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Update on Anticytokines

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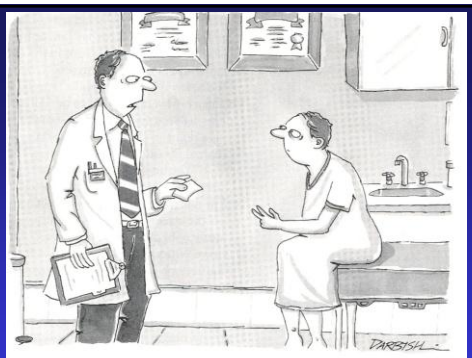


"Try this—I just bought a hundred shares."

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 ImmunityTargets

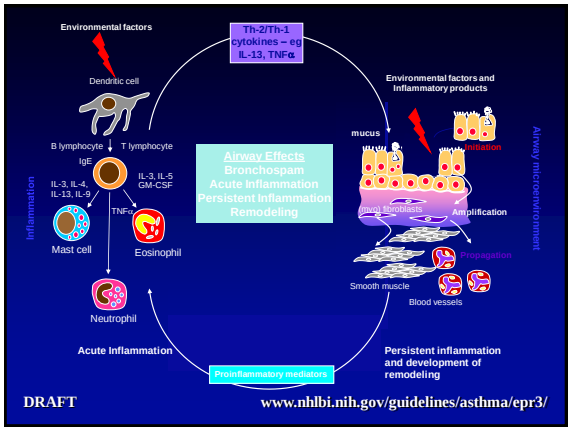
Th_2, Th_{17} Cytokines	IL-2, 4,5,9,13,17,25,33
Cellular	DC, T, B

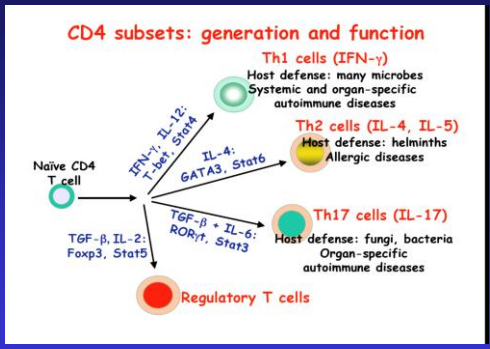
Other Targets
- TSLP
- Adipokines
- Growth and Differentiation Factors

Characteristics of Asthma

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

NHLBI, NAEPP, 1997.





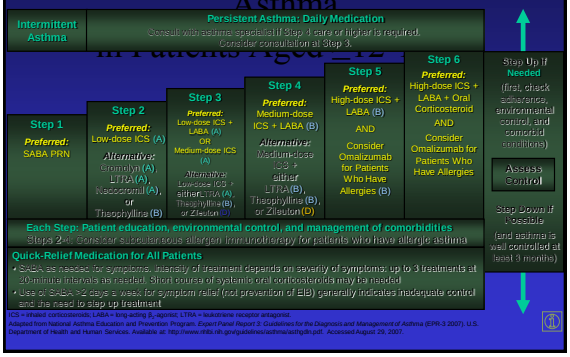
Regulatory T Lymphocytes

$CD4^+$, $CD25^+$ 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 in Patients Aged ≥12 Years



ICS = inhaled corticosteroids; LABA = long-acting β_2-agonist; LTRA = leukotriene receptor antagonist.

Adapted from National Asthma Education and Prevention Program. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma* (EPR-3 2007). U.S. Department of Health and Human Services. Available at: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf. Accessed August 29, 2007.

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-I
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. IV. Enhancement of Muriine T-Cell Antigen Recognition by Human Leukocitic Pyrogen. Rosenwasser, Lanny J. Dinarello, Charles A. Rosenthal Alan S. *The Journal of Experimental Medicine* – Vol. 150, 1979

Detection of Alveolar Macrophage-Derived IL-β in Asthma¹ Inhibition with Corticosteroids. Borish, Larry. Mascal James J. Dishuck, John. Beam, Martin , Richard J. Rosenwasser, Lanny J. *The American Association of Immunologists* Vol 149. 3076-3082; N0 9. November 1, 1992.

IL-1 acts directly on CD4 T cells to enhance their antigen-driven expansion and Differentiation. Shlomo , Z. Sasson, Ben. Hu-Li, Jane. Quiel, Juan. Cauchetaux, Stephane. Ratner, Maya. Shapira, Hana. Dinarello, Charles A. Paul, William E. *PNAS* April 28, 2009 Vol. 106 No. 17. 7119-7124

Cytokine . IL-1 acts on T cells to enhance the magnitude of in vivo immune Responses. S.Z. Sasson-Ben. Cauchetaux, Stephanie, Crank, Michelle. Jane, Hu-Li. Paul, William. *Elsevier Ltd.* 56 (2011) 122-125

Pathogen-induced human T_H17 cells produce IFN-γ or IL-10 and are regulated by IL-1β. Zielinski, Christina E. Mele , Federico. Aschenbrenner, Dominik, Jarrossay, David, Jarrossay, Francesca, Ronchi, Gattorno, Marco, Nonticelli, Silvia, Lanzavecchia, Antonio. Sallusto, Frederica. *Nature* 2012

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

New Name	Other Name	Property
IL-1F1	IL-1α	Agonist
IL-1F2	IL-1β	Agonist
IL-1F3	IL-1Ra	Receptor antagonist
IL-1F4	IL-18	Agonist
IL-1F5	FIL1δ	Anti-inflammatory
IL-1F6	FIL-1ε	Agonist
IL-1F7	IL-37	Anti-inflammatory
IL-1F8	IL-1H2	Agonist
IL-1F9	IL-1ε	Agonist
IL-1F10	IL1HY2	Receptor antagonist
IL-1F11	IL-33	Agonist

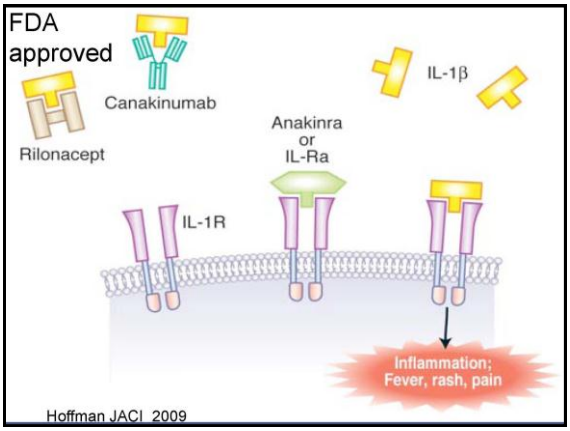
Gene	Cytokine
IL1F5	IL-36 Ra
IL-1F6	IL-36
1F8	IL-36
1F9	IL-36
IL-1F7	IL-37
IL-1F10	IL-38

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

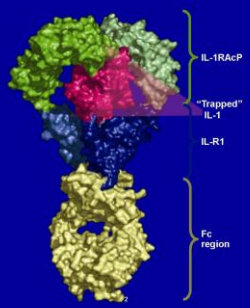
Potential disease targets for IL-1 directed therapy

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

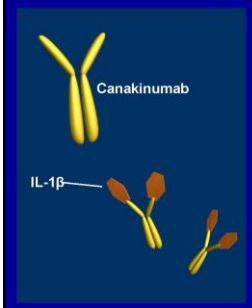


Rilonacept IL-1 TRAP

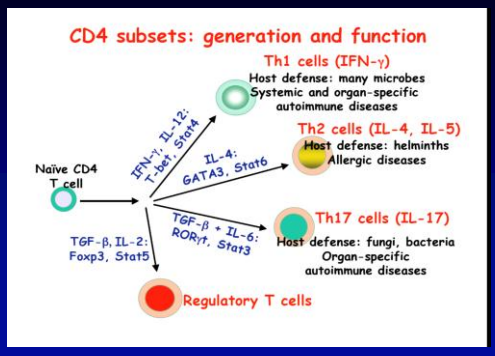
- Rilonacept: a dimeric fusion protein (251 kDa) that is a specific blocker of IL-1 - incorporating components required for IL-1 signalling
  - IL-1 receptor subtype
  - IL-1 receptor accessory protein
- Prolonged circulation half-life in-vivo (8.6 days)
- Approved for CAPS in 4/08
- Currently over 100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

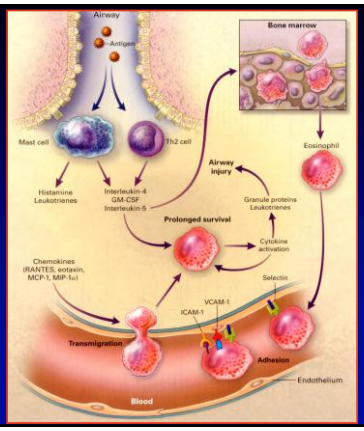
- 20-30 кd
- IL-17A, IL-17F – profibrotic activate chemokines (IL-8) and IL-6
- IL-17E – IL-25
- IL-25 associated with eosinophilia, airways hyperresponsiveness
- Genetics of IL-17 family linked to asthma

Therapy of Th17 Mediated Autoimmune Disease

Antibody	Target
Ixekizumab	IL-17
Brodalumab	IL-17R
Tocilzumab	IL-6R

Psoriasis, RA, SLE

Key Central Role of IL-5 in Asthma

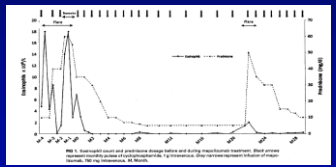


IL-5 pathway inhibition in the treatment of asthma and Churg-Strauss syndrome

TABLE 1. Promising anti–IL-5 drugs, anti–IL-5Rα drugs, or both

Drug	Target	Mode of action	Recent results	References
Mepolizumab	IL-5	Neutralizing	Steroid sparing and reduction of exacerbations in eosinophilic asthma; steroid sparing in patients with CSS and HES	1-4, 8
Reslizumab	IL-5	Neutralizing	Steroid sparing and reduction of exacerbations	9
MEDI-563	IL-5Rα	Cytotoxic and neutralizing	Reduction of eosinophilia	6, 7

HES, Hypereosinophilic syndrome.



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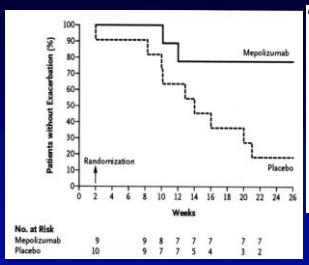
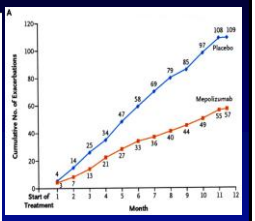
Anti-IL-5 in Human Asthma: Reduction in Exacerbations

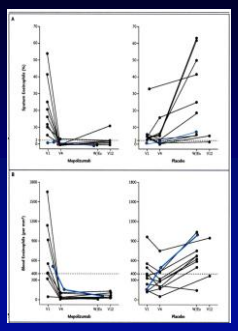


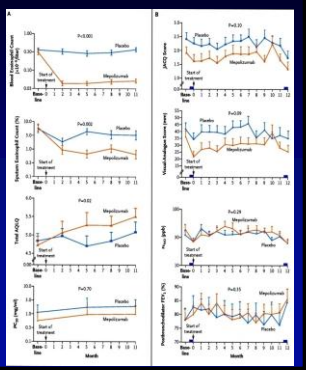


- Severe (CCS-dependent) asthma
- Sputum eosinophilia required for enrollment
- No improvement in FEV1, control, symptoms

Haldar P et al. *New Engl J Med* 2009;360:973
Nair P et al. *New Engl J Med* 2009;360:985

Anti-IL-5 in Human Asthma:





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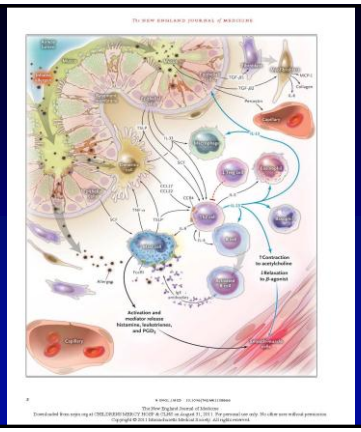

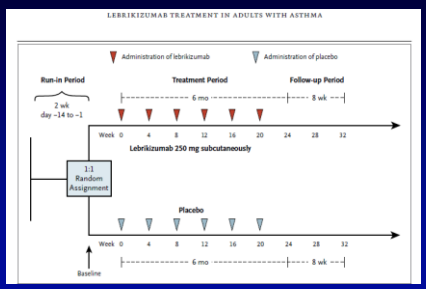

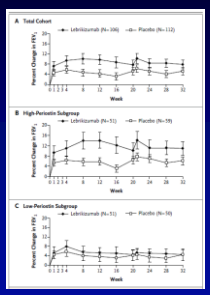

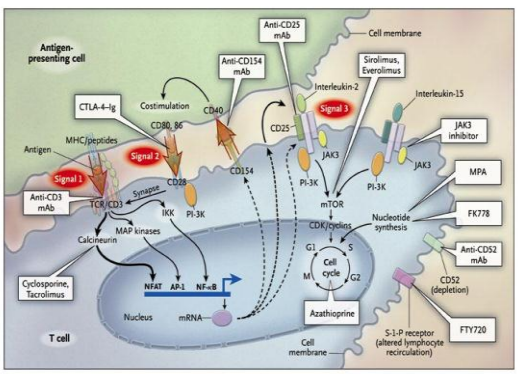

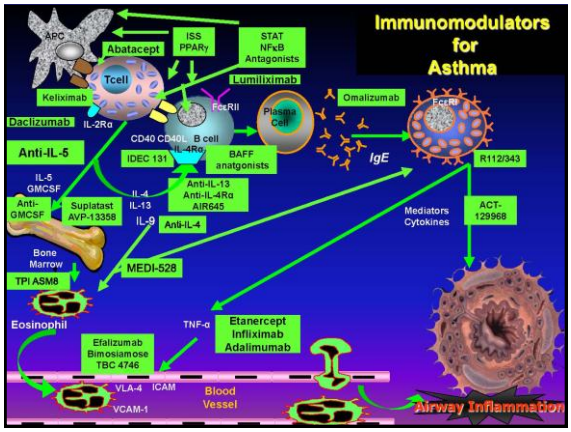

Allergy - 2030

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