DISCLOSURE

Dr. Fahy has declared no conflicts of interest related to the content of his presentation.
Clinical and molecular phenotypes of asthma

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Outline

1. Background: Asthma and asthma heterogeneity

2. “Th2-high” and “Th2-low” asthma, and the periostin story.

3. Persistent and intermittent eosinophil phenotypes of asthma.

4. Conceptualizing asthma heterogeneity
Asthma

- Disease of the airways
- Affects 23 million Americans (including 7 million children).
- 1.8 million ED visits for exacerbation per year in the US.
- 400,000 hospitalizations/yr in the US.
- Costs (US): $56 billion annually.
Asthma

Physiology:
- Reversible airflow obstruction
- Airway hyperresponsiveness.

Pathology:
- Allergic airway inflammation (eosinophils, T cells, mast cells).
- Airway remodeling (fibrosis, mucus, muscle, blood vessels).
- Does not lead to emphysema

Exacerbations
- Commonly precipitated by viral infections.

Treatment:
- Beta agonists, corticosteroids
Asthma is treated empirically

• Standard of care guidelines:

  
  asthma is treated empirically according to clinical severity and response to treatment, not according to underlying biology

  
  NHLBI Guidelines for the Diagnosis and Management of Asthma, Oct 2007
Cluster Analysis and Clinical Asthma Phenotypes


2. Moore et al. AJRCCM 2010; 181:315 (726 asthmatics - 304 with severe asthma)

Analysis of multiple clinical variables shows that patients cluster into multiple groups characterized by:

- Age of asthma onset
- Gender
- Atopy
- Body weight
- Lung function abnormality & reversibility
- Symptoms
- Health care utilization
Phenotype Vs Endotype

**Phenotype**: Any observable characteristic of a disease (morphology, biochemical or physiological properties) without any implication for mechanism.

**Endotype**: A subtype of a condition, defined by a distinct functional or pathobiological mechanism.
Searching for Asthma Endotypes

![Chart comparing outcomes of Healthy and Asthma groups with a significance mark (*)]
Searching for Asthma Endotypes
Searching for Asthma Endotypes

The diagram illustrates a comparison between Healthy and Asthma groups in terms of an outcome variable. TheHealthy group shows a spread of data points, indicating variability, while the Asthma group has a more concentrated distribution, highlighted by a red circle, suggesting a possible endotype distinction.
Searching for Asthma Endotypes
Asthma Treatment- Where do we need to go? Personalized Medicine based on endotype
Outline

1. Background.

2. “Th2-high” and “Th2-low” asthma, and the periostin story.

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Analyzing the gene expression profile of the airway epithelium in asthma

- Epithelial cells collecting using bronchial brushes from 42 asthmatic and 24 healthy controls

- Brushes from asthmatics analyzed before and after randomization to fluticasone or placebo

- Genome wide profiling using Affymetrix microarrays.

Woodruff et al. PNAS 2007; 104: 15858–15863
Woodruff et al. Am J Respir Crit Care Med. 2009;180:388-95

Sidhu SS et al. PNAS 2010;107:14170-5
Profiling gene expression in airway epithelial brushings

Epithelial cell count: 209,659 ± 135,954 /mL
Epithelial cell %: 96.7 ± 3.8%
Genes upregulated in airway epithelial brushings in asthma

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<tr>
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<th>Gene Symbol</th>
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Woodruff et al. PNAS 2007; 104: 15858–15863
The gene expression profile of epithelial brushings from asthmatic subjects

Woodruff et al. PNAS 2007; 104: 15858–15863

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

Epithelial cell expression of these three genes is regulated by IL-13.
Epithelial cell expression of these three genes is suppressed by corticosteroids.
Clustering by expression levels of periostin, CLCA1 and serpinB2 in epithelial brushings identifies two asthma subgroups

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22 asthmatics ("Th2-High" Asthma)
20 asthmatics (Th2-Low Asthma)
28 Healthy subjects

**Th2-High Asthma**

- Airflow obstruction
- Eosinophils
- IgE
- Abnormal mucin gene expression
- Allergen skin test responses
- Subepithelial fibrosis
- Mast cells in epithelium

**Th2-Low Asthma**

- Airflow obstruction
- No Eosinophilia
- IgE
- Allergen skin test responses
- No Subepithelial fibrosis

Treatment response:
Th2 High asthma to responds to inhaled steroids, whereas Th2 Low asthma does not

![Graph showing treatment response with Fluticasone]
Th2-high asthma

- Specific endotype of asthma
- Steroid responsive.
- Likely to be responsive to treatment with Th2 inhibitors.
Q. Of the genes in the 3-gene Th2-high signature (periostin, CLCA1, Serpin B2), which is best blood biomarker?
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A. Periostin

secreted from epithelial cells in high concentrations and in a basal rather than apical direction.
Periostin immunolocalizes to the subepithelial region

Healthy

Asthma

Woodruff et al. PNAS 2007; 104: 15858–15863
Periostin is secreted by epithelial cells when activated by IL-13

Sidhu SS et al. PNAS 2010
Periostin is a diffusible signaling molecule secreted by IL-13 activated epithelial cells that can access subepithelial blood vessels.
Serum periostin levels are a biomarker of airway eosinophilia in moderately severe asthma.

Jia et al. JACI 2012 Sep;130(3):647-65.
Efficacy of a monoclonal antibody directed against IL-13 (Lebrikizumab) on airway function in asthma

Corren et al. NEJM 2011 Sep 22;365:1088-98

- 219 asthmatics
- Asthma inadequately controlled on steroids
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. Bohen, M.D., Ph.D., and John G. Matthews, M.B., B.S., Ph.D.
Serum periostin as predictor of response to Lebrikizumab

Corren et al. NEJM 2011
Summary (1)

• "Th2-high" asthma:
  - a common asthma endotype (50% of patients with mild/moderate disease) that can be identified using a 3-gene signature of IL-13 activation in airway epithelial cells.

• characterized by phenotypic characteristics that include airway eosinophilia, subepithelial fibrosis, & steroid responsiveness.
Periostin:

- epithelial protein secreted in large quantities upon IL-13 activation.

- blood periostin is a biomarker of Th2 high asthma.

- blood periostin is a biomarker of responsiveness to anti IL-13 treatment.
Outline

1. Background

2. “Th2-high” and “Th2-low” asthma, and the periostin story.

3. Persistent and intermittent eosinophil phenotypes of asthma.

4. Conceptualizing asthma heterogeneity
A Large Subgroup of Mild-to-Moderate Asthma Is Persistently Noneosinophilic

Kelly Wong McGrath¹, Nikolina Icitovic², Homer A. Boushey¹, Stephen C. Lazarus¹, E. Rand Sutherland³, Vernon M. Chinchilli², and John V. Fahy⁴, for the Asthma Clinical Research Network of the National Heart, Lung, and Blood Institute

¹Cardiovascular Research Institute, and ⁴Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of California San Francisco, San Francisco, California; ²Public Health Sciences, Penn State Hershey College of Medicine, Hershey, Pennsylvania; and ³Department of Medicine, National Jewish Health, Denver, Colorado

Repeated Measures Subjects had an average of 2.6 sputum inductions (range 2-4) collected in five studies of 9 to 52 weeks duration.
Highly Skewed Distribution of Eosinophils in Sputum from Asthmatic Subjects

ICS- (n=350)

ICS+ (n=645)
Sputum Eosinophilia: Repeated Measures Estimate vs Single Cross-sectional Estimate

Steroid Naïve Cross-sectional Analysis (n=157)
- 64%
- 36%

Steroid Naïve Repeated Measures Analysis (n=157)
- 47%
- 53%

Eosinophilic  Non-Eosinophilic
Persistent vs. Intermittent vs. Non-eosinophilic Asthma

Week

0 (n=145)  8 (n=68)  10 (n=68)  14 (n=66)  52 (n=77)

% Sputum Eosinophils

- Non-Eosinophilic (n=73)
- Intermittent (n=49)
- Persistent (n=35)

22%  31%  47%
Classifying eosinophilic asthma phenotypes

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Persistently Non Eosinophilic</td>
<td>22%</td>
</tr>
<tr>
<td>Intermittently Eosinophilic</td>
<td>31%</td>
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<tr>
<td>Persistently Eosinophilic</td>
<td>47%</td>
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</table>

Among subjects with eosinophilia, 60% have it intermittently.
Persistently Non-Eosinophilic Asthma has reversible airflow obstruction that is not resolved by currently used controller therapy.
Eosinophilia and Asthma

- **Eosinophilic asthma** = Th2-high asthma

- Persistently non-eosinophilic asthma – likely a collection of multiple different endotypes.
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• **Old Concept:** Asthma is a relatively homogenous disease characterized by allergic inflammation and responsiveness to steroids.

-Severe asthma is caused by severe allergic inflammation.
Asthma is a heterogeneous disease
Asthma is a heterogeneous disease
Heterogeneity of asthma

1. Half of asthma is eosinophilic.
   - these patients have “Th2 driven” disease, are steroid sensitive
     and are candidates for treatment with inhibitors of Th2 cytokines.
   - Serum periostin is a promising biomarker of this phenotype.

2. Half of asthma is non- eosinophilic
   - these patients have “? driven” disease, are not steroid sensitive
     and are not good candidates for treatment with inhibitors of
     Th2 cytokines.
Human Asthma
Core Asthma Phenotype

Hyperresponsiveness
Bronchoconstriction
Mucus
Conceptualizing Asthma Heterogeneity

Core Asthma Pathology

- Th2 inflammation/eos
- Other modifiers
Conceptualizing Asthma Heterogeneity

Core Asthma Pathology

- Obesity
- Cigarette Smoke
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Prescott Woodruff
Homer Boushey
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Sukh Sidhu
Erin Gordon
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