Biologic Targeted Therapy in Asthma

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Asthma Background

• The most common serious chronic lung disease
• Afflicts ~ 334 million people worldwide
• Unpreventable and incurable
• The number of people with asthma in the US is expected to grow by >100 million by 2025.

Asthma Definition

- Defined as a complex disorder characterized by:
  - Variable and recurring symptoms
  - Airflow obstruction
  - Bronchial hyperresponsiveness
  - Underlying inflammation
- Heterogeneous Disease
- Different phenotypes/endotypes can be recognized

Asthma is not just one disease

Phenotypes: Observable Manifestations of Disease(s)

Endotypes: Different Diseases With Different Causes
Common View of Asthma

Asthma is more than TH2 inflammatory response

(1) Auto-innate, Mφ, and DAMPs
(2) T-cell independent Th2-like

“Asthma” may be due to different biological pathways
Most Asthma is Controlled

- Most asthma is controlled with non-specific anti-inflammatories (steroids) and bronchodilators

Poor response to asthma treatment may be due to several reasons

- Comorbidities (Obesity, OSA, nasal polyps, Cardiovascular disease, allergic rhinitis)
- Social issues
- Smoking
- Adherence (medications, asthma action plan, steroidphobia, age)
- Host factors/Drugs (PK, PG)
- Allergen Exposures (Indoor and Outdoor)
- Healthcare System
Severe refractory asthma is uncommon

- Severe asthma represents ~5% of asthma patients
- Significant physical and socio-economic burden with severe asthma

Treatment of Severe Asthma

- Oral Corticosteroids

Complications: Infectious, Cardiovascular, Metabolic, Ocular, Gastrointestinal

- Steroid-resistant Asthma

Era of Precision Medicine

• Target molecule(s) involved in persistent airway inflammation in severe asthma by biological agents
What is a Biologic Product?

- Biologics are medical products made from a variety of natural sources
- Biological products are used to either:
  - Treat or cure diseases and medical conditions
  - Prevent diseases
  - Diagnose diseases
How are Biological Products Different?

**Small Molecule Drugs**
- Generally low molecular weight
- Usually organic or chemical synthesis
- Fewer critical process steps
- Well-characterized
- Known structure

**Biological Products**
- Generally high molecular weight
- Made with/from live cells/organisms → inherent & contamination risk
- Many critical process steps
- Less easily characterized
- Structure may or may not be completely defined of known
- Heterogeneous mixtures → may include variants
- Often Immunogenic
Biologics are larger and more complex

Size and Complexity of Proteins

Aspirin 180 Da

Monoclonal Antibody ~150,000 Da
# Nomenclature of Monoclonal Antibodies

<table>
<thead>
<tr>
<th>Prefix</th>
<th>Target</th>
<th>Source</th>
<th>Suffix</th>
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<tbody>
<tr>
<td>-o(s)-</td>
<td>bone</td>
<td>-u-</td>
<td>human</td>
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<tr>
<td>-vi(r)-</td>
<td>viral</td>
<td>-o-</td>
<td>mouse</td>
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<tr>
<td>-ba(c)-</td>
<td>bacterial</td>
<td>-a-</td>
<td>rat</td>
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<tr>
<td>-li(m)-</td>
<td>immune</td>
<td>-e-</td>
<td>hamster</td>
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<td>-le(s)-</td>
<td>infectious lesions</td>
<td>-i-</td>
<td>primate</td>
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<td>-ci(r)-</td>
<td>cardiovascular</td>
<td>-xi-</td>
<td>chimeric</td>
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<td>musculoskeletal</td>
<td>-zu-</td>
<td>humanized</td>
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<td>-ki(n)-</td>
<td>interleukin</td>
<td>-axo-</td>
<td>rat/murine hybrid</td>
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<td>-co(l)-</td>
<td>colonic tumor</td>
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<td>-me(l)-</td>
<td>melanoma</td>
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<td>mammary tumor</td>
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<td>testicular tumor</td>
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<td>ovarian tumor</td>
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<td>-pr(o)-</td>
<td>prostate tumor</td>
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<td>-tu(m)-</td>
<td>miscellaneous tumor</td>
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<tr>
<td>-neu(r)-</td>
<td>nervous system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-tox(a)-</td>
<td>toxin as target</td>
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</tbody>
</table>

**variable**
Asthma Phenotype: **Allergic**
Target: **IgE**

Anti-IgE (Omalizumab)

- Inhibits allergen bridging
- Suppress new IgE production
- Down regulates IgE receptor on Mast Cells/Basophils
- Reduce the efficiency of antigen presentation to T lymphocytes
Role in Omalizumab in Asthma

- Studies show inhibition of early and late phase allergen induced asthmatic reactions
- Serum-free IgE concentrations reduced to less than 5% of baseline
- Subsequent studies also showed decreases in sputum and tissue eosinophil counts and submucosal IgE and FcεRI cell counts
Omalizumab reduces allergen-induced exacerbations

**Omalizumab (n = 268)**

**Placebo (n = 257)**

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**Stable steroid phase**

- No. of subjects with exacerbation (%): 39 (14.6) vs. 60 (23.3)
- P value: 0.009
- Mean no. of exacerbations per subject: 0.28 vs. 0.54
- P value: 0.006
- Mean no. of days per exacerbation: 7.8 vs. 12.7
- P value: <0.001

**Steroid reduction phase**

- No. of subjects with exacerbation (%): 57 (21.3) vs. 83 (32.3)
- P value: 0.004
- Mean no. of exacerbations per subject: 0.39 vs. 0.66
- P value: 0.003
- Mean no. of days per exacerbation: 9.4 vs. 12.6
- P value: 0.021

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Omalizumab reduces asthma symptoms and allows for reduction in ICS dose

Clinical Use of Omalizumab

- FDA Approved in 2003 for uncontrolled allergic moderate persistent asthma in ages 12 and older
  - Atopy (presence of specific IgE measured by using skin or serum tests)
  - Total serum IgE level of between 30 and 700 IU/mL
- Dosing is based on IgE level and weight
- Administered every 2-4 weeks subcutaneously in health care setting
Adverse reactions to Omalizumab

- Common ADRs: Nasopharyngitis, headache, induration at injection site (<10%)

- Severe: Black Box Warning- Anaphylaxis-like reactions (0.09%)

  - Extended monitoring after first 1-3 doses and subsequent doses monitoring for 30 minutes

  - Recent 5-year safety study found a slightly higher rate of heart and brain blood vessel problems but no increased risk of cancer.
Asthma Phenotype: Eosinophilic
Target: IL-5
Eosinophils in Asthma

Use of IL-5 targeted therapies in clinical trials (SB-240563, mepolizumab)

1. Th2 Allergen model (SB-240563):
   ❖ Significant reduction in blood and sputum eosinophils
   ❖ No change in early or late asthmatic responses or airway hyperreactivity

2. Heterogeneous Asthma Population (mild to moderate asthma; Mepolizumab):
   ❖ Significant reduction in blood, bone marrow and airway eos
   ❖ No change in FEV$_1$ or clinical asthma measures
Use of IL-5 targeted therapies in clinical trials (mepolizumab, reslizumab)

3. Eosinophilic Asthma Phenotype (severe asthma with sputum eosinophils >3%, blood eosinophil counts or FENO levels; mepolizumab, reslizumab)

- Significant reduction in sputum and blood eosinophils with both biologics
Mepolizumab in Eosinophilic Asthma

- Significant decrease in asthma exacerbations (48%)
- Improvement in Asthma related Quality of Life
- Decrease in airway wall thickening on CT

Haldar et al NEJM 2009; 360: 973-84.
Nair et al NEJM 2009; 985-93.
Mepolizumab in Eosinophilic Asthma


Reslizumab in Eosinophilic Asthma

- Reduction in sputum and blood eosinophils
- Improved asthma symptom control (ACQ score)
- Improved FEV$_1$ from baseline
- 59% reduction in asthma exacerbations

# Clinical Use of anti-IL-5 therapies

**Mepolizumab**
- FDA approved in Nov 2015 for treatment of severe persistent asthma with exacerbation in patients 12 years and older
- Blood eosinophils >300 cells/mcL in the past 12 mo or >150 cells/mcL in the past 6 weeks
- Dose: 100 mg every 4 weeks, subcutaneously in health care setting
- Response may occur as early as 4 weeks

**Reslizumab**
- FDA approved in March 2016 for treatment of severe persistent asthma with exacerbations in patients 18 years and older
- Blood eosinophils >300 cells/mcL in the past 12 mo or >150 cells/mcL in the past 6 weeks
- Dose: 3 mg/kg once every 4 weeks administered by intravenous infusion over 20-50 minutes in health care setting
- Response may occur as early as 4 weeks
### Adverse Reactions to anti-IL-5 biologics

<table>
<thead>
<tr>
<th><strong>Mepolizumab</strong></th>
<th><strong>Reslizumab</strong></th>
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<tbody>
<tr>
<td>❖ Common ADRs: headache, injection site reactions back pain, and weakness (fatigue).</td>
<td>❖ Common ADR(s): oropharyngeal pain</td>
</tr>
<tr>
<td>❖ Severe reactions: Anaphylaxis (occurred in 1 patient), herpes zoster infections occurred in 2 patients receiving mepolizumab. Herpes zoster is the virus that causes shingles.</td>
<td>❖ Severe reactions: Anaphylaxis was reported at a rate of 0.3% (3 patients) in the placebo-controlled studies (n=1028). Malignancy was observed in the Phase III trials (reslizumab 0.6% and placebo 0.3%).</td>
</tr>
<tr>
<td>❖ Consider prescribing epinephrine autoinjector and monitoring patient for period of time of the injection</td>
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<tr>
<td>❖ Consider varicella vaccination if medically appropriate prior to starting therapy</td>
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</table>
Benralizumab in Eosinophilic Asthma

- Blocks IL-5R alpha
- Activates opsonization pathways to destroy eosinophils and basophils expressing the receptor
Benralizumab, an anti-interleukin 5 receptor α monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study

Decrease in exacerbations

Improved Asthma Symptom Control
Benrilizumab in Eosinophilic Asthma

- Awaiting results from Phase 3 study
- Not currently FDA approved
Biologics in the Pipeline
NOT FDA APPROVED
IL-4 and IL-13 in Asthma

- "Th2" Cytokines
- Produced by T cells, mast cells and innate lymphoid cells
- Important in eosinophil accumulation and IgE synthesis by B cells
IL-4 and IL-13 share a receptor

Targeting IL-4 and IL-13 in Asthma (Pitrakinra)

- Mutant IL-4 molecule that blocks binding of human IL-4 or IL-13 to bind to IL-4Ra
- Double-blind, randomized, placebo-controlled trial of inhaled pitrakinra in 534 patients:
  - Significant reduction in exacerbations rates and symptom scores in patients with eosinophilia
- Analysis of single nucleotide polymorphisms in the IL-4Rα gene identified a subgroup of patients who were significantly more responsive to pitrakinra therapy
Targeting IL-13 in Asthma (Tralokinumab, Lebrikizumab)

**Tralokinumab**
- Modest improvement in FEV1 and decrease in B-agonist use
- Greater improvement in FEV1 and asthma symptoms control in IL-13 positive vs. IL-13–negative tralokinumab vs. placebo groups

**Lebrikizumab**
- Improved FEV1 compared with placebo
- Sub analysis-patients with high periostin had greater improvement in FEV1 (8.2%) vs. placebo vs. low level
Lebrikizumab: Change in FEV1 greatest in high periostin subgroup

Targeting IL-4 and IL-13 in Asthma (Dupilumab)

- **IL-4R alpha antagonist**: Blocks both IL-4 and IL-13
- Fewer asthma exacerbations and improved asthma symptoms and FEV$_1$
- Irrespective of blood eosinophil count

Wenzel et al Lancet 2016
Targeting IL-4 and IL-13 in Asthma
(Dupilumab)
Tumor Necrosis Factor-α (TNF)

- TNF-α is proinflammatory effects on eosinophils, neutrophils, T cells, epithelial cells and endothelial cells

- TNF-α may contribute to airway hyperreactivity, airway remodeling and steroid resistance in asthma
Targeting TNF-α in Asthma (infliximab, etanercept, golimumab)

**Etanercept**
- ACQ score, FEV₁, PEF and bronchial hyperresponsiveness to methacholine were significantly improved
- Significantly improved outcomes on symptoms and lung function

- Larger trials did not show significant differences in lung function, airway hyperresponsiveness, quality of life and exacerbation rates

**Golimumab**
- Did not improve lung function or decrease exacerbations
- Associated with increases in systemic infections and cancer-trial was stopped prematurely!
Summary

- Asthma is not one disease yet we have been treating it as one.

- Identification of multiple different phenotypes and associated biomarkers (IgE, FeNO, sputum and blood eosinophils, periostin) may help us better identify which patients may be appropriate for targeted biologic therapy.

- Treatment with biologic agents targeting IgE and Th2 cytokines IL-4, IL-5, and IL-13 are emerging as efficacious asthma therapies.
Nonatopic asthma
- Anti-IL-5 and other anti-Th2 [A]
- Omalizumab (POC) [C]

Atopic asthma with eosinophilia
- Omalizumab [A]
- Anti-IL-5 and other anti-Th2 [A]

Th2-low asthma
- Bronchial thermoplasty [B]
- Macrolides [C]
- Weight loss [B]

Atopic asthma
- Omalizumab [A]
Questions?
Discordant Symptoms

- EARLY SYMPTOM PREDOMINANT
  - Early onset, atopic
  - Normal BMI
  - High symptom expression.
- OBESE NON-EOSINOPHILIC
  - Later onset, female preponderance
  - High symptom expression.

Concordant Disease

- Symptom-based approach to therapy titration may be sufficient.
- Monitoring inflammation allows down-titration of corticosteroids.

Early Onset Atopic Asthma

- Concordant symptoms, inflammation & airway dysfunction.
- Monitoring inflammation allows targeted corticosteroids to lower exacerbation frequency.

Benign Asthma

- Mixed middle-aged cohort
- Well controlled symptoms and inflammation. Benign prognosis.

Inflammation Predominant

- Late onset, greater proportion of males.
- Few daily symptoms but active eosinophilic inflammation.

Primary Care Asthma

Secondary Care Asthma

Eosinophilic Inflammation

Symptoms

Phenotypes in Asthma Based on Cluster Analysis in the Severe Asthma Research Program

1. Mild atopic (75%)
2. Mild-moderate atopic (87%)
3. Late onset Non-atopic (51%)
4. Severe atopic (72%)
5. Severe with fixed airflow obstruction (68%)