Management of Severe Asthma

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How to define severe asthma

- At least 3 of the following criteria:
  - Have been seen by a consultant in asthma for ≥ 2 yrs
  - Have persistent symptoms & decreased QOL
  - Have received maximal usual asthma therapy &/or medications (high doses of inhaled corticosteroids) with documented adherence to therapy
  - Have previous respiratory failure/intubations/near-fatal episodes
  - Have repeated low FEV1 < 70% predicted

ENFUMOSA
(European Network for Understanding Mechanisms of Severe Asthma)
How to define severe asthma

- Asthma severity

How to overcome severe asthma

- Is it really effective?
  - Asthma heterogeneity
- Phenotype dissection
- Biomarker/PGx approach

- Is it only effective?
  - Different approach
  - Reassessing known drugs
  - New drug development
Phenotype dissection

- Asthma heterogeneity

→ The elephant metaphor of reality

Lancet 2006;368:804-813

Biomarker-driven approach

- Anti-IL13 antibody treatment for asthma

Pharmacogenomics approach

- Molecular phenotyping for asthma

In this presentation...

- Our recent works focused on the strategy to overcome severe asthma
  - Pharmacogenetic approach (reassessing known drug)
    - Arg16Gly in ADRB2 vs. Tiotropium bromide
  - Biomarker-driven approach (overcoming steroid insensitivity)
    - FKBP51 expression in PBMC vs. steroid response
  - Different treatment approach (overcoming steroid insensitivity)
    - Signalings via TLR vs. steroid response
  - Newer modality for phenotyping
    - Xenon ventilation computed tomography

Am J Respir Crit Care Med 2009;180:388-395
Arg16Gly in ADRB2 vs. Tiotropium bromide

• Role of anti-cholinergic in the asthma management


Arg16Gly in ADRB2 vs. Tiotropium bromide

• Genetic variations in ADRB2 vs. anticholinergics

Lancet 2004;364:1505-1512
Arg16Gly in *ADRB2* vs. 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

- Tiotropium 18µg once a day lung functions every 4 weeks

- Responders - FEV1 improvement ≥ 15% & 200 ml - maintained for at least 8 successive weeks

11 SNPs in *CHRM1-3*, Arg16Gly & Gin27Glu in *ADRB2* scored in 80 of the 138 asthmatics


Arg16Gly in *ADRB2* vs. Tiotropium bromide

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

# Main findings
- As many as 30% of severe asthmatics on conventional medications with reduced lung function were found to respond to adjuvant tiotropium.
- Logistic regression analyses (controlled age, gender and smoking status) showed that Arg16Gly in ADRB2 [P = 0.003, OR (95% CI) = 0.21 (0.07-0.59) in a minor allele dominant model] was significantly association with response to tiotropium.

Arg16Gly in ADRB2 vs. Tiotropium bromide

- Crosstalk between muscarinic receptor & adrenergic receptor

![Crosstalk Diagram](image)

*Proc Am Thorac Soc 2005;2:305-310*

Arg16Gly in ADRB2 vs. Tiotropium bromide

- Tiotropium improves lung function in patients with severe uncontrolled asthma: A randomized controlled trial

![Lung Function Graph](image)

*J Allergy Clin Immunol 2011;128:308-314*
Arg16Gly in ADRB2 vs. Tiotropium bromide

- Tiotropium is noninferior to salmeterol in maintaining improved lung function in B16-Arg/Arg patients with asthma

FKBP51 expression vs. steroid response

- 1st Step... Changes in gene expression during steroid treatment (murine model of asthma & dexamethasone treatment)
FKBP51 expression vs. steroid response


FKBP51 expression vs. steroid response

- FKBP51 in cluster

FKBP51 expression vs. steroid response

• 2nd Step... Evaluations using human PBMC
  - FKBP51 expression on PBMC (controls vs. asthmatics)


FKBP51 expression vs. steroid response

• 2nd Step... Evaluations using human PBMC
  - FKBP51 expression on PBMC (steroid response)

  $R = -0.821$, $P = 0.045$

Signaling via TLS vs. steroid response

- The expressions of TLRs on PBMCs

  ![Graph showing the expression of TLRs on PBMCs](image1)


- The changes in TNF-α production after *in vitro* stimulation with TLR-specific ligands according to asthma severity

  ![Graph showing TNF-α production](image2)

Signaling via TLS vs. steroid response

- The changes in the expression of TLRs on PBMCs of asthmatics after oral prednisolone administration

![Graph showing changes in TLR expression](image)


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Signaling via TLS vs. steroid response

- The changes in TLR-specific ligands induced TNF-α and IFN-γ production after oral prednisolone administration

![Graph showing cytokine production](image)

Xenon ventilation computed tomography

- **Xenon ventilation CT** (Functional imaging)

Emphysema & bullae

<table>
<thead>
<tr>
<th>Wash-in phase</th>
<th>Wash-out phase</th>
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</thead>
<tbody>
<tr>
<td>Asthmatics</td>
<td>Controls</td>
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</table>

Xenon ventilation computed tomography

- **Xenon ventilation CT** (Functional imaging)
Xenon ventilation computed tomography

- Clinical meanings of air trapping within the lungs of asthmatics (A promising role of Xenon ventilation CT)

Park HW, et al. Manuscript in preparation

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
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<tbody>
<tr>
<td>66-yr, female</td>
<td>65-yr, female</td>
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<table>
<thead>
<tr>
<th>Parameter</th>
<th>Case 1</th>
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<tbody>
<tr>
<td>PC_{20} (mg/ml)</td>
<td>1.29</td>
<td>5.19</td>
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<tr>
<td>FEV1 % predicted</td>
<td>65</td>
<td>66</td>
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<tr>
<td>% increase in FEV1 after BD inhalation</td>
<td>5</td>
<td>-1</td>
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After 12-wk treatment

<table>
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<th>Parameter</th>
<th>Case 1</th>
<th>Case 2</th>
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</thead>
<tbody>
<tr>
<td>FEV1 % predicted</td>
<td>116</td>
<td>78</td>
</tr>
<tr>
<td>% increase in FEV1 after treatment</td>
<td>78</td>
<td>18</td>
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</tbody>
</table>

* Changes in total number of AIs on Xenon ventilation CT in WO phase at baseline

Park HW, et al. Manuscript in preparation
Xenon ventilation computed tomography

• Baseline characteristics associated with dyspnea measured by visual analogue scale

Park HW, et al. Manuscript in preparation

Xenon ventilation computed tomography

• Baseline characteristics associated with % increase in FEV1 after treatment

Park HW, et al. Manuscript in preparation
Conclusion

• **Pharmacogenetic approach**
  - help the positioning of tiotropium in asthma management

• **Dexamethasone-induced FKBP51 expression in PBMCs**
  - a reliable & practical biomarker in predicting the response to corticosteroids in asthmatics

• **A TLR-specific antagonist & glucocorticoid**
  - required for the effective control of airway inflammation in asthmatics

• **Xenon ventilation CT**
  - an objective & promising tool in identifying specific subset of asthma & treatment responses