



## Early View

Research letter

### **Epithelial dysregulation in obese severe asthmatics with gastro-oesophageal reflux**

Jeanne-Marie Perotin, James P.R. Schofield, Susan J. Wilson, Jonathan Ward, Joost Brandsma, Fabio Strazzeri, Aruna Bansal, Xian Yang, Anthony Rowe, Julie Corfield, Rene Lutter, Dominick E. Shaw, Per S. Bakke, Massimo Caruso, Barbro Dahlén, Stephen J. Fowler, Ildikó Horváth, Peter Howarth, Norbert Krug, Paolo Montuschi, Marek Sanak, Thomas Sandström, Kai Sun, Ioannis Pandis, Charles Auffray, Bertrand De Meulder, Diane Lefaudeux, John H. Riley, Ana R. Sousa, Sven-Erik Dahlen, Ian M. Adcock, Kian Fan Chung, Peter J. Sterk, Paul J. Skipp, Jane E. Collins, Donna E. Davies, Ratko Djukanović

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**Title: Epithelial dysregulation in obese severe asthmatics with gastro-oesophageal reflux**

**Authors:** Jeanne-Marie Perotin<sup>1\*</sup>, James PR Schofield<sup>1,2</sup>, Susan J Wilson<sup>3</sup>, Jonathan Ward<sup>3</sup>, Joost Brandsma<sup>1</sup>, Fabio Strazzeri<sup>4</sup>, Aruna Bansal<sup>5</sup>, Xian Yang<sup>6</sup>, Anthony Rowe<sup>7</sup>, Julie Corfield<sup>8</sup>, Rene Lutter<sup>9, 10</sup>, Dominick E Shaw<sup>11</sup>, Per S Bakke<sup>12</sup>, Massimo Caruso<sup>13,14</sup>, Barbro Dahlén<sup>15</sup>, Stephen J. Fowler<sup>16</sup>, Ildikó Horváth<sup>17</sup>, Peter Howarth<sup>1</sup>, Norbert Krug<sup>18</sup>, Paolo Montuschi<sup>18</sup>, Marek Sanak<sup>20</sup>, Thomas Sandström<sup>21</sup>, Kai Sun<sup>7</sup>, Ioannis Pandis<sup>7</sup>, Charles Auffray<sup>22</sup>, Bertrand De Meulder<sup>22</sup>, Diane Lefaudeux<sup>22</sup>, John H Riley<sup>23</sup>, Ana R Sousa<sup>23</sup>, Sven-Erik Dahlen<sup>24</sup>, Ian M Adcock<sup>25</sup>, Kian Fan Chung<sup>25</sup>, Peter J Sterk<sup>11</sup>, Paul J Skipp<sup>2</sup>, Jane E Collins<sup>1</sup>, Donna E Davies<sup>1</sup>, Ratko Djukanović<sup>1</sup> on behalf of the U-BIOPRED Study Group

**Affiliations:**

<sup>1</sup> NIHR Southampton Biomedical Research Centre, Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, UK

<sup>2</sup> Centre for Proteomic Research, Biological Sciences, University of Southampton, UK

<sup>3</sup> The Histochemistry Research Unit, Faculty of Medicine, University of Southampton

<sup>4</sup> Mathematical Sciences, University of Southampton, UK

<sup>5</sup> Acclarogen Ltd, Cambridge, UK

<sup>6</sup> Data Science Institute, Imperial College, London, UK

<sup>7</sup> Janssen Research & Development, Buckinghamshire, UK

<sup>8</sup> Areteva Ltd, Nottingham, UK

<sup>9</sup> Amsterdam UMC, Department of Experimental Immunology (Amsterdam Infection & Immunity Institute), University of Amsterdam, Amsterdam, The Netherlands

<sup>10</sup> Amsterdam UMC, Department of Respiratory Medicine, University of Amsterdam, Amsterdam, The Netherlands

<sup>11</sup>NIHR Biomedical Respiratory Research Centre, University of Nottingham, UK

<sup>12</sup>Institute of Medicine, University of Bergen, Bergen, Norway

<sup>13</sup>Dept. of Clinical and Experimental Medicine Hospital University, University of Catania, Catania, Italy.

<sup>14</sup>Dept. of Biomedical and Biotechnological Sciences (Biometec). University of Catania. Catania. Italy

<sup>15</sup>Department of Respiratory diseases and allergy, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden.

<sup>16</sup>Respiratory and Allergy Research Group, University of Manchester, Manchester, UK.

<sup>17</sup>Dept. of Pulmonology, Semmelweis University, Budapest, Hungary

<sup>18</sup>Fraunhofer Institute for Toxicology and Experimental Medicine Hannover, Hannover, Germany.

<sup>19</sup>Faculty of Medicine, Catholic University of the Sacred Heart, Fondazione Policlinico Universitario, Agostino Gemelli IRCCS, Rome, Italy.

<sup>20</sup>Laboratory of Molecular Biology and Clinical Genetics, Medical College, Jagiellonian University, Krakow, Poland

<sup>21</sup>Dept. of Medicine, Dept of Public Health and Clinical Medicine Respiratory Medicine Unit, Umeå University, Umeå, Sweden.

<sup>22</sup>European Institute for Systems Biology and Medicine, CNRS-ENS-UCBL-INSERM, Université de Lyon, France

<sup>23</sup>Respiratory Therapeutic Unit, GSK, Stockley Park, UK.

<sup>24</sup>The Centre for Allergy Research, The Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden.

<sup>25</sup>Cell and Molecular Biology Group, Airways Disease Section, National Heart and Lung Institute, Imperial College London, Dovehouse Street, London, UK

\* Corresponding author: [J-M.Perotin-Collard@soton.ac.uk](mailto:J-M.Perotin-Collard@soton.ac.uk).

**Dear Editor,**

Gastro-oesophageal reflux disease (GORD) and obesity are associated with frequent exacerbations and poor quality of life in asthmatics. Multiple mechanisms have been proposed for the effect of obesity, including modification of inflammation affecting epithelial cell proliferation and wound repair, while the role of GORD is poorly understood and proton pump inhibitor (PPI) are of variable efficacy. GORD might exert a deleterious effect by inducing vagal reflex, neuroinflammation and directly (via microaspiration) triggering airway inflammation. Studies of reflux in animal models and human bronchial epithelial cell culture show varying impact on inflammation and airway remodelling. We have recently demonstrated changes in the sputum proteome in severe asthmatics with GORD, providing supportive evidence for gastric secretions exerting a direct effect on the airways (1). The epithelium plays a key role in asthma, so in this study we speculated that severe asthma in obese patients with GORD would be associated with epithelial dysfunction. Because GORD is treated with PPI, drugs associated with risk of pneumonia and exacerbations of COPD and cystic fibrosis, the impact of PPI was also assessed.

We analyzed 61 never or ex-smoker asthmatics and 44 healthy never smokers from the U-BIOPRED study (2) who had undergone bronchoscopy, bronchial biopsy and epithelial brushing. Patients were categorised as obese if  $BMI \geq 30 \text{ kg/m}^2$ , having or not a physician's diagnosis of GORD, and treated or not for GORD. Epithelial brushings were processed into RNeasy for Affymetrix U133 Plus 2.0 microarray analysis (GSE76226) and bronchial biopsies were immunostained for CD3+, CD4+ and CD8+ lymphocytes and analysed for basement membrane thickness. The study was approved by national ethics committees. All participants provided consent.

Epithelial transcriptomic data were clustered by TDA using the Ayasdi Core software (Ayasdi, MenloPark, CA), with cluster boundaries defined by density using Morse theory (3). Paired t-tests were applied to log<sub>2</sub> transformed transcriptomic data. Clinical data were analyzed by Kruskal-Wallis, Mann-Whitney U or Student t tests depending on data distribution. False discovery rate correction was

applied to the differentially expressed genes (DEGs). Pathway signatures and upstream regulators were identified by Ingenuity Pathway Analysis (IPA) (QIAGEN, Redwood City, CA). Potential drug impact on DEGs was identified by Connectivity Map (CMap) analysis of DEG signatures.

TDA analysis produced three clusters of similar size (C1, 2 and 3), comprising 21 participants (34%) in C1, 23 (38%) in C2 and 22 (36%) in C3 (Fig 1). When compared to combined C2/3 clusters, C1 had a higher incidence of obesity (76% vs 47%,  $p=0.02$ ), GORD (85% vs 43%,  $p=0.04$ ) and GORD treatment (81% vs 36%,  $p=0.004$ ) and 48% were obese and had a diagnosis of GORD and GORD treatment (compared to 10% in C2/C3,  $p=0.0009$ ); this cluster was, therefore, termed the Obesity-GORD-PPI treatment [OGP] phenotype. When compared to C2/3, the OGP cluster had lower blood eosinophil counts ( $p=0.007$ ), but was similar in respect of corticosteroid treatment.

IPA identified 77 pathways dysregulated in the OGP cluster relative to health, the top being the WNT/ $\beta$ -catenin pathway (z-score: 2.2-fold difference vs. healthy participants). Amongst the 38 DEGs related to WNT/ $\beta$ -catenin signalling, *FZD3* and *WISP1* were amongst the top upregulated (Figure 1). Application of CMap analysis to these DEGs and comparison with the genes regulated by PPI and bile acids in A549 epithelial cells (Fig 1) showed that the WNT/ $\beta$ -catenin signalling pathway was not associated with PPI or bile acid effects. Furthermore, although evidence points to WNT/ $\beta$ -catenin signalling and the WNT target gene *WISP1* regulating airway remodelling and pulmonary myofibroblast proliferation in COPD and IPF (4), we did not find a difference in the thickness of the sub-epithelial *lamina reticularis* between the OGP cluster and the other patients.

*WISP1* has been shown to be upregulated in obese individuals but has also been identified as an inhibitor of adipocyte differentiation by blocking the induction of the adipogenic transcription factors PPAR $\gamma$  and C/EBP $\alpha$  (5), both of which were downregulated in the OGP cluster. Given that PPAR $\gamma$  expression in bronchial epithelial cells has been shown to protect against oxidative stress and suppress MUC5AC expression, these data suggested that the OGP phenotype should be associated with airways inflammation. However, our study showed that the OGP cluster had a predominantly pauci-

granulocytic sputum cell profile ( $p=0.017$ ) and fewer sub-mucosal T-cells when compared to health (CD8<sup>+</sup> cells: 10.2 vs. 20.4 cells/mm<sup>2</sup>,  $p=0.05$ ; CD4<sup>+</sup> cells: 7.2 vs 10.4,  $p=0.02$ ; CD3<sup>+</sup> cells: 23.0 vs 36.7,  $p=0.03$ ). This could be explained by the finding in the OGP cluster of downregulated immune response pathways, including proliferation, activation and survival of lymphocytes, leucocyte recruitment and transepithelial migration (IL-7, TREM1 (Triggering receptor expressed on myeloid cells 1), B cell receptor and Calcium signaling; z-scores -0.69, -2.18, -2.33, -3.66 respectively). When compared to health and C2/3, the OGP cluster also exhibited downregulation of CCL5, CXCL1 and CCL11. CMap analysis identified high connectivity scores between TREM1 and effects of bile acids (CMap score 99.2), and between PPI treatment and Calcium signaling (CMap score 76.6) (Fig 1), suggesting a direct impact of bile acids and PPI treatment on immune cell accumulation.

In support of our study, recent analysis of bile acid effects on LPS-stimulated macrophages identified downregulated genes involved in differentiation and migration of immune cells, including T-cells, and decreased chemokine expression, including CCL5 and CXCL1 (6). PPI-inhibition of H<sup>+</sup>/K<sup>+</sup> ATPase induces intracellular acidification that inhibits immune cell proliferation, decreases heparanase activation involved in ECM remodeling and degradation (7), and decreases intercellular adhesion molecule expression, resulting in reduced immune cell transmigration (8). In airway epithelial cells, TLR2 activation by DAMPs releases calcium from endoplasmic reticulum stores, resulting in chemokine regulation through activation of NFκB and calpains which cleave junctional proteins and facilitate immune cell transmigration (9). In our study, expression of TLR2, NFκB and NFκB-regulated chemokines (*CCL5*, *CXCL1*, *CXCL2*, *CCL11*, *CCL22*, *CXCL8*) was also downregulated in the OGP cluster. In contrast, expression of calreticulin and calnexin, two endoplasmic reticulum calcium storage proteins, whose expression is increased by low intracellular calcium storage (10), was upregulated in the OGP cluster, suggesting dysregulated intracellular calcium influx. This could be speculated to involve PPI-induced decrease of Ca<sup>2+</sup>-ATPase sensitivity as previously shown in myocytes (11).

The top upstream regulator for the OGP cluster was CD24 (activation z-score 2.2;  $p=0.0004$ ), a cell surface receptor involved in suppression of immune responses to DAMPs (12), organization of tight

junction proteins (13), regulation of adipogenesis, B-cell survival and T-cell activity (14). CD24 is a direct WNT target gene (15), which is consistent with our findings of upregulated WNT/ $\beta$  catenin signaling. Together, these associations suggest a central role for CD24 in the OGP phenotype.

In summary, this exploratory analysis of epithelial gene expression in severe asthma has identified 3 clusters, one of which is enriched for obesity, GORD and treatment with PPI, with an as yet unreported mechanism that could represent a new endotype. This potentially new endotype was shown to be pauci-granulocytic as a consequence of downregulated mechanisms of cell recruitment linked to bile acid exposure and PPI treatment. The implications of this endotype for virus-induced exacerbations, which are increased in asthmatics with GORD, remains to be elucidated.

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## Figure legend

Severe asthma clusters based on epithelial transcriptomics. (a) TDA network constructed with transcripts from bronchial brushings using density analysis by Morse theory, with (b) the identified clusters 1-3 colored yellow, pink and orange. (c-e) Applying BMI, GORD treatment and blood eosinophil counts as meta data, nodes are colored by intensity from blue (low intensity) to red (high intensity). (f) Heat map of the three top upregulated and three top downregulated differentially expressed genes of WNT/ $\beta$ -catenin, TREM1 and Calcium signalling in the OGP cluster and in airway epithelial cells exposed to PPI (column L for Lansoprazole and column R for Rabeprazole) and bile acids (column G for Glycodeoxycholic acid and T for Taurodeoxycholic acid).

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Catania, Catania, Italy; A. Chaiboonchoe, European Institute for Systems Biology and Medicine, CNRS-ENS-UCBL-INSERM, Lyon, France; P. Chanez, Assistance publique des Hôpitaux de Marseille - Clinique des bronches, allergies et sommeil, Aix Marseille Université, Marseille, France; K.F. Chung, National Heart and Lung Institute, Imperial College, London, UK; C.H. Compton, Respiratory Therapeutic Unit, GSK, London, UK; J. Corfield, Areteva R&D, Nottingham, UK; A. D'Amico, University of Rome 'Tor Vergata', Rome Italy; S.E. Dahlen, Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden; B. De Meulder, European Institute for Systems Biology and Medicine, CNRS-ENS-UCBL-INSERM, Lyon, France; R. Djukanovic, NIHR Southampton Respiratory Biomedical Research Unit and Clinical and Experimental Sciences, Southampton, UK; V.J. Erpenbeck, Translational Medicine, Respiratory Profiling, Novartis Institutes for Biomedical Research, Basel, Switzerland; D. Erzen, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany; K. Fichtner, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany; N. Fitch, BioSci Consulting, Maasmechelen, Belgium; L.J. Fleming, National Heart and Lung Institute, Imperial College, London, UK; Royal Brompton and Harefield NHS trust, UK; E. Formaggio, previously CROMSOURCE, Verona, Italy; S.J. Fowler, 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, UK; U. Frey, University Children's Hospital, Basel, Switzerland; M. Gahlemann, Boehringer Ingelheim (Schweiz) GmbH, Basel, Switzerland; T. Geiser, Dept of Respiratory Medicine, University Hospital Bern, Switzerland; Y. Guo, Data Science Institute, Imperial College, London, UK; S. Hashimoto, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands; J. Haughney, International Primary Care Respiratory Group, Aberdeen, UK; G. Hedlin, Dept Women's and Children's Health & Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden; P.W. Hekking, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands; T. Higenbottam, Allergy Therapeutics, West Sussex, UK; J.M. Hohlfeld, Fraunhofer Institute for Toxicology and Experimental Medicine, Hannover, Germany; C. Holweg, Respiratory and Allergy Diseases, Genentech, San Francisco, USA; I. Horváth, Semmelweis University, Budapest, Hungary; P. Howarth, NIHR Southampton Respiratory Biomedical Research Unit, Clinical and Experimental

Sciences and Human Development and Health, Southampton, UK; A.J. James, Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden; R. Knowles, Arachos Pharma, Stevenage, UK; A.J. Knox, Respiratory Research Unit, University of Nottingham, Nottingham, UK; N. Krug, Fraunhofer Institute for Toxicology and Experimental Medicine, Hannover, Germany; D. Lefaudeux, European Institute for Systems Biology and Medicine, CNRS-ENS-UCBL-INSERM, Lyon, France; M.J. Loza, Janssen R&D, USA; R. Lutter, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands; A. Manta, Roche Diagnostics GmbH, Mannheim, Germany; S. Masefield, European Lung Foundation, Sheffield, UK; J.G. Matthews, Respiratory and Allergy Diseases, Genentech, San Francisco, USA; A. Mazein, European Institute for Systems Biology and Medicine, CNRS-ENS-UCBL-INSERM, Lyon, France; A. Meiser, Data Science Institute, Imperial College, London, UK; R.J.M. Middelveld, Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden; M. Miralpeix, Almirall, Barcelona, Spain; P. Montuschi, Università Cattolica del Sacro Cuore, Milan, Italy; N. Mores, Università Cattolica del Sacro Cuore, Milan, Italy; C.S. Murray, 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, UK; J. Musial, Dept of Medicine, Jagiellonian University Medical College, Krakow, Poland; D. Myles, Respiratory Therapeutic Unit, GSK, London, UK; L. Pahun, Assistance publique des Hôpitaux de Marseille, Clinique des bronches, allergies et sommeil, Espace Éthique Méditerranéen, Aix-Marseille Université, Marseille, France; I. Pandis, Data Science Institute, Imperial College, London, UK; S. Pavlidis, National Heart and Lung Institute, Imperial College, London, UK; P. Powell, European Lung Foundation, Sheffield, UK; G. Praticò, CROMSOURCE, Verona, Italy; M. Puig Valls, CROMSOURCE, Barcelona, Spain; N. Rao, Janssen R&D, USA; J. Riley, Respiratory Therapeutic Unit, GSK, London, UK; A. Roberts, Asthma UK, London, UK; G. Roberts, NIHR Southampton Respiratory Biomedical Research Unit, Clinical and Experimental Sciences and Human Development and Health, Southampton, UK; A. Rowe, Janssen R&D, UK; T. Sandström, Dept of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden; W. Seibold, Boehringer Ingelheim Pharma GmbH, Biberach, Germany; A. Selby, NIHR Southampton Respiratory Biomedical Research Unit, Clinical and Experimental Sciences and Human Development and Health,

Southampton, UK; D.E. Shaw, Respiratory Research Unit, University of Nottingham, UK; R. Sigmund, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany; F. Singer, University Children's Hospital, Zurich, Switzerland; P.J. Skipp, Centre for Proteomic Research, Institute for Life Sciences, University of Southampton, Southampton, UK; A.R. Sousa, Respiratory Therapeutic Unit, GSK, London, UK; P.J. Sterk, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands; K. Sun, Data Science Institute, Imperial College, London, UK; B. Thornton, MSD, USA; W.M. van Aalderen, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands; M. van Geest, AstraZeneca, Mölndal, Sweden; J. Vestbo, 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, UK; N.H. Vissing, COPSAC, Copenhagen Prospective Studies on Asthma in Childhood, Herlev and Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark; A.H. Wagener, Academic Medical Center Amsterdam, Amsterdam, The Netherlands; S.S. Wagers, BioSci Consulting, Maasmechelen, Belgium; Z. Weiszhart, Semmelweis University, Budapest, Hungary; C.E. Wheelock, Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden; S.J. Wilson, Histochemistry Research Unit, Faculty of Medicine, University of Southampton, Southampton, UK.

Additional contributors: Antonios Aliprantis, Merck Research Laboratories, Boston, USA; David Allen, North West Severe Asthma Network, Pennine Acute Hospital NHS Trust, UK; Kjell Alving, Dept Women's & Children's Health, Uppsala University, Uppsala, Sweden; P. Badorrek, Fraunhofer ITEM, Hannover, Germany; David Balgoma, Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden; S. Ballereau, European institute for Systems Biology and Medicine, University of Lyon, France; Clair Barber, NIHR Southampton Respiratory Biomedical Research Unit and Clinical and Experimental Sciences, Southampton, UK; Manohara Kanangana Batuwitage, Data Science Institute, Imperial College, London, UK; An Bautmans, MSD, Brussels, Belgium; A. Bedding, Roche Diagnostics GmbH, Mannheim, Germany; A.F. Behndig, Umeå University, Umea, Sweden; Jorge Beleta, Almirall S.A., Barcelona, Spain; A. Berglind, MSD, Brussels, Belgium; A. Berton, AstraZeneca, Mölndal, Sweden; Grazyna Bochenek, II Dept of Internal Medicine, Jagiellonian University Medical College, Krakow, Poland; Armin Braun, Fraunhofer Institute for Toxicology and

Experimental Medicine, Hannover, Germany; D. Campagna, Dept of Clinical and Experimental Medicine, University of Catania, Catania, Italy; Leon Carayannopoulos, previously at MSD, USA; C. Casaulta, University Children's Hospital of Bern, Switzerland; Romanas Chaleckis, Centre of Allergy Research, Karolinska Institutet, Stockholm, Sweden; B. Dahlén, Karolinska University Hospital & Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden; Timothy Davison, Janssen R&D, USA; Jorge De Alba, Almirall S.A., Barcelona, Spain; Inge De Lepeleire, MSD, Brussels, Belgium; Tamara Dekker, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands; Ingrid Delin, Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden; P. Dennison, NIHR Southampton Respiratory Biomedical Research Unit, Clinical and Experimental Sciences, NIHR-Wellcome Trust Clinical Research Facility, Faculty of Medicine, University of Southampton, Southampton, UK; Annemiek Dijkhuis, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands; Paul Dodson, AstraZeneca, Mölndal, Sweden; Aleksandra Draper, BioSci Consulting, Maasmechelen, Belgium; K. Dyson, CROMSOURCE, Stirling, UK; Jessica Edwards, Asthma UK, London, UK; L. El Hadjam, European Institute for Systems Biology and Medicine, University of Lyon, France; Rosalia Emma, Dept of Clinical and Experimental Medicine, University of Catania, Catania, Italy; Magnus Ericsson, Karolinska University Hospital, Stockholm, Sweden; C. Faulenbach, Fraunhofer ITEM, Hannover, Germany; Breda Flood, European Federation of Allergy and Airways Diseases Patient's Associations, Brussels, Belgium; G. Galffy, Semmelweis University, Budapest, Hungary; Hector Gallart, Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden; D. Garissi, Global Head Clinical Research Division, CROMSOURCE, Italy; J. Gent, Royal Brompton and Harefield NHS Foundation Trust, London, UK; M. Gerhardsson de Verdier, AstraZeneca; Mölndal, Sweden; D. Gibeon, National Heart and Lung Institute, Imperial College, London, UK; Cristina Gomez, Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden; Kerry Gove, NIHR Southampton Respiratory Biomedical Research Unit and Clinical and Experimental Sciences, Southampton, UK; Neil Gozzard, UCB, Slough, UK; E. Guillmant-Farry, Royal Brompton Hospital, London, UK; E. Henriksson, Karolinska University Hospital & Karolinska Institutet, Stockholm, Sweden; Lorraine Hewitt, NIHR Southampton Respiratory Biomedical Research Unit, Southampton, UK; U. Hoda, Imperial College,

London, UK; Richard Hu, Amgen Inc. Thousand Oaks, USA; Sile Hu, National Heart and Lung Institute, Imperial College, London, UK; X. Hu, Amgen Inc., Thousand Oaks, USA; E. Jeyasingham, UK Clinical Operations, GSK, Stockley Park, UK; K. Johnson, Centre for Respiratory Medicine and Allergy, Institute of Inflammation and repair, University Hospital of South Manchester, NHS Foundation Trust, Manchester, UK; N. Jullian, European Institute for Systems Biology and Medicine, University of Lyon, France; Juliette Kamphuis, Longfonds, Amersfoort, The Netherlands; Erika J. Kennington, Asthma UK, London, UK; Dyson Kerry, CromSource, Stirling, UK; G. Kerry, Centre for Respiratory Medicine and Allergy, Institute of Inflammation and Repair, University Hospital of South Manchester, NHS Foundation Trust, Manchester, UK; M. Klüglich, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany; Hugo Knobel, Philips Research Laboratories, Eindhoven, The Netherlands; Johan Kolmert, Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden; J.R. Konradsen, Dept Women's and Children's Health & Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden; Maxim Kots, Chiesi Pharmaceuticals, SPA, Parma, Italy; Kosmas Kretsos, UCB, Slough, UK; L. Krueger, University Children's Hospital Bern, Switzerland; Scott Kuo, National Heart and Lung Institute, Imperial College, London, UK; Maciej Kupczyk, Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden; Bart Lambrecht, University of Gent, Gent, Belgium; A-S. Lantz, Karolinska University Hospital & Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden; Christopher Larminie, GSK, London, UK; L.X. Larsson, AstraZeneca, Mölndal, Sweden; P. Latzin, University Children's Hospital of Bern, Bern, Switzerland; N. Lazarinis, Karolinska University Hospital & Karolinska Institutet, Stockholm, Sweden; N. Lemonnier, European Institute for Systems Biology and Medicine, CNRS-ENS-UCBL-INSERM, Lyon, France; Saeeda Lone-Latif, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands; L.A. Lowe, Centre for Respiratory Medicine and Allergy, Institute of Inflammation and Repair, University Hospital of South Manchester, NHS Foundation Trust, Manchester, UK; Alexander Manta, Roche Diagnostics GmbH, Mannheim, Germany; Lisa Marouzet, NIHR Southampton Respiratory Biomedical Research Unit, Southampton, UK; Jane Martin, NIHR Southampton Respiratory Biomedical Research Unit, Southampton, UK; Caroline Mathon, Centre of Allergy Research, Karolinska Institutet, Stockholm, Sweden; L. McEvoy, University Hospital, Dept of

Pulmonary Medicine, Bern, Switzerland; Sally Meah, National Heart and Lung Institute, Imperial College, London, UK; A. Menzies-Gow, Royal Brompton and Harefield NHS Foundation Trust, London, UK; Leanne Metcalf, previously at Asthma UK, London, UK; Maria Mikus, Science for Life Laboratory & The Royal Institute of Technology, Stockholm, Sweden; Philip Monk, Synairgen Research Ltd, Southampton, UK; Shama Naz, Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden; K. Nething, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany; Ben Nicholas, University of Southampton, Southampton, UK; U. Nihlén, previously at AstraZeneca, Mölndal, Sweden; Peter Nilsson, Science for Life Laboratory & The Royal Institute of Technology, Stockholm, Sweden; R. Niven, North West Severe Asthma Network, University Hospital South Manchester, UK; B. Nordlund, Dept Women's and Children's Health & Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden; S. Nsubuga, Royal Brompton Hospital, London, UK; Jörgen Östling, AstraZeneca, Mölndal, Sweden; Antonio Pacino, Lega Italiano Anti Fumo, Catania, Italy; Susanna Palkonen, European Federation of Allergy and Airways Diseases Patient's Associations, Brussels, Belgium; J. Pellet, European Institute for Systems Biology and Medicine, CNRS-ENS-UCBL-INSERM, Lyon, France; Giorgio Pennazza, University of Rome 'Tor Vergata', Rome Italy; Anne Petrén, Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden; Sandy Pink, NIHR Southampton Respiratory Biomedical Research Unit, Southampton, UK; C. Pison, European Institute for Systems Biology and Medicine, CNRS-ENS-UCBL-INSERM, Lyon, France; Anthony Postle, University of Southampton, UK; Malayka Rahman-Amin, previously at Asthma UK, London, UK; Lara Ravanetti, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands; Emma Ray, NIHR Southampton Respiratory Biomedical Research Unit, Southampton, UK; Stacey Reinke, Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden; Leanne Reynolds, previously at Asthma UK, London, UK; K. Riemann, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany; Martine Robberechts, MSD, Brussels, Belgium; J.P. Rocha, Royal Brompton and Harefield NHS Foundation Trust, UK; C. Rossios, National Heart and Lung Institute, Imperial College, London, UK; Kirsty Russell, National Heart and Lung Institute, Imperial College, London, UK; Michael Rutgers, Longfonds, Amersfoort, The Netherlands; G. Santini, Università Cattolica del Sacro Cuore, Milan, Italy; Marco Santoninco, University of Rome 'Tor Vergata', Rome



Italy; M. Saqi, European Institute for Systems Biology and Medicine, CNRS-ENS-UCBL-INSERM, Lyon, France; Corinna Schoelch, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany; James P.R. Schofield, Centre for Proteomic Research, Institute for Life Sciences, University of Southampton, Southampton, UK; S. Scott, North West Severe Asthma Network, Countess of Chester Hospital, UK; N. Sehgal, North West Severe Asthma Network, Pennine Acute Hospital NHS Trust; Marcus Sjödin, Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden; Barbara Smids, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands; Caroline Smith, NIHR Southampton Respiratory Biomedical Research Unit, Southampton, UK; Jessica Smith, Asthma UK, London, UK; Katherine M. Smith, University of Nottingham, UK; P. Söderman, Dept Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden; A. Sogbessan, Royal Brompton and Harefield NHS Foundation Trust, London, UK; F. Spycher, University Hospital Dept of Pulmonary Medicine, Bern, Switzerland; Doroteya Staykova, University of Southampton, Southampton, UK; S. Stephan, Centre for Respiratory Medicine and Allergy, Institute of Inflammation and Repair, University Hospital of South Manchester, NHS Foundation Trust, Manchester, UK; J. Stokholm, University of Copenhagen and Danish Pediatric Asthma Centre Denmark; K. Strandberg, Karolinska University Hospital & Karolinska Institutet, Stockholm, Sweden; M. Sunther, Centre for Respiratory Medicine and Allergy, Institute of Inflammation and Repair, University Hospital of South Manchester, NHS Foundation Trust, Manchester, UK; M. Szentkereszty, Semmelweis University, Budapest, Hungary; L. Tamasi, Semmelweis University, Budapest, Hungary; K. Tariq, NIHR Southampton Respiratory Biomedical Research Unit, Clinical and Experimental Sciences, NIHR-Wellcome Trust Clinical Research Facility, Faculty of Medicine, University of Southampton, Southampton, UK; John-Olof Thörngren, Karolinska University Hospital, Stockholm, Sweden; Jonathan Thorsen, COPSAC, Copenhagen Prospective Studies on Asthma in Childhood, Herlev and Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark; S. Valente, Università Cattolica del Sacro Cuore, Milan, Italy; Marianne van de Pol, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands; C.M. van Drunen, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands; Jonathan Van Eyll, UCB, Slough, UK; Jenny Versnel, previously at Asthma UK, London, UK; Anton Vink, Philips Research Laboratories, Eindhoven, The

Netherlands; C. von Garnier, University Hospital Bern, Switzerland; A. Vyas, North West Severe Asthma Network, Lancashire Teaching Hospitals NHS Trust, UK; Frans Wald, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany; Samantha Walker, Asthma UK, London, UK; Jonathan Ward, Histochemistry Research Unit, Faculty of Medicine, University of Southampton, Southampton, UK; Kristiane Wetzel, Boehringer Ingelheim Pharma GmbH, Biberach, Germany; Coen Wiegman, National Heart and Lung Institute, Imperial College, London, UK; Siân Williams, International Primary Care Respiratory Group, Aberdeen, UK; Xian Yang, Data Science Institute, Imperial College, London, UK; Elizabeth Yeyasingham, UK Clinical Operations, GSK, Stockley Park, UK; W. Yu, Amgen Inc., Thousand Oaks, USA; W. Zetterquist, Dept Women's and Children's Health & Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden; Z. Zolkipli, NIHR Southampton Respiratory Biomedical Research Unit, Clinical and Experimental Sciences and Human Development and Health, Southampton, UK; A.H. Zwinderman, Academic Medical Centre, University of Amsterdam, The Netherlands. 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; Hvidovre Hospital, Hvidovre, 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, The Netherlands; 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, UK; Philips Research Laboratories, Eindhoven, The Netherlands; 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. Members of the ethics board: Jan-Bas Prins, biomedical research, LUMC, The Netherlands; Martina Gahlemann, clinical care, BI, Germany; Luigi Visintin, legal affairs, LIAF, Italy; Hazel Evans, paediatric care, Southampton, UK; Martine Puhl, patient representation (co-chair), NAF, The Netherlands; Lina Buzermaniene, patient representation, EFA, Lithuania; Val Hudson, patient representation, Asthma UK; Laura Bond, patient representation, Asthma UK; Pim de Boer, patient representation and pathobiology, IND; Guy Widdershoven, research ethics, VUMC, The Netherlands; Ralf Sigmund, research methodology and biostatistics, BI, Germany. The patient input platform: 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: 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.

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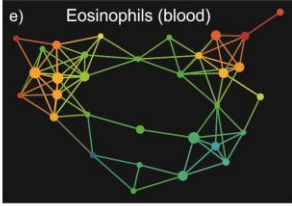
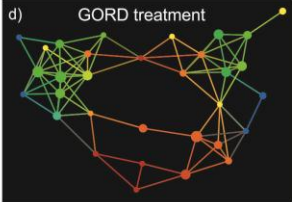
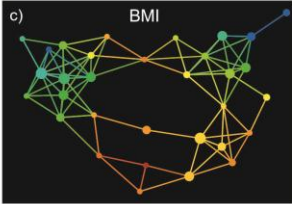
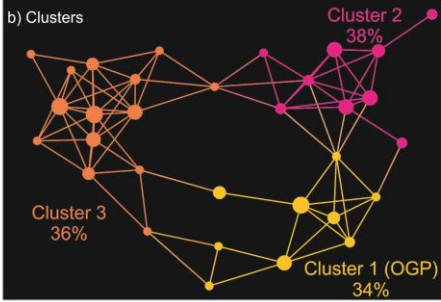
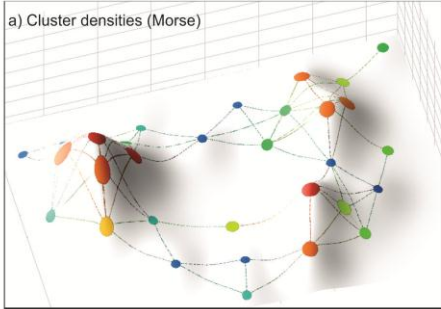
**Author contributions:**

Substantial contributions to the conception or design of the work: J.M.P, J.PR.S, D.E.D, R.D.

Acquisition, analysis, or interpretation of data: J.M.P, J.PR.S, J.B, F.S, A.B, Y.X, A.R, J.C, S.W, J.W, R.L, D.E.S, P.S.B, M.C, B.D, S.J.F, I.H, P.H, N.K, P.M, M.S, T.S, K.S, I.P, C.A, B.D.M, D.L, J.R, A.R.S, S.E.D, I.M.A, K.F.C, P.J.S, P.J. S, D.E.D, R.D

Drafting the manuscript or revising it critically for important intellectual content: J.M.P, J.PR.S, J.E.C, D.E.D, R.D.

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	OGP	L	R	G	T
<b>WNT/<math>\beta</math>-catenin genes</b>					
Cmap score		29.39	-14.77	0	-60.02
FZD3	Red	Blue	Blue	Blue	Blue
WISP1	Red	Blue	Red	Blue	Blue
ACVR1B	Red	Blue	Blue	Blue	Blue
SOX11	Blue	Blue	Blue	Blue	Blue
GNAO1	Blue	Blue	Blue	Blue	Blue
MDM2	Blue	Blue	Blue	Blue	Blue
<b>TREM1 Signaling genes</b>					
Cmap score		0	-80.47	97.51	99.23
MAPK1	Red	Blue	Blue	Blue	Red
TLR7	Red	Blue	Blue	Blue	Blue
STAT3	Red	Blue	Blue	Red	Red
CXCL8	Blue	Red	Red	Blue	Blue
TYROBP	Blue	Blue	Blue	Blue	Red
TREM1	Blue	Blue	Blue	Blue	Blue
<b>Calcium Signaling genes</b>					
Cmap score		76.57	71.01	0	39.63
CACNA1D	Red	Red	Red	Blue	Blue
CACNB3	Red	Blue	Blue	Blue	Red
TP63	Red	Blue	Blue	Blue	Blue
GRIN1	Blue	Blue	Blue	Blue	Blue
CACNG5	Blue	Blue	Blue	Blue	Blue
RAP1A	Blue	Blue	Blue	Blue	Blue