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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 ImmunityTargets

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

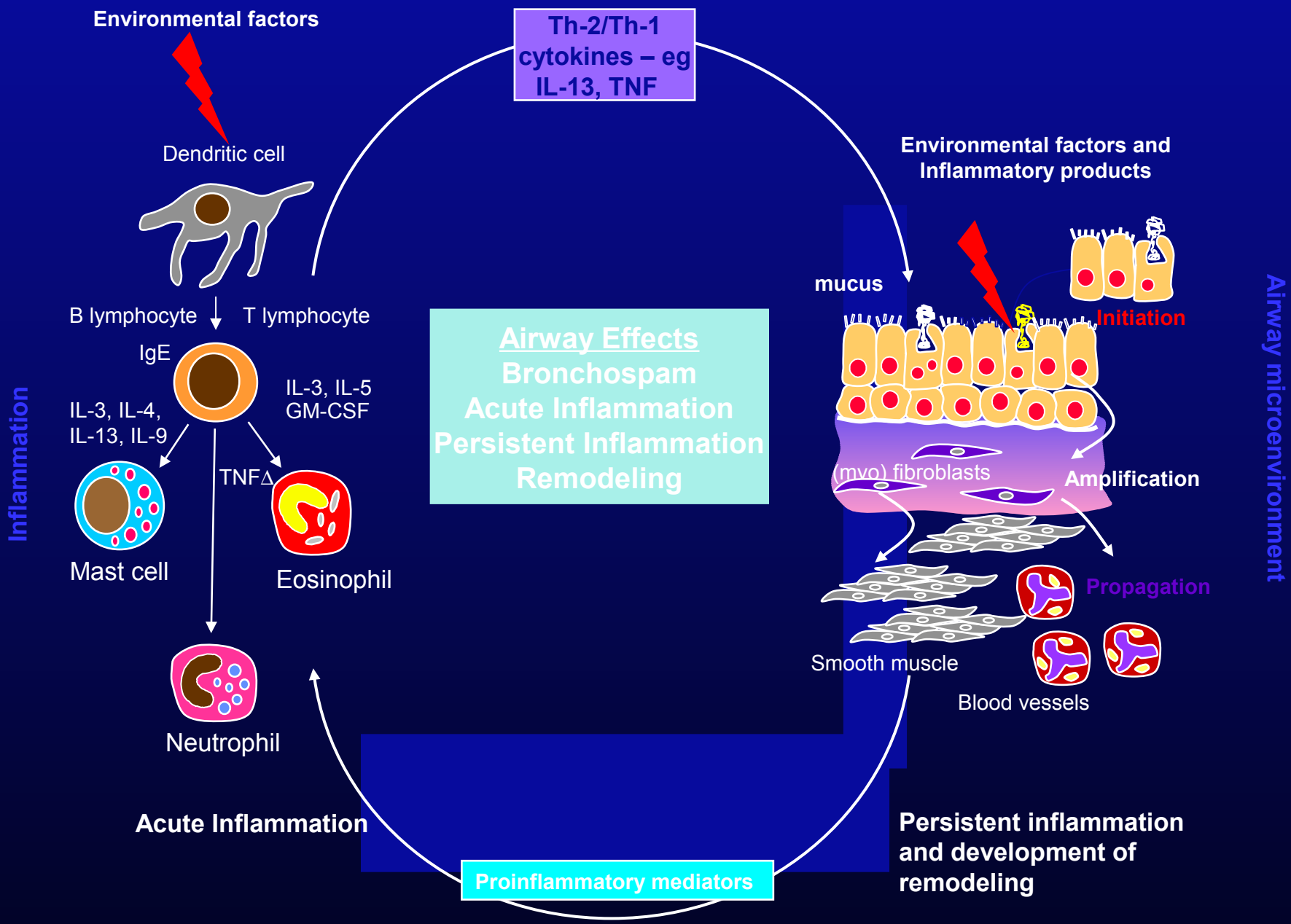
Other Targets

- TSLP
- Adipokines
- Growth and Differentiation Factors

Characteristics of Asthma

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

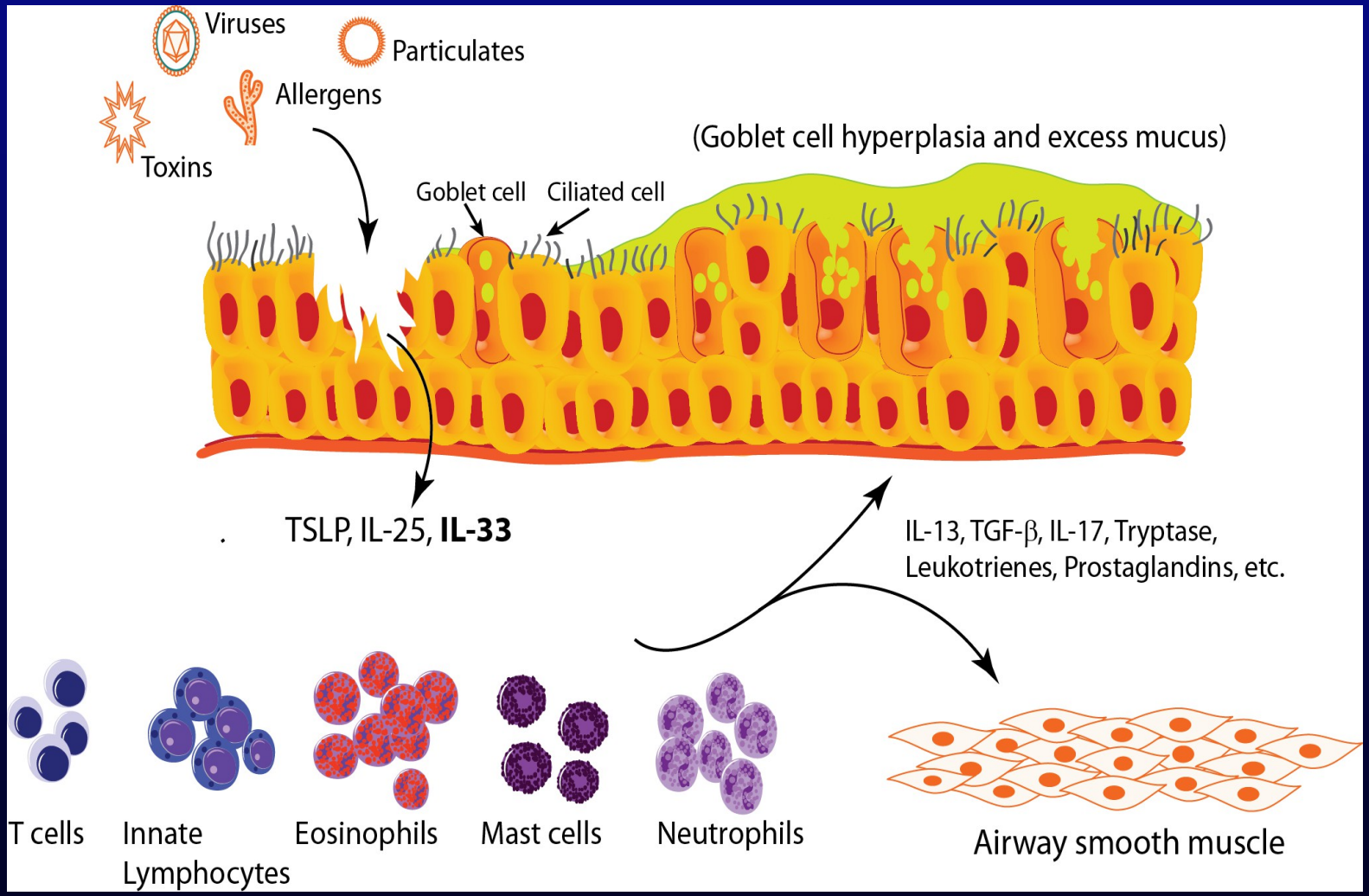
NHLBI, NAEPP, 1997.



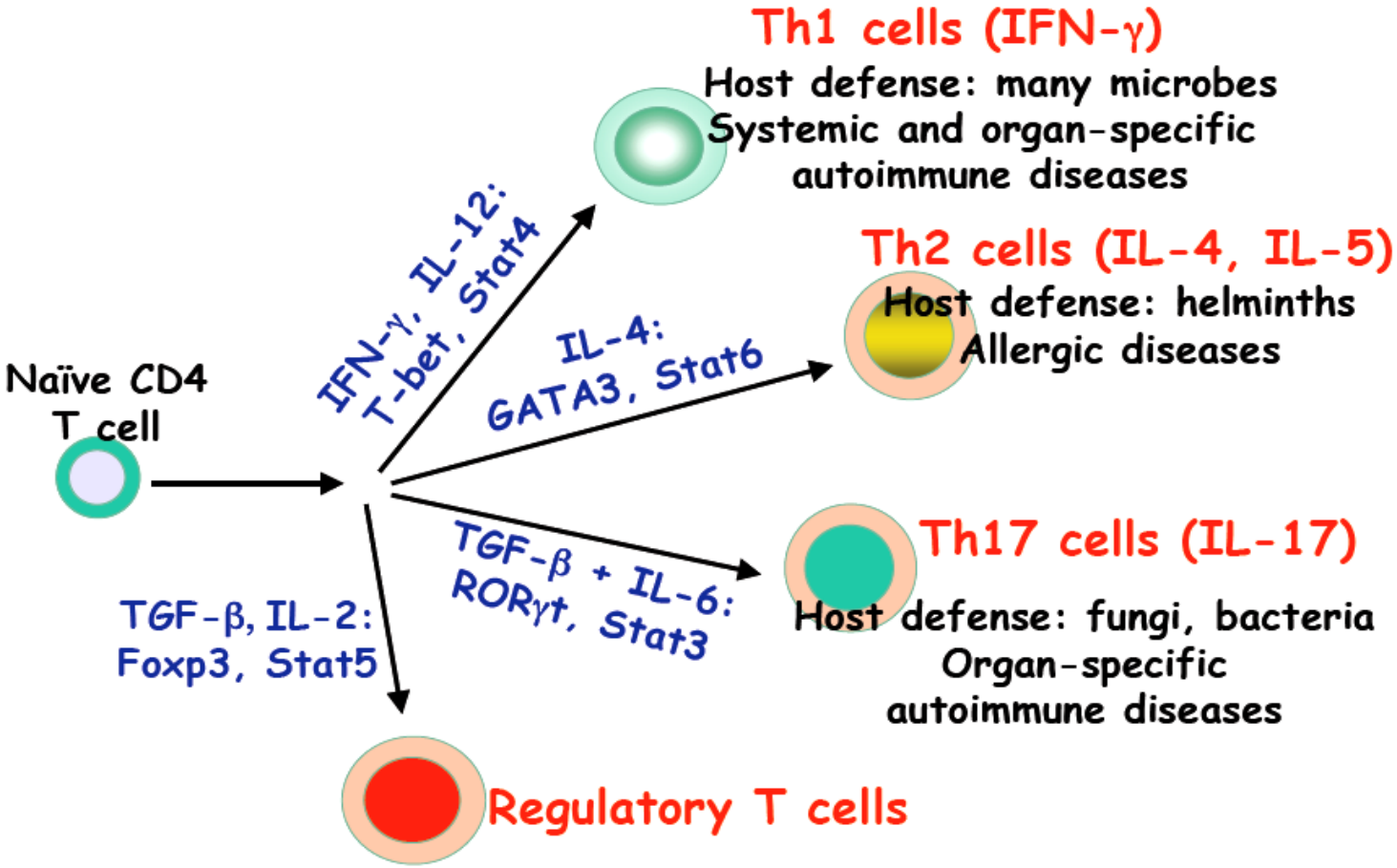
DRAFT

www.nhlbi.nih.gov/guidelines/asthma/epr3/

The role of the airway epithelium in asthma



CD4 subsets: generation and function



Regulatory T Lymphocytes

$CD4^+$, $CD25^+$ T lymphocytes

- Regulatory
- Express TGF ✔, 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 Years

Intermittent Asthma

Persistent Asthma: Daily Medication

Consult with asthma specialist if Step 4 care or higher is required.

Consider consultation at Step 3.

Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
Preferred: SABA PRN	***Preferred:*** Low-dose ICS (A)	***Preferred:*** Low-dose ICS + LABA (A) OR Medium-dose ICS (A)	***Preferred:*** Medium-dose ICS + LABA (B)	***Preferred:*** High-dose ICS + LABA (B) AND Consider Omalizumab for Patients Who Have Allergies (B)	***Preferred:*** High-dose ICS + LABA + Oral Corticosteroid AND Consider Omalizumab for Patients Who Have Allergies
	Alternative: Cromolyn (A), LTRA (A), Nedocromil (A), or Theophylline (B)	***Alternative:*** Low-dose ICS + either LTRA (A), Theophylline (B), or Zileuton (D)	***Alternative:*** Medium-dose ICS + either LTRA (B), Theophylline (B), or Zileuton (D)		

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)

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

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

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

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 Human and Health 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**

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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 alpha
1F8	IL-36 beta
1F9	IL-36 gamma
IL-1F7	IL-37
IL-1F10	IL-38

Successful IL-1 targeted therapy

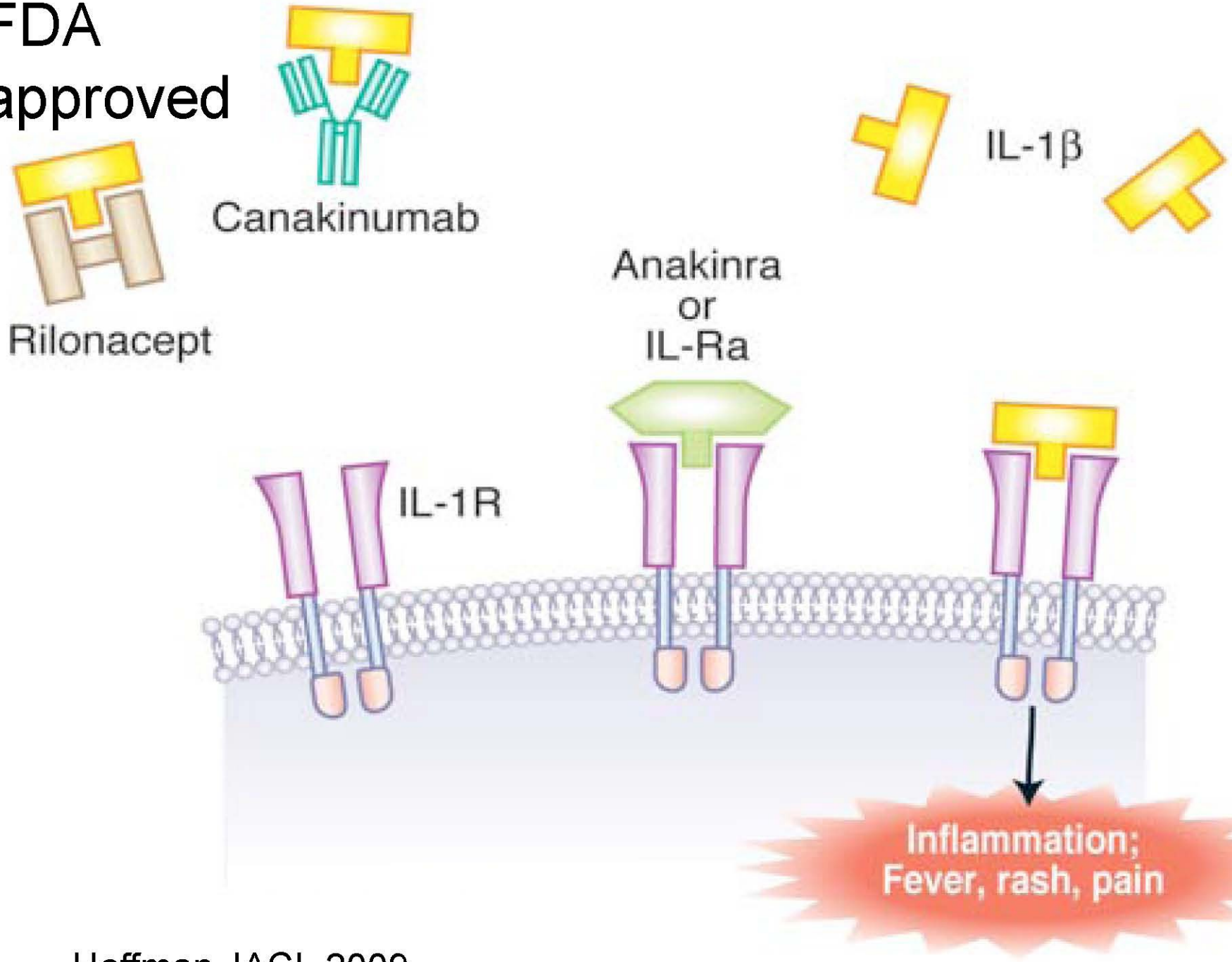
- Gout - acute and chronic
- Pseudogout
- Type 2 Diabetes
- Post MI remodeling

- 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

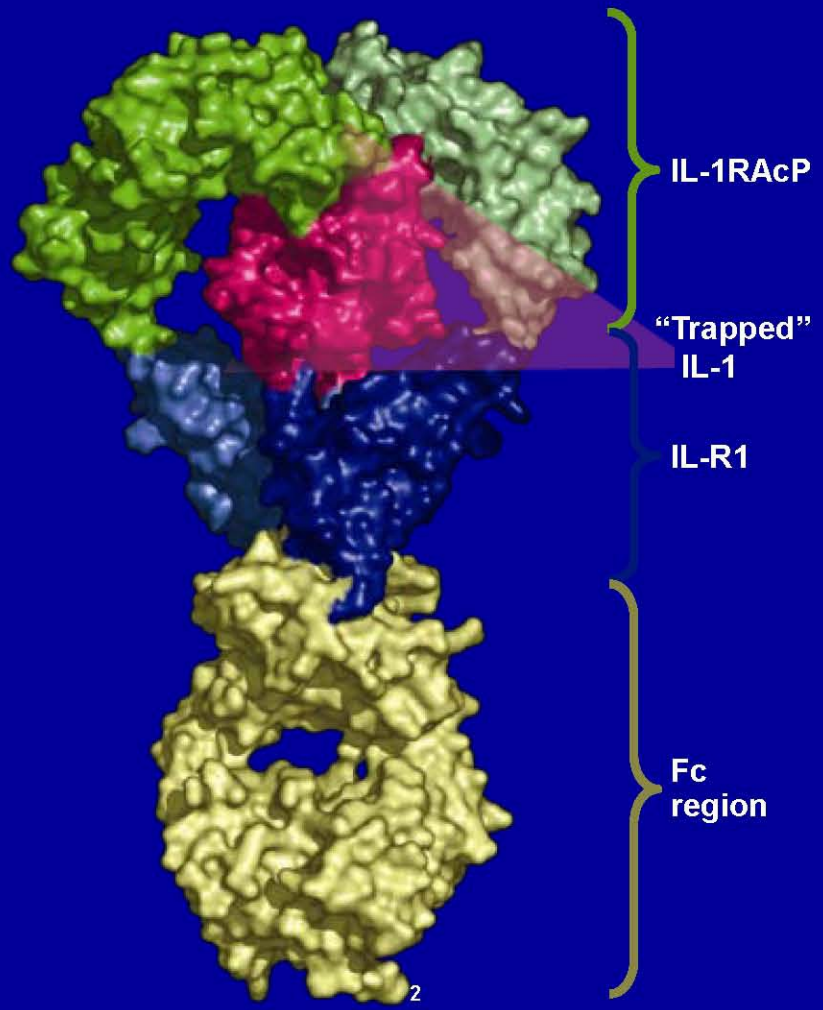
FDA approved



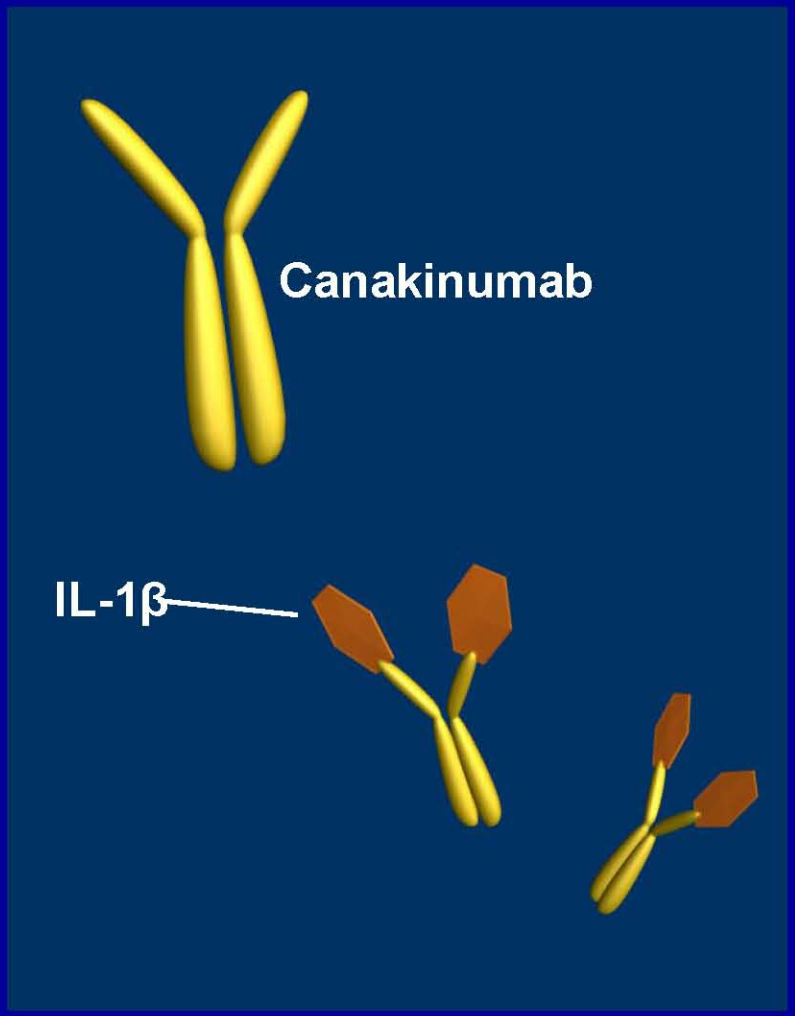
Hoffman JACI 2009

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



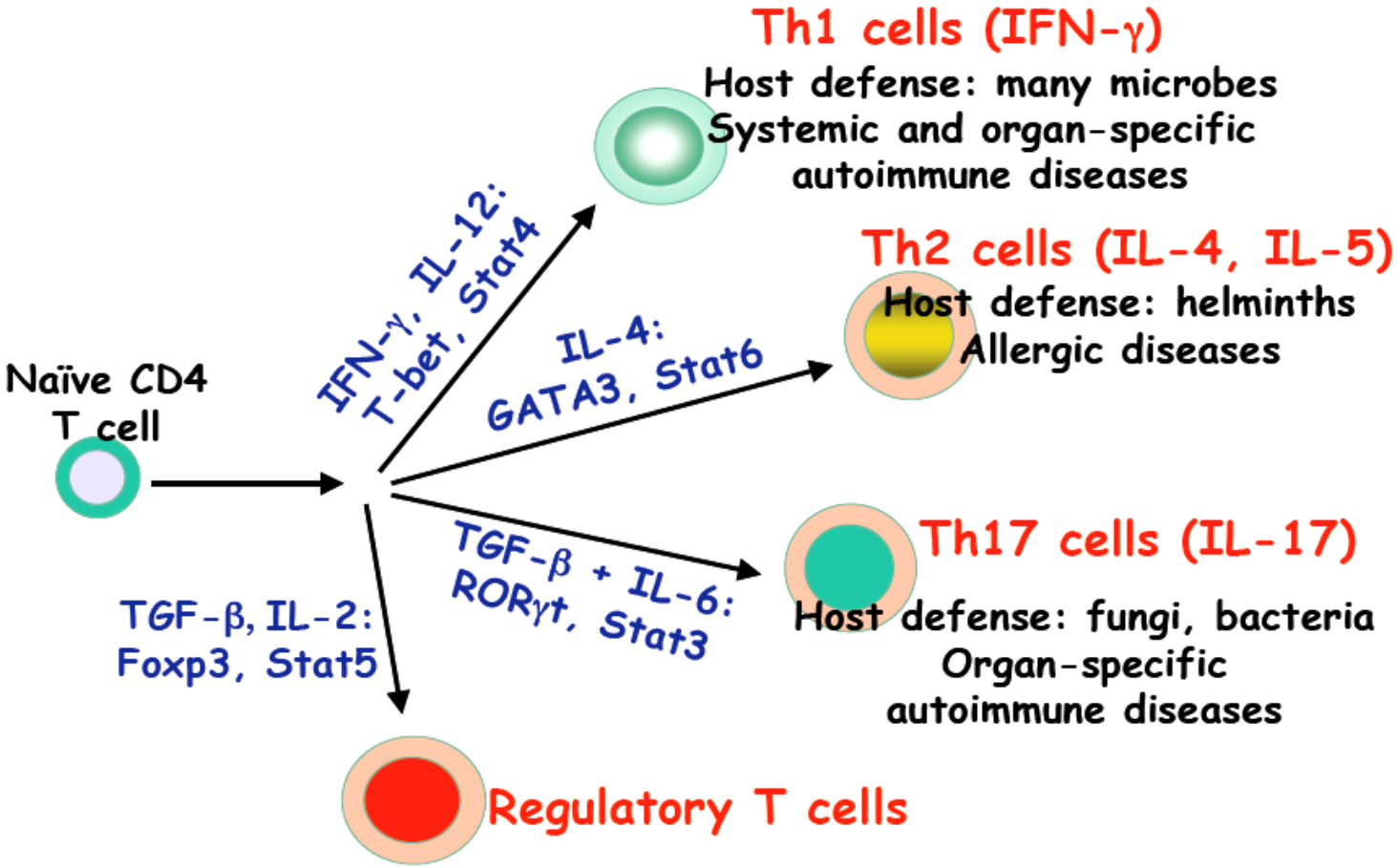
Canakinumab ACZ885



- 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



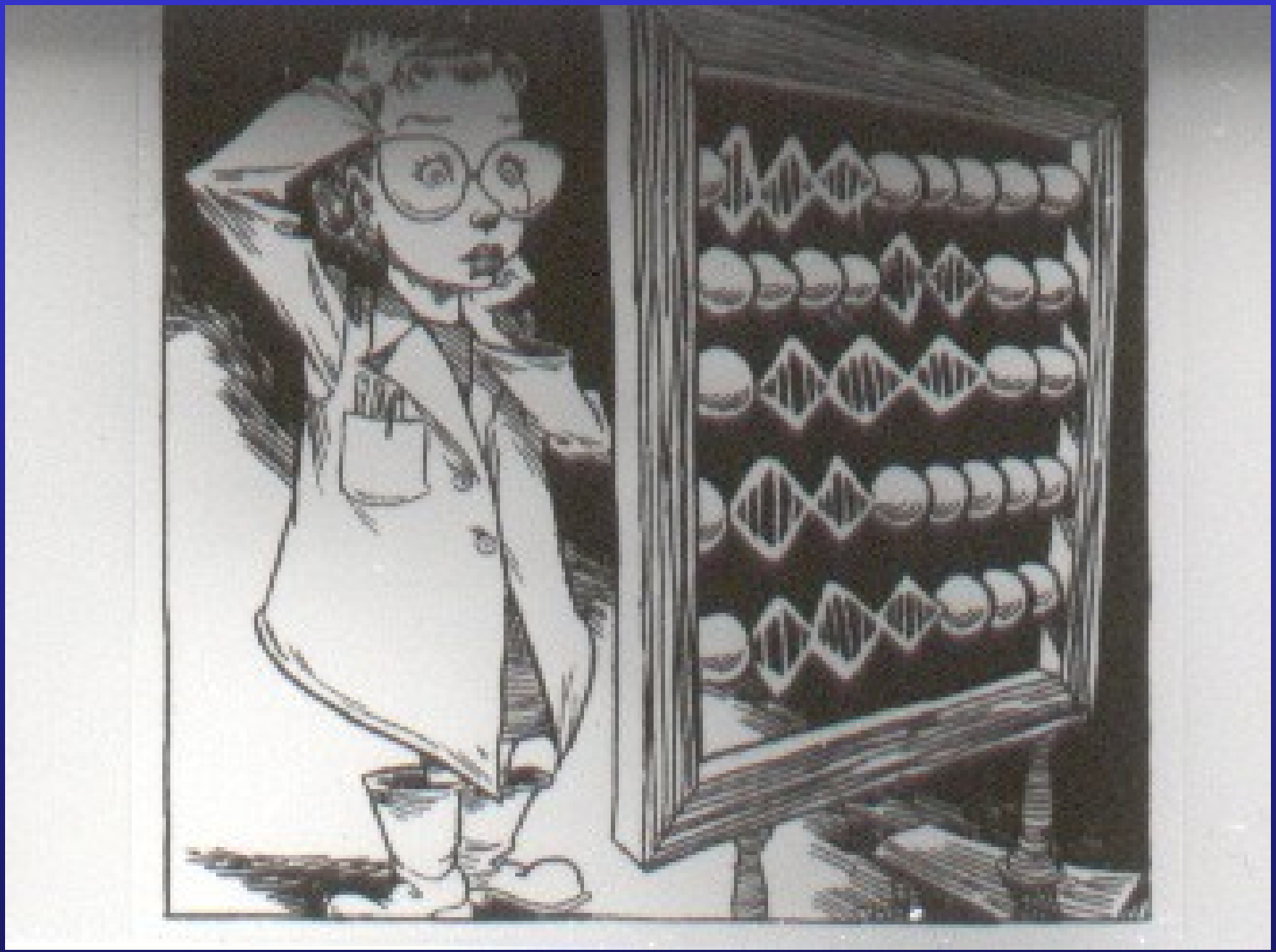
IL-17 Family

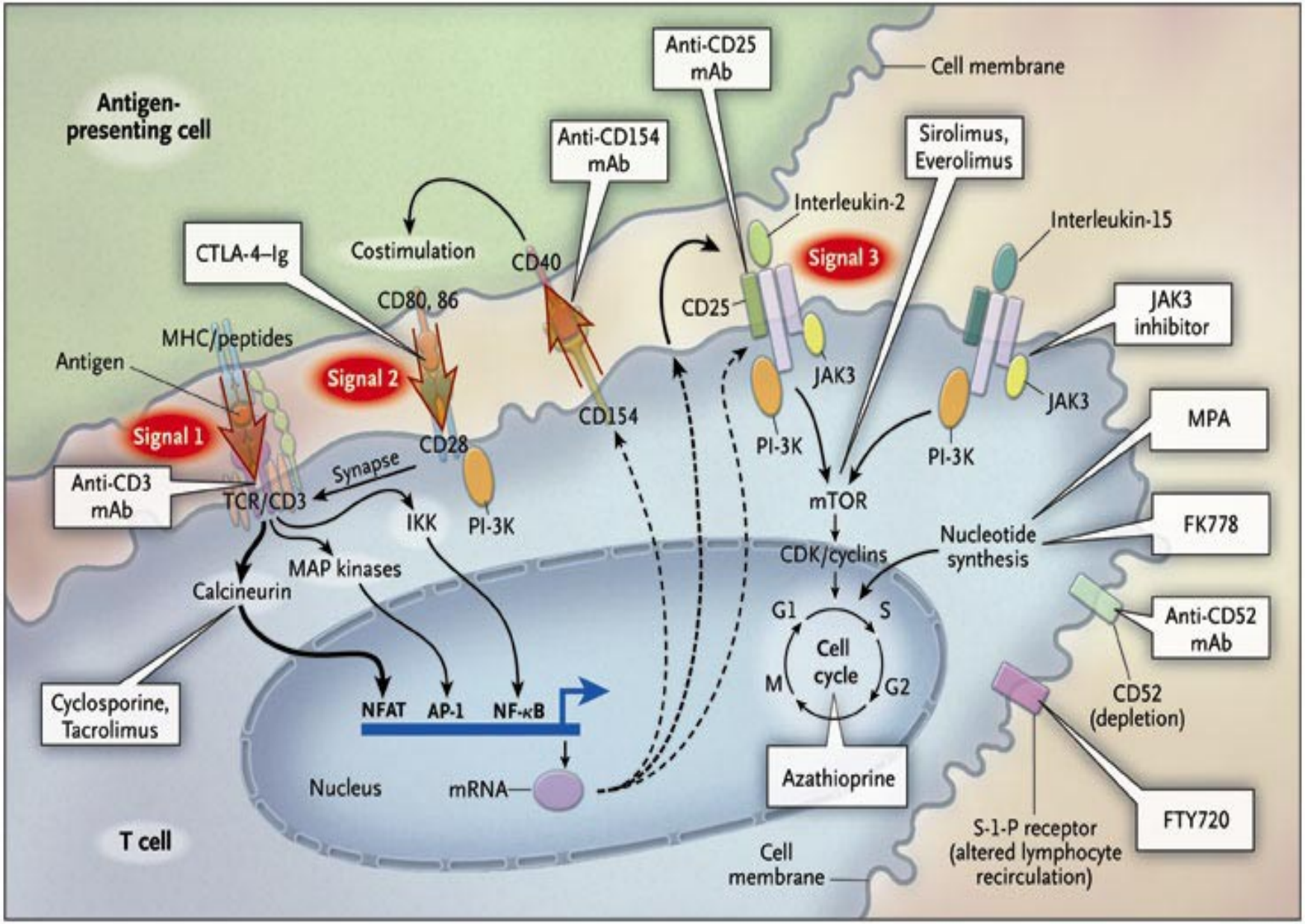
- 20-30 кd
- IL-17A, IL-17F – profibrotic activate chemokines (IL-8) and IL-6
- IL-17E – IL-25
- IL-25 associated with eosinophilia, airways hyperresponsiveness
- Genetics of IL-17 family linked to asthma

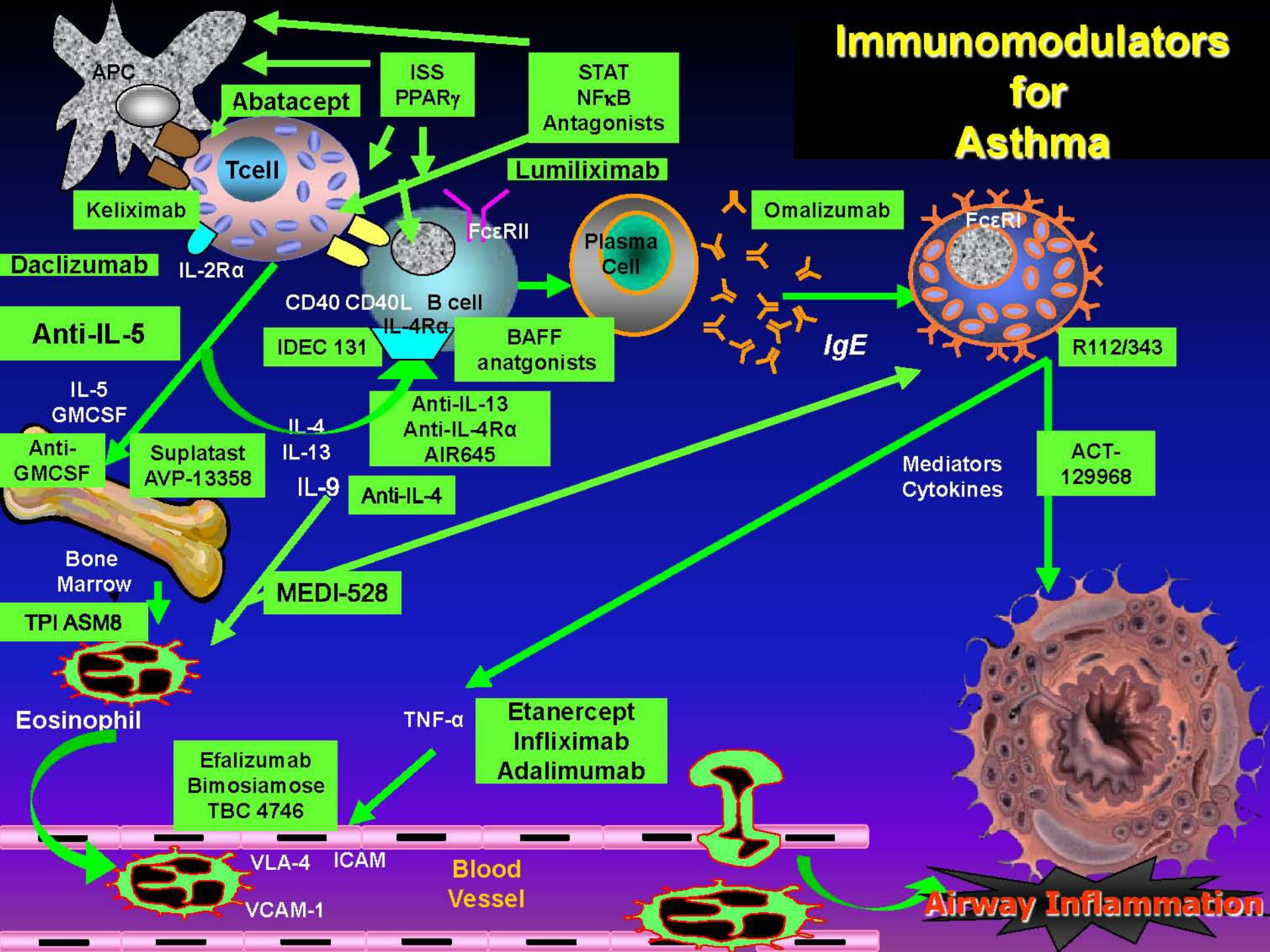
Therapy of Th17 Mediated Autoimmune Disease

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

Psoriasis, RA, SLE

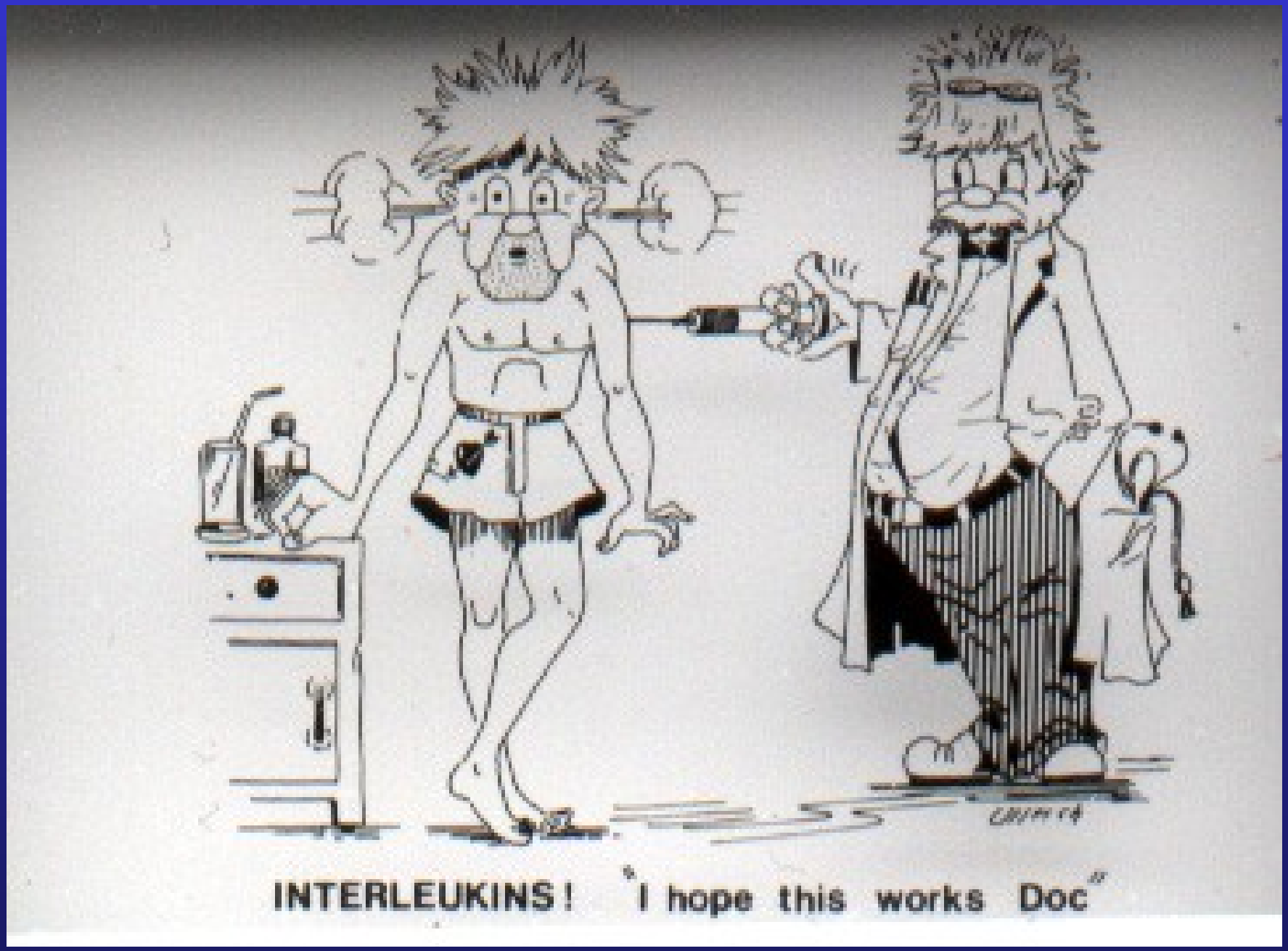



Antigen-presenting cell
Anti-CD25 mAb
Cell membrane
Anti-CD154 mAb
Sirolimus, Everolimus
Interleukin-2
Interleukin-15
CTLA-4–Ig
Costimulation
CD40
Signal 3
CD80, 86
CD25
JAK3 inhibitor
MHC/peptides
Antigen
Signal 2
JAK3
JAK3
MPA
CD154
Signal 1
CD28
PI-3K
PI-3K
Synapse
Anti-CD3 mAb
TCR/CD3
IKK
PI-3K
mTOR
FK778
Nucleotide synthesis
MAP kinases
CDK/cyclins
Calcineurin
G1
S
Anti-CD52 mAb
Cell cycle
M
G2
Cyclosporine, Tacrolimus
NFAT
AP-1
NF-κB
CD52 (depletion)
Azathioprine
Nucleus
mRNA
FTY720
T cell
S-1-P receptor (altered lymphocyte recirculation)
Cell membrane


Immunomodulators for Asthma
APC
Abatacept
ISS
PPARγ
STAT
NFκB
Antagonists
Tcell
Lumiliximab
Keliximab
FcεRII
Plasma Cell
Omalizumab
FcεRI
Daclizumab
IL-2Rα
CD40 CD40L B cell
IL-4Rα
IgE
Anti-IL-5
IDEC 131
BAFF
anatgonists
R112/343
IL-5
GMCSF
Anti-IL-13
Anti-IL-4Rα
AIR645
IL-4
IL-13
Anti-
GMCSF
Suplatast
AVP-13358
IL-9
Anti-IL-4
Mediators
Cytokines
ACT-
129968
Bone
Marrow
MEDI-528
TPI ASM8
Eosinophil
TNF-α
Etanercept
Infliximab
Adalimumab
Efalizumab
Bimosiamose
TBC 4746
VLA-4
ICAM
VCAM-1
Blood
Vessel
Airway Inflammation

Allergy - 2030

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


INTERLEUKINS!
"I hope this works Doc"

WISC 2014

2014 WAO International Scientific Conference


WAC 2015
XXIII World Allergy Congress
14–17 October 2015
Seoul, Korea
www.worldallergy.org/wac2015
A Meeting of
WAO
WORLD ALLERGY ORGANIZATION
A World Federation of Allergy, Asthma & Clinical Immunology Societies
in collaboration with
THE KOREAN ACADEMY OF ASTHMA, ALLERGY AND CLINICAL IMMUNOLOGY
1972