Redefining asthma: Identification of different types of asthma to realise personalised treatments

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The Unit for Experimental Asthma and Allergy Research at The National Institute for Environmental Medicine (NIEM) and CfA-The Centre for Allergy Research
1/3 of the population will get asthma, diabetes or cancer during their lifetime
(To et al Am J Respir Crit Care Med 181:337–343, 2010)

Asthma starts early and causes handicap all life
Large cumulated costs for society and individual
There are novel treatments under development!
The evolution of asthma treatments


Adrenaline
Oral steroids
Theophylline
Inhaled $\beta_2$-agonists
Inhaled anticholinergics
Inhaled steroids
Long-acting drugs

Sodium cromoglycate

Anti-IgE

Anti-Leukotrienes

Anti-IL5

New biologics
New combinations
Asthma as painted by a teenager with asthma
What is asthma?

“Airways that constrict too much, too often and too easily, resulting in impaired lung physiology and quality of life”

Ann J. Woolcock
Bronchoscopy of subject with asthma

Stable condition

Airway inflammation and oedema

Smooth Muscle Constriction

Asthma attack
Features in asthma:

- Bronchoconstriction
- Airway Hyperresponsiveness (AHR)
- Airway Inflammation
- Airway Remodelling
The current awareness

Asthma is not a homogenous disease but a syndrome comprised of many phenotypes!

<table>
<thead>
<tr>
<th>Allergic</th>
<th>Non-allergic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eosinophilic</td>
<td>Non-eosinophilic</td>
</tr>
<tr>
<td>Neutrophilic</td>
<td>Paucigranulocytic</td>
</tr>
<tr>
<td>Fatal</td>
<td>Near fatal</td>
</tr>
<tr>
<td>Brittle</td>
<td>Chronic severe</td>
</tr>
<tr>
<td>Cough-variant</td>
<td>Occupational</td>
</tr>
<tr>
<td>Leukotriene-dependent</td>
<td>Exercise-induced</td>
</tr>
<tr>
<td>Aspirin/NSAID-intolerant</td>
<td>Skier’s obstruction</td>
</tr>
<tr>
<td>Intermittent</td>
<td>Steroid-insensitive</td>
</tr>
</tbody>
</table>

Identification of phenotypes requires improved diagnostics
Challenges for asthma sub-phenotyping studies

1) There are as of date no specific biomarkers of asthma sub-phenotypes nor endotypes
2) The vast majority of studies are cross-sectional
3) Few studies include interventions
4) Most studies include only few biomarkers such as IgE, eosinophils and exhaled NO
The rapid development of ‘omics technology platforms

The ’omics cascade

Next “Genomics”

What can happen

- Genome
- Transcriptome
- Proteome
- Metabolome
- Phenotype

What appears to be happening

- Genome Resequencing
- mRNA Tag Profiling
- Small RNA Identification
- Methylation Analysis
- Functional Elements (ChIP-Seq, DNAse-Seq)
- Transcriptome Sequencing

What makes it happen

What has happened & is happening

SED Diagnostics WS July 2017
U-BIOPRED study of biomarkers in severe asthma

**SA**
Severe asthma non-smokers; n=311
Smokers; n=110

**MA**
Mild to moderate asthma n=88

**HC**
Healthy controls n=101

- Extensive investigation of clinical and physiological outcomes at baseline, including bronchoscopies
- Broad collection of biomarker samples for omics

PI Sir Peter Sterk
Amsterdam
U-BIOPRED Clinical clusters; Lefaudeux et al JACI 2017

**GRAPHICAL ABSTRACT**

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

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

**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
- Oral corticosteroid-dependent
- Moderate-severe airflow obstruction

**Phenotype T4**
- Severe
- Female
- Mild-none airflow obstruction
- Frequent exacerbations
Biomarker:

A molecule that may be measured to

- predict risk to develop disease
- establish diagnosis
- reflect severity
- relate to mechanisms
- identify pathobiology
- indicate drug target engagement
- assess effects of treatment
- monitor adherence to treatment
- monitor environmental exposure
Matrices for biomarkers of asthma

- **Bronchoscopy material** (Biopsies, Fluids, Cells)
- **Nasal material** (Cells & Fluids)
- **Induced sputum** (Cells & Fluids)
- **Saliva**
- **Blood**
- **Urine**
- **Exhaled air**

Invasive

Non-Invasive
Nasosorption

fibres  foam

CE-marked medical devices
Hunt Developments UK

Hansel TT, Johnston SL & Openshaw PJ. 
*Lancet* 2013; 381: 861-73
Induced sputum to monitor airway inflammation
**Figure 3:** Cumulative asthma exacerbations in the BTS management group and the sputum management group.
Half of the patients changed phenotype defined by sputum cells after 1 year of follow up.

Phenotypes should not be defined by single cross-sectional measurement.
Induced sputum to monitor airway inflammation: Opportunities by the use of ‘omics and bioinformatics but induction, processing and technologies for analysis need to be developed.
Breathomics

$F_{E\text{NO}}$

**Exhaled NO during repeated low dose allergen challenge**

- Placebo
- Formoterol
- Budesonide + Formoterol


**E-NOSE (VOCs)**

**Asthma**

**Healthy**

**PExA (particles)**

Fens N et al. *Am J Respir Crit Care Med* 2009;180:1076-82


SED Diagnostics WS July 2017
Single-breath nitric oxide measurements in asthmatic patients and smokers

Magnus G Persson, Olle Zetterström, Veronica Agrenius, Elisabeth Ihre, Lars E Gustafsson

Exhaled nitric oxide (NO) concentrations were measured in asthmatic outpatients and in non-smoking and smoking healthy controls. In single exhalations, NO showed a peak suggestive of airway origin in both controls and asthmatic patients. The peak NO concentration was higher in asthmatic patients and lower in smokers than in non-smoking controls \((p < 0.05)\). The findings support a role for NO in the host defence response in asthma and suggest that NO measurements can discriminate between different types of lung disorders.

*Lancet* 1994; **343**: 146–47
Management of asthma in pregnancy guided by measurement of fraction of exhaled nitric oxide: a double-blind, randomised controlled trial

Heather Powell, Vanessa E Murphy, D Robin Taylor, Michael J Hensley, Kirsten McCaffery, Warwick Giles, Vicki L Clifton, Peter G Gibson

Summary

Background Asthma exacerbations during pregnancy are common and can be associated with substantial maternal and fetal morbidity. Treatment decisions based on sputum eosinophil counts reduce exacerbations in non-pregnant women with asthma, but results with the fraction of exhaled nitric oxide ($F_eNO$) to guide management are equivocal. We tested the hypothesis that a management algorithm for asthma in pregnancy based on $F_eNO$ and symptoms would reduce asthma exacerbations.

Less exacerbations

Less steroid use
Triphasic pattern of FeNO levels during lifetime

Tiago Jacinto, Kjell Alving et al. Journal of Breath Research 2017 *in press*
The near future: Internet-aided transfer of biomarker status and airway function!
Internet-based monitoring of asthma using point-of-care biomarkers:

- Improves management
- Empowers the patient
- Cost-effective
- Round the clock
- Secures evidence-based treatments
Increased use of electronic medical records (EMR) in the US and decreased costs of whole genome sequencing

Lung function monitoring: 1 year of electronic diary data

Exacerbations
Detection of exacerbations in asthma based on electronic diary data: results from the 1-year prospective BIOAIR study

Maciej Kupczyk, Shushila Haque, Peter J Sterk, Ewa Niżankowska-Mogilnicka, Alberto Papi, Elisabeth H Bel, Pascal Chanez, Barbro Dahlén, Mina Gaga, Mark Gjomarkaj, Peter H Howarth, Sebastian L Johnston, Guy F Joos, Frank Kanniess, Eleni Tzortzaki, Anna James, Roelinde J M Middelveld, Sven-Erik Dahlén, on behalf of the BIOAIR investigators

What is the key question?

- Which variables (symptoms, rescue medication use or lung function) represent the highest sensitivity and specificity to detect severe exacerbations in asthma patients?
Fluctuation Based Clustering: Constructing lung function profiles for each patient

Delphine Meier, Edgar Delgado-Eckert & Urs Frey
>25000 antibodies targeting 17000 proteins

The Human Protein Atlas project is funded by the Knut & Alice Wallenberg foundation.
Severe asthma (n=362) vs mild-to-moderate asthma (n=94) in U-BIOPRED

Volcano plot

Fold change = log2(median group 1 / median group 2)

Maria Mikus et al, MS in preparation

Fold change = log2(median group 1 / median group 2)
UPLC-MS/MS platform for urinary lipid mediators
Balgoma et al Anal Chem 2013

Bronchoconstriction
Pro-inflammatory

Pro-protective

CysLTs
Isoprostanes

Oxidative stress

Bronchoconstriction

Vascular & Platelet effects + TXA₂ bronchoconstriction

Bronchoconstriction Pro-inflammatory
Broncho protective

UPLC-MS/MS platform for urinary lipid mediators
Balgoma et al Anal Chem 2013

Bronchoconstriction
Pro-inflammatory
Urinary LTE$_4$ monitoring CysLTs

- Healthy Control
- Mild Asthma
- Severe Asthma

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Extreme value analysis

Log (ng/mmol creatinine)

Cohort A
Cohort B
Cohort C
Cohort D

<Patient selection>

n=410

Sputum eosinophils (%)

High
Low

<25:th percentile
>75:th percentile

SA= Severe Asthma
ns=non-smoking
s=smokers
MA= Mild Asthma
HC=Healthy Controls

SEDiagnostics WS July 2017
Ubiased consensus clustering

Final model: PAM, log2, Z-scores, Euclidean distance, K=5
Molecular phenotyping in the U-BIOPRED study: Patient clusters identified urinary lipid mediator profiles

Kolmert et al, MS in preparation!
Improved asthma phenotyping

**Recommended strategies**

- Apply broad and unbiased biomarker panels
- Perform careful clinical investigations
- Aim for measures suitable at the point-of-care
- Prioritise:
  1) longitudinal studies with repeated measures
  2) Interventional trials
- Involve all stakeholders