Supplementary Materials:

Supplemental Table 1

Measure	**HV (N = 26)**	**Atopic Derm. (N = 20)**	**AD-HIES (N = 31)**
Colonization	8%	85%*	97%*
S. aureus abscess	0	10%	94%*
S. aureus pneumonia	0	0	42%*
Any pneumonia	0	0	81%*

Table S1: Clinical history of *S. aureus* complications. Healthy volunteers (HV), patients with atopic dermatitis without genetic mutations, and patients with hyper IgE syndrome (AD-HIES) underwent skin culture swabs as previously described (Myles, et al. *BMC Microbiol* 2016;16(1):60). Rates of *S. aureus* positivity on culture are shown. Chart review results from the same patients establishing history of *S. aureus* skin abscess, microbiologically confirmed *S. aureus* pneumonia, or total pneumonia (with and without identified pathogen). * = statistically significant versus HV by ANOVA with Bonferroni's adjustment.

705 Supplemental Table 2

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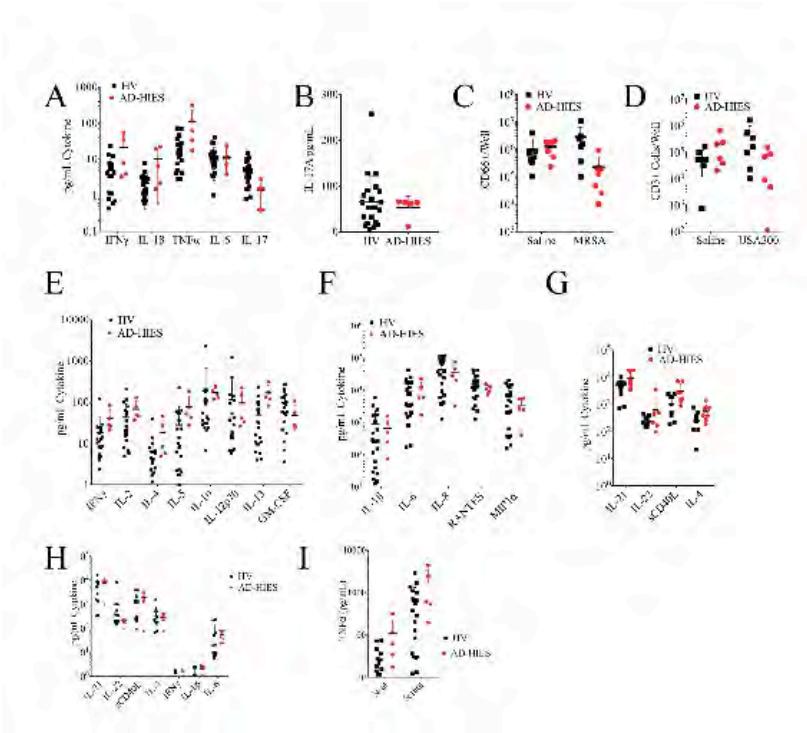
	17A (ng/mL)		**17F (ng/mL)**		**TNFα (ng/mL)**		
HV	Saline	MRSA	Saline	MRSA	Saline	MRSA	
1	0.30	0.52	1.43	0.67	0.69	0.07	
2	0.28	0.46	1.39	0.51	0.37	0.06	
3	0.40	1.10	1.92	2.50	0.08	0.27	
4	0.35	1.05	1.86	2.48	1.00	0.25	
5	0.31	0.33	0.59	0.32	0.03	0.10	
6	0.37	0.14	0.59	0.74	0.01	0.11	
7	0.12	0.50	0.27	0.11	0.55	0.21	
8	0.09	0.19	0.22	0.11	0.03	0.20	
9	0.20	0.16	0.21	0.12	0.36	0.30	
10	0.20	2.06	0.21	0.82	0.08	0.56	
11	0.13	0.73	0.26	1.75	0.16	0.13	
12	0.61	0.37	0.54	2.55	0.16	0.09	
	17A (ng/mL)		**17F (ng/mL)**		**TNFα (ng/mL)**		
AD-HIES	Saline	MRSA	Saline	MRSA	Saline	MRSA	Mutation
1	0.54	0.38	3.39	1.90	7.20	3.08	1144C>T; R382W
2	0.52	0.36	3.43	1.94	0.02	6.09	1145G>A; R382Q
3	0.82	0.50	1.97	1.08	0.41	0.89	1387delGTG; V463del
4	0.55	0.48	1.94	1.03	0.42	0.88	1909G>A; V637M
5	0.61	0.34	0.67	0.70	0.13	0.49	1861T>G; F621V
6	0.63	0.85	0.40	0.94	0.22	3.20	1970A>G; Y657C
7	0.30	0.49	0.60	0.62	0.31	1.29	c.1997T>C; p.L666R

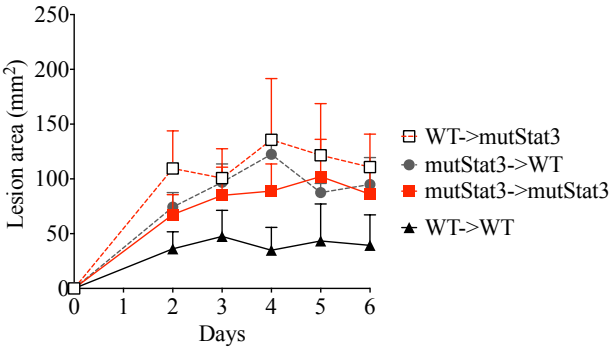
8	0.72	0.62	2.83	3.51	6.87	8.59	1853G>A; G618D

Table S2: STAT3 deficiency is associated with overproduction of TNF alpha**.** 12 healthy volunteers (HV) and eight patients with AD-HIES underwent blister induction and challenge of the wounded area with lethally irradiated bacteria or diluent control. IL-17A, IL-17F and TNFα concentrations in blister fluid after 20 hours of incubation with saline or irradiated methicillin resistant *S. aureus* (MRSA) are shown.

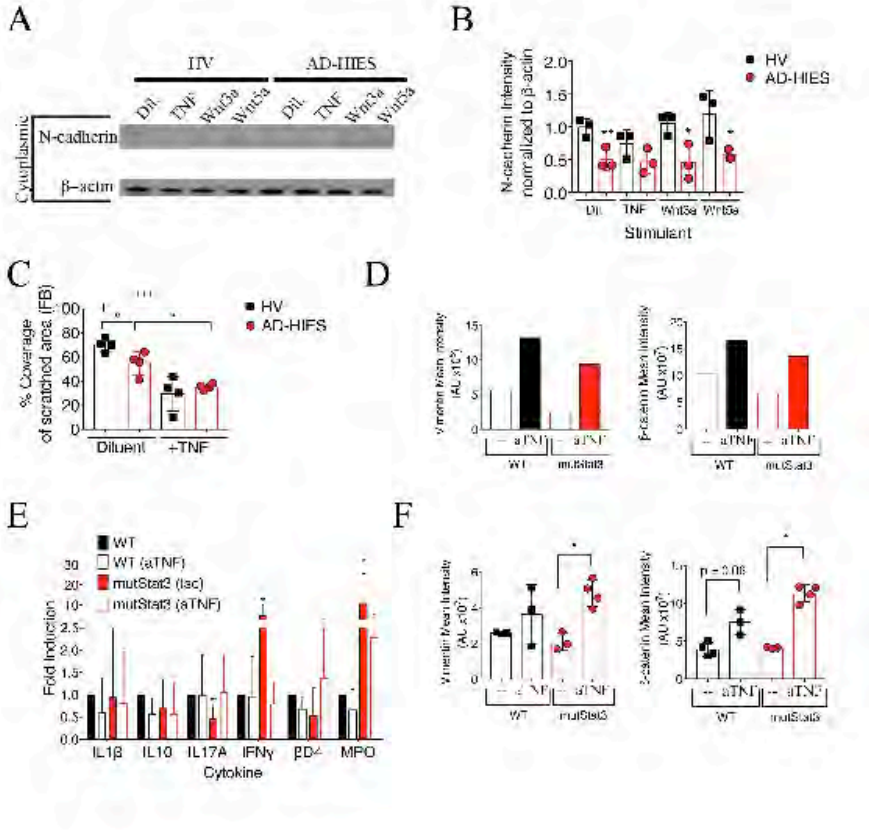
Supplemental Figure Legends:



Supplemental Figure 1: Cytokine responses in blister challenge fluid. 21 healthy volunteers (HV) and five patients with HIES underwent blister induction and challenge of the wound with 70% autologous serum. (A) Cytokine levels from resultant neat fluid, as well as IL-17A from 16 hours (B) are shown. (C-D) Flow cytometry on blister exudate cells was performed on a separate cohort of seven HV and seven patients with AD-HIES 20 hours after blister challenge with either saline or irradiated MRSA. Cell count numbers for CD66+ (C) and CD3+ cells (D) are shown. (E-F) Cytokine levels from 16-hour inflammatory exudates in response to autologous serum (21 HV and five AD-HIES patients). (G-H) Cytokines levels at 20 hours from 12 HV and 8 patients with HIES in response to saline (G) and irradiated MRSA (H). (I) TNFα concentrations in neat fluid and after 20 hours exposure to autologous serum for 21 HV and 5 patients with HIES. Data shown are a combination of experiments on individual patients and displayed as mean+sd. Significance determined by ANOVA with Bonferroni's correction versus HV.

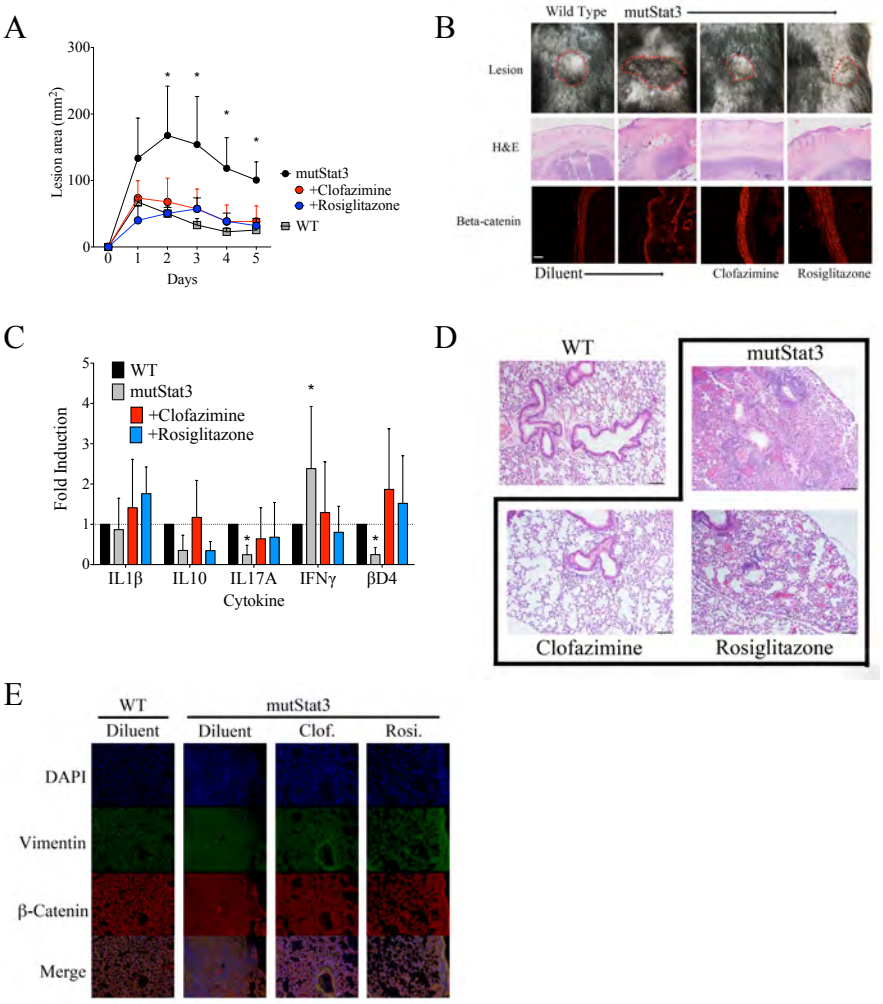


Supplemental Figure 2: Bone marrow transplantation fails to rescue WT responses in mutStat3 mice. MutStat3 and WT mice underwent bone marrow transplantation. WT bone marrow was transplanted into WT mice (WT->WT) or mutStat3 mice (WT-> mutStat3); bone marrow from mutStat3 mice was transplanted in mutStat3 (mutStat3->mutStat3) or WT mice (mutStat3->WT). Infections performed as in Fig. 2A.



Supplemental Figure 3: Epithelial cells from patients with HIES have disordered outcomes in EMT models. (A-B) Fibroblasts from two HV and two patients with AD-HIES were stimulated with diluent (Dil.), TNFα (TNF), Wnt3a, or Wnt5a. Western blot for N-cadherin (A) and fluorescent quantification normalized to beta-actin (B) are shown for one patient and one HV within one experiment. Experiments were identical for both patient and HV samples and reproducible between experiments. Nuclear fraction western blot did not reveal any N-cadherin (not shown). (C) As in Figure 3G using fibroblasts (FB) incubated with TNF (see Video S3), data pooled from two experiments using two independent cell lines per group per experiment. (D) Quantification of fluorescent intensity for vimentin and beta-catenin from Figure 4D; average intensity taken across entire image. Images are representative of two experiments. (E) Littermate wild type (WT) and mutStat3 mice were treated with daily intraperitoneal injection of anti-TNFα (aTNF) or isotype control (Iso) for four days prior to infection with 10^6 colony-forming units (CFU) of MRSA (N= 3-5 mice per group). Day 5 cytokine transcript levels relative to diluent treated (normalized to GAPDH). (F) Quantification of fluorescent intensity from Figure 4F as in panel D. Data shown are

representative of two or more independent experiments, unless indicated, and displayed as mean+sd. Significance determined by ANOVA with Bonferroni's correction versus corresponding HV diluent or isotype treated control. * = $p < 0.05$, ** = $p < 0.01$, ****=$p < 0.0001$.



Supplemental Figure 4: Drugs with reported EMT modulation improve outcomes in mutStat3 mice. (A-C) Wild type (WT) and mutStat3 mice were treated with daily gavage of clofazimine, rosiglitazone, or diluent control for four days prior to subcutaneous infection with 10^6 colony-forming units (CFU) of MRSA (N= 4-7 mice per group). Mean resultant lesion area over time (A), images of skin lesion, 20X H&E histology, and 10X immunofluorescent (IF) images for beta-catenin in median mouse (B), and day 5 cytokine transcript levels relative to diluent treated (normalized to GAPDH; C) are shown. (D-E) WT and mutStat3 mice were treated with clofazimine and rosiglitazone as above before nasal inoculation of 10^8 CFU of MRSA. Day 7 40X H&E (D) and 20X IF images (E) of lung are shown. Data shown are

779 representative of three independent experiments and displayed as mean+sd. Significance determined by
780 ANOVA with Bonferroni's correction versus WT diluent or isotype treated control. * = $p < 0.05$
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Video S1, S2, and S3 – uploaded separately

Supplemental video 1: Keratinocytes (KC) from healthy volunteers (HV) or patients with autosomal dominant Hyper IgE Syndrome (AD-HIES) were placed into the scratch assay as described in the methods. Cells were pre-incubated with diluent, clofazimine, or rosiglitazone prior to scratch assay. Video images run from time of scratch to 22 hours later. Dotted lines added digitally to indicate starting point of KC at time zero. Images are representative of three independent experiments.

Supplemental video 2: Fibroblasts from healthy volunteers (HV) or patients with autosomal dominant Hyper IgE Syndrome (AD-HIES) were placed into the scratch assay as described in the methods. Cells were pre-incubated with diluent, clofazimine, or rosiglitazone prior to scratch assay. Video images run from time of scratch to 24 hours later. Dotted lines added digitally to indicate starting point at time zero. Images are representative of three independent experiments.

Supplemental video 3: Fibroblasts from healthy volunteers (HV) or patients with autosomal dominant Hyper IgE Syndrome (AD-HIES) were placed into the scratch assay as described in the methods. Cells were pre-incubated with diluent or 2ng/mL of recombinant human TNFα. Video images run from time of scratch to 22 hours later. Dotted lines added digitally to indicate starting point at time zero. Images are representative of three independent experiments.