Precision medicine in allergy and asthma

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Precision medicine and precision health

- Personalized care based on molecular, immunologic and functional endotyping of the disease
- Participation of the patient in the decision making process
- Predictive aspects
- Preventive aspects

Asthma and allergic diseases are ideally suited for precision medicine

Umbrella of different diseases that partially share biological mechanisms (endotypes) and present similar visible properties (phenotypes) requiring an individualized approach for:

- *a better selection of treatment responders*
- *risk prediction*
- *design of disease-modifying strategies*

The audacious goal of PM

Offer the right medical care at the right time to the individual patient
What to we need to achieve the PM goal

- Global, multi-discipline partnerships
- Innovative health IT
- Rethinking healthcare

Right medical care at the right time to the individual patient

- Define
- Agree
- Implement

Research priorities

Policy priorities
A variety of stakeholders

Patients

Academia

Diagnostic and pharmaceutic industry

Ethics Committees

Regulators

Policy makers

Righ medical care at the right time to the individual patient

...needs agreement
A variety of tools

- Omics
- Health information technology
- Registries
- Biobanks
- Bioinformatics

Right medical care at the right time to the individual patient...needs coordination
Allergic diseases and asthma are extremely heterogeneous

- Disease phenotypes and endotypes
Disease phenotypes

- describe clinical, physiolologic and morphologic characteristics as well as unique responses to treatment

Visible properties

Asthma visible properties

- Onset
- Triggers
- Co-morbidities
- Inflammation type
- Remodeling
- Lung physiology

- Age, gender, race
- Long-term outcome
- Vital risk
- Response to treatment

Phenotypes

- Do not necessarily relate to or give insights into the underlying pathogenic mechanism

vs. endotypes

- Describe key pathogenic mechanisms

A successful endotype should LINK the key pathogenic mechanism with a clinical phenotype of asthma via BIOMARKERS

New approaches defining allergic diseases endotypes

- More accessible tools for human immunophenotyping
- Specific targeted immune therapies
- Application of omics
- Data driven disease endotyping
- New statistical tools

Agache I, Akdis C. Allergol Int. 2016 Jul;65(3):243-52
Personalized approach to allergic diseases

Phenotype/cluster approach
investigator-imposed subjective disease clustering
(hypothesis driven)

Endotype/biomarkers approach
unbiased, data-driven models

Agache I, Akdis C. Allergol Int. 2016 Jul;65(3):243-52
The ideal biomarker

Validity

- Reproducible (inter- and intra-coefficient of variability)
- Usable as diagnostic test (easily measurable, affordable)

Relevance

- Pathway specific
- Related to a relevant clinical end point (surrogate end points)
Current biomarkers in allergy and asthma

- The majority predict treatment response, very few forecast disease risk and progression

- Suitable for research settings

- Need to be validated and qualified

Agache I, Akdis C. Allergol Int. 2016 Jul;65(3):243-52
Validation and qualification of biomarkers

- **Validation** is the process of assessing the biomarker and its measurement performance characteristics, and determining the range of conditions under which the biomarker will give reproducible and accurate data.

- **Qualification** is the evidentiary process of linking a biomarker with biological processes and clinical end points.

Goodsaid FM, Frueh FW, Mattes W. Toxicology. 2008;245:219–23
<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Treatment expected to produce a response</th>
<th>Surrogate end-point value</th>
<th>Comments</th>
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<td>Anti IgE</td>
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<td>LF decline</td>
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<td>Corticosteroids (CS)</td>
<td>Fixed airway obstruction</td>
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<td>Anti IL-13</td>
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<td><strong>EXHALED BREATH</strong></td>
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<td>FeNO</td>
<td>Anti IL-5</td>
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<td>Anti IgE</td>
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<td>Point of care</td>
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<td>Metabolomics (VOC)</td>
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<td>Exacerbations in children</td>
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Allergic diseases endotypes – frameworks for research; are they ready for the clinic?
Factors modulating the disease endotype

- Anatomical factors
- Epithelial barrier
- Exposome (allergen, pollutants, irritants)
- Remodeled resident cells
- Genetic and epigenetic factors
- Innate and adaptive immune response
- Microbiome
- Nutrition
- Metabolic pathways
- Psychological factors

Agache I, Akdis C. Allergol Int. 2016 Jul;65(3):243-52
Simple and complex endotypes

- Single molecular mechanism (periostin high, IL-13 responsive asthma)

- Complex endotypes (type 2 asthma)
Type 2 inflammation

- Activation, chemokine, cytokine release
- Allergens
- Viruses
- Barrier defect

Epithelium

- TSLP
- IL-25
- IL-31
- IL-33

Submucosa

- ILC2
  - IL-4
  - IL-5

Tissue eosinophilia

- OX40L

Th2

- IL-4
- IL-5
- IL-9
- IL-13
- IL-4/IL-13

Vascular endothelium

- VLA-4 expression and tissue migration of Th2 cells, eosinophils and basophils

Mast cell degranulation

- TNF-α

Local IgE production
The complexity of the type 2 asthma endotype

The complex type 2 immune response driven endotype consists of several individual pathways with different preponderance in major allergic diseases.

Type 2 immune response driven complex endotype

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Multiple non-type 2-driven molecular sub-endotypes

Neutrophilic inflammation

Th17 pathway

Barrier defect

Neurogenic inflammation

Asthma

Rhinitis

CRS

AD

Non-type 2 immune response driven endotype

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Type 2 endotype: localised or systemic

**Localised inflammation**
- Predominance of the IL-4/IL-13-mediated pathway with eosinophilic inflammation localized in the bronchial mucosa

**Systemic inflammation**
- Driven by a strong chemokine signal (such as IL-5)
- More extensive eosinophilic airway inflammation involving the small airways
- Fixed airway obstruction
- Less responsive to ICS
- Risk of exacerbations requiring OCS/anti IL-5

Corticosteroid responsiveness of type 2 endotype depends on the subendotype

Responsive

Th2 and Eos

Less responsive

ILC2

Systemic eosinophilic inflammation responsive to anti IL-5

The mixed type 2 endotype

Is the targeted approach a disease modifier?

Critical issues for the endotype/biomarkers driven approach

1. Many options for similar patient population
   - No specific biomarkers; phenotype and endotype driven choices overlap

2. Treatment goals have not been reached yet
   - True immune modulation has to prevent/alter the course of the disease
3. Which asthma outcome to choose?

- Reflect the mechanistic intervention
- Is relevant for asthma
- Is relevant for that particular patient
Response to a targeted antiasthmatic drug

- Genetic and epigenetic background
- Immune-inflammatory pathway
- Remodeling phenotype (ASM, epithelium)
- Efficacy at the target site of the drug formulation

Inter- and intraindividual differences in response (dissociated effect)

Biomarker driven treatment

Outcome driven treatment
Suggested approach to PM in asthma

Diagnosis

Characterize phenotype
- Gender
- Age
- Race/Ethnicity
- Obesity
- Smoking status
- Early vs. late onset
- Atopic status
- Lung function/AHR

Characterize endotype
- Biomarkers:
  - blood
  - sputum
  - exhaled breath

Type 2 immune response
Non-Type 2 immune response

Prognostic BM

Primary and secondary prevention

Tailored therapy
Endotype-driven treatment of allergic diseases and asthma has improved the response rate but did not solve:

- the dissociated effect
- the variability in response due to drug efficacy at target site
Summary (2)

Key points for moving the field forward:

• Profiling type 2 and non-type 2 subendotypes (specific biomarkers)

• add new targets:
  • airway smooth muscle
  • epithelial components of asthma
  • epigenetic modifications

• systems pharmacology
Bring Precision Medicine to the clinic:

• Revised disease taxonomy including disease endotypes

• Full patient monitoring using novel digital technology and the concept of endotypes and novel biomarkers

• Improved understanding and common usage of disease phenotypes, endotypes and biomarkers at the point of care

• Biomarker and endotype-linked patient care and usage of precision therapies
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