Asthma Phenotypes

Prescott G. Woodruff, MD, MPH
UC San Francisco
Disclosures for:

Prescott Woodruff, MD

For the 12 months preceding this CME activity, I disclose the following types of financial relationships:

Honoraria received from: None
Consulted for: Boehringer Ingelheim, Kalobios, Merck
Held Common Stock in: None
Research, clinical trial, or drug study funds received from: Genentech

I will be discussing products that are investigational or not labeled for use under discussion.
Outline

- Heterogeneity in complex diseases
- Sub-phenotypes of asthma
  - Cellular
  - Molecular
- Periostin as a blood biomarker
- Summary
Background

Molecular mechanism

Targeted therapy

Cellular/pathological/physiological features

Clinical phenotype

Recognizable disease
Background

Molecular mechanism

Targeted therapy

Distinct molecular mechanism

Cellular/pathological/physiological features underlying phenotype A

Clinical phenotype A

Recognizable disease syndrome

Cellular/pathological/physiological features underlying phenotype B

Clinical phenotype B
Outline

- Heterogeneity in complex diseases
- Sub-phenotypes of asthma
  - Cellular
  - Molecular
- Periostin as a blood biomarker
- Summary
Cellular Phenotypes of Asthma

Based on studies of induced sputum
Sputum eosinophilia in asthma
Some have a lot
Sputum eosinophilia in asthma
Some have none
Eosinophil (+) and eosinophil (-) subgroups in asthma

Wenzel et al. AJRCCM 1999;160:1001
Characteristics of eosinophil (+) asthma

- More CD4\(^+\) and CD8\(^+\) T cells
- More mast cells
- More airway fibrosis (remodeling)

Wenzel et al. AJRCCM 1999;160:1001
**Treatment response:**

Anti–interleukin-5 monoclonal antibody (Mepolizumab) only effective against eosinophilic asthma


3. Significant effect on exacerbations in carefully selected patients. Sputum eosinophil percentage >3% on at least one occasion in the previous 2 years, despite high-dose corticosteroid treatment.

Haldar et al. NEJM 2009;360:985.
Characteristics of non-eosinophilic asthma

Non-eosinophilic asthma:

- pathologically distinct disease phenotype
- characterized by...
  - absence of airway eosinophilia
  - absence of fibrosis (remodeling)
  - poor short-term response to treatment with inhaled corticosteroids.
Sputum neutrophils are another inflammatory cell associated with airway obstruction in asthma.

Increased sputum neutrophil % is independently associated with lower FEV1 ($P = 0.04$)

Cellular Phenotypes of Asthma

1. Eosinophilic
2. Neutrophilic
3. Mixed inflammatory
4. Paucigranulocytic
Outline

- Heterogeneity in complex diseases
- Sub-phenotypes of asthma
  - Cellular
  - Molecular
- Periostin as a blood biomarker
- Summary
Dominant model: Asthma is caused by allergic inflammation driven by T-helper type 2 cytokines (IL-4, 5 and 13)
Interleukin-13 and asthma

Barnes, Nat Rev Drug Discovery 2004

Lee, J Exp Med 2001

Airway remodeling in IL-13tg mice

Nature Reviews | Drug Discovery

Mucus cell metaplasia

Subepithelial fibrosis
Increased messenger RNA for IL-13 in asthmatic airway biopsies

Humbert M et al, JACI 1997;99:657-65
Increased messenger RNA for IL-13 in asthmatic airway biopsies

Humbert M et al, JACI 1997;99:657-65
Increased messenger RNA for IL-13 in asthmatic airway biopsies

Humbert M et al, JACI 1997;99:657-65
Th-2 CD4+ T cells

IL-13 (or IL-4)

Mesenchyme

Asthma
Genome wide profiling in airway epithelial brushings

- Asthma (n=42) Vs placebo
- Healthy (n=28) Vs placebo
- Smokers (n=15)

Identify epithelial genes that are specifically differentially expressed in asthma and responsive to steroid treatment.
Inclusion criteria

(i) Prior physician diagnosis of asthma
(ii) No use of oral or inhaled corticosteroids for asthma in the past 6 wks
(iii) PC$_{20}$FEV$_1$ Methacholine $\leq$ 8.0 mg/mL
(iv) At least one of the following:
   - Asthma symptoms on at least two days per week
   - Beta agonist use on at least two days per week
   - FEV1 < 85% predicted
Differentially expressed genes in asthma that are steroid responsive

- Genes induced or repressed in asthma (n=22)
  - Bonferroni p<0.05
- Steroid responsive genes (n=30)
  - >2 fold difference for change in treatment vs placebo group

Woodruff, PNAS 2007
The gene expression profile of Epithelial brushings

Healthy (n = 28)  Asthma (n = 42)

Epithelial cell expression of these three genes is regulated by IL-13.

Woodruff et al. PNAS 2007
Expression levels of periostin, CLCA1 and serpinB2 in epithelial brushings are variable and highly correlated.
Clustering by expression levels of periostin, CLCA1 and serpinB2 in **epithelial brushings** identifies two groups of subjects with asthma

*Woodruff et al. AJRCCM 2009*
Confirmatory gene expression data from bronchial biopsies:

Expression levels of IL-13 and IL-5 (but not IL-4) are highly correlated and elevated in “Cluster 1” asthmatics.
**Clinical features:** Both Th2 High and Low asthma have abnormal lung function, bronchodilator responsiveness and allergen skin prick test reactivity.
Clinical Features: Th2 High asthma has greater AHR, IgE levels and Eosinophilia.
Features of these molecular phenotypes

*Both* Th2 High and Low asthma have:

- decrements in FEV$_1$
- bronchodilator responsiveness
- allergen skin prick test reactivity

Th2 High asthma has *greater*

- AHR
- IgE levels
- blood and especially BAL eosinophilia

Woodruff et al. AJRCCM 2009
Airway Remodeling: Sub-epithelial fibrosis

Woodruff et al. AJRCCM 2009
Implications of phenotyping based on molecular mechanism

1. Research on disease mechanisms
2. Treatment responses
Treatment response:
Th2 High asthma responds to inhaled steroids, whereas Th2 Low asthma does not

Woodruff et al. AJRCCM 2009
Th2 phenotyping in more severe disease

Periostin, CLCA1, SerpinB2 expression

Exhaled Nitric Oxide

Scaled 3 gene mean expression level

FENO (ppb)
Molecular phenotypes of asthma

**Th2 cytokines**

- Airway Eosinophilia
- Sub-epithelial Fibrosis
- ↑Mucin, altered airway mucin gene expression

**Th2 High asthma**
- ↑Serum IgE
- ↑AHR
- ↑Allergen skin test responses

**Th2 Low asthma**
- Indistinguishable based on demographics & clinical characteristics
- ↑Serum IgE
- AHR
- Allergen skin test responses

- Inhaled steroids
- Th2 cytokine blockade

- Airway infection?
- TH17?
- Neutrophilia?
- Innate immune dysfxn?

- Little Airway Eosinophilia
- No Sub-epithelial Fibrosis
- Normal airway mucin gene expression
Outline

- Heterogeneity in complex diseases
- Sub-phenotypes of asthma
  - Cellular
  - Molecular
- Periostin as a blood biomarker
- Summary
Assessment of phenotype-specific responses would be easier in trials and more practical in the clinic if we had a blood biomarker.

**Approach:** develop assays for secreted proteins in the signature

- **Periostin**
  - Secreted in the basolateral media in culture
  - Can be detected in the blood
  - Development of an ELISA sensitive for all 4 transcript variants
Serum periostin levels in mod/severe asthma Leicester cohort

Jia, G. JACI 2012
Serum periostin levels are a biomarker of airway eosinophilia in moderately severe asthma (BOBCAT study)

Jia, G. JACI 2012
Predictive capacity of serum periostin
Lebrikizumab phase IIa: bronchial allergen challenge

- Mild allergic asthma patients with specific aeroallergen sensitivity
- Instill aeroallergen, measure lung function over time
  - baseline and post-treatment (placebo:drug)
  - compare AUC of late-phase response
- Lebrikizumab (anti-IL13) study
  - N=12 active, 16 placebo
  - 13 week treatment course (5 mg/kg q4w)

![Graph showing allergen administered and changes in FEV1 (percentage change) over time. Immediate IgE-mast cell and delayed T cell, eosinophil response indicated.]

Genentech, AAAAI 2011

4/28/11
Predictive capacity of serum periostin
Lebrikizumab phase IIA: bronchial allergen challenge

Anti-IL13 Phase 2a allergen challenge study

Caveats
- Due to small N, median values selected to dichotomize groups (5-8 active subjects/group)
- Due to small N, outliers can skew results
- Unclear whether these cutoffs will translate to more severe asthmatics
- *Unclear whether these markers will predict benefit for clinical endpoints in target population (FEV1, exacerbation reduction)*

Zheng Su
Rich Erickson

Genentech
AAAAI/2011
Lebrikizumab Treatment in Adults with Asthma

Jonathan Corren, M.D., Robert F. Lemanske, Jr., M.D., Nicola A. Hanania, M.D., Phillip E. Korenblat, M.D., Merdad V. Parsey, M.D., Ph.D., Joseph R. Arron, M.D., Ph.D., Jeffrey M. Harris, M.D., Ph.D., Heleen Scheerens, Ph.D., Lawren C. Wu, Ph.D., Zheng Su, Ph.D., Sofia Mosesova, Ph.D., Mark D. Eisner, M.D., M.P.H., Sean P. Bohan, M.D., Ph.D., and John G. Matthews, M.B., B.S., Ph.D.
Serum periostin as predictor of response to lebrikizumab

A Total Cohort

B High-Periostin Subgroup

C Low-Periostin Subgroup

Corren et al. NEJM 2011
Serum periostin and FeNO as predictors of response to lebrikizumab: lung function

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Lebrikizumab (n=106)</th>
<th>Placebo (n=112)</th>
<th>Leb-placebo</th>
<th>Lebrikizumab (n=106)</th>
<th>Placebo (n=112)</th>
<th>Leb-placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>9.8%</td>
<td>4.3%</td>
<td>5.5% (0.8%,10.2%) p=0.02</td>
<td>8.4%</td>
<td>5.2%</td>
<td>3.1% (-1.4%, 7.6%) p=0.17</td>
</tr>
<tr>
<td>Periostin-high (≥ median)</td>
<td>14.0%</td>
<td>5.8%</td>
<td>8.2% (1.0%,15.4%) p=0.03</td>
<td>11.1%</td>
<td>6.9%</td>
<td>4.2% (-3.1%,11.5%) p=0.26</td>
</tr>
<tr>
<td>Periostin-low (&lt; median)</td>
<td>5.1%</td>
<td>3.5%</td>
<td>1.6% (-4.5%,7.7%) p=0.61</td>
<td>5.0%</td>
<td>3.5%</td>
<td>1.5% (-4.1%, 7.2%) p=0.59</td>
</tr>
<tr>
<td>FeNO-high (≥ median)</td>
<td>14.2%</td>
<td>5.6%</td>
<td>8.6% (1.3%,15.9%) p=0.02</td>
<td>10.7%</td>
<td>4.8%</td>
<td>5.9% (-0.9%, 12.7%) p=0.09</td>
</tr>
<tr>
<td>FeNO-low (&lt; median)</td>
<td>4.8%</td>
<td>2.9%</td>
<td>1.9% (-3.8%,7.5%) p=0.52</td>
<td>6.3%</td>
<td>5.7%</td>
<td>0.6% (-5.3%, 6.6%) p=0.84</td>
</tr>
</tbody>
</table>

Corren et al. NEJM 2011
Serum periostin and FeNO as predictors of response to lebrikizumab: Exacerbations

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Lebrikizumab n=106</th>
<th>Placebo n=112</th>
<th>% Reduction (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>0.2</td>
<td>0.3</td>
<td>43% (–10%, 71%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Periostin-high (≥ median)</td>
<td>0.1</td>
<td>0.3</td>
<td>67% (–15%, 90%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Periostin-low (&lt; median)</td>
<td>0.2</td>
<td>0.3</td>
<td>29% (–69%, 70%)</td>
<td>0.44</td>
</tr>
<tr>
<td>FeNO –high (≥ median)</td>
<td>0.1</td>
<td>0.4</td>
<td>79% (7%, 95%)</td>
<td>0.04</td>
</tr>
<tr>
<td>FeNO –low (&lt; median)</td>
<td>0.2</td>
<td>0.2</td>
<td>−4% (–128%, 53%)</td>
<td>0.92</td>
</tr>
</tbody>
</table>
Repeatability of Serum periostin and FeNO in lebrikizumab study run-in

Table S3. Intra-Patient Variability for Selected Biomarkers During Run-In Period

<table>
<thead>
<tr>
<th></th>
<th>Serum Periostin (n=201)</th>
<th>F\textsubscript{ENO} (n=212)</th>
<th>Blood Eosinophils (n=210)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean CV, %</td>
<td>5.0</td>
<td>19.8</td>
<td>21.3</td>
</tr>
<tr>
<td>95% CI for Mean CV, (%)</td>
<td>(4.4, 5.6)</td>
<td>(17.4, 22.2)</td>
<td>(18.7, 24.0)</td>
</tr>
</tbody>
</table>

CI, confidence interval; CV, coefficient of variation; F\textsubscript{ENO}, fractional exhaled nitric oxide; n = the number of patients with non-missing data at both the screening (Day 7) and Day 1 visits.
Summary

- **Molecular phenotyping: Th2-high asthma**
  - Largely overlapping with eosinophilic asthma
  - Also marked by increased FeNO
  - Present in at least ½ of patients mild asthma and persists despite ICS in some patients with more severe asthma

- **Serum periostin is a blood biomarker of Th2-high asthma**
  - Correlates well with airway eosinophilia and FeNO
  - Predicts treatment responses
    - Response to ICS in mild asthma
    - Response to Th2 cytokine blockade in mild and moderately severe asthma (two phase II studies to date)