Endotyping severe asthma: towards personalised medicine

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Declaration of interest

• Participation in Advisory Board meetings regarding treatments of asthma and COPD for GSK, AstraZeneca, TEVA, Novartis, Pfizer, Boehringer Ingelheim and Johnson & Johnson

• Research grant funding from Pfizer, GSK and Merck

• Speaking engagements: AstraZeneca, Merck, Novartis

• Investigator of IMI EU/EFPIA funded UBIOPRED Consortium on Severe Asthma
ERS/ATS definition of severe asthma

• A patient is deemed to have **uncontrolled asthma** if at least one of the following features is present:

<table>
<thead>
<tr>
<th>Poor symptom control</th>
<th>Frequent severe exacerbations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious exacerbations</td>
<td>Airflow limitation</td>
</tr>
</tbody>
</table>

A patient is deemed to have **severe asthma** if he/she has:

- Uncontrolled asthma while on **high-dose therapy**
- **OR:**
  - Controlled asthma that becomes uncontrolled on tapering of **high-dose corticosteroids**

GINA 2015
Stepwise management - pharmacotherapy

**Diagnosis**
- Symptom control & risk factors (including lung function)
- Inhaler technique & adherence
- Patient preference

**Response**
- Symptoms
- Exacerbations
- Side-effects
- Patient satisfaction
- Lung function

**Adjust treatment**

**Asthma medications**
- Non-pharmacological strategies
- Treat modifiable risk factors

**STEP 1**
- Low dose ICS

**STEP 2**
- Low dose ICS

**STEP 3**
- Med/high ICS/LABA

**STEP 4**
- High dose ICS

**Severe asthma**
- Add tiotropium
- Add low dose OCS

**Preferred controller choice**
- LABA: Long-acting beta-2 agonist
- LTRA: Leukotriene receptor antagonists
- OCS: Oral corticosteroids

**Other controller options**
- As-needed SABA or low dose ICS/formoterol

**As-needed short-acting beta-2-agonist (SABA)**

**Consider low dose ICS**

**Leukotriene receptor antagonists (LTRA)**

**Low dose theophylline**

**Med/high dose ICS**

**Low dose ICS + LTRA (or + theophylline)**

**Add tiotropium**

**Add low dose OCS**

**Refer for added treatment e.g. anti-IgE**
Characteristics of severe asthma: clinical (treatable) traits

- Late onset, non-atopic
- Atopic/high IgE, usually early onset
- Chronic airflow obstruction
- Recurrent exacerbations (≥ 2 /year)
- Eosinophilic asthma
- Obesity-associated
- Steroid-insensitive
Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes

Innovative Medicines Initiative call topic: Understanding Severe Asthma

www.ubiopred.eu
Demographics of UBIOPRED cohort

<table>
<thead>
<tr>
<th>Total: 617 participants</th>
<th>Severe asthma: non-smoking (308)</th>
<th>Severe asthma: smoking &amp; ex-smoking (110)</th>
<th>Moderate Asthma (98)</th>
<th>Non-asthma (101)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>50.9</td>
<td>54.5</td>
<td>42.4</td>
<td>38.9</td>
<td>2.9E-17</td>
</tr>
<tr>
<td>Female (%)</td>
<td>65.91</td>
<td>50.91</td>
<td>50.00</td>
<td>38.61</td>
<td>5.16E-06</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.08</td>
<td>29.56</td>
<td>25.88</td>
<td>25.31</td>
<td>2.02E-10</td>
</tr>
<tr>
<td>Exacerbations in past yr</td>
<td>2.48</td>
<td>2.55</td>
<td>0.37</td>
<td>0</td>
<td>2.51E-26</td>
</tr>
<tr>
<td>IgE (IU/ml)</td>
<td>119.5</td>
<td>126</td>
<td>89.4</td>
<td>23.45</td>
<td>5.40E-15</td>
</tr>
<tr>
<td>Atopy (%)</td>
<td>69</td>
<td>58</td>
<td>80</td>
<td>38</td>
<td>6.1E-066</td>
</tr>
<tr>
<td>Nasal polyps (%)</td>
<td>34.7</td>
<td>33.7</td>
<td>8.3</td>
<td>8.8</td>
<td>1.33E-06</td>
</tr>
<tr>
<td>FEV₁ (% pred)</td>
<td>67.42</td>
<td>67.25</td>
<td>88.37</td>
<td>101.76</td>
<td>1.81E-44</td>
</tr>
<tr>
<td>Oral corticosteroids (%)</td>
<td>50.68</td>
<td>46.08</td>
<td>1.06</td>
<td>0</td>
<td>9.73E-17</td>
</tr>
<tr>
<td>Sputum eosinophils (%)</td>
<td>2.75</td>
<td>4.13</td>
<td>1.05</td>
<td>0.00</td>
<td>2.69E-12</td>
</tr>
<tr>
<td>Exhaled NO</td>
<td>27</td>
<td>23.5</td>
<td>25.50</td>
<td>19.00</td>
<td>3.00E-04</td>
</tr>
</tbody>
</table>

UBIOPRED Training Cohort
- 163 non-smoking severe asthma
- 53 smoker/ex-smoker severe asthma
- 50 mild-moderate asthma

Parameters
- Age of asthma onset
- FEV₁/FVC ratio
- Pack-years of smoking
- Asthma Control Questionnaire-5
- Body Mass Index
- Exacerbations in past year
- FEV₁ % predicted
- Oral Corticosteroid daily dose

Partition-around-medoids clustering
- Flat middle-part of Cumulative Distribution Factor
- Well-defined squares within Consensus Matrix
- Deviation from Ideal Stability Test

Clinico-physiologic features

Clinical Phenotypes Or traits

Phenotype T1
- Moderate-severe
- Well-controlled
- Medium-to-high inhaled corticosteroids
- Mild-none airflow obstruction

Phenotype T2
- Severe
- Late onset
- Smoker or Ex-smoker
- Severe airflow obstruction
- High blood eosinophil count

Phenotype T3
- Severe
- Non-smoker
- Oral corticosteroid-dependent
- Moderate-severe airflow obstruction

Phenotype T4
- Severe
- Female Obese
- Mild-none airflow obstruction
- Frequent exacerbations

Cumulative Distribution Factor

Lefaudeux et al JACI 2017
Analyte biomarker levels by clinical cluster (C1 to C4)

- Serum CCL17
  - C1: n=89
  - C2: n=86
  - C3: n=92
  - C4: n=94
  - N: n=162

- Serum CCL18
  - C1: n=89
  - C2: n=86
  - C3: n=92
  - C4: n=94
  - N: n=162

- Serum IL-13
  - C1: n=89
  - C2: n=86
  - C3: n=92
  - C4: n=94
  - N: n=162

- Serum periostin
  - C1: n=90
  - C2: n=66
  - C3: n=93
  - C4: n=95
  - N: n=162

- Blood eosinophil count
  - C1: n=107
  - C2: n=84
  - C3: n=105
  - C4: n=114
  - N: n=197

- FeNO
  - C1: n=106
  - C2: n=83
  - C3: n=102
  - C4: n=106
  - N: n=187
Features of Th2-high asthma

- More blood and BAL eosinophils
- ↑ serum IgE
- ↑ mucin MUC5AC
- ↑ IL5 and IL13 in biopsies
- ↑ bronchial hyperresponsiveness
- FEV₁ increase with ICS

Woodruff et al AJRCCM 2009; 180:388
Supervised approach

*Gene set variation analysis* using gene signatures

Looking for Th2 high

<table>
<thead>
<tr>
<th>Name of signature</th>
<th>Details</th>
<th>Reference</th>
</tr>
</thead>
</table>
How common is a Th2 (IL-13) high in severe asthma?

**UBIOPRED**

Transcriptome analysis of bronchial brushings for Th2 signature from epithelial cells activated by IL-13 in vitro (IL13 IVS definition)

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Non Smoking Severe Asthma</th>
<th>Smoking Severe Asthma</th>
<th>Mild/Moderate Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL13 Th2 high %</td>
<td>37% (18/49)</td>
<td>17% (3/18)</td>
<td>25% (9/36)</td>
</tr>
</tbody>
</table>

- **Gene Set Variation Analysis**
- **U-BIOPRED Bronchial Brushings**
- Define “Th2(IL-13) High” as >95th %ile of Healthy controls

Stelios Pavlidis, Matthew Loza, Fred Baribaud for UBIOPRED
Distribution of high FeNO, high serum periostin and high blood eosinophil count in 312 severe asthma (UBIOPRED)

101 patients (32%) were low for all 3 biomarkers
High FeNO, high serum periostin and high blood eosinophil count linked to exacerbations and Th2 signature

101 patients (32%) were low for all 3 biomarkers

FeNO≥30 ppb

Th2 ES = 0.10
Exacerbations= 2.17/yr

Th2 ES = 0.36
Exacerbations= 2.83/yr

Th2 ES = 0.08
Exacerbations = 2.2/yr

Blood EOS≥300

Th2 ES = 0.29
Exacerbations = 2.2/yr

Th2 ES = 0.05
Exacerbations = 2/yr

Th2 ES = 0.00
Exacerbations = 3.25/yr

Serum Periostin≥55ug/l

Th2 ES = 0.13
Exacerbations = 1/yr

Combination of blood eos≥300
And FeNO ≥30 marks high Th2 in severe asthma

Constitutes the high Th2 associated exacerbations

Th2 expression score ES:
Using gene set variation analysis
With IL-13/epithelial cell
Gene expression in epithelial brushings
Precision Medicine

Precision medicine is an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person.

Personalised medicine is an older term for precision medicine.

4P Medicine: Predictive, Preventive, Personalised, Participatory
UBIOPRED PROCESS OF SYSTEMS MEDICINE

Patient recruitment

Sample collection

'Omics data acquisition

Severe asthmatics: Recruited from clinical centres across Europe

Multiple biomatrices:
- Plasma
- Sputum
- Urine

Tissue samples

Biobank: Sample shipping & storage

Knowledge management platform

Handprint of severe asthma

'Omics data integration:
networks, pathway mapping, statistical analyses

Wheelock et al. ERJ 2013;42:802

2013

2015

www.ubiopred.eu
A Transcriptome-driven Analysis of Epithelial Brushings and Bronchial Biopsies to Define Asthma Phenotypes in U-BIOPRED

Chih-Hsi Scott Kuo, Stelios Pavlidis, Matthew Loza, Fred Baribaud, Anthony Rowe, Ioannis Pandis, Uruj Hoda, Christos Rossios, Ana Sousa, Susan J Wilson, Peter Howarth, Barbro Dahlen, Sven-Erik Dahlen, Pascal Chanez, Dominick Shaw, Norbert Krug, Thomas Sandström, Bertrand De Meulder, Diane Lefaudeux, Stephen Fowler, Louise Fleming, Julie Corfield, Charles Auffray, Peter J Sterk, Ratko Djukanovic, Yike Guo, Ian M Adcock, Kian Fan Chung, and on behalf of the U-BIOPRED Project Team

Hybrid approach using both supervised and unsupervised method

Supervised
- Functional annotation of genes using gene set variation analysis (GSVA)
- 42 gene sets formed by *a priori* knowledge from 2,431 genes
- Gene sets related to immune cell characteristics and distinctive pathogenesis of asthma

Unsupervised
- Traditional clustering method
  -- hierarchical or K-means
- Topology data analysis (TDA)

Nicolau et al. *PNAS* 2011; April 26: 7265–7270
Hybrid approach using both *supervised* and *unsupervised* methods

**Supervised approach**

- Functional annotation of genes using gene set variation analysis (GSVA)
- 42 gene sets formed by *a priori* knowledge from 2,431 genes
- Gene sets (signatures) for mechanistic pathways related to severe asthma

**Unsupervised approach**

- Topological data analysis
- Hierarchical K-clustering
- Nearest shrunken centroid algorithm

**Examples of gene sets**

- **Th2.eosinophilic.inflammation (3 genes)**: POSTN, SERPINB2, CLCA1
- **Th2.rhesus (25 genes)**: CCL26, LOXL4, NOS2A, CD36, CDH13, CLCA1, CXCL6, IL1R2...
- **Fluticasone.salmeterol.down (36 genes)**: TMPRSS11D, SFRP1N813, SPINK5, KRT14, TMPRSS11A, CSTA...
- **PBMC.up (14 genes)**: EGR1, CXCL2, PTGS2, FOS, IFNGR2, IL8, IGH, SUCL3, TLR6...
- **PBMC.asthma.gluc.response (15 genes)**: CD83, STAT4, NFKB1, IL4R, DUSP2, DUSP4, TRAF1, JMJD6...
- **Ozone.Air.up (186 genes)**: KITH, Q3U4X8, CENPK, AGR2, CDK1, DYH8, CDD, TOPK...
9-gene set signature expression across combined airway biopsies and epithelial brushings using GSVA

<table>
<thead>
<tr>
<th>Group</th>
<th>Epithelial brushings</th>
<th>Bronchial biopsies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Group 2</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Group 3</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Group 4</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Kuo et al AJRCCM 2016, in press
Clinical features of groups by expression of 9-gene-set signature in bronchial biopsy and/or epithelial brushing

<table>
<thead>
<tr>
<th>Variables†</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>19 (23%)</td>
<td>17 (20%)</td>
<td>8 (10%)</td>
<td>39 (47%)</td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td>48.0 ± 13.6</td>
<td>47.4 ± 14.1</td>
<td>50.6 ± 13.4</td>
<td>44.0 ± 13.5</td>
<td>0.515</td>
</tr>
<tr>
<td>Female</td>
<td>7 (36.8)</td>
<td>8 (47.1)</td>
<td>3 (37.5)</td>
<td>24 (61.5)</td>
<td>0.268</td>
</tr>
<tr>
<td>BMI</td>
<td>27.8 ± 4.8</td>
<td>28.6 ± 4.9</td>
<td>33.1 ± 3.8</td>
<td>28.0 ± 5.9</td>
<td>0.043</td>
</tr>
<tr>
<td>Nasal polyps</td>
<td>8 (42.1)</td>
<td>6 (35.3)</td>
<td>2 (25.0)</td>
<td>9 (23.1)</td>
<td>0.476</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>8 (42.1)</td>
<td>8 (47.1)</td>
<td>6 (75.0)</td>
<td>16 (41.0)</td>
<td>0.476</td>
</tr>
<tr>
<td>Eczema</td>
<td>6 (31.6)</td>
<td>9 (52.9)</td>
<td>2 (25.0)</td>
<td>17 (43.6)</td>
<td>0.401</td>
</tr>
<tr>
<td>Severe asthma</td>
<td>14 (73.7)</td>
<td>10 (58.8)</td>
<td>6 (75.0)</td>
<td>20 (51.3)</td>
<td>0.323</td>
</tr>
<tr>
<td>Oral corticosteroid use</td>
<td>9 (47.4)</td>
<td>5 (29.4)</td>
<td>2 (25.0)</td>
<td>5 (12.8)</td>
<td>0.039</td>
</tr>
<tr>
<td>Atopy</td>
<td>11 (57.9)</td>
<td>12 (70.6)</td>
<td>6 (75.0)</td>
<td>30 (76.9)</td>
<td>0.742</td>
</tr>
<tr>
<td>Acute exacerbation (times/year)</td>
<td>3.0 (2.0-5.0)</td>
<td>2.0 (1.3-2.8)</td>
<td>3.0 (2.0-3.0)</td>
<td>1.5 (1.0-3.0)</td>
<td>0.084</td>
</tr>
<tr>
<td>FEV₁ (%)</td>
<td>68.1 (54.9-78.3)</td>
<td>90.4 (70.9-98.0)</td>
<td>80.3 (65.9-101.6)</td>
<td>79.7 (65.5-94.8)</td>
<td>0.151</td>
</tr>
<tr>
<td>Total IgE (IU/ml)</td>
<td>163 (42-231.5)</td>
<td>86.6 (24.0-196.0)</td>
<td>93.9 (41.3-879.8)</td>
<td>96 (44.3-278.5)</td>
<td>0.753</td>
</tr>
<tr>
<td>Blood eosinophil</td>
<td>3.5 (2.4-8.0)</td>
<td>1.7 (1.4-3.6)</td>
<td>3.4 (3.2-4.2)</td>
<td>2.4 (1.4-3.9)</td>
<td>0.085</td>
</tr>
<tr>
<td>Sputum eosinophil</td>
<td>8.2 (1.8-27.0)</td>
<td>0.6 (0.6-1.0)</td>
<td>15.8 (12.4-16.2)</td>
<td>0.6 (0-1.6)</td>
<td>0.014</td>
</tr>
<tr>
<td>FeNO (ppb)</td>
<td>56.5 (34.1-74.6)</td>
<td>22.0 (14.5-32.5)</td>
<td>35.5 (20.0-50.4)</td>
<td>19 (12.5-36.1)</td>
<td>0.003</td>
</tr>
<tr>
<td>Submucosal cells (count/mm²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eosinophil</td>
<td>6.1 (4.3-13.6)</td>
<td>2.2 (0-5.9)</td>
<td>2.7 (1.5-4.6)</td>
<td>1.0 (0-3.5)</td>
<td>8.94E-05</td>
</tr>
<tr>
<td>Neutrophil</td>
<td>11.0 (4.6-18.2)</td>
<td>9.8 (7.1-18.7)</td>
<td>12.1 (6.5-13.5)</td>
<td>12.1 (6.8-19.2)</td>
<td>0.933</td>
</tr>
<tr>
<td>CD4 T cell</td>
<td>15.4 (9.2-24.7)</td>
<td>5.8 (1.5-11.1)</td>
<td>9.2 (6.2-16.3)</td>
<td>10.2 (4.6-15.5)</td>
<td>0.046</td>
</tr>
<tr>
<td>CD8 T cell</td>
<td>45.3 (32.7-77.2)</td>
<td>21.8 (16.0-37.0)</td>
<td>41.9 (36.9-70.9)</td>
<td>33.3 (16.4-49.9)</td>
<td>0.041</td>
</tr>
</tbody>
</table>

9-gene signatures (Th2 high, Th1 high, steroid sensitivity, oxidative stress) in epithelial brushings and bronchial biopsies defines a distinct phenotype of asthma (Gp 1)
Decision tree using clinical parameters for inference of these unique cluster findings from machine learning

**Clinical Biomarkers**

**Molecular phenotypes**

In biopsies and brushings

Kuo et al AJRCCM 2016
Th2 and non-Th2 molecular phenotypes of asthma using sputum transcriptomics in UBIOPRED

Chih-Hsi Scott Kuo1,2, Stelios Pavlidis3, Matthew Loza3, Fred Baribaud3, Anthony Rowe3, Iaonnis Pandis2, Ana Sousa4, Julie Corfield5, Ratko Djukanovic6, Rene Lutter7, Peter J. Sterk7, Charles Auffray8, Yike Guo2, Ian M. Adcock1† & Kian Fan Chung1†# On behalf of the U-BIOPRED Study Group#

1Airways Disease, National Heart & Lung Institute, Imperial College London, & Biomedical Research Unit, Royal Brompton & Harefield NHS Trust, London, United Kingdom; 2Department of Computing & Data Science Institute, Imperial College London, United Kingdom; 3Janssen Research and Development, High Wycombe, Buckinghamshire

Eur Respir J 2017, in press
Defining ‘disease drivers’ from sputum inflammatory cell pattern: eosinophilic vs non-eosinophilic

- **Eosinophilic phenotype:**
  Sputum EOS ≥ 1.5%  (n=67)

- **Non-Eosinophilic phenotype:**
  Sputum EOS < 1.5%  (n=51)

- **Healthy Control**  (n=21)

- **Differentially expressed gene from 3 sets of comparison**

Number of differentially expressed genes

- EOS vs HC: 201 genes
- non-EOS vs HC: 145 genes
- non-EOS vs EOS: 197 genes

478 DEGs

Hierarchical Clustering

Kuo et al  ERJ 2017
Hierarchical clustering of differentially expressed genes between eosinophilic vs non-eosinophilic asthma in sputum cells

Genes in sputum cells

Molecular Phenotypes

Clinical Phenotypes

MOLECULAR PHENOTYPES

n=31

Associated clusters

TAC: Transcriptome-associated clusters

Clusters from disease drivers

Eosinophilic
non-Eosinophilic

478 DEGs

GENES

Kuo et al Eur Respir J 2017
Expression of gene signatures in the 3 TACs using gene set variation analysis

**TAC1:**
Th2 with ILC2
*Eosinophilic*

**TAC2:**
Inflammasome,
Neutrophil activation
*Neutrophilic*

**TAC3:**
Mitochondrial OXPHOS,
Th17,
Ageing genes
*Paucigranulocytic or eosinophilic*

Kuo and Pavlidis  ERJ 2017
Molecular Transcriptome-associated clusters (TACs) of moderate-severe asthma from sputum analysis in U-BIOPRED

<table>
<thead>
<tr>
<th>'Mechanisms'</th>
<th>TAC 1 (29%)</th>
<th>TAC 2 (21%)</th>
<th>TAC 3 (50%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Affymetrix Microarray</em></td>
<td>IL33R, TSLPR, CCR3, IL3RA</td>
<td>IFN &amp; TNF superfamily, CASP4</td>
<td>Mitochondrial Oxidative stress</td>
</tr>
<tr>
<td>Gene set variation analysis</td>
<td>Th2/ILC2</td>
<td>NLPR3/DAMP-associated</td>
<td>Th17; OXPHOS; ageing</td>
</tr>
<tr>
<td>Protein (Somalogic)</td>
<td>IL-16, Periostin, Serpin peptidase inhibitor 1, Adiponectin, PAPPA</td>
<td>TNFAIP6, MIF, Tyrosine kinase src</td>
<td>Cathepsin B, G</td>
</tr>
<tr>
<td>Blood eosinophils (/μL)</td>
<td>430</td>
<td>250</td>
<td>200</td>
</tr>
<tr>
<td>Sputum eosinophils (%)</td>
<td>30.9</td>
<td>0.6</td>
<td>1.0</td>
</tr>
<tr>
<td>FeNO (ppb)</td>
<td>29.5</td>
<td>22.0</td>
<td>27.5</td>
</tr>
<tr>
<td>Clinical features</td>
<td>Severe asthma Highest nasal polyps</td>
<td>Moderate-to-severe asthma Moderate airflow obstruction Less frequent exacerbations</td>
<td>Moderate-to-severe asthma Mild airflow obstruction Lowest oral prednisolone Less frequent exacerbations</td>
</tr>
</tbody>
</table>

Severe Asthma Molecular Phenotypes (from U-BIOPRED *sputum* analysis)

“Severe Asthma”

**Symptoms**
- Th2-like inflammation
  - Severe asthma
  - Airflow obstruction
  - Nasal polyps
  - High OCS use
  - Corticosteroid insensitivity
  - Highly Eosinophilic

**Exacerbations**
- Less Th2-like inflammation
  - Bacterial infection
  - Inflammasome
  - Moderate airflow obstruction
  - More eczema
  - Neutrophilic/Eosinophilic

- Oxidative stress/Ageing
  - Less exacerbations
  - Mild Airflow obstruction
  - Paucigranulocytic/eosinophilic

**FEV1**

**TAC1**
**TAC2**
**TAC3**
Mechanisms of severe asthma

- **Non-T2**
  - Growth factors: eg TGFβ
  - Fibroblast
  - Airway smooth muscle
  - Extracellular matrix

- **Th2**
  - IL-4, IL-13
  - Eosinophil
  - B-cell
  - Mast cell
  - Histamine
  - Leukotrienes

- **Non-T2**
  - IL-17A, IL-17F
  - Neutrophil

- **NLPR3 inflammasome**
  - Mitochondrial OXPHOS

**Allergens, Virus, Bacteria**
- Pollution & oxidants

**Remodeling/repair**
- Normal
- Eosinophilic inflammation
- Neutrophilic inflammation

**Treatable traits**
- Poor asthma control
- High treatment requirements
- Chronic airflow obstruction
- Recurrent exacerbations
- Poor response to corticosteroids
Conclusions

Endotypes of severe asthma will involve more than one pathway
We have defined non-Th2/T2 pathways

Identifiable molecular pathways contribute to clinical characteristics associated with molecular phenotypes (biomarkers)

- Understand what each compartment is telling us
- Need to prove that the pathways are underlying clinical traits
- Discover bedside biomarkers
- Find new targets for targeted therapy.

Precision Medicine
(Personalised Medicine)
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Barcelona 2013
Mepolizumab, an anti-IL5 antibody, in patients with severe eosinophilic asthma

- ≥ 2 exacerbations
- ≥ 1,000 µg FP/day
- Blood eos > 150/µl

**Ortega et al NEJM 2014; 371: 1198**
Can we define a Severe Eosinophilic Asthma phenotype?

**Major criteria:**
- Severe asthma (ERS/ATS definition)
- Exacerbation frequency $\geq 2$/year
- Dependence on OCS for asthma control
- High circulating eosinophils

**Minor criteria:**
- FeNO level increase
- Late onset disease
- Upper airway: nasal polyps
- Fixed airflow obstruction
- Air trapping/small airways obstruction/mucus plugging

European Consensus Project