Current and emerging updates in the management of asthma

Sang-Heon Cho, MD, PhD
Department of Internal Medicine
Seoul National University College of Medicine
Seoul, Korea
Overview

• Introduction
• Limitations of current asthma treatment
• New drugs improving what already exists
• Emerging roles of biologic therapy
• Phenotype- and endotype-based treatment
• Pharmacogenomic approach
Asthma cigarettes made from the leaves of *Datura stramonium* - Inhaled anti-muscarinic treatment effects
Advances in asthma treatment

Research Focus

Bronchospasm

Allergen - induced bronchospasm

Prevent and resolve inflammation

Asthma control
(Impairment ± Risk)

Allergen inflammation

Personalized medicine
Early intervention
Prevention

Treatment

Short-acting β-agonists
Theophylline

Cromolyn

Inhaled corticosteroids
Leukotriene modifiers

Long-acting β-agonists
Combination therapy

Anti-IgE

Patient characteristics
Biomarkers, Genetics
Immunomodulators

Global atlas of allergy, 2015
Pharmacotherapy of Asthma

- Stepwise treatment
- Preferred choice: ICS and ICS/LABA

<table>
<thead>
<tr>
<th>PREFERRED CONTROLLER CHOICE</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEP 1</td>
</tr>
<tr>
<td>Consider low dose ICS</td>
</tr>
<tr>
<td>Low dose ICS</td>
</tr>
<tr>
<td>As-needed short-acting beta₂-agonist (SABA)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RELIEVER</th>
</tr>
</thead>
<tbody>
<tr>
<td>As-needed SABA or low dose ICS/formoterol**</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>STEP 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukotriene receptor antagonists (LTRA)</td>
</tr>
<tr>
<td>Low dose theophylline*</td>
</tr>
<tr>
<td>Low dose ICS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>STEP 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Med/high dose ICS/LABA*</td>
</tr>
<tr>
<td>Med/high dose ICS+LTRA</td>
</tr>
<tr>
<td>(or + theoph*)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>STEP 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>High dose ICS+LTRA</td>
</tr>
<tr>
<td>(or + theoph*)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>STEP 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refer for add-on treatment e.g. anti-IgE</td>
</tr>
<tr>
<td>Add low dose OCS</td>
</tr>
</tbody>
</table>

*For children 0-4 years, theophylline is not recommended, and preferred Step 1 is medium dose ICS
**For patients prescribed SABA/formoterol or BUD/formoterol maintenance and reliever therapy

Stratifying patients for response

Percent of patients

FEV₁ percent change from baseline

Montelukast (n=350)
Beclomethasone (n=232)

Limitations of current treatment

- Heterogeneous individual response
- Considerable patients still do not achieve optimal control.
Several reasons for suboptimal control

- Suboptimal treatment
- Poor adherence
- Individual variation (heterogeneity)
- Treatment refractoriness (severe asthma)
Improving what already exists
Once daily ICS/LABA

Fluticasone propionate

Fluticasone furoate

17-α furoate ester occupies the 17-α pocket of the GR to a greater extent than FP

Vilanterol: ultra LABA with 24 hr duration

- Human small airway after contraction with 0.3 mM carbachol at t = 22 h

Slack RJ et al., J Pharmacol Exp Ther 2013; 344:218-30
Preference and error rates of inhalers

(A) Preference in asthma patients
(B) Error rates in asthma patients
(C) Error rates in COPD patients

• ATS 2016 conference abstract
  (A) Thomas et al.
  (B) Thomas et al.
  (C) Van Der Palen et al.
New LABAs and LAMAs

• Once daily LABA: indacaterol, vilanterol, olodaterol

• LAMA: recently approved for step 5 treatment
  - improve asthma control
  - reduce exacerbation
High lung deposition of small particle

- Total lung deposition, peripheral lung deposition, distal airway penetration are increased with smaller particles

<table>
<thead>
<tr>
<th>Particle size</th>
<th>1.5 μm</th>
<th>3 μm</th>
<th>6 μm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total lung deposition</td>
<td>56.3%</td>
<td>51.0%</td>
<td>46.0%</td>
</tr>
<tr>
<td>Peripheral lung deposition</td>
<td>24.7%</td>
<td>17.2%</td>
<td>10.9%</td>
</tr>
<tr>
<td>Penetration index</td>
<td>0.79</td>
<td>0.60</td>
<td>0.36</td>
</tr>
</tbody>
</table>

Usmani OS et al. Am J Respir Crit Care Med 2005
ICS/LABA fixed combination

- In a real-life, use of extrafine BDP/F results in a greater percentage of patients with controlled asthma compared to larger particle formulations $P=0.002$

Allegra et al. *Res med* 2012
Asthma heterogeneity is now widely recognized
<table>
<thead>
<tr>
<th>Cluster 1</th>
<th>Longstanding asthma with marked airway obstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cluster 2</td>
<td>Female predominant mild asthma</td>
</tr>
<tr>
<td>Cluster 3</td>
<td>Male predominant asthma with smoking history and airway obstruction</td>
</tr>
<tr>
<td>Cluster 4</td>
<td>Asthma associated with higher BMI and borderline lung functions</td>
</tr>
</tbody>
</table>

Park HW, Cho SH et al. ANAI 2014 In press
Cluster 1: exacerbation prone phenotype

Park HW, Cho SH et al. ANAI 2014 In press
Pharmacogenomics approach based on phenotypes

- Molecular phenotyping for asthma

Asthma Phenotyping ‘Th2-high’ vs. “Th2-low” Based on Epithelial Markers

Woodruff PG et al. Am J Respir Crit Care Med 2009
Endotype-based Approach: targets for severe asthma
Endotype-based approach

- Biomarker-guided treatment

### FDA-approved biologics for Th2 pathway

<table>
<thead>
<tr>
<th>Target</th>
<th>Compound</th>
<th>Cell targets</th>
<th>Efficacy in target population</th>
<th>Efficacy in allergen challenge</th>
<th>Biomarkers (predictive-responsive)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgE</td>
<td>Omalizumab</td>
<td>Mast cells/basophils</td>
<td>30% reduction in exacerbation in moderate-severe asthma</td>
<td>Inhibits early and late phase</td>
<td>FeNO, blood eosinophils, and periostin may better identify responders than IgE Predictive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Little effect on symptoms or lung function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-5 and IL-5 receptor</td>
<td>Mepolizumab, reslizumab, and benralizumab</td>
<td>Eosinophils (IL-5) Eosinophils/basophils (IL-5R)</td>
<td>50% reduction in exacerbation in high-eosinophil severe asthma Efficacy increases as eosinophil numbers increase, including effects on lung function Steroid sparing (mepolizumab)</td>
<td>No</td>
<td>Blood eosinophils (predictive and responsive)</td>
</tr>
</tbody>
</table>

- Mepolizumab — approved
- Reslizumab (approved by advisory committee)
- Benralizumab — filed

Clinical effects of omalizumab in asthma

- In patients on ICS alone, or in combination with other agents, addition of omalizumab
  - Reduced number of exacerbations (40-50%)
  - Reduced symptom scores
  - Reduced need for inhaled corticosteroids
  - Reduced use of rescue medication
  - Improved asthma-related quality of life

Busse et al. JACI 2001
Soler et al. Eur Respir J 2001
Humbert, et al. Allergy 2005
Asthma phenotype and anti-IgE: EXTRA study

- The difference in exacerbation frequency between omalizumab and placebo was greatest in the three high-biomarker subgroups. (FeNO, S-Eosinophil, Peiostin)

Hanania et al. Am J Respir Crit Care Med 2013
Asthma phenotype and anti-IL5: DREAM trial

Mepolizumab in severe eosinophilic asthma

Ian Pavord et al. Lancet 2012
# IL-5 target therapy: severe eosinophilic asthma

**Table 2**

Summary of anti-interleukin-5 clinical trial programs

<table>
<thead>
<tr>
<th></th>
<th>Phase 3</th>
<th>Phase 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biomarker (cutoff)</strong></td>
<td>Blood EOS $\geq$150/$\mu$L at initiation or Blood EOS $\geq$400/$\mu$L</td>
<td>Weighted for eosinophilic based on proprietary index or FeNO $\geq$40 ppb</td>
</tr>
<tr>
<td><strong>Baseline biomarker mean</strong></td>
<td>290 ± 1050</td>
<td>590 (100–2300)</td>
</tr>
<tr>
<td><strong>Background therapy</strong></td>
<td>$\geq$880 $\mu$g FP/d + another controller</td>
<td>$\geq$440 $\mu$g FP/d ± another controller</td>
</tr>
<tr>
<td><strong>Baseline patient demographics</strong></td>
<td>2–6 in last year</td>
<td>2–6 in last year</td>
</tr>
<tr>
<td>Exacerbations required for inclusion (mean observed)</td>
<td>Not reported</td>
<td>2.6</td>
</tr>
<tr>
<td>FEV₁ pre-BD (mL)</td>
<td>1730 ± 660 (FEV₁ $&lt;$80% predicted in adults)</td>
<td>2190</td>
</tr>
<tr>
<td>Asthma symptoms (ACQ5/6)</td>
<td>2.26 ± 1.27</td>
<td>Not reported</td>
</tr>
<tr>
<td>Asthma QOL (AQLQ)</td>
<td>Not reported</td>
<td>4.2</td>
</tr>
<tr>
<td>Maintenance OCS use % (mean dose, mg)</td>
<td>27%</td>
<td>Not reported</td>
</tr>
<tr>
<td>Age</td>
<td>$\geq$12 y</td>
<td>$\geq$12 y</td>
</tr>
</tbody>
</table>

## IL-5 target therapy

### Table 3
Summary of efficacy

<table>
<thead>
<tr>
<th></th>
<th>Phase 3</th>
<th>Phase 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mepolizumab (Anti-IL-5)</td>
<td>Reslizumab (Anti-IL-5)</td>
</tr>
<tr>
<td><strong>Exacerbation reduction relative to PBO</strong></td>
<td>54% (subcutaneously [SC]) and 47% (IV)</td>
<td>50%–60% (top-line data) at 400 cut-off</td>
</tr>
<tr>
<td><strong>FEV₁ improvement (% FEV₁)</strong></td>
<td>98 mL (6%) SC</td>
<td>160 mL (7%) and 270 mL (12%)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Asthma symptoms (ACQ5/6)</strong></td>
<td>0.44</td>
<td>0.36 PBO-corrected</td>
</tr>
<tr>
<td><strong>Asthma QOL</strong></td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Oral steroid sparing (min 5 mg/d prednisone)</strong></td>
<td>50% median reduction in baseline OCS dose</td>
<td>No OCS sparing study</td>
</tr>
<tr>
<td><strong>Expected frequency and dosage</strong></td>
<td>Every 4 wk 100 mg</td>
<td>Every 4 wk 3 mg/kg</td>
</tr>
<tr>
<td><strong>ROA</strong></td>
<td>SC lyophilized powder</td>
<td>IV</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>1 potential anaphylaxis case</td>
<td>1 case of anaphylaxis related to drug</td>
</tr>
</tbody>
</table>

<sup>a</sup> Data are from 211 subjects in the phase 2, 12-week randomized placebo-controlled trial (NCT01842387). Data were based on change from baseline in ACQ5/6 score (range: 0–1) and pooled 20% responders. Data are mean (95% CI) change from baseline in FEV₁ (L). Data are from 68 subjects in 3 different phase 3 trials (NCT02057271, NCT02488700, and NCT02976585). Data were based on change from baseline in ACQ5/6 score (range: 0–1) and pooled 20% responders. Data are mean (95% CI) change from baseline in FEV₁ (L). Data are from 38 subjects in the phase 2, 12-week randomized placebo-controlled trial (NCT01842387). Data were based on change from baseline in ACQ5/6 score (range: 0–1) and pooled 20% responders. Data are mean (95% CI) change from baseline in FEV₁ (L).
# Still unapproved biologics for Th2 pathway

<table>
<thead>
<tr>
<th>Biologic</th>
<th>Targets</th>
<th>Efficacy</th>
<th>Modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-13</td>
<td>Lebrikizumab, Tralokinumab</td>
<td>Structural cells, macrophages, B cells</td>
<td>~50% reduction in exacerbation in moderate-severe asthma, 8%-10% improvement in lung function</td>
</tr>
<tr>
<td>IL-4 receptor</td>
<td>Dupilumab, Pitrakinra (IL-4 mutant)</td>
<td>Structural cells, T cells, macrophages, B cells</td>
<td>60%-75% reduction in exacerbation in moderate-severe asthma, 10% improvement in lung function, Symptom improvement, Greater improvement in those with higher type 2 biomarkers</td>
</tr>
<tr>
<td>PGD2 receptor 2 (DP2)</td>
<td>OC000459, QAW039</td>
<td>T cells, eosinophils, ILC2 cells</td>
<td>Symptom and lung function improvement in mild CS naive asthma, Lung function improvement in severe asthma with decrease in eosinophils</td>
</tr>
<tr>
<td>GATA3</td>
<td>SB010</td>
<td>Th2 cells, ILC2 cells</td>
<td>Not available</td>
</tr>
<tr>
<td>TSLP</td>
<td>AMG 157</td>
<td>Epithelial cells, macrophages, dendritic cells</td>
<td>Not available</td>
</tr>
</tbody>
</table>

Asthma phenotype and anti-IL13

High-Periostin Subgroup

- Lebrikizumab (N=51)
- Placebo (N=59)

Percent Change in FEV₁

Week

0 1 2 3 4 8 12 16 20 24 28 32

8.2%↑

Low-Periostin Subgroup

- Lebrikizumab (N=51)
- Placebo (N=50)

Percent Change in FEV₁

Week

0 1 2 3 4 8 12 16 20 24 28 32

1.6%↑

### Phase III for lebrikizumab (LAVOLTA I and II)

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Adjusted exacerbation rate (per patient per year)</th>
<th>Rate difference (lebrikizumab-placebo)</th>
<th>Rate reduction (%)</th>
<th>Rate ratio (lebrikizumab vs placebo, 95% CI)</th>
<th>p value</th>
<th>Rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LAVOLTA I</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biomarker high</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>256</td>
<td>0.94</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lebrikizumab 37.5 mg</td>
<td>251</td>
<td>0.46</td>
<td>-0.48</td>
<td>51%</td>
<td>0.49 (0.34-0.69)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Lebrikizumab 125 mg</td>
<td>255</td>
<td>0.66</td>
<td>-0.28</td>
<td>30%</td>
<td>0.70 (0.51-0.95)</td>
<td>0.0232</td>
<td></td>
</tr>
<tr>
<td>Biomarker low</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>106</td>
<td>0.60</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lebrikizumab 37.5 mg</td>
<td>109</td>
<td>0.33</td>
<td>-0.27</td>
<td>45%</td>
<td>0.55 (0.32-0.95)</td>
<td>0.0318</td>
<td></td>
</tr>
<tr>
<td>Lebrikizumab 125 mg</td>
<td>104</td>
<td>0.44</td>
<td>-0.17</td>
<td>28%</td>
<td>0.72 (0.44-1.19)</td>
<td>0.2013</td>
<td></td>
</tr>
<tr>
<td><strong>LAVOLTA II</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biomarker high</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>247</td>
<td>0.72</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lebrikizumab 37.5 mg</td>
<td>257</td>
<td>0.54</td>
<td>-0.19</td>
<td>26%</td>
<td>0.74 (0.54-1.01)</td>
<td>0.0609</td>
<td></td>
</tr>
<tr>
<td>Lebrikizumab 125 mg</td>
<td>251</td>
<td>0.54</td>
<td>-0.19</td>
<td>26%</td>
<td>0.74 (0.54-1.02)</td>
<td>0.0626</td>
<td></td>
</tr>
<tr>
<td>Biomarker low</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>107</td>
<td>0.34</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lebrikizumab 37.5 mg</td>
<td>99</td>
<td>0.50</td>
<td>0.16</td>
<td>-46%</td>
<td>1.46 (0.87-2.45)</td>
<td>0.1519</td>
<td></td>
</tr>
<tr>
<td>Lebrikizumab 125 mg</td>
<td>106</td>
<td>0.36</td>
<td>0.02</td>
<td>-6%</td>
<td>1.06 (0.61-1.83)</td>
<td>0.8346</td>
<td></td>
</tr>
</tbody>
</table>

*Figure 2: Rate of asthma exacerbations over 52 weeks by biomarker group*
 Dupilumab (anti-IL-4Rα) phase IIa

A Exacerbations — Primary End Point

Proportion of Patients with Exacerbation

- Placebo (N=52): 44%
- Dupilumab (N=52): 6%

87% reduction
P<0.001

Wenzel et al. NEJM 2013
Neutrophilic asthma (Macrolide): AZISAST

Non-eosinophilic severe asthma (blood eosinophilia ≤200/ml)

Brusselle et al. Thorax 2013
# Asthma phenotyping and Specifically-targeted treatments

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Biomarkers</th>
<th>Specifically-targeted treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Allergic asthma</strong></td>
<td>Serum IgE↑</td>
<td>Anti-immunoglobulin E (omalizumab)</td>
</tr>
<tr>
<td></td>
<td>Atopy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Blood eosinophil↑</td>
<td></td>
</tr>
<tr>
<td><strong>Eosinophilic asthma</strong></td>
<td>Exacerbations↑</td>
<td>Anti-interleukin-4 receptor α (dupilumab) / Anti-interleukin-5</td>
</tr>
<tr>
<td></td>
<td>Sputum eosinophils↑</td>
<td></td>
</tr>
<tr>
<td></td>
<td>steroid-dependent asthma</td>
<td></td>
</tr>
<tr>
<td><strong>Neutrophilic asthma</strong></td>
<td>Sputum neutrophils↑</td>
<td>Macrolide antibiotics (azithromycin)</td>
</tr>
<tr>
<td><strong>Chronic airflow obstruction</strong></td>
<td>FEV1↓</td>
<td>Anti-interleukin-13 (lebrikizumab)</td>
</tr>
<tr>
<td></td>
<td>Serum periostin↑</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Airway remodelling</td>
<td></td>
</tr>
<tr>
<td><strong>Recurrent exacerbations</strong></td>
<td>Sputum eosinophils↑</td>
<td>Anti-interleukin-5 (mepolizumab)</td>
</tr>
<tr>
<td></td>
<td>oral corticosteroid dose</td>
<td></td>
</tr>
</tbody>
</table>

*Chung KF et al. The Lancet Respiratory Medicine, 2013*
Personalized therapy
Based on Pharmacogenetics

- Predict responders
- Avoid adverse reactions
- Develop new drugs

Acquired factors: renal, hepatic function, drug interaction, weight, age, sex etc

Genetic factors
Variable Steroid Response in Asthma

Genetic variation of CRHR1

Tantisira KG et al. Human Molecular Genetics 2004
GLCCI1 and Response to Glucocorticoid in Asthma

Promoter SNP in the glucocorticoid induced transcript-1 gene (rs37972) → Changes in Lung Function with Glucocorticoid Therapy

Steroid pharmacogenetics

- Study design

Steroid naïve severe asthmatics (N=35)

Oral prednisolone 30mg qd x 7 days

Measurements
1. FEV1 pred. %
2. induced sputum (IS)
   - eosinophil %
   - IFN-γ & IL-4 mRNA expression

- HDAC1-3 genetic polymorphism screening
  : on 24 healthy Korean adults by direct sequencing
  → -1332 C>T on HDAC 1 was selected for scoring
Steroid pharmacogenetics

-1332C>T genotype

- **IS eosinophil decrease %**

- **IS IL-4 mRNA decrease %**

\[
\text{P} = 0.006
\]

\[
\text{P} = 0.035
\]

\*[(baseline-F/U)/baseline] x 100
Arg16Gly in ADRB2 and Tiotropium bromide

- Additive role of tiotropium in severe asthmatics and Arg16Gly in ADRB2 as a potential marker to predict response

- 138 severe asthmatics
  - decreased lung function
  - on conventional medications

- Responders
  - FEV1 improvement ≥ 15% & 200 ml maintained ≥ 8 wks

11 SNPs in CHRM1-3, Arg16Gly & Gin27Glu in ADRB2 scored in 80/138 asthmatics

Park HW, Cho SH et al. Allergy 2009
Role of tiotropium in severe asthma

- Responders based on genotype-difference

**b2ADR16**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Responder %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arg16Arg (N=22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arg16Gly+Gly16Gly (N=57)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**-146359C>A in CHRM2**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Responder %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC (N=61)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CA+AA (N=19)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Bonferroni-corrected P = 0.018*

*Park HW, Cho SH et al., Allergy 2009:64:778-7*
Pitrakinra Pharmacogenetics

**Figure A**

- **rs8832**
  - GGP = 0.009
  - AG/AA P = 0.58

**Figure B**

- **rs1029489**
  - GGP = 0.005
  - AG/AA P = 0.29

Slager RE et al, JACI 2012 130: 516-22
Single gene alone?

Gene-environment interaction

-159C>T in CD14

<CC genotype in the promoter region of the CD14>

Simpson A et al, Am J Respir Crit Care Med 2006
Genetic modeling to predict the drug response

Multifactor-Dimensionality Reduction Model
Take home messages

• Asthma is a heterogeneous disease with complex pathophysiology.

• Phenotype and Endotype-based approach is showing promise, particularly in targeting Th2 pathway such as IL5 and IL-4Rα in severe eosinophilic asthma.

• Pharmacogenomic approach may reveal better indication of conventional therapeutics and new biologic agents.