Dr. Holguin graduated from La Salle University School of Medicine in Mexico City and continued his subspecialty training in Internal medicine, Pulmonary and Critical Care at Emory University in Atlanta Georgia. He subsequently returned to Mexico as a researcher in the National Institute of Public Health. He then rejoined the Pulmonary and critical Care Faculty at Emory in 2002 and was also recruited as an adjunct researcher at the Centers for Disease Control and Prevention and the Rollins School of Public Health at Emory University, where he completed his MPH in Epidemiology. During his faculty tenure at Emory University, Dr. Holguin Directed the Adult Asthma and Allergy Clinics at Grady Memorial Hospital. Currently, Dr. Holguin works in clinical and translational asthma research with Dr. Sally Wenzel, Directs the Pulmonary Translational Research Core at UPMC and Montefiore’s Clinical Translational Research Center. He is the Associate Director of the Asthma Institute <http://www.asthmainstitute.pitt.edu/>.

OBJECTIVES:

Participants should be better able to:

1. To understand the basic asthma clinical phenotypes;

2. To become familiar with new biological therapies for asthma;

3. Understand how phenotyping patients can determine the best treatment selection.
Asthma Update: Emphasis on Biologics and Phenotypes.

Fernando Holguin M.D. M.P.H.
Asthma Institute
University of Pittsburgh

Dr. Holguin has declared no conflicts of interest related to the content of his presentation.
Asthma is a heterogeneous disease
The underlying inflammatory pattern, determines steroid responsiveness

Several therapies will be available (Anti-IL5, IL-13, IL-4)

Th2 High Blood Eos

Th2 low Blood Eos

Prescott G. Woodruff et al, AJRCCM 2009
There is significant heterogeneity in response to ICS; can we predict who responds better?

Asthma is not one disease, but rather a clinical syndrome in which many different diseases (with different mechanisms & response to therapy) share features of intermittent airway obstruction with varying degree of severity.
What makes a phenotype?

“The observable properties of an organism that are produced by the interaction of the genotype and the environment” (Medline Plus, NIH, NLM).

Severe Asthma Phenotyping

- Genetics
  - Epigenetics
  - Transcriptome
  - Proteome
  - Microbiome
- Microbiome
  - Immunity
  - Inflammation
- Remodeling
  - Airway obstruction
  - BHR
- Symptoms
  - Comorbidities
- Environment

Adapted from ATS/ERS Task Force on Severe Asthma 2014

Unsupervised analysis

Input

- Patient demographics
- biomarkers
- Atopy
- Lung function
- Age of onset
- Obesity

Methods

- Hierarchical cluster
- Factor analysis
- PCA

Cluster A
Cluster B
Cluster C
Cluster D

The use of different unsupervised statistical learning methods and different variable sets and encodings can lead to multiple and inconsistent subgroupings of asthma, not necessarily correlated with severity.

These reductionist methods are susceptible to variable transformation, coding, and types of variables. Prosperi et al, AJRCCM 2013
Severe asthma SARP phenotypes + and healthy controls

<table>
<thead>
<tr>
<th></th>
<th>Cluster 1</th>
<th>Cluster 2</th>
<th>Cluster 3</th>
<th>Cluster 4</th>
<th>Cluster 5</th>
<th>Cluster 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>29 (11)</td>
<td>31 (11)</td>
<td>33 (10)</td>
<td>39 (12)</td>
<td>47 (10)</td>
<td>43 (11)</td>
</tr>
<tr>
<td>Male/Female</td>
<td>41/59</td>
<td>43/57</td>
<td>16/84</td>
<td>25/75</td>
<td>60/40</td>
<td>25/75</td>
</tr>
<tr>
<td>FEV1% Pre</td>
<td>100 (11)</td>
<td>88 (15)</td>
<td>93 (13)</td>
<td>71 (14)</td>
<td>65 (17)</td>
<td>50 (21)</td>
</tr>
</tbody>
</table>

Healthy control: 98%

Severe asthma (%) - 7, 52, 54, 86, 100

Wu, W; et al JACI 2014

A. Age asthma onset (age)
B. Number of skin reactions to allergens
C. Allergy symptoms in winter (score)
D. Asthma symptoms caused by animal exposure (%)
A
Prebronchodilator FEV1/FVC (ratio)

C
Exhaled NO (parts per billion)

Discordant Symptoms

- **EARLY SYMPTOM PREDOMINANT**
  - Early onset, severe
  - Normal BMI
  - High symptom expression

- **OBESITY NON-COSINOPHILIC**
  - Late onset, female preponderance
  - High symptom expression

- **EARLY ONSET ATOPIC ASTHMA**
  - Mixed symptom presentation
  - Early onset
  - Asthma

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

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

Monitoring inflammation allows down-titration of corticosteroids.

Concordant Disease

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

Concordant Inflammation

- Monitoring inflammation allows targeted corticosteroids to lower exacerbation frequency.
Asthma phenotypes

Cluster 5
- 
- 
- 
- 

Cluster 6
- 
- 
- 
- 

Wenzel S et al.
Algorithm to assign Clusters with 3 variables

Moore et al. AJRCCM 2010;181:315-323.

SARP I, II Asthma Cluster Analysis: 5 Clusters

1 Mild Allergic Asthma
   Early onset asthma (EOA); Normal lung function; Atopic ≤ 2 Controller (medication use); Minimal Health Care Utilization (HCU); sputum eosinphils (EOS)

2 Mild-Moderate Allergic Asthma
   Most common cluster; EOA; Borderline normal FEV1 but reverses to normal; Atopic; ≤ 2 Controllers; Very low HCU, but some oral steroid bursts (OCS); sputum eosinophils

3 More Severe Older Onset Asthma
   Older; Late onset (LOA); higher BMI; Less atopic; Moderately low FEV1 with some reversibility; Higher dose ICS; ≥ 3 Controllers, but despite this more OCS bursts; increased sputum eosinophils

4 Severe Variable Allergic Asthma
   EOA; 53% male; Severely decreased FEV1, but very reversible to near normal; Atopic; “Variable” with need for frequent OCS; High beta agonist use, HCU and symptoms; increased sputum EOS

5 Severe Fixed Airflow Asthma
   Older; long duration; 63% female; higher BMI; GERD; HTN.; Less atopic; Severely decreased FEV1 less reversibility; On OCS; High beta-agonist use, HCU, symptoms; increased sputum PMN, EOS

Moore et al. AJRCCM 2010;181:315-323.
VIDA – Trial Design

• **Population**: Adults with asthma and vitamin D insufficiency (<30 ng/mL)

• **Intervention**: Vitamin D (100,000 U load then 4,000 U daily or matching placebo added to low-dose ICS (ciclesonide))

• **Primary outcome**: Post-randomization treatment failure

![Trial Design Diagram](image)


---

Response to corticosteroid characterization differs by Cluster

![Response Chart](image)

Only 18% of all subjects had a >=5% change in FEV1 after 5 days of prednisone

Wendy Moore et al., with permission
Asthma exacerbations during ICS reduction withdrawal phases differ by Cluster

Asthma Exacerbation defined by ≥ 1 of the following criteria:
- Failure to respond to rescue algorithm
- FEV1 < 50% baseline on 2 serial measurements
- >=16 puffs/d levalbuterol for 2d
- Physician opinion
- Use of systemic CS

Wendy Moore et al, with permission

A Study to Evaluate Safety and Efficacy of Mepolizumab in Patients with Moderate Persistent Asthma

There were no statistically significant changes in any of the clinical end points measured.

There was a nonsignificant trend for decrease in exacerbation rates in the mepolizumab 750-mg treatment group \((p=0.065)\).

Enrolled into the study were nonsmoking subjects, aged 18–55 years, with asthma managed with inhaled corticosteroids (maximum dose of beclomethasone dipropionate [BDP] or equivalent, 1,000 mg/d), had to be symptomatic.

Mepolizumab treatment for patients with severe eosinophilic asthma

This was multicenter, randomized, double-blind, double-dummy, phase 3, placebo-controlled Trial 32-week treatment phase and a follow-up 8-week safety phase (Fig. 1A).

Study population:
- Asthma diagnosis
- At least 1 exacerbation requiring systemic corticosteroids while on high dose ICS and at least 3 months of an additional controller
- Eosinophils in blood > 150 at screening or > 300 cells/micro liter during the preceding year

Outcomes:
- Primary: annualized frequency of clinically significant exacerbations, which were defined as requiring systemic glucocorticoids for at least 3 days or requiring emergency department or hospitalization
- Secondary: ACQ, St George’s
Results Mepolizumab treatment for eosinophilic asthma

- Significant improvements over placebo in SGRQ and ACQ scores
- Subgroup analyses: greater efficacy in patients with Eos > 500

Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial, Pavord I et al
Lancet 2012; 380:651-59

Multicenter, double-blind, placebo-controlled trial at 81 centers in 13 countries
- Patients ages 12 – 74 were enrolled to randomly receive 75, 250, 750mg of Mepolizumab, for a total of 13 infusions at 4-week intervals.

Study population:
Dx asthma based on standard BDR, PC20 or PEF variability x > 3 days in a two – week period. In addition had two or more asthma exacerbation requiring systemic steroids. One or more of: eNO > 50 ppb, peripheral eos > 0.3x10^9, sputum eos > 3%. All patients were on high dose ICS and an additional controller.

Outcomes:
Primary: protocol defined rate of significant asthma exacerbations.
Secondary outcomes were rate of exacerbations requiring admission, visits to the emergency department, blood and sputum eosinophil counts, prebronchodilator FEV1, and scores on AQLQ and ACQ.
Results: DREAM study
What this study adds to field:

- Largest study to date
- Effective in reducing asthma exacerbations, yet has small effects on lung function and symptoms.
- No safety dose – response
- 75mg appears to be ceiling effect in reducing eos.
- Secondary analysis showed that the main predictors of response are a) previous number of exacerbations, and high eosinophils

New, phenotype-driven treatments that target specific inflammatory pathways


The Steroid Reduction with Mepolizumab Study (SIRIUS),
- Randomized double blind, placebo controlled study
- compare mepolizumab vs. placebo in reducing the use of maintenance oral glucocorticoids while maintaining asthma control in patients with severe eosinophilic asthma

Study populations:
- Adults with severe asthma requiring systemic glucocorticosteroids (5 – 35mg/day of prednisone or equivalent).
- Evidence of eosinophilic inflammation (300 cells/µl) at screening or within the preceding 12 months, OR 150 cells/µl during the study optimization phase.
Study design

Run-in Period (3–8 wk before start of study)  

<table>
<thead>
<tr>
<th>Study Drug Administered</th>
</tr>
</thead>
<tbody>
<tr>
<td>wk 0</td>
</tr>
<tr>
<td>-------------------------</td>
</tr>
<tr>
<td>Visit 1</td>
</tr>
<tr>
<td>Visit 2</td>
</tr>
<tr>
<td>Optimization phase</td>
</tr>
<tr>
<td>Induction phase</td>
</tr>
<tr>
<td>Reduction phase</td>
</tr>
<tr>
<td>Maintenance phase</td>
</tr>
</tbody>
</table>

Primary Efficacy Outcome (exit visit)

- Mepolizumab 100 mg, subcutaneously every 4 wk
- Placebo subcutaneously every 4 wk

Weekly steroid reduction until exacerbation occurred or control worsened (change in ACQ > 0.5)

Steroids further reduced every 4 weeks (1.5 mg – 10 mg prednisone/equivalent), on the bases of ACQ and symptoms of adrenal insufficiency

No further steroid reduction

Maintained ICS dose

During the optimization phase

Mepolizumab, systemic steroid sparing

Primary efficacy outcome:  
the % reduction in daily oral glucocorticoid dose during weeks 20 to 24 (maintenance phase) as compared with the dose determined during the optimization phase

Secondary prespecified outcomes: proportions of patients who:

- reduction of 50% or more in the oral glucocorticoid
- reduction in the oral glucocorticoid dose to a value of 5.0 mg or less per day,
- had a total cessation in oral glucocorticoid use
- median percentage reduction in the oral glucocorticoid dose.

- Other outcomes included: annualized rates of asthma exacerbations, the mean change from baseline in the FEV\textsubscript{1} before and after bronchodilation, ACQ-5 score, SGRQ score, safety, and immunogenicity
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo (N=66)</th>
<th>Mepolizumab (N=69)</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in oral glucocorticoid dose at 20 to 24 wk: primary outcome — no. (%) †</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90 to 100%</td>
<td>7 (11)</td>
<td>16 (23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75 to &lt;90%</td>
<td>5 (8)</td>
<td>12 (17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 to &lt;75%</td>
<td>10 (15)</td>
<td>9 (13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;0 to &lt;50%</td>
<td>7 (11)</td>
<td>7 (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No decrease in oral glucocorticoid dose, a lack of asthma control, or withdrawal from treatment</td>
<td>37 (56)</td>
<td>25 (36)</td>
<td>2.39 (1.25–4.56)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Secondary outcomes

| Reduction in daily oral glucocorticoid dose of ≥50% — no. (%) ‡       | 22 (33)        | 37 (54)           | 2.26 (1.10–4.65)    | 0.03    |
| Reduction in daily oral glucocorticoid dose to a level ≤5 mg — no. (%) ‡ | 21 (32)        | 37 (54)           | 2.45 (1.12–5.37)    | 0.02    |
| Reduction of 100% in oral glucocorticoid dose — no. (%) ‡             | 5 (8)          | 10 (14)           | 1.67 (0.49–5.75)    | 0.41    |

Median percent reduction from baseline in daily oral glucocorticoid dose (95% CI) §  

<table>
<thead>
<tr>
<th>Median percent reduction from baseline</th>
<th>Placebo (N=66)</th>
<th>Mepolizumab (N=69)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0 (±20.0 to 33.3)</td>
<td></td>
<td>50.0 (±20.0 to 75.0)</td>
<td>NA</td>
</tr>
</tbody>
</table>

### A. Change from Baseline in Glucocorticoid Dose

- Placebo (N=66)
- Mepolizumab (N=69)

- Maintenance dose
- Optimized dose

Week: 0 4 8 12 16 20 24

Median Change (%): -80 -60 -40 -20 0 20 40 60 80
Mepolizumab steroid sparing effect

What this study adds to the field:

Mepolizumab effectively reduces exposure to systemic steroids among patients with severe, steroid-dependent asthma

Mepolizumab will likely prevent long term complications associated with chronic systemic steroids.

Limitations:

Limited duration. Does not address long term efficacy

Efficacy on patients taking 35 mg prednisone or equivalent/day is not known.
New, phenotype-driven treatments that target specific inflammatory pathways


Phase IIb, double blind, placebo – controlled study to determine the safety and efficacy of Benralizumab (IL5rα ab)

Study population:
- Medium to high ICS and on a LABA
- 2 to 6 exacerbations requiring systemic steroids preceding year
- ACQ > 1.5 on two separate screening times

Primary outcome
Compared to placebo: annual exacerbation rate
Secondary outcomes: FEV₁ & ACQ (change from baseline)

964 screened

ELEN index stratified: Eosinophilic vs non-eosinophilic Or FeNO 50ppb

Non-eosinophilic (n=285)
100 mg or placebo

Eosinophilic

Block randomized To: placebo or 2,20,100 mg

(n=324)

Procedures: SC injections every 4 weeks for the 1st 3 doses
Subsequently every 8 weeks
52 weeks of follow up
Subjects maintained on ICS, LABA doses

Planned post hoc analysis included evaluation of primary and secondary outcomes based on baseline blood eosinophil levels (≥ 300 cells μl)
Annual exacerbation rate by eosinophilic status and treatment allocation

n=232 eosinophilic (count ≥ 300 per µL) randomized to Benralizumab
Benralizumab for asthma

**What this study adds to the field**

Benralizumab is safe effective in improving lung function, quality of life and reducing exacerbations among patients with eosinophilic asthma.

The 100 mg dose may be effective in improving health outcomes in non-eosinophilic asthma.

Blood eosinophil count is a good biomarker to determine therapeutic response to this drug.

**Limitations**

The results obtained from the subgroups post hoc analysis require longitudinal validation.

Relatively small study, larger phase III underway.

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**Lebrikizumab treatment for adults with asthma**


Multicenter, double-blind, parallel study of adult patients with asthma, randomized to either monthly SQ lebrikizumab for 6 months vs placebo.

**Study population**

- Adult patients with asthma with at least > 6 months of ICS treatment
- Uncontrolled asthma at the time of randomization

**Outcomes:**

- Primary: relative change in FEV1 (L)
- Secondary: Asthma exacerbations, ACQ, asthma symptoms, rescue inhaler use
Study design

Results: Primary outcome

Secondary outcomes:
- No significant reductions in exacerbations
- No improvement in control

In the High periostin group:
- Significant reduction in exacerbation
- Steeper FeNO reduction
What this study adds to the field:

Anti IL-13 Lebrikizumab is effective in improving FEV1 (L) vs placebo in patients with asthma. Though the effect was small, it was significantly larger in patients with high periostin. No significant changes were observed in the low periostin group.

May be useful to reduce exacerbation and airway inflammation in patients with greater Th-2 driven inflammation.

Limitations:
- Relatively small number of patients.
- Need to validate secondary outcomes in larger study populations of patients with predominant Th-2 driven inflammation.


Phase 2A double – blind, placebo-controlled parallel study of Dupilumab 300 mg vs. placebo for 12 weeks or until protocol defined exacerbation.

**Study population**
- Adults with moderate to severe asthma
- Poorly controlled asthma (ACQ 1.5 – 3)
- On medium to high dose ICS + LABA.
- Peripheral eosinophils ≥ 300 or Sputum ≥ 3%

**Study outcomes:**
- Primary outcome: Protocol defined asthma exacerbation
- Changes from baseline in lung function, ACQ, SABA, time to first exacerbation
Dopilumab study design

A

Screening and Run-In Period

Intervention Period

After Intervention Period

Up to approximately 65 patients: dupilumab, 300 mg, subcutaneously, weekly
Up to approximately 65 patients: placebo, subcutaneously, weekly

Randomization

Day 29
Wk 4

Day 43
Wk 6

Day 50
Wk 7

Day 57
Wk 8

Day 64
Wk 9

Day 71
Wk 10

Day 78
Wk 11

Day 85
Wk 12

Day 127
Wk 18

Day 141
Wk 20

Dopilumab study design

Dopilumab vs placebo

Time to Exacerbation

Stable background therapy

LABA withdrawal

Tapering of inhaled glucocorticoid

Dupilumab monotherapy

Placebo

Hazards ratio, 0.10
(95% CI, 0.03–0.34)
P < 0.001

Cumulative Exacerbation Rate (%)
Local injection sites reactions, nasopharyngits, nausea and headache were more frequent on the treatment arm.

What this study adds to the field

- Dupilumab is remarkably effective in reducing exacerbations, though it is also effective in improving lung function and symptoms.
- It may be more effective than anti IL-13 and IL-5, given that IL-4Rα blocks the IL-4/13 receptor ligand system.
- It is safe and well tolerated.

Limitations:

- Small sample size
- Needs to be replicated in larger and longer studies.
Omalizumab, monoclonal ab to IgE.
prevents an interaction with its high-affinity receptor (FcεRI) on mast cells, basophils, eosinophils, Langerhans cells, and dendritic cells.

Currently approved for moderate to severe allergic asthma not adequately controlled
- Most effective in reducing exacerbations. Not so for other secondary outcomes.
- Very effective in reducing seasonally-related increases in asthma exacerbations.
- IgE and allergic sensitization may not adequately predict response.

Randomized Trial of Omalizumab (Anti-IgE) for Asthma in Inner-City Children

EXTRA omalizumab study enrolled 800 patients (aged 12–75 yr); Analyses were performed evaluating treatment effects in relation to FeNO, blood eosinophils, and serum periostin at baseline. Patients received 48 weeks of treatment.
High blood eosinophil counts predict sputum eosinophilia in patients with severe asthma

163 patients with asthma managed with high dose ICS

ROC to predict 2% sputum eosinophils

Fowler et al, JACI 2015
Summary:

1) Asthma is complex. A multitude of diseases sharing similar clinical manifestations

2) Therefore, NO SINGLE Rx will be universally helpful

3) We have a long way to go in terms of linking phenotyping to drug choices. However, change is happening and several options are being developed. Consider determining what kind of asthma your patient has. Particularly among those that don’t respond to steps 1 – 3

4) Peripheral eos are helpful, so are FeNO, periostin, age of onset.

5) If your patient has severe eosinophilic asthma, we now have new, non steroid options

6) If your patients falls in the non Th-2 asthma phenotype, unfortunately there are not great options available (Bronchial Thermoplasty?).

QUESTION 1

What are important factors (s) in classifying different asthma clinical phenotypes (can choose more than one)?

a. Age of asthma onset
b. Atopy
c. BMI
d. FEV1 (%)
e. All the above
**QUESTION 1**
What are important factors (s) in classifying different asthma clinical phenotypes (can choose more than one)?

a. Age of asthma onset  
b. Atopy  
c. BMI  
d. FEV1 (%)  
e. All the above

**QUESTION 2**
What factor (s) are important for endotyping asthma (can choose more than one)?

a. periostin  
b. Sputum eosinopohils  
c. FeNO  
d. Peripheral eosinophils  
e. All the above
QUESTION 2
What factor(s) are important for endotyping asthma (can choose more than one)?

a. Periostin
b. Sputum eosinopohils
c. FeNO
d. Peripheral eosinophils
e. All the above

QUESTION 3
What determines response to mepolizumab?

a. Peripheral eos
b. IgE
c. Previous asthma exacerbations
d. a and b
QUESTION 3
What determines response to mepolizumab?

a. Peripheral eos
b. IgE
c. Previous asthma exacerbations
d. a and b