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1     **Identification of the major immune differences in severe asthmatic children**  
2                                   **according to their atopic dermatitis status**

3                                   **Running title: Children with severe asthma and atopic dermatitis**

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34    **Author contributions**

35    G.L., K.A.P., and M.L.M. designed research; M.G., and C.D., performed research; G.L., C.P., K.A.P., and  
36    M.L.M. analyzed data; and G.L., K.A.P., and M.L.M. wrote the paper.

37 **ABSTRACT**

38 Severe asthma (SA) affects 2% to 5% of asthmatic children. Atopic dermatitis can affect up to 34% of  
39 children with SA (cwSA). Atopic dermatitis and asthma share common genetic and immunological  
40 features. However, not all children with SA suffer from AD, and it remains unclear whether the overall  
41 immune profiles of these children are similar. In this study, seventeen cwSA (9.8 [7.1-13.2] years; seven  
42 with and ten without AD) were enrolled. Bronchoalveolar lavage (BAL) and blood samples were  
43 collected from these patients. Seventy-three cytokines/chemokines and distinct immune T cell  
44 populations were evaluated in blood and BAL. We found that BAL and blood immune profiles of cwSA  
45 with and without AD were globally similar. However, specific differences were observed, namely lower  
46 frequency of Tc2, Th17 and IL-17-producing mucosal associated invariant T (MAIT-17) cells and higher  
47 CD8/CD4 ratio and IL-22 concentrations in BAL and of CCL19 concentrations in plasma from cwSA with  
48 AD. Further, in contrast with cwSA without AD, we found a positive correlation between a set of plasma  
49 cytokines and almost all cytokines in BAL in cwSA with AD. In conclusion, this study shows the major  
50 immune differences between cwSA with and without AD in BAL and blood suggesting that distinct  
51 endotypes may be implicated in the inflammatory responses observed in these pediatric patients.

52

53 **Keywords:**

54 Asthma; atopic dermatitis; children; Bronchoalveolar lavage; T cells

55

56 **Abbreviations:**

57 AD, atopic dermatitis; BAL, Bronchoalveolar lavage; cwSA, children with SA; ILT, innate-like T (ILT) cells;  
58 MAIT, mucosal-associated invariant T; SA; severe asthma

59

60

## 61 1. Introduction

62 Asthma is a heterogeneous immunological condition usually characterized by a chronic airway  
63 inflammation, with different underlying disease processes. It is defined by the history of respiratory  
64 symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in  
65 intensity, together with variable expiratory airflow limitation (1-3). Asthma is a common chronic  
66 respiratory disease affecting 1 to 18% of the general population depending on the country (4,5). The  
67 prevalence of asthma in childhood is elevated and up to 7% of adolescents had severe asthma symptoms  
68 (5).

69 It is currently accepted that the term asthma refers to several conditions with distinct mechanistic  
70 pathways (endotypes) and variable clinical presentations (phenotypes) (6,7). This is why a better  
71 understanding of the immune mechanisms involved in each endotype is crucial to the management of  
72 asthma (8,9). Severe asthma (SA) affects 2% to 5% of children with asthma. Children with SA (cwSA)  
73 suffer from frequent exacerbations despite being treated with inhaled corticosteroids and at least  
74 another controller, good treatment adherence and technique and removal of environmental factors  
75 such as tobacco (10,11). cwSA have a reduced quality of life. Association between asthma and other  
76 atopic conditions such as atopic dermatitis (AD) was described in children (5,12). AD, also known as  
77 eczema and atopic eczema, is one of the most common inflammatory disorders characterized by  
78 intense itching and recurrent eczematous lesions (5,13). AD affects up to 20% of children and 10% of  
79 adults in high-income countries (5,14,15). Previous studies described the progression of atopic  
80 disorders from AD in infants to allergic rhinitis and asthma in children (16,17). In addition, it was  
81 reported that up to 25% of children with current AD also have asthma (18).

82 Asthma and AD share common genetic and immunological features (19,20). These two pathologies  
83 were originally considered to be mediated by an imbalance towards a T helper 2 (Th2) and exaggerated  
84 IgE responses to allergens (8,12,13,20,21). In this context, biologics such as dupilumab (anti-IL-4Ra)  
85 and omalizumab (anti-IgE) are effective treatments of moderate to severe asthma and AD (22-24).  
86 However, not all cwSA have AD, and clinical responses to biologics may vary among cwSA, children  
87 with AD or both (25). In addition, it remains unclear whether cwSA with current AD and cwSA without  
88 AD have distinct local and systemic immune profiles. Here, we carried out an in-depth analysis of the  
89 immune profile of cwSA according to the presence or absence of AD to determine the main immune  
90 features they share and those that distinguish them. For this, we analyzed distinct T cell populations,  
91 including innate-like T (ILT) cells as mucosal-associated invariant T (MAIT), invariant Natural Killer T  
92 (iNKT) and  $\gamma\delta$  T cells (26-29), and cytokine levels in both bronchoalveolar lavage (BAL) and blood from  
93 cwSA with current AD and cwSA without AD.

94 **2. Materials and Methods**

95 **2.1. Subjects and sample collection**

96 CwSA included in this study were from the CLASSE (Cellules Lymphoïdes Innées dans l'Asthme Sévère  
97 de l'Enfant) cohort (ClinicalTrials.gov Identifier: NCT03784781). They were recruited in the department  
98 of Paediatric Pulmonology and Allergy of Necker Hospital (Paris, France). Institutional ethical approval  
99 and written informed consent were obtained.

100 SA was defined by the persistence of symptoms despite the use of high doses of inhaled corticosteroid  
101 (ICS) and another controller medication (10), confirmation of good adherence and inhalation  
102 technique and control of underlying modifiable factors and environmental factors. Indeed, patients  
103 were not included if their adherence or technique was considered poor by medical doctors, based on  
104 both their history and how parents and children used the inhaler. Number of severe exacerbations  
105 (SE), defined as exacerbations requiring bursts of systemic corticosteroids ( $\geq 3$  days), were recorded.  
106 Asthma control was assessed using the Asthma Control Test (ACT) based on a response scale from 1 to  
107 25, where a score higher than 21 over the last 4 weeks, indicated complete control, between 16 to 20  
108 somewhat controlled, below 15 poorly controlled, and below 7.5 not controlled (score 1).  
109 Demographic data, age at asthma onset, total serum IgE and medication were recorded for each  
110 patient. Children underwent clinical investigations, including flexible endoscopy with bronchoalveolar  
111 lavage (BAL) collection and blood sampling, as previously described (30).

112 Moreover, atopic dermatitis (AD) status was defined by clinician's assessment as recommended (13)  
113 and cwSA were divided into two groups based on their current AD. No cwSA had symptoms or findings  
114 suggestive of current infection at the time of the bronchoscopy.

115 **2.2. Flow cytometry**

116 Blood and BAL were obtained from each patient on the same day. Freshly isolated peripheral blood  
117 mononuclear cells (PBMC) were obtained by using Ficoll-Paque density centrifugation (1.077 g/mL;  
118 PAA Laboratories GmbH, Velizy Villacoublay, France). BAL was immediately filtered through MACS  
119 SmartStrainers (100  $\mu$ m) (Miltenyi Biotec, Paris, France) to remove mucus. BAL was centrifuged to  
120 separate cells from fluids. BAL and blood samples were obtained at the same time and immediately  
121 analyzed for T cells. No cells were frozen/thawed.

122 PBMC and BAL cells were washed in fluorescence-activated cell sorting buffer (2% w/v BSA, 0.1%  
123  $\text{NaN}_3$  sodium azide in PBS) and then stained with eFluor506–fixable viability dye (ThermoFisher  
124 Scientific, Illkirch, France) for 10 minutes at 4°C. Then, cells were stained with the following  
125 fluorochrome-conjugated antibodies for 30 min at 4°C: anti-CD3, anti-CD4, anti-CD8, anti-CD161, anti-

126 V $\delta$ 2 and anti-TCRV $\alpha$ 7.2. Doublets were excluded using pulse-width and pulse-area and side scatter  
127 properties. MAIT and V $\delta$ 2 cells were identified as CD3<sup>+</sup>TCRV $\alpha$ 7.2<sup>+</sup>CD161<sup>+</sup> and CD3<sup>+</sup>V $\delta$ 2<sup>+</sup> cells,  
128 respectively. For intracellular cytokine analysis allowing the identification of IL-4, IL-13, IL-17A, and  
129 IFN $\gamma$ -producing T cells, PBMC and BAL cells were cultured during 5h with 25 ng/ml phorbol 12-  
130 myristate 13-acetate (PMA) and 1  $\mu$ M ionomycin, in the presence of 10 ng/ml Brefeldin A (all from  
131 Sigma-Aldrich, Saint-Quentin Fallavier, France). Events were acquired on a FACS LSR Fortessa (BD  
132 Biosciences) and analyzed using FlowJo software v10.8.1 (Becton, Dickinson and Company, Ashland,  
133 USA). CD8<sup>+</sup>/CD4<sup>+</sup> ratio was calculated as the percentage of CD8<sup>+</sup> among gated CD3<sup>+</sup> cells divided by  
134 the percentage of CD4<sup>+</sup> among gated CD3<sup>+</sup> cells. Gate strategies are showed in **Figure 1** and the  
135 antibodies and reagents used for flow cytometry analysis are listed in **Supplementary Table 1**.

### 136 **2.3. Cytokines in BAL and plasma**

137 Cytokines were analysed using xMAP<sup>®</sup> Luminex technology and the associated apparatus  
138 (Bioplex<sup>®</sup>200, Biorad, Marnes-la-Coquette, France). Forty chemokines (Bio-Plex Pro<sup>™</sup> Human  
139 chemokine assays, 40-plex; BioRad) and 37 inflammation markers (Bio-Plex Pro<sup>™</sup> Human Inflammation  
140 Panel I, 37-plex; BioRad) were analysed on BAL diluted 1/2 and plasma diluted 1/4, following the  
141 manufacturer's recommendations, as previously reported (20). Due to a small amount of redundancy  
142 between the two multiplex assays used, 73 cytokines were assayed: APRIL/TNFSF13, BAFF/TNFSF13B,  
143 sCD30/TNFRSF8, sCD163, Chitinase 3-like 1 (CHI3L1), CCL21 (6Ckine), CXCL13 (BCA-1), CCL27 (CTACK),  
144 CXCL25 (ENA-78), CCL11 (Eotaxin), CCL24 (Eotaxin-2), CCL26 (Eotaxin-3), CX3CL1 (Fractalkine), CXCL6  
145 (GCP-2), GM-CSF, CXCL1 (Gro- $\alpha$ ), CXCL2 (Gro- $\beta$ ), CCL1 (I-309), gp130/sIL-6RB, sIL-6RA, IFN $\alpha$ 2, IFN $\beta$ ,  
146 IFN $\gamma$ , IL-1 $\beta$ , IL-2, IL-4, IL-6, IL-8 (CXCL8), IL-10, IL-11, IL-12p40, IL-12p70, IL-16, IL-19, IL-20, IL-22, IL-26,  
147 IL-27 (p28), IL-28A (IFN- $\lambda$ 2), IL-29 (IFN- $\lambda$ 1), IL-32, IL-34, IL-35, CXCL10 (IP-10), CXCL11 (I-TAC), CCL2  
148 (MCP-1), CCL8 (MCP-2), CCL7 (MCP-3), CCL13 (MCP4), CCL22 (MDC), MIF, CXCL9 (MIG), CCL3 (MIP-1 $\alpha$ ),  
149 CCL15 (MIP-1 $\delta$ ), CCL20 (MIP-3 $\alpha$ ), CCL19 (MIP-3 $\beta$ ), CCL23 (MPIF-1), CXCL16 (SCYB16), CXCL12 (SDF-  
150 1 $\alpha$ + $\beta$ ), CCL17 (TARC), CCL25 (TECK), LIGHT/TNFSF14, MMP-1, MMP-2, MMP-3, Osteocalcin,  
151 Osteopontin, Pentraxin-3, sTNF-R1, sTNF-R2, TLSP, TNF $\alpha$  and TWEAK/TNFSF12.

### 152 **2.4. Statistical analysis**

153 Data were expressed as the median (interquartile range). Differences between groups were assessed  
154 with the Mann-Whitney or Fischer's exact test (two tailed) for categorical data. Correlation analyses  
155 were made using Spearman rank correlation analysis (two tailed).  $p < 0.05$  was considered to be  
156 significant. The Benjamini-Hochberg FDR method was used to correct for multiple comparisons. Data  
157 were analysed using GraphPad Prism version 10.1.0 (GraphPad Software, Inc, San Diego, Calif).

158

159 **3. Results**

160 **3.1. Clinical characteristics of patients**

161 Data from seventeen cwSA (9.8 [7.1-13.2] years) were analyzed. Seven children had concomitant AD  
162 (cwSA with AD) and ten did not (cwSA without AD). Demographic and clinical characteristics are  
163 summarized in **Table 1**. The number of severe exacerbations in the past year, the number of  
164 exacerbators among cwSA, ACT score, lung function, IgE levels and the number of blood cells  
165 (leukocytes, eosinophils, neutrophils and lymphocytes) did not differ between groups. Among the  
166 clinical parameters, only the dose of ICS was higher in cwSA with AD ( $p=0.03$ ).

167 **3.2. The frequency of IL-17-producing MAIT (MAIT-17) and CD4+ (Th17) cells was significantly lower**  
168 **in BAL from cwSA with AD**

169 Here, we systematically profiled in BAL Th1, Th2 and Th17 cells identified as IFN $\gamma$ -, IL-4- and IL-13- and  
170 IL-17-producing CD4+ T cells, respectively. Type 1 and Type 2 cytotoxic (Tc1 and Tc2) CD8+ T cells (IFN $\gamma$   
171 and IL-4 producers, respectively) were also analyzed. Among ILT cells, we focused on IFN $\gamma$ - and IL-17-  
172 producing MAIT and on IFN $\gamma$ -producing V $\delta$ 2+  $\gamma\delta$  T cells. No significant differences were observed  
173 between the frequency of the majority of these T cell populations in BAL (**Table 2**). Despite all these  
174 similarities, the ratio CD8/CD4 was higher while the frequency of Tc2, Th17 and IL-17-producing MAIT  
175 (MAIT-17) cells in BAL was lower in cwSA with AD than in those without AD (**Figure 2A – 2D**). Further,  
176 we found a negative correlation between the frequency of Th2 and Th17 cells in BAL from cwSA with  
177 AD ( $p=0.048$ ,  $r= -0.786$ ) but not without AD ( $p=0.263$ ,  $r= 0.394$ ).

178 The analysis of circulating Th1, Th2, Th17, Tc1, Tc2 and cytokine-producing MAIT and V $\delta$ 2+  $\gamma\delta$  T cells  
179 showed no significant difference between these populations in the peripheral blood of cwSA with AD  
180 compared to those without AD (**Table 3**).

181 **3.3. IL-22 and CCL19 were significantly enhanced in cwSA with AD**

182 Further, we analyzed distinct cytokines in BAL and plasma from cwSA with versus without AD. No major  
183 differences were observed except for IL-22 and CCL19 levels that were respectively higher in BAL and  
184 plasma from cwSA with AD compared to cwSA without AD (**Table 4**). A positive correlation was  
185 observed between the levels of BAL and plasma CCL19 in cwSA with AD ( $r=0.793$ ;  $p=0.04$ ) but not in  
186 CwSA without AD ( $r=0.292$ ;  $p=0.56$ ).

187 **3.4. Correlation of soluble cytokines between BAL and plasma**

188 Spearman correlations showed that most of the cytokines analyzed were positively correlated with  
189 each other in BAL from cwSA without AD (**Figure 3A**) and with AD (**Figure 3B**). In plasma, a particular

190 core of cytokines was more strongly positively correlated with each other, mainly in samples from  
191 cwSA with AD (**Figure 3B**). This core included IFN $\alpha$ 2, IFN $\beta$ , IFN $\delta$ 1, IFN $\delta$ 2, IFN $\gamma$ , IL-10, IL-11, IL-12p70, IL-  
192 19, IL-2, IL-20, IL-22, IL-27p28, IL-32, IL-34, IL-35, IL-4, IL-6 (green square).

193 We also determined whether correlations could also exist between cytokines present in BAL and those  
194 present in plasma. This was not the case for the majority of cytokines from cwSA without AD (**Figure**  
195 **3A**). However, we found in cwSA with AD a clear positive correlation between a set of plasma cytokines  
196 (IFN $\alpha$ 2, IFN $\beta$ , IFN $\delta$ 1, IFN $\delta$ 2, IFN $\gamma$ , IL-11, IL-12p40, IL-19, IL-2, IL-20, IL-22, IL-32, IL-34, IL-35, IL-4 and IL-  
197 6) and almost all cytokines present in BAL (**Figure 3B**, orange rectangle).



198 **4. Discussion**

199 Our study provided a deep comparative analyze of the immune profile of cwSA with versus without  
200 AD. A large set of variables, including cytokines, chemokines, immune cells, and immunoglobulins,  
201 were analyzed both in periphery and in BAL. The access to these samples is crucial because the levels  
202 of many variables in the airways and blood did not correlate with each other in cwSA (30-32) and here  
203 we measured several variables in both BAL and blood. Among the immune parameters analyzed, six  
204 were significantly different between the groups and among them five in BAL. In fact, cwSA with AD had  
205 less Th17, MAIT-17 and Tc2 cells but enhanced CD8/CD4 T cell ratio and IL-22 in BAL and higher levels  
206 of CCL19 in plasma compare to cwSA without AD. This confirms that invasive analyses performed in  
207 BAL are necessary for a better understanding of the local actors and mechanisms responsible for SA  
208 associated with other pathologies as AD.

209 The analysis of T cell populations showed that the ratio CD8/CD4 was significantly higher in BAL from  
210 cwSA with AD than without AD. It is possible that the balance between these cells reflects the  
211 involvement of distinct immune mechanisms. CD8+ T cells, mainly Tc1 cells, are critical to anti-viral  
212 defense (33), but cwSA presented no viral infection at the time of the bronchoscopy. Nevertheless,  
213 CD8+ Tc2 cells, another subset of CD8+ T cells, produce type 2 cytokines (34). The implication of type  
214 2 cytokines on atopic diseases including asthma and AD was confirmed by the efficacy and safety of  
215 dupilumab (anti-IL-4R $\alpha$ ) treatment (22,35,36). Th2 cells are commonly considered as a major source  
216 of IL-4 in asthma. However, Tc2 cells may also play an important role in asthma pathogenesis (34,37).  
217 Indeed, Tc2 cells have been detected in blood and lung samples from adult asthmatic patients, their  
218 numbers often correlating with long-term decline in lung function, poor symptom control or death  
219 (34,38,39). Tc2 cells were also associated with severe AD (40). Here, we found that Tc2 cells were  
220 reduced in BAL from cwSA with AD. It was suggested that Tc2 cells could be more steroid-resistant  
221 type 2 cytokine producers than Th2 cells (34). However, this does not seem to explain our results, since  
222 cwSA with AD received higher doses of ICS than cwSA without AD. Future studies focused at the in-  
223 depth molecular and functional characterization of Tc2 cells and their role in pediatric SA will likely  
224 provide valuable new insight into the pathophysiology of uncontrolled disease.

225 In addition to the implication of Th2-type cytokines in SA and AD, the involvement of Th17 cells in the  
226 pathogenesis of these pathologies have also been reported (41-43). The percentage of circulating Th17  
227 cells in AD patients was higher and associated with disease severity, but it has also been suggested  
228 that the presence of IL-17 in the skin may be primarily a defense mechanism against infection (44,45).  
229 Concerning pediatric SA, it was reported that the frequency of Th17 cells in the bronchial mucosa and  
230 BAL did not differ between asthmatics and controls and we did not find significant association between

231 the frequency of Th17 cells and the number of severe exacerbations in cwSA (30-32). Here, we found  
232 that cwSA with AD presented lower frequency of Th17 cells in BAL and that the frequency of Th17 and  
233 Th2 negatively correlated in BAL from cwSA with AD. It is possible that in cwSA with AD, the  
234 differentiation of CD4<sup>+</sup> Th2 cells was favored at the expense of CD4 Th17 cells.

235 MAIT cells are currently described as being implicated on the mucosal defense against infections  
236 (46,47) but they can also contribute to SA pathology since they are present in BAL from cwSA (30). Our  
237 previous report (30) identified two groups of cwSA according to MAIT-17 frequency in BAL: a group  
238 with high (MAIT-17<sup>high</sup>) and a group with low (MAIT-17<sup>low</sup>) frequency of MAIT-17 cells. Children in the  
239 MAIT-17<sup>high</sup> group was more prone to severe exacerbations (30). Here, the frequency of MAIT-17 was  
240 lower in BAL from cwSA with DA, but no significant difference in the number of severe exacerbations  
241 was observed between the two groups of patients. It was reported in adults with SA that oral  
242 corticosteroid (OCS) could decrease the frequency of circulating MAIT cells, but this study did not  
243 analyze MAIT-17 cells (48). Here, we found that cwSA with AD used higher doses of ICS (not of OCS)  
244 than cwSA without AD. We therefore cannot exclude that ICS may contribute to the reduced frequency  
245 of MAIT-17 cells observed in BAL from cwSA with DA.

246 IL-22 belongs to the IL-10 cytokine family and is produced by T cells as Th17, type 3 innate lymphoid  
247 cells as well as neutrophils (49). Elevated BAL and serum IL-22 levels in adult patients with SA have  
248 been reported (50,51). It was suggested that IL-22 could play a role in certain endotypes of asthma as  
249 neutrophilic asthma (52). Further, IL-22 was reported to be implicated in AD and the anti-IL-22  
250 monoclonal antibody (fezakinumab) improved AD clinical scores (53,54). The levels of IL-22 were  
251 higher in BAL from cwSA with DA but these patients presented no significant increase in the frequency  
252 of neutrophils in BAL when compared to cwSA without DA. Experimental models reported that IL-22  
253 promoted allergic airway inflammation and hyperreactivity in intranasal antigen challenge of mice  
254 sensitized epicutaneously (55). These results associated with our observations suggest that cutaneous  
255 sensitization, as can occur in cwSA with AD, may elicit IL-22 production in BAL then contributing to lung  
256 inflammation.

257 CCL19, which primarily regulates cell trafficking, plays an important role in the balance between  
258 immunity and tolerance (56,57). The higher levels of CCL19 in the plasma of cwSAs with AD could result  
259 from the production of this chemokine by fibroblasts in the area infiltrated by leukocytes in AD lesions,  
260 since it has been described that CCL19 gene expression was strongly upregulated in the lesions of adult  
261 AD patients (58). A positive correlation was found between CCL19 levels in BAL and plasma of cwSA  
262 with AD, suggesting that this chemokine may also be involved in airway inflammation in these patients.

263 A compelling finding of the present study is the observed positive correlation between a panel of  
264 cytokines present in plasma, namely IFN $\alpha$ 2, IFN $\beta$ , IFN $\delta$ 1, IFN $\delta$ 2, IFN $\gamma$ , IL-11, IL-12p40, IL-19, IL-2, IL-20,  
265 IL-22, IL-32, IL-34, IL-35, IL-4 and IL-6, with the majority of cytokines present in BAL from cwSA with  
266 AD. This phenomenon was specific to this group, as it was not observed in cwSA without AD. Prior to  
267 the present study, the correlation between BAL and plasma cytokines in cwSA with AD have not been  
268 studied in detail. In our previous study, we reported that almost no correlation between BAL and blood  
269 concentrations of any soluble constituents was observed in cwSA (31,32). Our results may indicate  
270 that, in cwSA with AD, increased levels of this group of cytokines in their plasma may reflect increased  
271 levels of these cytokines in their BAL. These observations could provide valuable information on airway  
272 inflammation in cwSA with AD. The present results need to be confirmed in another cohort with more  
273 patients but, if confirmed, it could contribute to better understand the global immune profile from  
274 cwSA with compared to without AD.

275 Our study has limitations. We are aware that our sample size was small and future studies performed  
276 on independent cohorts are required to confirm our results. However, we would like to draw attention  
277 to the fact that it is difficult to obtain BAL samples from cwSA and that this may explain the limited  
278 number of studies on T cells present in this type of invasive sample. The severity of AD was not assessed  
279 and no healthy controls were included due to ethical reasons, so we were not able to distinguish  
280 pathological variation from normal expression.

281 In summary, this study compared for the first time the immune profile in BAL and blood of cwSA with  
282 or without AD. Our results showed that immune profiles of these groups were globally similar but  
283 specific differences were observed, namely lower frequency of Tc2, Th17 and MAIT-17 cells and higher  
284 CD8/CD4 ratio and IL-22 concentrations in BAL and enhanced CCL19 concentrations in plasma from  
285 cwSA with AD.

286 Our results support the idea that targeted analyses in cwSA with versus without AD will potentially  
287 allow us to dissect the relative contribution of different endotypes to the inflammatory responses  
288 observed in these patients.

289

290 **References**

- 291 [1] I.D. Pavord, R. Beasley, A. Agusti, G.P. Anderson, E. Bel, G. Brusselle, P. Cullinan, A. Custovic, F.M.  
292 Ducharme, J.V. Fahy, U. Frey, P. Gibson, L.G. Heaney, P.G. Holt, M. Humbert, C.M. Lloyd, G. Marks,  
293 F.D. Martinez, P.D. Sly, E. von Mutius, S. Wenzel, H.J. Zar, A. Bush, After asthma: redefining airways  
294 diseases, *Lancet*, 391 (2018) 350-400. 10.1016/S0140-6736(17)30879-6.
- 295 [2] C. Porsbjerg, E. Melen, L. Lehtimaki, D. Shaw, *Asthma, Lancet*, 401 (2023) 858-873.  
296 10.1016/S0140-6736(22)02125-0.
- 297 [3] M.L. Levy, L.B. Bacharier, E. Bateman, L.P. Boulet, C. Brightling, R. Buhl, G. Brusselle, A.A. Cruz,  
298 J.M. Drazen, L. Duijts, L. Fleming, H. Inoue, F.W.S. Ko, J.A. Krishnan, K. Mortimer, P.M. Pitrez, A.  
299 Sheikh, A. Yorgancioglu, H.K. Reddel, Key recommendations for primary care from the 2022 Global  
300 Initiative for Asthma (GINA) update, *NPJ Prim Care Respir Med*, 33 (2023) 7. 10.1038/s41533-023-  
301 00330-1.
- 302 [4] M.I. Asher, L. Garcia-Marcos, N.E. Pearce, D.P. Strachan, Trends in worldwide asthma prevalence,  
303 *Eur Respir J*, 56 (2020). 10.1183/13993003.02094-2020.
- 304 [5] L. Garcia-Marcos, M.I. Asher, N. Pearce, E. Ellwood, K. Bissell, C.Y. Chiang, A. El Sony, P. Ellwood,  
305 G.B. Marks, K. Mortimer, A.E. Martinez-Torres, E. Morales, V. Perez-Fernandez, S. Robertson, C.E.  
306 Rutter, R.J. Silverwood, D.P. Strachan, I.S.G. Global Asthma Network Phase, The burden of asthma,  
307 hay fever and eczema in children in 25 countries: GAN Phase I study, *Eur Respir J*, 60 (2022)  
308 2102866. 10.1183/13993003.02866-2021.
- 309 [6] J. Lotvall, C.A. Akdis, L.B. Bacharier, L. Bjermer, T.B. Casale, A. Custovic, R.F. Lemanske, Jr., A.J.  
310 Wardlaw, S.E. Wenzel, P.A. Greenberger, Asthma endotypes: a new approach to classification of  
311 disease entities within the asthma syndrome, *J Allergy Clin Immunol*, 127 (2011) 355-360.  
312 10.1016/j.jaci.2010.11.037.
- 313 [7] J. Lotvall, C.A. Akdis, L.B. Bacharier, L. Bjermer, T.B. Casale, A. Custovic, R.F. Lemanske, Jr., A.J.  
314 Wardlaw, S.E. Wenzel, P.A. Greenberger, Asthma endotypes: a new approach to classification of  
315 disease entities within the asthma syndrome, *J Allergy Clin Immunol*, 127 (2011) 355-360.  
316 10.1016/j.jaci.2010.11.037.
- 317 [8] T. Boonpiyathad, Z.C. Sozener, P. Satitsuksanoa, C.A. Akdis, Immunologic mechanisms in asthma,  
318 *Semin Immunol*, 46 (2019) 101333. 10.1016/j.smim.2019.101333.
- 319 [9] H. Hammad, B.N. Lambrecht, The basic immunology of asthma, *Cell*, 184 (2021) 1469-1485.  
320 10.1016/j.cell.2021.02.016.
- 321 [10] K.F. Chung, S. Wenzel, F. European Respiratory Society/American Thoracic Society Severe Asthma  
322 International Guidelines Task, From the authors: International European Respiratory  
323 Society/American Thoracic Society guidelines on severe asthma, *Eur Respir J*, 44 (2014) 1378-  
324 1379. 10.1183/09031936.00120714.
- 325 [11] F. Holguin, J.C. Cardet, K.F. Chung, S. Diver, D.S. Ferreira, A. Fitzpatrick, M. Gaga, L. Kellermeier,  
326 S. Khurana, S. Knight, V.M. McDonald, R.L. Morgan, V.E. Ortega, D. Rigau, P. Subbarao, T. Tonia,  
327 I.M. Adcock, E.R. Bleecker, C. Brightling, L.P. Boulet, M. Cabana, M. Castro, P. Chanez, A. Custovic,  
328 R. Djukanovic, U. Frey, B. Frankemolle, P. Gibson, D. Hamerlijnck, N. Jarjour, S. Konno, H. Shen, C.  
329 Vitary, A. Bush, Management of severe asthma: a European Respiratory Society/American  
330 Thoracic Society guideline, *Eur Respir J*, 55 (2020). 10.1183/13993003.00588-2019.
- 331 [12] S.K. Bantz, Z. Zhu, T. Zheng, The Atopic March: Progression from Atopic Dermatitis to Allergic  
332 Rhinitis and Asthma, *J Clin Cell Immunol*, 5 (2014). 10.4172/2155-9899.1000202.
- 333 [13] S.M. Langan, A.D. Irvine, S. Weidinger, Atopic dermatitis, *Lancet*, 396 (2020) 345-360.  
334 10.1016/S0140-6736(20)31286-1.

- 335 [14] M.R. Laughter, M.B.C. Maymone, S. Mashayekhi, B.W.M. Arents, C. Karimkhani, S.M. Langan, R.P.  
336 Dellavalle, C. Flohr, The global burden of atopic dermatitis: lessons from the Global Burden of  
337 Disease Study 1990-2017, *Br J Dermatol*, 184 (2021) 304-309. 10.1111/bjd.19580.
- 338 [15] A. Mosam, G. Todd, Global epidemiology and disparities in atopic dermatitis, *Br J Dermatol*, 188  
339 (2023) 726-737. 10.1093/bjd/ljad042.
- 340 [16] J.M. Spergel, A.S. Paller, Atopic dermatitis and the atopic march, *J Allergy Clin Immunol*, 112  
341 (2003) S118-127. 10.1016/j.jaci.2003.09.033.
- 342 [17] A.S. Paller, J.M. Spergel, P. Mina-Osorio, A.D. Irvine, The atopic march and atopic multimorbidity:  
343 Many trajectories, many pathways, *J Allergy Clin Immunol*, 143 (2019) 46-55.  
344 10.1016/j.jaci.2018.11.006.
- 345 [18] J.I. Silverberg, E.L. Simpson, Association between severe eczema in children and multiple  
346 comorbid conditions and increased healthcare utilization, *Pediatr Allergy Immunol*, 24 (2013) 476-  
347 486. 10.1111/pai.12095.
- 348 [19] S. Weidinger, S.A. Willis-Owen, Y. Kamatani, H. Baurecht, N. Morar, L. Liang, P. Edser, T. Street, E.  
349 Rodriguez, G.M. O'Regan, P. Beattie, R. Folster-Holst, A. Franke, N. Novak, C.M. Fahy, M.C. Winge,  
350 M. Kabesch, T. Illig, S. Heath, C. Soderhall, E. Melen, G. Pershagen, J. Kere, M. Bradley, A. Lieden,  
351 M. Nordenskjold, J.I. Harper, W.H. McLean, S.J. Brown, W.O. Cookson, G.M. Lathrop, A.D. Irvine,  
352 M.F. Moffatt, A genome-wide association study of atopic dermatitis identifies loci with  
353 overlapping effects on asthma and psoriasis, *Hum Mol Genet*, 22 (2013) 4841-4856.  
354 10.1093/hmg/ddt317.
- 355 [20] H. Hammad, B.N. Lambrecht, Barrier Epithelial Cells and the Control of Type 2 Immunity,  
356 *Immunity*, 43 (2015) 29-40. 10.1016/j.immuni.2015.07.007.
- 357 [21] C.A. Akdis, P.D. Arkwright, M.C. Bruggen, W. Busse, M. Gadina, E. Guttman-Yassky, K. Kabashima,  
358 Y. Mitamura, L. Vian, J. Wu, O. Palomares, Type 2 immunity in the skin and lungs, *Allergy*, 75 (2020)  
359 1582-1605. 10.1111/all.14318.
- 360 [22] M. Castro, J. Corren, I.D. Pavord, J. Maspero, S. Wenzel, K.F. Rabe, W.W. Busse, L. Ford, L. Sher,  
361 J.M. FitzGerald, C. Katelaris, Y. Tohda, B. Zhang, H. Staudinger, G. Pirozzi, N. Amin, M. Ruddy, B.  
362 Akinlade, A. Khan, J. Chao, R. Martincova, N.M.H. Graham, J.D. Hamilton, B.N. Swanson, N. Stahl,  
363 G.D. Yancopoulos, A. Teper, Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled  
364 Asthma, *N Engl J Med*, 378 (2018) 2486-2496. 10.1056/NEJMoa1804092.
- 365 [23] E.L. Simpson, A.S. Paller, E.C. Siegfried, M. Boguniewicz, L. Sher, M.J. Gooderham, L.A. Beck, E.  
366 Guttman-Yassky, D. Pariser, A. Blauvelt, J. Weisman, B. Lockshin, T. Hultsch, Q. Zhang, M.A. Kamal,  
367 J.D. Davis, B. Akinlade, H. Staudinger, J.D. Hamilton, N.M.H. Graham, G. Pirozzi, A. Gadkari, L.  
368 Eckert, N. Stahl, G.D. Yancopoulos, M. Ruddy, A. Bansal, Efficacy and Safety of Dupilumab in  
369 Adolescents With Uncontrolled Moderate to Severe Atopic Dermatitis: A Phase 3 Randomized  
370 Clinical Trial, *JAMA Dermatol*, 156 (2020) 44-56. 10.1001/jamadermatol.2019.3336.
- 371 [24] A. Blauvelt, M. de Bruin-Weller, M. Gooderham, J.C. Cather, J. Weisman, D. Pariser, E.L. Simpson,  
372 K.A. Papp, H.C. Hong, D. Rubel, P. Foley, E. Prens, C.E.M. Griffiths, T. Etoh, P.H. Pinto, R.M. Pujol,  
373 J.C. Szepietowski, K. Ettlner, L. Kemeny, X. Zhu, B. Akinlade, T. Hultsch, V. Mastey, A. Gadkari, L.  
374 Eckert, N. Amin, N.M.H. Graham, G. Pirozzi, N. Stahl, G.D. Yancopoulos, B. Shumel, Long-term  
375 management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical  
376 corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-  
377 controlled, phase 3 trial, *Lancet*, 389 (2017) 2287-2303. 10.1016/S0140-6736(17)31191-1.
- 378 [25] M. Boguniewicz, L.A. Beck, L. Sher, E. Guttman-Yassky, D. Thaci, A. Blauvelt, M. Worm, J. Corren,  
379 W. Soong, P. Lio, A.B. Rossi, Y. Lu, J. Chao, L. Eckert, A. Gadkari, T. Hultsch, M. Ruddy, L.P. Mannent,

380 N.M.H. Graham, G. Pirozzi, Z. Chen, M. Ardeleanu, Dupilumab Improves Asthma and Sinonasal  
381 Outcomes in Adults with Moderate to Severe Atopic Dermatitis, *J Allergy Clin Immunol Pract*, 9  
382 (2021) 1212-1223 e1216. 10.1016/j.jaip.2020.12.059.

383 [26] D.I. Godfrey, J. Le Nours, D.M. Andrews, A.P. Uldrich, J. Rossjohn, Unconventional T Cell Targets  
384 for Cancer Immunotherapy, *Immunity*, 48 (2018) 453-473. 10.1016/j.immuni.2018.03.009.

385 [27] A. Toubal, I. Nel, S. Lotersztajn, A. Lehuen, Mucosal-associated invariant T cells and disease, *Nat*  
386 *Rev Immunol*, 19 (2019) 643-657. 10.1038/s41577-019-0191-y.

387 [28] J.R. Victor, G. Lezmi, M. Leite-de-Moraes, New Insights into Asthma Inflammation: Focus on iNKT,  
388 MAIT, and gammadeltaT Cells, *Clin Rev Allergy Immunol*, 59 (2020) 371-381. 10.1007/s12016-020-  
389 08784-8.

390 [29] J.C. Ribot, N. Lopes, B. Silva-Santos, gammadelta T cells in tissue physiology and surveillance, *Nat*  
391 *Rev Immunol*, 21 (2021) 221-232. 10.1038/s41577-020-00452-4.

392 [30] G. Lezmi, R. Abou-Taam, N. Garcelon, C. Dietrich, F. Machavoine, C. Delacourt, K. Adel-Patient, M.  
393 Leite-de-Moraes, Evidence for a MAIT-17-high phenotype in children with severe asthma, *J Allergy*  
394 *Clin Immunol*, 144 (2019) 1714-1716 e1716. 10.1016/j.jaci.2019.08.003.

395 [31] K. Adel-Patient, M. Grauso, R. Abou-Taam, B. Guillon, C. Dietrich, F. Machavoine, M. Briard, N.  
396 Garcelon, H. Faour, A. Neuraz, C. Delacourt, T.J. Molina, M. Leite-de-Moraes, G. Lezmi, A  
397 Comprehensive Analysis of Immune Constituents in Blood and Bronchoalveolar Lavage Allows  
398 Identification of an Immune Signature of Severe Asthma in Children, *Front Immunol*, 12 (2021)  
399 700521. 10.3389/fimmu.2021.700521.

400 [32] K. Adel-Patient, M. Grauso, R. Abou-Taam, B. Guillon, C. Dietrich, F. Machavoine, N. Garcelon, M.  
401 Briard, H. Faour, A. Neuraz, C. Delacourt, T.J. Molina, M. Leite-de-Moraes, G. Lezmi, Immune  
402 signatures distinguish frequent from non-frequent exacerbators among children with severe  
403 asthma, *Allergy*, 76 (2021) 2261-2264. 10.1111/all.14759.

404 [33] M.A. Cox, S.M. Kahan, A.J. Zajac, Anti-viral CD8 T cells and the cytokines that they love, *Virology*,  
405 435 (2013) 157-169. 10.1016/j.virol.2012.09.012.

406 [34] T.S.C. Hinks, R.D. Hoyle, E.W. Gelfand, CD8(+) Tc2 cells: underappreciated contributors to severe  
407 asthma, *Eur Respir Rev*, 28 (2019). 10.1183/16000617.0092-2019.

408 [35] E.L. Simpson, T. Bieber, E. Guttman-Yassky, L.A. Beck, A. Blauvelt, M.J. Cork, J.I. Silverberg, M.  
409 Deleuran, Y. Kataoka, J.P. Lacour, K. Kingo, M. Worm, Y. Poulin, A. Wollenberg, Y. Soo, N.M.  
410 Graham, G. Pirozzi, B. Akinlade, H. Staudinger, V. Mastey, L. Eckert, A. Gadkari, N. Stahl, G.D.  
411 Yancopoulos, M. Ardeleanu, Solo, S. Investigators, Two Phase 3 Trials of Dupilumab versus Placebo  
412 in Atopic Dermatitis, *N Engl J Med*, 375 (2016) 2335-2348. 10.1056/NEJMoa1610020.

413 [36] L.B. Bacharier, J.F. Maspero, C.H. Katelaris, A.G. Fiocchi, R. Gagnon, I. de Mir, N. Jain, L.D. Sher, X.  
414 Mao, D. Liu, Y. Zhang, A.H. Khan, U. Kapoor, F.A. Khokhar, P.J. Rowe, Y. Deniz, M. Ruddy, E. Laws,  
415 N. Patel, D.M. Weinreich, G.D. Yancopoulos, N. Amin, L.P. Mannent, D.J. Lederer, M. Hardin, V.I.  
416 Liberty Asthma, Dupilumab in Children with Uncontrolled Moderate-to-Severe Asthma, *N Engl J*  
417 *Med*, 385 (2021) 2230-2240. 10.1056/NEJMoa2106567.

418 [37] E.K. van der Ploeg, L. Krabbendam, H. Vroman, M. van Nimwegen, M.J.W. de Bruijn, G.M. de Boer,  
419 I.M. Bergen, M. Kool, G.A. Tramper-Standers, G.J. Braunstahl, D. Huylebroeck, R.W. Hendriks, R.  
420 Stadhouders, Type-2 CD8(+) T-cell formation relies on interleukin-33 and is linked to asthma  
421 exacerbations, *Nat Commun*, 14 (2023) 5137. 10.1038/s41467-023-40820-x.

422 [38] S.H. Cho, L.A. Stanciu, S.T. Holgate, S.L. Johnston, Increased interleukin-4, interleukin-5, and  
423 interferon-gamma in airway CD4+ and CD8+ T cells in atopic asthma, *Am J Respir Crit Care Med*,  
424 171 (2005) 224-230. 10.1164/rccm.200310-1416OC.

- 425 [39] S. Ying, M. Humbert, J. Barkans, C.J. Corrigan, R. Pfister, G. Menz, M. Larche, D.S. Robinson, S.R.  
426 Durham, A.B. Kay, Expression of IL-4 and IL-5 mRNA and protein product by CD4+ and CD8+ T cells,  
427 eosinophils, and mast cells in bronchial biopsies obtained from atopic and nonatopic (intrinsic)  
428 asthmatics, *J Immunol*, 158 (1997) 3539-3544.
- 429 [40] T. Czarnowicki, J. Gonzalez, A. Shemer, D. Malajian, H. Xu, X. Zheng, S. Khattri, P. Gilleaudeau, M.  
430 Sullivan-Whalen, M. Suarez-Farinas, J.G. Krueger, E. Guttman-Yassky, Severe atopic dermatitis is  
431 characterized by selective expansion of circulating TH2/TC2 and TH22/TC22, but not TH17/TC17,  
432 cells within the skin-homing T-cell population, *J Allergy Clin Immunol*, 136 (2015) 104-115 e107.  
433 10.1016/j.jaci.2015.01.020.
- 434 [41] J. Chesne, F. Braza, G. Mahay, S. Brouard, M. Aronica, A. Magnan, IL-17 in severe asthma. Where  
435 do we stand?, *Am J Respir Crit Care Med*, 190 (2014) 1094-1101. 10.1164/rccm.201405-0859PP.
- 436 [42] H. Esaki, P.M. Brunner, Y. Renert-Yuval, T. Czarnowicki, T. Huynh, G. Tran, S. Lyon, G. Rodriguez,  
437 S. Immaneni, D.B. Johnson, B. Bauer, J. Fuentes-Duculan, X. Zheng, X. Peng, Y.D. Estrada, H. Xu, C.  
438 de Guzman Strong, M. Suarez-Farinas, J.G. Krueger, A.S. Paller, E. Guttman-Yassky, Early-onset  
439 pediatric atopic dermatitis is T(H)2 but also T(H)17 polarized in skin, *J Allergy Clin Immunol*, 138  
440 (2016) 1639-1651. 10.1016/j.jaci.2016.07.013.
- 441 [43] J. Ostling, M. van Geest, J.P.R. Schofield, Z. Jevnikar, S. Wilson, J. Ward, R. Lutter, D.E. Shaw, P.S.  
442 Bakke, M. Caruso, S.E. Dahlen, S.J. Fowler, I. Horvath, N. Krug, P. Montuschi, M. Sanak, T.  
443 Sandstrom, K. Sun, I. Pandis, C. Auffray, A.R. Sousa, Y. Guo, I.M. Adcock, P. Howarth, K.F. Chung,  
444 J. Bigler, P.J. Sterk, P.J. Skipp, R. Djukanovic, O. Vaarala, U.B.S. Group, IL-17-high asthma with  
445 features of a psoriasis immunophenotype, *J Allergy Clin Immunol*, 144 (2019) 1198-1213.  
446 10.1016/j.jaci.2019.03.027.
- 447 [44] C. Koga, K. Kabashima, N. Shiraishi, M. Kobayashi, Y. Tokura, Possible pathogenic role of Th17 cells  
448 for atopic dermatitis, *J Invest Dermatol*, 128 (2008) 2625-2630. 10.1038/jid.2008.111.
- 449 [45] M. Sugaya, The Role of Th17-Related Cytokines in Atopic Dermatitis, *Int J Mol Sci*, 21 (2020).  
450 10.3390/ijms21041314.
- 451 [46] M. Salou, K. Franciszkiewicz, O. Lantz, MAIT cells in infectious diseases, *Curr Opin Immunol*, 48  
452 (2017) 7-14. 10.1016/j.coi.2017.07.009.
- 453 [47] N. Hartmann, M.J. Harriff, C.P. McMurtrey, W.H. Hildebrand, D.M. Lewinsohn, M. Kronenberg,  
454 Role of MAIT cells in pulmonary bacterial infection, *Mol Immunol*, 101 (2018) 155-159.  
455 10.1016/j.molimm.2018.06.270.
- 456 [48] T.S. Hinks, X. Zhou, K.J. Staples, B.D. Dimitrov, A. Manta, T. Petrossian, P.Y. Lum, C.G. Smith, J.A.  
457 Ward, P.H. Howarth, A.F. Walls, S.D. Gadola, R. Djukanovic, Innate and adaptive T cells in  
458 asthmatic patients: Relationship to severity and disease mechanisms, *J Allergy Clin Immunol*, 136  
459 (2015) 323-333. 10.1016/j.jaci.2015.01.014.
- 460 [49] W. Ouyang, A. O'Garra, IL-10 Family Cytokines IL-10 and IL-22: from Basic Science to Clinical  
461 Translation, *Immunity*, 50 (2019) 871-891. 10.1016/j.immuni.2019.03.020.
- 462 [50] D. Pennino, P.K. Bhavsar, R. Effner, S. Avitabile, P. Venn, M. Quaranta, V. Marzaioli, L. Cifuentes,  
463 S.R. Durham, A. Cavani, K. Eyerich, K.F. Chung, C.B. Schmidt-Weber, S. Eyerich, IL-22 suppresses  
464 IFN-gamma-mediated lung inflammation in asthmatic patients, *J Allergy Clin Immunol*, 131 (2013)  
465 562-570. 10.1016/j.jaci.2012.09.036.
- 466 [51] A.G. Besnard, R. Sabat, L. Dumoutier, J.C. Renauld, M. Willart, B. Lambrecht, M.M. Teixeira, S.  
467 Charron, L. Fick, F. Erard, K. Warszawska, K. Wolk, V. Quesniaux, B. Ryffel, D. Togbe, Dual Role of  
468 IL-22 in allergic airway inflammation and its cross-talk with IL-17A, *Am J Respir Crit Care Med*, 183  
469 (2011) 1153-1163. 10.1164/rccm.201008-1383OC.

470 [52] Y.E. Badi, A.B. Pavel, S. Pavlidis, J.H. Riley, S. Bates, N.Z. Kermani, R. Knowles, J. Kolmert, C.E.  
471 Wheelock, S. Worsley, M. Uddin, K. Alving, P.S. Bakke, A. Behndig, M. Caruso, P. Chanez, L.J.  
472 Fleming, S.J. Fowler, U. Frey, P. Howarth, I. Horvath, N. Krug, A.H. Maitland-van der Zee, P.  
473 Montuschi, G. Roberts, M. Sanak, D.E. Shaw, F. Singer, P.J. Sterk, R. Djukanovic, S.E. Dahlen, Y.K.  
474 Guo, K.F. Chung, E. Guttman-Yassky, I.M. Adcock, U.B.S. Group, Mapping atopic dermatitis and  
475 anti-IL-22 response signatures to type 2-low severe neutrophilic asthma, *J Allergy Clin Immunol*,  
476 149 (2022) 89-101. 10.1016/j.jaci.2021.04.010.

477 [53] E. Guttman-Yassky, P.M. Brunner, A.U. Neumann, S. Khattri, A.B. Pavel, K. Malik, G.K. Singer, D.  
478 Baum, P. Gilleaudeau, M. Sullivan-Whalen, S. Rose, S. Jim On, X. Li, J. Fuentes-Duculan, Y. Estrada,  
479 S. Garcet, C. Traidl-Hoffmann, J.G. Krueger, M.G. Lebwohl, Efficacy and safety of fezakinumab (an  
480 IL-22 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately  
481 controlled by conventional treatments: A randomized, double-blind, phase 2a trial, *J Am Acad*  
482 *Dermatol*, 78 (2018) 872-881 e876. 10.1016/j.jaad.2018.01.016.

483 [54] D. Bakker, M. de Bruin-Weller, J. Drylewicz, F. van Wijk, J. Thijs, Biomarkers in atopic dermatitis, *J*  
484 *Allergy Clin Immunol*, 151 (2023) 1163-1168. 10.1016/j.jaci.2023.01.019.

485 [55] J.M. Leyva-Castillo, J. Yoon, R.S. Geha, IL-22 promotes allergic airway inflammation in  
486 epicutaneously sensitized mice, *J Allergy Clin Immunol*, 143 (2019) 619-630 e617.  
487 10.1016/j.jaci.2018.05.032.

488 [56] R. Forster, A.C. Davalos-Miszlitz, A. Rot, CCR7 and its ligands: balancing immunity and tolerance,  
489 *Nat Rev Immunol*, 8 (2008) 362-371. 10.1038/nri2297.

490 [57] A. Link, T.K. Vogt, S. Favre, M.R. Britschgi, H. Acha-Orbea, B. Hinz, J.G. Cyster, S.A. Luther,  
491 Fibroblastic reticular cells in lymph nodes regulate the homeostasis of naive T cells, *Nat Immunol*,  
492 8 (2007) 1255-1265. 10.1038/ni1513.

493 [58] Y. Mitamura, M. Reiger, J. Kim, Y. Xiao, D. Zhakparov, G. Tan, B. Ruckert, A.O. Rinaldi, K.  
494 Baerenfaller, M. Akdis, M.C. Bruggen, K.C. Nadeau, P.M. Brunner, D. Roqueiro, C. Traidl-Hoffmann,  
495 C.A. Akdis, Spatial transcriptomics combined with single-cell RNA-sequencing unravels the  
496 complex inflammatory cell network in atopic dermatitis, *Allergy*, 78 (2023) 2215-2231.  
497 10.1111/all.15781.

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501 **Legends to figures.**

502 **Figure 1.** Representative flow cytometric gating strategies used to identify distinct BAL and circulating  
503 T cell populations. (A) Flow cytometric gating strategy to identify CD3<sup>+</sup> T cells among gated CD45<sup>+</sup>  
504 cells. Debris, dead cells and doublets were gated out. (B) Flow cytometric gating strategy to identify  
505 invariant Natural Killer T (iNKT) (CD1d-PBS-57 tetramers+CD3<sup>+</sup>), V $\delta$ 2<sup>+</sup>  $\gamma\delta$  T cells, mucosal-associated  
506 invariant T (MAIT) (TCRV $\alpha$ 7.2+CD161+iNKT-V $\delta$ 2<sup>-</sup>), CD4<sup>+</sup> and CD8<sup>+</sup> cells within CD3<sup>+</sup> T cells (MAIT-iNKT-  
507 V $\delta$ 2<sup>-</sup>). (C) Gate strategy to identify IL-4<sup>-</sup>, IL-13<sup>-</sup>, IL-17A<sup>-</sup> and IFN $\gamma$ -producing cells among gated CD4<sup>+</sup>,  
508 CD8<sup>+</sup>, MAIT, V $\delta$ 2<sup>+</sup> as represented in B. Data represent PBMC cells.

509

510 **Figure 2.** Ratio and frequency of distinct T cell populations present in BAL from cwSA without (green  
511 circles) and with (blue squares) AD. **A.** Ratio of CD8<sup>+</sup>/CD4<sup>+</sup> among gated CD3<sup>+</sup> T cells. **B-D.** Percentages  
512 of Tc2 (IL-4<sup>+</sup> among gated CD8<sup>+</sup> T cells), Th17 (IL-17A<sup>+</sup> among gated CD4<sup>+</sup> T cells) and MAIT-17 (IL-17<sup>+</sup>  
513 among gated CD3<sup>+</sup>TCRV $\alpha$ 7.2<sup>+</sup>CD161<sup>+</sup> MAIT cells) in BAL from cwSA with or without AD. p values are  
514 indicated. p<0.05 was considered as significant. Mann-Whitney test.

515

516 **Figure 3.** Heatmap of Spearman correlations for cytokines analyzed in BAL and plasma from cwSA  
517 without (**A**) and with (**B**) AD. Data for 66 cytokines, representing the most significant correlations, are  
518 shown. Positive correlations are shown in red, the absence of a correlation in white, and negative  
519 correlations in blue. The intensity of the color indicates the intensity of the correlation. Blue squares  
520 indicate correlations between soluble components from BAL and BAL and plasma and plasma, while  
521 yellow and green squares indicate respectively the major correlations between soluble components  
522 from BAL and plasma or plasma and plasma.

523

524

525 **Table I.** Demographic and clinical characteristics of children with SA belonging to the group with AD  
 526 or the group without AD.

Characteristics	cwSA without AD	cwSA with AD	p value
Study participants, n	10	7	
Age (y)	9.7 (7.7 - 11.4)	12 (7-14.6)	0.59
Sex: Female/male	4/6	2/5	>0.99
BMI (kg/m <sup>2</sup> )	16 (15 - 22)	21 (16 - 28)	0.25
Post-BD FEV1 (%)	113 (98 - 118)	109 (99 - 116)	0.94
Post-BD FEV1/FVC (%)	87 (79 - 92)	91 (81.7 - 95.9)	0.41
SE in the past year, n	5 (1 - 10)	3 (2 - 7)	0.87
Exacerbators, n	7	4	0.64
ACT score	18 (13 - 21)	14 (8 - 22)	0.42
Allergic rhinitis	7/10	6/7	0.60
ICS (mg/d equivalent fluticasone)	500 (500 - 500)	750 (500 - 1000)	<b>0.03</b>
Circulating total IgE levels (ku/ L)	801 (229 - 1016)	1054 (150 - 1432)	0.51
Blood leukocytes (x 10 <sup>-3</sup> /mL)	6.8 (5 - 7.8)	6.6 (4.6 - 7.8)	>0.99
Blood eosinophils x 10 <sup>-3</sup> /mL)	0.6 (0.25 - 1.15)	0.4 (0.3 - 1)	0.87
Blood neutrophils x 10 <sup>-3</sup> /mL)	2.7 (1.95 - 3.95)	2.9 (1.9 - 3.8)	>0.99
Blood lymphocytes x 10 <sup>-3</sup> /mL)	2.6 (1.80 - 2.95)	2.2 (1.6 - 2.8)	0.63

527 Exacerbators: > 2 SE in the past year

528 *Abbreviations:* AD, atopic dermatitis; BMI, body mass index; BD, bronchodilator; cwSA, children with  
 529 severe asthma; FVC, force vital capacity; ICS, inhaled corticosteroid; SA, severe asthma; SE, severe  
 530 exacerbations. Data are represented as the median (interquartile range). Mann-Whitney test (2-  
 531 tailed) or Fischer exact test (2-tailed) were used. Boldface denotes statistical significance (p<0.05).

532

533 **Table 2.** Frequency of immune cells in bronchoalveolar lavage of children with severe asthma (cwSA)  
 534 with or without atopic dermatitis (AD).

Cell type (%)	cwSA without AD	cwSA with AD	p value
CD3+/CD45+	81.9 (77.8-90.3)	81.6 (66.2-91.4)	0.89
CD4+/CD3+	33.1 (31.5-39.1)	30.7 (19.9-35)	0.19
IFN $\gamma$ +/CD4+ (Th1)	33.5 (18.4-75.1)	46.0 (15.2-60.7)	0.36
IL-4+/CD4+ (Th2)	3.7 (1.9-4.8)	2.9 (0.9-10.5)	0.60
IL-13+/CD4+	3.3 (1.4-5.8)	4.7 (1.5-19.6)	0.54
CD8+/CD3+	54.7 (45.1-59.7)	61.3 (54.8-72)	0.23
IFN $\gamma$ +/CD8+ (Tc1)	56.2 (23.7-92)	44.4 (32.8-90.8)	0.54
IL-13+/ CD8+	0.3 (0.1-1.1)	0.1 (0.1-1.1)	0.87
IL-17+/ CD8+	1.9 (0.6-7.3)	1.1 (0.6-4.1)	0.54
iNKT/CD3+	0.06 (0.02-0.1)	0.01 (0-0.10)	0.30
MAIT/CD3+	1.1 (0.8-2.1)	1.3 (0.9-2.3)	0.74
IFN $\gamma$ +/MAIT	50.1 (30.1-61.9)	57.9 (45-74.6)	0.23
IL-4+/ MAIT	1.6 (0.4-3.3)	0.6 (0-15)	0.79
IL-13+/ MAIT	2.4 (0-5.6)	5.0 (0.9-12.9)	0.43
V $\delta$ 2+/CD3+	1.4 (0.3-9.1)	1.3 (0.5-2.2)	0.72
IFN $\gamma$ +/V $\delta$ 2+	54.0 (43.3-72.5)	66.7 (23.9-74.6)	>0.99
IL-4+/ V $\delta$ 2+	0.4 (0-1.9)	0 (0-0.6)	0.12
IL-13+/ V $\delta$ 2+	0.2 (0-0.9)	0.41 (0-7.7)	0.39

535

536 *Abbreviations:* MAIT, mucosal associated invariant T; Th, T helper; Tc, T cytotoxic.

537 In the column "cell type (%)", the symbol "/" means "among gated".

538 Data are represented as the median (interquartile range). Mann-Whitney test (2-tailed) was used.

539

540

541 **Table 3.** Frequency of immune cells in peripheral blood of children with severe asthma (cwSA) with or  
 542 without atopic dermatitis (AD).

Cell type (%)	cwSA without AD	cwSA with AD	p value
CD3+/CD45+	70.9 (65.6-77.2)	67 (65.2-69.4)	0.23
CD4+/CD3+	63.8 (57.8-68.6)	64.7 (61.2-69.9)	0.98
IFN $\gamma$ +/CD4+ (Th1)	6.2 (4.2-13.1)	7.5 (5.9-10)	0.69
IL-4+/CD4+ (Th2)	2.1 (1.5-3.1)	2 (1.7-2.5)	0.94
IL-13+/CD4+	2.4 (1.6-3.1)	2.5 (2.3-2.9)	0.81
IL-17+/CD4+ (Th17)	0.6 (0.5-1.2)	0.9 (0.5-1.4)	0.58
CD8+/CD3+	30.8 (24.7-35.3)	29 (24.7-34.2)	0.94
IFN $\gamma$ +/CD8+ (Tc1)	21.1 (10.6-33.1)	24.3 (11.9-30.7)	>0.99
IL-4+/CD8+ (Tc2)	0.4 (0.2-0.6)	0.3 (0.2-1.3)	0.65
IL-13+/CD8+	0.4 (0.3-0.9)	0.3 (0.3-0.6)	0.58
IL-17+/CD8+	0.1 (0-0.1)	0.1 (0-0.2)	0.65
Ratio CD8+/CD4+	0.5 (0.4-0.6)	0.4 (0.3-0.6)	0.96
iNKT/CD3+	0.09 (0-0.1)	0.05 (0-0.1)	0.11
MAIT/CD3+	1.2 (0.6-2.8)	2.1 (1.2-4.2)	0.36
IFN $\gamma$ +/MAIT	49.6 (40.1-63.6)	50.6 (18.4-65.3)	>0.99
IL-4+/MAIT	0.5 (0.2-0.8)	0.4 (0.2-0.8)	0.67
IL-13+/MAIT	0.8 (0.2-1.5)	0.7 (0.3-1.2)	0.89
IL-17+/MAIT	2.5 (1.7-3.2)	1.2 (0.7-2.4)	0.13
V $\delta$ 2+/CD3+	5.8 (3.2-7.7)	2.9 (2.7-7.9)	0.36
IFN $\gamma$ +/V $\delta$ 2+	65 (48.3-85.6)	83 (66.4-84.7)	0.23
IL-4+/V $\delta$ 2+	0.6 (0-1.7)	0.3 (0-0.4)	0.40
IL-13+/V $\delta$ 2+	0.2 (0-1.2)	0.2 (0.1-0.4)	0.76

543

544 *Abbreviations: MAIT, mucosal associated invariant T; Th, T helper; Tc, T cytotoxic.*

545 In the column “cell type (%)”, the symbol “/” means “among gated”.

546 Data are represented as the median (interquartile range). Mann-Whitney test (2-tailed) was used.

547

548 **Table 4.** Cytokine levels in BAL and plasma from children with severe asthma (cwSA) with or without atopic  
549 dermatitis (AD).

	BAL			Plasma		
	cwSA without AD	cwSA withAD	<i>p</i>	cwSA without AD	cwSA withAD	<i>p</i>
<b>APRIL*</b>	81.7 (26.1-114.8)	107.8 (42.2-310.3)	0.315	101.4 (75.6-132.3)	106.1 (96.4-122.4)	0.618
<b>BAFF*</b>	0.87 (0.79-2.21)	1.48 (0.97-2.41)	0.459	6.46 (5.02-16.57)	6.55 (5.99-7.32)	0.813
<b>CCL1</b>	39 (36-66)	42 (36-48)	0.812	70 (57-87)	59 (50-78)	0.490
<b>CCL11</b>	13 (12-25)	19 (16-20)	0.459	78 (61-112)	74 (54-104)	>0.999
<b>CCL13</b>	88 (43-158)	114 (78-139)	0.601	200 (183-234)	213 (142-305)	0.740
<b>CCL15</b>	307 (202-866)	643 (460-831)	0.133	3079 (2493-5421)	2931 (2280-4080)	0.669
<b>CCL17</b>	16 (14-19)	19 (18-23)	0.126	83 (72-182)	197 (65-219)	0.459
<b>CCL19</b>	21 (18-74)	45 (26-47)	0.377	138 (115-164)	175 (174-188)	<b>0.031</b>
<b>CCL2</b>	12 (8-19)	23 (12-26)	0.161	93 (66-535)	86 (81-129)	0.887
<b>CCL20</b>	17 (8-318)	21 (15-81)	0.887	18 (13-61)	16 (12-21)	0.832
<b>CCL21*</b>	0.35 (0.27-1.01)	0.64 (0.46-0.74)	0.601	7.59 (5.64-10.07)	11.12 (8.66-12.22)	0.070
<b>CCL22</b>	38 (28-80)	47 (40-71)	0.650	455 (387-585)	595 (564-621)	0.133
<b>CCL23</b>	32 (13-42)	36 (28-57)	0.230	182 (35-231)	114 (95-335)	0.813
<b>CCL24</b>	290 (70-660)	172 (126-344)	0.740	215 (117-493)	205 (129-254)	0.813
<b>CCL25</b>	246 (136-442)	217 (186-273)	0.690	325 (274-392)	256 (219-420)	0.270
<b>CCL26</b>	17 (10-36)	14 (11-17)	0.685	114 (87-136)	152 (87-199)	0.230
<b>CCL27</b>	11 (8-26)	17 (16-20)	0.268	401 (321-558)	472 (372-570)	0.315
<b>CCL3</b>	6 (4-14)	7 (6-11)	0.740	7 (6-118)	7 (6-12)	0.514
<b>CCL7</b>	47(33-97)	52 (40-66)	0.905	87 (70-131)	80 (66-87)	0.581
<b>CCL8</b>	1 (1-3)	1 (1-2)	0.867	17 (11-28)	20 (17-30)	0.364
<b>CHI3L1*</b>	3.97 (2.66-7.40)	6.62 (4.32-13.3)	0.315	9.98 (6.42-13.6)	13.3 (8.06-19.3)	0.364
<b>CX3CL1</b>	129 (69-664)	157 (117-224)	0.601	277 (210-424)	277 (218-326)	0.867
<b>CXC13</b>	4 (3-40)	4 (2-8)	0.431	165 (155-276)	160 (155-221)	0.813
<b>CXCL1</b>	3437 (1840-5101)	6592 (2472-20079)	0.669	49 (38-61)	42 (30-99)	0.887
<b>CXCL10</b>	128 (63-466)	143 (136-354)	0.887	68 (51-98)	87 (46-112)	>0.999
<b>CXCL11</b>	6 (2-23)	7 (3-20)	0.793	463 (357-521)	542 (463-609)	0.193
<b>CXCL12</b>	56 (46-97)	68 (51-76)	0.757	17 (13-25)	17 (13-24)	0.962
<b>CXCL16</b>	1254 (802-1385)	1376 (642-1582)	0.417	958 (718-1109)	1061 (854-1233)	0.315
<b>CXCL2</b>	19 (16-39)	27 (16-42)	0.457	49 (35-62)	43 (33-54)	0.826
<b>CXCL5</b>	418 (229-879)	697 (463-924)	0.193	168 (124-844)	97 (0-386)	0.254
<b>CXCL6</b>	673 (293-4442)	1298 (461-1875)	0.364	53 (31-112)	54 (49-98)	0.721
<b>CXCL9</b>	423 (102-1624)	575 (230-1165)	0.813	223 (159-272)	227 (220-475)	0.535
<b>GMCSF</b>	29 (24-49)	33 (26-40)	>0.999	29 (26-39)	28 (19-31)	0.458
<b>IFN<math>\alpha</math>2</b>	2 (1-2)	2 (1-2)	0.868	10 (8-12)	7 (5-10)	0.161
<b>IFN<math>\beta</math></b>	28 (21-40)	39 (17-42)	0.584	130 (102-169)	123 (115-147)	0.813
<b>IFN<math>\delta</math>1</b>	9 (0-37)	22 (9-35)	0.473	228 (199-401)	200 (183-288)	0.402
<b>IFN<math>\delta</math>2</b>	8 (5-13)	14 (4-19)	0.459	111 (97-152)	94 (67-116)	0.260
<b>IFN<math>\gamma</math></b>	11 (10-22)	13 (9-16)	0.867	62 (55-74)	60 (41-63)	0.417
<b>IL-10</b>	19 (17-30)	25 (23-29)	0.417	46 (39-66)	33 (30-43)	0.070
<b>IL-11</b>	1 (0-2)	1 (1-2)	0.549	24 (19-39)	20 (19-30)	0.489
<b>IL-12p40</b>	58 (45-89)	61 (40-81)	>0.999	525 (461-780)	481 (420-517)	0.520
<b>IL-12p70</b>	5 (0-5)	5 (1-5)	0.117	5 (0-15)	5 (0-5)	0.531
<b>IL-16</b>	437 (291-844)	545 (315-698)	0.887	291 (246-904)	410 (214-547)	0.962
<b>IL-17</b>	4 (3-5)	6 (5-7)	0.059	5 (0-12)	3 (2-135)	0.990
<b>IL-19</b>	69 (40-403)	101 (65-177)	0.417	211 (185-245)	175 (146-226)	0.298
<b>IL-1<math>\beta</math></b>	67 (46-134)	101 (78-109)	0.536	20 (16-53)	17 (14-21)	0.403
<b>IL-2</b>	4 (3-6)	5 (4-5)	0.489	26 (23-32)	21 (20-35)	0.536
<b>IL-20</b>	14 (12-16)	14 (14-16)	0.722	92 (85-113)	87 (62-126)	0.475
<b>IL-22</b>	11 (9-12)	14 (12-21)	<b>0.013</b>	109 (85-133)	96 (73-154)	0.618

<b>IL-26*</b>	0.52 (0.35-0.69)	0.49 (0.35-0.79)	0.865	7.54 (6.63-7.92)	7.08 (5.94-7.50)	0.364
<b>IL-27p28</b>	72 (52-84)	82 (67-111)	0.183	335 (289-384)	316 (242-371)	0.758
<b>IL-32</b>	291 (268-352)	326 (288-432)	0.364	659 (590-912)	616 (421-799)	0.459
<b>IL-34</b>	384 (353-514)	407 (384-529)	0.349	729 (570-960)	562 (480-937)	0.521
<b>IL-35</b>	133 (97-188)	138 (108-214)	0.489	963 (828-1117)	698 (639-903)	0.059
<b>IL-4</b>	34 (20-48)	20 (15-30)	0.228	40 (29-56)	26 (23-44)	0.165
<b>IL-6</b>	3 (2-7)	6 (3-6)	0.304	4 (3-62)	4 (3-6)	0.128
<b>IL-8</b>	86 (52-444)	159 (91-367)	0.417	182 (146-1449)	127 (117-221)	0.984
<b>MIF*</b>	34.6 (26.9-49.3)	36.7 (18.2-47.7)	0.962	1.45 (0.81-4.38)	2.22 (1.22-3.90)	0.549
<b>MMP1</b>	119 (94-143)	95 (82-127)	0.349	529 (494-723)	475 (419-689)	0.364
<b>MMP2*</b>	0.78 (0.51-0.99)	0.60 (0.15-0.94)	0.304	105.9 (89.7-139.3)	90.6 (62.6-136.8)	0.459
<b>MMP3*</b>	0.32 (0.02-0.78)	0.63 (0.02-0.86)	0.518	7.93 (6.28-9.80)	7.41 (6.77-9.16)	0.315
<b>Osteocalcin*</b>	0.05 (0.03-0.07)	0.02 (0.09-0.05)	0.103	28.4 (13.4-33.1)	23.5 (16.9-27.1)	0.887
<b>Osteopontin*</b>	0.56 (0.37-0.86)	0.57 (0.46-0.61)	0.718	132.5 (73.5-194.4)	93.0 (60.9-139.3)	0.813
<b>Pentraxin3*</b>	0.43 (0.21-1.16)	0.78 (0.35-1.47)	0.377	45.1 (36.1-54.1)	38.5 (21.1-57.7)	0.417
<b>sCD163*</b>	43.8 (26.6-80.8)	75.7 (28-84.5)	0.620	180.5 (119.2-219.7)	175.6 (121-195)	0.364
<b>sCD30</b>	39 (27-44)	38 (27-47)	0.982	3497 (2502-4651)	3266 (1929-5143)	0.601
<b>sIL-16RB*</b>	5.66 (2.53-9.67)	7.20 (3.61-12.1)	0.475	118.3 (83.4-141.1)	99.1 (85.8-127.7)	0.601
<b>sIL-6RA*</b>	0.38 (0.23-0.65)	0.39 (0.20-0.91)	0.740	28.4 (23.0-42.9)	31.7 (23.4-53.8)	0.887
<b>sTNFR1</b>	251 (131-407)	245 (224-379)	0.813	1470 (1049-1895)	1335 (1008-1602)	0.887
<b>sTNFR2</b>	112 (100-156)	136 (100-164)	0.553	957 (914-1080)	945 (807-965)	0.962
<b>TNF<math>\alpha</math></b>	13 (10-35)	19 (13-21)	0.490	26 (23-39)	25 (14-36)	0.364
<b>TNFSF14</b>	22 (20-24)	25 (21-26)	0.258	78 (66-114)	95 (60-133)	0.651
<b>TSLP</b>	9 (6-13)	10 (6-12)	0.981	78 (66-96)	57 (55-87)	0.757
<b>TWEAK</b>	313 (313-170)	402 (258-680)	0.377	977 (784-1110)	620 (571-899)	0.193

550 All cytokine values are expressed in pg/ml, except those marked with \*, which are expressed in ng/ml. Data are represented  
551 by the median (interquartile range). The Mann-Whitney test (two-tailed) was used. p-values are indicated. p<0.05 was  
552 considered significant and indicated in bold.

553