ADVANCES IN BIOLOGIC THERAPEUTICS IN ATOPIC DISEASE

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Objectives

- A brief review of atopic disease
- Review the history of immunotherapy; where we came from and where we are now.
- Define the term biologic
- What is a biomarker
- Understand what a monoclonal antibody is and the nomenclature
- Bonus material

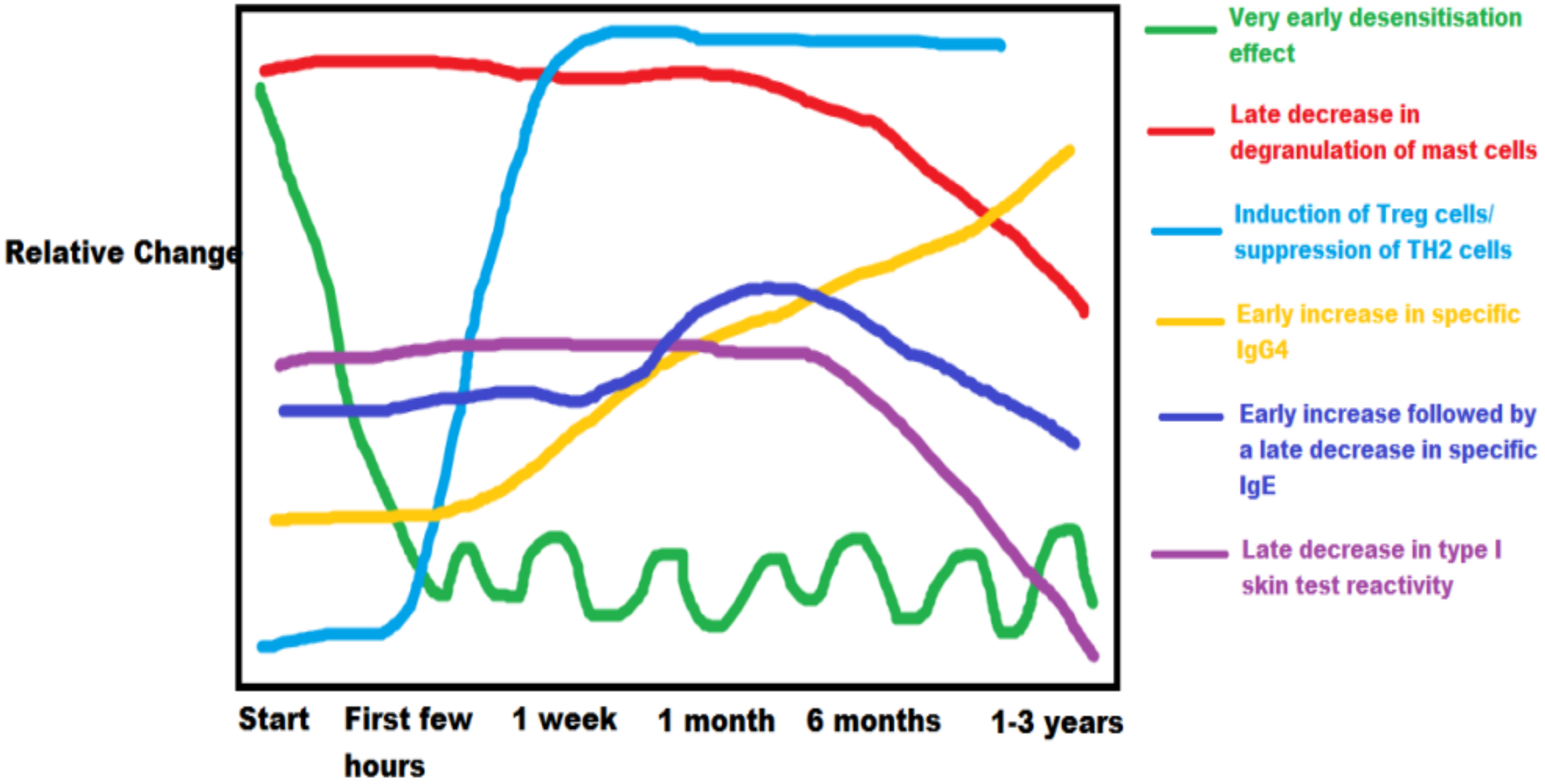
Atopic disease: Immunologic pathways are the key to diagnosis and treatment

- Allergic rhinitis
- Atopic dermatitis/eczema
- Asthma
- Food allergy
- Urticaria

Immunotherapy: 100 years of proven success

- Regulatory T cells
- Increase in T regulatory cells (CD4+CD25+)
- Produce increased levels of IL-10 which suppresses TH2 (allergic) immune response
- Produce TGFβ which also decreases TH2 response
- Increase TH1 cytokine production (IFN γ)

- Immunoglobulin class switch deviation
- Increase in allergen specific IgA and IgG levels (esp. IgG4)
- Early rise in specific IgE followed by a decline


Relative Change
Start
First few hours
1 week
1 month
6 months
1-3 years
Very early desensitisation effect
Late decrease in degranulation of mast cells
Induction of Treg cells/ suppression of TH2 cells
Early increase in specific IgG4
Early increase followed by a late decrease in specific IgE
Late decrease in type I skin test reactivity

Then and Now

- TH1 Vs. TH2-is old nomenclature
- Now we talk more specifically about T2 High and T2 low

What is the definition of a BIOLOGIC?

- A biologic drug is a product that's produced from living organisms contains components of living organisms. Examples include vaccines or blood components.
- In the case of allergy and asthma, biologics monoclonal antibodies, allergy immunotherapy, Immunoglobulin G infusions.

How is a BIOLOGIC different from other therapies?

- A biologic is produced from a living organism
- In contrast, something like and inhaled corticosteroid or leukotriene inhibitor is something that would be synthesized in the lab.

THE BIOLOGIC NAME GAME

An introduction to the future of biotherapeutics

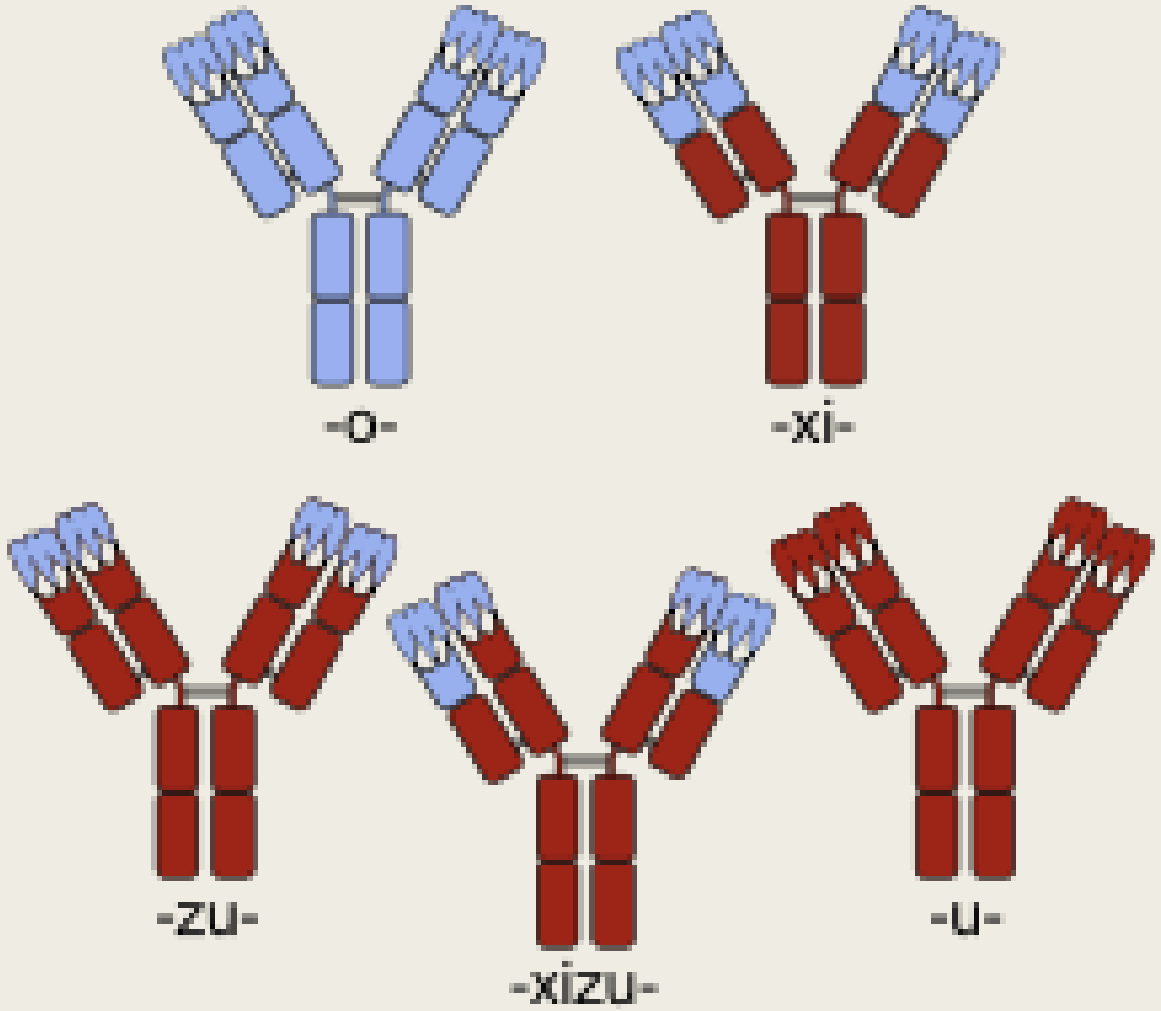
Monoclonal antibodies (mAb's)

- Lab produced antibodies that target a specific protein involved in a disease
- mAbs are created typically by injecting a mouse with target protein found in humans
- The mouse makes antibodies from B lymphocytes to this protein
- These antibodies (b lymphocytes) are harvested
- A hybridoma is produced which then divides repeatedly producing multiple clones (aka monoclonal antibodies)

- In order to get around the issue of the human recipient creating antibdoies to the biologic, the antibodies are “humanized” by replacing as much of the mouse portion of the antibody as possible

STEM=MAB

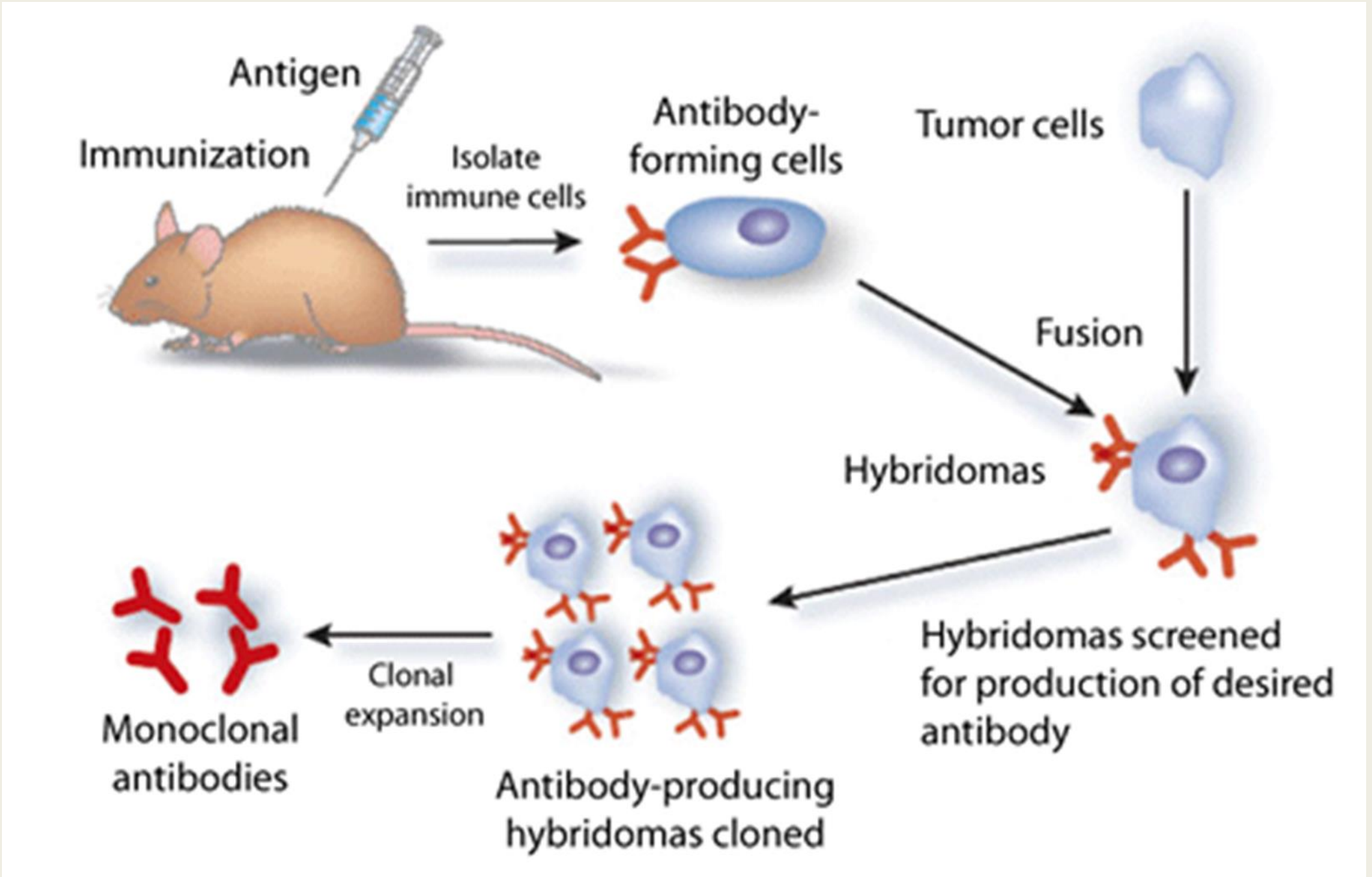
- SUBSTEMS:
- Mouse=O
- Human=U
- Humanized=ZU
- Chimeric=XI
- Chimeric humanized=XIZU



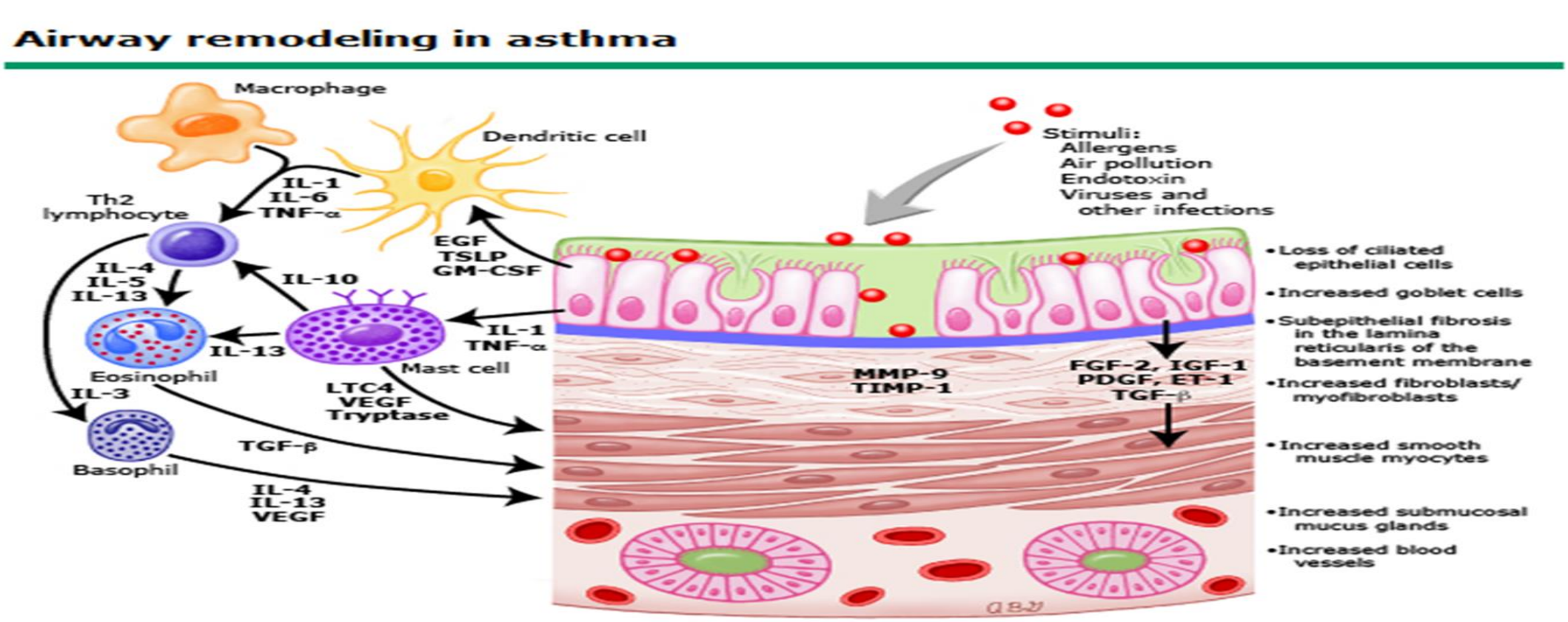
- The prefix carries no special significance, but is unique for each drug.

Subsets for target

- LI/LU=immune system/lymphocyte
- CI (r)=circulatory system
- NE (r)=Nervous system
- T=tumor
- And so on.....


Antigen
Immunization
Isolate immune cells
Antibody-forming cells
Tumor cells
Fusion
Hybridomas
Hybridomas screened for production of desired antibody
Antibody-producing hybridomas cloned
Clonal expansion
Monoclonal antibodies

Pathways in atopic disease that can be targeted by BIOLOGIC therapies

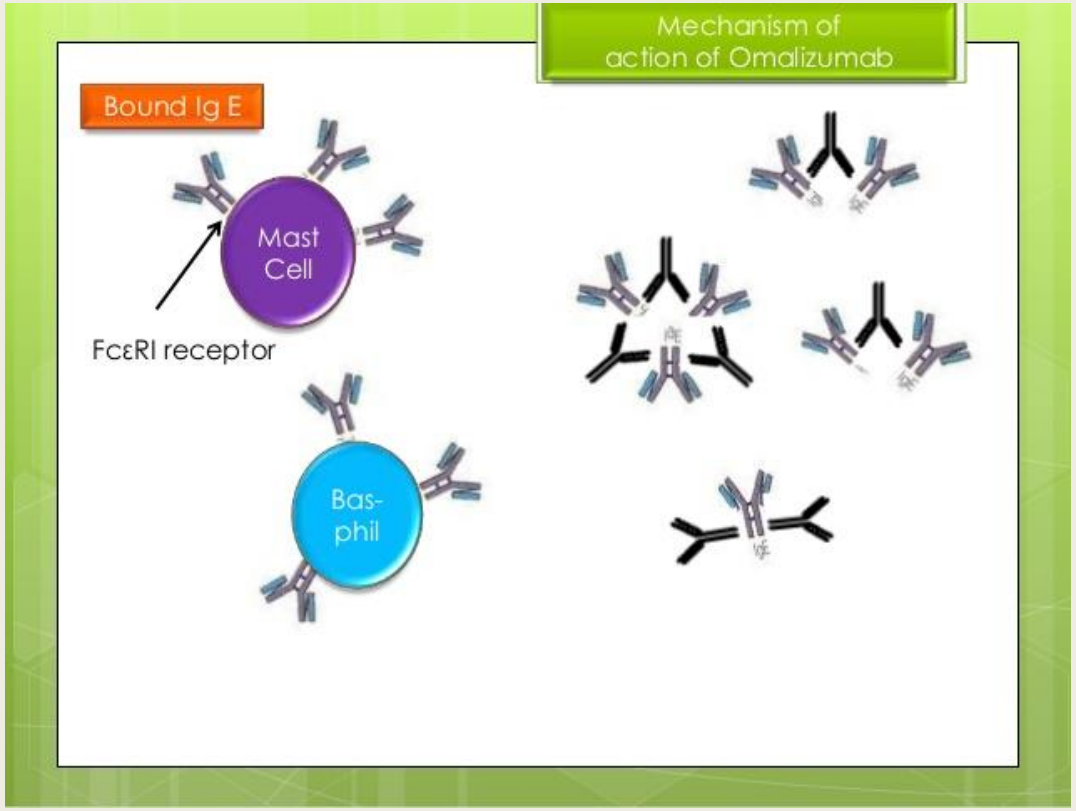


ET-1: endothelin-1; FGF-2: fibroblast growth factor; IGF-1: insulin-like growth factor-1; IL: interleukin; LTC4: leukotriene C4; MMP-9: matrix metalloproteinase-9; PDGF: platelet-derived growth factor; TGFβ: transforming growth factor β; TNFα: tumor necrosis factor α; TIMP-1: tissue inhibitor of metalloproteinase-1; EGF: epidermal growth factor; GM-CSF: granulocyte macrophage colony stimulating factor; VEGF: vascular endothelial growth factor.

BIOLOGIC	Target	Approval	Indication	Age	Home admin.
Omalizumab	IGE	2003	+ perennial allergy	≥6 yo	No approval, subcutaneous in office
Mepolizumab	IL-5	2015	Add on maintenance, eosinophilic phenotype	≥6 yo	Yes- subcutaneous at home or office
Resilizumab	IL-5	2016	Add on maintenance, eosinophilic phenotype	≥18 yo	No-Intravenous
Benralizumab	IL-5 R alpha	2017	Add on maintenance, eosinophilic phenotype	≥12 yo	Yes- subcutaneous at home or office
Dupilumab	IL-4 R alpha	2018	Add on main, steroid dependent regardless phenotype	≥12 yo	Yes
Tezepelumab	TSLP	TBD	Add on Main regardless phenotype		

Anti Ige (Omalizumab)

- Monoclonal antibody that binds the Fc portion of IGE and prevents activating the high-affinity IGE receptor (FcER1) on mast cells, dendritic cells and other cells.
- Numerous studies: reduced ICS dose, oral steroids and exacerbations/hospitalization (down by 25%) and improved QOL



Anti Ige (Omalizumab)

- Allergic asthma since 2003
- IGE range 70-300 IU/ml
- Perennial allergy
- No biomarker known that will predict good response
- Omalizumab is also used in chronic urticaria

IL-5

- Drugs are those that block the IL-5 pathway
- interleukin-5 is very important for eosinophil growth and differentiation.
- 3 available:
  - *Two, reslizumab and mepolizumab, target and block IL-5 itself*
  - *The other one is benralizumab and which binds to the IL-5 R-alpha which is present on eosinophils and basophils and actually causes antibody dependence cell-mediated cytotoxicity.*

IL 4 IL13

- Dupilumab works by effecting the IL-4 and IL-13 pathways, because it binds to the common alpha chain for signaling for those two cytokines, interleukins 4 and 13.
- It binds with the IL-4 alpha receptor and prevents the IL-4 or IL-13 from acting on that cell causing downstream effects.
- In the case of interleukin-4 that's important for switching from making IgM to IgE, among other things; and IL-13 is important for a number of different things including airway hyper-responsiveness.

TSLP-Thymic Stromal Lymphopoietin

- A newer biologic indicated for the treatment of atopic disease with it’s first approved indication being asthma.
- TSLP is an epithelial-cell-derived protein belonging to c

Identifying patients who are candidates for biologic medications

- Once you have identified a patient with severe atopic disease, the challenge becomes how to identify the best personalized treatment plan
- Issues include
  - *Optimizing control*
  - *Patient needs*
  - *Patient preference*
  - *Location of administration-home, office, infusion center*
  - *Identifying appropriate biomarkers*
  - *Expanding therapeutic options*
  - *Where to refer*

Initial considerations when choosing a biologic

- Adherence
- Side effects and safety
- Testing for biomarkers
- Has there been chronic steroid use over the last 3-6 months
- Other diagnosis to be considered: AERD, ABPA, Chronic rhinosinusitis, nasal polyps, atopic dermatitis, and so on…
- Is treatment with a biologic affordable?

Additional considerations with choosing a biologic

- Stop therapy that is ineffective
- Education and training on current medication administration
- Use of non biologics indicated or exhausted? (LABA, tiotropium, LAMA,LTRA, macrolides, low dose OCS with strategies to minimize side effects

What is a BIOMARKER

- A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic response to a therapeutic intervention
- Any substance, structure or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease
- Naturally occurring biologic materials

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