

Management of Severe Asthma

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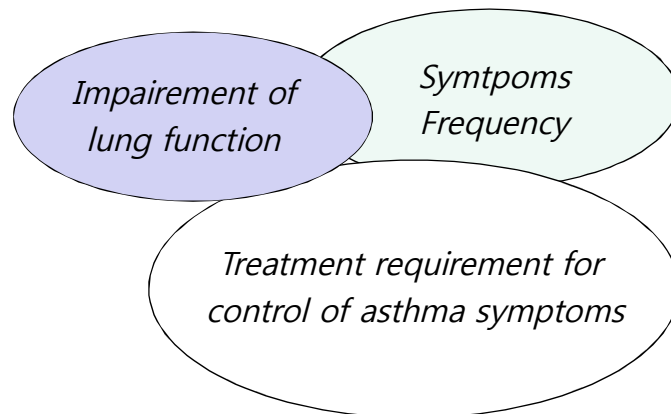
How to define severe asthma

- **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

Treatment requirement for control of asthma symptoms

Corticosteroid

- **Is it really effective ?**

→ Asthma heterogeneity

- Phenotype dissection
- Biomarker/PGx approach

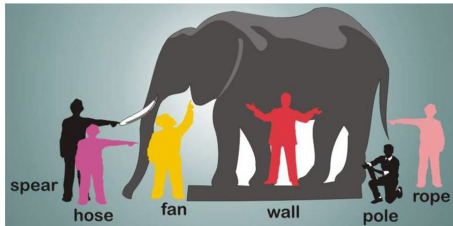
- **Is it only effective ?**

→ Different approach

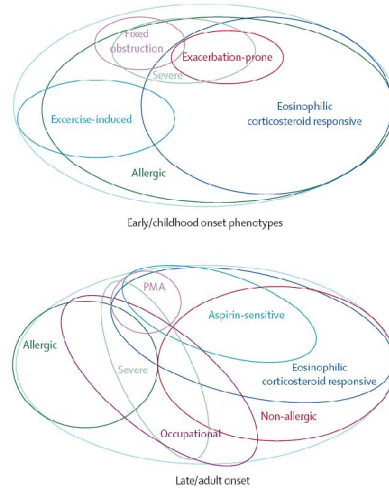
- Reassessing known drugs
- New drug development

Phenotype dissection

- Asthma heterogeneity**



→ The elephant metaphor of reality

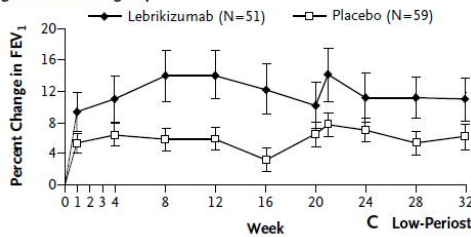


Lancet 2006;368:804-813

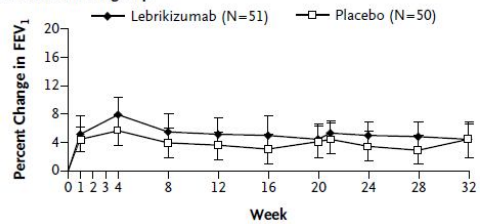
Biomarker-driven approach

- Anti-IL13 antibody treatment for asthma**

B High-Periostin Subgroup



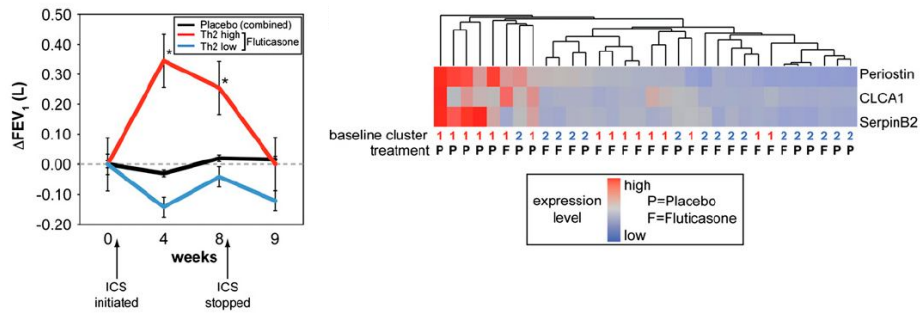
C Low-Periostin Subgroup



N Engl J Med 2011;365:1088-1098

Pharmacogenomics approach

- Molecular phenotyping for asthma



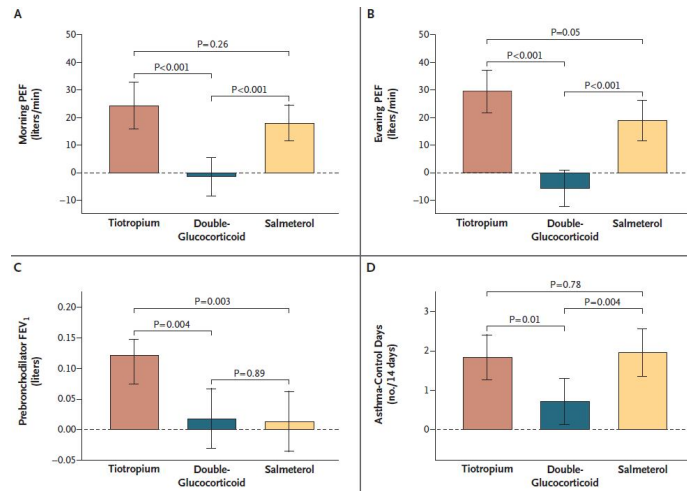
Am J Respir Crit Care Med 2009;180:388-395

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)
Singalings via TLR vs. steroid response
 - Newer modality for phenotyping
Xenon ventilation computed tomography

Arg16Gly in *ADRB2* vs. Tiotropium bromide

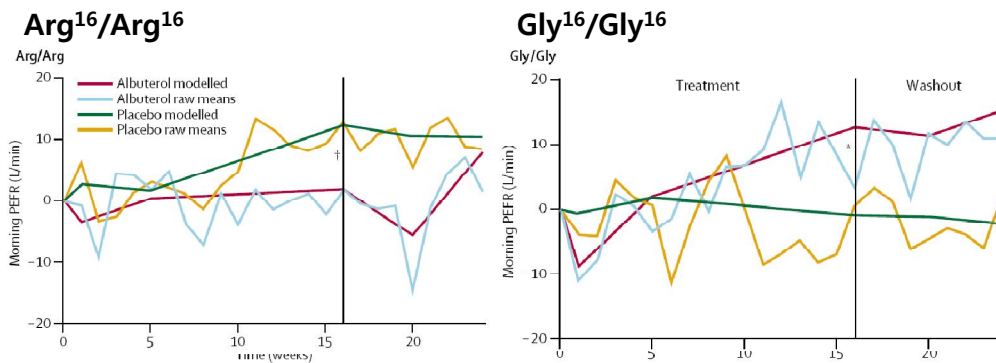
- Role of anti-cholinergic in the asthma management



N Engl J Med 2010;363:1715-1726

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

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

Tiotropium 18µg once a day
lung functions every 4 weeks

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

Park HW, et al. *Allergy* 2009;64:778-783

Arg16Gly in *ADRB2* vs. Tiotropium bromide

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

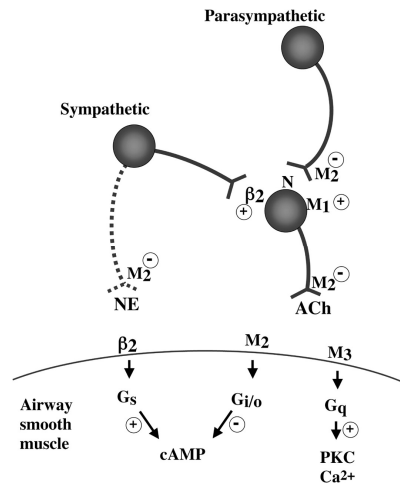
Main findings

- 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

Park HW, et al. *Allergy* 2009;64:778-783

Arg16Gly in *ADRB2* vs. Tiotropium bromide

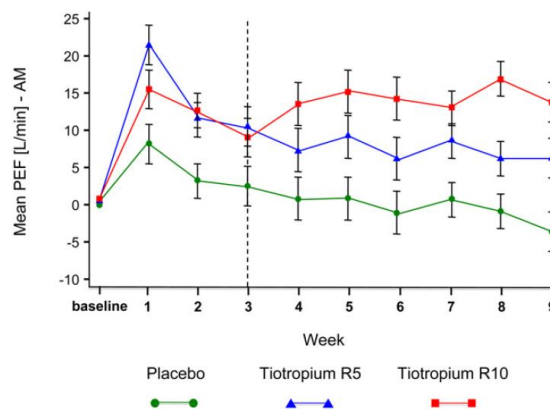
- Crosstalk between muscarinic receptor & adrenergic receptor



Proc Am Thorac Soc 2005;2:305-310

Arg16Gly in *ADRB2* vs. Tiotropium bromide

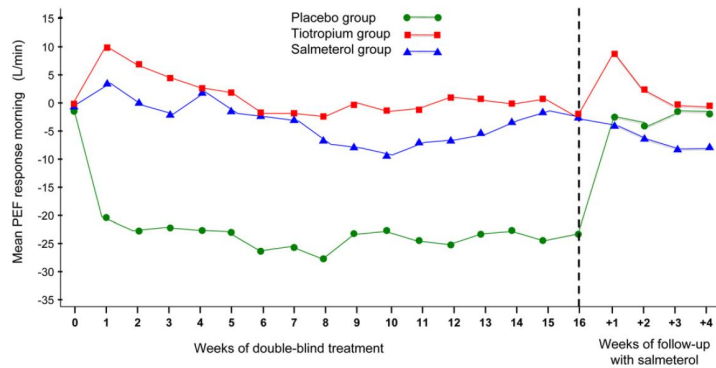
- Tiotropium improves lung function in patients with severe uncontrolled asthma: A randomized controlled trial



J Allergy Clin Immunol 2011;128:308-314

Arg16Gly in *ADRB2* vs. Tiotropium bromide

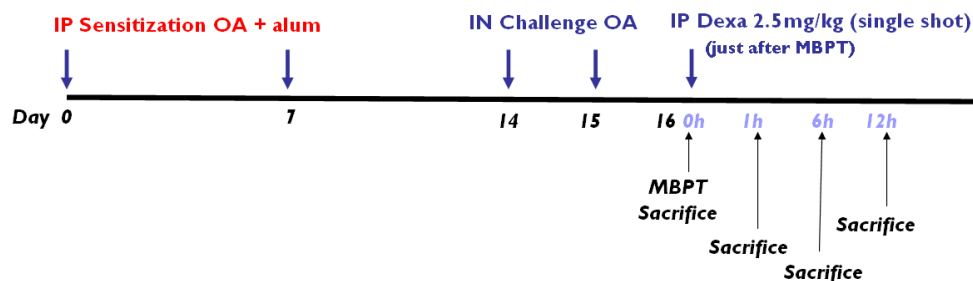
- Tiotropium is noninferior to salmeterol in maintaining improved lung function in B16-Arg/Arg patients with asthma



J Allergy Clin Immunol 2011;128:315-322

FKBP51 expression vs. steroid response

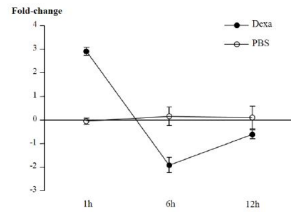
- 1st Step... Changes in gene expression during steroid treatment (murine model of asthma & dexamethasone treatment)



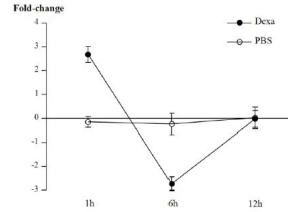
Park HW, et al. J Clin Immunol 2011;31:122-127

FKBP51 expression vs. steroid response

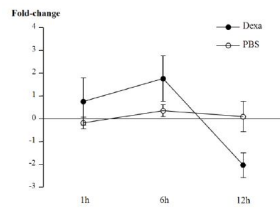
a. cluster 1 (64)



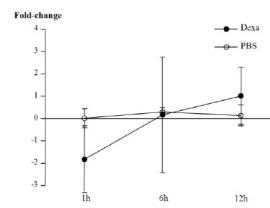
b. cluster 2 (65)



c. cluster 3 (28)



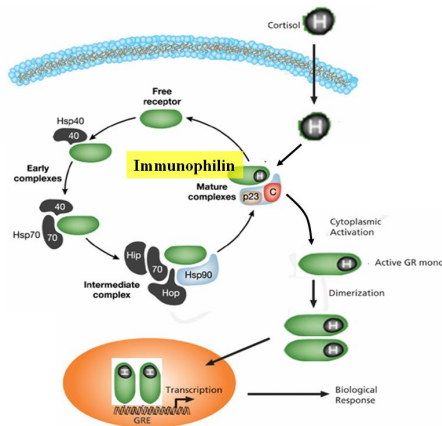
d. cluster 4 (29)



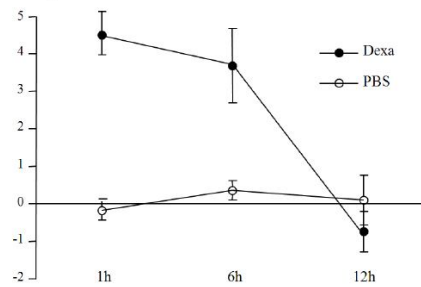
Park HW, et al. *J Clin Immunol* 2011;31:122-127

FKBP51 expression vs. steroid response

• FKBP51 in cluster



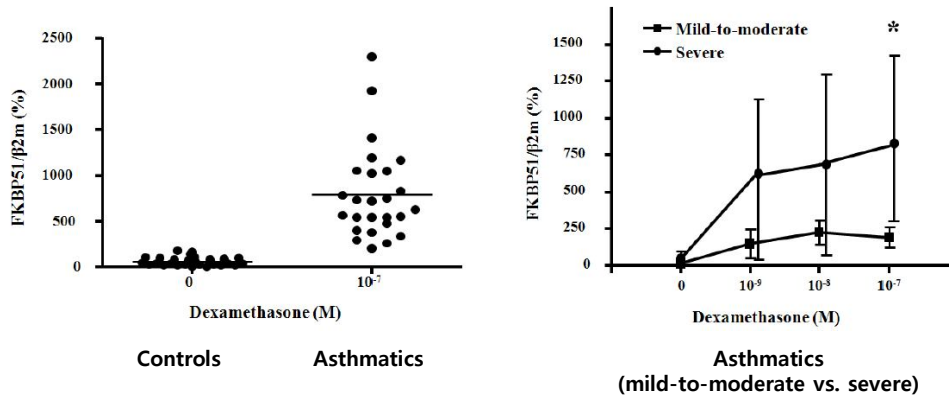
Fold-change



Park HW, et al. *J Clin Immunol* 2011;31:122-127

FKBP51 expression vs. steroid response

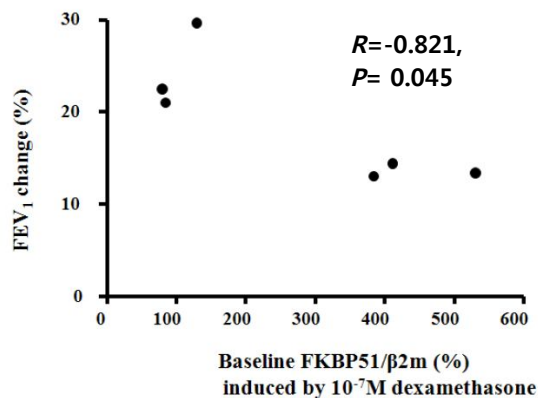
- 2nd Step... Evaluations using human PBMC
 - FKBP51 expression on PBMC (controls vs. asthmatics)



Park HW, et al. *J Clin Immunol* 2011;31:122-127

FKBP51 expression vs. steroid response

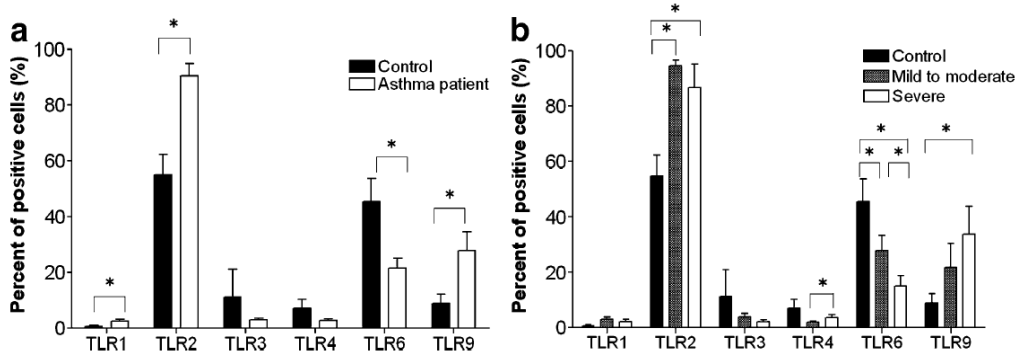
- 2nd Step... Evaluations using human PBMC
 - FKBP51 expression on PBMC (steroid response)



Park HW, et al. *J Clin Immunol* 2011;31:122-127

Signaling via TLS vs. steroid response

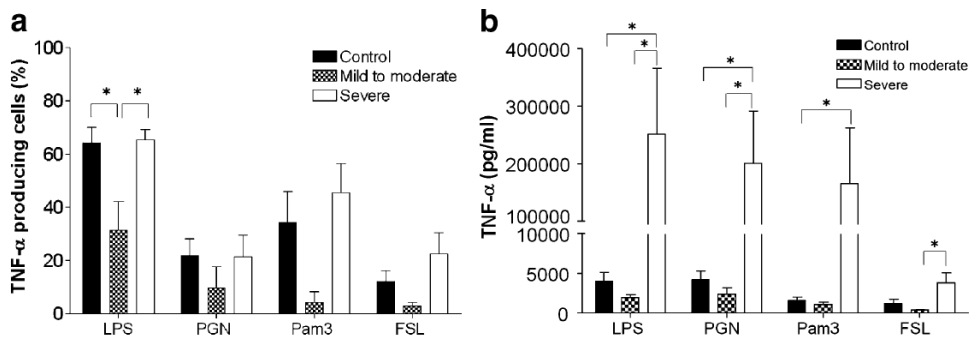
- The expressions of TLRs on PBMCs



Park HW, et al. *J Clin Immunol* 2010;30:459-464

Signaling via TLS vs. steroid response

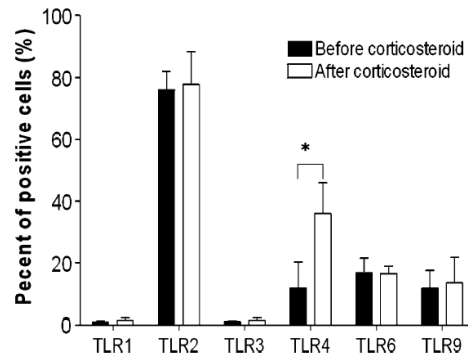
- The changes in TNF- α production after *in vitro* stimulation with TLR-specific ligands according to asthma severity



Park HW, et al. *J Clin Immunol* 2010;30:459-464

Signaling via TLS vs. steroid response

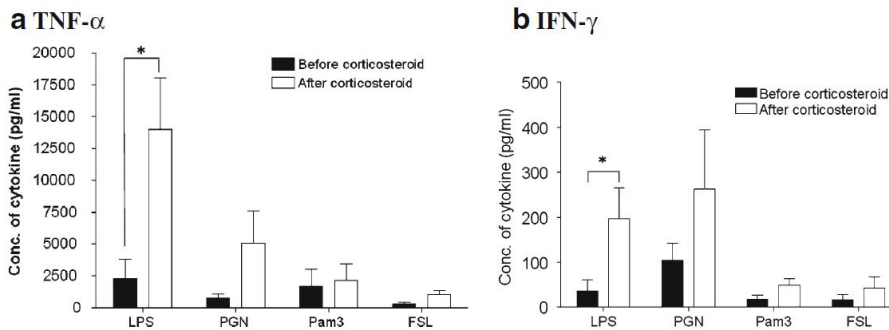
- The changes in the expression of TLRs on PBMCs of asthmatics after oral prednisolone administration



Park HW, et al. *J Clin Immunol* 2010;30:459-464

Signaling via TLS vs. steroid response

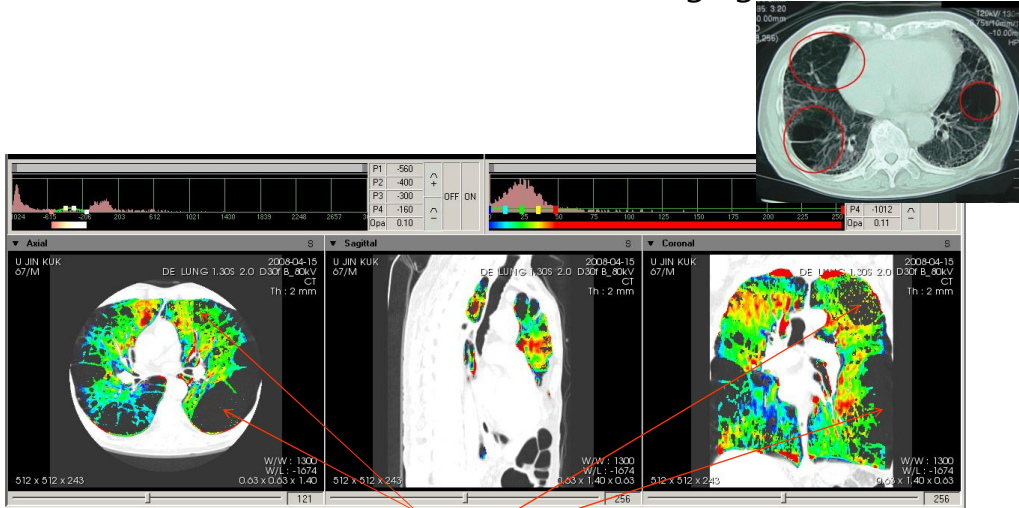
- The changes in TLRspecific ligands induced TNF- α and IFN- γ production after oral prednisolone administration



Park HW, et al. *J Clin Immunol* 2010;30:459-464

Xenon ventilation computed tomography

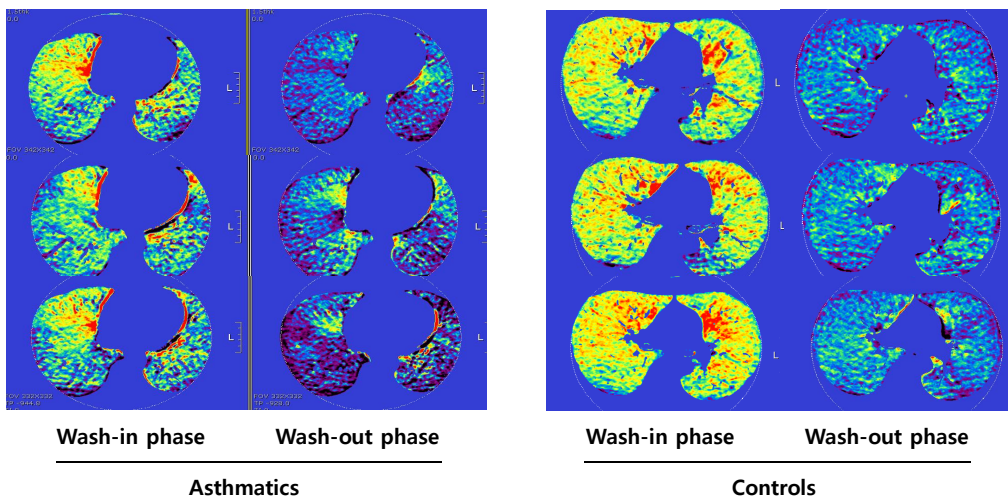
- Xenon ventilation CT (Functional imaging)



Emphysema & bullae

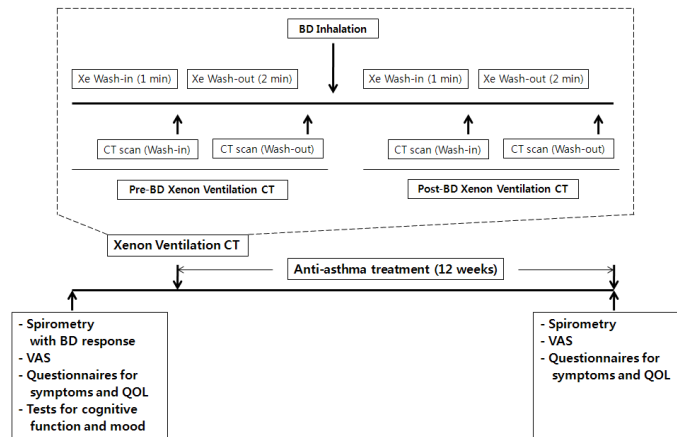
Xenon ventilation computed tomography

- 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)

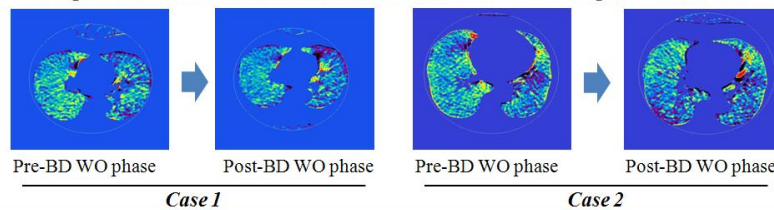


Park HW, et al. Manuscript in preparation

Xenon ventilation computed tomography

	Case 1 66-yr, female	Case 2 65-yr, female
At baseline		
PC ₂₀ (mg/ml)	1.29	5.19
FEV1 % predicted	65	66
% increase in FEV1 after BD inhalation	5	-1
After 12-wk treatment		
FEV1 % predicted	116	78
% increase in FEV1 after treatment	78	18

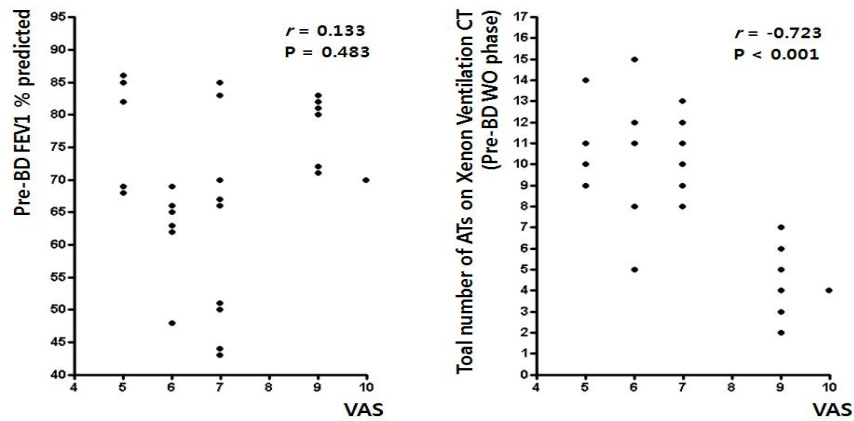
* Changes in total number of ATs on Xenon ventilation CT in WO phase at baseline



Park HW, et al. Manuscript in preparation

Xenon ventilation computed tomography

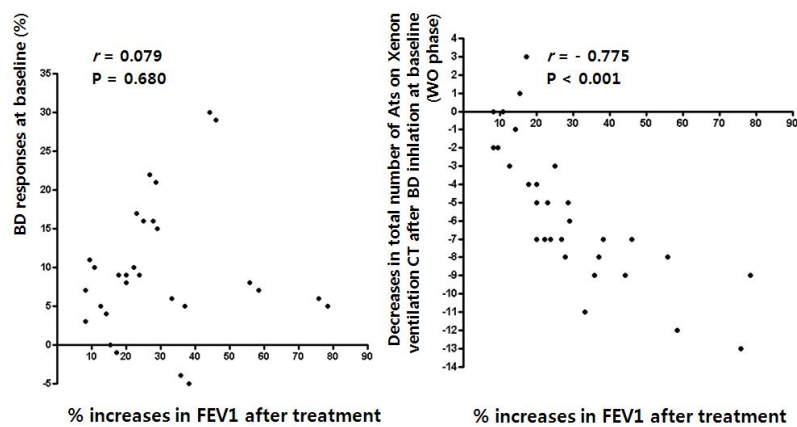
- Baseline characteristics associated with dyspnea measured by visual analogue scale



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