Impact of biomarkers on asthma phenotypes

Professor Kian Fan Chung MD DSc
Experimental Studies, National Heart & Lung Institute,
Imperial College London;
Biomedical Research Unit, Royal Brompton Hospital,
London, UK

f.chung@imperial.ac.uk
Declaration of interest

• Participation in Advisory Board meetings regarding treatments of asthma and COPD for GSK, AstraZeneca, Novartis 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
How many phenotypes of asthma that clinicians can recognise?

- Late onset non-atopic asthma
- Early onset childhood atopic asthma
- Aspirin-induced asthma: Samter’s triad
- Corticosteroid-sensitive asthma associated with eosinophilia
- Asthma associated with chronic airflow obstruction
- Asthma with frequent exacerbations
Severe asthma

For children 6-11 years, theophylline is not recommended, and preferred Step 3 is medium dose ICS

**For patients prescribed BDP/formoterol or BUD/formoterol maintenance and reliever therapy

# Tiotropium by soft-mist inhaler is indicated as add-on treatment for adults (≥18 yrs) with a history of exacerbations

GINA 2015, Box 3-5 (2/8) (upper part)
Why do we need a systems medicine approach in severe asthma?

• A complex common disease with difficult definition
• Gene-environment interactions
• Variable disease with chronic changes
• Heterogeneous presentation
• Variable response to drugs
• Severe asthma, less responsive to current medications, need for new medications
Characteristics of severe asthma clinical traits

- Early onset/childhood asthma vs late onset
- Chronic airflow obstruction vs normal lung function (Increased decline in FEV$_1$)
- Recurrent exacerbations vs occasional exacerbations
- Atopic/high IgE vs non-atopic
- Eosinophilic vs non-eosinophilic
- Obese vs non-obese
- Steroid-insensitive vs steroid-sensitive
- β-adrenergic bronchodilation vs no bronchodilation
Molecular phenotyping

Th2-high vs Th2-low in mild-moderate asthma

Transcriptomic analysis of epithelial brushings: expression of Th2 cytokines

Features of Th2-high asthma

- More blood and BAL eosinophils
- ↑ serum IgE
- ↑ mucin MUC5AC
- ↑ IL5 and IL13 in biopsies
- ↑ bronchial hyperresponsiveness
- FEV$_1$ increase with ICS

Woodruff et al AJRCCM 2009; 180:388
How common is a Th2 (IL-13) high in severe asthma?

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

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

<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>

Stelios Pavlidis, Matthew Loza, Fred Baribaud for UBIOPRED
Potential Severe Asthma Phenotypes

“Severe Asthma”

Treatments

Symptoms

Exacerbations

FEV$_1$

Th2-high inflammation

Th2-low inflammation

Early onset allergic

Late onset eosinophilic

Obese Oxidative stress

Neutrophilic Bacterial infection

Adapted from Wenzel 2013
Mechanisms of severe asthma

Allergens, Virus, Bacteria
Pollution & oxidants

Non-T2

Eosinophilic inflammation

Remodeling/repair

Eosinophilic inflammation

Neutrophilic inflammation

Poor asthma control  High treatment requirements  
Chronic airflow obstruction  Recurrent exacerbations  Poor response to corticosteroids
New asthma treatments: targeting INTERLEUKINS/CYTOKINES

T2 (ILC2)

- IL-13
- IL-4
- IL-5
- IL-5Rα
- TSLP

- AMG157
- Mepolizumab
- Reslizumab
- Benralizumab
- Omalizumab
- QGE031
- Quilizumab

Non-T2

- IL-17
- TNFα
- CXCR8

- GSK679586
- Lebrikizumab
- Tralokinumab

- IL-4Rα
- IL-13
- IL-17
- IL-4

- Brodalumab

- AMG317
- Dupilumab

- Etanercept
- Golimumab

- CXCR2 Antagonist (SCH527123)
Mepolizumab, an anti-IL5 antibody, in patients with severe eosinophilic asthma

Ortega et al NEJM 2014; 371: 1198

- ≥ 2 exacerbations
- ≥ 1,000 µg FP/day
- Blood eos > 150/µl
Currently-available biomarkers to select patients for each specific anti-Th2 target?

Biomarkers of response to therapy

1. Blood eosinophil count: for anti-IL5, anti-IgE, Anti-IL4Rα (blocks IL4/IL-13)

2. Serum periostin: for anti-IL13

3. FeNO: for anti-IgE/anti-IL4Rα

4. Other biomarkers?
## Demographics of UBIOPRED cohort

<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>Total: 617 participants</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>


www.ubiopred.eu
Potential anti-Th2 treatment approaches in severe asthma (1)

Assuming anti-IL5, anti-IgE and anti-IL13 available: application to UBIOPRED cohort

Anti-IL5 vs Anti-IgE

<table>
<thead>
<tr>
<th></th>
<th>Total 418</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-IL5</td>
<td>111 (26%)</td>
</tr>
<tr>
<td>Anti-IgE</td>
<td>154 (37%)</td>
</tr>
<tr>
<td>IgE 30-1300 IU/ml Atopic</td>
<td>66(16%)</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>EOS ≥150 /ul</td>
<td>90 (21%)</td>
</tr>
</tbody>
</table>

Anti-IL-13 vs Anti IL-5

<table>
<thead>
<tr>
<th></th>
<th>Total 418</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-IL5</td>
<td>44 (10%)</td>
</tr>
<tr>
<td>Anti-IgE</td>
<td>115 (27%)</td>
</tr>
<tr>
<td>Anti-IL-13</td>
<td>150 (36%)</td>
</tr>
</tbody>
</table>

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<td>EOS ≥150 /ul</td>
<td>112 (27%)</td>
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</table>

Data from UBIOPRED

Stelios Pavlidis
Distribution of high FeNO, high serum periostin and high blood eosinophil count in 418 severe asthma (UBIOPRED)

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

FeNO≥30 ppb

Blood EOS≥300

Serum Periostin≥55
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

Th2 expression score (ES): Using gene set variation analysis with IL-13/epithelial cell gene expression in epithelial brushings

FeNO≥30 ppb

Blood EOS≥300

Serum Periostin≥50 µg/l

Th2 ES 0.10
Exacerbations 2.17

Th2 ES 0.36
Exacerbations 2.83

Th2 ES 0.08
Exacerbations 2.2

Th2 ES 0.29
Exacerbations 2.2

Th2 ES 0.05
Exacerbations 2

Th2 ES 0.13
Exacerbations 1

Th2 ES -0.11
Exacerbations 3.07

Th2 ES 0.00
Exacerbations 3.25
UBIOPRED PROCESS OF SYSTEMS MEDICINE

Patient recruitment

Severe asthmatics: Recruited from clinical centres across Europe

Sample collection

Multiple biomatrices:
- Plasma
- Sputum
- Urine

Biobank: Sample shipping & storage

'Oomics data acquisition

Knowledge management platform

Handprint of severe asthma

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

Tissue samples

2013

Wheelock et al. ERJ 2013;42:802

2015

www.ubiopred.eu
Analysis of sputum inflammatory cells transcriptomics and proteome: ‘sputum fingerprint’

Christos Rossios, Stelios Pavlidis, Chihhsi Kuo, Uruj Hoda
Distribution of neutrophilic and eosinophilic inflammation in sputum

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

B - Severe Smokers
- NEU & EOS: 53%
- NEU ONLY: 11%
- EOS ONLY: 8%
- NORMAL (PAUCI-GRANULOCYTIC): 28%

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

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

Uruj Hoda
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**

Kuo et al 2016
Hierarchical clustering of differentially expressed genes between eosinophilic vs non-eosinophilic asthma in sputum cells

Kuo et al 2016
Transcriptome-associated clusters (TAC) of moderate-severe asthma from sputum analysis

<table>
<thead>
<tr>
<th>Mechanisms</th>
<th>TAC 1</th>
<th>TAC 2</th>
<th>TAC 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>‘T-2 associated’</td>
<td>‘Inflammasome’</td>
<td>‘Mitochondrial’</td>
<td></td>
</tr>
<tr>
<td>Epithelial driven</td>
<td>Macrophage driven</td>
<td>Oxidative stress</td>
<td></td>
</tr>
<tr>
<td>Sputum inflammation</td>
<td>Eosinophilic/Mixed</td>
<td>Neutrophilic/Mixed</td>
<td>Eosinophilic/Paucigranulocytic</td>
</tr>
<tr>
<td>Microarray</td>
<td>IL33R, TSLPR, CCR3, IL3RA</td>
<td>IFN &amp; TNF superfamily, CASP4</td>
<td>Metabolic genes</td>
</tr>
<tr>
<td>GSVA</td>
<td>Th2/ILC2</td>
<td>NLPR3/DAMP-associated</td>
<td>Th17; OXPHOS; ageing</td>
</tr>
<tr>
<td>Protein (Somalogics)</td>
<td>IL-16, Periostin, Serpin peptidase inhibitor 1, ADIPOQ</td>
<td>TNFAIP6, MIF, Tyrosine kinase src</td>
<td>Cathepsin B, G</td>
</tr>
<tr>
<td>Clinical features</td>
<td>Severe asthma; Highest nasal polyps and OCS use; Severe airflow obstruction</td>
<td>Moderate-to-severe asthma Mild airflow obstruction</td>
<td>Moderate-to-severe asthma Mild airflow obstruction</td>
</tr>
</tbody>
</table>

Kuo et al 2016
Systems Medicine: finding biomarker(s)
Systems medicine for precision medicine of asthma

From multi-omics analysis to point-of-care biomarker
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 Méditerranee 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 Bergen, Semmelweis University Budapest, Jagiellonian University Krakow, University Hospital Bern, University of Ghent.

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

EFPIA Partners
Novartis
Almirall
Amgen

SME’s
Aerocrine
BioSci Consulting
Synairgen

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

Barcelona 2013

website hosted by the ELF: www.ubiopred.eu