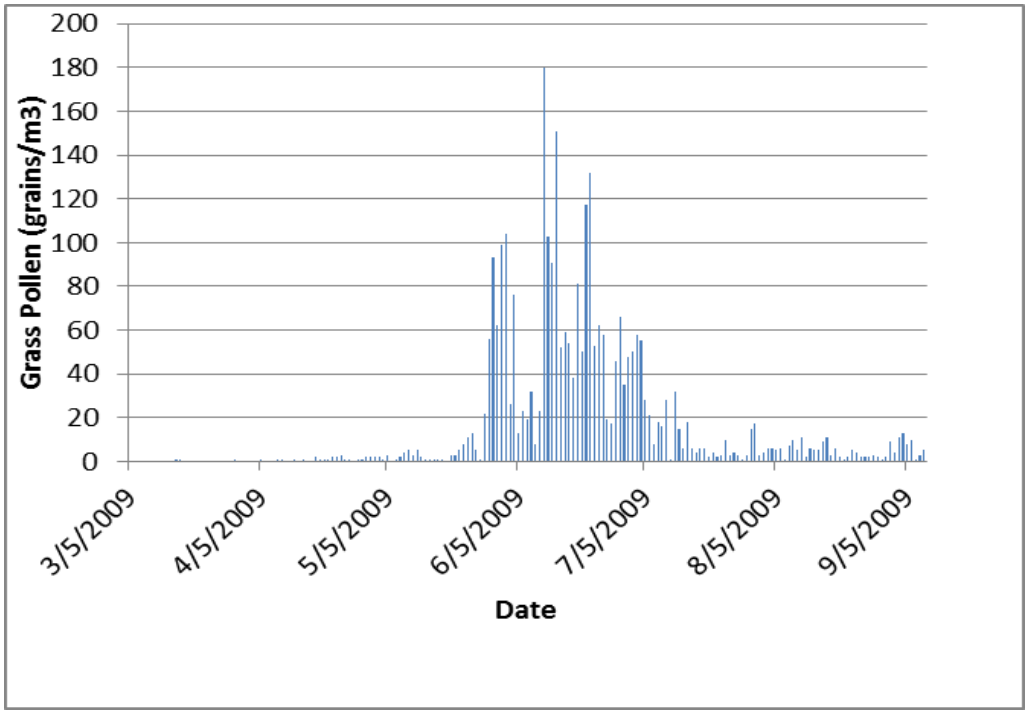


Figure E1. Daily grass pollen counts for North London in 2009

All nasal allergen challenges were completed in the study between January and late April 2009. It was found that grass pollen counts of >30 grains/m3 were only present after late May, 2009. Please note that the date format is month/day/year. This data is courtesy of Dr. Jean Emberlin, former Director of the National Pollen and Aerobiology Research Unit, Worcester.

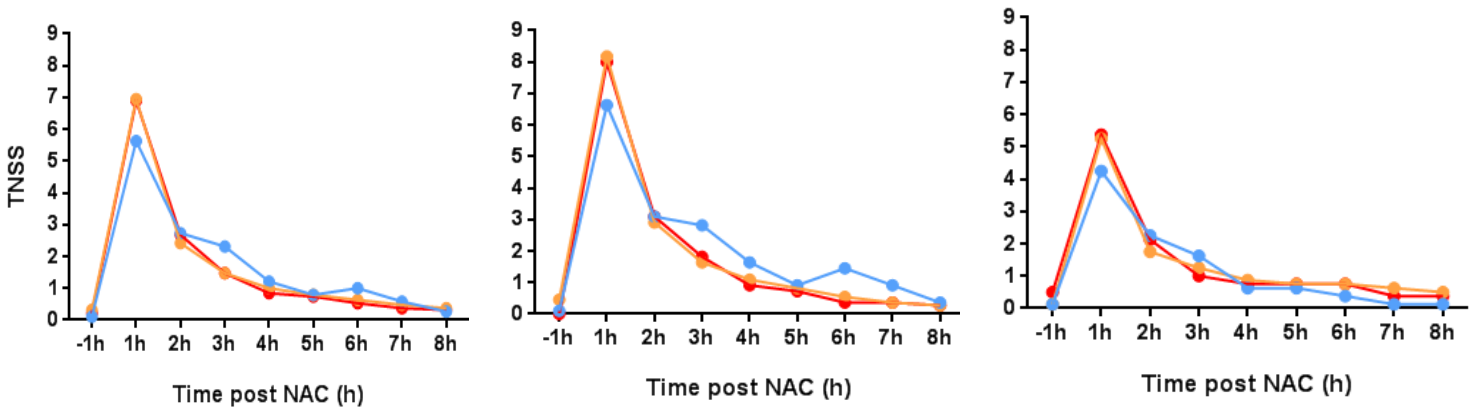


Figure E2. Total nasal symptom scores (TNSS) after nasal allergen challenge (NAC)

"Non-Responders" (n=8) and "Responders" (n=11) are defined on the basis of their IL-13 levels in nasal MLF at 2-8h post NAC (see text). Blue = placebo followed by NAC, Orange = 10mg prednisone followed by NAC, Red = 25mg prednisone followed by NAC

Following NAC participants had early (within the first hour) nasal symptoms: generally consisting of sneezing for a few minutes with rhinorrhea and nasal and soft palate itching for up to 30 mins, that largely resolved within an hour. Symptoms are subjective in rhinitis, especially during the late phase (2-8h post NAC), that consists largely of a slight nasal obstruction. Some AR patients had an early symptomatic response with little or no late symptomatic response. TNSS are displayed as means over time, graded 0 to 3 for nasal itch, nasal obstruction, nasal discharge and sneezing: this corresponds to a maximal TNSS of 12. TNSS in the late phase are variable and of low magnitude: reaching only mean levels of around 2 out of 12, and largely due to obstruction alone.

There were trends for increased early (1h) and late (2-8h) TNSS in the Responder group, when compared to the Non-Responder group (these did not reach statistical significance).
In the responder group area under the curve (AUC) analysis showed a trend for decreased TNSS levels following prednisone administration, relative to placebo.

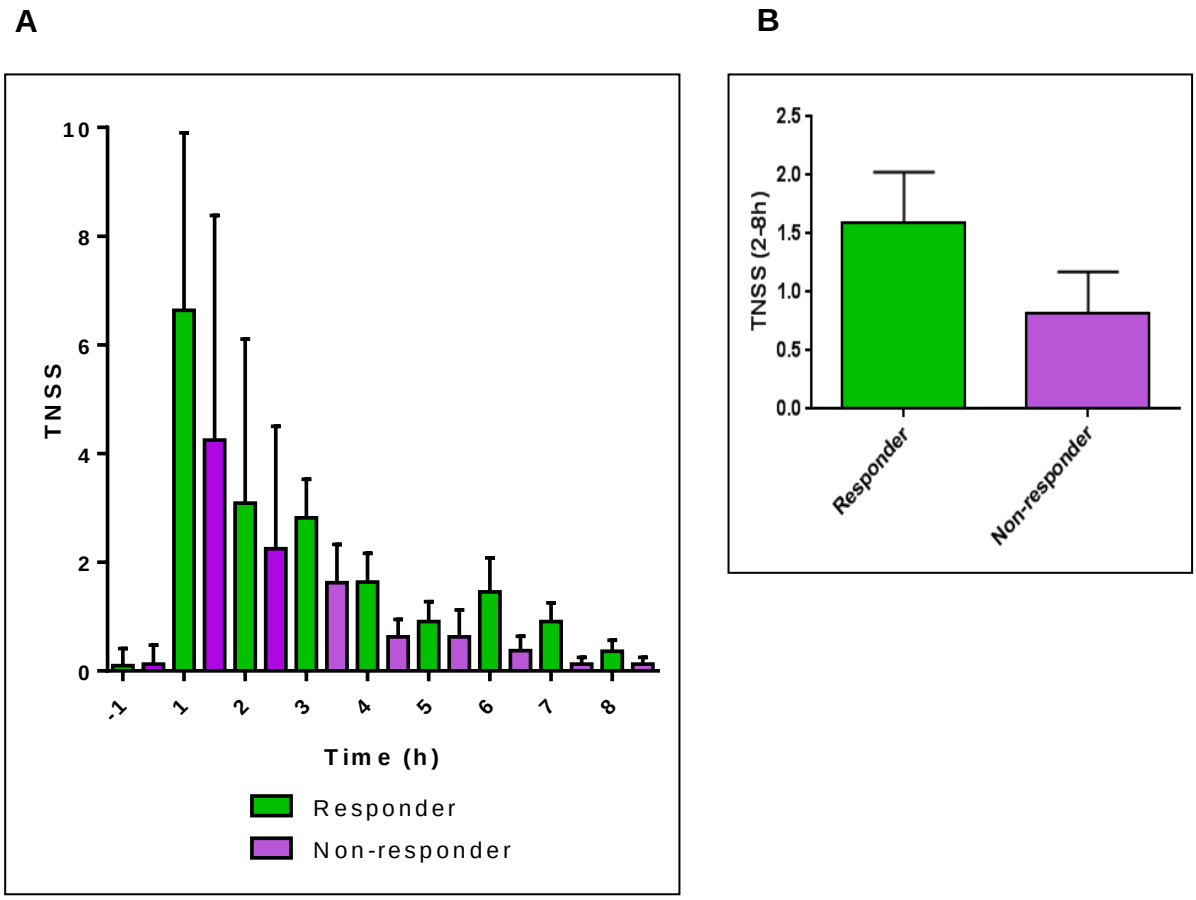


Figure E3. Total nasal symptom scores (TNSS) after nasal allergen challenge (NAC)

A. TNSS scores over time (at each hour in the late phase) in Responders (green) versus Non-Responders (purple), in the placebo followed by NAC arm, shown as means and SEM.
At all timepoints after NAC there is a trend for reduced TNSS in Non-Responders.

B. TNSS scores (means) in the late phase (2-8h) in Responders (green) versus Non-Responders (purple), showing a trend for greater TNSS in the Responder group that did not achieve statistical significance. On the right we see that and there were approximately double the mean levels of TNSS evaluated by AUC 2-8h in the Responder versus Non-Responder group.

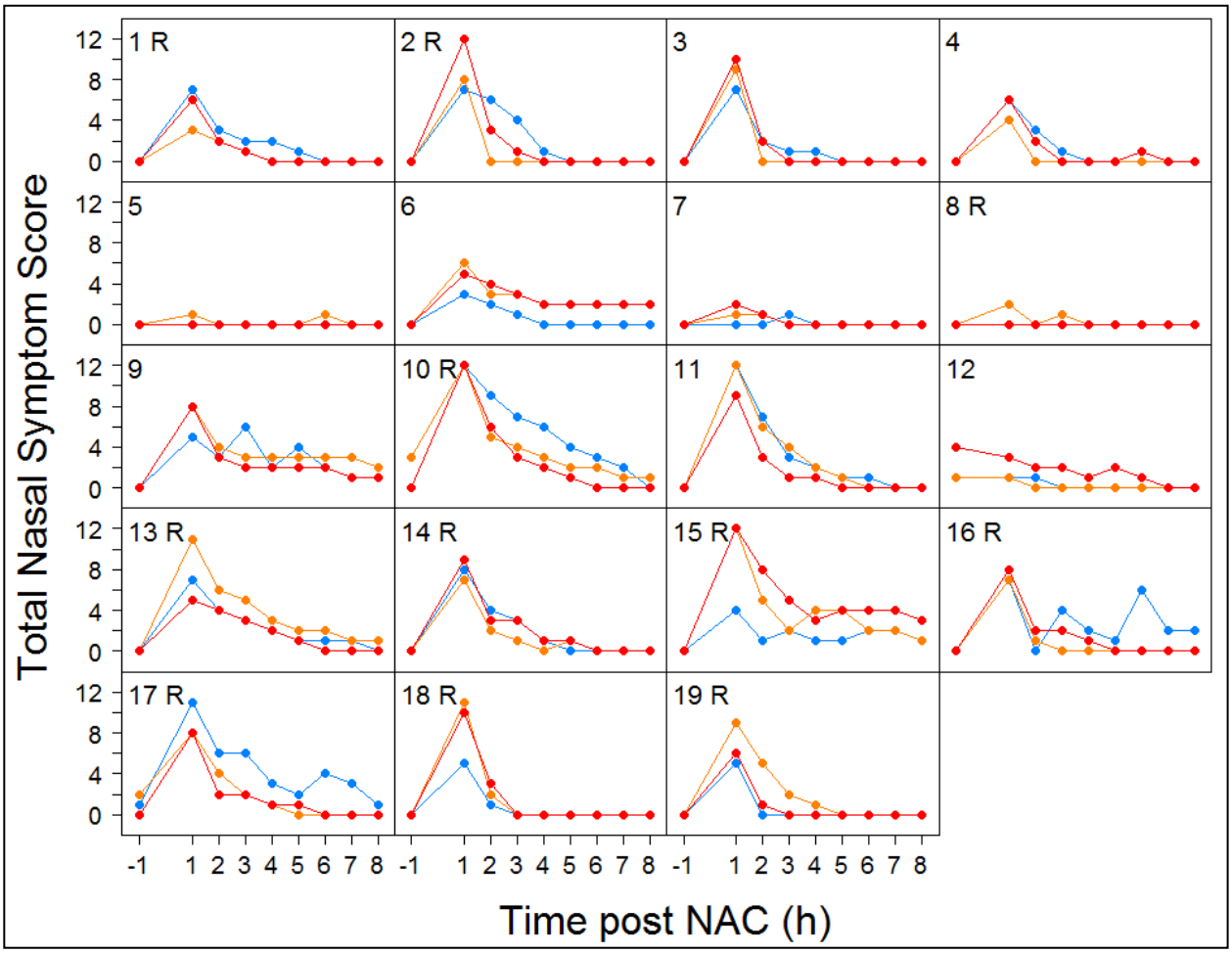


Figure E4. Individual total nasal symptom scores (TNSS) after nasal allergen challenge (NAC)

"Non-Responders" (n=8) and "Responders" (n=11) are defined on the basis of their IL-13 levels in nasal MLF (see text).

Blue = placebo followed by NAC
Orange = 10mg prednisone followed by NAC
Red = 25mg prednisone followed by NAC

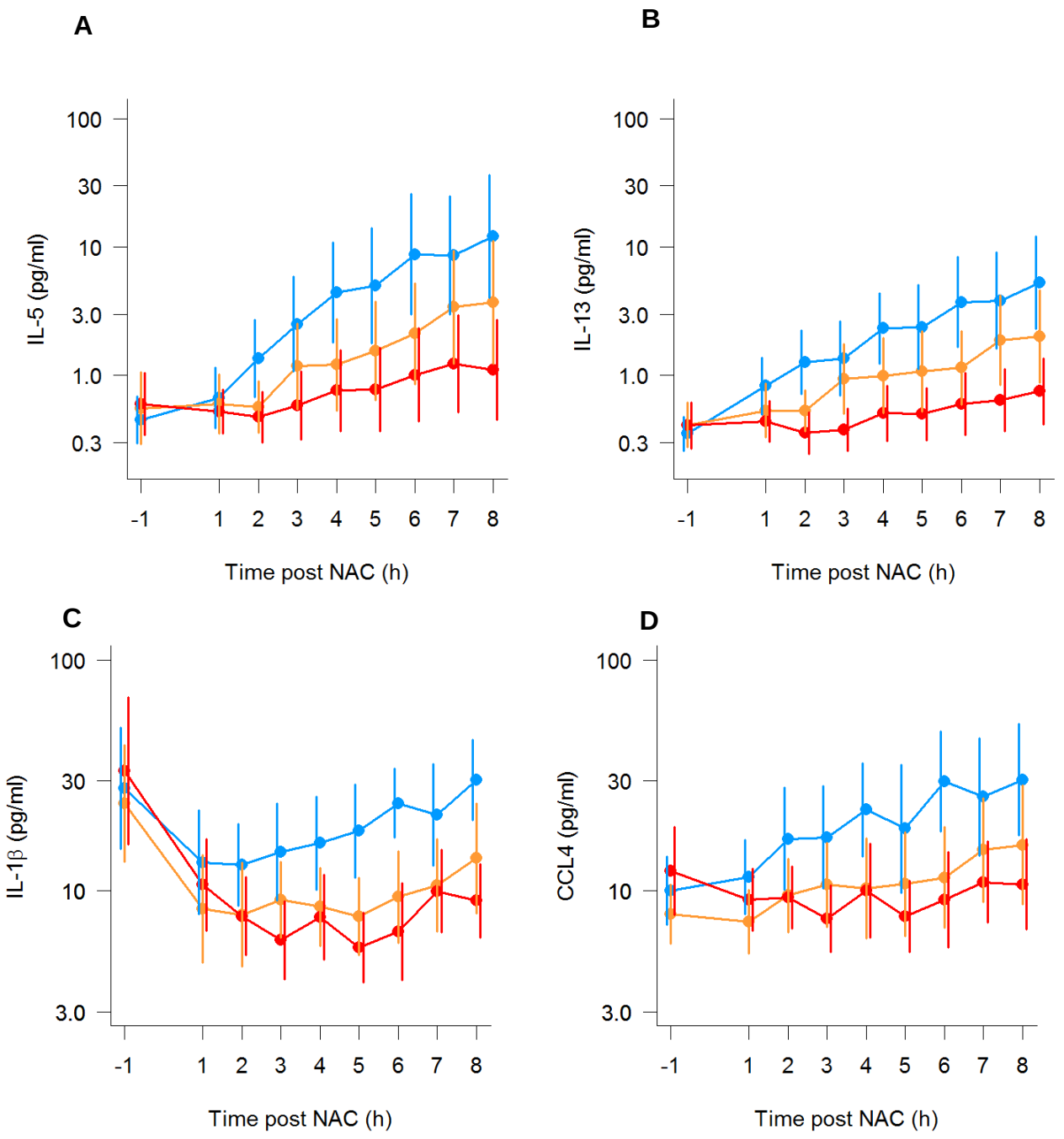


Figure E5. Time courses of geometric mean absolute cytokine levels in MLF following nasal allergen challenge

Levels of cytokines and CCL4 were measured by immunoassay in eluted nasosorption samples. In all panels, blue denotes placebo pretreatment, orange denotes 10mg prednisone pretreatment, and red denotes 25mg prednisone pretreatment.

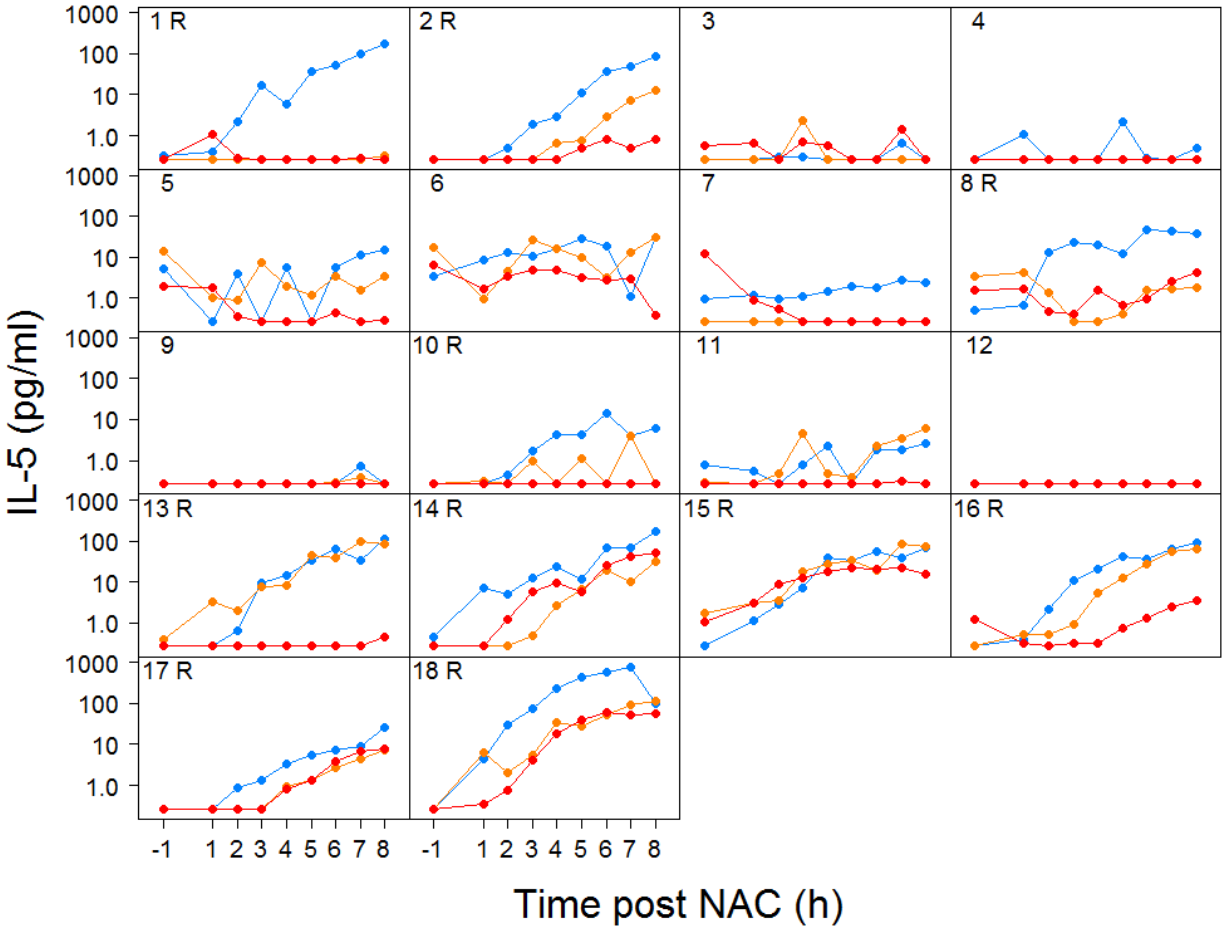


Figure E6. Time courses of individual IL-5 responses to NAC

Blue denotes placebo pretreatment, orange denotes 10mg prednisone pretreatment, and red denotes 25mg prednisone pretreatment.

“R” denotes IL-13 Responder status as explained in the main text. There are 18 subjects, with subject 19R having insufficient sample for IL-5 measurement, but included in Fig 2C in the main manuscript.

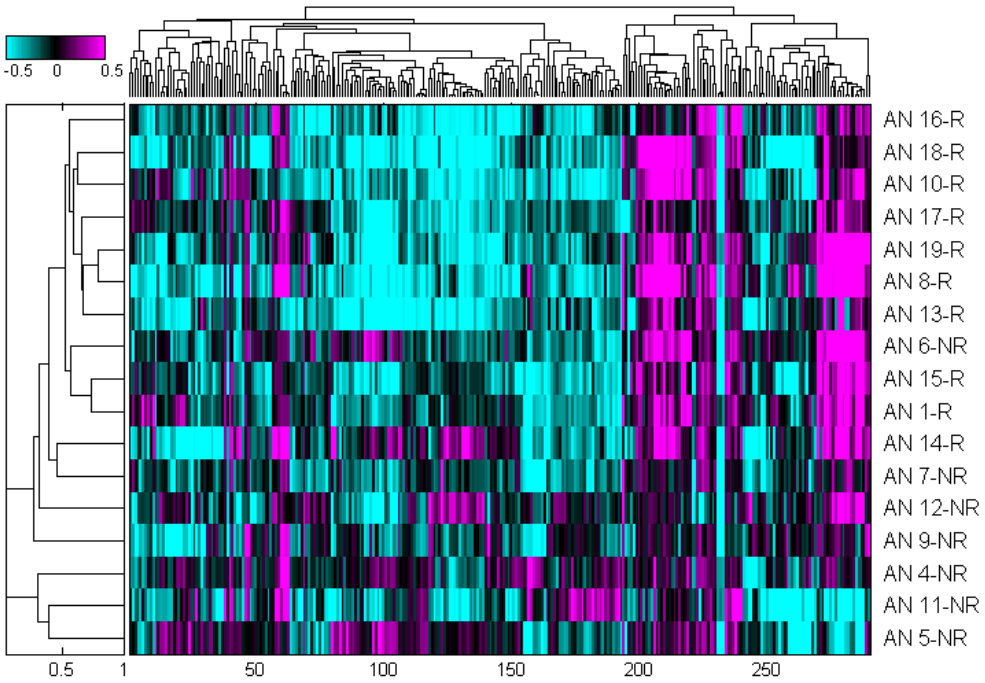


Figure E7. Unsupervised hierarchical clustering heatmap of NAC-induced gene expression changes with probesets as columns and study participants as rows

Color coded values are fold changes (log_{10}) of 8h post-NAC probeset expression compared with common study baseline (Figure 1). Participants are listed by study allocation number ("AN") and by nasal cytokine IL-13 Responder status ("R" or "NR") as defined in the manuscript.

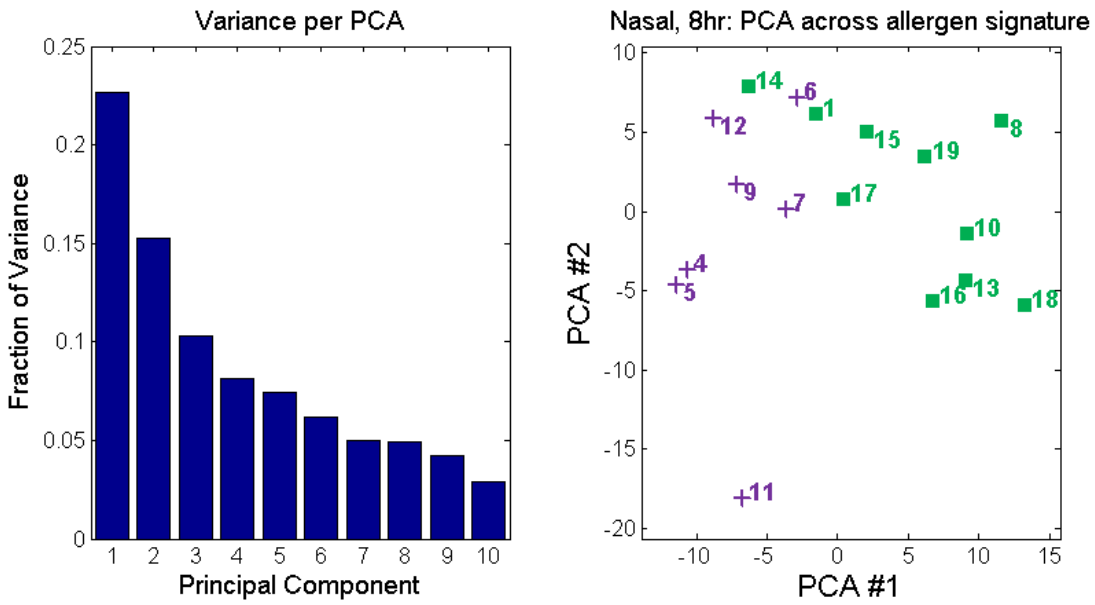


Figure E8. Principal components analysis (PCA) of changes in probeset expression levels following NAC (placebo pretreatment)

Left panel: Fraction of total gene expression variance explained by the first 10 principal components.

Right panel: Principal component coefficients of subjects in the two dimensional space made up of principal components 1 and 2. Each cross symbol corresponds to a patient – identified with an adjacent allocation number: green squares correspond to IL-13 Responders and purple crosses correspond to Non-Responders.

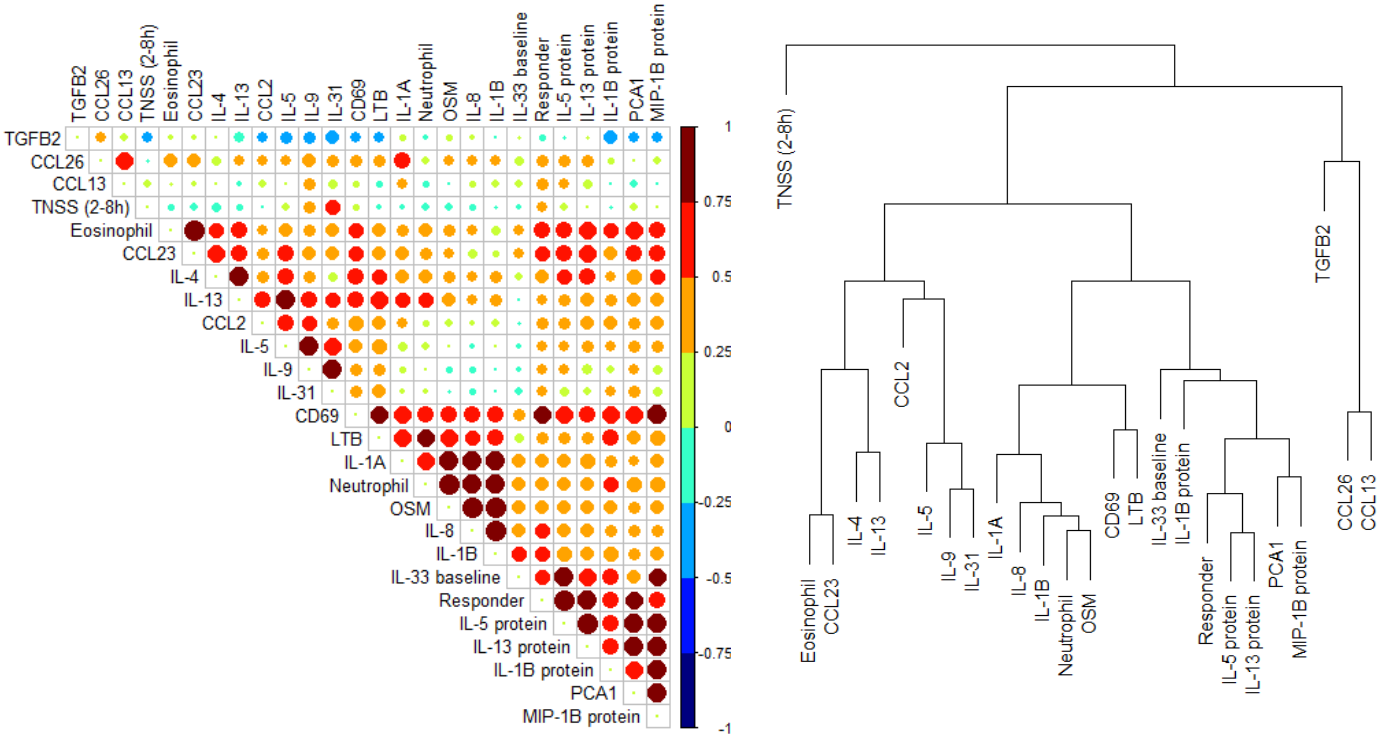
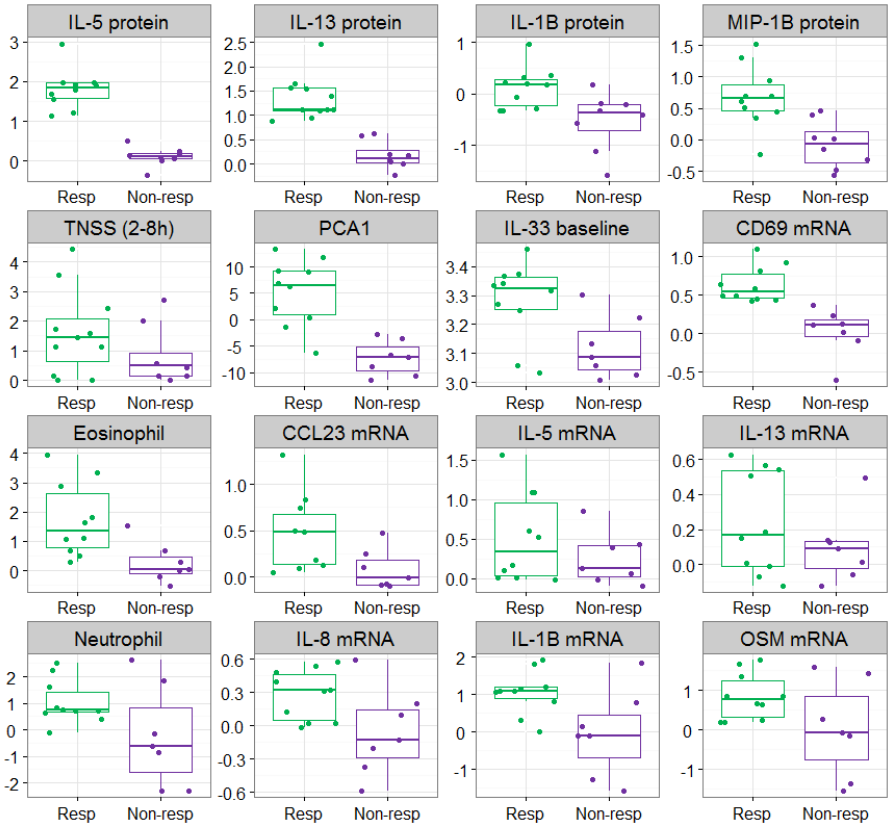


Figure E9. Correlation matrix and dendrogram for key parameters of the nasal allergen challenge (NAC)

Correlation Matrix (left) in which the magnitude of Pearson correlation ("r") is reflected in colour (see scale bar) and also by the diameter of circles. Analysis was carried out on data from the placebo period, thus reflecting NAC biology in the absence of any treatment. This illustrates correlations between total nasal symptom scores (TNSS) in the late phase (2-8h) after NAC, IL-33 mRNA at baseline, the first transcriptional principal component (PCA1, Figure E8) across the allergen gene expression signature, post-NAC change from baseline in several immunologically relevant mRNAs including neutrophil and eosinophil mRNA-derived markers; and selected cytokine and chemokine protein levels (IL-5, IL-13, IL-1β and CCL4/MIP-1β: geometric mean time weighted average, GMTWA, 2-8hr).
Nomenclature for chemokines: CCL2/MCP-1, CCL4/MIP-1β, CCL13/MCP-4, CCL23/MIP-3, CCL26/eotaxin-3. IL-33 gene expression is at baseline.
"Responders" were based on IL-13 protein levels after NAC, assessed by geometric mean time weighted averages (GMTWA) at 2-8h post placebo NAC (see manuscript for definition).

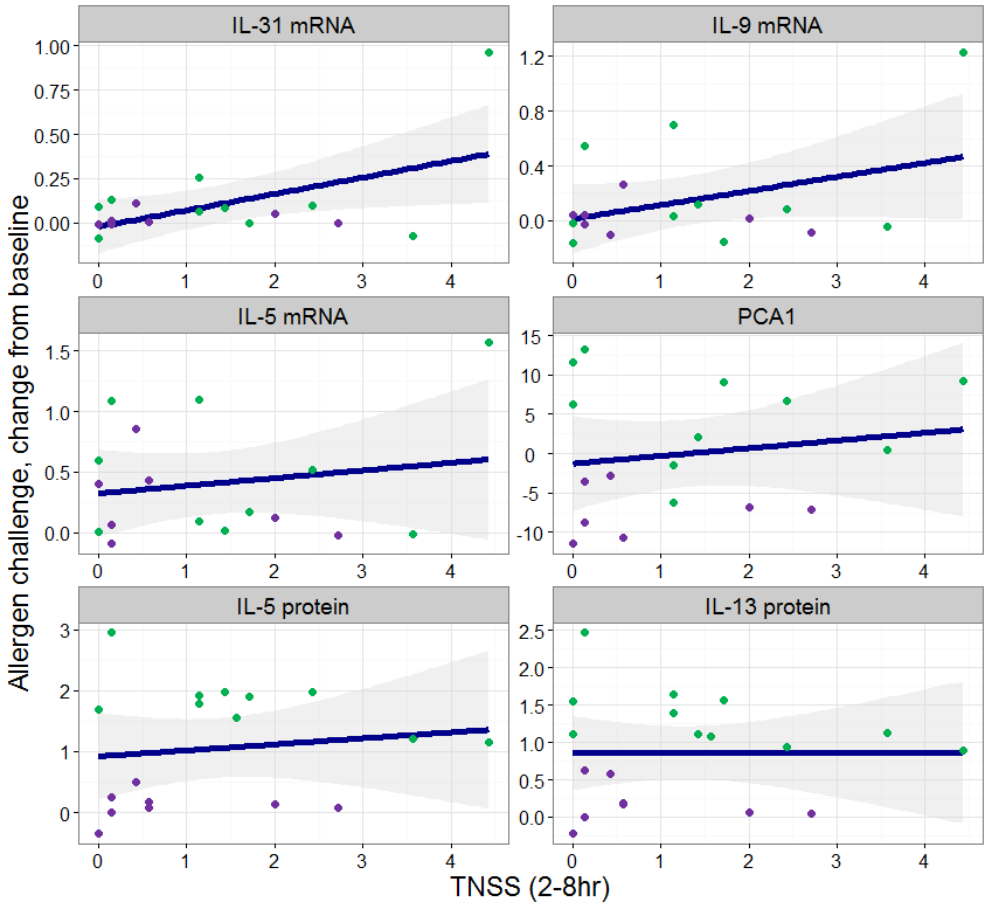
Dendrogram (right) of hierarchical clustering, showing correlation distances and average link. The eosinophil mRNA derived marker is clustered with gene expression (change from baseline) for type 2 inflammation. The neutrophil gene signature is clustered with oncostatin M (OSM), IL-1B, IL-8, IL-1A gene expression. IL-33 baseline gene expression clusters with IL-5, IL-13, CCL4/MIP-1β and IL-1β protein levels (GMTWA, 2-8h): and therefore with IL-13 Responders.



Endpoint	p-value
IL-5 protein	Used for Responder stratification
IL-13 protein	
IL-1β protein	1.74E-02
MIP-1β protein	2.00E-03
TNSS (2-8h)	1.79E-01
PCA1	1.00E-04
IL-33 baseline	1.65E-02
CD69	1.16E-03
eosinophil	7.93E-03
CCL23	1.84E-02
IL-5	2.49E-01
IL-13	2.61E-01
neutrophil	1.31E-01
IL-8	7.03E-02
IL-1β	5.29E-02
OSM	1.37E-01

Figure E10. Comparison of "IL-13 Responders" and Non-Responders with regard to responses after nasal allergen challenge (NAC)

Post hoc stratification of IL-13 protein Responders after NAC is reflected in key endpoints. Post NAC (preceded by placebo) across key endpoints. Selected proteins: IL-5, IL-13, IL-1β and CCL4/MIP-1β (pg/ml) (geometric mean time weighted average, log10 transformed (GMTWA, 2-8hr). TNSS: total nasal symptom scores in the late phase (2-8h). PCA1: first principal components analysis across the NAC gene expression signature (change from baseline). mRNA genes and neutrophil and eosinophil mRNA derived markers (change from baseline, log10 transformed). IL-33 gene expression is shown at baseline. *P*-values in this situation should be interpreted with caution, as these are nominal, not adjusted for multiplicity and performed *post hoc*.



Endpoint	Correlation	*P*-value
IL-31mRNA	0.530	0.029
IL-9mRNA	0.384	0.129
IL-5mRNA	0.175	0.501
PCA1	0.164	0.530
IL-5 and IL-13 protein	Used for Responder stratification	

Figure E11. Pearson correlation between total nasal symptom scores TNSS (2-8hr) and key gene expression and cytokine levels after nasal allergen challenge (NAC)

IL-13 Responders (defined in the manuscript, green dots) and Non-Responders (purple dots) are shown. This confirms that TNSS in the late phase (2-8hr) are not associated with changes from baseline in levels of IL-5 and IL-13. The correlation of TNSS with IL-31 is weak and based mainly on a single point, and has not been corrected for multiple testing. Values for mRNA and proteins are log10 transformed NAC fold change from baseline.

Table E1. Baseline demographics

Participant number	Age_(yr)	Sex	Race category	Baseline blood eosinophil count (thousands/μL)
1	41	M	white	0.11
2	35	F	white	0.13
3	52	M	white	0.24
4	36	M	black	0.17
5	49	M	white	0.07
6	46	M	white	0.18
7	29	M	white	0.14
8	55	M	white	0.04
9	44	M	white	0.08
10	39	M	black	0.38
11	36	M	white	0.07
12	53	F	black	0.05
13	47	M	white	0.38
14	38	M	white	0.85
15	33	M	white	0.07
16	51	M	white	0.09
17	29	M	white	0.31
18	32	M	white	0.08
19	22	M	Asian	0.17

Table E2. Geometric mean time weighted average (hours 2-8) fold differences from baseline in allergen-induced inflammatory markers, as measured in MLF: Treatment group comparisons

Analyte	Treatment Group Comparison	GM FD	90% CI for GM FD	1-sided P-value	Effect Size (log scale)
IL-5	10 mg prednisone vs. Placebo	0.27	(0.14, 0.52)	0.001	-1.109
	25 mg prednisone vs. Placebo	0.12	(0.06, 0.24)	<0.001	-1.779
	25 mg prednisone vs. 10 mg prednisone	0.45	(0.23, 0.88)	0.027	-0.669
IL-13	10 mg prednisone vs. Placebo	0.38	(0.23, 0.62)	0.001	-1.098
	25 mg prednisone vs. Placebo	0.17	(0.11, 0.28)	<0.001	-1.980
	25 mg prednisone vs. 10 mg prednisone	0.46	(0.28, 0.75)	0.005	-0.881
MIP-1β	10 mg prednisone vs. Placebo	0.66	(0.41, 1.06)	0.072	
	25 mg prednisone vs. Placebo	0.34	(0.21, 0.54)	<0.001	-1.306
	25 mg prednisone vs. 10 mg prednisone	0.51	(0.32, 0.82)	0.011	-0.808
MCP-1	10 mg prednisone vs. Placebo	0.95	(0.60, 1.52)	0.430	
	25 mg prednisone vs. Placebo	0.52	(0.32, 0.83)	0.012	-0.795
	25 mg prednisone vs. 10 mg prednisone	0.54	(0.34, 0.87)	0.017	-0.735
ENA-78	10 mg prednisone vs. Placebo	1.18	(0.62, 2.24)	0.664	
	25 mg prednisone vs. Placebo	0.94	(0.49, 1.79)	0.436	
	25 mg prednisone vs. 10 mg prednisone	0.80	(0.42, 1.52)	0.279	
IL-6	10 mg prednisone vs. Placebo	1.16	(0.78, 1.72)	0.736	
	25 mg prednisone vs. Placebo	0.75	(0.50, 1.11)	0.109	
	25 mg prednisone vs. 10 mg prednisone	0.64	(0.44, 0.95)	0.034	-0.632
MIP-1α	10 mg prednisone vs. Placebo	0.96	(0.89, 1.05)	0.230	
	25 mg prednisone vs. Placebo	0.91	(0.84, 0.98)	0.025	-0.678
	25 mg prednisone vs. 10 mg prednisone	0.94	(0.87, 1.02)	0.104	
IL-4	10 mg prednisone vs. Placebo	0.99	(0.98, 1.00)	0.115	
	25 mg prednisone vs. Placebo	0.99	(0.98, 1.00)	0.115	
	25 mg prednisone vs. 10 mg prednisone	1.00	(0.99, 1.01)	0.500	
RANTES	10 mg prednisone vs. Placebo	1.18	(1.01, 1.39)	0.955	
	25 mg prednisone vs. Placebo	1.16	(0.99, 1.36)	0.936	
	25 mg prednisone vs. 10 mg prednisone	0.98	(0.84, 1.15)	0.425	
IL-1β	10 mg prednisone vs. Placebo	0.58	(0.35, 0.95)	0.037	-0.617
	25 mg prednisone vs. Placebo	0.33	(0.20, 0.54)	<0.001	-1.251
	25 mg prednisone vs. 10 mg prednisone	0.57	(0.34, 0.94)	0.033	-0.634
IL-8	10 mg prednisone vs. Placebo	1.29	(0.84, 1.99)	0.841	
	25 mg prednisone vs. Placebo	0.74	(0.48, 1.14)	0.123	
	25 mg prednisone vs. 10 mg prednisone	0.57	(0.37, 0.88)	0.018	-0.731

GM FD = Geometric Mean Fold Difference, CI = Confidence Interval
Effect sizes shown on log scale for statistically significant comparisons.
Final Results, Date: 09/03/2009

Table E3. Geometric mean fold differences from baseline at hour 7 in allergen-induced inflammatory markers, as measured in MLF: Treatment group comparisons

Analyte	Treatment Group Comparison	GM FD	90% CI for GM FD	1-sided P-value	Effect Size (log scale)
IL-5	10 mg prednisone vs. Placebo	0.32	(0.14, 0.71)	0.011	-0.806
	25 mg prednisone vs. Placebo	0.11	(0.05, 0.24)	<0.001	-1.579
	25 mg prednisone vs. 10 mg prednisone	0.34	(0.15, 0.74)	0.013	-0.774
IL-13	10 mg prednisone vs. Placebo	0.41	(0.22, 0.76)	0.010	-0.798
	25 mg prednisone vs. Placebo	0.14	(0.08, 0.26)	<0.001	-1.748
	25 mg prednisone vs. 10 mg prednisone	0.34	(0.19, 0.64)	0.003	-0.950
MIP-1β	10 mg prednisone vs. Placebo	0.75	(0.41, 1.37)	0.211	
	25 mg prednisone vs. Placebo	0.35	(0.19, 0.65)	0.003	-0.971
	25 mg prednisone vs. 10 mg prednisone	0.47	(0.26, 0.87)	0.022	-0.700
ENA-78	10 mg prednisone vs. Placebo	1.01	(0.41, 2.49)	0.508	
	25 mg prednisone vs. Placebo	0.95	(0.39, 2.31)	0.463	
	25 mg prednisone vs. 10 mg prednisone	0.94	(0.38, 2.32)	0.456	
MCP-1	10 mg prednisone vs. Placebo	0.97	(0.49, 1.94)	0.474	
	25 mg prednisone vs. Placebo	0.65	(0.33, 1.30)	0.152	
	25 mg prednisone vs. 10 mg prednisone	0.67	(0.34, 1.34)	0.168	
IL-6	10 mg prednisone vs. Placebo	1.32	(0.83, 2.09)	0.840	
	25 mg prednisone vs. Placebo	0.69	(0.43, 1.09)	0.089	
	25 mg prednisone vs. 10 mg prednisone	0.52	(0.33, 0.83)	0.011	-0.797
MIP-1α	10 mg prednisone vs. Placebo	0.92	(0.80, 1.05)	0.148	
	25 mg prednisone vs. Placebo	0.87	(0.76, 1.00)	0.049	-0.567
	25 mg prednisone vs. 10 mg prednisone	0.95	(0.83, 1.09)	0.264	
IL-4	10 mg prednisone vs. Placebo	0.97	(0.93, 1.01)	0.115	
	25 mg prednisone vs. Placebo	0.97	(0.93, 1.01)	0.115	
	25 mg prednisone vs. 10 mg prednisone	1.00	(0.96, 1.05)	0.500	
RANTES	10 mg prednisone vs. Placebo	1.05	(0.87, 1.26)	0.669	
	25 mg prednisone vs. Placebo	1.20	(0.99, 1.44)	0.944	
	25 mg prednisone vs. 10 mg prednisone	1.14	(0.95, 1.37)	0.879	
IL-1β	10 mg prednisone vs. Placebo	0.58	(0.32, 1.04)	0.062	
	25 mg prednisone vs. Placebo	0.39	(0.22, 0.71)	0.005	-0.900
	25 mg prednisone vs. 10 mg prednisone	0.68	(0.38, 1.22)	0.135	
IL-8	10 mg prednisone vs. Placebo	1.34	(0.77, 2.34)	0.811	
	25 mg prednisone vs. Placebo	0.93	(0.53, 1.63)	0.417	
	25 mg prednisone vs. 10 mg prednisone	0.70	(0.40, 1.21)	0.139	

GM FD = Geometric Mean Fold Difference, CI = Confidence Interval
Effect sizes shown on log scale for statistically significant comparisons.
Final Results, Date: 09/03/2009

Table E4. Geometric mean fold differences from baseline at hour 8 in allergen-induced inflammatory markers, as measured in MLF: Treatment group comparisons

Analyte	Treatment Group Comparison	GM FD	90% CI for GM FD	1-sided P-value	Effect Size (log scale)
IL-5	10 mg prednisone vs. Placebo	0.25	(0.12, 0.54)	0.002	-1.021
	25 mg prednisone vs. Placebo	0.07	(0.03, 0.15)	<0.001	-1.962
	25 mg prednisone vs. 10 mg prednisone	0.28	(0.13, 0.60)	0.004	-0.941
IL-13	10 mg prednisone vs. Placebo	0.32	(0.18, 0.56)	0.001	-1.106
	25 mg prednisone vs. Placebo	0.12	(0.07, 0.22)	<0.001	-2.021
	25 mg prednisone vs. 10 mg prednisone	0.39	(0.22, 0.68)	0.004	-0.915
MIP-1β	10 mg prednisone vs. Placebo	0.66	(0.37, 1.18)	0.116	
	25 mg prednisone vs. Placebo	0.29	(0.16, 0.51)	<0.001	-1.219
	25 mg prednisone vs. 10 mg prednisone	0.44	(0.25, 0.78)	0.010	-0.813
MCP-1	10 mg prednisone vs. Placebo	1.00	(0.55, 1.82)	0.496	
	25 mg prednisone vs. Placebo	0.63	(0.35, 1.15)	0.102	
	25 mg prednisone vs. 10 mg prednisone	0.63	(0.35, 1.15)	0.104	
IL-6	10 mg prednisone vs. Placebo	1.29	(0.77, 2.13)	0.797	
	25 mg prednisone vs. Placebo	0.65	(0.39, 1.08)	0.080	
	25 mg prednisone vs. 10 mg prednisone	0.51	(0.30, 0.84)	0.015	-0.760
ENA-78	10 mg prednisone vs. Placebo	1.08	(0.43, 2.75)	0.556	
	25 mg prednisone vs. Placebo	1.08	(0.42, 2.73)	0.552	
	25 mg prednisone vs. 10 mg prednisone	0.99	(0.39, 2.53)	0.496	
IL-1β	10 mg prednisone vs. Placebo	0.53	(0.31, 0.93)	0.033	-0.637
	25 mg prednisone vs. Placebo	0.25	(0.14, 0.44)	<0.001	-1.399
	25 mg prednisone vs. 10 mg prednisone	0.47	(0.27, 0.82)	0.014	-0.762
MIP-1α	10 mg prednisone vs. Placebo	0.99	(0.91, 1.07)	0.401	
	25 mg prednisone vs. Placebo	0.92	(0.85, 1.00)	0.046	-0.575
	25 mg prednisone vs. 10 mg prednisone	0.93	(0.86, 1.01)	0.074	
RANTES	10 mg prednisone vs. Placebo	1.09	(0.95, 1.25)	0.843	
	25 mg prednisone vs. Placebo	0.99	(0.87, 1.14)	0.473	
	25 mg prednisone vs. 10 mg prednisone	0.91	(0.80, 1.05)	0.142	
IL-8	10 mg prednisone vs. Placebo	1.32	(0.72, 2.41)	0.777	
	25 mg prednisone vs. Placebo	0.77	(0.42, 1.40)	0.232	
	25 mg prednisone vs. 10 mg prednisone	0.58	(0.32, 1.07)	0.070	

GM FD = Geometric Mean Fold Difference, CI = Confidence Interval
Effect sizes shown on log scale for statistically significant comparisons.
Final Results, Date: 09/03/2009

Table E5. Gene transcripts included in prospectively defined mRNA derived markers of eosinophils, neutrophils, and mast cells

Eosinophil-associated	Mast Cell-Associated	Neutrophil-Associated
CLC	MS4A2	FCGR2A
SIGLEC8	TPSAB1	FCGR2C
EMR1	TPSB2	CXCR1
EMR4P	CPA3	CXCR2
LGALS12	RGS13	FPR1
HRH4	C1orf186	MME
CEBPE		GLT1D1
DACH1		TREM1
VSTM1		SLC2A3
		SIRPB1
		DYSF
		MEFV
		IFITM2
		FOS

Table E6. Table of genes known to be genetic modifiers of asthma: association of baseline nasal gene expression (mRNA) with magnitude of the NAC response (IL-5 and IL-13 protein, change from baseline)

Gene	Probeset	Transcript	Correlation with IL-13 protein NAC		Correlation with IL-5 protein NAC	
			Pearson, r	p-value	Pearson, r	p-value
ADAMTS4	100127399_TGI_at	NM_005099	-0.326	0.217	-0.376	0.167
ADAMTS4	100302649_TGI_at	NM_005099	-0.322	0.223	-0.391	0.149
BACH2	100155509_TGI_at	NM_021813	-0.207	0.442	-0.031	0.913
CLEC16A	100149696_TGI_at	NM_015226	0.315	0.235	0.288	0.298
D2HGDH	100154978_TGI_at	NM_152783	-0.044	0.872	0.035	0.901
FCER1G	100160419_TGI_at	NM_004106	0.024	0.93	-0.029	0.919
GAPT	100125122_TGI_at	NM_152687	-0.028	0.919	-0.077	0.785
GATA3	100160989_TGI_at	NM_001002295	0.234	0.384	0.042	0.881
GATA3	100303528_TGI_at	NM_001002295	0.227	0.397	0.064	0.821
GSDMB	100144966_TGI_at	NM_001042471	0.171	0.526	0.138	0.625
IL33	100159118_TGI_at	NM_033439	0.685	0.0034	0.808	0.0003
LRP1	100302931_TGI_at	NM_002332	0.256	0.338	0.377	0.166
RAD50	100132153_TGI_at	NM_133482	0.117	0.666	0.199	0.478
SMAD3	100134075_TGI_at	NM_005902	-0.199	0.459	-0.035	0.902
STAT6	100156721_TGI_at	NM_003153	0.077	0.777	-0.056	0.843

Since these genetic drivers of asthma have been demonstrated to alter the risk of development of asthma, baseline expression level might affect the magnitude of the subsequent allergen response up to 12 weeks later. Only genetics findings with measurable expression at baseline were included in this correlation analysis. Within this list IL-33 mRNA at baseline is strongly associated with IL-5 and IL13 protein responses after NAC. These correlations remain statistically significant after Bonferroni correction for multiple hypothesis-testing.

Table E7. Baseline gene expression and prediction of IL-5/IL-13 protein responses after NAC.

Statistical test	MAS5 present	Whole array
Responder ~ Baseline	1.000	1.000
Baseline ~ Responder	1.000	1.000
IL-5 protein ~ Baseline	0.666	0.716
IL-13 protein ~ Baseline	1.000	1.000
TNSS (2-8hr) ~ Baseline	1.000	1.000

Values represent the smallest Benjamini-Hochberg false discovery rate (FDR) (SAS Proc Mult Test procedure) observed across the whole array of the genome (52,369 probe sets) as observed in baseline prediction tests. MAS5 was present in 31,892 probe sets. Given the small sample size, we cannot identify a *de novo* gene signature with a reasonable FDR (i.e. <0.2) that would predict subsequent NAC Responders. The study sample size was based on the primary end-point (PEP), and was not powered to detect the baseline gene expression prediction signal for IL-13 Responders.

Data File S1

Data File S1. Expression patterns (aggregate amongst all subjects) of probesets regulated by allergen challenge and/or 25mg prednisone – with MAS5 present call in >50% of samples in a treatment group (placebo and/or 25mg prednisone), |fold change| >1.5, and FDR < 10%.

Data File S2

Data File S2. Expression patterns (amongst Responders only) of probesets regulated by allergen challenge (FDR <5%) used for Ingenuity analysis.

Data File S3

Data File S3. Data table of gene symbols and respective z-scores and FDR (< 0.05) of prednisone effects (prednisone *vs*. placebo pretreatment) used for Ingenuity Pathway Analysis.