Heterogeneity of COPD and Asthma

from Heterogeneity to Stratification

Dr. Y-M Oh
Asan Medical Center
Seoul
Congratulations & Welcome

Airway Vista 2017
March 25(SAT) - March 26(SUN)
ASAN MEDICAL CENTER, SEOUL

IWPFI 2017
8th International Workshop on Pulmonary Functional Imaging
& 16th Meeting of Korean Society of Thoracic Radiology
March 24 (Fri) - 26 (Sun), 2017

Lee, SD
Ohno, Y
Park, JS
Seo, JB
Heterogeneity of COPD and Asthma

Oh my god

어떻게 하지
Hurray! 만세

Meilan Han:
COPD Phenotypes to Endotype
Early COPD

Fan Chung:
Endotyping Severe Asthma

Norbert F. Voelkel:
COPD-vascular alterations

Hae Sim Park:
Phenotypes & endotypes of AERD

David Lynch:
CT imaging in COPD

Yasutaka Nakano:
Practical approach to ACOS

Edwin Silverman:
Network Medicine Approaches to COPD
Genetics in COPD
Heterogeneity is **NOT** my goal.

- Heterogeneity
- Stratification
- Best Treatment

Complex

Phenotype

Endotype

Precise
To Overcome Heterogeneity

① Phenotype stratification

② Endotype stratification
   “Molecular pathogenesis”

③ Treatability stratification
   “Treatable traits”

④ ...

Best Treatment
COPD Phenotypes

- **Frequent Exacerbation** → LAMA + LABA
- **Severe Emphysema** → Lung Vol. Reduction
- **Asthma - COPD overlap** → Inhaled Steroid + BD

*CS, corticosteroid; BD, bronchodilator of LAMA or LABA*

*GOLD 2017 update*
To Overcome Heterogeneity

① Phenotype stratification

② Endotype stratification
  “Pathobiological mechanism”

③ Treatability approach
  “Treatable traits”

④ …

GOLD 2017
Asthma Endotypes

$T_H2$-high

$T_H2$-low
Asthma Endotypes

Unsupervised Hierarchical Clustering

$\Delta$ Lung Function

$\Delta$ FEV$_1$

$T_H2$-high

$T_H2$-low

Ideal $\rightarrow$ Practical!

POSTN
CLCA1
SERPINB2

8wks

ICS initiated

To Overcome Heterogeneity

① Phenotype stratification

② Endotype stratification
   “Molecular pathogenesis”

③ Treatability stratification
   “Treatable traits”

④ ...

→ Practical
→ Ideal
→ Individualized
COPD Treatable Traits for each individual patient

- Smooth m. contraction
- Emphysema
- Airway eosinophilia
- Chronic bronchitis
- Hypoxemia

- Bronchodilator
- Lung Vol. Reduction
- Smoking Cessation
- Oxygen

- Inhaled Steroid

Individualized → Validation

*Modified. Agusti A. Eur Respir J 2016; 47: 410*
To Overcome Heterogeneity

① Phenotype
② Endotype
③ Treatability
④ Severity

Best or Precise Treatment
COPD, Progress & Heterogeneity

- **Predisposition**
  - Genetic
  - Small Lung
  - ...

- **Etiology**
  - Heterogeneity

- **Exposure**
  - Cigarette
  - Biomass
  - ...

- **Molecular & cellular change**
  - Bronchitis & -olitis
  - Emphysema
  - ...

- **Pathology**
  - Heterogeneity

- **Morphologic change**
  - Bronchitis & -olitis
  - Emphysema
  - ...

- **Dyspnea**
  - Airflow limitation
  - Hyperinflation
  - ...

- **Exacerbation**
  - Heterogeneity

- **Phenotype**
  - Heterogeneity

- **Treatability**
  - Heterogeneity

- **Severity**

- **Time**
COPD Heterogeneity in Pathology

There are non-obstructive chr. bronchitis, chr. bronchiolitis, & emphysema.
COPD Heterogeneity in Pathology

A patient may have all pathologies or may not
Stratification & Current Therapy

- Emphysema
  - LVR, ...
- Chronic Bronchiolitis
  - LAMA/LABA, ICS, PDE4I, ...
- Vascular Alteration
  - O2, ...
- Chronic Bronchitis
  - Mucolytics, PDE4I
COPD Heterogeneity in Pathology

Stratification & Future Therapy

- Emphysema → Alveolar Regeneration
- Chronic Bronchiolitis → Anti-Neutrophilic, Anti-Fibrotic
- Vascular Alteration → Vascular targeting
- Chronic Bronchitis → Anti-mucus
Diagnostic Tools

- **Emphysema**
- **Chronic Bronchiolitis**
- **Vascular Change**
- **Chronic Bronchitis**

**Biomarkers**
- CT
- Spirometry
- Echocardiography

**Outcomes**
- Symptoms, QoL
- Exacerbation

**Sputum amount**
Emphysema vs. Bronchiolitis

Emphysema severity by CT

Bronchiolitis

FEV₁ % by Spirometry

Emphysema may NOT be treatable with Inhaler Therapy

Emphysema severity by CT

Bronchiolitis

FEV1 %

ICS & LABA

FEV1 increase %pred.

Vascular Alteration in COPD patients

KOLD COPD pts

s PA Pressure mmHg by Echocardiography

High PA pressure

FEV1 %

sPAP 15~30mmHg

Lee JW. IJTLID 2011
COPD Heterogeneity in Treatability

- Treatable with inhaled CS
  Sputum/blood eosionphilia or ACOS

- Treatable with bronchodilators
  LABA vs. LAMA
COPD Heterogeneity in Treatability

Treatable w/ LABA or LAMA

Δ FEV1, liter

0.8
0.4
0.2
0.0
-0.2
-0.4
-0.6

LAMA -only Responders
Non-Responders
LABA -only Responders
Both Responders

Δ FEV1, liter

0.1 liter

r = -0.14, p = 0.26

4, p = 0.26
COPD Heterogeneity in Treatability

Cross-over Design

73 COPD pts. w/ Tx Naïve or Wash-out

Δ FEV1

LABA

LAMA

4wks

4wks

4wks

① FEV₁, 70 % pred. (Post-BD)
② CAT score, 10

Unpublished data
Prediction of Treatability

LABA vs. LAMA

To Find Treatable Traits

• Clinical Characteristics  ➔  13 Variables
• Gene Expression  ➔  Microarray
• Gene Damage Score  ➔  Exome Seq.
### Clinical Variables, Factor Analysis

#### 13 → 6 variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>-0.09</td>
<td>0.35</td>
<td>0.66</td>
<td>0.32</td>
<td>0.01</td>
<td>0.15</td>
</tr>
<tr>
<td>Ex-smoker vs. current</td>
<td>0.13</td>
<td>0.17</td>
<td>-0.47</td>
<td>0.55</td>
<td>-0.32</td>
<td>0.23</td>
</tr>
<tr>
<td>Cigarette smoke, PYs</td>
<td>0.24</td>
<td>0.28</td>
<td>0.20</td>
<td>0.45</td>
<td>-0.30</td>
<td>-0.47</td>
</tr>
<tr>
<td>CAT</td>
<td>0.20</td>
<td>0.09</td>
<td>-0.41</td>
<td>0.12</td>
<td>0.63</td>
<td>0.40</td>
</tr>
<tr>
<td>mMRC</td>
<td>0.19</td>
<td>-0.25</td>
<td>0.43</td>
<td>-0.23</td>
<td>0.43</td>
<td>-0.27</td>
</tr>
<tr>
<td>FEV1 %pred</td>
<td>-0.70</td>
<td>0.61</td>
<td>-0.16</td>
<td>-0.09</td>
<td>0.18</td>
<td>-0.23</td>
</tr>
<tr>
<td>post-BD FEV1 %pred</td>
<td>-0.59</td>
<td>0.65</td>
<td>-0.12</td>
<td>-0.39</td>
<td>-0.04</td>
<td>-0.08</td>
</tr>
<tr>
<td>BDR %pred</td>
<td>0.35</td>
<td>-0.01</td>
<td>0.11</td>
<td>-0.60</td>
<td>-0.48</td>
<td>0.35</td>
</tr>
<tr>
<td>DLCO %pred</td>
<td>-0.32</td>
<td>0.48</td>
<td>0.36</td>
<td>0.19</td>
<td>0.15</td>
<td>0.32</td>
</tr>
<tr>
<td>TLC %pred</td>
<td>0.57</td>
<td>0.67</td>
<td>-0.20</td>
<td>-0.24</td>
<td>-0.03</td>
<td>-0.12</td>
</tr>
<tr>
<td>IC/TLC</td>
<td>-0.58</td>
<td>-0.03</td>
<td>0.28</td>
<td>-0.01</td>
<td>-0.15</td>
<td>0.46</td>
</tr>
<tr>
<td>RV %pred</td>
<td>0.85</td>
<td>0.42</td>
<td>0.13</td>
<td>-0.05</td>
<td>0.03</td>
<td>0.12</td>
</tr>
<tr>
<td>RV/TLC</td>
<td>0.86</td>
<td>0.22</td>
<td>0.15</td>
<td>0.01</td>
<td>0.15</td>
<td>0.09</td>
</tr>
</tbody>
</table>
Gene Expression

• **Correlation**
  - $\Delta$ FEV1 & expression level
  - $P < 0.05$
  - highest $|R| \rightarrow 28$ genes

• **Linear Regression**
  $$Y = \Delta \text{ FEV1}$$
  $$X = \text{expression level of 28 genes}$$
  $\rightarrow 7$ genes

• **Factor analysis**
  - $7 \rightarrow 3$ genes

---

**Treatability with LABA**

- CLN8
- PCSK5
- SKP2
Predict Treatability \( w/ \) LABA

\[ Y = \Delta \text{FEV}1, \text{liter} \]

Correlation or Regression Analyses
Predict Treatability with LAMA

Δ FEV₁, liter

Correlation or Regression Analyses
Prediction of Treatability
LABA or LAMA

Clinical + Expression + Gene Damage

R= 0.6 for LABA
R= 0.7 for LAMA

$R^2 \ 0.36 \sim 0.49$

Not Sufficient
COPD Heterogeneity in Etiology

- Cigarette Smoke
- Biomass Combustion
- Pollutants
- Extracellular Vesicles in Indoor Dusts

~100 nm
Extracellular Vesicles in Indoor Dusts

COPD Heterogeneity in Etiology

Gho YS. Proteomics 2009
IgG of Anti-Extracellular Vesicles in Indoor Dusts → higher risk of COPD

Risk Factors for COPD

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>1.2</td>
<td>1.1 - 1.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Female</td>
<td>1.0</td>
<td>0.3 - 2.8</td>
<td>0.93</td>
</tr>
<tr>
<td>Cigarette smoke</td>
<td>3.7</td>
<td>1.4 - 10.1</td>
<td>0.01</td>
</tr>
<tr>
<td>High anti-dust EV*</td>
<td>8.0</td>
<td>2.0 - 32.5</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Kim YS, et.al. Allergy Asthma Immunol Res. 2016:8;198
Extracellular Vesicles in Indoor Dusts


Asthma Heterogeneity & Progress

Predisposition
- Genetic
- ...

Exposure
- Allergen
- ...

Molecular & cellular change
- Th2 inflammation
- ...

Morphologic change
- Airflow limitation
- Hyperresponsive
- ...

Functional change
- ...

Symptoms
- ...

Phenotype Heterogeneity

Exacerbation

Treatability Heterogeneity

Pathology Heterogeneity

Severity

Etiology Heterogeneity

Time
Asthma Heterogeneity in Pathology

- Pauci-granulocytic
- Eosinophilic
- Mixed or Neutrophilic

Controlled

Uncontrolled

Severe
Proportion of *Eosionphilic* or Th2 Asthma in a General Population, NHANES, US

- High blood Eosinophil $\geq 300$/mL: 41%
- High specific IgE to any 9 allergens: 61%
- High serum IgE & blood eosinophil: 37%

Any of 3 = 73%
Most of pts. = atopic early onset, on ICS with well controlled

Asthma Heterogeneity in Pathology

Stable Persistent, Controlled Asthma

Subject No.

Withdrawal of ICS or LABA for 4wks

<table>
<thead>
<tr>
<th></th>
<th>Eosionphilic</th>
<th>Paucigranulocytic</th>
<th>Mixed</th>
<th>Neutrophilic</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>63</td>
<td>29</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>29</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Eosinophilic Asthma
Stable Persistent, Controlled Asthma

Withdrawal of ICS or LABA for 4wks

Fluticasone 1000 µg for 4wks

Pauci-granulocytic Asthma

Stable Persistent, Controlled Asthma

Subject No.

Withdrewal of ICS or LABA for 4wks

Fluticasone 1000 µg for 4wks
Global Asthma Guidelines, GINA 2016 Update

Stratification ➞ Treatment

Controlled vs. Uncontrolled ➞ ICS → + LABA → + LAMA

High IgE, severe uncontrolled ➞ Anti-IgE

High eosinophil, severe uncontrolled ➞ Anti-IL5

Aspirin exacerbated ➞ LTRA
Summary

Heterogeneity → Stratification → Best Treatment

① Etiology
② Pathology
...

① Phenotype
② Endotype
③ Treatability
...

...
Conclusion

‘Heterogeneity’ expands understandings on COPD & asthma.

Keep you not overwhelmed by heterogeneity but with ‘stratification’ for best treatment
Thank you for KOLD & ANOLD Researchers
Treatability w/ LABA

Δ FEV1, liter

Δ FEV1, liter

Δ FEV1, liter

CLN8  

PCSK5  

SKP2  

Gene Expression
Asthma Heterogeneity in Pathology

**Current & Future Therapy**

- **Eosinophilic** → Inhaled Steroid, LTRA
- **Smooth m.** → LABA, LAMB, Thermoplasty
- **Neutrophilic** → Anti-Neutrophilic
- **Mucus** → Anti-mucus
Asthma Heterogeneity in Pathology

Diagnostic Tools

- **Eosinophilic**
  - Smooth m.
  - Sputum eosino., eNO

- **Neutrophilic**
  - Mucus
  - Sputum neutro.
  - Sputum amount

- Spirometry
- ACQ, ACT
- Exacerbation