Precision Asthma Therapy:
Picking the Right Biologic for the Right Patient

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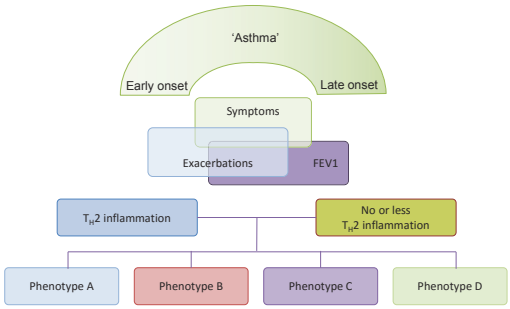
The Asthma Umbrella



Wenzel S. Nature Medicine 18, 716–725 (2012)

Precision Asthma Therapy: The Path Forward

Clinical phenotypes

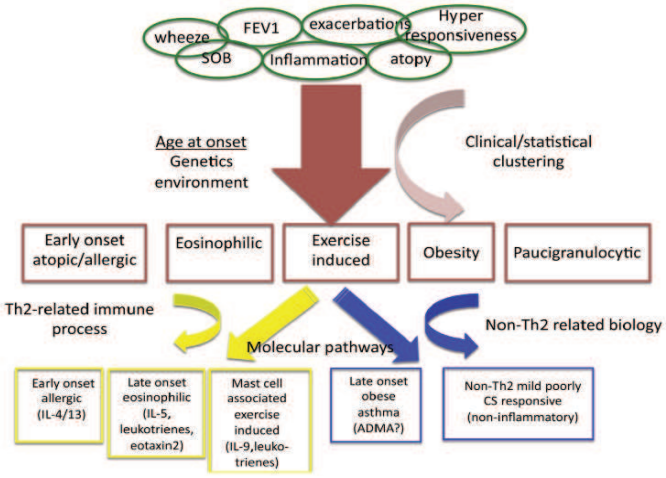
Treatable traits

Molecular endotypes

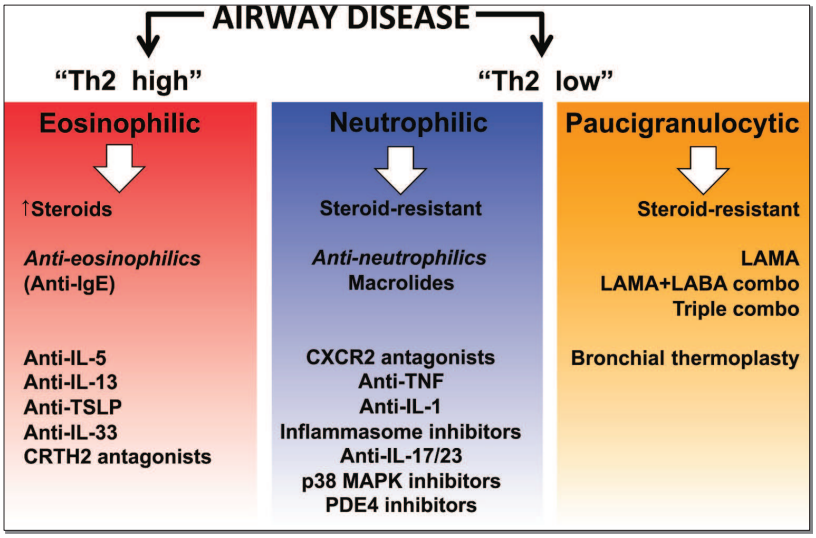
Precision medicines

Remissions and cures

Phenotypes to Endotypes



Wenzel SE. *Pulm Pharmacol Ther.* 2013;26:710-715.



PRACTALL consensus report

Precision medicine in patients with allergic diseases: Airway diseases and atopic dermatitis—PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology

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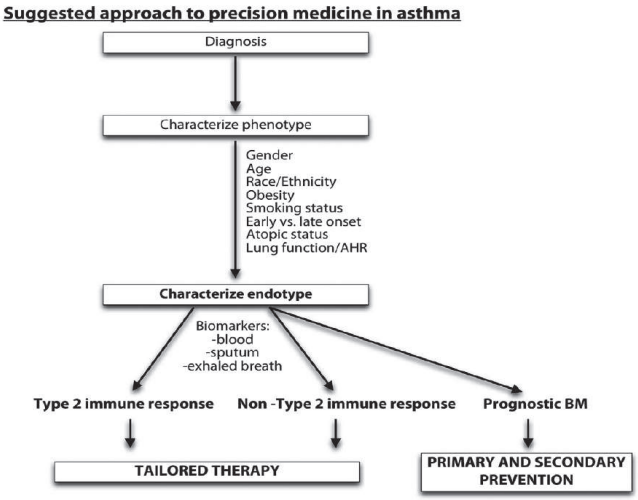
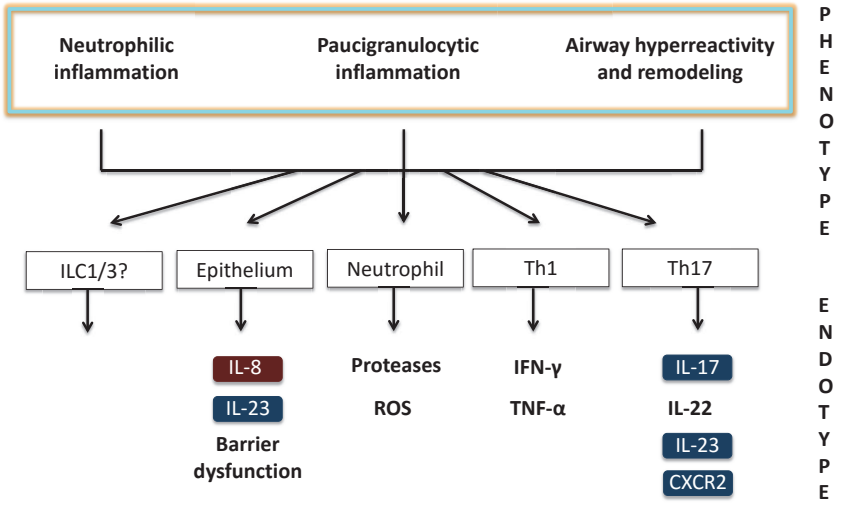


JACI, May 2016

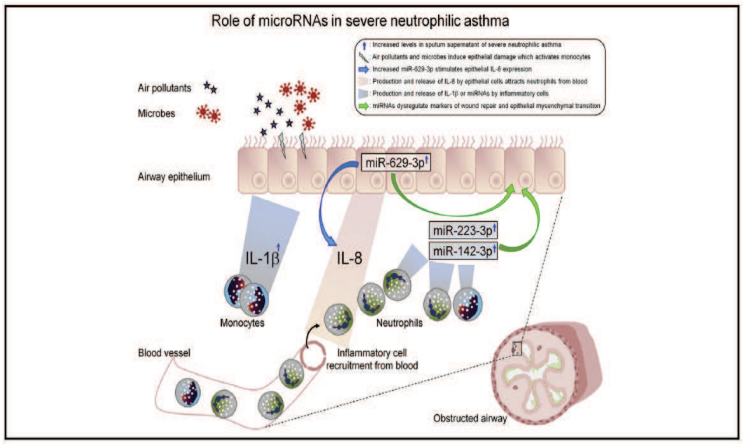
Type 2 Low Asthma



JACI, May 2016

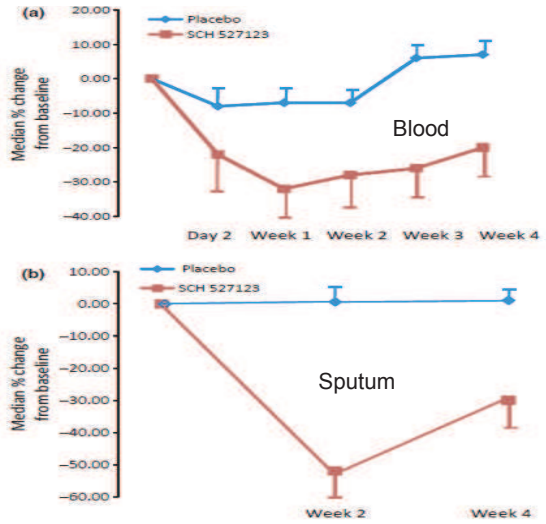
Approved treatment targets | Under investigation treatment targets | Potential treatment targets

Neutrophilic Asthma: A Potential Biomarker for Disease



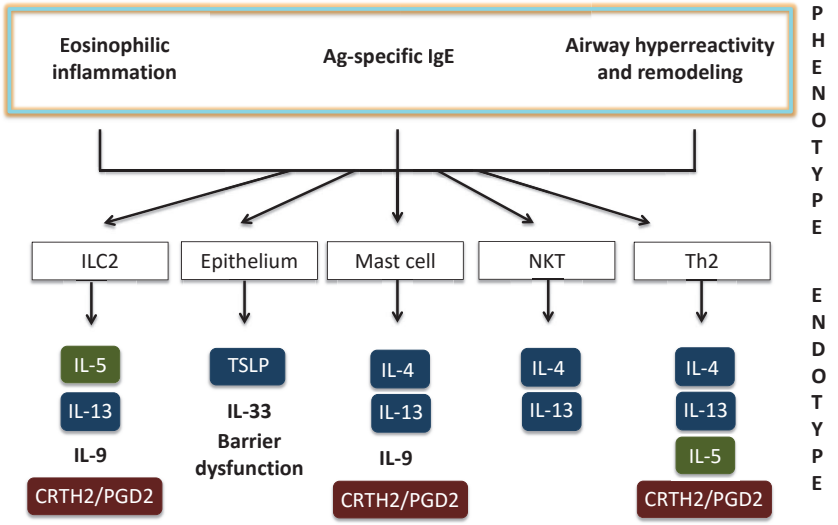
Maes et al, JACI, May, 2016

Efficacy Of A CXCR2 (IL-8) Antagonist In Severe Asthma With Sputum Neutrophils



Nair P, et al. Clin Exp Allergy. 2012 Jul;42(7):1097-103.

Type 2 Hi Asthma



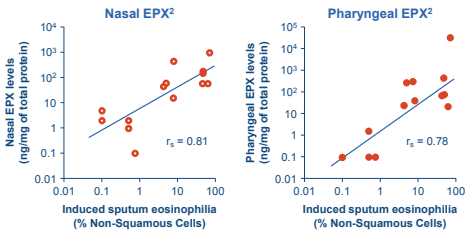
JACI, May 2016

Approved treatment targets | Under investigation treatment targets | Potential treatment targets

Biomarker	Treatment expected to produce a response	Associations	Comments (point of care, variability/fluctuation)
BLOOD			
Eosinophil	Anti-IL5 Anti -IgE Anti- IL-4/IL-13 Corticosteroids (CS) CRTH2 antagonists	Exacerbations LF decline Fixed airway obstruction	Easily available Significant fluctuation
Specific IgE	Anti-IgE AIT	Exacerbations AHR (AIT)	
Periostin Dipeptidyl peptidase-4 (DPP-4)	Anti-IL-13	LF decline Exacerbations	Research type Assay dependent
INDUCED SPUTUM			
Eosinophils	Anti IL-5 ICS	Exacerbations	Research type Significant fluctuation
IL-13	Anti IL-13	?	Research type
EXHALED BREATH			
FeNO	Anti IL-5 Anti IgE Anti IL-13 ICS	Exacerbations, LF decline	Easily available Point of care Significant fluctuation
Metabolomics (VOC)	ICS	?	Research type

Novel Ways to Measure Eosinophils in Clinical Practice

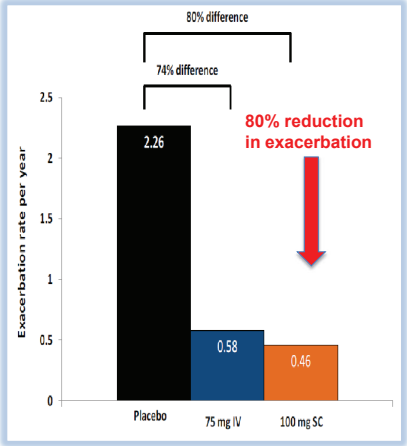
- Inexpensive, point-of-care diagnostic tools being developed to improve management of patients with respiratory diseases
- Bioactive paper[1]
  - "Bio-inks" on paper strip measures quantity of eosinophil peroxidase (EPX) in sputum
- Throat or nasal swabs[2]
  - Strong association between nasal and pharyngeal EPX levels and percentage of induced sputum eosinophils
  - Potentially clinically relevant diagnostic metric; simplicity of use provides potential novel point-of-care assay for management of poorly controlled patients

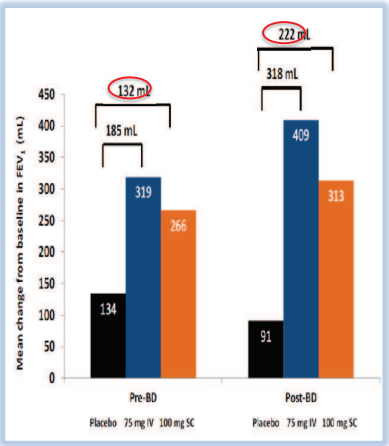


1. Bioactive Paper Will Revolutionize Point-of-Care Diagnostics. http://dailynews.mcmaster.ca/article/bioactive-paper-will-revolutionize-point-of-care-diagnostics/. March 7, 2016. 2. Rank MA et al. *Allergy*. 2016;71(4):567-570.

Potential for application in doctor's offices, outpatient clinics, and by patients themselves for self-management[1]

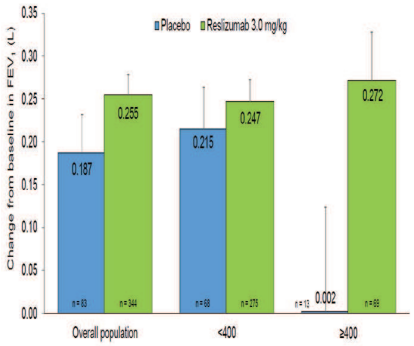
Subgroup Analysis Of 177 Patients With Blood Eosinophils ≥500 Cells/mL From MENSA Population

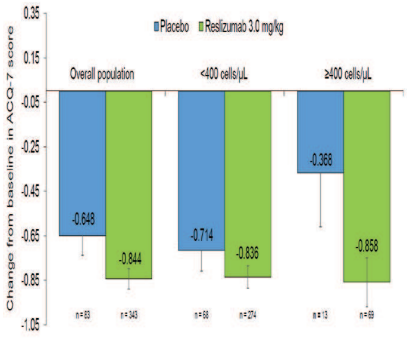




Source: Ortega et al . N Engl J Med 2014; 371:1198-1207

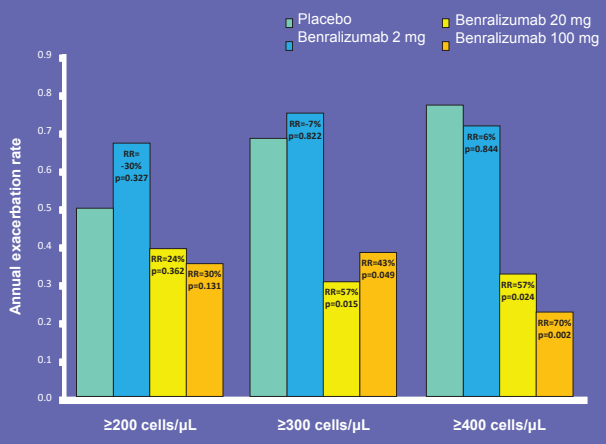
Reslizumab Effects on FEV1 and ACQ Based On Bld Eos: 16-Week Studies





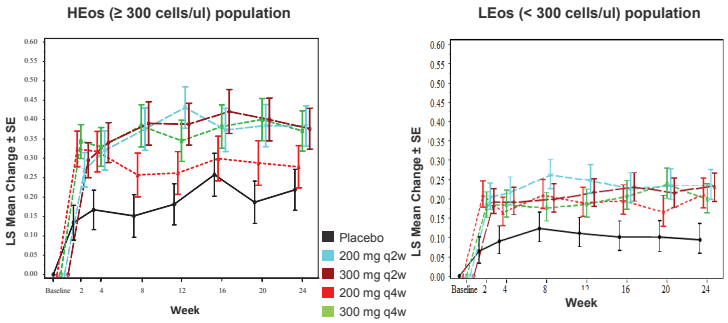
Corren et al, Chest, 2016, In Press

Benralizumab's Effects on Annual Exacerbation Rate By Eosinophil Level



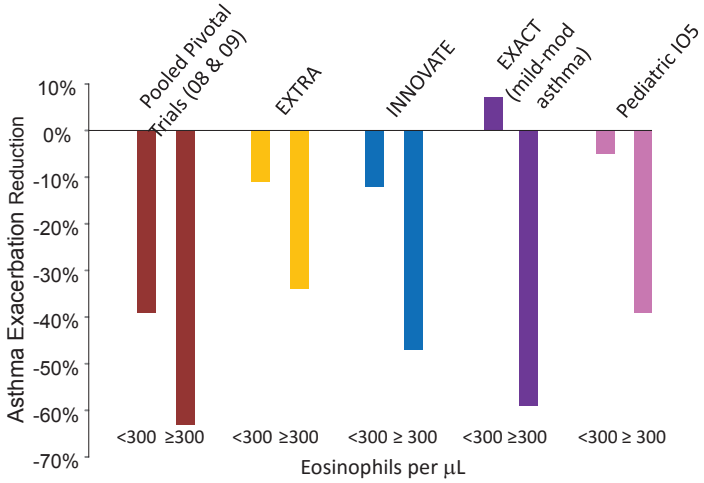
RR, rate ratio
Castro et al. Lancet Resp Med 2014; 2: 879–90

Dupilumab-Induced Changes From Baseline in Absolute FEV_1 By Eosinophils



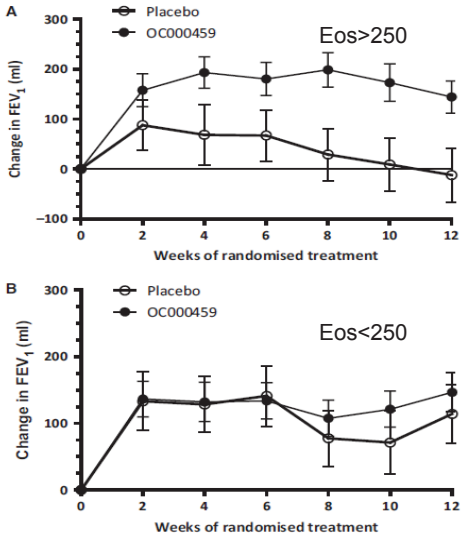
Wenzel, et al, Lancet, 2016

Asthma Exacerbation Reductions in Omalizumab Clinical Trials by Eosinophil Strata



Sources: Hanania et al. *AJRCCM* 2013; Busse et al. *JACI* 2013; Genentech and Novartis Data on File

Heightened Response Of Eosinophilic Asthmatics To CRTH2 Antagonist OC000459



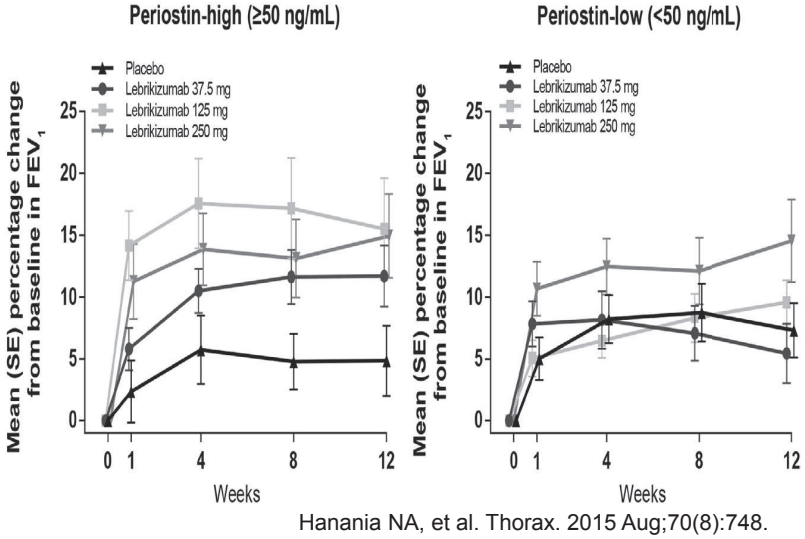
Pettipher R, et al. Allergy. 2014 Sep;69(9):1223-32.

Endotype-Driven Treatment In T2 Asthma

Predictive biomarker	Drug	Target	Effects
Blood eosinophils Periostin FENO	Omalizumab	IgE	Reduces exacerbations Improves symptoms and quality of life
Blood/sputum eosinophils FENO	Mepolizumab	IL-5	Reduces eosinophil counts, exacerbations, and OCS Improves FEV_1
Blood eosinophils	Reslizumab	IL-5	Reduces eosinophil counts, exacerbations Improves FEV_1
Blood eosinophils	Benralizumab	IL-5Rα	Reduces eosinophil and basophil counts, exacerbations Improves FEV_1
Blood eosinophils	Dupilumab	IL-4Rα	Reduces exacerbations Improves FEV_1 Improves symptoms and quality of life
Periostin DPP-4	Tralokinumab	IL-13	Reduces eosinophil counts and exacerbations Improves FEV_1
Periostin	Lebrikizumab	IL-13	Reduces exacerbations Improves FEV_1

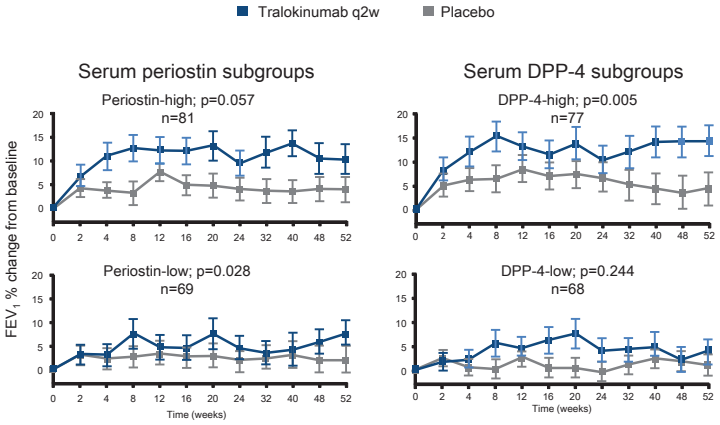
JACI, May 2016

52-Week Replicate Lebrikizumab Trials in Adults with Asthma



Hanania NA, et al. Thorax. 2015 Aug;70(8):748.

Changes In FEV_1 In Subgroups Treated With Tralokinumab for 52 Weeks



Brightling CE, et al. Lancet Respir Med 2015;DOI:10.1016/S2213-2600(15)00197-6

Critical Issues /Questions for Th2 Blockers

- Many options for similar patient populations.
  - Phenotype/Endotype (Biomarker) driven choices overlap: *No specific biomarkers*
- Optimal treatment goals have not yet been met:
  - True Immunomodulation: prevent/alter disease course
- Th2 blockers likely have favorable risk/benefit ratio

Why Precision Medicine is Important