Re-defining Asthma –
What’s all the fuss about?

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**Conflict of interest**

- Participation in Advisory Board meetings regarding treatments of asthma and COPD for GSK, AstraZeneca, Boehringer Ingelheim, TEVA, Novartis, 4D.
- Research grant funding from Pfizer, GSK and Merck
- Speaking engagements: AstraZeneca, Merck, Novartis, TEVA
- Investigator of IMI EU/EFPIA funded UBIOPRED Consortium on Severe Asthma
Asthma is a **heterogeneous** disease, usually characterized by **chronic airway inflammation**.

It is defined by the history of **respiratory symptoms** such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable **expiratory airflow limitation**.

**GINA 2017: Global Initiative for Asthma**
GLOBAL INITIATIVE FOR ASTHMA

Stepwise management - pharmacotherapy

**Not for children <12 years**
**For children 6-11 years, the preferred Step 3 treatment is medium dose ICS**
**For patients prescribed BDP/formoterol or BUD/formoterol maintenance and reliever therapy**
**Add tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations**

GINA 2017

Mild-moderate asthma

Severe asthma

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

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

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

**Step 1**
Low dose ICS
Consider low dose ICS

**Step 2**
Low dose ICS/LABA**
Leukotriene receptor antagonists (LTRA)
Low dose theophylline

**Step 3**
Med/high ICS/LABA
Med/high dose ICS/LTRA (or + theophylline)
Add tiotropium
Add low dose OCS

**Step 4**
Refer for add-on treatment e.g. tiotropium,**omalizumab, mepolizumab,**

**Step 5**
High dose ICS + LTRA (or + theophylline)
Add low dose OCS

**Other controller options**

<table>
<thead>
<tr>
<th>RELIEVER</th>
<th>PREFERRED CONTROLLER CHOICE</th>
</tr>
</thead>
<tbody>
<tr>
<td>As-needed short-acting beta²-agonist (SABA)</td>
<td>As-needed SABA or low dose ICS/formoterol**</td>
</tr>
</tbody>
</table>
ERS/ATS international 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 (ACQ)</th>
<th>Frequent severe exacerbations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious exacerbations</td>
<td>Airflow limitation (FEV1)</td>
</tr>
</tbody>
</table>

- **Uncontrolled asthma while on high-dose therapy**
  - (GINA Step 4/5)

- **Controlled asthma that becomes uncontrolled on tapering of high-dose corticosteroids**
  - (GINA Step 5)
Severe asthma clinical phenotypes

- Late onset, non-atopic
- Atopic/high IgE, usually early onset
- Chronic airflow obstruction
- Recurrent exacerbations (≥ 2/year)
- Eosinophilic asthma
- Obesity-associated
- Steroid-insensitive
<table>
<thead>
<tr>
<th></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><strong>Total: 617 participants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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>

U-BIOPRED clinical adult asthma clusters

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
### Mechanisms and targets in severe asthma

<table>
<thead>
<tr>
<th>Remodeling/repair</th>
<th>Eosinophilic inflammation</th>
<th>Neutrophilic inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor asthma control</td>
<td>High treatment requirements</td>
<td>Chronic airflow obstruction Recurrent exacerbations Poor response to corticosteroids</td>
</tr>
</tbody>
</table>

#### 'Unknown Mechanisms'

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

- **TSLP, IL-33, IL-25**
  - TGFβ
  - Eotaxin
  - RANTES

- **T2 high**
  - IL-5
  - IL-4
  - IL-13
  - B-cell
  - IgE

- **Th2**
  - Histamine
  - Leukotrienes

- **Macrophage**
  - TNFα
  - IL-1β

- **Epithelium**
  - Allergens, Virus, Bacteria

- **Pollution & oxidants**

- **Dendritic cells**
  - MHC I
  - Peptide
  - TCR
  - B7.2
  - CD28

- **Th0**

- **Th1**
  - IFNγ, TNFα
  - IL-12

- **Th17**
  - IL-17A, E, F
  - IL-8

- **Neutrophil**

- **Eosinophil**

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- **Neutrophil**

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- **Unknown Mechanisms**

- **T2: Type 2**
  - Th2: T-helper
GLOBAL INITIATIVE FOR ASTHMA

Stepwise approach to control asthma symptoms and reduce risk

CLINICAL APPROACH

PHARMACOLOGICAL APPROACH

GINA 2017
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
Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β₂-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial

At least 2 exacerbations in past year while on high dose ICS+LABA

Benralizumab = Anti-IL-5Rα antibody

Exacerbations
Definition of ‘Severe Eosinophilic Asthma’ phenotype

**Major criteria:**
- Severe asthma (ERS/ATS definition)
- Exacerbation frequency ≥ 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

Eur Respir J. 2017;49(5). pii: 1700634.
## T2 current biologic therapies for severe asthma

**FDA and EMA-approved**

<table>
<thead>
<tr>
<th>Biologic</th>
<th>Target</th>
<th>Patient type &amp; biomarker</th>
<th>Exacerbations</th>
<th>FEV&lt;sub&gt;1&lt;/sub&gt;</th>
<th>Symptoms</th>
<th>QoL</th>
<th>Oral Corticosteroid dose</th>
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</thead>
<tbody>
<tr>
<td>Omalizumab</td>
<td>IgE</td>
<td>High serum IgE Allergies</td>
<td>↓</td>
<td>↑</td>
<td>↑Symptom score, AQLQ</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(↓)</td>
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<tr>
<td>Mepolizumab</td>
<td>IL-5</td>
<td>Exacerbation ≥ 2; Blood eos ≥150/μL</td>
<td>↓</td>
<td>↑</td>
<td>↑SGRQ, ACQ5</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓</td>
</tr>
<tr>
<td>Reslizumab</td>
<td>IL-5</td>
<td>Exacerbation ≥ 1; Blood eos ≥400/μL</td>
<td>↓</td>
<td>↑</td>
<td>↑ACQ7, AQLQ</td>
<td>Not done</td>
<td></td>
</tr>
<tr>
<td>Benralizumab</td>
<td>IL-5Rα</td>
<td>Exacerbation ≥ 2; Blood eos ≥300/μL</td>
<td>↓</td>
<td>↑</td>
<td>↑ACQ6, AQLQ</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓</td>
</tr>
<tr>
<td>Dupilumab</td>
<td>IL-4Rα</td>
<td>Exacerbation ≥ 1; Blood eos ≥150/μL</td>
<td>↓</td>
<td>↑</td>
<td>↑ACQ5, AQLQ</td>
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</tbody>
</table>
Personalised approach to Severe asthma in UK

Severe refractory asthma ERS/ATS definition 2014

Optimise treatment (Step 5)
Adherence

T2 biomarker high
Blood eosinophil count
FeNO

T2 biomarker high
Eosinophilic asthma
Recurrent exacerbations

Consideration of anti-T2 treatment strategy

Anti-IgE, Anti-IL5, Anti-IL5Ra

T2 biomarker low

Consider reducing Corticosteroid dosage

T2 biomarker remains low

Trial of azithromycin
?Bronchial thermoplasty
Other non-T2 targets
The Problem

- Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation
- Cost of asthma (15-65 years old) in Europe (2014) = 21 billion Euros
- 5-10% suffers from severe asthma, unresponsive to current treatments
- Urgent need to identify the endotypes of asthma

The Vision

Bringing Precision Medicine to asthma

- Biomarker identification of endotypes
- Treatment targeted towards disease mechanisms
- Leading to improved outcomes

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.
U-BIOPRED Systems Biology approach to molecular phenotypes

Patient recruitment
Sample collection

‘Omics data acquisition

‘Omics data integration
Networks, pathways, statistical analysis

Knowledge Management Platform

Multiple Biomatrix:
Plasma, Sputum, Urine
Biopsy, Bronchial/nasal brushings

GWAS
Focussed lipidomics
Unbiased lipidomics
Unbiased proteomics
Somalogics
Transcriptomics
Metagenomics

Data Science Institute, Imperial College (Prof Yike Guo)
Translational Bioinformatics

Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes
Supervised approach:
How common is a Type 2 (IL-13) high in U-BIOPRED severe asthma?

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

<table>
<thead>
<tr>
<th>Name of signature</th>
<th>Details</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL13 Th2: Effect of IL-13 on airway epithelial cells</td>
<td>CST1, CCL26, PRB2, PRB1, PRB3, POSTN, PRB4, ITIN1, ALOX15, SH2D1B, CA2, NOS2, FCGBP, FOXA3, SPDEF, CAPN14, DUOX2, CLDN5, PADI3, TSPAN8, ALPL, KCNJ16, FETUB, B3GNT6, CDH26, LRRRC31, MUC13, VSIG2, C3TA, FAM138, SLC9B2, NTRK1, KLF4, HPDL, SDC51, TRNP1, H35ST1, VWF, DUOX2, CDH1, ATP13A5, ZNF108, RNASE4, CCBL1, DDB3P5, TIPR5S2, HYAL1, CDC109B, FAM83D, TRAK1, TPK1, SLCA7A1, CYP2C18, CDC42EPS5, KCN53, ADRA2A, MRAP2, SLC2A10, PPARG, FAM266, ADCY4, WNT3, SLC04A1, ALDH1A2, C10or99, WDFY2</td>
<td>Alevy YG, Patel AC, Romero AG, Patel DA; Tucker J, Roswit WT, Miller CA, Heier RF, Byers DE, Brett TJ, Holtzman MS. IL-13-induced airway mucus production is attenuated by MAPK13 inhibition. J Clin Invest 2012; 122: 4555-4568.</td>
</tr>
</tbody>
</table>

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

**Enrichment score for IL-13 IVS signature**

- Non-smoking Severe asthma: 37% (18/49)
- Smoking Severe asthma: 17% (3/18)
- Mild-Moderate asthma: 25% (9/36)
- Healthy

Stelios Pavlidis et al ERJ 2018 In press
Distribution of neutrophilic and eosinophilic inflammation in sputum

**A - Severe Asthma**
- NEU & EOS: 12%
- NEU ONLY: 23%
- EOS ONLY: 50%
- NORMAL (PAUCI-GRANULOCYTIC): 15%

**B - Severe Smokers**
- NEU & EOS: 11%
- NEU ONLY: 28%
- EOS ONLY: 11%
- NORMAL (PAUCI-GRANULOCYTIC): 8%

**C - Mild/Moderate Asthma**
- NEU & EOS: 14%
- NEU ONLY: 44%
- EOS ONLY: 2%
- NORMAL (PAUCI-GRANULOCYTIC): 2%

**D - Health Volunteers**
- NEU & EOS: 2%
- NEU ONLY: 3%
- EOS ONLY: 2%
- NORMAL (PAUCI-GRANULOCYTIC): 93%

Rossios et al JACI 2017
Systems Biology approach to molecular phenotypes

Bioinformatic analyses

Hierarchical clustering of genes from sputum transcriptomics

Gene set variation analysis (GSVA)
Transcriptome-associated clusters (TAC) from *sputum* transcriptome analysis

"Severe Asthma"

Kuo et al. Eur Respir J 2017, 49, 1602135

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<table>
<thead>
<tr>
<th>TAC 1 (29%)</th>
<th>TAC 2 (21%)</th>
<th>TAC 3 (50%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanisms</strong></td>
<td><strong>T-2 associated</strong></td>
<td><strong>T2/ILC2</strong></td>
</tr>
<tr>
<td>Sputum inflammation</td>
<td>'High' eosinophilic/Mixed</td>
<td>Neutrophilic/Mixed</td>
</tr>
<tr>
<td>Affymetrix Microarray</td>
<td>IL33R, TSLPR, CCR3, IL3RA</td>
<td>IFN &amp; TNF superfamily, CASP4</td>
</tr>
<tr>
<td>Gene set variation analysis</td>
<td>Th2/ILC2</td>
<td>NLPR3/DAMP-associated</td>
</tr>
<tr>
<td>Protein (Somalogic)</td>
<td>IL-16, Peristin, Serpin peptidase inhibitor 1, Adiponectin, PAPPA</td>
<td>TNFAIP6</td>
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<tr>
<td>Clinical features</td>
<td>Highest nasal polyps Oral CS dependent Severe airflow obstruction</td>
<td>Moderate airflow obstruction High blood CRP levels More eczema</td>
</tr>
</tbody>
</table>

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**Symptoms**

**Exacerbations**

**FEV1**
Precision medicine translated to severe asthma

EXPOSOME + GENOME

**Biological responses**

- Immunological/Inflammatory responses
- Cellular/Molecular events
- Disease characteristics discriminant

**Endotypes**

**Clinical phenotypes**

- Mechanisms Pathways
- Specific Treatments
- Biomarker

Treatable trait
The definition of asthma has been descriptive without any pathophysiology.
Re-defining Asthma – What’s all the fuss about?

• Asthma is an evolving concept based on symptoms, physiology and inflammation that continues to be useful for clinicians

• Endotypes, mechanism-based phenotypes, by looking at the genes, proteins, metabolites, microbiome involved in the disease should be included in a new definition

• This will form the basis for personalised/precision medicine with targeted therapies for specific endotypes
Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes

University of Amsterdam, University of Southampton, Imperial College London, University of Manchester, University of Nottingham, Fraunhofer Institute Hannover, Centre Nat Recherche Sc. Villejuif Paris, Université de Méditerranée Montpellier, Karolinska Institute Stockholm, University Hospital Umea, University Tor Vergata Rome, Università Cattolica del Sacro Cuore Rome, University of Catania, Hvidore Hospital Copenhagen, University Hospital Copenhagen, Haukeland University Bergen, Semmelweis University Budapest, Jagiellonian University Krakow, University Hospital Bern, University of Ghent

EFPIA Partners
Novartis
Almirall
Amgen
AstraZeneca
Boehringer Ingelheim
Chiesi
GlaxoSmithKline
Johnson & Johnson / Janssen
Merck
UCB
Roche / Genentech

Patient organisations
Asthma UK
European Lung Foundation
EFA
Int Primary Care Respiratory Group
Lega Italiano Anti Fumo
Netherlands

Scientists, biologists, physiologists, statisticians, bioinformaticians, computer scientists, clinicians, clinical trialists, managers, patients