Disclosure Statement
Lanny J. Rosenwasser, MD

- RESEARCH STUDIES
  Genentech, Novartis, National Institutes of Health
- CONSULTANT
  A-Z, Genentech, Novartis, Regeneron, Sanofi-Aventis
- SPEAKERS’ BUREAU
  Alcon, A-Z, Genentech, Novartis

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
- Th1, Th2 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

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

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**

- **Step 1: Preventive Management**
  - Patient education, environmental control, and management of comorbidities

- **Step 2:**
  - SABA PRN (as needed for symptoms)

- **Step 3:**
  - Long-acting β2 agonist (LABA) + inhaled corticosteroid (ICS)

- **Step 4:**
  - LABA + Oral Steroids + Other controller medication

- **Step 5:**
  - Oral Steroids + Omalizumab (Anti-IgE)

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**Emerging Biotherapeutics**

- Anti-IL-1
- Anti-IL-5
- Anti-IL-17
- Anti-IL-13

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**Extended IL-1 Family**

- 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

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**Anti IgE**

- Targets IgE, FcεRI
- Rhu Mab - E25 - Omalizumab, Xolair
- Reduces Free IgE (allergen specific)
- Reduces Eos (sputum, BAL, blood)
- Reduces FcεRI and FcεRII expression
- Efficacy - Asthma, AR

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**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 in asthma and allergy

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**IL-1 family members – Chr. 2q13**

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**References**

- Allergic Cell Activation in Mouse T Cell Suppresses Allergen Recognition
- Allergen-Specific Phagocyte Responses in Human Volunteers
- Allergen, Neutrophils, and Lysozyme
- The American Journal of Respiratory and Critical Care Medicine

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Image credits: [Adapted from National Asthma Education and Prevention Program](http://www.nia.nih.gov/niahealth)
<table>
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<td>IL-1F10</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
IL-17 Family

- 20-30KD
- 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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Psoriasis, RA, SLE

Key Central Role of IL-5 in Asthma

Anti-IL-5 in Human Asthma: Reduction in Exacerbations

- Severe (CCS-dependent) asthma
- Sputum eosinophilia required for enrollment
- No improvement in FEV1, control symptoms
Anti-IL-5 in Human Asthma:

Allergy - 2030

- Systems Biology Approach to Allergic Cascades
- Bio Therapeutics
- Pharmacogenetic Profiling
- Early Intervention

Introducing the World Allergy Organization Journal
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