Biomarkers for Asthma: Myths & Reality

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pulmonologist – clinical pharmacologist

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UMCG & QPS-NL, Groningen, The Netherlands

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Zuzana Diamant MD PhD Professor
Executive Medical Director Respiratory & Allergy QPS-NL
- 2014 GCP-Certified Principle Investigator, Amsterdam, NL
- 2002, 2012 Board-certified Pulmonologist, Rotterdam, NL
- 2006, 2011 Clinical Pharmacologist, Leiden, NL

Academic Affiliations
- Guest Professor Respiratory Allergy Research: Skane University, Dept Respiratory Medicine & Allergology, Lund, Sweden;
- Affiliated Scientist and Supervisor, Dept of Pharmacy & Clinical Pharmacology, University Medical Center, Groningen, Netherlands.

Research experience & Scientific Performance
- >25 year clinical trials; focus: asthma/allergy/(COPD)
- >10 years Research Director Respiratory Allergy (CRO); PI
- Phase 0-II (human disease models, non-invasive biomarkers)
- EAACI Asthma Section Secretary
- EAACI TF chair (Biomarkers) and member of 3 other EAACI TFs
- ERS TF member (Bronchoprovocation tests);
- Editorial board member (3 international journals)
- Several scientific advisory boards
- >100 scientific publications
- Scientific lectures, refereeships, chairs at international congresses
Disclosures

• Collaboration with QPS-NL (CRO), work with different pharma companies
• None related to this lecture
Lecture Highlights

• Unidimensional Paradigms vs Complex Reality
• Biomarkers & Asthma Phenotypes/Endotypes
• Application of Biomarkers in Clinical Drug Development and Personalized Medicine
Shifting Paradigm of Asthma: From one Clinical Syndrome to different Inflammatory Phenotypes
Evolution of Asthma Paradigm: From pattern recognition to understanding

Clinical phenotypes
Clinical and physiological characteristics

Bio-clinical phenotypes
Includes cellular biomarkers

Endotypes
Linking to molecular pathways
Until 1980s: Generalistic Concept of asthma = Clinical Syndrome

Traditional Pillars in...

Asthma Diagnosis, Treatment and Clinical Trials:

- Symptoms
- Rescue Medication Use
- Lung Function Measurements
- Exacerbations

GINA www.ginasthma.org
Classical Concept in 1990s-early 2000s: Asthma = Allergen-driven TH2 Disease

Genes predisposing to allergies

Lack of early Th1 stimulation

Triggers:
- Allergens, viruses, cold, irritants, exercise

Hyperactive response
- Bronchospasm
- Edema
- Airway obstruction

Physiologic Effects

Chronic inflammation & Tissue remodeling

Allergen-induced TH2-response as Asthma POC model in Drug Development

### Increased Sputum Eosinophils at 24 and 7 h post-Allergen Challenge following P and FP treatment

<table>
<thead>
<tr>
<th>Sputum Biomarker</th>
<th>Treatment</th>
<th>Estimate (90% CI)</th>
<th>Change from Baseline (90% CI)</th>
<th>1-sided p-value</th>
<th>Effect Size*</th>
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<td></td>
<td></td>
<td></td>
<td>Fluticasone - Placebo</td>
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<td>Hour 24</td>
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<tr>
<td>Eosinophils</td>
<td>Placebo</td>
<td>250.8 (165.5, 336.1)</td>
<td>-277 (-394, -160)</td>
<td>0.002</td>
<td>-2.1</td>
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<tr>
<td></td>
<td>Fluticasone (500 mcg bid)</td>
<td>-25.9 (-106, 54.5)</td>
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<td>Eosinophils</td>
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<td>11.5 (5.7, 17.4)</td>
<td>-11.8 (-19.9, -3.8)</td>
<td>0.014</td>
<td>-1.3</td>
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<td>-0.3 (-5.8, 5.2)</td>
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<tr>
<td>Neutrophils</td>
<td>Placebo</td>
<td>173.6 (62.5, 284.8)</td>
<td>-101 (-253, 52.0)</td>
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<td>Neutrophils</td>
<td>Placebo</td>
<td>-5.5 (-18.8, 7.9)</td>
<td>6.3 (-9.3, 21.8)</td>
<td>0.768</td>
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<td>Hour 7</td>
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* Effect size for Fluticasone shown on analysis scale for markers with statistically significant treatment effects (1-sided alpha < 0.05)

Cell count estimates were analyzed after a square root transformation

CI = Confidence Interval, Final Results Date: 08/28/2009

Life was simple:

1990s-early 2000s:
Uni-dimensional Concept of Asthma & Asthma Management:

- Mainly allergic
- Th2-driven (major cytokines: IL-4, IL-5 and IL-13)
- Eosinophilic
- ICS-responsive condition
One-Size-fits-All Treatment of Asthma according to Guidelines based on Disease severity

Step 1
Intermitterend astma

Step 2
Licht persisterend astma

Symptomen ≤ 1x per week

β₂-kort
ICS 400-800 µg bud/becl; 200-500 µg flu

Niet bereiken streefdoel ondanks stap 3 medicatie

Step 3
Matig persisterend astma

Symptomen > 1x per week

β₂-kort
ICS 1600 µg bud/becl; 1000 µg flu

ICS 1600 µg bud/becl; 1000 µg flu

Niet bereiken streefdoel ondanks 3 maanden matige dosis ICS

Step 4
Ernstig persisterend astma

β₂-kort
ICS 1600 µg bud/becl; 1000 µg flu

ipratropium of theoph en β₂-lang

ICS 800 µg bud/becl; 500 µg flu en β₂-lang

ICS 1600 µg bud/becl; 1000 µg flu en β₂-lang

Controle
Step omlaag

Stepdown:
Indien astma na 3 maanden onder controle, dan stap omlaag overwegen

Niet bereiken streefdoel ondanks stap 3 medicatie

Niet bereiken streefdoel ondanks 3 maanden matige dosis ICS

Symptomen ≤ 1x per week
Despite almost complete, prolonged depletion of eosinophils from sputum and blood
No effect on allergen-induced late response or AHR
Study results question the role of eosinophils in LAR/asthma
Effect of two anti-IL13 mAbs on Allergen Challenge

- Pts inclusion based on clinical/physiological criteria
- Both anti-IL13 mABs inhibit the LAR (+/- EAR)
- No effect on allergen-induced AHR
- No effect on allergen-induced sputum eosinophils
- No effect on allergen-induced blood eos
• Polosa R (Curr Opin Pulm Med 2007):
  ‘Monotherapy with LTRA in asthma is not effective except for specific populations e.g. aspirin-intolerant asthma and asthma with concomitant allergic rhinitis’.

• Chauhan & Ducharme: (Cochrane report 2012):
  ‘As monotherapy, inhaled corticosteroids display superior efficacy to anti-leukotrienes in adults and children with persistent asthma; the superiority is particularly marked in patients with moderate airway obstruction.’
Is Life (so) simple?

• Still too many asthmatics, especially those with severe asthma, are suboptimally controlled despite potent ICS + LABA combi therapy
  • [Rabe KF, et al ERJ 2000;16:802-7].

• Several biologicals development programs have been suspended due to discordant results and hence negative POC in allergen challenge model
Conclusion: Asthma is more Heterogeneous than originally thought; time for a Rethink?
1990-early 2000
New Dimension: Airway Sampling

**Invasive**
- Bronchial biopsy
- Bronchial wash
- Bronchial brushing
- Bronchoalveolar lavage (BAL)
- Lung biopsy

**Non-invasive**
- Exhaled air analysis
- (EBC, FeNO, eNose)

Sputum analysis
Two different pathways (TH2 and ILC2) produce type2-cytokines and result in eosinophilia.
From pattern recognition to understanding asthma

Clinical and physiological characteristics

Clinical phenotypes

Bio-clinical phenotypes
Includes cellular and other inflammatory biomarkers

Endotypes
Linking to molecular pathways
Characteristics of an “ideal” Biomarker

- Involved in the disease’s pathophysiology
- Responsive to changes in disease activity and...
- Responsive to (targeted) treatment
- Simple
- Minimally invasive
- Properly validated
- Repeatable
- Cost-effective

Th2-phenotype-linked Biomarkers: for phenotyping and monitoring

- Sputum eosinophils (>2 or 3%)
- Exhaled nitric oxide (FeNO; >30 ppb)
- Blood eosinophils (150-400/mcL)
- Periostin
- IgE
- Allergen skin prick testing
Blood eosinophils: back on stage

Diagnostic accuracy to discriminate between eosinophilic vs non-eosinophilic airway inflammation*) was assessed by ROC AUC for:
- Blood eosinophils: 89%
- FeNO: 78%
- Serum periostin (inhouse periostin assay): 55% (NS)

*) defined by sputum eosinophilia (≥3 and 2%)

Cluster Analysis and Clinical Asthma Phenotypes

Pranab Haldar*, Ian D. Pavord*, Dominic E. Shaw, Michael A. Berry, Michael Thomas, Christopher E. Brightling, Andrew J. Wardlaw, and Ruth H. Green*

1Institute for Lung Health, Glenfield Hospital, Leicester, United Kingdom; and 2Department of General Practice, University of Aberdeen, Aberdeen, United Kingdom

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**Discordant Symptoms**

- **Early Symptom Predominant**
  - Early onset, atopic
  - Normal BMI
  - High symptom expression

- **Obese Non-Eosinophilic**
  - Later onset, female preponderance
  - High symptom expression

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**Concordant Disease**

- Symptom-based approach to therapy titration may be sufficient.

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**Benign Asthma**

- Mixed middle-aged cohort
- Well controlled symptoms and inflammation
- Benign prognosis

**Early Onset Atopic Asthma**

- Concordant symptoms, inflammation & airway dysfunction

**Inflammation Predominant**

- Late onset, greater proportion of males
- Few daily symptoms but active eosinophilic inflammation

**Monitoring inflammation allows down-titration of corticosteroids.**

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**Eosinophilic Inflammation**

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Take home messages from Haldar study

• Different inflammatory phenotypes based on airway inflammation (eosinophilic vs non-eosinophilic)
  • ICS responders
  • ICS non-responders

• Different asthma phenotypes require different management strategy (concordant vs discordant disease)
  • Symptoms/lung function-driven strategy
  • Biomarkers-driven strategy

Moderate-severe Asthma profits from Biomarker guided Treatment Strategy

\[ \text{Jayaram L, et al. ERJ 2006;27:483-94.} \]
Bio-Clinical Phenotypes of Asthma

Mild-mod early onset
Young
Allergic
Normal LF

Mild-mod early onset
Older
Allergic
Reversible LF

Higher BMI later onset
Older
High ICS
Reversible LF

Severe
Obese
Oldest
ICS, OCS, +
Impaired LF

Moore WC, JACI 2014; 133:1557-63.
From pattern recognition to understanding asthma

Clinical phenotypes
Clinical and physiological characteristics

Bio-clinical phenotypes
Includes cellular biomarkers

Endotypes
Linking to molecular pathways
T-helper Type 2–driven Inflammation Defines Major Subphenotypes of Asthma

Prescott G. Woodruff1,2, Barmak Modrek3, David F. Choy4, Guiquan Jia4, Alexander R. Abbas3, Almut Ellwanger1, Joseph R. Arron4*, Laura L. Koth1,5, and John V. Fahy1,2*

Objectives:
• To study the heterogeneity of Th2-related molecular mechanisms and
• The relationship on patient responsiveness to ICS

Methods:
* Investigating the gene expression in epithelial brushings from 42 patients with mild-moderate asthma and 28 non-asthmatics controls

Molecular markers identify Th2-type asthma

C/3 gene expression signature correlates with:
- Th2 profile: IL5 and IL13 expression, eosinophilia
- BHR, airway remodeling

Woodruff P, et al AJRCCM 2009
Only asthmatics with “Th2 High” profile responded to anti-inflammatory therapy with ICS

After 8 weeks of FP 2x500 mcg BID, increased FEV1 was found only in TH2-high asthmatics

Non-Th2/Th2 low asthma:
- approx. 50% of asthmatics
- Associated with infections, occupational irritants, oxidative stress, neutrophils, TH1-17, ASM changes
- Modest or no response to ICS and/or targeted TH2-therapeutics
- Still insufficiently defined in contrast to Th2high asthma
IMI project U-Biopred: from Systems Biology to Handprints of Severe Asthma

Kaminsky, Irvin, Sterk, JAP 2011.
Asthma is a heterogeneous disease consisting of $\geq 4(-5)$ clinical phenotype clusters. Within the clinical phenotypes there are different inflammatory phenotypes. Neutrophilic inflammatory phenotypes present in more severe disease. Th2’-high’ asthma is presently the only ‘well-defined’ endotype characterized by increased levels of type2-inflammation; usually well-responsive to ICS. Well-defined biomarkers for type2-inflammation include FeNO, eosinophils, periostin, IgE. ‘Th2-low/non-Th2’ asthma does not respond to ICS and represents an unmet need.
New Era: Applying Biomarkers for Personalized Medicine (& Drug Development)

**YESTERDAY**

Traditional Medicine

One size fits all treatment

**TODAY**

Stratified Medicine

Relatively homogeneous patient groups (biomarkers, phenotypes)

**TOMORROW**

Personalized Medicine

Single individuals with a disease or risk of a disease (treatment/prevention)

Revival of Biomarker-guided Therapy (since 1958)

Dr Harry Morrow Brown 1917-2013

Application and Impact of Type2-biomarkers for Targeted Monoclonal Antibody Therapy in Type2-eosinophilic asthma
Inclusion criteria:
• Uncontrolled (symptomatic) asthma with persistent sputum eosinophilia (>3%) while on oral prednisone (5-25 mg/day) and high-dosed ICS

Effect on Exacerbations:
• In placebo group: 10 (of 11) pts had 12 exa’s; all received extra prednisone or antibiotics;
• in Mepo group only 1 pt experienced an exa
Mepolizumab (anti-IL5) reduces exacerbations in patients with severe eosinophilic asthma (DREAM study: >600 pts)


>600 pts
Eosinophil asthma (sputum eosinophils; blood eos or FeNO) on high doses of ICS +/- OCS
N=135 randomized; pts with eosinophilic SA; (Blood eos >300 cells/mL (prev) or >150 mL (optim phase); OCS + high dosed ICS

32% exacerbations

Phase II
N=219 poorly controlled asthma (ICS mean dose: 580 mcg/day); Lebrikizumab 250 mg sc/month during 6 months

Lebrikizumab (anti-IL13) effective in Th2-high vs Th2-low moderate-severe asthma on top of high doses ICS.

Setipiprant, a selective CRTH2 antagonist, reduces allergen-induced airway responses in allergic asthmatics

Z. Diamant¹, P. N. Sidharta², D. Singh³, B. J. O’Connor⁴, R. Zuiker¹, B. R. Leaker⁴, M. Silkey² and J. Dingemanse²

N=15 HDM allergic asthmatics; no pre-phenotyping

25.6% LAR (AUC3-10h)
No effect on FeNO or blood eosinophils
Exit for CRTH2 antagonists?

- Overall modest efficacy data from 2 POCs (Singh D, ERJ 2013; Diamant, CEA 2014) and
- Little/no efficacy in clinical asthma studies (non-phenotyped asthmatics)
- Caused the development of several CRTH2-antagonists to be put on hold
Phenotyping saves CRTH2 clinical program

CRTH2 antagonist OC000459 effective in eosinophilic, but not in non-eosinophilic asthma.

A: effect of CRTH2-inhibition vs P in ‘eosinophilic’ asthmatics
(≥250 blood eosinophils/mcL)

B: effect of CRTH2-inhibition vs P in ‘non-eosinophilic’ asthmatics
(<250 blood eosinophils/mcL)

Emerging and Current Targeted type 2-treatments for Severe Asthma

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Biomarker</th>
<th>Development Phase (EU)</th>
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<tbody>
<tr>
<td>Mepolizumab¹</td>
<td>IL-5</td>
<td>Blood eosinophilia</td>
<td>Recommended for approval</td>
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<tr>
<td>Reslizumab²</td>
<td>IL-5</td>
<td>Blood eosinophilia</td>
<td>Pre-registration (Filed)</td>
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<tr>
<td>Benralizumab³</td>
<td>IL-5Rα</td>
<td>Blood eosinophilia</td>
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<tr>
<td>Lebrikizumab⁴</td>
<td>IL-13</td>
<td>Periostin</td>
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<td>Tralokinumab⁵</td>
<td>IL-13</td>
<td>FeNO (?)</td>
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<td>Dupilumab⁶</td>
<td>IL-13, IL-4</td>
<td>FeNO (?)</td>
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<tr>
<td>QAW039⁷,⁸</td>
<td>CRTH2</td>
<td>Blood eosinophilia (?)</td>
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<tr>
<td>Omalizumab⁸</td>
<td>IgE</td>
<td>FeNO</td>
<td>Approved</td>
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</table>

¹ As of December 2015.
² Orally active.
Summing up

• Q: Do we need biomarkers in asthma management?
• A: Yes, in selected phenotypes

• Q: De we *always* need biomarkers to manage asthma?
• A: Probably not, only in non-responsive patients
Proposed Algorithm for Clinical Application of Biomarkers in Asthma

For a patient who is uncontrolled on high dose ICS or oral CS

Make sure the patient has good
- Compliance
- Inhalation technique
- Knowledge of his or her condition

Check
- IgE
- Eosinophils
- FeNO
- Periostin

If high levels, start relevant anticytokine antibody treatment (as available in your country)
Back up
Identification of Asthma Phenotypes Using Cluster Analysis in the Severe Asthma Research Program

5 different subphenotypes within the SA phenotype with clinically similar characteristics

Moore WC, AJRCCM 2010; 181:315-23.
Biomarkers, Cluster analysis

Current Concept of Asthma based on recent Insights

omics techniques

personalized medicine

Response (stimuli, targeted Rx)

Genes

Environmental factors, triggers

Biomarkers, Cluster analysis
Effects of an Anti-TSLP Antibody on Allergen-Induced Asthmatic Responses

N=31 mild asthmatics
3 monthly IV doses of anti-TSLP mAb or P

34% inhibition of the LAR (day 42) and 46% inhibition of the LAR on day 84.

Also inhibition of sputum & blood eosinophils and FeNO.

Biomarkers $\Rightarrow$ Phenotypes $\Rightarrow$ Personalized Medicine

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Bio-clinical phenotypes
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