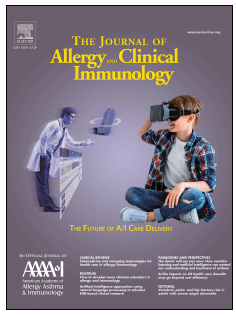
Journal Pre-proof



Mapping atopic dermatitis and anti-IL-22 response signatures to Type 2-low severe neutrophilic asthma

Yusef Eamon Badi, MSc, Ana B. Pavel, PhD, Stelios Pavlidis, PhD, John H. Riley, PhD, Stewart Bates, PhD, Nazanin Zounemat Kermani, PhD, Richard Knowles, PhD, Johan Kolmert, PhD, Craig E. Wheelock, PhD, Sally Worsley, MSc, Mohib Uddin, PhD, Kjell Alving, PhD, Per S. Bakke, MD, Annelie Behndig, MD, PhD, Massimo Caruso, MD, Pascal Chanez, MD, Louise J. Fleming, MD, Stephen J. Fowler, MD, PhD, Urs Frey, MD, PhD, Peter Howarth, MD, PhD, Ildikó Horváth, MD, PhD, Norbert Krug, MD, Anke H. Maitland-van der Zee, PharmD, PhD, Paolo Montuschi, MD, Graham Roberts, MD, PhD, Marek Sanak, MD, Dominick E. Shaw, MD, PhD, Florian Singer, MD, PhD, Peter J. Sterk, MD, PhD, Ratko Djukanovic, MD, PhD, Sven-Eric Dahlen, MD, PhD, Yi-Ke Guo, PhD, Kian Fan Chung, MD, DSc, Emma Guttman-Yassky, MD, PhD, Ian M. Adcock, PhD, on behalf of the U-BIOPRED study group

PII: S0091-6749(21)00648-5

DOI: https://doi.org/10.1016/j.jaci.2021.04.010

Reference: YMAI 15078

To appear in: *Journal of Allergy and Clinical Immunology*

Received Date: 12 November 2020

Revised Date: 11 March 2021

Accepted Date: 9 April 2021

Please cite this article as: Badi YE, Pavel AB, Pavlidis S, Riley JH, Bates S, Kermani NZ, Knowles R, Kolmert J, Wheelock CE, Worsley S, Uddin M, Alving K, Bakke PS, Behndig A, Caruso M, Chanez P, Fleming LJ, Fowler SJ, Frey U, Howarth P, Horváth I, Krug N, Maitland-van der Zee AH, Montuschi P, Roberts G, Sanak M, Shaw DE, Singer F, Sterk PJ, Djukanovic R, Dahlen S-E, Guo Y-K, Chung KF, Guttman-Yassky E, Adcock IM, on behalf of the U-BIOPRED study group, Mapping atopic dermatitis and anti-IL-22 response signatures to Type 2-low severe neutrophilic asthma, *Journal of Allergy and Clinical Immunology* (2021), doi: https://doi.org/10.1016/j.jaci.2021.04.010.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of

record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2021 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology.

Journal Pre-proof

Mapping atopic dermatitis and anti-IL-22 response signatures to Type 2-low severe neutrophilic asthma

Yusef Eamon Badi MSc[1,2], *Ana B. Pavel PhD[3,4], **Stelios Pavlidis PhD[2], John H Riley PhD[5], Stewart Bates PhD[5], Nazanin Zounemat Kermani PhD[2], Richard Knowles PhD[6], Johan Kolmert PhD[7,8], Craig E. Wheelock PhD[8], Sally Worsley MSc[9], Mohib Uddin PhD[10], Kjell Alving PhD[11], Per S Bakke MD[12], Annelie Behndig MD, PhD[13], Massimo Caruso MD[14], Pascal Chanez MD[15], Louise J Fleming MD[1], Stephen J Fowler MD, PhD[16], Urs Frey MD, PhD[17], Peter Howarth MD, PhD[18], Ildikó Horváth MD, PhD[19], Norbert Krug MD[20], Anke H. Maitland-van der Zee PharmD, PhD[21], Paolo Montuschi MD[22], Graham Roberts MD, PhD[18], Marek Sanak MD[23], Dominick E Shaw MD, PhD[24], Florian Singer MD, PhD[25], Peter J Sterk MD, PhD[21], Ratko Djukanovic MD, PhD[18], Sven-Eric Dahlen MD, PhD[7], Yi-Ke Guo PhD[2], Kian Fan Chung MD, DSc[1], Emma Guttman-Yassky MD, PhD[3], Ian M. Adcock PhD[1] on behalf of the U-BIOPRED study group[#]

[1]National Heart and Lung Institute, Imperial College London, London and the NIHR Imperial Biomedical Research Centre, London, UK.

[2]Data Science Institute, Imperial College London, London, UK.

[3]Laboratory of Inflammatory Skin Diseases, Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, NY, USA.

[4]Department of Biomedical Engineering, The University of Mississippi, University, MS, USA.

[5]GSK Respiratory Therapeutic Area Unit, Stevenage, UK

[6]Knowles Consulting, Stevenage, UK.

[7]Centre for Allergy Research, Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden.

[8]Division of Physiological Chemistry 2, Department of Medical Biochemistry and Biophysics, Karolinska Institute, 171 77, Stockholm, Sweden

[9]GSK Value Evidence and Outcomes, GSK House, Brentford, UK

[10]Respiratory Global Medicines Development, AstraZeneca, Gothenburg, Sweden

[11]Uppsala University, Dept. of Women's and Children's Health: Paediatric Research, Uppsala, Sweden.

[12]Department of Clinical Science, University of Bergen, Bergen, Norway.

32 [13]Department of Public Health and Clinical Medicine, Division of Medicine/Respiratory
33 Medicine, Umeå University, Umeå, Sweden.
34 [14]University of Catania, 9298, Department of Biomedical and Biotechnological Sciences,
35 Catania, Italy.
36 [15]Aix-Marseille Universite, 128791, Assistance Publique des Hopitaux de Marseille, Clinic des
37 Bronches, Allergies et Sommeil, Marseille, France.
38 [16]Division of Infection, Immunity and Respiratory Medicine, School of Biological Sciences,
39 Faculty of Biology, Medicine and Health, University of Manchester, and Manchester
40 Academic Health Science Centre and NIHR Biomedical Research Centre, Manchester
41 University Hospitals NHS Foundation Trust, Manchester, UK.
42 [17]University Children's Hospital Basel, University of Basel, Basel, Switzerland.
43 [18]Clinical and Experimental Sciences and Human Development in Health, University of
44 Southampton Faculty of Medicine, Southampton; NIHR Southampton Biomedical Research
45 Centre, University Hospital Southampton NHS Foundation Trust, Southampton; and David
46 Hide Asthma and Allergy Research Centre, St Mary's Hospital, Newport, Isle of Wight. UK.
47 [19]Semmelweis University, Department of Public Health, Budapest, Hungary.
48 [20]Fraunhofer ITEM, Hannover, Germany.
49 [21]Department of Respiratory Medicine, Amsterdam UMC, University of Amsterdam,
50 Amsterdam, The Netherlands.
51 [22]Pharmacology, Catholic University of the Sacred Heart, Agostino Gemelli University
52 Hospital Foundation, Roma, Italy.
53 [23]Jagiellonian University Medical College, Department of Internal Medicine, Cracow, Poland.
54 [24]University of Nottingham, NIHR Biomedical Research Centre, Nottingham, UK.
55 [25]Division of Respiratory Medicine, Department of Paediatrics, Inselspital, University of
56 Bern, Bern, Switzerland.
57
58 [#]Members of the U-BIOPRED study group are listed in the Appendix
59
60

Journal Pre-proof

Author for Correspondence:
Professor Ian Adcock
National Heart and Lung Institute
Imperial College London
Dovehouse Street
London
SW3 6LY UK
Tel +44 (0)20 7594 7840
Fax +44 (0)20 7351 8126
email: ian.adcock@imperial.ac.uk

Total word count: 4715 words
Graphical presentations: 5 Figures and 3 Tables

*Current address: Department of Biomedical Engineering, The University of Mississippi, MS, USA
**Current address: Janssen Research & Development Ltd, High Wycombe, United Kingdom

Author contributions: EGY, JHR, KFC and IMA conceived the study; YEB, ABP, SP and SB made substantial contributions to the acquisition and analysis of the data, KFC, IMA, SED and RD generated and provided the asthma datasets and EGY, JHR, YG, SW, YEB, Johan, KFC and IMA made substantial contributions to the interpretation of the work. YEB, KFC and IMA drafted the initial manuscript and all authors provided substantial input into the revision and interpretation of the manuscript. All authors approved the final version for submission and accept responsibility for the accuracy and integrity of the work.

Conflict of Interest statement.
JH Riley, S Bates and S Worsley are employees and shareholders of GlaxoSmithKline. Dr. Uddin reports he is an employee of AstraZeneca and holds shares in the company. Dr. Knowles reports being a former employee of GlaxoSmithkline. Dr. Singer reports personal fees from Vertex Pharmaceuticals Switzerland, personal fees from Novartis Pharma Switzerland , outside the submitted work. Dr. Fowler reports personal fees from AstraZeneca, grants and personal fees from Boehringer Ingelheim, personal fees from

93 Chiesi, personal fees from GSK, personal fees from Novartis, personal fees from Teva
94 outside the submitted work. Dr. Chanez reports grants and personal fees from Almirall,
95 grants and personal fees from BI, grants and personal fees from ALK, grants and personal
96 fees from GSK, grants and personal fees from AstraZeneca, grants and personal fees from
97 Novartis, grants and personal fees from Teva, grants and personal fees from Chiesi, outside
98 the submitted work. Dr. Kolmert reports personal fees from Gesynta Pharma AB outside the
99 submitted work. Dr. Shaw reports speaker fees from Sanofi, AZ and Novartis and travel fees
100 from AZ and Novartis. KFC has received honoraria for participating in Advisory Board
101 meetings of GSK, AZ, Roche, Novartis, Merck, BI and Shionogi regarding treatments for
102 asthma, COPD and chronic cough and has also been renumerated for speaking
103 engagements. AH Maitland-van der Zee has received research grants outside the submitted
104 work from GSK, Boehringer Íngelheim and Vertex, she is the PI of a P4O2 (Precision
105 Medicine for more Oxygen) public private partnership sponsored by Health Holland
106 involving many private partners that contribute in cash and/or in kind (Boehringer
107 Ingelheim, Breathomix, Fluidda, Ortec Logiqcare, Philips, Quantib-U, Smartfish, SODAQ,
108 Thirona, TopMD and Novartis), and she has served in advisory boards for AstraZeneca, GSK
109 and Boehringer Ingelheim with money paid to her institution. R. Djukanovic has received
110 fees for lectures at symposia organized by Novartis, AstraZeneca, and TEVA, as well as
111 consultation fees for serving as a member of advisory boards TEVA and Novartis and
112 participating in a scientific discussion about asthma organized by GlaxoSmithKline.
113 R.Djukanovic is a cofounder and current consultant of and has shares in Synairgen, a
114 University of Southampton spinout company. S-E. Dahlen reports personal fees from
115 AstraZeneca, GlaxoSmithKline, Merck & Company, Novartis, Regeneron, Sanofi, and Teva
116 outside the submitted work. Dr. Guttman-Yassky reports grants from Abbvie, grants from
117 Celgene, grants from Eli Lilly, grants from Janssen, grants from Medimmune/Astra Zeneca,
118 grants from Novartis, grants from Pfizer, grants from Regeneron, outside the submitted
119 work; and EGY is an employee of Mount Sinai and has received research funds (grants paid
120 to the institution) from: Abbvie, Celgene, Eli Lilly, Janssen, Medimmune/Astra Zeneca,
121 Novartis, Pfizer, Regeneron, Vitae, Glenmark, Galderma, Asana, Innovaderm, Dermira, UCB.
122 EGY is also a consultant for Sanofi Aventis, Regeneron, Stiefel/GlaxoSmithKline,
123 MedImmune, Celgene, Anacor, AnaptysBio, Dermira, Galderma, Glenmark, Novartis, Pfizer,
124 Vitae, Leo Pharma, Abbvie, Eli Lilly, Kyowa, Mitsubishi Tanabe, Asana Biosciences, and

Promius. IM Adcock, G Roberts and PJ Sterk received grants from Innovative Medicines Initiative during the conduct of the study. The remaining authors declare that they have no relevant conflicts of interest.

Journal Pre-proof

Abstract

Background: Transcriptomic changes in patients who respond clinically to biological therapies may identify responses in other tissues or diseases.

Objective: To determine whether a disease signature identified in atopic dermatitis (AD) is seen in adults with severe asthma (SA) and whether a transcriptomic signature for AD patients who respond clinically to anti-IL-22 (Fezakinumab, FZ) is enriched in SA.

Methods: An AD disease signature was obtained from analysis of differentially expressed genes (DEGs) between AD lesional and non-lesional skin biopsies. DEGs from lesional skin from therapeutic super-responders before and after 12 weeks FZ treatment defined the FZ-response signature. Gene Set Variation Analysis (GSVA) was used to produce enrichment scores (ES) of AD and FZ-response signatures in the U-BIOPRED asthma cohort.

Results: The AD disease signature (112 up-regulated genes) encompassing inflammatory, T-cell, Th2 and Th17/Th22 pathways was enriched in the blood and sputum of asthmatics with increasing severity. Asthmatics with sputum neutrophilia and mixed granulocyte phenotypes were the most enriched ($p<0.05$). The FZ-response signature (296 down-regulated genes) was enriched in asthmatic blood ($p<0.05$) and particularly in neutrophilic and mixed granulocytic sputum ($p<0.05$). These data were confirmed in sputum of the ADEPT (Airway Disease Endotyping for Personalized Therapeutics) cohort. IL-22 mRNA across tissues did not correlate with FZ-response ES, but this response signature correlated with Th22/IL-22 pathways.

Conclusions: The FZ-response signature in AD identifies severe neutrophilic asthmatics as potential responders to FZ therapy. This approach will help identify patients for future asthma clinical trials of drugs used successfully in other chronic diseases

Abstract word count: 249

Journal Pre-proof

156 **Clinical implications**

157 Identification of transcriptomic drug-response signatures in the target tissue of one chronic
158 immune disease may be utilised in another disease to stratify subjects for subsequent
159 clinical trials or treatment.

160

161 **Capsule Summary:**

162 We used a signature defined by clinical and transcriptomic super-responders to
163 Fezakinumab in atopic dermatitis to identify severe neutrophilic asthmatics as subjects most
164 suitable for testing the efficacy of the drug in asthmatics.

165

166 **Key words**: Anti-IL-22 antibody, atopic dermatitis, gene set variation analysis, IL-22, severe
167 asthma.

168

169 **Abbreviations:**

170 AD	Atopic dermatitis
171 ADEPT	Airway Disease Endotyping for Personalized Therapeutics
172 ASM	Airway smooth muscle
173 BAL	Bronchoalveolar lavage
174 ES	Enrichment score
175 FC	Fold-change
176 FDR	False discovery rate
177 FeNO	Fractional exhaled nitric oxide
178 FZ	Fezakinumab
179 HC	Healthy control
180 ILC	innate lymphoid cell
181 LS	Lesional
182 MADAD	meta-analysis derived atopic dermatitis
183 MMA	Mild-moderate asthma
184 NL	Non-lesional
185 PNR	Potential non-responder
186 PR	Potential responder
187 SA	Severe asthma

Journal Pre-proof

SAs/ex	Severe asthmatic smoker/ex-smoker
T2	Type 2
TAC	Transcriptome-Associated Cluster
U-BIOPRED	Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes
DEGS	Differentially expressed genes
GSVA	Gene Set Variation Analysis

Journal Pre-proof

195 **Introduction**

196 Asthma is phenotyped according to clinical treatable traits and physiological markers
197 including eosinophilic and non-eosinophilic phenotypes (1,2). The Type 2 (T2) inflammatory
198 phenotype characterised by high expression of an interleukin (IL)-13 stimulated bronchial
199 epithelial cell signature (3,4) and elevated urinary leukotriene (LT)E_4 (5), is a molecular
200 phenotype characterised by high eosinophilic inflammation. However, the molecular
201 phenotypes of non-T2 inflammation remain unclear although one phenotype has been
202 characterised by inflammasome, tumour necrosis factor (TNF)α and interferon (IFN)
203 pathway activation associated with neutrophilic asthma (3,6,7). An IL-17 phenotype
204 characterised by neutrophilic inflammation has also been described (8).

205 IL-22 belongs to the IL-10 cytokine family and is produced by T helper (Th)17 and
206 Th22 cells, γδ-T cells and Type 3 innate lymphoid cells (ILCs) as well as neutrophils (9).
207 Elevated bronchoalveolar lavage (BAL) (10) and serum IL-22 levels (11,12) in patients with
208 severe asthma has been reported. Neutrophil-high asthmatics show an upregulated
209 presence of bronchial and nasal cells staining positive for IL-22 expression(13,14). IL-22
210 suppresses IFN-γ-induced pro-inflammatory mediator expression by human bronchial
211 epithelial cells (10) indicating a potential protective role in asthma, but IL-22 also enhances
212 the proliferation and migration of human airway smooth muscle (ASM) cells which may
213 induce airway wall remodelling (15,16). This suggests that IL-22 could play a role in certain
214 endotypes of asthma.

215 IL-22 is implicated in other chronic inflammatory diseases including atopic dermatitis
216 (AD), a closely-related condition to asthma, often preceding it, in the atopic march (17).
217 Epicutaneous sensitization in mice promotes the generation of antigen-specific IL-22-
218 producing T cells leading to airway inflammation and airway hyperresponsiveness following
219 allergen challenge (18). This suggests that IL-22 may be important in the atopic march. The
220 anti-IL-22 monoclonal antibody, fezakinumab (FZ), improves AD clinical scores (19) whilst AD
221 patients with high baseline IL-22 expression showed the greatest clinical response with
222 down-regulation of transcriptomic features associated with immune pathways involved in T-
223 cell and dendritic cell activation (20).

224 The atopic march is a term used to describe the progression of allergic disease from
225 the early presence of atopic dermatitis, food allergies and rhinitis through to asthma (21). A
226 recent *in silico* analysis of the protein interaction networks in these diseases identified the

227 presence of pathways contributing to the allergic multimorbidity of these diseases (22). We
228 hypothesised that a gene signature from AD patients who respond to fezakinumab will be
229 up-regulated in other chronic inflammatory diseases such as asthma. Furthermore, analysis
230 of these 'responder signatures' will select patients most likely to respond to fezakinimab.
231 We analysed differentially expressed genes (DEGs) in eczematous skin lesions of IL-22 high
232 responders between baseline and after 12 weeks of FZ treatment in order to obtain a FZ-
233 response signature. This FZ signature was used to probe the transcriptomes of the lungs
234 and blood of the Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes
235 (U-BIOPRED) asthma cohort to identify features of asthmatic subjects who may respond to
236 FZ. The results were validated in the independent Airway Disease Endotyping for
237 Personalized Therapeutics (ADEPT) cohort.
238

Journal Pre-proof

239 **Methods (word count=709)**

240 **Determination of AD disease and anti-IL-22 responsive signature**

241 Full details of AD patient demographics, samples, transcriptomic analyses and clinical
242 response (NCT01941537) are provided elsewhere (20). The AD disease signature was
243 defined by DEGs identified between eczematous or lesional (LS) skin and non-lesional (NL)
244 skin samples with a fold-change (FC) ≥2 or ≤-2 and a false discovery rate (FDR) ≤0.05 for the
245 whole AD cohort. We also used a composite AD signature derived by comparing the lesional
246 and non-lesional skin transcriptome from 4 microarray studies (MADAD, meta-analysis
247 derived AD)(23).

248 We defined a FZ treatment response signature by analysis of the LS biopsy data of
249 AD patients at baseline and after 12 weeks of FZ treatment to identify DEGs (FC ≥2 or ≤-2
250 and FDR<0.05) (20). Patients with high levels of IL-22 mRNA in lesional tissue at baseline had
251 the greatest response to FZ at both the clinical and transcriptomic level. We used DEGS from
252 the IL-22^{high} AD patients to derive a FZ 'super responder' signature (20)(**Supplementary**
253 **Table 1**).

254

255 **Asthma cohorts**

256 The U-BIOPRED cohort consists of severe non-smoking asthma (SAn); smokers and
257 ex-smokers with severe asthma (SAs/ex); mild/moderate non-smoking asthmatics (MMA)
258 and healthy non-smoking controls (HC) (24). Expression profiling was performed on RNA
259 extracted from blood cells, sputum cells, epithelial brushings and bronchial biopsies (8)(24).
260 Clinical characteristics and sputum and blood proteomic (SomaLogic) metadata are stored
261 within TransMART as part of the eTRIKs project (25). For validation, the ADEPT cohort
262 (NCT01274507) was analysed (26).

263

264 **Protein and other assays**

265 The SOMAscan proteomic assay of 1129 analytes was performed on sputum
266 supernatants (SomaLogic, Boulder, CO, USA) (3). The fraction of exhaled nitric oxide (FeNO)
267 was measured online using an electrochemical analyser (NIOX MINO; Aerocrine, Solna,
268 Sweden) at an expiratory flow rate of 50ml/s according to ATS/ERS guidelines (27). Serum
269 IgE was measured using the Thermo Fisher (Uppsala, Sweden) CAP system. Biomarker and

270 sputum and urinary eicosanoid data were generated by multiplex analysis and mass
271 spectrometry (5).
272
273 **Data analysis**
274 Analysis was performed in R version 3.5.0 (28). Gene set variation analysis (GSVA)
275 was run using the R Bioconductor GSVA package (29) to calculate sample-wise enrichment
276 scores (ES). The ES for AD disease, FZ response and immunological pathway signatures was
277 calculated for each subject across the U-BIOPRED sample compartments. We used a linear
278 model adjusted for age and gender and used the least squares means (30) with the Tukey p-
279 value adjustment method for comparisons of families of estimates (4 for cohort, 5 for
280 granulocyte subtype, and 4 for Transcriptome-Associated Cluster (TAC) group (3)) to analyse
281 the ES differences between groups. Differential expression between sputum transcriptomics of
282 subjects with eosinophilic inflammation against those with non eosinophilic inflammation and
283 subsequent clustering revealed 3 groups. TAC1 contains patients with a high enrichment for the
284 Woodruff Th2-high gene signature with a very high sputum eosinophilia. The TAC2 is characterised
285 by inflammasome-associated pathways and high sputum neutrophilia whilst TAC3 is associated with
286 high levels of macrophages and a mainly paucigranulocytic phenotype (3). Visualization of the
287 distribution of ES was performed with the ggplot2 R package (31). The GSVA signatures are
288 listed in **Supplementary Table 1**.
289 The FZ response signature in U-BIOPRED sputum subjects was used to categorise SA
290 patients as being predicted-responders (PRs) (n=26, ES ≥+0.1) or predicted non-responders
291 (PNRs) (n=18, ES ≤-0.1) whilst filtering out patients with undirected ES (>+0.1 and >-0.1),
292 MMAs and HCs. All categorical variables were analysed using Fisher's exact test. A T-test
293 was used for continuous clinical variables with normal distribution (Shapiro-Wilk test p-
294 value >0.05), whilst the Wilcoxon rank sum test with continuity correction was used for
295 variables with a skewed distribution.
296 Differential gene (for all PRs and PNRs) and protein (for those PRs and PNRs with
297 proteomics data) expression analysis was performed using limma 3.38.3 (32) for linear
298 model fitting for each gene or protein. Empirical Bayes moderation of standard errors was
299 used to produce tables of significant DEGs and proteins. P-values were adjusted with the
300 Benjamini–Hochberg False Discovery Rate (FDR-BH) procedure (33). Age and gender were
301 not confounding variables. Significantly up and downregulated genes were determined by a

302 log2 fold change of ≥1 or ≤-1 and an FDR-BH adjusted p≤0.05. Pathway enrichment analysis
303 was performed using ReactomePA (34), utilising the human Reactome ontology (35) with p-
304 value FDR-BH adjustment and cut-off of 0.05.
305

Journal Pre-proof

306 **Results**

307 **AD signature in asthma**

308 We defined an AD disease signature (**Supplementary Table 1**) according to whether
309 DEGs were significantly up- (112 DEGS, AD-UP) or down-regulated (29 DEGs, AD-DOWN)
310 between lesional and non-lesional skin with a fold-change (FC) ≥2 or ≤-2 and an FDR≤0.05
311 for the whole AD cohort. T-cell, Th2, Th17/Th22 and general inflammatory genes were up-
312 regulated in the AD-UP signature whereas AD-DOWN reflected lipid pathways and pathways
313 associated with dysregulated dermal epithelial function (20).

314 This signature was applied to blood (**Fig 1A**) and sputum (**Fig 1B**) of the U-BIOPRED
315 cohort. The AD-UP signature ES trended with severity: significantly enriched in the blood of
316 severe, but not MMA, asthmatics irrespective of smoking status (**Fig 1A**). A similar trend
317 was seen in the sputum of severe asthmatics (**Fig 1B**). When compared by sputum TACs (3)
318 there was an enrichment of the AD-UP signature in sputum from TAC2 (adj.p=2.87×10^{-6})
319 subjects (**Fig 1C**) compared to healthy controls. Assessment based on sputum granulocytes
320 further highlighted the greater enrichment of the AD-UP score in granulocytic asthma (**Fig**
321 **1D**) with a greater ES in neutrophilic (adj.p=6.83×10^{-5}) and mixed granulocytic
322 (adj.p=0.0005) asthma compared to healthy controls. The enrichment of the AD lesion
323 signature in asthma reflects a composite of the cells within blood and sputum.

324 We confirmed the appropriateness of the AD-UP signature by using the previously
325 defined MADAD-UP pooled signature (**Fig 1E-H**). The MADAD-UP signature is a consensus
326 disease signature of the pathologically upregulated genes which characterise atopic dermatitis
327 across several studies (23). The overlap between the AD-UP and MADAD-UP gene signatures
328 consisted of 84 genes. This signature was enriched in both blood (**Fig 1E**) and sputum (**Fig**
329 **1F**) of severe asthmatics irrespective of smoking status, mirroring results seen in AD-UP
330 blood. Classifying asthmatics according to sputum molecular phenotype or to sputum
331 granulocytes also demonstrated enrichment of the MADAD-UP signature in TAC2 (**Fig 1G**)
332 and neutrophilic/mixed granulocytic subjects (**Fig 1H**). Overall, the AD disease signature was
333 enriched in severe neutrophilic asthma.

334

335 **Derivation of an FZ super-responder signature in AD**

336 The FZ treatment super-response was defined by those subjects with a good clinical
337 response who also had a good transcriptomic response comparing lesional biopsies at

338 baseline and after 12 weeks FZ treatment in AD patients to identify the significant DEGs
339 (FC≥2 or ≤-2 and FDR<0.05)(20). The highest clinical and transcriptomic effect was seen in
340 baseline IL-22^{high} lesional tissue and the transcriptomic changes seen in patients with a high
341 clinical and transcriptomic response was used to generate the FZ-super-responder
342 signature.

343 We identified 417 DEGs (121 up- and 296 or down-regulated by FZ) in lesional AD
344 skin tissue biopsies from patients with the greatest clinical response to FZ at 12 weeks
345 (**Supplementary Table 1**). This FZ-response signature (FZ-DOWN) represents a key
346 proportion of the AD-UP disease signatures. In particular, the AD-UP signature (112 genes)
347 had 74 genes overlapping with the FZ-DOWN (296 genes, 25%) whilst the MADAD-UP
348 signature (405 genes) had 196 genes overlapping with the FZ-DOWN signature (48.4%). A
349 strong correlation existed between the AD-UP and FZ-DOWN ES in asthmatic sputum
350 (R^2=0.8326, p=2.2x10^{-16}) (**Supplementary Fig 1A**) and between MADAD-UP and FZ-DOWN
351 (R^2=0.9156, p=2.2x10^{-16}) (**Supplementary Fig 1B**). The FZ-DOWN signature included
352 pathways associated with general inflammation, T-cell, Th2 and Th17/Th22 activation
353 (**Supplementary Fig 2, Supplementary Table 2**), which are all up-regulated within the AD
354 disease signatures. No pathways were significantly associated with FZ-UP genes although
355 relaxing the FDR threshold identified pathways associated with epidermal signalling
356 (**Supplementary Fig 3, Supplementary Table 3**), which justifies the focus on the FZ-DOWN
357 signature. To test whether the FZ-DOWN signature predicted the response in AD patients,
358 we examined the ES of FZ DOWN in lesional AD baseline samples (20). This was significantly
359 (p=0.0496, adjusted for age and gender) positively associated with the AD SCORAD score
360 after treatment.

361 In summary, **Supplemental Table 1** provides a list of all the gene signatures used in
362 this analysis including the sets of genes up-regulated (AD-UP) or down-regulated (AD-
363 DOWN) in AD whilst **Supplemental Table 2** provides a list of all the pathways that the FZ-
364 DOWN gene signature corresponds to and highlights the importance of immune pathways.
365 **Supplementary Table 3** is a list of all the pathways that relate to the FZ-UP gene signature.
366 None of these pathways was significantly enriched and are mostly skin-related.
367

368 **Enrichment of the FZ super-responder signature from AD in U-BIOPRED**

369 The FZ-DOWN signature was significantly enriched in the blood of U-BIOPRED severe
370 asthmatics (adj.p<0.05) (**Fig 2A**) despite the wide variability in ES scores, which may reflect
371 the different types of immune cells found in blood and lesional tissue. The skin contains a
372 mixture of epithelial cell-like and immune cells but the enrichment observed in blood may
373 indicate detection of the immune components.

374 The FZ-DOWN signature was significantly enriched in the blood of TAC2 patients
375 (adj.p=0.015, **Fig 2B**). The response in blood when subjects were stratified according to
376 sputum granulocytes was variable and although there was a trend towards enrichment in
377 asthma subtypes, this did not reach significance (**Fig 2C**). There was a greater degree of
378 enrichment in sputum samples compared to blood (compare Fig 3A-C with Fig 3D-F). The ES
379 for FZ-DOWN had a stepwise association with severity and was highly enriched TAC2
380 patients (adj.p=0.002, **Fig 2E**), and neutrophilic (adj.p=0.0002, **Fig 2F**) and mixed
381 granulocytic (adj.p=0.0098, **Fig 2F**) asthma compared with healthy controls. The good
382 correlation between the TAC2 signature and the FZ-DOWN signature in sputum ($p<2.2x10^{-16}$,
383 r=0.784) was not due to overlapping signatures as only 3 genes were common between the
384 two genesets – CASP4, KCNJ15 and SAMSN1. Importantly, we were able to show that the
385 AD-UP and MADAD-UP (**Fig 3A**) and the FZ-DOWN (**Fig 3B**) signatures were also enriched
386 within the sputum neutrophilic (adj.p<0.05) and mixed granulocytic patients within the
387 ADEPT cohort (**Fig 3A-B**).

388 To ensure against a confounding effect of tissue heterogeneity we removed the 4 skin-
389 specific genes identified by comparing the FZ-DOWN signature with a published skin transcriptomic
390 profile (36). There were 4 overlapping genes (WFDC12, TYR, S1PR5, LYPD5) and removal of these 4
391 genes from the FZ-DOWN signature had minimal effect on the analysis (**Supplementary Fig 4**).

392 Since the FZ-DOWN signature was associated with neutrophilic asthma we checked whether
393 this and the AD disease signatures correlated with 3 neutrophil signatures from the Human Cell Atlas
394 (37), an immune cell gene-signature database (38) and a Th17 signature (39) that consists of genes
395 for neutrophil chemoattractants (CXCL1, CXCL2, CXCL3, CXCL8 and CFS3). We observed a high
396 correlation between FZ-DOWN ES and neutrophil signature ES and also AD disease signature ES and
397 neutrophil signature ES, indicating that the disease signatures reflected tissue neutrophilia. In
398 particular Pearson's correlation between the FZ-DOWN ($p=1.25 x10^{-9}$, r=0.519), AD-UP ($p<2.2x10^{-16}$,
399 r=0.754) and the MADAD-UP ($p<2.2x10^{-16}$, r=0.684) signatures were very significantly correlated with
400 the immune cell database neutrophil signature. In addition, the FZ-DOWN ($p<2.2x10^{-16}$, r= 0.691),

401 AD-UP ($p=4.479x10^{-7}$, r=0.441) and the MADAD-UP ($p=4.304x10^{-7}$, r=0.442) signatures were also
402 significantly correlated with the Human Cell Atlas neutrophil signature.
403 However, neutrophil levels in the skin were not significantly reduced after FZ treatment
404 (**Supplementary Fig 5**) which suggests that despite neutrophil genes contributing to the AD disease
405 signature and some neutrophil genes being present in the FZ response signature, the FZ response
406 phenomenon is unlikely to be driven by neutrophil levels alone. This corroborates with a positive but
407 non-significant correlation between sputum neutrophils and sputum IL-22 protein in U-BIOPRED
408 subjects (p=0.0699, r=0.184). We also examined the correlation between sputum neutrophils and
409 the FZ-DOWN signature in the validation ADEPT cohort and found no significant correlation (%
410 segmented neutrophils; p=0.911, r=0.0186).
411
412 **Clinical features of predicted responders and non-responders in U-BIOPRED**
413 We next examined whether the FZ-DOWN signature was associated with a specific
414 subset of SA patients as the most clinically relevant group. Highly-enriched patients (PRs)
415 were compared with those least-enriched (PNRs) for the FZ-DOWN signature
416 (**Supplementary Fig 6, Supplementary Table 4**). The enrichment score of the FZ-DOWN
417 signature in sputum was used to categorise SA patients as being predicted-responders (PRs)
418 (n=26, ES ≥+0.1) or predicted non-responders (PNRs) (n=18, ES ≤-0.1) whilst filtering out
419 patients with an undirected ES (<+0.1 and >-0.1), MMAs and HCs. The clinical comparison
420 revealed that PRs had more frequent LABA use and significantly elevated sputum
421 neutrophils and lower sputum eosinophils and macrophages in addition to lower IgE levels
422 in contrast to PNRs (**Table 1**). Furthermore, PRs had lower levels of plasma eotaxin-3 and
423 serum IL-13 biomarkers as measured by Luminex or MSD analysis. PRs also had elevated
424 sputum levels of 11-dehydro-TXB_2, 5-HETE and LTB_4 (p=0.0526) but lower LTE_4 reflecting the
425 neutrophilic and low eosinophilic nature of the PR population (**Table 2**).
426 In a linear model (LM) of asthmatic sputum FZ-DOWN ES and medication usage,
427 corrected for age, gender and BMI, we found no significant association between FZ-DOWN
428 ES and OCS use (p=0.702). However, we did find a significant association between FZ-DOWN
429 ES and LABA use (p=0.0243) where FZ-DOWN ES was elevated in the twice daily LABA use
430 group (reflecting severity of disease, LM estimate=0.112) and least in the group not taking
431 LABA at all (mildest subjects, LM estimate=-0.117).
432

433 **DEGs between Predicted Responder (PR) and Predicted Non-Responder (PNR) severe**
434 **asthmatics**
435 We performed DEG analysis between PR and PNR patients and identified 431 up and 19
436 down sputum DEGs which were significant with a log2 FC of over 1 or below -1 respectively.
437 These are reported in **Supplementary Table 5**. ReactomePA pathway analysis on the up
438 DEGs indicates a strong neutrophilic component with neutrophil degranulation, cytokine
439 and chemokine receptor and Toll-like receptor (TLR) signalling as well as IL-10 and IFN
440 pathways being highly enriched in PR subjects (**Fig 4, Supplementary Table 6**). The IL-33
441 receptor (IL1RL1, ST2) was greatly downregulated in the PR group.
442
443 **Sputum proteomic enrichment of FZ-DOWN signature**
444 We then selected PRs and PNRs who had SomaLogic sputum proteomics data
445 available (n=32) (**Supplementary Table 7**)**.** Differential protein analysis on the sputum
446 SomaLogic data confirmed a strong neutrophilic component (**Table 3**). Significantly
447 upregulated sputum proteins included the neutrophil modulator Sialic acid-binding
448 immunoglobulin-type lectins 9 (siglec-9), the neutrophil serine proteases cathepsin G and
449 azurocidin involved in neutrophil degranulation and microbial killing, B7_H2 which is a
450 costimulatory ligand for CD28, IL-6 which is involved in neutrophilic asthma and increased
451 differentiation of Th17 cells and Oxidized Low Density Lipoprotein Receptor 1 (OLR1) which
452 is involved in tissue remodelling. These proteins together with the enhanced expression of
453 neutrophil degranulation products implicate neutrophil activation as being a key component
454 of asthmatic subjects who are highly enriched for the FZ-DOWN signature.
455
456 **FZ-DOWN signature markers in blood**
457 We then selected PRs and PNRs who had blood proteomics data available (n=42)
458 (**Supplementary Table 8**)**.** Differential protein analysis on blood SomaLogic data
459 (**Supplementary Table 9**) defined potential FZ responders from non-responders as
460 possessing lower blood IgE and a trend towards elevated expression of the neutrophil
461 modulator siglec-9 and I-TAC as seen in the sputum proteomics analysis.
462
463 **IL-22 pathway and protein correlates with FZ-DOWN enrichment**

464 In AD skin (20), IL-22 gene expression alone predicts the response to FZ. However, IL-
465 22 gene expression was not enriched in blood (**Supplementary Fig 7A**) or sputum according
466 to asthma severity (**Supplementary Fig 7B**) or in TAC2 asthmatics (**Supplementary Fig 7C**).
467 There was no correlation between FZ-DOWN and IL-22 gene expression in blood
468 (**Supplementary Fig 7D**), sputum **(Supplementary Fig 7E**), bronchial brushings
469 (**Supplementary Fig 7F**) or nasal brushings (**Supplementary Fig 7G**).
470 In contrast, the ES of the Th22/IL-22 signature was significantly correlated with FZ-
471 DOWN ES in asthmatic sputum ($p=4.31x10^{-14}$, r=0.656)(**Fig 5A**), bronchial brushings
472 ($p<2.2x10^{-16}$, r=0.753)(**Fig 5B**), nasal brushings ($p=8.53x10^{-13}$, r=0.755)(**Fig 5C**) and blood
473 ($p=5.06x10^{-6}$, r=0.223). The Th22/IL-22 signature (**Supplementary Table 1**) consists of 16
474 genes including IL-22 itself and the Th22-specific marker CCR10 (20). Pathway analysis
475 identified several significantly enriched pathways including 'IL22 Induces Keratinocyte
476 Proliferation in Psoriasis', 'Interleukin-19, 20, 22, 24 Homo sapiens R-HSA-8854691' and 'IL-
477 the 17 signaling pathway'.
478 Importantly, sputum IL-22 protein was significantly enriched in patients with TAC2
479 asthma compared to those with TAC1 asthma (p=0.0112) and there was a significant
480 correlation between sputum IL-22 protein expression and the FZ-DOWN ES when controlled
481 for age, sex and BMI (p=0.0360, r=0.133)(**Fig 5D**). IL-22 protein in sputum also significantly
482 correlated with FZ-DOWN ES in nasal brushings for all subjects (p=0.0443, r=0.423).

Journal Pre-proof

483 **DISCUSSION**

484 We demonstrate that an AD disease signature was enriched in severe neutrophilic
485 asthma in both the U-BIOPRED and ADEPT asthma cohorts and that these subjects were also
486 highly enriched for a gene signature indicative of a super-response to FZ. Pathway analysis
487 indicated that the AD-UP disease signature and the FZ-DOWN-response signature were a
488 composite of Th1, Th2, Th17, Th22 and general inflammatory processes and that sputum
489 proteins linked with a potential FZ response in asthma were associated with neutrophil
490 recruitment and activation. The FZ super-response signature did not correlate with IL-22
491 gene expression itself although there was a good correlation with the Th22/IL-22 gene
492 signature in nasal and bronchial brushings. Sputum IL-22 protein correlated significantly
493 with FZ-DOWN. Re-purposing transcriptomic data that defines a treatment response across
494 therapeutic areas may aid the stratification of patients for future clinical trials.

495 Early transcriptomic analysis of skin samples from psoriasis and AD subjects
496 identified neutrophil chemoattractant genes as being highly expressed in both AD and
497 psoriatic skin lesions (40). Furthermore, neutrophil elastase staining is elevated in lesional
498 compared with non-lesion skin in AD patients but to a much lesser extent than seen in
499 patients with psoriasis. This enhanced neutrophilia in AD may reflect concurrent infection
500 with Staphylococcus aureus infection (41). Enhanced neutrophilia may reflect an enhanced
501 Th1/Th17 drive.

502 The Th2/Th22 pathway is the major pathway in AD as recently confirmed using single cell
503 RNA-sequencing (42). This is seen across all age-groups, however, an enrichment of
504 Th1/Th17 genes is seen in lesional compared to non-lesional skin in adults (43). Indeed, the
505 usual Th2/Th22 drive in AD is skewed towards a Th1/Th17 phenotype with increasing age
506 (44) and severity of disease. For example, enhanced Th1/Th17 mediator expression is
507 reported in the blood of AD patients with severe but not mild disease (45). Importantly,
508 there was a good correlation between Th2/Th22/Th1/Th17 gene and protein expression
509 profiles in lesional and non-lesional AD samples (46).

510 Severe asthmatic PRs to FZ had neutrophilic or mixed granulocytic asthma, poor lung
511 function and a low asthma quality of life despite frequent LABA use. These subjects also
512 had lower serum IgE levels but with relatively greater atopic disposition, in contrast to
513 subjects with T2 eosinophilic asthma (≥300 cells/µl), suggesting that an anti-IL-22
514 intervention may be targeted to non-T2 asthmatics with low IgE as opposed to those with a

515 high IgE neutrophilic phenotype (14,47). Gender, BMI and age did not affect the enrichment
516 of the FZ response signature. Comparison of biomarkers between PRs and PNRs indicated
517 that PR subjects had elevated levels of 11-dehydro-TXB_2, 5-HETE and LTB_4 although the
518 latter did not quite reach significance. Leukotrienes are formed via a 5-LOX dependent
519 process in which arachidonic acid is converted to the unstable epoxide intermediate LTA_4,
520 which can then be converted by either LTC_4 synthase (LTC_4S) to form the cysteinyl-
521 leukotrienes or via LTA_4-hydrolase (LTA_4H) to form LTB_4. Neutrophils have known LTA_4H
522 activity and sputum neutrophils have been previously reported to produce LTB_4 (48).
523 Accordingly, the elevated sputum LTB_4 levels in combination with the lower LTE_4 levels
524 among PR subjects collectively point towards a specific elevation of LTA_4H activity within
525 these neutrophilic subjects, which further support a non-T2 phenotype (49).

526 We have previously defined asthmatics according to their sputum molecular
527 phenotypes (3). The FZ-DOWN signature was enriched in TAC2 patients that suggests that
528 FZ may be useful for T2-low severe neutrophilic asthmatics. Pathway analysis of the
529 potential FZ responders versus non-responders highlighted the importance of neutrophil
530 degranulation products along with signalling downstream of TLRs, cytokine/chemokines
531 including neutrophil-associated mediators and chemoattractant receptors such as CXCL10,
532 CXCL11, CXCR1 and CXCR2, suggesting an activated neutrophil phenotype. Although
533 previously-defined pathways such as the NLRP3 inflammasome within TAC2 were not
534 specifically enriched in the FZ predicted responder versus non-responder subjects, factors
535 associated with inflammasome activation including IL-1α and IL-1RAP are present (50).

536 At the cellular level, a significant increase in the percentage of airway neutrophils
537 (75.5% *vs* 35.6%) and a significant decrease in the percentage of airway macrophages
538 (18.9% *vs* 32.5%) in the FZ predicted responders group were observed. Macrophages
539 phagocytose apoptotic neutrophils and contribute to inflammation resolution. It is
540 interesting to speculate whether a reduced number of airway macrophages observed could
541 adversely impede neutrophil clearance, thus promoting the elevated levels of airway
542 neutrophils in this endotype of asthma. Defects in neutrophil apoptosis and/or clearance
543 leading to airway neutrophilia have previously been reported in a small cohort of severe
544 atopic asthmatics with a low-eosinophilic phenotype (≤3% sputum eosinophils) (51).

545 We have previously shown that GM-CSF/CSF2RB- and IFN-activated macrophages as
546 well as lower enrichment of eosinophils were associated with childhood asthma (52). The

547 AD disease signature indicates that AD, although generally seen as a T2-dominant disease,
548 also has different degrees of non-T2 driving pathways including Th1, Th17, Th22 and
549 inflammatory pathways (20). Both GM-CSF and IFN pathways were also enriched within the
550 FZ predicted responder population and interestingly, the potential responder-non-
551 responder pathways also indicated the enrichment of IL-10 signalling which is involved in
552 the suppression of IL-5 and GM-CSF expression and eosinophil apoptosis (53). These
553 pathways may also represent therapeutic targets in these SA patients.

554 The AD-DOWN signature is not enriched in asthmatic peripheral blood but shows
555 some enrichment in airway samples. This signature includes lipid pathways and pathways
556 associated with dysregulated dermal epithelial function that indicates remodelling of
557 epithelial tissues is more prevalent in severe neutrophilic asthma airways. These pathways
558 are also up-regulated by FZ which suggests that FZ may also impact upon asthmatic airway
559 epithelial cell barrier function.

560 IL-22 possesses potential pro- and anti-inflammatory roles in asthma (11,15,16). In
561 mouse models of allergic sensitisation and challenge, IL-22 attenuates established Th2 cell-
562 mediated allergic inflammation *in vivo* (11,54). However, IL-22 promotes allergic
563 inflammation in similar mouse models at the onset of allergic asthma (11,18), supporting
564 the view that IL-22 may be involved in the atopic march (17). While data from mouse
565 models suggest that anti-IL-22 may be efficacious in early onset allergic asthma, our analysis
566 would indicate that IL-22 might have a pathogenic role in those with neutrophilic
567 inflammation with lower IgE levels.

568 In our analysis, IL-22 mRNA expression did not correlate with FZ response signatures
569 in blood, sputum, nasal and bronchial brushings whereas there was a significant correlation
570 with sputum IL-22 protein and with the Th22/IL-22 gene signature in sputum, bronchial and
571 nasal brushings. This may reflect the local expression of IL-22 protein in the airways which is
572 not detected at the mRNA level or is not observed due to lack of proteomics data for
573 bronchial and nasal brushings. However, the up-regulation of the FZ-DOWN signature does
574 indicate a significant impact of IL-22 on downstream signalling.

575 This study has several strengths and also some limitations. We derived a gene
576 signature from skin lesions of AD subjects (AD-UP) and also from patients with a good
577 clinical response and a clear transcriptomic response to FZ after 12 weeks of treatment (FZ-
578 DOWN) to provide evidence for target engagement in the lesional tissue. We utilised the

579 large data-rich U-BIOPRED cohort to define subsets of patients who are more likely to
580 respond to FZ and validated this in a separate cohort of severe asthmatics. Importantly, we
581 were able to demonstrate markers of high enrichment of this response signature in nasal
582 brushings and peripheral blood. However, we do not have evidence that the changes seen
583 in the lesional skin of AD patients with FZ also occur in the airways of asthmatics. Animal
584 models of severe neutrophilic or mixed granulocytic asthma may be used to address this
585 issue. In asthma, baseline levels of IL-22 mRNA did not correlate with FZ-DOWN signature as
586 predicted from the AD data. This suggests that additional mechanisms may occur in the
587 asthmatic airway compared to the skin. These mechanisms may be linked since there is a
588 strong correlation between the Th22/IL-22 and FZ-DOWN signatures. The good correlation
589 of both IL-22 sputum protein abundance and Th22/IL-22 signature ES with the FZ-DOWN
590 signature ES within nasal brushings indicates a potential alternative readily accessible
591 approach for identifying possible responder populations. Although this data was validated in
592 a separate SA cohort we have not measured the stability of the FZ-response signature over
593 time and whether this changes with T2-directed biologics.

594 This novel approach of molecularly characterising clinical super-responders to an
595 antibody drug in one disease followed by probing other disease databases may be a more
596 effective way of identifying predicted-responders at the endotypes level compared to
597 looking at drug-target levels alone. By exploiting pre-existing databases and clinical trial
598 data, this approach could lead to a reduction in drug development time and in research
599 costs. The greatest enrichment of the FZ PR signature was observed in severe neutrophilic
600 asthmatics. Furthermore, we found that blood and sputum gene expression and the
601 expression of several proteins in sputum can predict asthmatics with a high enrichment of a
602 FZ response signature in the airway. This stratification process will need validation in a
603 controlled clinical trial, while at the same time examining the long-term efficacy and side-
604 effect profile of FZ in endotypes of severe asthma.

605
606

Journal Pre-proof

Acknowledgements

This study was supported by the Biotechnology and Biological Sciences Research Council Studentship (BBSRC-NPIF studentship /BIDS3000032503) to YB. U-BIOPRED was supported by an Innovative Medicines Initiative Joint Undertaking (No.115010), resources from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in-kind contribution (www.imi.europa.eu). We acknowledge the contribution of the whole U-BIOPRED team. SED and IMA are supported by the 3TR (Taxonomy, Treatment, Targets and Remission) project funded by the Innovative Medicines Initiative 2 Joint Undertaking (JU) under grant agreement No 831434.

Journal Pre-proof

619 **References**

620 1. Holguin F, Cardet JC, Chung KF, Diver S, Ferreira DS, Fitzpatrick A, et al. Management
621 of severe asthma: A European Respiratory Society/American Thoracic Society
622 guideline. Eur Respir J. 2020;**55**(1):pii: 1900588.
623 2. Papi A, Brightling C, Pedersen SE, Reddel HK. Asthma. Lancet. 2018;**391**:783–800.
624 3. Kuo CHS, Pavlidis S, Loza M, Baribaud F, Rowe A, Pandis I, et al. T-helper cell type 2
625 (Th2) and non-Th2 molecular phenotypes of asthma using sputum transcriptomics in
626 U-BIOPRED. Eur Respir J. 2017;**49**(2):pii: 1602135.
627 4. Woodruff PG, Modrek B, Choy DF, Jia G, Abbas AR, Ellwanger A, et al. T-helper type 2-
628 driven inflammation defines major subphenotypes of asthma. Am J Respir Crit Care
629 Med. 2009;**180**(5):388–95.
630 5. Kolmert J, Gómez C, Balgoma D, Sjödin M, Bood J, Konradsen JR, et al. Urinary
631 Leukotriene E4 and Prostaglandin D2 Metabolites Increase in Adult and Childhood
632 Severe Asthma Characterized by Type-2 Inflammation. Am J Respir Crit Care Med.
633 2020;
634 6. Bhakta NR, Christenson SA, Nerella S, Solberg OD, Nguyen CP, Choy DF, et al. IFN-
635 stimulated gene expression, type 2 inflammation, and endoplasmic reticulum stress
636 in asthma. Am J Respir Crit Care Med. 2018;**197**(3):313–24.
637 7. Gauthier M, Chakraborty K, Oriss TB, Raundhal M, Das S, Chen J, et al. Severe asthma
638 in humans and mouse model suggests a CXCL10 signature underlies corticosteroid-
639 resistant Th1 bias. JCI insight. 2017;**2**(13):pii: 94580.
640 8. Östling J, van Geest M, Schofield JPR, Jevnikar Z, Wilson S, Ward J, et al. IL-17–high
641 asthma with features of a psoriasis immunophenotype. J Allergy Clin Immunol.
642 2019;**144**(5):1198–213.
643 9. Zenewicz LA. IL-22: There Is a Gap in Our Knowledge. ImmunoHorizons.
644 2018;**2**(6):198–207.
645 10. Pennino D, Bhavsar PK, Effner R, Avitabile S, Venn P, Quaranta M, et al. IL-22
646 suppresses IFN-γ-mediated lung inflammation in asthmatic patients. J Allergy Clin
647 Immunol. 2013;**131**(2):P562-570.
648 11. Besnard AG, Sabat R, Dumoutier L, Renauld JC, Willart M, Lambrecht B, et al. Dual
649 role of IL-22 in allergic airway inflammation and its cross-talk with IL-17A. Am J Respir
650 Crit Care Med. 2011;**183**(9).

651 12. Sherkat R, Yazdani R, Ganjalikhani Hakemi M, Homayouni V, Farahani R, Hosseini M,
652 et al. Innate lymphoid cells and cytokines of the novel subtypes of helper T cells in
653 asthma. Asia Pac Allergy. 2014;**4**(4):212–21.
654 13. Ricciardolo FLM, Sorbello V, Folino A, Gallo F, Massaglia GM, Favatà G, et al.
655 Identification of IL-17F/frequent exacerbator endotype in asthma. J Allergy Clin
656 Immunol. 2017;**140**(2):P395-406.
657 14. Bullone M, Carriero V, Bertolini F, Folino A, Mannelli A, Stefano A Di, et al. Elevated
658 serum IgE, oral corticosteroid dependence and IL-17/22 expression in highly
659 neutrophilic asthma. Eur Respir J. 2019;**54**(5).
660 15. Chang Y, Al-Alwan L, Risse PA, Halayko AJ, Martin JG, Baglole CJ, et al. Th17-
661 associated cytokines promote human airway smooth muscle cell proliferation. FASEB
662 J. 2012;**26**(12):5152–60.
663 16. Chang Y, Al-Alwan L, Risse PA, Roussel L, Rousseau S, Halayko AJ, et al. TH17 cytokines
664 induce human airway smooth muscle cell migration. J Allergy Clin Immunol.
665 2011;**127**(4):1046-53.e1-2.
666 17. Aw M, Penn J, Gauvreau GM, Lima H, Sehmi R. Atopic March: Collegium
667 Internationale Allergologicum Update 2020. Int Arch Allergy Immunol. 2020;**181**(1):1–
668 10.
669 18. Leyva-Castillo JM, Yoon J, Geha RS. IL-22 promotes allergic airway inflammation in
670 epicutaneously sensitized mice. J Allergy Clin Immunol. 2019;**143**(2):619-630.e7.
671 19. Guttman-Yassky E, Brunner PM, Neumann AU, Khattri S, Pavel AB, Malik K, et al.
672 Efficacy and safety of fezakinumab (an IL-22 monoclonal antibody) in adults with
673 moderate-to-severe atopic dermatitis inadequately controlled by conventional
674 treatments: A randomized, double-blind, phase 2a trial. J Am Acad Dermatol.
675 2018;**78**(5):872–81.
676 20. Brunner PM, Pavel AB, Khattri S, Leonard A, Malik K, Rose S, et al. Baseline IL-22
677 expression in patients with atopic dermatitis stratifies tissue responses to
678 fezakinumab. J Allergy Clin Immunol. 2019;**143**:142–54.
679 21. Davidson WF, Leung DYM, Beck LA, et al. Report from the National Institute of Allergy
680 and Infectious Diseases workshop on "Atopic dermatitis and the atopic march:
681 Mechanisms and interventions". J Allergy Clin Immunol 2019; **143**(3): 894-913.
682 22. Aguilar D, Pinart M, Koppelman GH, et al. Computational analysis of multimorbidity

683 between asthma, eczema and rhinitis. PLoS One 2017; **12**(6): e0179125.
684 23. Ewald DA, Malajian D, Krueger JG, Workman CT, Wang T, Tian S, et al. Meta-analysis
685 derived atopic dermatitis (MADAD) transcriptome defines a robust AD signature
686 highlighting the involvement of atherosclerosis and lipid metabolism pathways. BMC
687 Med Genomics. 2015;**8**(60).
688 24. Shaw DE, Sousa AR, Fowler SJ, Fleming LJ, Roberts G, Corfield J, et al. Clinical and
689 inflammatory characteristics of the European U-BIOPRED adult severe asthma cohort.
690 Eur Respir J. 2015;**46**(5):1308–21.
691 25. Athey BD, Braxenthaler M, Haas M, Guo Y. tranSMART: An Open Source and
692 Community-Driven Informatics and Data Sharing Platform for Clinical and
693 Translational Research. AMIA Jt Summits Transl Sci proceedings AMIA Jt Summits
694 Transl Sci. 2013;**2013**(6–8).
695 26. Silkoff PE, Strambu I, Laviolette M, Singh D, FitzGerald JM, Lam S, et al. Asthma
696 characteristics and biomarkers from the Airways Disease Endotyping for Personalized
697 Therapeutics (ADEPT) longitudinal profiling study. Respir Res. 2015;**16**(142).
698 27. Araya-Cloutier C, Vincken JP, Van De Schans MGM, Hageman J, Schaftenaar G, Den
699 Besten HMW, et al. ATS/ERS recommendations for standardized procedures for the
700 online and offline measurement of exhaled lower respiratory nitric oxide and nasal
701 nitric oxide, 2005. Am J Respir Crit Care Med 2005;171:912–30.
702 doi:10.1164/rccm.200406-710ST.
703 28. Core Team R. R: A Language and Environment for Statistical Computing [Internet]. R
704 Foundation for Statistical Computing, Vienna, Austria. 2018. Available from:
705 http://www.r-project.org/
706 29. Hänzelmann S, Castelo R, Guinney J. GSVA: Gene set variation analysis for microarray
707 and RNA-Seq data. BMC Bioinformatics. 2013;**14**(7).
708 30. Lenth R V. Least-squares means: The R package lsmeans. J Stat Softw. 2016;**69**(1).
709 31. Wickham H. ggplot2: Elegant Graphics for Data Analysis [Internet]. Springer-Verlag
710 New York; 2016. Available from: https://ggplot2.tidyverse.org
711 32. Ritchie ME, Phipson B, Wu D, Hu Y, Law CW, Shi W, et al. Limma powers differential
712 expression analyses for RNA-sequencing and microarray studies. Nucleic Acids Res.
713 2015;**43**(7):e47.
714 33. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and

715 Powerful Approach to Multiple Testing. J R Stat Soc Ser B. 1995;**57**(1).
716 34. Yu G, He QY. ReactomePA: An R/Bioconductor package for reactome pathway
717 analysis and visualization. Mol Biosyst. 2016;**2016**(2):477–9.
718 35. Fabregat A, Jupe S, Matthews L, Sidiropoulos K, Gillespie M, Garapati P, et al. The
719 Reactome Pathway Knowledgebase. Nucleic Acids Res. 2018;**46**(D1):D649–55.
720 36. Edqvist PH, Fagerberg L, Hallström BM, et al. Expression of human skin-specific genes
721 defined by transcriptomics and antibody-based profiling. J Histochem Cytochem
722 2015; **63**(2): 129-41.
723 37. Hay SB, Ferchen K, Chetal K, Grimes HL, Salomonis N. The Human Cell Atlas bone
724 marrow single-cell interactive web portal. Exp Hematol 2018; **68:51-61.**
725 38. Abbas AR, Baldwin D, Ma Y, et al. Immune response in silico (IRIS): immune-specific
726 genes identified from a compendium of microarray expression data. Genes Immun
727 2005; **6**(4): 319-31.
728 39. Choy DF, Hart KM, Borthwick LA, et al. TH2 and TH17 inflammatory pathways are
729 reciprocally regulated in asthma. Sci Transl Med 2015; **7**(301): 301ra129.
730 40. Choy DF, Hsu DK, Seshasayee D, et al. Comparative transcriptomic analyses of atopic
731 dermatitis and psoriasis reveal shared neutrophilic inflammation. J Allergy Clin
732 Immunol 2012; **130**(6): 1335-43.e5.
733 41. Dhingra N, Suárez-Fariñas M, Fuentes-Duculan J, et al. Attenuated neutrophil axis in
734 atopic dermatitis compared to psoriasis reflects TH17 pathway differences between
735 these diseases. J Allergy Clin Immunol 2013; **132**(2): 498-501.e3.
736 42. He H, Suryawanshi H, Morozov P, et al. Single-cell transcriptome analysis of human
737 skin identifies novel fibroblast subpopulation and enrichment of immune subsets in
738 atopic dermatitis. *J Allergy Clin Immunol* 2020; **145**(6): 1615-28.
739 43. Renert-Yuval Y, Del Duca E, Pavel AB, et al. The molecular features of normal and
740 atopic dermatitis skin in infants, children, adolescents, and adults. *J Allergy Clin*
741 *Immunol* 2021; **13**(21): 00007-5.
742 44. Zhou L, Leonard A, Pavel AB, et al. Age-specific changes in the molecular phenotype
743 of patients with moderate-to-severe atopic dermatitis. J Allergy Clin Immunol 2019;
744 **144**(1): 144-56.
745 45. He H, Del Duca E, Diaz A, et al. Mild atopic dermatitis lacks systemic inflammation and
746 shows reduced nonlesional skin abnormalities. J Allergy Clin Immunol 2020; **1**(20):

747 31334-8.
748 46. Pavel AB, Zhou L, Diaz A, et al. The proteomic skin profile of moderate-to-severe
749 atopic dermatitis patients shows an inflammatory signature. J Am Acad Dermatol
750 2020; **82**(3): 690-9.
751 47. Kuruvilla ME, Lee FEH, Lee GB. Understanding Asthma Phenotypes, Endotypes, and
752 Mechanisms of Disease. Clin Rev Allergy Immunol. 2019;**56**(2):219–33.
753 48. Gabrijelcic J, Acuña A, Profita M, Paternò A, Chung KF, Vignola AM, et al. Neutrophil
754 airway influx by platelet-activating factor in asthma: Role of adhesion molecules and
755 LTB4 expression. Eur Respir J. 2003;**22**(2):290–7.
756 49. Araújo AC, Wheelock CE, Haeggström JZ. The Eicosanoids, Redox-Regulated Lipid
757 Mediators in Immunometabolic Disorders. Antioxidants Redox Signal.
758 2018;**29**(3):275–96.
759 50. Rossios C, Pavlidis S, Hoda U, Kuo CH, Wiegman C, Russell K, et al. Sputum
760 transcriptomics reveal upregulation of IL-1 receptor family members in patients with
761 severe asthma. J Allergy Clin Immunol. 2018;**141**(2):P560-570.
762 51. Uddin M, Nong G, Ward J, Seumois G, Prince LR, Wilson SJ, et al. Prosurvival activity
763 for airway neutrophils in severe asthma. Thorax. 2010;**65**(8):684–9.
764 52. Hekking PP, Loza MJ, Pavlidis S, de Meulder B, Lefaudeux D, Baribaud F, et al.
765 Pathway discovery using transcriptomic profiles in adult-onset severe asthma. J
766 Allergy Clin Immunol. 2018;**141**(4):1280–90.
767 53. Ogawa Y, Duru E, Ameredes B. Role of IL-10 in the Resolution of Airway Inflammation.
768 Curr Mol Med. 2008;**8**(5).
769 54. Takahashi K, Hirose K, Kawashima S, Niwa Y, Wakashin H, Iwata A, et al. IL-22
770 attenuates IL-25 production by lung epithelial cells and inhibits antigen-induced
771 eosinophilic airway inflammation. J Allergy Clin Immunol. 2011;**128**(5):P1067-1076.
772
773

Journal Pre-proof

774 **Table 1.** Clinical differences of predicted responders versus non-responders to Fezikinumab
775 in U-BIOPRED.
776

Characteristic	FZ Predicted Responders	FZ Predicted Non-Responders	p value
Total (n)	26	18	
Age (years)	51.8 (12.7)	55.3 (14)	NS
BMI	28 (4.65)	26.3 (3.39)	NS
Gender: Female (n)	16	9	NS
Severe asthma, non-smokers (n)	18	13	NS
Severe asthma, smokers/ex-smokers (n)	8	5	NS
Severe exacerbation in previous year	2.27 (2.38)	1.72 (2.02)	NS
Nasal polyps (n)	8	6	NS
Eczema (n)	8	7	NS
Allergic rhinitis (n)	9	4	NS
Non-allergic rhinitis (n)	5	3	NS
Gastro-esophageal reflux (n)	12	7	NS
Hay fever (n)	11	5	NS
Positive atopic status (n)	11	6	NS
ACQ5 score	2.44 (1.23)	1.79 (1.31)	NS
AQLQ score	4.35 (1.22)	4.98 (1.41)	NS
HADS score	12.3 (8.16)	10.5 (8.91)	NS
SNOT score	31.2 (18.2)	22.6 (10.8)	NS
FEV1 (% predicted)	63.7 (24.3)	67.2 (17.5)	NS
FVC (% predicted)	86.9 (20.4)	95.3 (17.4)	NS
FEV1/FVC	59.3 (13.1)	57.2 (8.79)	NS
FeNO (ppb)	35 (33)	54.7 (46.9)	NS
Serum IgE (IU/L)	204 (358)	332 (294)	0.02
Blood eosinophil (/10-9L)	0.277 (0.155)	0.401 (0.305)	NS
Blood neutrophil (/10-9L)	4.93 (1.93)	5.41 (2.44)	NS
Blood lymphocyte (/10-9L)	2.12 (0.936)	2.1 (0.9)	NS
Blood monocyte (/10-9L)	0.634 (0.278)	0.581 (0.222)	NS
Sputum neutrophils (%)	75.7 (16.6)	35.6 (18)	2.26E-08
Sputum eosinophils (%)	3.9 (5.55)	30.4 (26.5)	0.0009
Sputum lymphocyte (%)	1.5 (1.6)	1.46 (1.26)	NS
Sputum macrophage (%)	18.9 (14.4)	32.5 (20.8)	0.025
Sputum mast cell (%)	0.0346 (0.087)	0.0333 (0.101)	NS
Oral corticosteroid use daily (n)	12	9	NS
LABA use twice a day (n)	12	2	0.039

777 ACQ: Asthma Control Questionnaire; AQLQ: Asthma Quality of Life Questionnaire; BMI:
778 Body Mass Index; FEV1: Forced expiratory volume in one second; FVC: Forced vital capacity;
779 FeNO: Fractional exhaled nitric oxide; HADS: Hospital Anxiety and Depression Scale; ICS:

780 Inhaled corticosteroids; LABA: long-acting beta agonist; SNOT: SinoNasal Outcome Test.
781 Data shown as mean (Standard Deviation).
782
783

Journal Pre-proof

784 **Table 2.** Molecular marker differences of Predicted Responders versus Predicted Non-
785 Responders to Fezakinumab in the U-BIOPRED severe asthma patients.
786

Biomarker	FZ Predicted Responders	FZ Predicted Non-Responders	p value
α1 microglobulin (pg/ml) Luminex (serum)	6120 (2210)	7500 (2390)	NS
C5a (pg/ml) Luminex (serum)	50.8 (33.4)	38.9 (21.6)	NS
CD30 (pg/ml) Luminex (serum)	38.9 (17.1)	42.5 (14.7)	NS
CD40L (pg/ml) Luminex (serum)	4420 (1990)	5210 (2300)	NS
DPPIV (pg/ml) Luminex (serum)	98500 (48100)	91500 (24300)	NS
Galectin 3 (pg/ml) Luminex (serum)	5550 (2050)	5770 (1470)	NS
IL-18 (pg/ml) Luminex (serum)	247 (152)	234 (73.8)	NS
IL-1α (pg/ml) Luminex (serum)	35.5 (9.95)	36.2 (6.12)	NS
IL-6Rα (pg/ml) Luminex (serum)	10600 (2450)	10900 (2020)	NS
LBP (pg/ml) Luminex (serum)	2110000 (891000)	1820000 (668000)	NS
Lumican (pg/ml) Luminex (serum)	131000 (37000)	136000 (25300)	NS
MCP4 (pg/ml) Luminex (serum)	142 (44.7)	168 (71.2)	NS
MMP3 (pg/ml) Luminex (serum)	21400 (18300)	24500 (17900)	NS
RAGE (pg/ml) Luminex (serum)	1260 (414)	1320 (382)	NS
Serpin E1 (pg/ml) Luminex (serum)	95000 (30400)	97600 (19900)	NS
SHBG (pg/ml) Luminex (serum)	3640000 (2840000)	4780000 (4670000)	NS
CCL17 (pg/ml) MSD (plasma)	77.5 (70.8)	134 (120)	NS
CCL22 (pg/ml) MSD (plasma)	796 (316)	866 (218)	NS
EOTAXIN (pg/ml) MSD (plasma)	118 (60.1)	140 (67.6)	NS
EOTAXIN3 (pg/ml) MSD (plasma)	15 (15.4)	72.4 (130)	0.00097
IFNγ (pg/ml) MSD (plasma)	12.2 (12.8)	7.44 (6.18)	NS
IL-6 (pg/ml) MSD (plasma)	1.21 (1.01)	0.804 (0.335)	NS
IL-8 (pg/ml) MSD (plasma)	6.02 (9.75)	3.78 (1.86)	NS
IP10 (pg/ml) MSD (plasma)	386 (250)	305 (183)	NS
MCP1 (pg/ml) MSD (plasma)	117 (36.8)	119 (38.4)	NS
MIP1β (pg/ml) MSD (plasma)	56.1 (18.1)	63.5 (29.8)	NS
TNFα (pg/ml) MSD (plasma)	1.84 (0.483)	1.94 (0.632)	NS
CCL18 (pg/ml) IMPACT serum	169 (63.3)	228 (106)	NS
IL-13 (pg/ml) IMPACT serum	0.608 (0.494)	0.942 (0.384)	0.0074
IL-17A (pg/ml) SINGULEX serum	0.58 (0.381)	0.455 (0.258)	NS
Periostin (ng/ml) ELECSYS serum	51.2 (19.5)	54.2 (16.5)	NS
hCRP (mg/L)	6.29 (11)	1.69 (1.33)	NS
11-dehydroTXB$_2$ (ng/ml) urine	13.9 (8.96)	14.2 (10.5)	NS

Journal Pre-proof

2,3 dinor-11β PGF2α (ng/ml) urine	73.8 (30.9)	94.8 (86)	NS
2,3 dinor 8isoPGF2α (ng/ml) urine	244 (137)	296 (319)	NS
2,3 dinor TXB_2 (ng/ml) urine	68.1 (46.6)	52.2 (41.3)	NS
8,12 isoPGF2α (ng/ml) urine	386 (240)	430 (408)	NS
8 isoPGF2α (ng/ml) urine	29.3 (11.8)	32.3 (19.6)	NS
LTE_4 (ng/ml) urine	9.28 (8.35)	10 (6.13)	NS
PGE2 (ng/ml) urine	20.2 (23.2)	18.5 (14.8)	NS
PGF2α (ng/ml) urine	132 (102)	130 (75.1)	NS
Tetranor PGDM (ng/ml) urine	299 (115)	305 (257)	NS
tetranorPGEM (ng/ml) urine	1180 (1190)	1030 (539)	NS
11 dehydroTXB_2 (pg/mL) sputum	231 (283)	63.4 (23.9)	0.00438
12-HETE (pg/mL) sputum	1470 (1300)	1980 (1410)	NS
15-HETE (pg/mL) sputum	4490 (6900)	7180 (9130)	NS
5-HETE (pg/mL) sputum	1570 (1500)	964 (1630)	0.0322
6-ketoPGF1α (pg/mL) sputum	58.6 (27.1)	53.7 (23.6)	NS
LTB_4 (pg/mL) sputum	801 (756)	774 (1540)	NS
LTE_4 (pg/mL) sputum	319 (372)	763 (1030)	0.0312
PGD2 (pg/mL) sputum	269 (317)	174 (159)	NS
PGE2 (pg/mL) sputum	390 (363)	202 (135)	NS
Tetranor PGDM (pg/mL) sputum	66 (57.4)	54.8 (51.9)	NS
Tetranor PGEM (pg/mL) sputum	76.3 (49.1)	67.6 (53.3)	NS

787

Journal Pre-proof

Table 3. Top and bottom 20 differentially expressed sputum proteins that differentiate U-BIOPRED asthmatic FZ predicted responders (PRs) from predicted non-responders (PNRs) defined from asthma sputum GSVA FZ response signature ES which had sputum proteomic data available (see Supplementary Table 7, see Supplementary Figure 4). Genes are ranked according to log_2 fold change.

Upregulated

Gene Symbol	Log2 Fold Change	Fold Change	P value	FDR-BH adjusted P value
Siglec_9	2.04	4.11	0.0066	0.1928
Hemoglobin	1.98	3.96	0.01807	0.2210
PSA1	1.75	3.37	0.01409	0.2059
Cathepsin_G	1.70	3.25	0.00048	0.1368
Carbonic_anhydrase_I	1.45	2.74	0.00081	0.1370
SRCN1	1.43	2.70	0.00702	0.1928
Azurocidin	1.40	2.65	0.00251	0.1661
PLCG1	1.30	2.46	0.01068	0.2059
resistin	1.29	2.45	0.09375	0.3715
Factor_I	1.28	2.44	0.14821	0.4261
IL_6	1.28	2.43	0.00390	0.1869
B7_H2	1.19	2.29	0.04214	0.2830
Ferritin	1.18	2.27	0.0127	0.2059
IP_10	1.15	2.23	0.01319	0.2059
Elastase	1.08	2.12	8.53E-05	0.0959
Transferrin	1.06	2.09	0.16571	0.4476
OLR1	1.02	2.03	0.00309	0.1735
I_TAC	0.99	1.99	0.04652	0.2875
Granzyme_B	0.99	1.98	0.03350	0.2599
Esterase_D	0.97	1.96	0.06937	0.338

Downregulated

Gene Symbol	Log2 Fold Change	Fold Change	P value	FDR-BH adjusted P value
a2_Antiplasmin	-1.28	0.40	0.02414	0.2441
Fucosyltransferase_3	-1.29	0.40	0.28234	0.5445
PCSK9	-1.29	0.40	0.00876	0.2017
CATZ	-1.29	0.40	0.04350	0.2830
Kininogen_HMW	-1.37	0.38	0.08360	0.3495
IGFBP_4	-1.37	0.38	0.03957	0.2800
Cathepsin_B	-1.38	0.38	0.00473	0.1869
Phosphoglycerate_mutase_1	-1.46	0.36	0.0435	0.2830
Histone_H2A_z	-1.51	0.34	0.00838	0.2007
FETUB	-1.52	0.34	0.05755	0.3169
Clusterin	-1.55	0.34	0.00521	0.1892

Plasminogen	-1.56	0.33	0.00596	0.1928
amyloid_precursor_protein	-1.60	0.32	0.0251	0.2441
PCI	-1.62	0.32	0.01463	0.2079
Integrin_aVb5	-1.62	0.32	0.00678	0.1928
PTHrP	-1.65	0.31	0.00122	0.1370
CD39	-1.72	0.30	0.00039	0.1368
MIS	-1.73	0.30	0.00130	0.1370
PAPP_A	-1.76	0.29	0.01554	0.2079
Antithrombin_III	-2.31	0.20	0.00490	0.1869

794

Journal Pre-proof

795 **Figure legends**

796 **Figure 1.** Gene Set Variation Analysis (GSVA) showing enrichment scores (ES) of gene
797 signatures derived from genes up-regulated (UP) in lesional versus non-lesional tissue from
798 atopic dermatitis (AD). Disease signatures are derived from either the Brunner paper (AD-
799 UP, **A-D**) or from an AD meta-analysis-derived AD (MADAD, **E-H**). The ES for these signatures
800 in U-BIOPRED blood (**A, E**) and sputum (**B-D** and **F-H**) according to severity (**A, B, E, F**),
801 Transcriptome-Associated Cluster (TAC) (**C, G**) and sputum granulocyte subtype (**D, H**).
802 Between group adjusted p values are provided compared to HC values. *p<0.05, **p<0.01,
803 ***p<0.001 and ****p<0.0001). Abbreviations: HC; Healthy Control, MMA; Mild-Moderate
804 Asthma. SAs/ex; Severe Asthma smoker/ex-smoker. SAns; Severe Asthma non-smoker, P;
805 pauci-granulocytic, E; eosinophilic, N; neutrophilic and M; Mixed.

806

807 **Figure 2.** Gene Set Variation Analysis (GSVA) showing enrichment scores (ES) of
808 Fezakinumab (FZ) treatment response signatures of downregulated genes (FZ-DOWN) in
809 lesion versus non-lesional tissue from atopic dermatitis (AD). ES for AD-UP signatures are
810 given for U-BIOPRED blood (**A-C**) and sputum (**D-F**) according to asthma severity (**A, D**),
811 Transcriptome-Associated Clusters (TAC) (**B, E**) and granulocyte subtype (**C, F**). Between
812 group adjusted p values are provided compared to HC values. *p<0.05, **p<0.01,
813 ***p<0.001 and ****p<0.0001). Abbreviations: HC; Healthy Control, MMA; Mild-Moderate
814 Asthma. SAs/ex; Severe Asthma smoker/ex-smoker. SAns; Severe Asthma non-smoker, P;
815 Pauci-granulocytic, E; Eosinophilic, N; Neutrophilic and M; Mixed.

816

817 **Figure 3.** Gene Set Variation Analysis (GSVA) showing enrichment scores (ES) of gene
818 signatures derived from genes up-regulated (UP) in lesion versus non-lesional tissue from
819 atopic dermatitis (AD) in the ADEPT (Airway Disease Endotyping for Personalized
820 Therapeutics) cohort by granulocytic subtype. Disease signatures are derived from either
821 the Brunner paper (AD-UP, **A, upper panel**) or from an AD meta-analysis-derived AD
822 (MADAD, **A, lower panel**). ES of the Fezakinumab (FZ)-DOWN signature obtained from
823 lesional versus non-lesion tissue after 12 weeks treatment (**B**). Between group adjusted p
824 values are provided compared to HC values. *p<0.05. Abbreviations: HC; Healthy Control,
825 P; Pauci-granulocytic, E; Eosinophilic, N; Neutrophilic and M; Mixed.

826

827 **Figure 4.** Protein pathway analysis using ReactomePA of differentially-expressed genes
828 (false discovery rate, FDR<0.05) that distinguish asthmatic patients highly-enriched
829 (Predicted Responders, PRs) for the Fezakinumab (FZ)-response signature (FZ-DOWN) from
830 those poorly-enriched (Predicted Non-Responders, PNRs) for this signature.
831
832 **Figure 5.** Correlation of the transcriptomic enrichment score (ES) of the signature of genes
833 down-regulated by Fezakinumab (FZ) treatment (FZ-DOWN) in lesional samples from atopic
834 dermatitis patients against the ES of the Th22/IL-22 pathway genes in (A) sputum (B)
835 bronchial brushings and (C) nasal brushings of asthmatic subjects and against sputum IL-22
836 protein abundance in the sputum of asthmatic subjects (D). The correlation for sputum IL-22
837 protein was controlled for age, gender and body mass index.

Journal Pre-proof

Journal Pre-proof

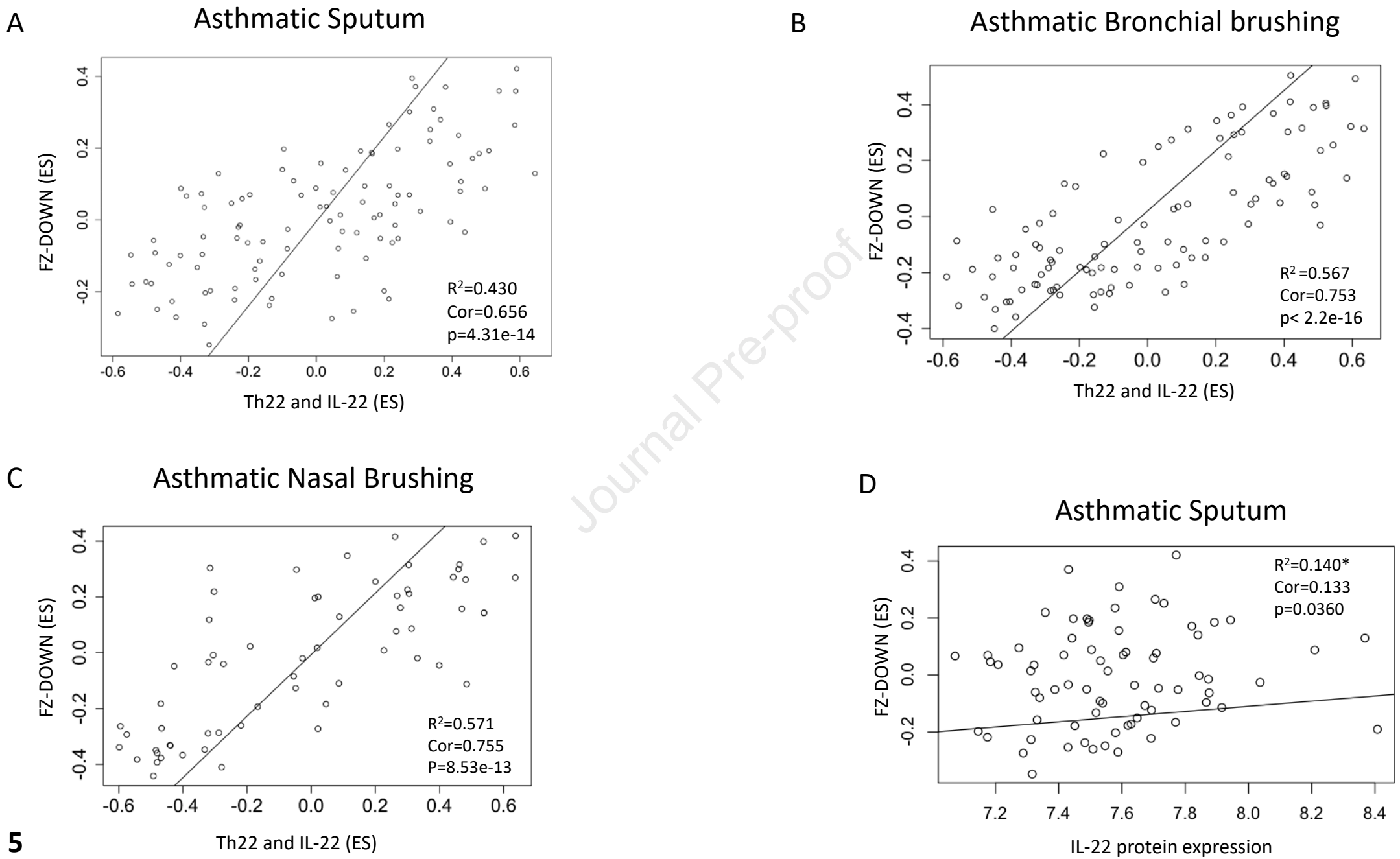


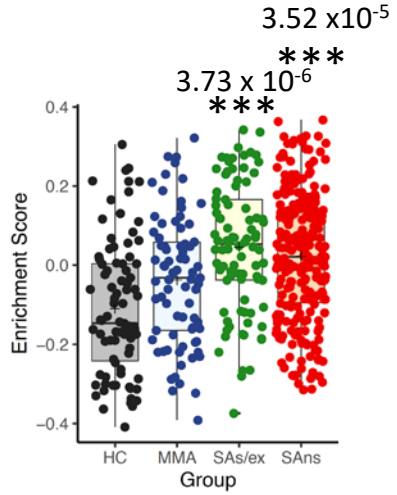
Figure 5

Journal Pre-proof

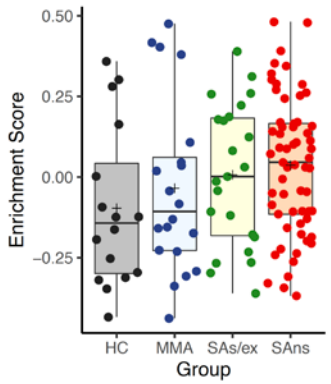
Journal Pre-proof

AD-UP

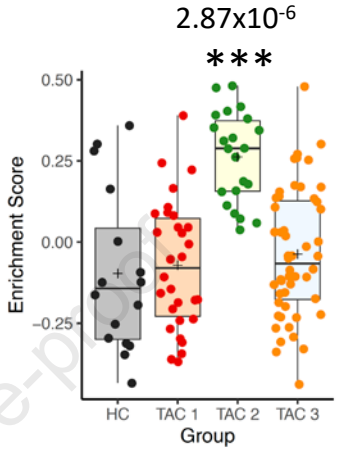
A Blood



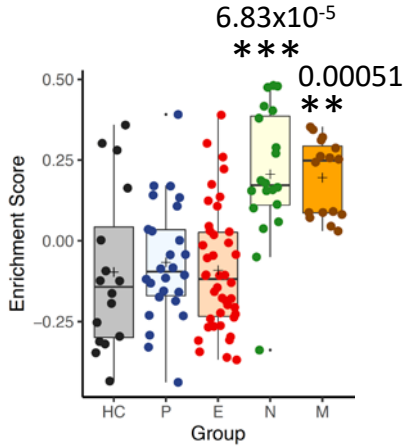
B Sputum



C Sputum

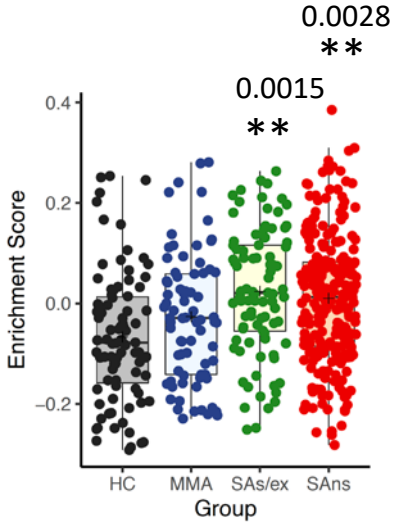


D Sputum

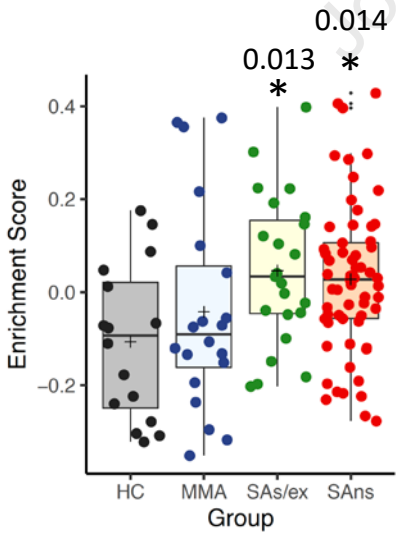


MADAD-UP

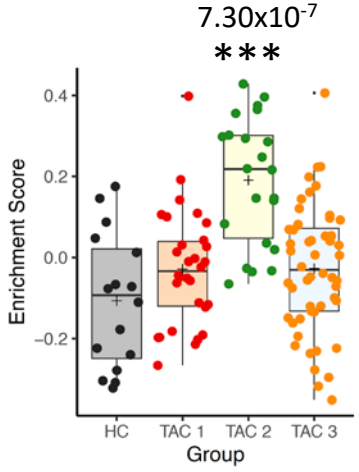
E Blood



F Sputum



G Sputum



H Sputum

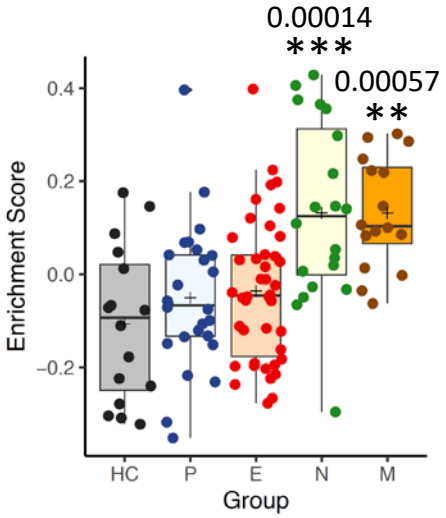


Figure 1

Journal Pre-proof

FZ-DOWN signature

Blood

Sputum

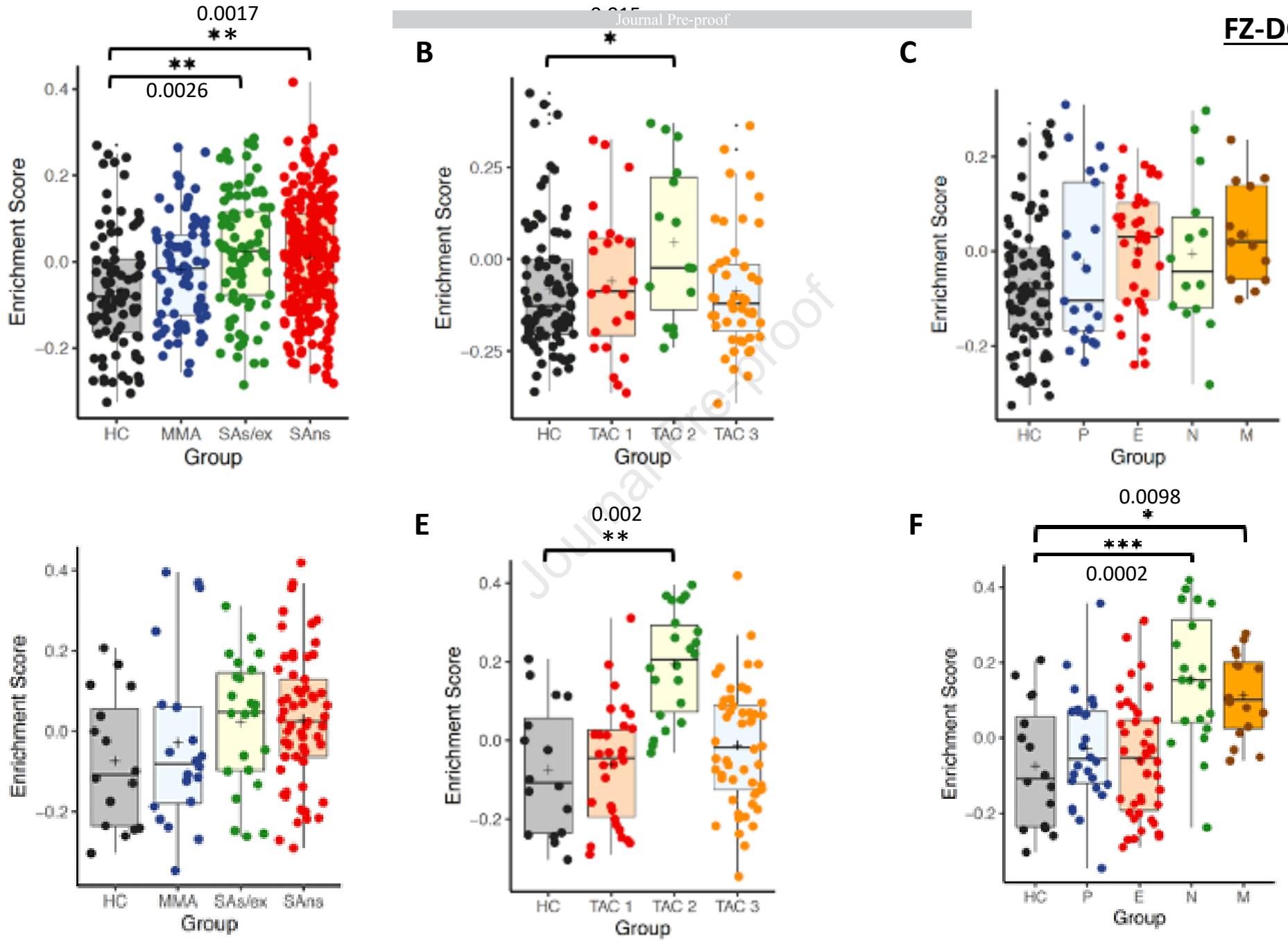
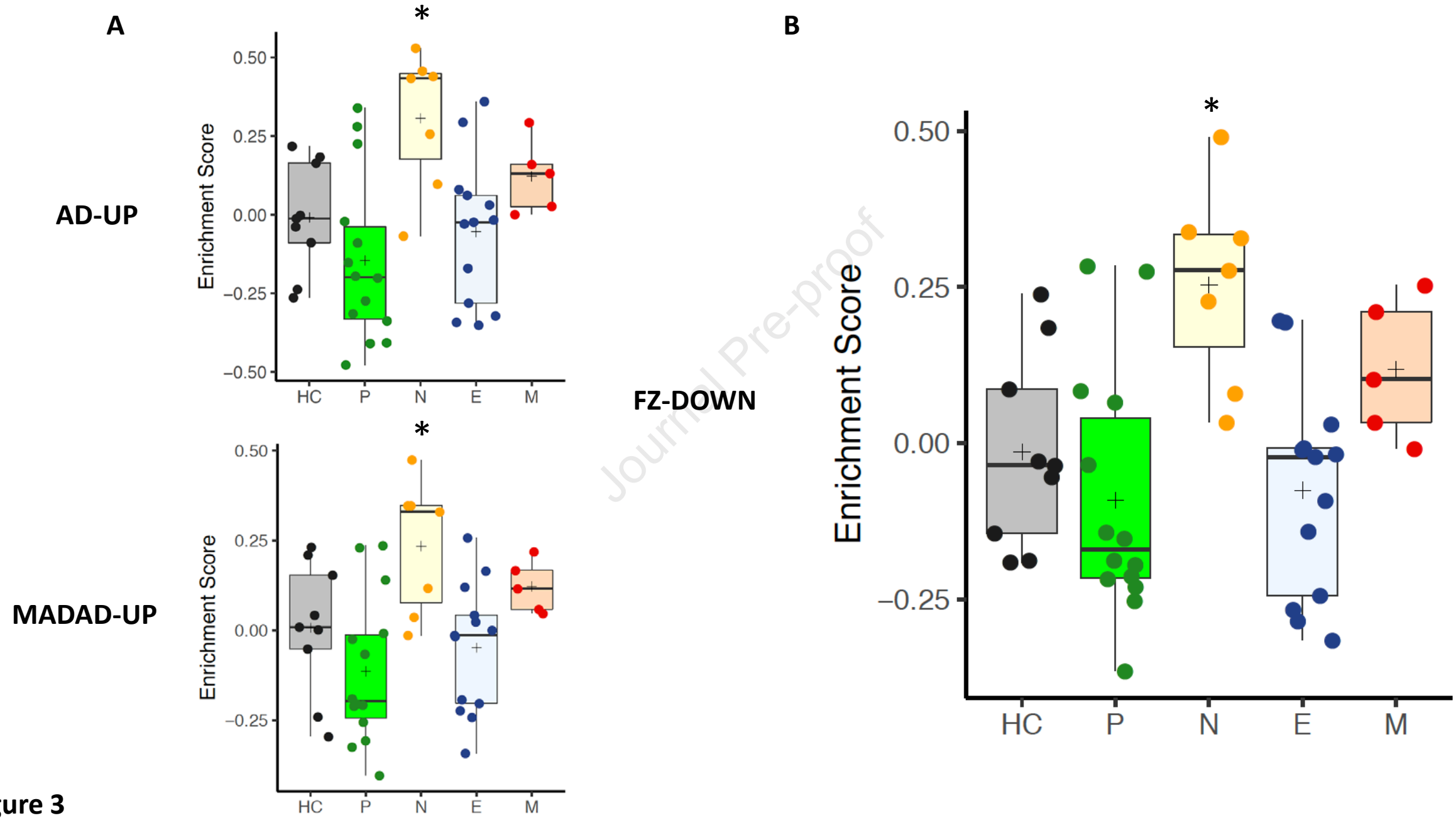


Figure 2

Journal Pre-proof



Journal Pre-proof

Figure 3

Journal Pre-proof

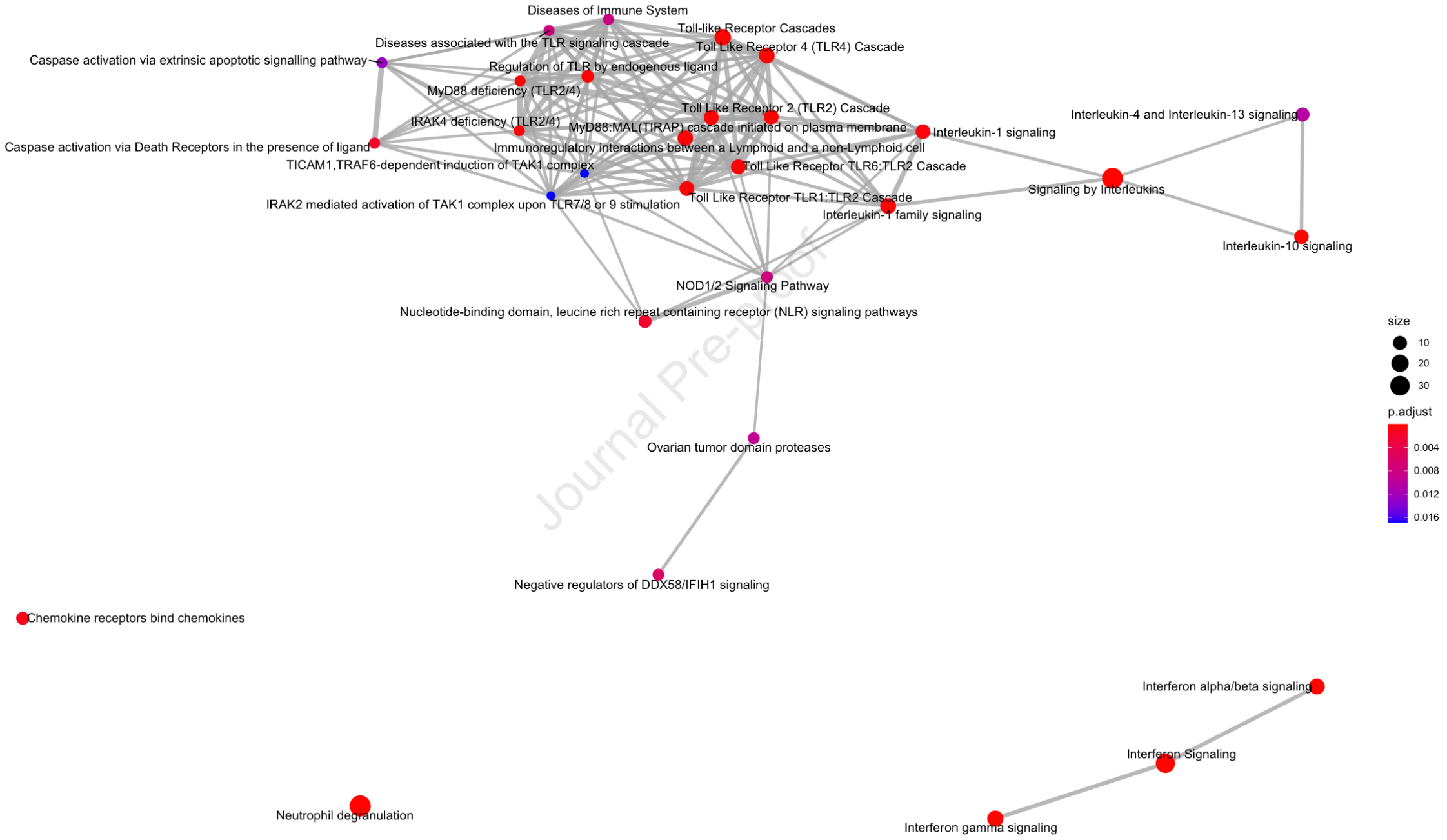


Figure 4

Journal Pre-proof

Supplementary data

Mapping atopic dermatitis and anti-IL-22 response signatures to Type 2-low asthma

Yusef Eamon Badi[1,2], *Ana B. Pavel[3,4], **Stelios Pavlidis[2], John H Riley[5], Stewart Bates[5], Nazanin Zounemat Kermani[2], Richard Knowles[6], Johan Kolmert[7,8], Craig E. Wheelock[8], Sally Worsley[4], Mohib Uddin[9], Kjell Alving[10], Per S Bakke[11], Annelie Behndig[12], Massimo Caruso[13], Pascal Chanez[14], Louise J Fleming[1], Stephen J Fowler[15], Urs Frey[16], Peter Howarth[17], Ildikó Horváth[18], Norbert Krug[19], Anke-Hilse Maitland[20], Paolo Montuschi[21], Graham Roberts[17], Marek Sanak[22], Dominick E Shaw[23], Florian Singer[24], Peter J Sterk[20], Ratko Djukanovic[17], Sven-Eric Dahlen[7], Yi-Ke Guo[2], Kian Fan Chung[1], Emma Guttman-Yassky[3], Ian M. Adcock[1] on behalf of the U-BIOPRED study group[#]

Journal Pre-proof

Supplementary Table 1. Gene signatures

Signature name	Gene list	Reference
Brunner AD disease signature UP	S100A9 OASL C10orf99 AKR1B10 PRSS53 LINC01094 TEX101 TMPRSS4 SERPINB4 TRIM10 SERPINB3 KRT16 S100A8 CLEC7A KYNU SPRR2C IGFL1 S100A7A PI3 TFEC SERPINB13 EPSTI1 TCN1 FBN2 CCNA2 PTPRC SELL SAMSN1 HAS3 ICOS IL7R GZMB NELL2 CD274 CTLA4 RGS1 MMP12 LGALS2 CXCL2 CD2 DSC2 PI15 LILRB2 CST7 SERPINA1 COL6A5 GPR65 SASH3 RGS18 CXCL1 COL6A6 COL4A4 MMP1 GALNT6 DPY19L1 SPC25 BATF3 OAS2 PLAU STEAP4 RTP4 PLAC8 UBD ICAM1 SLAMF7 BCL2A1 UPP1 ADAM23 ITGAX CLEC4A LAIR2 GNLY CFB CYTIP SNX20 CH25H SAMD9L IL2RG ADAM19 ADAM8 MNDA XCL1 ST8SIA4 IL24 CCL5 XCL2 CD52 SELE CYP27B1 JAML IL15 JAK3 MIR155HG GPRIN3 IFI44 TNFAIP6 PIK3R5 IL13RA2 FAM129C MARK1 ARHGAP9 PRKCQ PLXDC1 RUBCNL TNC CD47 APELA ADAMTS12 CPXM1SPINK6 KLHL6 TDO2	1
Brunner AD disease signature DOWN	AGFG2 IL34 C5orf46 SCIN ARFGEF3 SYNE1 CPEB3 LOC284578 CHPT1 ST6GAL2 GPLD1 PNPLA3 SEMA3E LOC100996902 C1QTNF7 MFSD4A PSORS1C2 MACROD2 SCGB2A1 WIF1 FMO5 ZNF254 FABP7 MYOT FOLR1 NELL1 BTC PHYHIP IL37	1
MADAD UP signature	DEFB4A DEFB4B SERPINB4 S100A9 SERPINB3 MMP1 S100A7A IGFL1 MMP12 AKR1B10 C10orf99 PI3 OASL TMPRSS4 DSC2 GZMB SERPINB13 FOSL1 LCE3D SPRR2D SPRR2B SELE ARNTL2 SPRR3 SPRR1A COL4A4 CLEC7A COL6A5 CXCL10 CCL18 HPSE S100A8 RRM2 IL36G APELA NR4A3 PRSS53 APOBEC3A APOBEC3A_B KRT16 COL6A6 RGS1 EPSTI1 KLHDC7B HAS3 CXCL1 GALNT6 DLGAP5 CD274 CTLA4 CD1B SLAMF7 CEP55 LTF ASPM KIF4A MKI67 SLC2A1 CH25H ZBED2 GPR171 SAMSN1 KIF20A CDCA2 SPRR1B CENPE CXCL8 CCL22 S100A7 BUB1 RTP4 RGS20 NETO2 TRIP13 APOBEC3B CDK1 PKP1 PRKCQ IVL CDKN3 BCL2A1 TYMP ISG20 FCHSD1 IL7R SLC26A9 LGALS2 OAS2 NAPSB MMP9 CASC5 KIAA0101 RAB27A CST7 GPRIN1 TTC39A TGM1 INA VMP1 MIR21 CCL17 BLM NDC80 UGT1A1 UGT1A10 UGT1A8 UGT1A7 UGT1A6 UGT1A5 UGT1A9 UGT1A4 UGT1A3 MIR155HG MIR155 CXCL2 IL13RA2 CD28 CYTIP PRSS27 KLK8 KLK9 ITK NUF2 MPZL2 BIRC5 PI15 HMMR MXD1 HS3ST3A1 PRKCQ-AS1 MIAT ADAM19 GZMA SH3PXD2A-AS1 GPR183 BATF3 CNFN KIF14 SOCS3 AURKA IRF7 LCK NCAPG CENPF WNT5A OAS3 PRR11 PCDH7 MELK CDCA5 MOXD1 CCL26 KYNU MS4A14 SELL LTB KCNJ15 ANGPTL4 TNC CCNB1 STAT1 CCL2 SERPINA1 SASH3 ADAM8 IL36RN RSAD2 SMC4 IFI44 FOSB IRF1 CEMIP CD2 TEX101 TMEM45B F12 CCNB2 UBD GABBR1 C12orf56 PTPN7 ECT2 KLK10 PLAUR SPC25 FAM83A PLAU WWTR1 POLQ C9orf84 FGFBP1 SFT2D2 FPR1 C21orf91 SPTLC2 IL18RAP CCR7 CCL13 DSG3 PTPRC TOP2A KIF2C KIAA1644 SPRR2C CDC20 ASF1B SNX20 LINC01094 UBE2T CXorf65 CD3D TTK LILRB2 CCNA2 CENPA SLC35F6 HERC6 IL12RB1 SLC28A3 HBEGF CLEC10A OAS1 POLR3G IL2RG CDH3 XCL2 XCL1 CCL5 TNFRSF12A KRT6A MIR142 BUB1B NUSAP1 CYP27B1 CACNB4 ADAMDEC1 DIAPH3 SCO2 ADAM10 CD69 TIFAB PML MX1 SLC5A1 SLAMF1 CORO1A C12orf29 C12orf5 SAMD9 UBE2C DNASE1L3 ZC3H12A MIR6732 NEIL3 SLFN5 CKAP2L KRT6B P2RY1 P2RY2 FAS PLXDC1 LRP8 HJURP	2

	IL12RB2 PIK3CG ADAM23 THBD DEFB103B DEFB103A FAM124B FAM26F ITGAX LCN2 NAPG CHEK1 MNDA FOXM1 AIM2 SLAMF8 NUP50 IL4R FAIM3 CXADR ZBED6CL PBK PARVG CA2 GTSE1 DCAF8 GNLY GPSM3 SH3TC1 MND1 PARP9 STK17B KLK13 TAGAP AREG RALGPS2 CPEB2 CENPN CENPW HCK KLRB1 LOC100288860 HAL GK LCP2 01-Mar JAK3 MMP3 DEPDC1B SH2D5 C17orf96 FAM111B TBC1D10C LMNB2 FYB ITGAL CD1E RIT1 DUOXA1 MYO1B PHF19 UBE3C CCNE1 GNA15 KLRK1 KLRC4-KLRK1 IQGAP3 GBP1 SAMD9L KIF18B TFEC PDPN PTAFR PGF SYNCRIP ADAP2 SMOX CFB NOD2 CDT1 IL23A TRBC1 FLVCR2 ELL2 CDK5R1 MFHAS1 STAM2 LYN MMP19 DCTN5 THBS1 TPX2 E2F7 DCANP1 XAF1 CCL8 RELB MCOLN2 CHI3L2 GPR65 DPP4 ICOS ARHGAP9 AMD1 ACPP TRAT1 CCL19 ISG15 NDC1 ACAP1 CTSC PNPT1 PTX3 CD48 CDCA3 TK1 PIK3R5 FPR3 IFI27 TGM3 RAD51AP1 VSNL1 CXCL11 PLAGL2 CDC45 IL27RA MAP4K1 CD6 RASGRP1 SELPLG SNHG3 SNORA73A POC1A THAP2 LAMP3 UBA6 PRDM1 ZC3H12D RNF144B TMC5 PPP2R2C C15orf48	
MADAD DOWN Signature	LMOD1 MYRIP KIAA1324 RORC SLC13A2 FAXDC2 NALCN MEGF10 SEMA3E FAM189A2 LOC100507311 CYP2J2 ZNF471 LINC00663 AQP5 PRKAA2 TRHDE-AS1 GPRC5A CEACAM6 TIMP3 TMC4 FASN AWAT1 SHROOM3 RHPN2 SEMA3B MIR6872 AR SERHL2 SERHL ERBB4 PLCB4 SORBS2 KLRG2 KCNIP2 FGF1 ACVR1C IL20RA SSPN COCH EFHD1 FOXC1 LOC100507557 SYT17 EDAR PIP KRT77 GPRASP1 CA6 TLN2 C1orf95 NSUN7 MOGAT1 NEDD4L SCGB2B2 MAPT ATP6V1B1 CHRM3 CALB2 HSPB6 KRT19 CASQ2 FHL1 COPG2 COPG2IT1 CLIC5 MAP6 PER1 MIR6883 SNCA MUC20 PPARG MIR181A2HG GALNT15 OBP2B OBP2A SH3BGRL2 HRCT1 PPARGC1A CORO2B PSORS1C2 GYG2 GCHFR TRIM2 ACOX2 MRAP SLITRK4 TUSC5 CNKSR2 GPC4 FMO5 SCN7A ADH1B FST C14orf180 CD300LG SCIN MGST1 PLEKHB1 PRB1 STK32A SHANK2 ALDH1A2 LOC101928635 CES1 ATP6V0A4 CKMT2 TG DGAT2 ID4 C2orf40 MFSD4 SCGB1D2 ACADL GSTM5 RNF150 RNF128 LPL RERGL ATP1A2 PDK3 PNPLA3 ABHD12B MIR4454 GPAM C1orf115 MACROD2 FRZB MYBPC1 FA2H PRR4 PRH1-PRR4 VTCN1 SYNE1 BTNL9 TMEM56 PTCSC1 MUC7 ESRRG MYH11 C5orf46 ARFGEF3 HIF3A SGCG PRR15L LGALS12 FAR2 ACOT2 ACOT1 BPY2 PPP1R1B CFTR ALDH1L1 FADS1 MIR1908 KLB YBX2 MSMB ADAMTS9-AS2 01-Mar LGR5 ATP13A5 NR3C2 SGK2 PLEKHA6 AQP7 LOC100509620 LOC101930168 PON3 CUX2 PPP1R1A TMEM132C C1QTNF7 SYN2 ANGPTL7 CIDEA MYEOV ENPP5 ADIPOQ TSPAN8 FABP4 TMEM139 IL37 TF ADRB1 FADS2 RBP4 FGFBP2 LOC284578 C9orf152 FOLR1 HSPB7 MYOC TNMD THRSP PHYHIP GPD1 HAO2 GPIHBP1 CYP4F8 CLDN8 CIDEC SLC14A1 ELOVL3 WDR72 HMGCS2 TIMP4 ZBTB16 PLIN4 SCGB2A1 KANK4 LEP FABP7 PLIN1 GAL KRT79 BTC WIF1 HSD11B1 PM20D1	2
High IL-22 FZ response signature UP	CD300LG FOXC1 CLCNKB HIF3A FOXP2 ADAMTS9-AS2 FBXL13 LOC284578 SORBS2 SNRPN LINC01091 ZNF208 CAPN6 TG FRZB SLC17A7 LMO3 SSPN TRIL NR3C2 GLRB PHYHIP HSD11B1 RUNX1T1 WNT2 GSTM5 GAS2 TPM1 ESRRG KRT7 ADGRL3 CRISP2 GPRC5A SHANK2 ADAM22 ERBB4 TF SPDEF CHRM3 CLDN8 SCAI	1

	TSHR PLA2G5 MUC7 OGN PRR15L FA2H NDNF VTCN1 TGFB2 CNTNAP3P2 IL37 ALDH6A1 KIAA1324 PRND ISYNA1 CRISPLD1 KIAA1549 MMP16 RASD2 ROPN1 FZD8 H19 PPP1R1B LONRF2 PRICKLE1 COL8A1 TMC4 LRRN1 NEDD4L GPC6 WDR72 MYEOV TMEM139 ENPP5 FARP1 PPP1R9A TET1 DACH1 CNTN4 CNKSR2 PRRG3 PLEKHA6 THRSP STK32A C9orf152 B3GALT5 FREM2 KLRG2 ZNF582-AS1 ARFGEF3 PCDH20 SNORD114-3 MIR181A2HG MEGF10 RASSF6 HAND2-AS1 GRIA2 PRDM6 IL34 SLC25A36 GPIHBP1 PRKAA2 SLC26A7 ZNF542P C1QTNF7 HS3ST6 NEGR1 TMEM213 CPEB3 FLG-AS1 TBX18 PTPN14 EBF2 TBXA2R C5orf46 BTC AGFG2 ST6GAL2 PAK3 TMEM56	
High IL-22 FZ response signature DOWN	CLEC7A SAMSN1 SRGN MX1 CFB IRF1 LYN ICAM1 S100A8 RGS1 PLEK S100A9 PI3 IL2RG KYNU IFI6 CXCL1 MMP1 SELL CD52 SASH3 MNDA OAS2 LCP2 LRP8 GPR183 CD3E GZMA TCN1 OAS1 OASL CD2 UBD IL13RA2 SELE XCL1 CCL13 IGSF6 CD28 AKR1B10 TFEC PTPRC DEFB4A LGALS2 SPRR2D CORO1A IFI35 CYTIP SERPINB3 KRT16 GOSR2 CCL19 SH2D1A CST7 GZMB SERPINB4 ICOS PLAUR ITK CERKL PRSS53 XCL2 FAS SERPINB13 OAS3 TMPRSS4 RTP4 IL36G BATF3 ZNF557 TRIM10 CLEC4A CYLD HAS3 RGS18 TEX101 LCE3D IL7R ALYREF MIAT IKZF1 CD274 EPSTI1 JAK3 C10orf99 GALNT6 MIR155HG LINC01094 PRKCQ-AS1 S100A7A MTFR2 LINC01215 CTLA4 TIFAB SLAMF1 IGFL1 RSAD2 ST8SIA4 CCL18 CYP2E1 IL12RB1 WFDC12 PDZK1IP1 ACTR2 UBE3C ABCD3 PLA2G4D NAMPT ITGB2 SYNCRIP TYR MS4A4A LYZ CDKN3 MYRFL FAM111B SH3PXD2A-AS1 LOC100506411 NOP56 SLC2A1 TOP2A PPIF SMC4 LTF BIRC5 GBP1 CCNB2 SERPINA1 CXCL8 SPTLC2 FBN2 CDK1 CCNA2 BUB1B DLGAP5 MPZL2 CXCL9 MMP9 NDC80 FOSL1 INA SAMHD1 UGT1A9 CXCL10 MMP12 CCL5 TTK MELK LCK CENPE CCR1 CHEK1 CCL20 PLAU GNLY DSG3 BCL2A1 CD86 BLM CD8A KLK13 S100A12 S100A7 TGM3 TGM1 UGT1A6 P2RY2 SLC5A1 APOBEC3B ZNF165 CD1B RAB27B UGT1A1 ATP12A CENPF CCL22 CCL17 CYP2C18 UGT1A3 STAT3 RAB27A BUB1 CD24 RRM2 RIT1 SPC25 PRKCQ NAPG TPX2 KCNJ15 RGS20 LILRB2 CXCL11 CHRNA3 CSF2RA BIRC3 TTC39A APOBEC3A IL13RA1 MKI67 VEGFA LCN2 JMJD6 CEBPD CHI3L2 DOCK2 CD3D CASP4 CCL8 FUT3 CCNB1 SOD2 YME1L1 HTR3A TRAT1 TYMP RAB31 CEP55 NCAPG KIF20A PLAC8 RHOF TIGAR PBK SLAMF7 HERC6 HPSE CENPN TMC5 DHRS9 ASPM HS3ST3A1 CARD14 ARNTL2 SPRR2C C21orf91 ANGPTL4 IL26 UGT1A8 GPATCH4 RBM8A PLBD1 DTL NETO2 FLVCR2 EHF XPO5 CDCA3 NUF2 LYAR MCM10 MND1 SNHG12 DEFB103B FAM83D RPS16 TMEM45B CDCA2 FCHSD1 ARHGAP9 PTAFR ZBED6CL RAB7A GPRIN1 NAPSB C17orf96 DDIAS LRG1 DIAPH3 CKAP2L S1PR5 DUOXA2 DSC2 PRSS27 GRHL3 SULF2 KLK8 RNASE7 DENR LEO1 PANX1 RNF144B LYPD5 KLHDC7B KIF14 ULBP2 FAM83A LINC01214 LOC101927972 EPHA1 PPARD SLC26A9 RALGPS2 HBEGF TEAD4 STAT1	1
IL-22/Th22 signature gene list	AHR CALML5 CCR10 FLG IL22 IL32 KRT1 KRT10 LOR S100A7 S100A8 S100A9 S100P SERPINB1 SERPINB4 S100A12	1

Supplementary Table 2. ReactomePA pathway enrichment FZ-DOWN signature. P values adjusted by FDR-BH with cutoff <0.05.

ID	Description	Gene Ratio	Bg Ratio	P value	p. djust	Q value	geneID	Count
R-HSA-6783783	Interleukin-10 signaling	12/212	47/10554	8.90E-11	3.03E-08	2.68E-08	ICAM1/CXCL1/CCL19/CXCL8/CXCL10/CCL5/CCR1/CCL20/CD86/CCL22/STAT3/PTAFR	12
R-HSA-380108	Chemokine receptors bind chemokines	12/212	48/10554	1.16E-10	3.03E-08	2.68E-08	CXCL1/XCL1/CCL13/CCL19/XCL2/CXCL8/CXCL9/CXCL10/CCL5/CCR1/CCL20/CXCL11	12
R-HSA-449147	Signaling by Interleukins	33/212	462/10554	1.61E-10	3.03E-08	2.68E-08	LYN/ICAM1/IL2RG/CXCL1/MMP1/IL13RA2/CCL19/IL36G/IL7R/JAK3/IL12RB1/ITGB2/BIRC5/CXCL8/MMP9/CXCL10/CCL5/LCK/CCR1/CCL20/CD86/S100A12/CCL22/STAT3/CSF2RA/IL13RA1/VEGFA/LCN2/CEBPD/SOD2/IL26/PTAFR/STAT1	33
R-HSA-6785807	Interleukin-4 and Interleukin-13 signaling	16/212	108/10554	3.98E-10	5.59E-08	4.95E-08	ICAM1/IL2RG/MMP1/IL13RA2/JAK3/ITGB2/BIRC5/CXCL8/MMP9/CCL22/STAT3/IL13RA1/VEGFA/LCN2/CEBPD/STAT1	16
R-HSA-6798695	Neutrophil degranulation	29/212	479/10554	9.37E-08	1.02E-05	9.04E-06	S100A8/S100A9/CXCL1/SELL/MNDA/TCN1/PTPRC/SERPINB3/PLAUR/ACTR2/ITGB2/LYZ/LTF/SERPINA1/MMP9/PLAU/S100A12/S100A7/RAB27A/LCN2/DOCK2/RAB31/PLAC8/RHOF/HPSE/ARHGAP9/PTAFR/RAB7A/LRG1	29
R-HSA-909733	Interferon alpha/beta	11/212	69/10554	1.08E-07	1.02E-05	9.04E-06	MX1/IRF1/IFI6/OAS2/OAS1/OASL/IFI35/OAS3/RSAD2/SAMHD1/ST	11

Journal Pre-proof

	signaling						AT1	
R-HSA-6803157	Antimicrobial peptides	12/212	97/10554	5.02E-07	4.03E-05	3.57E-05	S100A8/S100A9/PI3/DEFB4A/S100A7A/LYZ/LTF/GNLY/S100A7/LCN2/DEFB103B/RNASE7	12
R-HSA-2514853	Condensation of Prometaphase Chromosomes	5/212	11/10554	1.30E-06	9.17E-05	8.13E-05	SMC4/CCNB2/CDK1/CCNB1/NCAPG	5
R-HSA-2500257	Resolution of Sister Chromatid Cohesion	12/212	124/10554	6.98E-06	0.00043	0.00038	BIRC5/CCNB2/CDK1/BUB1B/NDC80/CENPE/CENPF/BUB1/SPC25/CCNB1/CENPN/NUF2	12
R-HSA-913531	Interferon Signaling	15/212	197/10554	9.82E-06	0.00051	0.00045	MX1/IRF1/ICAM1/IFI6/OAS2/OAS1/OASL/IFI35/OAS3/TRIM10/RSAD2/GBP1/SAMHD1/PTAFR/STAT1	15
R-HSA-388841	Costimulation by the CD28 family	9/212	70/10554	1.01E-05	0.00051	0.00045	LYN/CD3E/CD28/ICOS/CD274/CTLA4/LCK/CD86/CD3D	9
R-HSA-877300	Interferon gamma signaling	10/212	92/10554	1.48E-05	0.00069	0.00061	IRF1/ICAM1/OAS2/OAS1/OASL/OAS3/TRIM10/GBP1/PTAFR/STAT1	10
R-HSA-9020958	Interleukin-21 signaling	4/212	10/10554	3.02E-05	0.00130	0.00115	IL2RG/JAK3/STAT3/STAT1	4
R-HSA-68877	Mitotic Prometaphase	14/212	198/10554	4.46E-05	0.00179	0.00158	SMC4/BIRC5/CCNB2/CDK1/BUB1B/NDC80/CENPE/CENPF/BUB1/SPC25/CCNB1/NCAPG/CENPN/NUF2	14
R-HSA-156588	Glucuronidation	5/212	25/10554	0.00011	0.00424	0.00376	UGT1A9/UGT1A6/UGT1A1/UGT1A3/UGT1A8	5
R-HSA-141424	Amplification of signal from the	9/212	96/10554	0.00012	0.00424	0.00376	BIRC5/BUB1B/NDC80/CENPE/CENPF/BUB1/SPC25/CENPN/NUF2	9

Journal Pre-proof

	kinetochores							
R-HSA-141444	Amplification of signal from unattached kinetochores via a MAD2 inhibitory signal	9/212	96/10554	0.00012	0.00424	0.00376	BIRC5/BUB1B/NDC80/CENPE/CENPF/BUB1/SPC25/CENPN/NUF2	9
R-HSA-1433557	Signaling by SCF-KIT	6/212	43/10554	0.00020	0.00626	0.00554	LYN/MMP9/LCK/CHEK1/STAT3/STAT1	6
R-HSA-451927	Interleukin-2 family signaling	6/212	44/10554	0.00022	0.00675	0.00598	IL2RG/JAK3/LCK/STAT3/CSF2RA/STAT1	6
R-HSA-69620	Cell Cycle Checkpoints	16/212	293/10554	0.00027	0.00772	0.00684	BIRC5/CCNB2/CDK1/CCNA2/BUB1B/NDC80/CENPE/CHEK1/BLM/CENPF/BUB1/SPC25/CCNB1/CENPN/NUF2/MCM10	16
R-HSA-418594	G alpha (i) signalling events	19/212	396/10554	0.00038	0.0104	0.00920	RGS1/CXCL1/LRP8/GPR183/CCL13/AKR1B10/CCL19/RGS18/CXCL8/CXCL9/CXCL10/CCL5/CCR1/CCL20/PRKCQ/RGS20/CXCL11/DHRS9/S1PR5	19
R-HSA-69618	Mitotic Spindle Checkpoint	9/212	112/10554	0.00041	0.0105	0.00932	BIRC5/BUB1B/NDC80/CENPE/CENPF/BUB1/SPC25/CENPN/NUF2	9
R-HSA-375276	Peptide ligand-binding receptors	12/212	190/10554	0.00044	0.0105	0.00932	CXCL1/XCL1/CCL13/CCL19/XCL2/CXCL8/CXCL9/CXCL10/CCL5/CCR1/CCL20/CXCL11	12
R-HSA-5663220	RHO GTPases Activate Formins	10/212	138/10554	0.00045	0.0105	0.00932	BIRC5/BUB1B/NDC80/CENPE/CENPF/BUB1/SPC25/CENPN/NUF2/DIAPH3	10
R-HSA-202433	Generation of second messenger	5/212	33/10554	0.00046	0.0105	0.00932	LCP2/CD3E/ITK/LCK/CD3D	5

Journal Pre-proof

	molecules							
R-HSA-389513	CTLA4 inhibitory signaling	4/212	21/10554	0.00072	0.0157	0.0139	LYN/CTLA4/LCK/CD86	4
R-HSA-373076	Class A/1 (Rhodopsin-like receptors)	16/212	324/10554	0.00082	0.0172	0.0153	CXCL1/GPR183/XCL1/CCL13/CCL19/XCL2/CXCL8/CXCL9/CXCL10/CCL5/CCR1/CCL20/P2RY2/CXCL11/PTAFR/S1PR5	16
R-HSA-202427	Phosphorylation of CD3 and TCR zeta chains	4/212	22/10554	0.00087	0.0175	0.0155	CD3E/PTPRC/LCK/CD3D	4
R-HSA-389948	PD-1 signaling	4/212	23/10554	0.00103	0.0201	0.0178	CD3E/CD274/LCK/CD3D	4
R-HSA-6809371	Formation of the cornified envelope	9/212	129/10554	0.00114	0.0215	0.0191	PI3/SPRR2D/KRT16/LCE3D/DSG3/KLK13/TGM1/DSC2/KLK8	9
R-HSA-198933	Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell	9/212	132/10554	0.00135	0.0245	0.0217	ICAM1/SELL/CD3E/SH2D1A/ITGB2/CD8A/CD1B/CD3D/SLAMF7	9
R-HSA-69273	Cyclin A/B1/B2 associated events during G2/M transition	4/212	25/10554	0.00143	0.0245	0.0217	CCNB2/CDK1/CCNA2/CCNB1	4
R-HSA-8854691	Interleukin-20 family signaling	4/212	25/10554	0.00143	0.0245	0.0217	JAK3/STAT3/IL26/STAT1	4
R-HSA-389359	CD28 dependent Vav1 pathway	3/212	12/10554	0.00153	0.0247	0.0219	CD28/LCK/CD86	3
R-HSA-9020558	Interleukin-2 signaling	3/212	12/10554	0.00153	0.0247	0.0219	IL2RG/JAK3/LCK	3
R-HSA-75035	Chk1/Chk2(Cds1)	3/212	13/10554	0.00196	0.0307	0.0272	CDK1/CHEK1/CCNB1	3

Journal Pre-proof

	mediated inactivation of Cyclin B:Cdk1 complex							
R-HSA-162658	Golgi Cisternae Pericentriolar Stack Reorganization	3/212	14/10554	0.00246	0.0365	0.0324	CCNB2/CDK1/CCNB1	3
R-HSA-8983432	Interleukin-15 signaling	3/212	14/10554	0.00246	0.0365	0.0324	IL2RG/JAK3/STAT3	3
R-HSA-202403	TCR signaling	8/212	119/10554	0.00270	0.0390	0.0345	LCP2/CD3E/PTPRC/ITK/LCK/PRKCQ/CD3D/TRAT1	8
R-HSA-2219530	Constitutive Signaling by Aberrant PI3K in Cancer	6/212	71/10554	0.00295	0.0416	0.0368	CD28/ICOS/LCK/CD86/TRAT1/HBEGF	6

Journal Pre-proof

Supplementary Table 3. ReactomePA pathway enrichment FZ-UP signature. P values adjusted by FDR-BH with cutoff <0.2.

ID	Description	Gene Ratio	Bg Ratio	P value	p. adjust	Q value	geneID	Count
R-HSA-1250342	PI3K events in ERBB4 signaling	2/60	10/10554	0.00138	0.108	0.102	ERBB4/BTC	2
R-HSA-163125	Post-translational modification: synthesis of GPI-anchored proteins	4/60	92/10554	0.00181	0.108	0.102	PRND/CNTN4/GPIHBP1/NEGR1	4
R-HSA-8847993	ERBB2 Activates PTK6 Signaling	2/60	13/10554	0.00238	0.108	0.102	ERBB4/BTC	2
R-HSA-1250347	SHC1 events in ERBB4 signaling	2/60	14/10554	0.00276	0.108	0.102	ERBB4/BTC	2
R-HSA-200425	Import of palmitoyl-CoA into the mitochondrial matrix	2/60	14/10554	0.00276	0.108	0.102	THRSP/PRKAA2	2
R-HSA-6785631	ERBB2 Regulates Cell Motility	2/60	15/10554	0.00318	0.108	0.102	ERBB4/BTC	2
R-HSA-1963640	GRB2 events in ERBB2 signaling	2/60	16/10554	0.00362	0.108	0.102	ERBB4/BTC	2
R-HSA-1963642	PI3K events in ERBB2 signaling	2/60	16/10554	0.00362	0.108	0.102	ERBB4/BTC	2
R-HSA-9008059	Interleukin-37 signaling	2/60	21/10554	0.00622	0.163	0.153	IL37/PTPN14	2
R-HSA-1250196	SHC1 events in ERBB2 signaling	2/60	22/10554	0.00682	0.163	0.153	ERBB4/BTC	2

Journal Pre-proof

Supplementary Table 4. Clinical characteristics of U-BIOPRED asthmatic Predicted Responders (PRs, ES of ≥ +0.1) against predicted non-responders (PNRs, ES of ≤ -0.1) defined from sputum transcriptomic GSVA of the FZ-DOWN signature. See main paper Table 1 for full breakdown.

	Predicted responders	**Predicted non-responders**
n	26	18
Sex		
Male	10	9
Female	16	9
Age mean, yrs	51.8	55.3
Cohort		
Severe Asthma non-smoker (SAns)	18	13
Severe Asthma smoker / ex-smoker (SAs/ex)	8	5

Journal Pre-proof

Supplementary Table 5. Top 431 sputum and 19 down transcriptomic DEGS which differentiate U-BIOPRED asthmatic FZ predicted responders (PRs) from predicted non-responders (PNRs). Genes are ranked according to log_2 fold change. All results are significant by FDR adjusted p value.

Upregulated Genes

Gene Symbol	Log_2 Fold Change	FDR-BH adjusted p value
KCNJ2	2.89	1.57E-08
ANXA3	2.87	2.87E-07
CXCL10	2.60	2.72E-05
LRRK2	2.48	1.50E-06
IFIT2	2.44	4.57E-06
GCH1	2.44	1.39E-07
S100A12	2.42	1.05E-06
GRIP1	2.41	2.33E-07
IFIH1	2.37	2.19E-07
HS3ST3B1	2.34	1.29E-08
CXCL11	2.34	5.47E-04
RSAD2	2.34	2.77E-04
GBP5	2.31	2.83E-07
TNFAIP6	2.31	2.60E-08
CALHM6	2.23	8.43E-05
PTGS2	2.21	2.08E-06
LOC105372881	2.17	1.78E-06
TNFSF10	2.15	4.59E-06
IFIT3	2.09	1.59E-04
CCL8	2.08	6.15E-03
FAS	2.06	2.60E-08
DOCK4	2.04	4.55E-06
ISG20	2.03	1.05E-06
KCNJ15	2.01	9.25E-06
STEAP4	2.00	2.52E-06
CLEC4E	1.96	1.50E-06
SELL	1.95	2.74E-06
CXCR2	1.95	7.26E-06
IFITM1	1.95	2.85E-07
GPR84	1.90	1.32E-05
SLC30A4	1.90	1.50E-06
APOBEC3A	1.89	1.85E-06
TNIP3	1.88	3.09E-04
UBD	1.87	1.05E-06
CXCL9	1.86	8.52E-04
TNFRSF10C	1.86	1.13E-03

Journal Pre-proof

ACOD1	1.85	3.68E-03
CMPK2	1.82	1.98E-03
AIM2	1.82	1.77E-06
LIMK2	1.81	4.45E-07
PDE4B	1.79	1.99E-06
TIFA	1.78	8.83E-06
VNN3	1.78	3.93E-05
IRAK2	1.77	2.43E-05
IFIT1	1.76	2.43E-03
HIVEP2	1.75	4.52E-06
LINC01270	1.75	7.31E-05
GBP1	1.74	1.17E-06
PROK2	1.73	7.05E-05
WDFY3	1.72	3.96E-07
GJB2	1.71	5.33E-04
LMNB1	1.70	1.07E-06
RAB33B	1.70	6.48E-05
IDO1	1.69	1.35E-03
HPSE	1.69	2.72E-05
N4BP1	1.69	3.77E-06
ZNF200	1.68	7.95E-06
PI3	1.67	6.13E-04
ANKRD22	1.66	4.28E-04
CASP4	1.66	6.41E-08
ALPL	1.64	4.30E-04
SERPINB9	1.64	1.70E-03
GBP4	1.64	6.35E-05
FPR2	1.63	7.13E-06
CXCR1	1.63	2.32E-04
FAM8A1	1.63	1.12E-05
TAGAP	1.63	2.43E-05
BAZ1A	1.63	4.67E-07
ARL5B	1.62	6.74E-06
BMT2	1.61	1.77E-06
LINC00266-1	1.61	4.00E-05
UBE2D1	1.60	1.05E-06
FBXO6	1.60	5.03E-04
MX2	1.59	6.30E-05
P2RY14	1.59	7.08E-04
MGAM	1.58	5.07E-04
LINC01215	1.58	8.85E-04
VNN2	1.58	4.52E-06
TSPAN2	1.57	7.10E-04

Journal Pre-proof

ORM1	1.57	3.98E-03
HAL	1.57	9.59E-04
SPATA13	1.57	2.79E-04
MRVI1	1.57	5.33E-04
KLHL15	1.57	1.54E-04
STAT4	1.57	1.86E-04
HERC5	1.56	1.41E-03
CEP83	1.55	9.96E-06
TMEM154	1.55	2.22E-04
FAM129A	1.55	1.68E-06
CMTM2	1.55	2.15E-05
LILRA2	1.55	1.50E-05
SP110	1.54	7.99E-05
CD274	1.54	1.19E-05
KRT23	1.54	7.26E-06
GLT1D1	1.54	1.45E-04
NBN	1.54	8.17E-06
KATNBL1	1.54	4.16E-04
QPCT	1.54	7.14E-07
MANSC1	1.54	1.04E-03
LINC01093	1.53	2.34E-03
ZNF267	1.53	2.33E-07
SMA5	1.53	2.88E-03
IL6ST	1.53	1.96E-05
MSRB1	1.53	6.35E-05
PLXNC1	1.53	8.43E-05
ARHGEF40	1.53	1.42E-04
NMI	1.53	4.14E-07
CCDC71L	1.53	1.42E-04
TLR1	1.52	2.33E-04
PTX3	1.52	2.50E-03
FFAR2	1.52	6.17E-04
BATF	1.52	1.46E-05
TNFSF13B	1.52	7.26E-06
GBP1P1	1.51	2.99E-04
ERV3-2	1.51	1.93E-03
ARFIP1	1.51	5.41E-05
PFKFB3	1.51	5.33E-06
RUBCNL	1.50	1.64E-03
CSGALNACT1	1.50	2.24E-04
IRF1	1.50	2.88E-05
LOC399716	1.50	1.05E-04
NAIP	1.50	1.15E-05

Journal Pre-proof

KIAA1551	1.49	9.48E-05
CLEC2B	1.49	4.43E-08
CD177	1.49	2.88E-03
LRG1	1.48	6.00E-05
NLRC5	1.47	4.47E-05
C5orf58	1.47	1.23E-05
LILRA1	1.47	9.06E-04
THAP2	1.46	2.22E-04
CREB5	1.46	4.29E-05
CLEC4D	1.46	1.02E-04
PLEK	1.46	6.41E-08
GALNT3	1.46	6.09E-04
GNG2	1.45	2.83E-04
LOC145474	1.45	5.33E-04
CSF3R	1.45	1.05E-04
MIR29A	1.44	1.51E-04
DGAT2	1.44	1.31E-05
TRIM22	1.43	1.48E-04
CR1	1.43	1.51E-04
GIMAP4	1.43	9.40E-06
C15orf48	1.43	9.25E-06
TMCC3	1.43	5.04E-04
RAPGEF2	1.42	6.41E-05
TANK	1.42	2.10E-05
SORL1	1.41	8.43E-05
BATF2	1.41	1.32E-03
RHOH	1.41	4.14E-04
RNF175	1.41	2.60E-05
HCAR3	1.40	5.99E-05
LOC114224	1.40	5.72E-05
AQP9	1.40	1.30E-06
IFI16	1.40	2.63E-06
LOC254896	1.39	5.47E-04
IL1A	1.38	8.26E-03
ZC3H12D	1.38	8.83E-05
HES1	1.38	2.46E-03
CARD16	1.38	5.24E-06
TOPORS	1.38	2.92E-04
KREMEN1	1.38	1.92E-04
PDP1	1.38	1.42E-03
OSM	1.38	5.72E-05
TREML4	1.38	1.05E-04
CXCL1	1.38	1.92E-04

Journal Pre-proof

GTF2IP12	1.37	9.25E-06
CR1L	1.36	1.34E-03
MIR155HG	1.36	4.14E-04
IL18RAP	1.36	7.52E-03
JAK3	1.36	1.21E-04
TNFAIP3	1.36	4.73E-04
NSMAF	1.36	2.20E-04
EIF4E3	1.36	1.27E-05
SGTB	1.36	1.32E-03
MCTP2	1.35	1.10E-02
SLPI	1.35	7.69E-04
IL1B	1.35	1.92E-04
LY96	1.34	3.77E-05
IFITM2	1.34	4.52E-06
ANTXR2	1.33	1.44E-05
SERPINB9P1	1.33	5.19E-03
CASP5	1.32	1.86E-04
SCLT1	1.32	1.72E-03
IFITM3	1.32	3.77E-06
NLRP3	1.32	2.51E-03
EREG	1.32	1.44E-03
P2RY13	1.32	2.73E-03
FAM126B	1.31	3.67E-04
RPGR	1.31	2.29E-04
SNX18	1.31	6.08E-05
PELI2	1.31	4.72E-04
MNDA	1.31	3.93E-05
LINC00528	1.31	9.56E-04
ACAT2	1.30	1.74E-03
PSMB9	1.30	2.09E-05
KCNH7	1.30	9.73E-05
HMGN2P46	1.30	9.87E-03
CLOCK	1.30	4.45E-04
PML	1.29	4.28E-04
IL1R2	1.29	2.93E-04
CYP4F3	1.28	8.08E-03
SNN	1.28	4.67E-07
WTAP	1.28	4.52E-06
SLC7A5	1.28	3.42E-04
IRAK3	1.28	3.67E-03
SLC40A1	1.28	7.56E-03
ADGRE2	1.28	7.95E-06
LRRC70	1.27	3.26E-02

Journal Pre-proof

CD48	1.27	1.81E-05
PPP1R3B	1.27	8.77E-03
PIP4P2	1.27	1.27E-03
ADAMDEC1	1.27	1.37E-02
LILRA5	1.27	1.14E-03
ATG3	1.27	4.49E-07
CD8A	1.27	1.22E-05
CSF2RB	1.27	1.05E-06
FCAR	1.26	4.20E-04
GZMB	1.26	8.76E-03
NFKBIZ	1.26	1.05E-06
TRAPPC13	1.26	4.08E-04
CCRL2	1.26	5.40E-04
TRAF1	1.26	9.95E-04
FCGR1B	1.26	3.58E-04
CASP1	1.26	4.35E-05
DYSF	1.25	6.05E-04
SIGLEC5	1.25	8.35E-04
CPD	1.25	8.63E-04
SAMD9	1.25	2.11E-04
BRE-AS1	1.25	1.76E-03
DAPP1	1.25	3.37E-05
C1D	1.25	2.76E-03
TBK1	1.24	1.36E-03
LINC00641	1.24	4.49E-04
LOC100289230	1.24	3.73E-03
POLB	1.24	9.88E-08
SBF2	1.24	1.69E-03
SLC39A8	1.23	7.05E-05
RAB5A	1.23	3.04E-04
PELI1	1.23	1.56E-04
TMEM185B	1.23	7.95E-06
RNF149	1.23	1.27E-05
SAMD9L	1.22	8.40E-04
TLR4	1.22	3.24E-05
USP10	1.22	1.92E-04
XRN1	1.22	1.85E-03
ZC3H12C	1.22	2.84E-03
SERPINB2	1.21	1.40E-02
STAT1	1.21	9.43E-05
PREX1	1.21	3.18E-04
SMCHD1	1.21	6.63E-05
PSMB8-AS1	1.21	8.07E-04

Journal Pre-proof

TMEM71	1.21	3.03E-03
OAS3	1.21	8.26E-03
RASSF2	1.21	1.63E-04
S100A8	1.20	2.28E-05
KCNJ2-AS1	1.20	1.56E-03
NFAM1	1.20	8.83E-06
RNF19B	1.20	6.68E-04
CCL5	1.20	1.13E-03
ZNF292	1.20	1.42E-03
BICRAL	1.20	9.02E-05
FLJ32255	1.19	2.89E-04
S100P	1.19	2.03E-03
SLC22A4	1.19	9.43E-05
SCARF1	1.19	2.66E-03
EGR3	1.19	2.67E-03
PLSCR1	1.19	2.03E-07
LAMP3	1.19	1.54E-02
TRIM5	1.19	7.52E-03
HSD17B11	1.19	4.48E-04
GSEC	1.18	1.14E-03
HNRNPH2	1.18	6.36E-05
GBP2	1.18	1.22E-06
LOC100130357	1.18	2.33E-03
CREM	1.18	5.99E-05
S100A9	1.18	9.16E-06
GIMAP8	1.18	2.05E-03
MIR3945HG	1.17	4.73E-04
UBR1	1.17	2.25E-03
LINC01003	1.17	4.15E-03
TCP11L2	1.17	2.36E-03
CNOT11	1.17	1.86E-04
COQ10B	1.17	2.62E-05
PCBP1-AS1	1.16	2.06E-02
ICAM1	1.16	1.74E-06
RNF213	1.16	9.69E-04
IPO11	1.16	5.41E-03
ABHD3	1.15	2.50E-03
RABGAP1L	1.15	9.11E-03
CDC42SE2	1.15	7.86E-05
ST8SIA4	1.15	1.53E-04
NFE2L2	1.15	8.17E-06
SEMA4A	1.15	2.60E-05
PRKCB	1.15	4.20E-03

Journal Pre-proof

CEP68	1.15	3.01E-05
RGL4	1.15	9.09E-03
IRF2	1.14	1.35E-05
PARP14	1.14	3.67E-05
RIPOR2	1.14	4.05E-03
GTF2B	1.14	1.20E-04
MAP3K13	1.13	8.25E-04
MARCKS	1.13	4.67E-07
GBP3	1.13	2.88E-02
SP100	1.13	1.26E-04
FGL2	1.13	4.51E-04
TAB2	1.13	1.92E-04
SECTM1	1.13	1.11E-04
ELF2	1.13	2.29E-04
PAK1	1.13	1.72E-03
TCFL5	1.13	6.43E-03
GPR27	1.13	5.34E-04
FPR1	1.13	8.68E-06
DNTTIP2	1.13	3.01E-05
PTEN	1.12	5.67E-04
GZMA	1.12	1.26E-04
LINC00877	1.12	6.10E-04
VAV1	1.12	2.02E-05
TMEM88	1.12	3.85E-04
TLR2	1.12	6.85E-04
CD93	1.11	5.08E-03
BTBD19	1.11	1.14E-03
DDX60L	1.11	1.74E-04
ZBTB21	1.11	3.68E-03
PHF11	1.11	1.44E-04
CHD1	1.11	7.04E-05
PARP8	1.11	4.20E-04
MAK	1.11	9.43E-05
ZNF107	1.11	2.06E-02
TAP1	1.11	8.51E-06
SUSD6	1.10	3.42E-05
CFLAR	1.10	2.60E-05
SNORD89	1.10	1.23E-03
ACSL1	1.10	9.16E-06
BCL10	1.10	4.05E-04
RIN2	1.10	6.61E-03
SLAMF7	1.10	1.05E-02
TECPR2	1.10	2.30E-03

Journal Pre-proof

TET3	1.10	1.58E-03
CNTNAP3	1.09	3.94E-02
CHMP2B	1.09	1.35E-03
IDI2-AS1	1.09	2.73E-03
ICAM3	1.09	2.43E-03
EPM2AIP1	1.09	7.35E-03
DTX3L	1.09	5.29E-06
FCN1	1.09	1.42E-03
G0S2	1.09	4.74E-05
SPATA1	1.09	1.23E-05
CHST15	1.08	2.13E-03
TNF	1.08	1.09E-02
SLC15A4	1.08	3.56E-04
HSD11B1-AS1	1.08	3.78E-03
BTNL8	1.08	6.11E-03
TIMP1	1.08	1.21E-04
STX3	1.07	8.73E-03
BCL2A1	1.07	2.85E-07
CDC42EP2	1.07	3.95E-03
PTENP1	1.07	4.54E-04
ERI1	1.07	5.18E-03
AGTPBP1	1.07	9.43E-05
SPAG9	1.07	3.58E-04
GPR65	1.07	5.48E-04
IL1RAP	1.07	2.79E-03
AP1AR	1.06	5.33E-03
LOC441081	1.06	3.57E-03
C16orf54	1.06	7.31E-03
BID	1.06	3.63E-05
NFE2L3	1.06	5.24E-04
TULP2	1.06	1.90E-02
MX1	1.06	6.15E-03
HCG26	1.06	1.52E-03
ZC3HAV1	1.05	6.33E-04
NAF1	1.05	5.17E-03
APOBEC3G	1.05	1.40E-03
C11orf54	1.05	2.76E-03
CHSY1	1.05	1.33E-03
HCK	1.05	4.47E-06
CEACAM1	1.05	5.10E-03
PSTPIP2	1.05	1.72E-03
DLEU2L	1.05	9.65E-03
RNF141	1.05	4.04E-04

Journal Pre-proof

PPA1	1.05	3.52E-03
LAP3	1.05	5.84E-03
LOC101928361	1.04	3.60E-03
PPP2R2A	1.04	2.73E-03
CHI3L1	1.04	4.93E-02
PJA2	1.04	2.60E-05
MITD1	1.04	1.29E-04
RALB	1.04	5.21E-05
SMA4	1.04	7.45E-03
BCL3	1.04	1.48E-04
KDM6A	1.04	5.95E-05
LCP2	1.04	7.04E-06
AMPD3	1.04	2.82E-04
PPIF	1.04	3.01E-04
SECISBP2	1.04	1.22E-04
CFP	1.03	3.01E-04
ELOVL5	1.03	1.74E-06
CYSTM1	1.03	1.96E-05
DENND5A	1.03	4.90E-05
ASPRV1	1.03	1.44E-03
IDI1	1.03	1.21E-04
IGSF6	1.03	3.38E-05
MMP25	1.03	5.80E-03
NKG7	1.03	1.48E-04
KDM7A	1.03	1.59E-03
NFE4	1.03	2.35E-02
PHF20L1	1.02	1.33E-04
LYRM1	1.02	1.04E-03
NOD2	1.02	1.64E-03
MIA3	1.02	1.78E-03
GK3P	1.02	1.66E-04
PPP4R2	1.02	3.06E-05
CD55	1.02	8.79E-05
MIER1	1.02	5.94E-05
MLKL	1.02	1.24E-03
PIK3AP1	1.02	1.68E-05
ESCO1	1.01	2.59E-03
TREML2	1.01	1.70E-03
FCGR1A	1.01	3.45E-04
DDX60	1.01	1.34E-02
SRSF12	1.01	2.69E-03
DLGAP1-AS2	1.01	1.45E-03
WASHC2A	1.01	1.69E-03

Journal Pre-proof

USP32	1.01	3.95E-03
SPTY2D1	1.01	1.52E-03
ZFX	1.00	5.01E-04
CSRNP1	1.00	2.64E-04
PPP3CA	1.00	3.95E-03
SLAMF1	1.00	4.26E-03
TDP2	1.00	3.68E-03
TLR6	1.00	4.16E-04

Downregulated Genes

Gene Symbol	**Log_2 Fold Change**	**FDR-BH adjusted p value**
TMC6	-1.01	5.61E-05
RNA45SN5	-1.01	1.33E-03
DTX4	-1.01	2.30E-02
TPSAB1	-1.05	4.41E-03
BHLHE41	-1.06	4.39E-02
SPOCD1	-1.08	9.65E-03
FIG4	-1.10	1.58E-02
TGM2	-1.12	4.09E-03
SLC7A8	-1.13	3.43E-04
CD1C	-1.15	3.78E-02
CCL17	-1.22	5.59E-03
HMG20B	-1.25	2.29E-04
PNPLA6	-1.25	1.07E-04
LPL	-1.34	2.59E-02
CHML	-1.43	9.61E-04
TPSB2	-1.51	1.30E-03
PDK4	-1.66	6.45E-03
PRSS33	-1.78	3.12E-02
IL1RL1	-1.91	1.17E-02

Journal Pre-proof

Supplementary Table 6. ReactomePA pathway enrichment of the 431 upregulated sputum transcriptomic DEGS which differentiate predicted U-BIOPRED asthmatic FZ predicted responder (PR) from predicted non-responder (PNR) patients (see supplementary Table 5). Pathway enrichment P values adjusted by FDR-BH with cut-off <0.05.

ID	Description	Gene Ratio	BgRatio	P value	P .adjust	Q value	geneID	Count
R-HSA-913531	Interferon Signaling	28/268	197/10554	9.04E-14	6.15E-11	5.45E-11	IFIT2/RSAD2/GBP5/IFIT3/ISG20/IFITM1/IFIT1/GBP1/GBP4/MX2/HERC5/IRF1/TRIM22/EIF4E3/IFITM2/IFITM3/PML/FCGR1B/STAT1/OAS3/TRIM5/GBP2/ICAM1/IRF2/GBP3/SP100/MX1/FCGR1A	28
R-HSA-909733	Interferon alpha/beta signaling	15/268	69/10554	1.32E-10	4.50E-08	3.98E-08	IFIT2/RSAD2/IFIT3/ISG20/IFITM1/IFIT1/MX2/IRF1/IFITM2/IFITM3/STAT1/OAS3/GBP2/IRF2/MX1	15
R-HSA-6798695	Neutrophil degranulation	38/268	479/10554	3.13E-10	7.09E-08	6.28E-08	S100A12/TNFAIP6/SELL/CXCR2/GPR84/HPSE/FPR2/CXCR1/MGAM/ORM1/QPCT/PTX3/CD177/LRG1/CLEC4D/CR1/CXCL1/SLPI/MNDA/FCAR/SIGLEC5/S100A8/NFAM1/S100P/S100A9/FGL2/FPR1/TLR2/CD93/FCN1/SLC15A4/CEACAM1/CHI3L1/AMPD3/CFP/CYSTM1/MMP25/CD55	38
R-HSA-877300	Interferon gamma signaling	16/268	92/10554	1.07E-09	1.82E-07	1.61E-07	GBP5/GBP1/GBP4/IRF1/TRIM22/PML/FCGR1B/STAT1/OAS3/TRIM5/GBP2/ICAM1/IRF2/GBP3/SP100/FCGR1A	16
R-HSA-449147	Signaling by Interleukins	36/268	462/10554	1.57E-09	2.14E-07	1.90E-07	CXCL10/S100A12/PTGS2/IRAK2/LMNB1/STAT4/IL6ST/BATF/CSF3R/IL1A/OSM/CXCL1/IL18RAP/JAK3/IL1B/PELI2/PSMB9/IL1R2/IRAK3/CSF2RB/CASP1/TBK1/PELI1/SERPINB2/STAT1/CCL5/ICAM1/TAB2/FPR1/VAV1/TNF/TIMP1/STX3/IL1RAP/HCK/NOD2	36

Journal Pre-proof

R-HSA-6783783	Interleukin-10 signaling	11/268	47/10554	1.79E-08	2.02E-06	1.79E-06	CXCL10/PTGS2/IL1A/CXCL1/IL1B/IL1R2/CCL5/ICAM1/FPR1/TNF/TIMP1	11
R-HSA-5686938	Regulation of TLR by endogenous ligand	7/268	19/10554	2.44E-07	2.37E-05	2.10E-05	TLR1/LY96/TLR4/S100A8/S100A9/TLR2/TLR6	7
R-HSA-168898	Toll-like Receptor Cascades	17/268	155/10554	3.85E-07	3.27E-05	2.90E-05	S100A12/IRAK2/UBE2D1/TLR1/TANK/LY96/PELI2/IRAK3/TBK1/PELI1/TLR4/S100A8/S100A9/TAB2/TLR2/NOD2/TLR6	17
R-HSA-166016	Toll Like Receptor 4 (TLR4) Cascade	15/268	130/10554	9.86E-07	7.45E-05	6.59E-05	S100A12/IRAK2/UBE2D1/TLR1/TANK/LY96/PELI2/IRAK3/TBK1/PELI1/TLR4/TAB2/TLR2/NOD2/TLR6	15
R-HSA-5602498	MyD88 deficiency (TLR2/4)	5/268	10/10554	2.31E-06	1.43E-04	1.27E-04	TLR1/LY96/TLR4/TLR2/TLR6	5
R-HSA-446652	Interleukin-1 family signaling	15/268	139/10554	2.32E-06	1.43E-04	1.27E-04	S100A12/IRAK2/IL1A/IL18RAP/IL1B/PELI2/PSMB9/IL1R2/IRAK3/CASP1/TBK1/PELI1/TAB2/IL1RAP/NOD2	15
R-HSA-5603041	IRAK4 deficiency (TLR2/4)	5/268	11/10554	4.15E-06	2.29E-04	2.03E-04	TLR1/LY96/TLR4/TLR2/TLR6	5
R-HSA-166058	MyD88:MAL(TIRAP) cascade initiated on plasma membrane	12/268	95/10554	4.71E-06	2.29E-04	2.03E-04	S100A12/IRAK2/TLR1/LY96/PELI2/IRAK3/PELI1/TLR4/TAB2/TLR2/NOD2/TLR6	12
R-HSA-168188	Toll Like Receptor TLR6:TLR2 Cascade	12/268	95/10554	4.71E-06	2.29E-04	2.03E-04	S100A12/IRAK2/TLR1/LY96/PELI2/IRAK3/PELI1/TLR4/TAB2/TLR2/NOD2/TLR6	12
R-HSA-198933	Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell	14/268	132/10554	6.21E-06	2.62E-04	2.32E-04	SELL/IFITM1/LILRA2/CLEC2B/LILRA1/TREML4/LILRA5/CD8A/SIGLEC5/ICAM1/SLAMF7/ICAM3/TREML2/FCGR1A	14
R-HSA-168179	Toll Like Receptor TLR1:TLR2 Cascade	12/268	98/10554	6.55E-06	2.62E-04	2.32E-04	S100A12/IRAK2/TLR1/LY96/PELI2/IRAK3/PELI1/TLR4/TAB2/TLR2/NOD2/TLR6	12
R-HSA-181438	Toll Like Receptor 2 (TLR2) Cascade	12/268	98/10554	6.55E-06	2.62E-04	2.32E-04	S100A12/IRAK2/TLR1/LY96/PELI2/IRAK3/PELI1/TLR4/TAB2/TLR2/NOD2/TLR6	12

Journal Pre-proof

R-HSA-9020702	Interleukin-1 signaling	12/268	103/10554	1.10E-05	4.16E-04	3.68E-04	S100A12/IRAK2/IL1A/IL1B/PELI2/PSMB9/IL1R2/IRAK3/PELI1/TAB2/IL1RAP/NOD2	12
R-HSA-380108	Chemokine receptors bind chemokines	8/268	48/10554	2.43E-05	8.71E-04	7.72E-04	CXCL10/CXCL11/CXCR2/CXCL9/CXCR1/CXCL1/CCRL2/CCL5	8
R-HSA-140534	Caspase activation via Death Receptors in the presence of ligand	5/268	17/10554	4.90E-05	1.67E-03	1.48E-03	TNFSF10/FAS/LY96/TLR4/CFLAR	5
R-HSA-168643	Nucleotide-binding domain, leucine rich repeat containing receptor (NLR) signaling pathways	8/268	55/10554	6.74E-05	2.18E-03	1.93E-03	AIM2/IRAK2/CASP4/TNFAIP3/NLRP3/CASP1/TAB2/NOD2	8
R-HSA-936440	Negative regulators of DDX58/IFIH1 signaling	6/268	34/10554	1.87E-04	5.79E-03	5.13E-03	IFIH1/UBE2D1/HERC5/NLRC5/TNFAIP3/TBK1	6
R-HSA-168638	NOD1/2 Signaling Pathway	6/268	36/10554	2.60E-04	7.69E-03	6.81E-03	IRAK2/CASP4/TNFAIP3/CASP1/TAB2/NOD2	6
R-HSA-5260271	Diseases of Immune System	5/268	24/10554	2.91E-04	7.91E-03	7.01E-03	TLR1/LY96/TLR4/TLR2/TLR6	5
R-HSA-5602358	Diseases associated with the TLR signaling cascade	5/268	24/10554	2.91E-04	7.91E-03	7.01E-03	TLR1/LY96/TLR4/TLR2/TLR6	5
R-HSA-5689896	Ovarian tumor domain proteases	6/268	38/10554	3.53E-04	9.24E-03	8.18E-03	IFIH1/TNIP3/UBE2D1/TNFAIP3/PTEN/NOD2	6
R-HSA-6785807	Interleukin-4 and Interleukin-13 signaling	10/268	108/10554	4.09E-04	1.03E-02	9.12E-03	PTGS2/BATF/IL1A/OSM/JAK3/IL1B/STAT1/ICAM1/TNF/TIMP1	10
R-HSA-5357769	Caspase activation via extrinsic apoptotic signalling pathway	5/268	27/10554	5.19E-04	1.26E-02	1.12E-02	TNFSF10/FAS/LY96/TLR4/CFLAR	5
R-HSA-9014325	TICAM1,TRAF6-dependent induction of TAK1 complex	4/268	17/10554	7.45E-04	1.69E-02	1.50E-02	IRAK2/LY96/TLR4/TAB2	4
R-HSA-975163	IRAK2 mediated activation	4/268	17/10554	7.45E-04	1.69E-02	1.50E-02	IRAK2/LY96/TLR4/TAB2	4

Journal Pre-proof

	of TAK1 complex upon TLR7/8 or 9 stimulation							
R-HSA-168928	DDX58/IFIH1-mediated induction of interferon-alpha/beta	8/268	78/10554	7.85E-04	1.72E-02	1.52E-02	S100A12/IFIH1/UBE2D1/HERC5/NLRC5/TANK/TNFAIP3/TBK1	8
R-HSA-1236975	Antigen processing-Cross presentation	9/268	99/10554	9.04E-04	1.74E-02	1.54E-02	TLR1/LY96/PSMB9/FCGR1B/TLR4/TLR2/TAP1/FCGR1A/TLR6	9
R-HSA-168164	Toll Like Receptor 3 (TLR3) Cascade	9/268	99/10554	9.04E-04	1.74E-02	1.54E-02	S100A12/IRAK2/UBE2D1/TANK/LY96/TBK1/TLR4/TAB2/NOD2	9
R-HSA-73887	Death Receptor Signalling	11/268	141/10554	9.18E-04	1.74E-02	1.54E-02	TNFSF10/FAS/ARHGEF40/TNFAIP3/NSMAF/TRAF1/PREX1/TAB2/VAV1/CFLAR/TNF	11
R-HSA-936964	Activation of IRF3/IRF7 mediated by TBK1/IKK epsilon	4/268	18/10554	9.39E-04	1.74E-02	1.54E-02	TANK/LY96/TBK1/TLR4	4
R-HSA-937072	TRAF6-mediated induction of TAK1 complex within TLR4 complex	4/268	18/10554	9.39E-04	1.74E-02	1.54E-02	IRAK2/LY96/TLR4/TAB2	4
R-HSA-166166	MyD88-independent TLR4 cascade	9/268	100/10554	9.72E-04	1.74E-02	1.54E-02	S100A12/IRAK2/UBE2D1/TANK/LY96/TBK1/TLR4/TAB2/NOD2	9
R-HSA-937061	TRIF(TICAM1)-mediated TLR4 signaling	9/268	100/10554	9.72E-04	1.74E-02	1.54E-02	S100A12/IRAK2/UBE2D1/TANK/LY96/TBK1/TLR4/TAB2/NOD2	9
R-HSA-5213460	RIPK1-mediated regulated necrosis	4/268	20/10554	1.43E-03	2.43E-02	2.15E-02	TNFSF10/FAS/CFLAR/MLKL	4
R-HSA-5218859	Regulated Necrosis	4/268	20/10554	1.43E-03	2.43E-02	2.15E-02	TNFSF10/FAS/CFLAR/MLKL	4
R-HSA-9020958	Interleukin-21 signaling	3/268	10/10554	1.70E-03	2.82E-02	2.50E-02	STAT4/JAK3/STAT1	3
R-HSA-3371378	Regulation by c-FLIP	3/268	11/10554	2.30E-03	3.55E-02	3.14E-02	TNFSF10/FAS/CFLAR	3
R-HSA-5218900	CASP8 activity is inhibited	3/268	11/10554	2.30E-03	3.55E-02	3.14E-02	TNFSF10/FAS/CFLAR	3

Journal Pre-proof

R-HSA-69416	Dimerization of procaspase-8	3/268	11/10554	2.30E-03	3.55E-02	3.14E-02	TNFSF10/FAS/CFLAR	3
R-HSA-975138	TRAF6 mediated induction of NFkB and MAP kinases upon TLR7/8 or 9 activation	8/268	93/10554	2.46E-03	3.72E-02	3.29E-02	S100A12/IRAK2/LY96/PELI2/PELI1/TLR4/TAB2/NOD2	8
R-HSA-168181	Toll Like Receptor 7/8 (TLR7/8) Cascade	8/268	94/10554	2.63E-03	3.81E-02	3.37E-02	S100A12/IRAK2/LY96/PELI2/PELI1/TLR4/TAB2/NOD2	8
R-HSA-975155	MyD88 dependent cascade initiated on endosome	8/268	94/10554	2.63E-03	3.81E-02	3.37E-02	S100A12/IRAK2/LY96/PELI2/PELI1/TLR4/TAB2/NOD2	8
R-HSA-8984722	Interleukin-35 Signalling	3/268	12/10554	3.01E-03	4.26E-02	3.77E-02	STAT4/IL6ST/STAT1	3
R-HSA-5621481	C-type lectin receptors (CLRs)	10/268	142/10554	3.31E-03	4.59E-02	4.07E-02	CLEC4E/UBE2D1/CLEC4D/IL1B/PSMB9/TAB2/PAK1/BCL10/ICAM3/PPP3CA	10
R-HSA-168138	Toll Like Receptor 9 (TLR9) Cascade	8/268	98/10554	3.41E-03	4.64E-02	4.11E-02	S100A12/IRAK2/LY96/PELI2/PELI1/TLR4/TAB2/NOD2	8
R-HSA-1169410	Antiviral mechanism by IFN-stimulated genes	7/268	78/10554	3.58E-03	4.77E-02	4.23E-02	IFIT1/MX2/HERC5/EIF4E3/STAT1/OAS3/MX1	7

Journal Pre-proof

Supplementary Table 7. Clinical characteristics of U-BIOPRED asthmatic predicted responders and predicted non-responders who have sputum proteomic data in addition to the sputum transcriptomic data from which they were defined.

	Predicted responders	**Predicted non-responders**
n	18	14
Sex		
Male	13	7
Female	5	7
Age mean, years	49.33	56.29
Cohort		
SAns	10	9
SAs/ex	8	5

Journal Pre-proof

Supplementary Table 8. Clinical characteristics of U-BIOPRED asthmatic predicted responders and predicted non-responders who have blood proteomic data in addition to the sputum transcriptomic data from which they were defined.

	Predicted responders	**Predicted non-responders**
n	24	18
Sex		
Male	9	9
Female	15	9
Age mean, yrs	53.71	55.28
Cohort		
SAns	17	13
SAs/ex	7	5

Journal Pre-proof

Supplementary Table 9. Top and bottom 25 differentially expressed blood proteins that differentiate U-BIOPRED asthmatic FZ predicted responders (PRs) from predicted non-responders (PNRs) defined from asthma sputum GSVA FZ response signature ES which had serum proteomic data available (see Supplementary Table 4). Genes are ranked according to log_2 fold change.

Upregulated

Gene Symbol	Log2 Fold Change	Fold Change	P value	FDR-BH adjusted P value
Siglec_9	0.73	1.65	0.05	0.92
ARTS1	0.65	1.57	0.00	0.50
SSRP1	0.61	1.52	0.07	0.92
GSTA3	0.54	1.45	0.02	0.92
TECK	0.52	1.44	0.00	0.72
Glucagon	0.51	1.42	0.03	0.92
SORC2	0.49	1.40	0.14	0.92
b_Endorphin	0.48	1.39	0.05	0.92
GM_CSF	0.47	1.38	0.17	0.92
MICA	0.40	1.32	0.02	0.92
PAK6	0.40	1.32	0.13	0.92
MK08	0.37	1.30	0.03	0.92
vWF	0.37	1.30	0.08	0.92
TSP2	0.37	1.29	0.01	0.92
CRP	0.36	1.29	0.26	0.92
FSH	0.35	1.28	0.45	0.93
TLR2	0.35	1.28	0.28	0.92
C3d	0.34	1.27	0.35	0.92
pTEN	0.34	1.27	0.26	0.92
Aminoacylase_1	0.34	1.26	0.13	0.92
Fas_ligand_soluble	0.33	1.26	0.03	0.92
IL_8	0.33	1.26	0.09	0.92
COMMD7	0.33	1.26	0.12	0.92
I_TAC	0.32	1.25	0.19	0.92
BRF_1	0.32	1.25	0.15	0.92

Downregulated

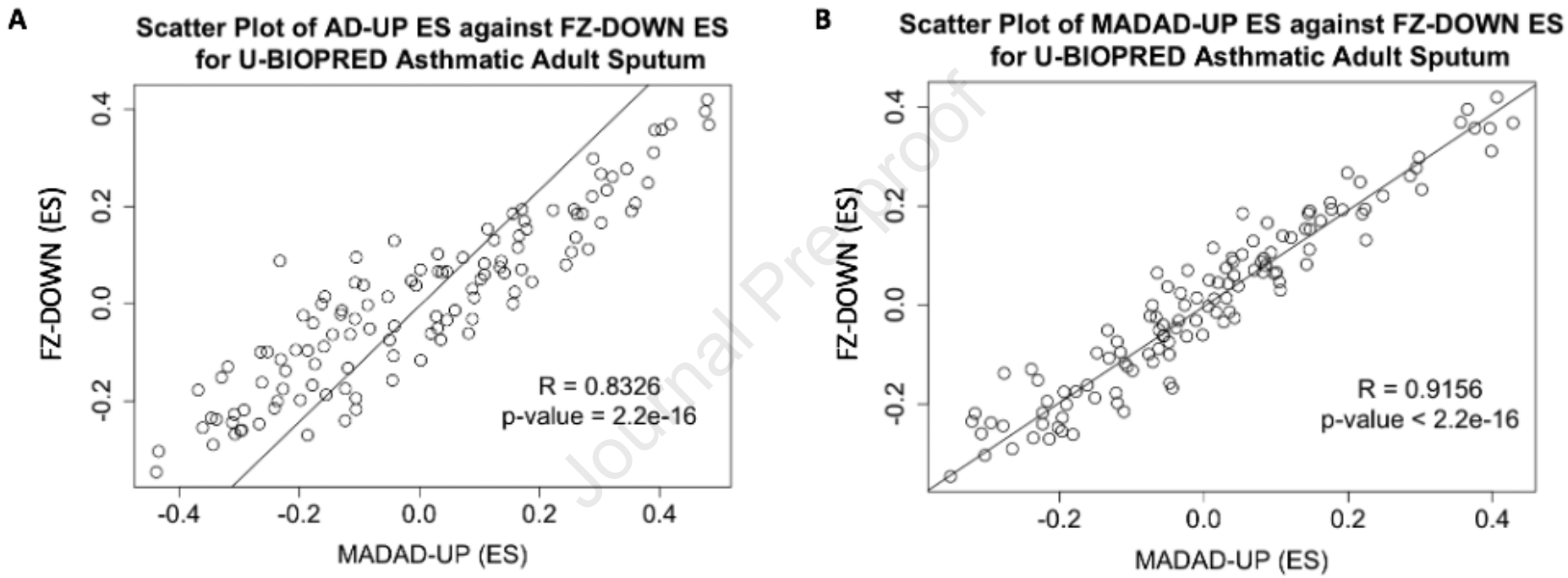
Gene Symbol	Log2 Fold Change	Fold Change	P value	FDR-BH adjusted P value
CD5L	-0.23	0.85	0.30	0.92
PSA	-0.24	0.85	0.06	0.92
Carbonic_anhydrase _III	-0.24	0.85	0.19	0.92

Journal Pre-proof

PARC	-0.24	0.85	0.16	0.92
Renin	-0.24	0.85	0.24	0.92
MDC	-0.24	0.84	0.13	0.92
BCMA	-0.25	0.84	0.11	0.92
Trypsin	-0.25	0.84	0.08	0.92
BMPER	-0.25	0.84	0.04	0.92
LKHA4	-0.27	0.83	0.11	0.92
MMP_10	-0.27	0.83	0.09	0.92
MIP_3b	-0.28	0.82	0.16	0.92
BSP	-0.29	0.82	0.09	0.92
IgD	-0.31	0.81	0.64	0.96
C3a	-0.32	0.80	0.24	0.92
BLC	-0.35	0.79	0.26	0.92
Chk2	-0.35	0.78	0.33	0.92
PAPP_A	-0.36	0.78	0.10	0.92
Haptoglobin_Mixed_ Type	-0.37	0.77	0.06	0.92
IL_5_Ra	-0.41	0.75	0.01	0.92
NEUREGULIN_1	-0.48	0.72	0.19	0.92
TARC	-0.51	0.70	0.00	0.72
CYTT	-0.53	0.69	0.01	0.92
CYTN	-0.58	0.67	0.00	0.72
IgE	-1.14	0.45	0.06	0.92

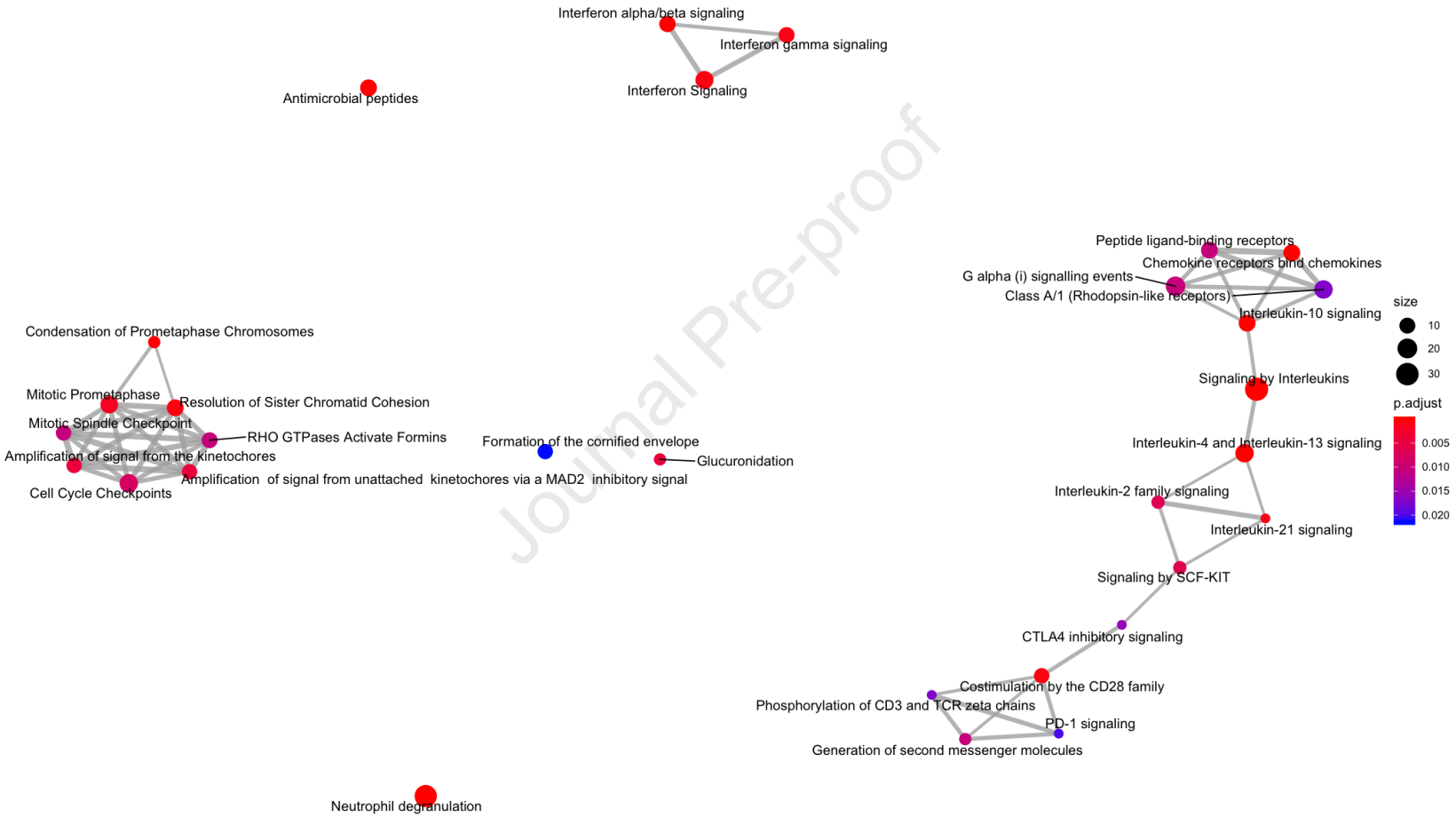
Journal Pre-proof

Supplementary Figure 1. Correlation of the enrichment score (ES) of genes down-regulated by fezikinumab (FZ) (FZ-DOWN) in adult asthmatic sputum against (A) the ES of genes up-regulated in lesional compared to non-lesional atopic dermatitis (AD) skin (AD-UP) and (B) the ES of a consensus AD gene signature (MADAD-UP).



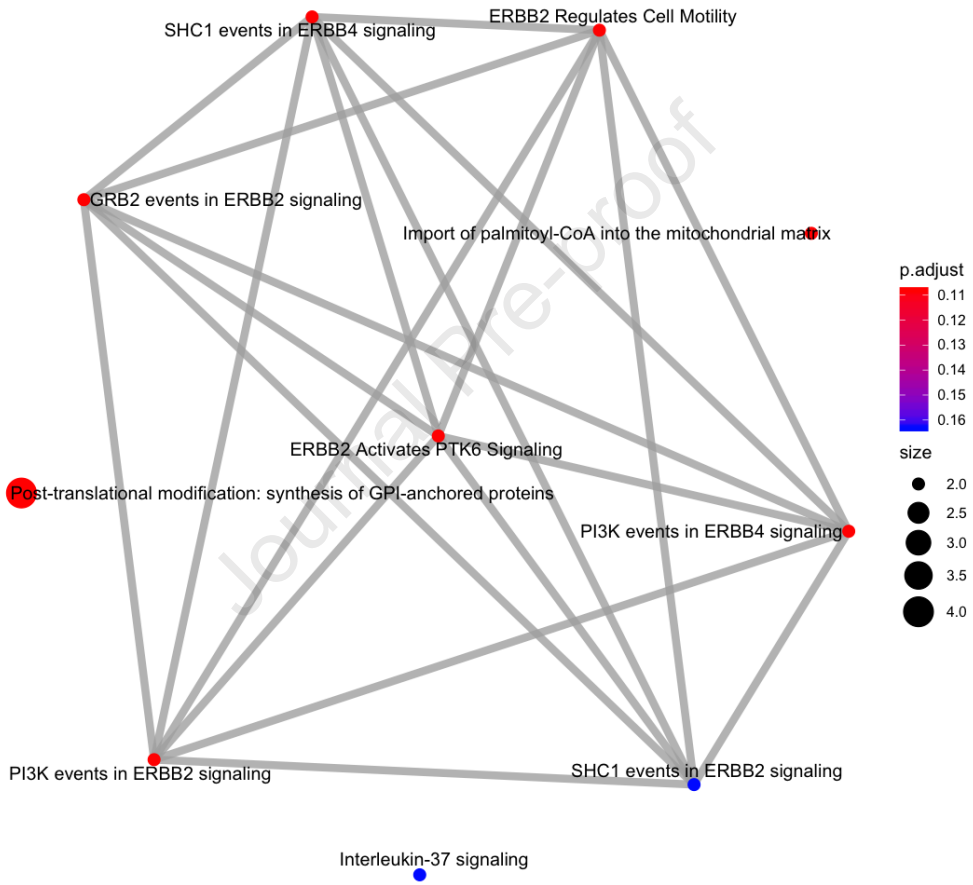
Journal Pre-proof

Supplementary Figure 2. Protein pathway analysis of the 40 significantly enriched pathways (false discovery rate, FDR<0.05) for differentially expressed genes down-regulated in atopic dermatitis lesional tissue following 12 weeks Fezakinumab treatment. See **Supplementary Table 8** for more details of these pathways.

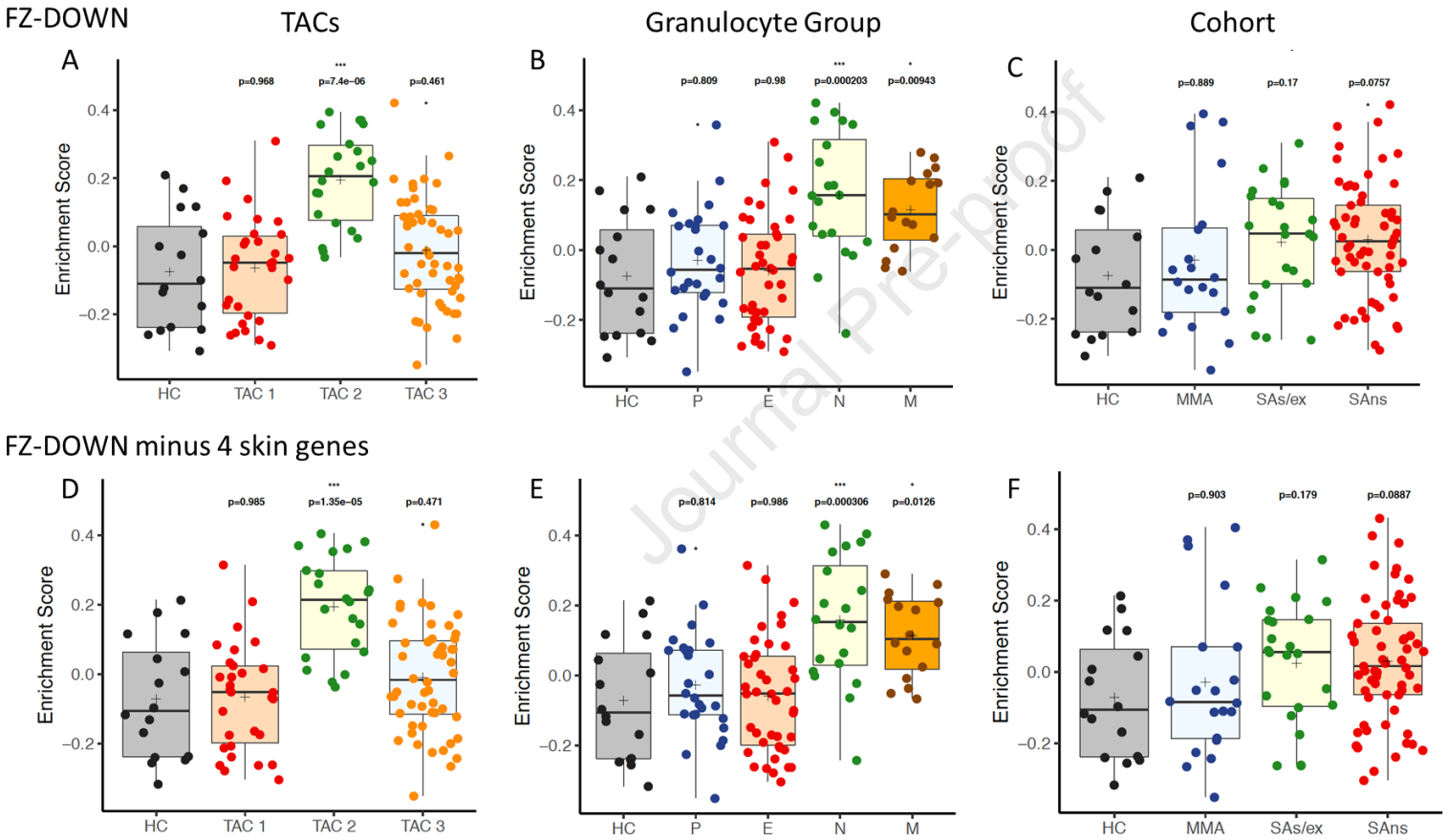


Journal Pre-proof

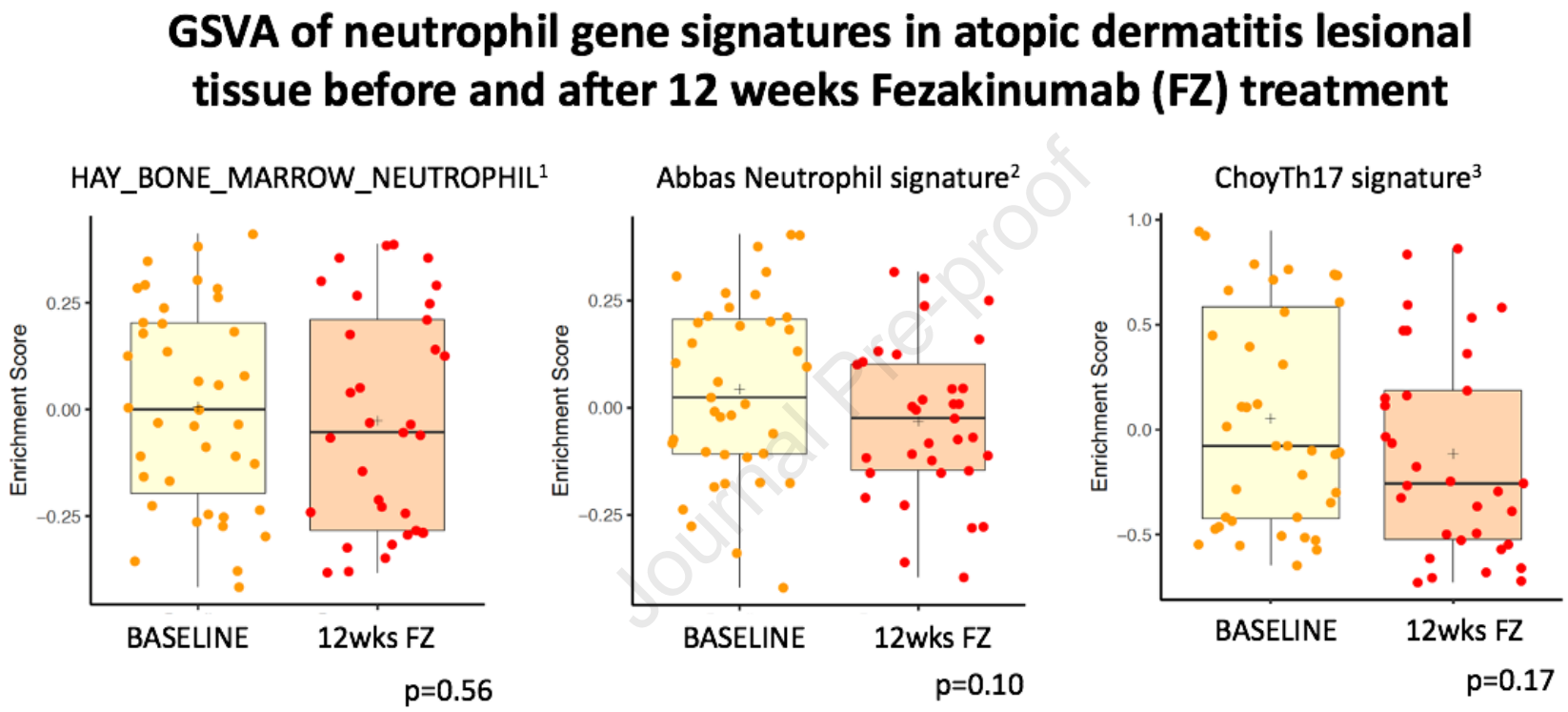
Supplementary Figure 3. Protein pathway analysis at a false discovery rate (FDR)<0.02 for differentially expressed genes up-regulated in atopic dermatitis lesional tissue following 12 weeks Fezakinumab treatment. See **Supplementary Table 9** for more details of these pathways. No pathways were enriched at a FDR<0.05.



Supplementary Figure 4. Minimal effect on the FZ-DOWN signature enrichment scores (A-C) in the sputum of asthmatic and healthy subjects with the removal of 4 skin-specific genes (D-F) when assessed by transcriptome associated cluster (TAC) status (A and D), sputum granulocyte group (B and E) or by asthma severity (C and F). SAns – severe asthma non-smoker; SAs/ex – severe asthma current or ex-smoker; MMA – mild-moderate asthma and HC – healthy control. P - paucigranulocytic; E – eosinophilic; N – neutrophilic and M – mixed granulocytic.

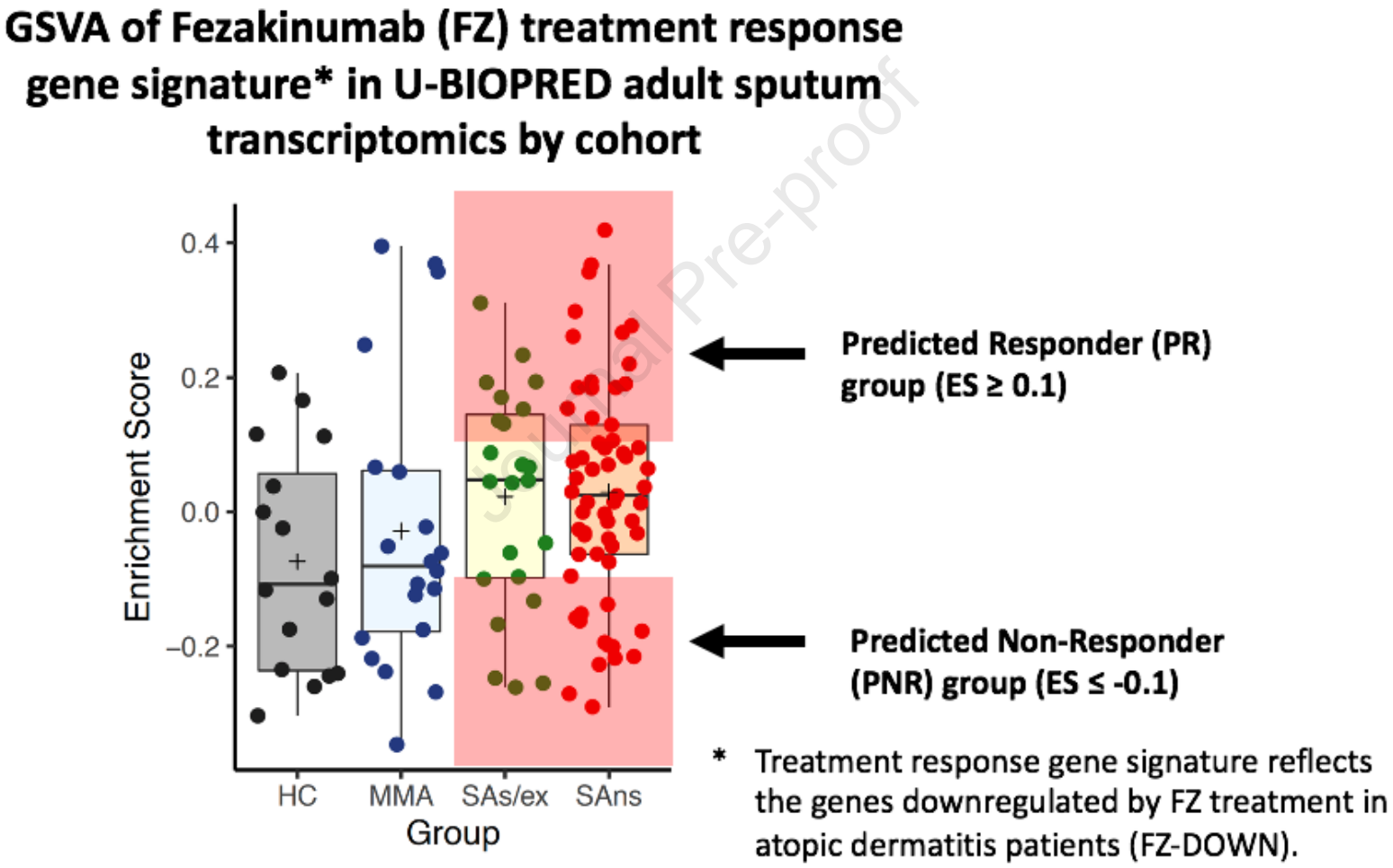


Supplementary Figure 5. Gene set variation analysis (GSVA) show no significant change in enrichment scores for neutrophil signatures in atopic dermatitis skin lesional tissue at baseline and after 12 weeks of Fezikinumab (FZ) treatment. The references from which the neutrophil signatures were obtained are provided beneath the figure.

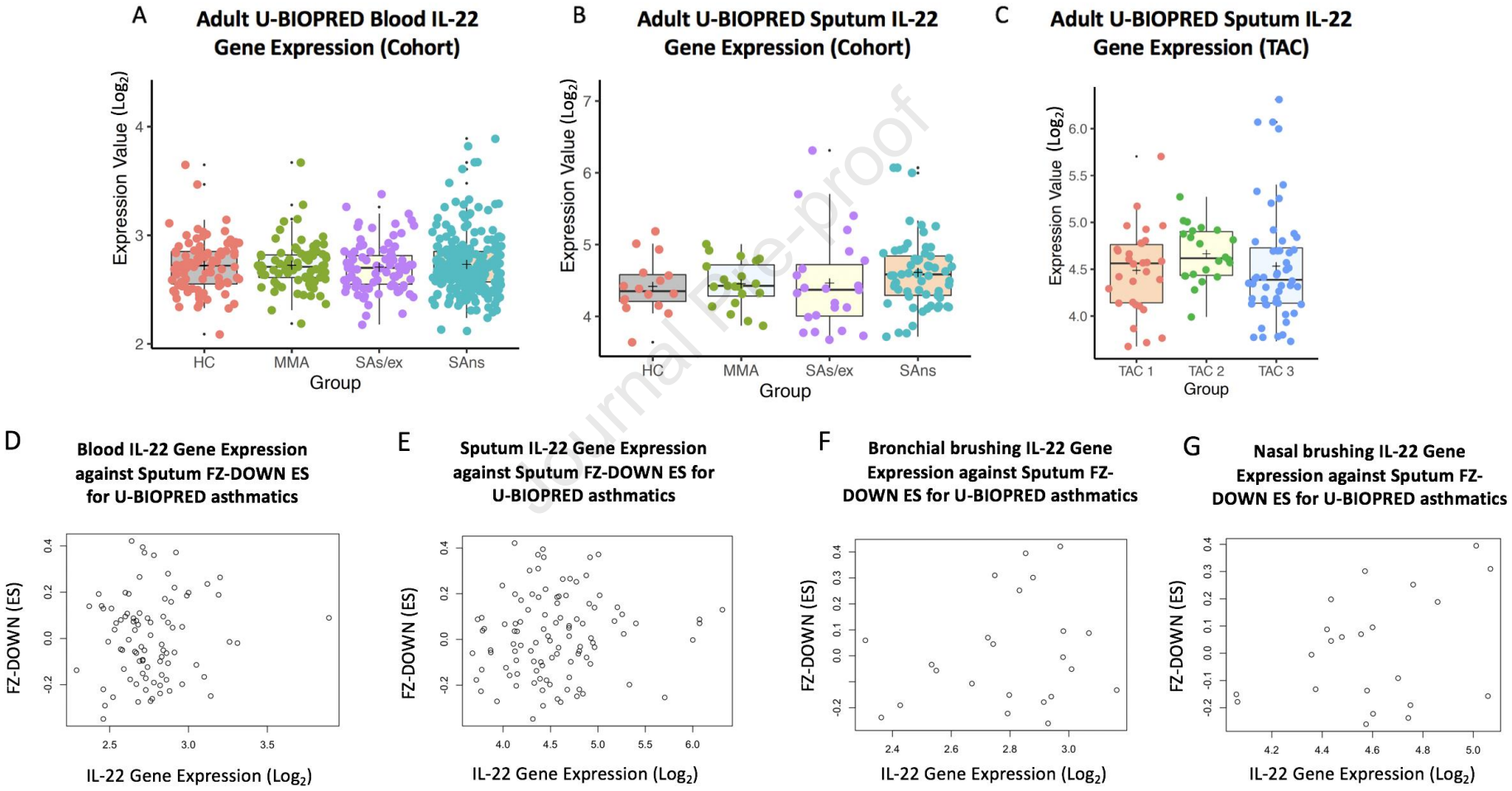


1. Hay SB, Ferchen K, Chetal K, Grimes HL, Salomonis N. The Human Cell Atlas bone marrow single-cell interactive web portal. Exp Hematol 2018; 68:51-61.
2. Abbas AR, Baldwin D, Ma Y, et al. Immune response in silico (IRIS): immune-specific genes identified from a compendium of microarray expression data. Genes Immun 2005; 6(4): 319-31.
3. Choy DF, Hart KM, Borthwick LA, et al. TH2 and TH17 inflammatory pathways are reciprocally regulated in asthma. Sci Transl Med 2015; 7(301): 301ra129.

Supplementary Figure 6. Schematic of selection of patients with a high versus low enrichment score (ES) for the gene signature of genes down-regulated by Fezakinumab (FZ) in atopic dermatitis patients. Predicted responders (PRs) were considered as patients most highly enriched (n=26, ES ≥ +0.1) whilst predicted non-responders were defined as those lowly enriched (n=18, ES ≤ -0.1). Clinical and omics variables that defined these patients were then obtained from the U-BIOPRED dataset.



Supplementary Figure 7. IL-22 gene expression in blood (A) and sputum (B, C) is not significantly up-regulated according to asthma severity (B) or transcriptome associated cluster (TAC) status (C). IL-22 gene expression in blood (D), sputum (E), bronchial (F) and nasal (G) brushings does not correlate with the Fezakinumab (FZ)-DOWN signature sputum ES. SAns – severe asthma non-smoker; SAs/ex – severe asthma current or ex-smoker; MMA – mild-moderate asthma and HC – healthy control.



References

1. Brunner, P. M. *et al.* Baseline IL-22 expression in patients with atopic dermatitis stratifies tissue responses to fezakinumab. *J. Allergy Clin. Immunol.* **143**, 142–154 (2019).
2. Ewald, D. A. *et al.* Meta-analysis derived atopic dermatitis (MADAD) transcriptome defines a robust AD signature highlighting the involvement of atherosclerosis and lipid metabolism pathways. *BMC Med. Genomics* (2015). doi:10.1186/s12920-015-0133-x

Journal Pre-proof

U-BIOPRED project team

U-BIOPRED Supplementary authors	
Name	**Affiliation**
Adcock I M	National Heart and Lung Institute, Imperial College, London, UK;
Ahmed H	European Institute for Systems Biology and Medicine, CNRS-ENS-UCBL-INSERM, Lyon, France;
Auffray C	European Institute for Systems Biology and Medicine, CNRS-ENS-UCBL-INSERM, Lyon, France;
Bakke P	Department of Clinical Science, University of Bergen, Bergen, Norway;
Bansal A T	Acclarogen Ltd, St. John's Innovation Centre, Cambridge, UK;
Baribaud F	Janssen R&D, LLC, Spring House, PA, USA
Bates S	Respiratory Therapeutic Unit, GSK, London, UK;
Bel E H	Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands;
Bigler J	*Previously Amgen Inc*
Bisgaard H	COPSAC, Copenhagen Prospective Studies on Asthma in Childhood, Herlev and Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark
Boedigheimer M J	Amgen Inc.; Thousand Oaks, USA
Bønnelykke K	COPSAC, Copenhagen Prospective Studies on Asthma in Childhood, Herlev and Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark;
Brandsma J	University of Southampton, Southampton, UK
Brinkman P	Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands;
Bucchioni E	Chiesi Pharmaceuticals SPA, Parma, Italy
Burg D	Centre for Proteomic Research, Institute for Life Sciences, University of Southampton, Southampton, UK
Bush A	National Heart and Lung Institute, Imperial College, London, UK; Royal Brompton and Harefield NHS trust, UK
Caruso M	Dept. Clinical and Experimental Medicine, University of Catania, Catania, Italy;
Chaiboonchoe A	European Institute for Systems Biology and Medicine, CNRS-ENS-UCBL-INSERM, Lyon, France;
Chanez P	Assistance publique des Hôpitaux de Marseille - Clinique des bronches, allergies et sommeil, Aix Marseille Université, Marseille, France
Chung F K	National Heart and Lung Institute, Imperial College, London, UK;
Compton C H	Respiratory Therapeutic Unit, GSK, London, UK
Corfield J	Areteva R&D, Nottingham, UK;
Cunoosamy D	Sanofi, Cambridge, USA
D'Amico A	University of Rome 'Tor Vergata', Rome Italy;
Dahlén B	Karolinska University Hospital & Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden
Dahlén S E	Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden
De Meulder B	European Institute for Systems Biology and Medicine, CNRS-ENS-UCBL-INSERM, Lyon, France;
Djukanovic R	NIHR Southampton Respiratory Biomedical Research Unit and Clinical and Experimental Sciences, Southampton, UK;
Erpenbeck V J	Translational Medicine, Respiratory Profiling, Novartis Institutes for Biomedical Research, Basel, Switzerland;
Erzen D	Boehringer Ingelheim Pharma GmbH & Co. KG; Biberach, Germany
Fichtner K	Boehringer Ingelheim Pharma GmbH & Co. KG; Biberach, Germany
Fleming L J	National Heart and Lung Institute, Imperial College, London, UK;

	Royal Brompton and Harefield NHS trust, UK
Formaggio E	*Previously CROMSOURCE, Verona Italy*
Fowler S J	Division of infection, immunity and respiratory medicine, School of biological sciences, University of Manchester, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, United Kingdom
Frey U	University Children's Hospital, Basel, Switzerland;
Gahlemann M	Boehringer Ingelheim (Schweiz) GmbH,Basel, Switzerland;
Geiser T	Department of Pulmonary Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland.
Giovonni M	Chiesi
Goss V	NIHR Respiratory Biomedical Research Unit, University Hospital Southampton NHS Foundation Trust, Integrative Physiology and Critical Illness Group, Clinical and Experimental Sciences, Sir Henry Wellcome Laboratories, Faculty of Medicine, University of Southampton, Southampton, UK;
Guo Y	Data Science Institute, Imperial College, London, UK;
Hashimoto S	Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands;
Haughney J	International Primary Care Respiratory Group, Aberdeen, Scotland;
Hedlin G	Dept. Women's and Children's Health & Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden;
Hekking P W	Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands;
Higenbottam T	Allergy Therapeutics, West Sussex, UK;
Hohlfeld J M	Fraunhofer Institute for Toxicology and Experimental Medicine, Hannover, Germany
Holweg C	Respiratory and Allergy Diseases, Genentech, San Francisco, USA
Horváth I	Semmelweis University, Budapest, Hungary
Howarth P	NIHR Southampton Respiratory Biomedical Research Unit, Clinical and Experimental Sciences and Human Development and Health, Southampton, UK
James A J	Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden;
Knowles RG	Knowles Consulting Ltd, Stevenage. UK;
Knox A J	Respiratory Research Unit, University of Nottingham, Nottingham, UK;
Kots M	Chiesi
Krug N	Fraunhofer Institute for Toxicology and Experimental Medicine, Hannover, Germany;
Lefaudeux D	European Institute for Systems Biology and Medicine, CNRS-ENS-UCBL-INSERM, Lyon, France;
Loza M J	Janssen R&D, LLC, Spring House, PA, USA
Lutter R	Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands;
Manta A	Roche Diagnostics GmbH, Mannheim, Germany
Masefield S	European Lung Foundation, Sheffield, UK;
Matthews J G	Respiratory and Allergy Diseases, Genentech, San Francisco, USA;
Mazein A	European Institute for Systems Biology and Medicine, CNRS-ENS-UCBL-INSERM, Lyon, France
Meiser A	Data Science Institute, Imperial College, London, UK
Middelveld R J M	Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden
Miralpeix M	Almirall, Barcelona, Spain;
Montuschi P	Università Cattolica del Sacro Cuore, Milan, Italy;
Mores N	Università Cattolica del Sacro Cuore, Milan, Italy;
Murray C S	Division of infection, immunity and respiratory medicine, School of biological sciences, University of Manchester, Manchester University NHS Foundation Trust, and Manchester Academic Health

	Science Centre, Manchester, United Kingdom
Musial J	Dept. of Medicine, Jagiellonian University Medical College, Krakow, Poland
Myles D	Respiratory Therapeutic Unit, GSK, London, UK;
Pahus L	Assistance publique des Hôpitaux de Marseille, Clinique des bronches, allergies et sommeil Espace Éthique Méditerranéen, Aix-Marseille Université, Marseille, France;
Pandis I	Data Science Institute, Imperial College, London, UK
Pavlidis S	National Heart and Lung Institute, Imperial College, London, UK
Postle A	University of Southampton, UK
Powel P	European Lung Foundation, Sheffield, UK;
Praticò G	CROMSOURCE, Verona, Italy
Puig Valls M	CROMSOURCE, Barcelona, Spain
Rao N	Janssen R&D, LLC, Spring House, PA, USA
Riley J	Respiratory Therapeutic Unit, GSK, London, UK;
Roberts A	Asthma UK, London, UK;
Roberts G	NIHR Southampton Respiratory Biomedical Research Unit, Clinical and Experimental Sciences and Human Development and Health, Southampton, UK;
Rowe A	Janssen R&D, UK;
Sandström T	Dept of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden;
Schofield JPR	Centre for Proteomic Research, Institute for Life Sciences, University of Southampton, Southampton, UK
Seibold W	Boehringer Ingelheim Pharma GmbH, Biberach, Germany
Selby A	NIHR Southampton Respiratory Biomedical Research Unit, Clinical and Experimental Sciences and Human Development and Health, Southampton, UK;
Shaw D E	Respiratory Research Unit, University of Nottingham, UK;
Sigmund R	Boehringer Ingelheim Pharma GmbH & Co. KG; Biberach, Germany
Singer F	Pediatric Respiratory Medicine, Department of Pediatrics, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland.
Skipp P J	Centre for Proteomic Research, Institute for Life Sciences, University of Southampton, Southampton, UK
Smicker M	Sanofi, Cambridge, USA
Sousa A R	Respiratory Therapeutic Unit, GSK, London, UK;
Sterk P J	Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands;
Sun K	Data Science Institute, Imperial College, London, UK
Thornton B	MSD, USA
van Aalderen W M	Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands;
van Geest M	AstraZeneca, Mölndal, Sweden;
Vestbo J	Centre for Respiratory Medicine and Allergy, Institute of Inflammation and Repair, University of Manchester and University Hospital of South Manchester, Manchester Academic Health Sciences Centre, Manchester, United Kingdom
Vissing N H	COPSAC, Copenhagen Prospective Studies on Asthma in Childhood, Herlev and Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark;
Wagener A H	Academic Medical Center Amsterdam, Amsterdam, The Netherlands
Wagers S S	BioSci Consulting, Maasmechelen, Belgium
Weiszhart Z	Semmelweis University, Budapest, Hungary;
Wheelock C E	Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden;
Wheelock A M	Division of Respiratory Medicine and Allergy, Department of

	Medicine, and Center for Molecular Medicine, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden
Wilson S J	Histochemistry Research Unit, Faculty of Medicine, University of Southampton, Southampton, UK;

Contributors

Aliprantis Antonios, Merck Research Laboratories, Boston, USA;
Allen David, North West Severe Asthma Network, Pennine Acute Hospital NHS Trust, UK
Alving Kjell, Dept Women's & Children's Health, Uppsala University, Uppsala, Sweden
Badorrek P, Fraunhofer ITEM; Hannover, Germany
Balgoma David, Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden
Ballereau S, European institute for Systems Biology and Medicine, University of Lyon, France
Barber Clair, NIHR Southampton Respiratory Biomedical Research Unit and Clinical and Experimental Sciences, Southampton, UK;
Batuwitage Manohara Kanangana, Data Science Institute, Imperial College, London, UK
Bautmans An, MSD, Brussels, Belgium
Bedding A, Roche Diagnostics GmbH, Mannheim, Germany
Behndig AF, Umeå University, Umea, Sweden
Beleta Jorge, Almirall S.A., Barcelona, Spain;
Berglind A, MSD, Brussels, Belgium
Berton A, AstraZeneca, Mölndal, Sweden
Bochenek Grazyna, II Department of Internal Medicine, Jagiellonian University Medical College, Krakow, Poland;
Braun Armin, Fraunhofer Institute for Toxicology and Experimental Medicine, Hannover, Germany;
Campagna D, Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy;
Carayannopoulos Leon, Previously at: MSD, USA;
Casaulta C, University Children's Hospital of Bern, Switzerland
Chaleckis Romanas, Centre of Allergy Research, Karolinska Institutet, Stockholm, Sweden
Davison Timothy Janssen R&D, LLC, Spring House, PA, USA
De Alba Jorge, Almirall S.A., Barcelona, Spain;
De Lepeleire Inge, MSD, Brussels, BE
Dekker Tamara, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands;
Delin Ingrid, Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden
Dennison P, NIHR Southampton Respiratory Biomedical Research Unit, Clinical and Experimental Sciences, NIHR-Wellcome Trust Clinical Research Facility, Faculty of Medicine, University of Southampton, Southampton, UK;
Dijkhuis Annemiek, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands;
Dodson Paul, AstraZeneca, Mölndal, Sweden
Draper Aleksandra, BioSci Consulting, Maasmechelen, Belgium;

Journal Pre-proof

Dyson K, CROMSOURCE; Stirling, UK
Edwards Jessica, Asthma UK, London, UK;
El Hadjam L, European Institute for Systems Biology and Medicine, University of Lyon
Emma Rosalia, Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy;
Ericsson Magnus, Karolinska University Hospital, Stockholm, Sweden
Faulenbach C, Fraunhofer ITEM; Hannover, Germany
Flood Breda, European Federation of Allergy and Airways Diseases Patient's Associations, Brussels, Belgium
Galffy G, Semmelweis University, Budapest, Hungary;
Gallart Hector, Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden
Garissi D, Global Head Clinical Research Division, CROMSOURCE, Italy
Gent J, Royal Brompton and Harefield NHS Foundation Trust, London, UK;
Gerhardsson de Verdier M, AstraZeneca; Mölndal, Sweden;
Gibeon D, National Heart and Lung Institute, Imperial College, London, UK;
Gomez Cristina, Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden
Gove Kerry, NIHR Southampton Respiratory Biomedical Research Unit and Clinical and Experimental Sciences, Southampton, UK;
Gozzard Neil, UCB, Slough, UK;
Guillmant-Farry E, Royal Brompton Hospital, London, UK
Henriksson E, Karolinska University Hospital & Karolinska Institutet, Stockholm, Sweden
Hewitt Lorraine, NIHR Southampton Respiratory Biomedical Research Unit, Southampton, UK
Hoda U, Imperial College, London, UK
Hu Richard, Amgen Inc. Thousand Oaks, USA
Hu Sile, National Heart and Lung Institute, Imperial College, London, UK;
Hu X, Amgen Inc.; Thousand Oaks, USA
Jeyasingham E, UK Clinical Operations, GSK, Stockley Park, UK
Johnson K, Centre for respiratory medicine and allergy, Institute of Inflammation and repair, University Hospital of South Manchester, NHS Foundation Trust, Manchester, UK
Jullian N, European Institute for Systems Biology and Medicine, University of Lyon
Kamphuis Juliette, Longfonds, Amersfoort, The Netherlands;
Kennington Erika J., Asthma UK, London, UK;
Kerry Dyson, CromSource, Stirling, UK;
Kerry G, Centre for respiratory medicine and allergy, Institute of Inflammation and repair, University Hospital of South Manchester, NHS Foundation Trust, Manchester, UK
Klüglich M, Boehringer Ingelheim Pharma GmbH & Co. KG; Biberach, Germany
Knobel Hugo, Philips Research Laboratories, Eindhoven, The Netherlands;
Kolmert Johan, Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden
Konradsen J R, Dept. Women's and Children's Health & Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden
Kots Maxim, Chiesi Pharmaceuticals, SPA, Parma, Italy;

Journal Pre-proof

Kretsos Kosmas, UCB, Slough, UK
Krueger L, University Children's Hospital Bern, Switzerland
Kuo Scott, National Heart and Lung Institute, Imperial College, London, UK;
Kupczyk Maciej, Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden
Lambrecht Bart, University of Gent, Gent, Belgium;
Lantz A-S, Karolinska University Hospital & Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden
Larminie Christopher, GSK, London, UK
Larsson L X, AstraZeneca, Mölndal, Sweden
Latzin P, University Children's Hospital of Bern, Bern, Switzerland
Lazarinis N, Karolinska University Hospital & Karolinska Institutet, Stockholm, Sweden
Lemonnier N, European Institute for Systems Biology and Medicine, CNRS-ENS-UCBL-INSERM, Lyon, France
Lone-Latif Saeeda, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands;
Lowe L A, Centre for respiratory medicine and allergy, Institute of Inflammation and repair, University Hospital of South Manchester, NHS Foundation Trust, Manchester, UK
Manta Alexander, Roche Diagnostics GmbH, Mannheim, Germany
Marouzet Lisa, NIHR Southampton Respiratory Biomedical Research Unit, Southampton, UK
Martin Jane, NIHR Southampton Respiratory Biomedical Research Unit, Southampton, UK
Mathon Caroline, Centre of Allergy Research, Karolinska Institutet, Stockholm, Sweden
McEvoy L, University Hospital, Department of Pulmonary Medicine, Bern, Switzerland
Meah Sally, National Heart and Lung Institute, Imperial College, London, UK;
Menzies-Gow A, Royal Brompton and Harefield NHS Foundation Trust, London, UK;
Metcalf Leanne, Previously at: Asthma UK, London, UK;
Mikus Maria, Science for Life Laboratory & The Royal Institute of Technology, Stockholm, Sweden;
Monk Philip, Synairgen Research Ltd, Southampton, UK;
Naz Shama, Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden
Nething K, Boehringer Ingelheim Pharma GmbH & Co. KG; Biberach, Germany
Nicholas Ben, University of Southampton, Southampton, UK
Nihlén U, *Previously AstraZeneca; Mölndal, Sweden;*
Nilsson Peter, Science for Life Laboratory & The Royal Institute of Technology, Stockholm, Sweden;
Niven R, North West Severe Asthma Network, University Hospital South Manchester, UK
Nordlund B, Dept. Women's and Children's Health & Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden
Nsubuga S, Royal Brompton Hospital, London, UK
Östling Jörgen, AstraZeneca, Mölndal, Sweden;
Pacino Antonio, Lega Italiano Anti Fumo, Catania, Italy;
Palkonen Susanna, European Federation of Allergy and Airways Diseases Patient's Associations, Brussels, Belgium.

Journal Pre-proof

Pellet J, European Institute for Systems Biology and Medicine, CNRS-ENS-UCBL-INSERM, Lyon, France
Pennazza Giorgio, Unit of Electronics for Sensor Systems, Department of Engineering, Campus Bio-Medico University of Rome, Rome, Italy
Petrén Anne, Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden
Pink Sandy, NIHR Southampton Respiratory Biomedical Research Unit, Southampton, UK
Pison C, European Institute for Systems Biology and Medicine, CNRS-ENS-UCBL-INSERM, Lyon, France
Rahman-Amin Malayka, Previously at: Asthma UK, London, UK;
Ravanetti Lara, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands;
Ray Emma, NIHR Southampton Respiratory Biomedical Research Unit, Southampton, UK
Reinke Stacey, Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden
Reynolds Leanne, Previously at: Asthma UK, London, UK;
Riemann K, Boehringer Ingelheim Pharma GmbH & Co. KG; Biberach, Germany
Robberechts Martine, MSD, Brussels, Belgium
Rocha J P, Royal Brompton and Harefield NHS Foundation Trust
Rossios C, National Heart and Lung Institute, Imperial College, London, UK;
Russell Kirsty, National Heart and Lung Institute, Imperial College, London, UK;
Rutgers Michael, Longfonds, Amersfoort, The Netherlands;
Santini G, Università Cattolica del Sacro Cuore, Milan, Italy;
Santonico Marco, Unit of Electronics for Sensor Systems, Department of Engineering, Campus Bio-Medico University of Rome, Rome, Italy
Saqi M, European Institute for Systems Biology and Medicine, CNRS-ENS-UCBL-INSERM, Lyon, France
Schoelch Corinna, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany
Scott S, North West Severe Asthma Network, Countess of Chester Hospital, UK
Sehgal N, North West Severe Asthma Network; Pennine Acute Hospital NHS Trust
Sjödin Marcus, Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden
Smids Barbara, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands;
Smith Caroline, NIHR Southampton Respiratory Biomedical Research Unit, Southampton, UK
Smith Jessica, Asthma UK, London, UK;
Smith Katherine M., University of Nottingham, UK;
Söderman P, Dept. Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden
Sogbesan A, Royal Brompton and Harefield NHS Foundation Trust, London, UK;
Spycher F, University Hospital Department of Pulmonary Medicine, Bern, Switzerland
Staykova Doroteya, University of Southampton, Southampton, UK
Stephan S, Centre for respiratory medicine and allergy, Institute of Inflammation and repair, University Hospital of South Manchester, NHS Foundation Trust, Manchester, UK
Stokholm J, University of Copenhagen and Danish Pediatric Asthma Centre Denmark
Strandberg K, Karolinska University Hospital & Karolinska Institutet, Stockholm, Sweden

Journal Pre-proof

Sunther M, Centre for respiratory medicine and allergy, Institute of Inflammation and repair, University Hospital of South Manchester, NHS Foundation Trust, Manchester, UK
Szentkereszty M, Semmelweis University, Budapest, Hungary;
Tamasi L, Semmelweis University, Budapest, Hungary;
Tariq K, NIHR Southampton Respiratory Biomedical Research Unit, Clinical and Experimental Sciences, NIHR-Wellcome Trust Clinical Research Facility, Faculty of Medicine, University of Southampton, Southampton, UK;
Thörngren John-Olof, Karolinska University Hospital, Stockholm, Sweden
Thorsen Jonathan, COPSAC, Copenhagen Prospective Studies on Asthma in Childhood, Herlev and Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark;
Valente S, Università Cattolica del Sacro Cuore, Milan, Italy;
van de Pol Marianne, Academic Medical Centre, University of Amsterdam, Amsterdam ,The Netherlands;
van Drunen C M, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands;
Van Eyll Jonathan, UCB, Slough, UK
Versnel Jenny, Previously at: Asthma UK, London, UK;
Vink Anton, Philips Research Laboratories, Eindhoven, The Netherlands;
von Garnier C, University Hospital Bern, Switzerland;
Vyas A, North west Severe Asthma Network, Lancashire Teaching Hospitals NHS Trust, UK
Wald Frans, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany
Walker Samantha, Asthma UK, London, UK;
Ward Jonathan, Histochemistry Research Unit, Faculty of Medicine, University of Southampton, Southampton, UK;
Wetzel Kristiane, Boehringer Ingelheim Pharma GmbH, Biberach, Germany
Wiegman Coen, National Heart and Lung Institute, Imperial College, London, UK;
Williams Siân, International Primary Care Respiratory Group, Aberdeen, Scotland;
Yang Xian, Data Science Institute, Imperial College, London, UK
Yeyasingham Elizabeth, UK Clinical Operations, GSK, Stockley Park, UK;
Yu W, Amgen Inc.; Thousand Oaks, USA
Zetterquist W, Dept. Women's and Children's Health & Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden
Zolkipli Z, NIHR Southampton Respiratory Biomedical Research Unit, Clinical and Experimental Sciences and Human Development and Health, Southampton, UK;
Zwinderman A H, Academic Medical Centre, University of Amsterdam, The Netherlands;

Journal Pre-proof

Partner organisations	
Novartis Pharma AG	University of Southampton, Southampton, UK
Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands	Imperial College London, London, UK
University of Catania, Catania, Italy	University of Rome 'Tor Vergata', Rome, Italy
Hvidore Hospital, Hvidore, Denmark	Jagiellonian Univ. Medi.College, Krakow, Poland
University Hospital, Inselspital, Bern, Switzerland	Semmelweis University, Budapest, Hungary
University of Manchester, Manchester, UK	Université d'Aix-Marseille, Marseille, France
Fraunhofer Institute, Hannover, Germany	University Hospital, Umea, Sweden
Ghent University, Ghent, Belgium	Ctr. Nat. Recherche Scientifique, Lyon, France
Università Cattolica del Sacro Cuore, Rome, Italy	University Hospital, Copenhagen, Denmark
Karolinska Institutet, Stockholm, Sweden	Nottingham University Hospital, Nottingham, UK
University of Bergen, Bergen, Norway	Netherlands Asthma Foundation, Leusden, NL
European Lung Foundation, Sheffield, UK	Asthma UK, London, UK
European. Fed. of Allergy and Airways Diseases Patients' Associations, Brussels, Belgium	Lega Italiano Anti Fumo, Catania, Italy
International Primary Care Respiratory Group, Aberdeen, Scotland	Philips Research Laboratories, Eindhoven, NL
Synairgen Research Ltd, Southampton, UK	Aerocrine AB, Stockholm, Sweden
BioSci Consulting, Maasmechelen, Belgium	Almirall
AstraZeneca	Boehringer Ingelheim
Chiesi	GlaxoSmithKline
Roche	UCB
Janssen Biologics BV	Amgen NV
Merck Sharp & Dome Corp	

Journal Pre-proof

MEMBERS OF THE ETHICS BOARD			
Name	**Task**	**Affiliation**	**e-mail**
Jan-Bas Prins	Biomedical research	LUMC/the Netherlands	J.B.Prins@lumc.nl
Martina Gahlemann	Clinical care	BI/Germany	Martina.Gahlemann@boehringer-ingelheim.com
Luigi Visintin	Legal affairs	LIAF/Italy	visintin@inrete.it
Hazel Evans	Paediatric care	Southampton/UK	hazel.evans@uhs.nhs.uk
Martine Puhl	Patient representation (co chair)	NAF/ the Netherlands	martine@puhl.nl
Lina Buzermaniene	Patient representation	EFA/Lithuania	lina.buzermaniene@pavb.lt
Val Hudson	Patient representation	Asthma UK	hudsonval7@gmail.com
Laura Bond	Patient representation	Asthma UK	lvbond22@googlemail.com
Pim de Boer	Patient representation and pathobiology	IND	deboer.pim@hetnet.nl
Guy Widdershoven	Research ethics	VUMC/the Netherlands	g.widdershoven@vumc.nl
Ralf Sigmund	Research methodology and biostatistics	BI/Germany	ralf.sigmund@boehringer-ingelheim.com

THE PATIENT INPUT PLATFORM	
Name	**Country**
Amanda Roberts	UK
David Supple (chair)	UK
Dominique Hamerlijnck	The Netherlands
Jenny Negus	UK
Juliëtte Kamphuis	The Netherlands
Lehanne Sergison	UK
Luigi Visintin	Italy
Pim de Boer (co-chair)	The Netherlands
Susanne Onstein	The Netherlands

MEMBERS OF THE SAFETY MONITORING BOARD	
Name	**Task**
William MacNee	Clinical care
Renato Bernardini	Clinical pharmacology
Louis Bont	Paediatric care and infectious diseases
Per-Ake Wecksell	Patient representation
Pim de Boer	Patient representation and pathobiology (chair)
Martina Gahlemann	Patient safety advice and clinical care (co-chair)
Ralf Sigmund	Bio-informatician

Journal Pre-proof