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		Placebo arm	Dupilumab arm	Total
		N=47 (50%)	N=47 (50%)	N=94 (100%)
Demographic characteristics				
Gender, n (%)				
Male		23 (48.9%)	14 (29.8%)	37 (39.4%)
Female		24 (51.1%)	33 (70.2%)	57 (60.6%)
Age in years (mean (SD))		41.1 (15.86)	37.8 (13.60)	39.5 (14.79)
Phototype, n (%)				
1-4		45 (95.8%)	46 (97.9%)	91 (96.8%)
5-6		2 (4.2%)	1 (2.1%)	3 (3.2%)
Profession, n (%)				
Office worker		18 (38.3%)	19 (40.4%)	37 (39.4%)
Healthcare professional		5 (10.6%)	6 (12.8%)	11 (11.7%)
Manual workers (construction, mechanics, electrician, wood)		5 (10.6%)	4 (8.5%)	9 (9.6%)
Restauration		4 (10.6%)	4 (8.5%)	9 (9.6%)
Cleaning agent		3 (6.4%)	5 (10.6%)	8 (8.5%)
Hairdresser, Beautician		1 (2.1%)	1 (2.1%)	2 (2.1%)
Farmer		1 (2.1%)	1 (2.1%)	2 (2.1%)
Retired/Unemployed		6 (12.8%)	6 (12.8%)	12 (12.8%)
Other		3 (6.4%)	1 (2.1%)	4 (4.3%)
History of personal atopy, n (%)		37 (78.7%)	41 (87.2%)	78 (83.0%)
Atopic dermatitis		30 (63.8%)	34 (72.3%)	64 (68.1%)
Allergic rhinitis		28 (59.6%)	25 (53.2%)	53 (56.4%)
Asthma		17 (36.2%)	16 (34.0%)	33 (35.1%)
Allergic conjunctivitis		14 (29.8%)	12 (25.5%)	26 (27.7%)
Food allergy		5 (10.6%)	10 (21.3%)	15 (16.0%)
Known sensitization to pneumallergens (prick or IgE-confirmed)		23 (48.9%)	20 (42.6%)	43 (45.7%)
Family history of atopy, n (%)		22 (46.8%)	30 (63.8%)	52 (55.3%)
History of CHE disease				
Time since diagnosis in years (mean (SD))		9.24 (13.037)	8.20 (8.909)	8.72 (11.118)
Previous treatment for CHE, n (%)	Therapeutic education	9 (19.1%)	8 (17.0%)	17 (18.1%)
	Potent or very potent topical corticosteroids	47 (100.0%)	47 (100.0%)	94 (100.0%)
	Topical tacrolimus	13 (28.9%)	18 (40.0%)	31 (34.4%)
	Ciclosporin	3 (6.4%)	2 (4.3%)	5 (5.3%)
	Methotrexate	6 (12.8%)	1 (2.1%)	7 (7.4%)
	Alitretinoin	12 (25.5%)	14 (29.8%)	26 (27.7%)
	Oral corticosteroid	5 (10.6%)	8 (17.0%)	13 (13.8%)
	Phototherapy	5 (11.1%)	6 (13.3%)	11 (12.2%)
Irritative aggravating cofactors, n (%)		22 (46.8%)	22 (46.8%)	44 (46.8%)
Allergic aggravating cofactors, n (%)		6 (12.8%)	5 (10.6%)	11 (11.7%)
Working test *(active CHE at work and improvement/ regression offsite work),* **n (%)**				
Positive		2 (5.9%)	5 (12.5%)	7 (9.5%)
Negative		25 (73.5%)	27 (67.5%)	52 (70.3%)
Doubtful		7 (20.6%)	8 (20.0%)	15 (20.3%)
Currently off work due to CHE, n (%)		5 (10.6%)	7 (14.9%)	12 (12.8%)

Supplementary Table 1. Baseline patients characteristics.

CHE: chronic hand eczema, SD: standard deviation.

		Placebo arm	Dupilumab arm	Total
		N=47 (50%)	N=47 (50%)	N=94 (100%)
CHE examination				
Unilateral involvement, n (%)		1 (2.1%)	3 (6.4%)	4 (4.3%)
Bilateral involvement, n (%)		46 (97.9%)	44 (93.6%)	90 (95.7%)
Palmar involvement only, n (%)		6 (12.8%)	6 (12.8%)	12 (12.8%)
Dorsal involvement only, n (%)		5 (10.6%)	5 (10.6%)	10 (10.6%)
Palmar and dorsal involvements, n (%)		36 (76.6%)	36 (76.6%)	72 (76.6%)
Vesicles, n (%)		20 (42.6%)	18 (38.3%)	38 (40.4%)
Cracks, n (%)		34 (72.3%)	30 (63.8%)	64 (68.1%)
Hyperkeratosis, n (%)		31 (66.0%)	19 (40.4%)	60 (63.8%)
Pulpitis, n (%)		22 (46.8%)	21 (44.7%)	43 (45.7%)
Nails affected, n (%)		13 (27.7%)	20 (42.6%)	33 (35.1%)
Eczema on feet, n (%)		18 (38.3%)	10 (21.3%)	28 (29.8%)
Disease severity scoring				
mTLSS - Modified total lesion symptom score (mean (SD)) / 25		12.5 (2.71)	12.0 (3.15)	12.2 (2.93)
IGA - Investigator global assessment (mean (SD)) / 4		3.3 (0.48)	3.3 (0.51)	3.3 (0.49)
PaGA - Patient Global Assessment of disease severity (mean (SD)) / 4		3.3 (0.67)	3.3 (0.66)	3.3 (0.66)
Visual analogue scales of pruritus (mean (SD)) / 100		63.1 (23.63)	60.8 (29.73)	62.0 (26.70)
Visual analogue scales of pain (mean (SD)) / 100		53.5 (27.61)	60.2 (27.32)	56.8 (27.53)
Visual analogue scales of sleep loss (mean (SD)) / 100		41.3 (27.37)	39.8 (30.52)	40.5 (28.85)
EASI – Eczema area and severity index (mean (SD)) / 72		7.13 (5.969)	5.36 (4.100)	6.3 (5.216)
EQ-VAS – EuroQol-visual analogue scales (mean (SD)) / 100		61.8 (19.43)	68.9 (21.20)	65.3 (20.54)
DLQI - Dermatology life quality index (mean (SD)) / 30		12.1 (5.38)	13.0 (5.21)	12.5 (5.28)
WPAI - Work productivity and activity impairment questionnaire	Work time missed (%) (mean (SD))	10.1 (28.83)	8.9 (26.16)	9.4 (27.10)
	Impairment while working due to health (%) (mean (SD))	33.5 (25.34)	41.6 (25.31)	38.1 (25.41)
	Overall work impairment due to health (%) (mean (SD))	2.3 (10.42)	3.0 (11.81)	2.7 (11.14)
	Activity impairment due to health (%) (mean (SD))	50.9 (25.89)	57.8 (25.31)	54.3 (25.70)
Biological routine atopic traits				
Eosinophils blood count (G/L)				
Mean (SD)		0.24 (0.118)	0.17 (0.139)	0.20 (0.132)
Min ; Max		0.1 ; 0.5	0.0 ; 0.8	0.0 ; 0.8
Total IgE serum level (kUI/L)				
Mean (SD)		742.26 (1050.5)	221.84 (386.9)	467.6 (812.1)
> 150		21 (44.7%)	26 (61.9%)	47 (52.8%)
< 150		26 (55.3%)	16 (38.1%)	42 (47.2%)

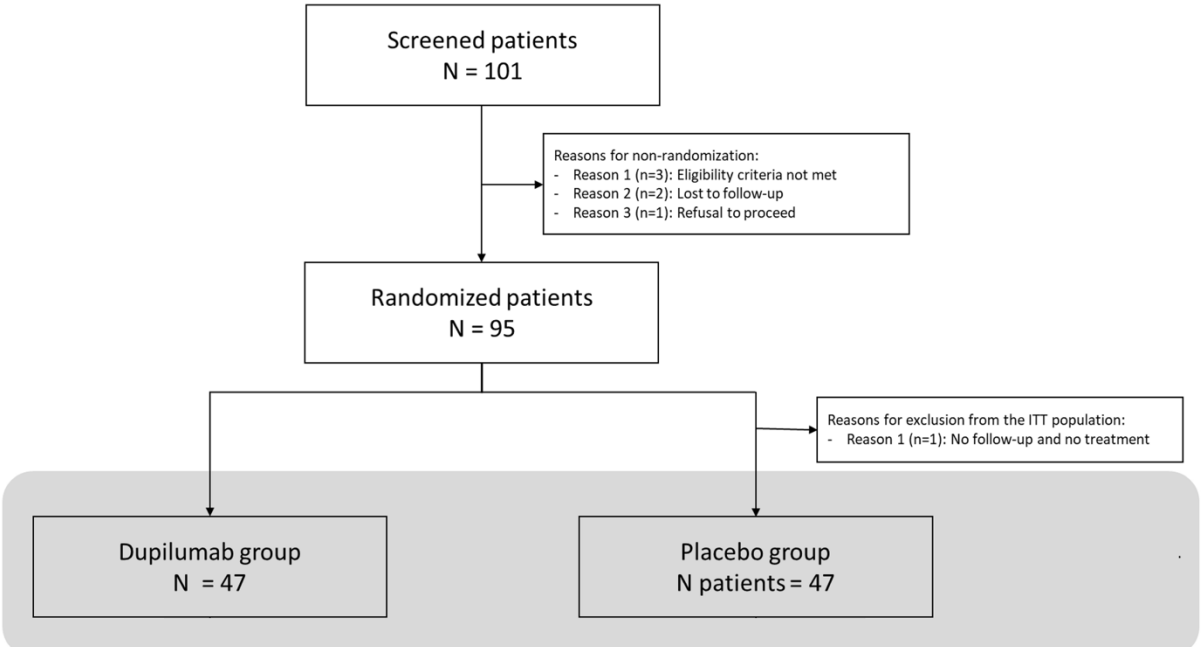
Supplementary Table 2. Baseline CHE disease characteristics.

IgE: Immunoglobulin E, CHE: chronic hand eczema, SD: standard deviation, VAS: Visual analogue scales.

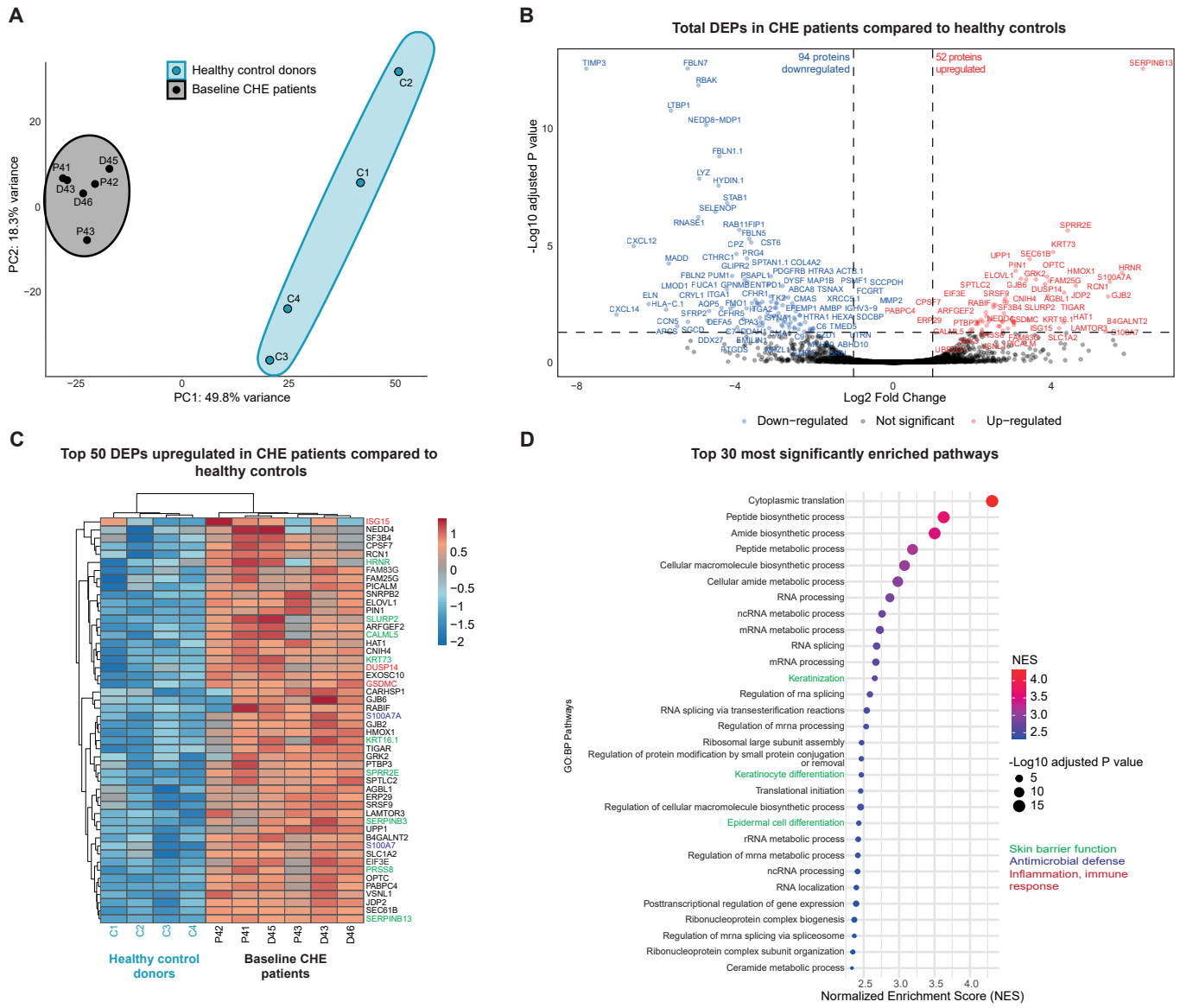
Patients included in the molecular study	Group	Analysis performed								History of AD	Irritative factors	Proven contact allergy	mTLSS		IGA	
		Skin total RNA sequencing			Blood immune cells phenotyping by spectral cytomety	Skin LC-MS/MS shotgun proteomic		Serum LC-MS/MS shotgun proteomic	Meso Scale Discovery multiplex assay				W0	W16	W0	W16
		x	Matched healthy donor skin	Biopsy site		x	Matched healthy donor skin									
P1	Placebo	x	From abdomen or arm n=15	P/B interface	x		From the back of the hand n=4		x	yes	no	no	11	8	3	2
P2		x		B	x				x	no	yes	no	15	8	4	3
P3		x		B					x	yes	no	no	15	12	4	3
P4		x		P	x				x	yes	no	no	13	11	3	3
P6		x		P	x					no	yes	yes	15	13	3	3
P9		x		NA	x					yes	no	yes	10		3	
P13					x				x	yes	no	no	14	17	4	4
P14					x				x	no	yes	no	17	12	4	4
P15					x					yes	no	no	9	6	3	2
P17					x				x	yes	yes	yes	14	11	3	3
P18									x	yes	yes	yes	14	2	3	1
P21					x			x	x	yes	yes	no	11	19	3	4
P41						x		x		no	yes	yes	12	13	3	3
P42					x	x		x		yes	no	no	12		3	
P43					x	x		x		yes	no	no	18	15	4	4
P47		x		NA	x					yes	no	yes	14		3	
D1	Dupilumab	x		P/B interface					x	yes	yes	yes	17	5	4	1
D2		x		P/B interface	x					yes	yes	yes	9	3	3	1
D4		x		P/B interface					x	yes	yes	no	10	5	3	2
D5		x		B	x					yes	yes	no	12	7	4	2
D6		x		B					x	no	no	yes	14	6	4	2
D7					x				x	yes	yes	no	10	3	3	1
D8		x		B	x				x	yes	no	yes	13	2	3	1
D10		x		B	x					yes	yes	no	12	2	3	1
D12		x		NA						no	no	yes	7	4	3	2
D14					x					no	no	yes	15	1	4	0
D15					x				x	yes	no	no	16	6	4	1
D16					x					yes	yes	no	11	5	3	1
D19					x				x	yes	yes	no	12	3	3	1
D20					x					yes	no	yes	6	2	3	1
D22					x				x	no	no	yes	13	0	4	0
D24					x					yes	no	no	11	7	3	3
D43						x		x		yes	yes	yes	15	3	4	1
D45					x	x		x		no	yes	yes	11	2	3	1
D46					x	x		x		yes	yes	no	14	6	4	2

Supplementary Table 3. Overview of the patients included in the molecular phenotyping study.

X indicates the analyses completed by each patient. P: palm, B: back, AD: atopic dermatitis, W: week., mTLSS: modified Total Lesional Severity Score, IGA: Investigator Global Assessment. History of AD was defined as a diagnosis of AD including mild or intermittent forms, made prior to the diagnosis of CHE. Black squares indicate a premature end of study (no score available at week 16 and no paired sample).



Supplementary Figure 1. Flow chart of the clinical study.

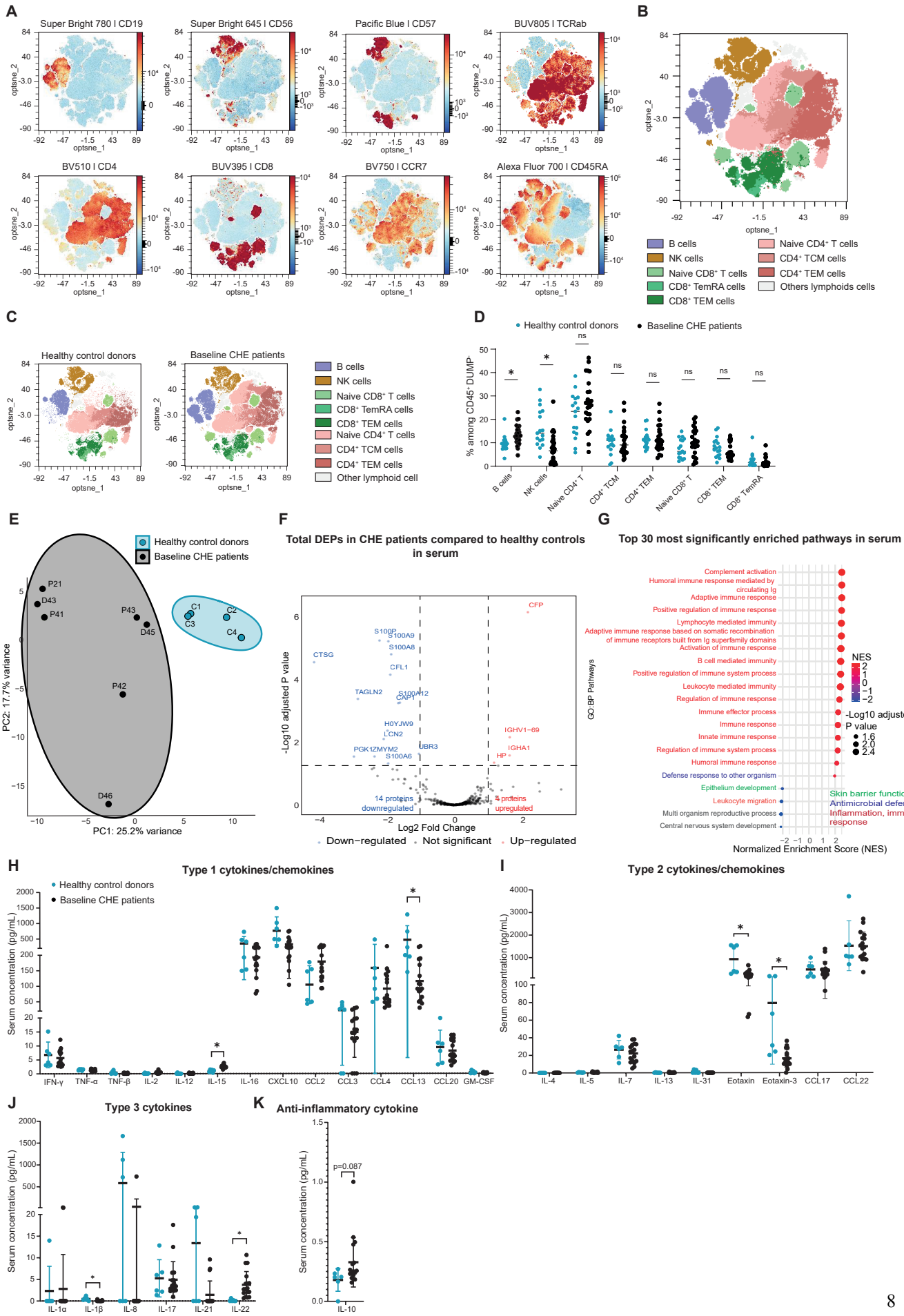


35

36 **Supplementary Figure 2. Baseline whole skin proteomic signature in CHE patients**
37 **compared to healthy controls was restricted to a strongly compromised skin barrier.**

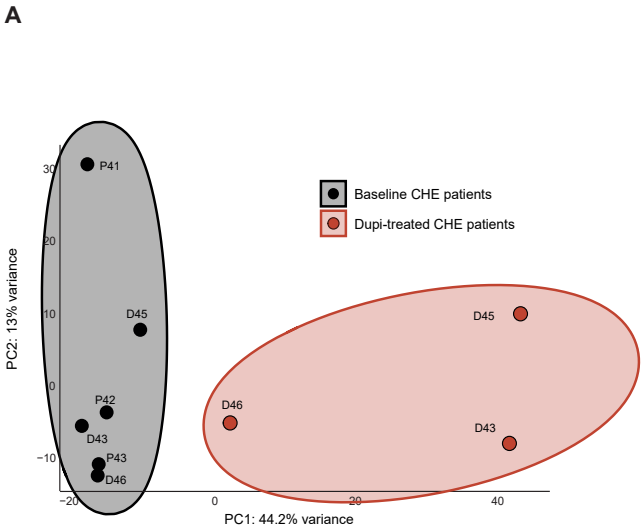
38 **A. PCA approach on all variable proteins obtained from LC-MS/MS shotgun proteomic in the skin,**
39 **showing the segregation between CHE patients at baseline and healthy donor controls.** Patient and control
40 numbers are reported above each sample. **B. Volcanoplot representation of differentially expressed proteins**
41 **(DEPs) between CHE patients and healthy controls at baseline.** Log2-FC threshold : < -1 and > 1, adjusted
42 *P* value threshold < 0.05. **C. Hierarchically clustered heatmap representation of top 50 upregulated DEPs**
43 **in CHE patients compared to controls.** Characteristic genes involved in skin barrier functions (green),
44 antimicrobial defense (blue) or inflammation/ immune response processes (red) are highlighted. Red and blue
45 represent up- and downregulated expression, respectively. **D. Top 30 most enriched pathways from Gene set**

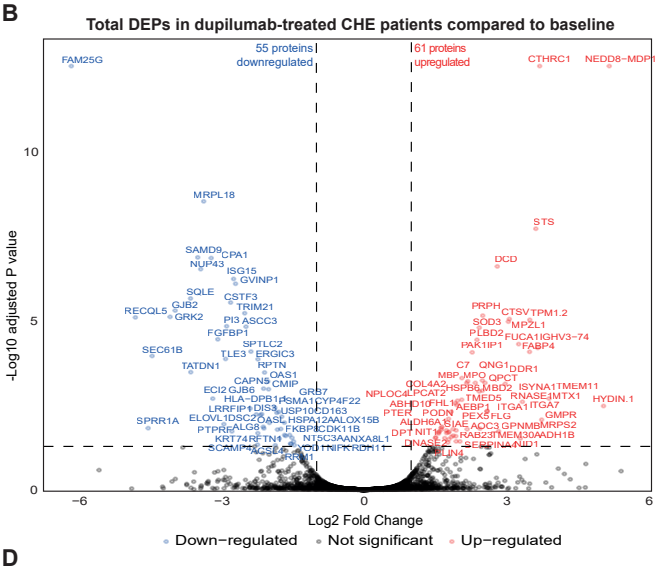
enrichment analysis (GSEA) in CHE patients at baseline. Y-axis represents ranked pathways, and X-axis shows the normalized enrichment score (NES). Blue to red colors represent low to high NES, respectively. The size of the bubbles is associated with the *P* value. Characteristic genes involved in skin barrier functions (green), antimicrobial defense (blue) or inflammation/ immune response processes (red) are highlighted. (A-D) n = 4 controls and 6 baseline CHE patients.

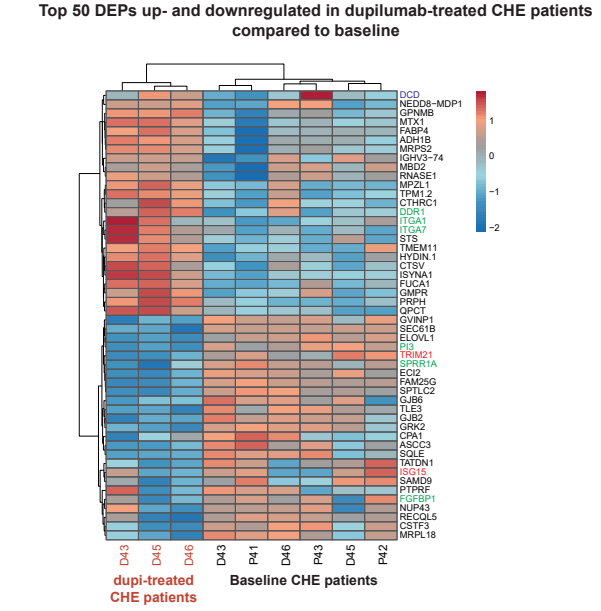

A
Super Bright 780 I CD19
Super Bright 645 I CD56
Pacific Blue I CD57
BUV805 I TCRab
BV510 I CD4
BUV395 I CD8
BV750 I CCR7
Alexa Fluor 700 I CD45RA
optsne_1
optsne_2
B
B cells
NK cells
Naive CD8⁺ T cells
CD8⁺ TemRA cells
CD8⁺ TEM cells
Naive CD4⁺ T cells
CD4⁺ TCM cells
CD4⁺ TEM cells
Others lymphoids cells
C
Healthy control donors
Baseline CHE patients
Other lymphoid cell
D
Healthy control donors
Baseline CHE patients
% among CD45⁺ DUMP⁻
B cells
NK cells
Naive CD4⁺ T
CD4⁺ TCM
CD4⁺ TEM
Naive CD8⁺ T
CD8⁺ TEM
CD8⁺ TemRA
ns
E
Healthy control donors
Baseline CHE patients
PC1: 25.2% variance
PC2: 17.7% variance
F
Total DEPs in CHE patients compared to healthy controls in serum
-Log10 adjusted P value
Log2 Fold Change
14 proteins downregulated
4 proteins upregulated
Down−regulated
Not significant
Up−regulated
G
Top 30 most significantly enriched pathways in serum
GO:BP Pathways
Normalized Enrichment Score (NES)
-Log10 adjusted P value
Skin barrier function
Antimicrobial defense
Inflammation, immune response
H
Type 1 cytokines/chemokines
Healthy control donors
Baseline CHE patients
Serum concentration (pg/mL)
IFN-γ
TNF-α
TNF-β
IL-2
IL-12
IL-15
IL-16
CXCL10
CCL2
CCL3
CCL4
CCL13
CCL20
GM-CSF
I
Type 2 cytokines/chemokines
IL-4
IL-5
IL-7
IL-13
IL-31
Eotaxin
Eotaxin-3
CCL17
CCL22
J
Type 3 cytokines
IL-1α
IL-1β
IL-8
IL-17
IL-21
IL-22
K
Anti-inflammatory cytokine
p=0.087
IL-10

Supplementary Figure 3. Baseline CHE patients showed less circulating NK cells, more B cells and a global immune activated profile in the serum compared to healthy controls.

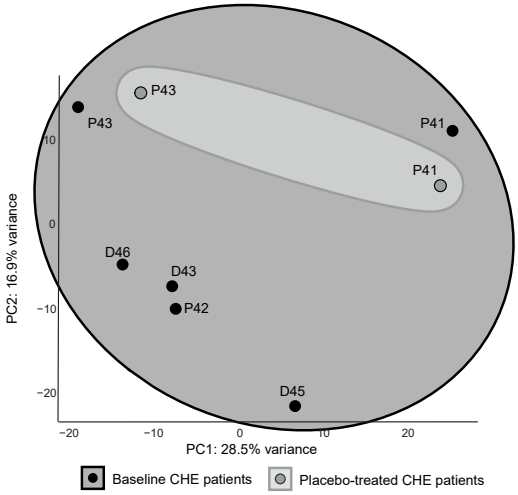
A-C. Opt-sne concatenation of circulating lymphoid populations of baseline CHE patients compared to healthy controls. (A) Relative expression of lymphoid biomarkers (CD19, CD56, CD57, TCRab, CD4, CD8 and CCR7) was assessed to determine lymphoid populations. Red and blue represent high and low expression levels of markers, respectively. (B, C) Distribution of major lymphoid populations in opt-sne. Biomarkers allow discriminating between B cells, NK cells, naïve/TEMRA/TEM $CD8^+$ T cells and naïve/TEMRA/TEM $CD4^+$ T cells. **D. Quantification of major circulating lymphoid populations in baseline CHE patients compared to healthy controls.** Percentage of each population among lymphoid cells. DUMP = CD14, CD11c, CD1a, CD34. Data are presented as mean ± standard deviation. **P*<0.05, ns: not significant. Mann–Whitney U test. (A-D) n = 16 controls and 25 baseline CHE patients. **E. PCA approach on all variable proteins obtained from LC-MS/MS shotgun proteomic in the serum, showing the segregation between CHE patients at baseline and healthy donor controls.** Patient and control numbers are reported above each sample. **F. Volcanoplot representation of differentially expressed proteins (DEPs) between CHE patients and healthy controls.** Log2-FC threshold : < -1 and > 1, adjusted *P* value threshold < 0.05. **G. Top 30 most enriched pathways from Gene set enrichment analysis (GSEA) in CHE patients.** Y-axis represents ranked pathways, and X-axis shows the normalized enrichment score (NES). Blue to red colors represent low to high NES, respectively. The size of the bubbles is associated with the *P* value. Characteristic genes involved in skin barrier functions (green), antimicrobial defense (blue) or inflammation/ immune response processes (red) are highlighted. (E-G) n = 4 controls and 7 baseline CHE patients. **H-K. Serum concentration of chemokines and cytokines in baseline CHE patients compared to healthy controls obtained from Meso Scale Discovery multiplex assay.** Type 1 (H), 2 (I), 3 (J) and anti-inflammatory (K) cytokines/chemokines were assessed in serum. n = 6 controls and 17 baseline CHE patients. Data are presented as mean ± standard deviation. **P*<0.05. Student's t-test.


A
Baseline CHE patients
Dupi-treated CHE patients
PC2: 13% variance
PC1: 44.2% variance
P41
D45
P42
D43
P43
D46
D45
D46
D43


B
Total DEPs in dupilumab-treated CHE patients compared to baseline
55 proteins downregulated
61 proteins upregulated
-Log10 adjusted P value
Log2 Fold Change
Down−regulated
Not significant
Up−regulated

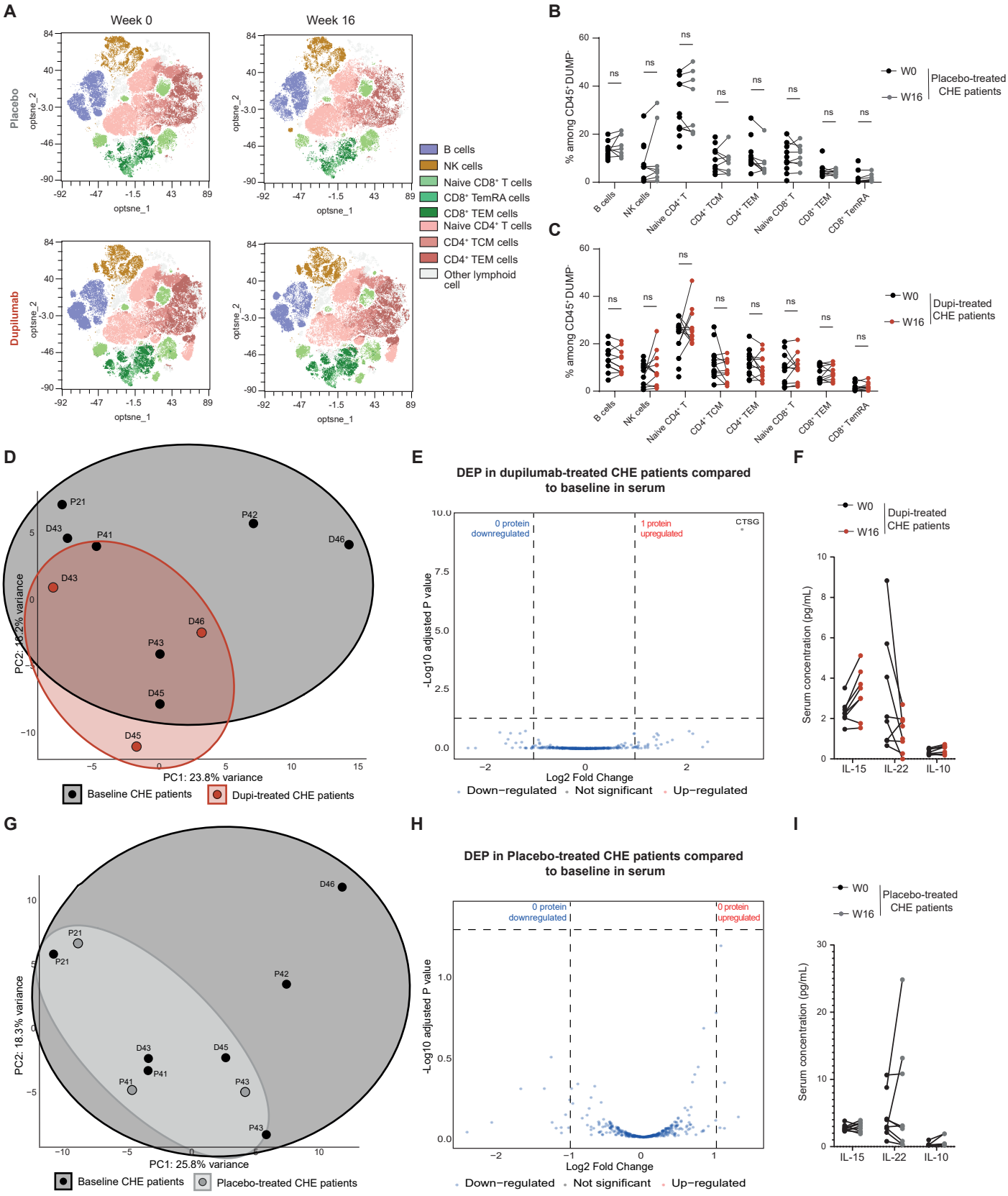

C
Top 50 DEPs up- and downregulated in dupilumab-treated CHE patients compared to baseline
dupi-treated CHE patients
Baseline CHE patients


D
Top 30 most significantly enriched pathways
GO:BP Pathways
External encapsulating structure organization
Humoral immune response
Electron transport chain
Cellular respiration
Response to toxic substance
Complement activation
Biological adhesion
Aminoglycan metabolic process
Respiratory electron transport chain
Negative regulation of locomotion
Aerobic respiration
Mitochondrial electron transport nadh to ubiquinone
Basement membrane organization
Energy derivation by oxidation of organic compounds
Small molecule catabolic process
Modification dependent macromolecule catabolic process
Protein modification by small protein conjugation
RNA splicing
Rna splicing via transesterification reactions
mRNA processing
Ribonucleoprotein complex subunit organization
Protein modification by small protein conjugation or removal
RNA processing
mRNA metabolic process
Regulation of cellular macromolecule biosynthetic process
Peptide metabolic process
Amide biosynthetic process
Peptide biosynthetic process
Cytoplasmic translation
Cellular macromolecule biosynthetic process
NES
-Log10 adjusted P value
Skin barrier function
Antimicrobial defense
Inflammation, immune response
Normalized Enrichment Score (NES)


E
PC2: 16.9% variance
PC1: 28.5% variance
P43
P43
P41
P41
D46
D43
P42
D45
Baseline CHE patients
Placebo-treated CHE patients

Supplementary Figure 4. Skin barrier defect proteomic signature was restored after 16 weeks-dupilumab treatment compared to placebo.

A. PCA approach on all variable proteins obtained from LC-MS/MS shotgun proteomic in the skin, showing the segregation between baseline CHE patients and dupilumab-treated CHE patients. Patient numbers are reported above each sample. **B. Volcanoplot representation of DEPs in dupilumab-treated CHE patients compared to baseline.** Log2-FC threshold : < -1 and > 1, adjusted *P* value threshold < 0.05. **C. Hierarchically clustered heatmap of the top 50 up- and downregulated DEPs in dupilumab-treated CHE patients compared to baseline.** Characteristic genes involved in skin barrier functions (green), antimicrobial defense (blue) or inflammation/ immune response processes (red) are highlighted. Patient numbers are reported at the bottom of the figure. Red and blue represent up- and downregulated expression, respectively. **F. Top 30 most significantly enriched pathways from GSEA in dupilumab-treated CHE patients compared to baseline.** Y-axis represents ranked pathways, and X-axis shows NES. Blue to red colors represent low to high NES, respectively. The size of the bubbles is related to the *P* value. Characteristic genes involved in skin barrier functions (green), antimicrobial defense (blue) or inflammation/ immune response processes (red) are highlighted. (A-D) n = 6 baseline CHE patients and 3 dupilumab-treated CHE patients. **E. PCA approach on all variable proteins obtained from LC-MS/MS shotgun proteomic in the skin, showing no segregation between baseline CHE patients and placebo-treated CHE patients.** Patient numbers are reported above each sample. N = 6 baseline CHE patients and 2 placebo-treated CHE patients.


A
Week 0
Week 16
Placebo
Dupilumab
optsne_1
optsne_2
B cells
NK cells
Naive CD8+ T cells
CD8+ TemRA cells
CD8+ TEM cells
Naive CD4+ T cells
CD4+ TCM cells
CD4+ TEM cells
Other lymphoid cell
B
% among CD45+DUMP-
ns
W0
W16
Placebo-treated CHE patients
B cells
NK cells
Naive CD4+ T
CD4+ TCM
CD4+ TEM
Naive CD8+ T
CD8+ TEM
CD8+ TemRA
C
Dupi-treated CHE patients
D
PC1: 23.8% variance
PC2: 16.2% variance
Baseline CHE patients
Dupi-treated CHE patients
E
DEP in dupilumab-treated CHE patients compared to baseline in serum
0 protein downregulated
1 protein upregulated
CTSG
-Log10 adjusted P value
Log2 Fold Change
Down−regulated
Not significant
Up−regulated
F
Serum concentration (pg/mL)
IL-15
IL-22
IL-10
G
PC1: 25.8% variance
PC2: 18.3% variance
Placebo-treated CHE patients
H
DEP in Placebo-treated CHE patients compared to baseline in serum
0 protein downregulated
0 protein upregulated
I

Supplementary Figure 5. No major change was observed in circulating immune cells or serum proteins in dupilumab-treated patients compared to placebo at week 16.

A-C. Distribution of major circulating lymphoid populations in CHE patients treated with dupilumab or placebo. Opt-sne concatenation representation (A) and percentage of each population among lymphoid cells at week 0 and 16 in (B) placebo-treated and (C) dupilumab-treated CHE patients. DUMP = CD14, CD11c, CD1a, CD34. N = 12 at week 0 (W0) and 9 at week 16 (W16) for placebo, and 13 at week 0 and 10 at week 16 for dupilumab-treated CHE patients. Data are presented as mean ± standard deviation. (B,C) **P*<0.05, ns: not significant. Mann–Whitney U test. **D. PCA approach on all variable proteins obtained from LC-MS/MS shotgun proteomic in the serum, showing no segregation between baseline CHE patients and dupilumab-treated CHE patients.** Patient numbers are reported above each sample. **E. Volcanoplot representation of DEPs in dupilumab-treated CHE patients compared to baseline.** Log2-FC threshold : < -1 and > 1, adjusted *P* value threshold < 0.05. **F. Serum concentration of chemokines and cytokines in dupilumab-treated CHE patients compared to baseline obtained from Meso Scale Discovery multiplex assay.** N = 17 baseline and 8 dupilumab-treated CHE patients. **G. PCA approach on all variable proteins obtained from LC-MS/MS shotgun proteomic in the serum, showing no segregation between baseline CHE patients and placebo-treated CHE patients.** Patient numbers are reported above each sample. N = 6 baseline CHE patients and 2 placebo-treated CHE patients. **H. Volcanoplot representation of DEPs in placebo-treated CHE patients compared to baseline.** Log2-FC threshold : < -1 and > 1, adjusted *P* value threshold < 0.05. **I. Serum concentration of chemokines and cytokines in placebo-treated CHE patients compared to baseline obtained from Meso Scale Discovery multiplex assay.** N = 17 baseline and 9 placebo-treated CHE patients. B, C, F, I: ns= not significant. Student's t-test.