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

**The Asthma Umbrella**

![Diagram of the Asthma Umbrella](image)

**Precision Asthma Therapy: The Path Forward**

- Clinical phenotypes
- *Treatable traits*
- Molecular endotypes
- Precision medicines
- Remissions and cures

_Wenzel S. Nature Medicine 18, 716–725 (2012)_)
Phenotypes to Endotypes


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
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


**Type 2 Hi Asthma**

- Eosinophilic inflammation
- Ag-specific IgE
- Airway hyperreactivity and remodeling

**Phenotype**

- ILC2
- Epithelium
- Mast cell
- NKT
- Th2

**Endotype**

- IL-5
- IL-13
- IL-9
- CRTH2/PGD2

**Biomarker**

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

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

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

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Benralizumab’s Effects on Annual Exacerbation Rate By Eosinophil Level

RR, rate ratio

Dupilumab-Induced Changes From Baseline in Absolute FEV₁ By Eosinophils


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

Endotype-Driven Treatment In T2 Asthma

<table>
<thead>
<tr>
<th>Predictive biomarker</th>
<th>Drug</th>
<th>Target</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood eosinophils</td>
<td>Omalizumab</td>
<td>IgE</td>
<td>Reduces exacerbations</td>
</tr>
<tr>
<td>Periostin</td>
<td></td>
<td></td>
<td>Improves symptoms and quality of life</td>
</tr>
<tr>
<td>Fino</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Blood/sputum eosinophils</td>
<td>Mepolizumab</td>
<td>IL-5</td>
<td>Reduces eosinophil counts, exacerbations, and OCS</td>
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<tr>
<td>Fino</td>
<td></td>
<td></td>
<td>Improves FEV₁</td>
</tr>
<tr>
<td>Blood eosinophils</td>
<td>Reslizumab</td>
<td>IL-5</td>
<td>Reduces eosinophil counts, exacerbations</td>
</tr>
<tr>
<td>Blood eosinophils</td>
<td>Benralizumab</td>
<td>IL-5-Rx</td>
<td>Reduces eosinophil and basophil counts, exacerbations</td>
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<tr>
<td>Blood eosinophils</td>
<td>Dupilumab</td>
<td>IL-4-Rx</td>
<td>Reduces exacerbations</td>
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<td>Periostin</td>
<td>Tralokinumab</td>
<td>IL-13</td>
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JACI, May 2016

52-Week Replicate Lebrikizumab Trials in Adults with Asthma

Changes In FEV₁ In Subgroups Treated With Tralokinumab for 52 Weeks

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

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