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IL-1 and IL-17 Cytokine Families: New Targets for Allergy Treatment

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“Try this—I just bought a hundred shares.”
Disclosure Statement
Lanny J. Rosenwasser, MD

• RESEARCH STUDIES
  Novartis, National Institutes of Health

• CONSULTANT
  A-Z, Genentech/Roche, Novartis, Regeneron, Sanofi-Aventis, Tunitas
Learning Objectives

• Understand the concept of biotherapeutics

• Understand the application of biotherapeutics to allergic disease and asthma

• Review current preliminary studies of potential biotherapeutics in asthma

• Understand complex cascades of allergy/asthma pathogenesis and implications for biotherapeutics
**Biotherapeutics**

A field encompassing materials, usually proteins, produced by biological means including recombinant DNA technology. The agents and agonists/antagonists for treatment are usually biological.
Biotherapeutic Agents

- Monoclonal Antibodies
  - cell surface receptors, ligands, microorganisms
- Cytokines
- Soluble Receptors
- Natural and Synthetic Antagonists
- SiRNA
- Designer Modeled Small Molecules
- Oligonucleotides
- Transcriptional Inhibitors
Biotherapeutic Targets in Immune Allergic Disorders, Anti-IgE

**Innate Immunity Targets**
- IL-1, TNF, IL-6
- TLR, Adhesion Molecules
- IFN Modulation
- Chemokines

**Acquired Immunity Targets**
- Th$_2$, Th$_{17}$ Cytokines
- IL-2, 4, 5, 9, 13, 17, 25, 33
- Cellular
- DC, T, B

**Other Targets**
- TSLP
- Adipokines
- Growth and Differentiation Factors
Characteristics of Asthma

- Narrowing of the airways
- Airway obstruction
- Airway inflammation
- Increased airway responsiveness

Environmental factors

B lymphocyte
IgE
IL-3, IL-4, IL-13, IL-9

Mast cell

T lymphocyte
IL-3, IL-5, GM-CSF

Dendritic cell

Neutrophil

Eosinophil

Airway Effects
Bronchospasm
Acute Inflammation
Persistent Inflammation
Remodeling

Proinflammatory mediators

Initiation
Amplification
Propagation

Airway microenvironment

Environmental factors and Inflammatory products

mucus

Smooth muscle
Blood vessels

Airway Effects

Acute Inflammation

Persistent inflammation and development of remodeling
The role of the airway epithelium in asthma

- Viruses
- Particulates
- Allergens
- Toxins

(Goblet cell hyperplasia and excess mucus)

- TSLP, IL-25, IL-33

- IL-13, TGF-β, IL-17, Tryptase, Leukotrienes, Prostaglandins, etc.

- T cells
- Innate Lymphocytes
- Eosinophils
- Mast cells
- Neutrophils

Airway smooth muscle
CD4 subsets: generation and function

Th1 cells (IFN-γ)
- Host defense: many microbes
- Systemic and organ-specific autoimmune diseases

Th2 cells (IL-4, IL-5)
- Host defense: helminths
- Allergic diseases

Th17 cells (IL-17)
- Host defense: fungi, bacteria
- Organ-specific autoimmune diseases

Naïve CD4 T cell
- TGF-β, IL-2: Foxp3, Stat5

IFN-γ, IL-12: T-bet, Stat4
- IL-4: GATA3, Stat6
- TGF-β + IL-6: RORγt, Stat3

Regulatory T cells
Regulatory T Lymphocytes

CD4⁺, CD25⁺ T lymphocytes

- Regulatory
- Express TGFβ, IL-10
- Suppressive to other T cells
- Express Foxp3 transcription factor
- IL-35 growth factor
Other T Cell Subsets

• NKT/iNKT
• Gamma Delta T cells
• Th22-CD4 T cells
• Th9-CD4 T cells
• Tfh-CD4 follicular T Cells
Innate Lymphoid Cells

• ILC group 1- Th1 cytokines
• ILC group 2- Th2 cytokines
• ILC group 3- IL-17, IL-22
Complexity of Asthma

- Several orders of magnitude more complex
- Microbiome, Proteome, Transcriptome, Genome
- Tissues, Organs, Whole Body, Brain
- Third and Fourth Dimensions
Stepwise Approach for Managing Asthma in Patients Aged ≥ 12

### Intermittent Asthma

**Step 1**  
**Preferred:** Low-dose ICS (A)  
**Alternative:** Cromolyn (A), LTRA (A), Nedocromil (A), or Theophylline (B)  

**Step 2**  
**Preferred:** Low-dose ICS + LABA (A)  
**Alternative:** Medium-dose ICS (A)  

**Step 3**  
**Preferred:** Medium-dose ICS + LABA (B)  
**Alternative:** Low-dose ICS + either LTRA (B), Theophylline (B), or Zileuton (D)  

**Step 4**  
**Preferred:** High-dose ICS + LABA (B)  
**Alternative:** Consider Omalizumab for Patients Who Have Allergies (B)  

**Step 5**  
**Preferred:** High-dose ICS + LABA + Oral Corticosteroid AND Consider Omalizumab for Patients Who Have Allergies  

**Step 6**  
**Preferred:** High-dose ICS + LABA + Oral Corticosteroid AND Consider Omalizumab for Patients Who Have Allergies  

### Persistent Asthma: Daily Medication

Consult with asthma specialist if Step 4 care or higher is required. Consider consultation at Step 3.

### Quick-Relief Medication for All Patients

- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of systemic oral corticosteroids may be needed.  
- Use of SABA >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment  

### Each Step: Patient education, environmental control, and management of comorbidities

Steps 2-4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma

### Step Up If Needed

(first, check adherence, environmental control, and comorbid conditions)

Assess Control

### Step Down If Possible

(and asthma is well controlled at least 3 months)

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ICS = inhaled corticosteroids; LABA = long-acting β₂-agonist; LTRA = leukotriene receptor antagonist.

Anti IgE

• Targets IgE, FCeRI
• Rhu Mab - E25 - Omalizumab, Xolair
• Reduces Free IgE (allergen specific)
• Reduces Eos (sputum, BAL, blood)
• Reduces FCeRI and FCeRII expression
• Efficacy - Asthma, AR
Emerging Biotherapeutics

Anti-IL-1
Anti-IL-5
Anti-IL-17
Anti-IL-13
IL-1 and Allergy/Asthma

- IL-1 in a critical co-factor for Th2 and Th17 T cell activation in vivo and in vitro for Humans and Mice

• Airway and tissue involvement n asthma and allergy

References

Adherent Cell Function in Murine T-Lymphocyte Antigen Recognition.

Detection of Alveolar Macrophage-Derived IL-8 in Asthma


Extended IL-1 Family

(Caspase 3 Dependent)

• IL-18 – shared receptor and genetics (IL-18bp)
• IL-32 – TNF inducer
• IL-33 – Ligand for ST2 Induces TH2 Cytokines
• IL-37 – Downregulation of IL-1 family activities
### IL-1 family members – Chr. 2q13

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<th>Other Name</th>
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<td>IL-1F10</td>
<td>IL-38</td>
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Successful
IL-1 targeted therapy

- Gout - acute and chronic
- Pseudogout
- Type 2 Diabetes
- Post MI remodeling
- Systemic onset juvenile idiopathic arthritis (Still’s)
- Adult onset Still’s disease
- Schnitzler’s Disease
Potential disease targets for IL-1 directed therapy

- Neutrophilic urticaria
  - Chronic urticaria
- Neutrophilic lung disorders
  - COPD
  - Neutrophilic asthma
  - Acute Chest syndrome
- Neutrophilic CNS disease
  - Acute Hemorrhagic Leukoencephalitis
Rilonacept

IL-1 TRAP

- Rilonacept: a dimeric fusion protein (251 kDa) that is a specific blocker of IL-1 - incorporating components required for IL-1 signalling
  - IL-1 receptor subtype
  - IL-1 receptor accessory protein
- Prolonged circulation half-life in-vivo (8.6 days)
- Approved for CAPS in 4/08
- Currently over 100 patients on therapy
Canakinumab ACZ885

- Fully human IgG1 anti-IL-1β mAb
- Direct binding to IL-1β
- Half life > 21 days
- No cross-reactivity with human IL-1α or IL-1Ra
- Approved for CAPS in 6/09
- Currently over 100 patients on therapy
CD4 subsets: generation and function

Th1 cells (IFN-γ)
- Host defense: many microbes
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Regulatory T cells
IL-17 Family

- 20-30 kDa
- IL-17A, IL-17F – profibrotic activate chemokines (IL-8) and IL-6
- IL-17E – IL-25
- IL-25 associated with eosinophilia, airways hyperresponsiveness
- Genetics of IL-17 family linked to asthma
## Therapy of Th17 Mediated Autoimmune Disease

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<tr>
<th>Antibody</th>
<th>Target</th>
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<tr>
<td>Ixekizumab</td>
<td>IL-17</td>
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<tr>
<td>Brodalumab</td>
<td>IL-17R</td>
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<tr>
<td>Tocilzumab</td>
<td>IL-6R</td>
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Psoriasis, RA, SLE
Allergy - 2030

- Systems Biology Approach to Allergic Cascades
- Bio Therapeutics
- Pharmacogenetic Profiling
- Early Intervention
INTERLEUKINS! "I hope this works Doc"
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