

清華大學
當代生命科學課程
2011年6月1日

新藥免疫療法
發展治療哮喘與過敏的抗體藥物

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我們應重視生命科學的跨領域教學



新竹清大與北京清大領先世界發展用於
工學院科系的生命科學教科書

Allergy: a very prevalent modern malady

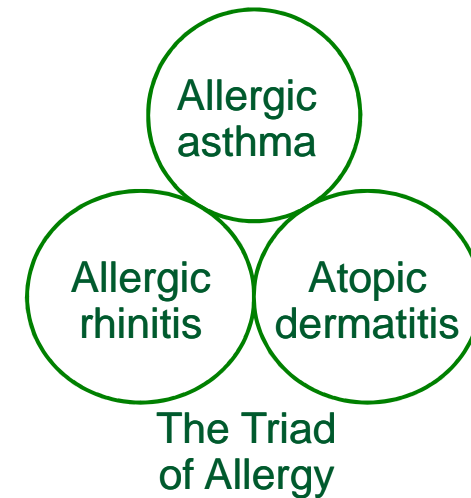
- Allergic asthma
- Atopic dermatitis
- Allergy to latex
- Others
- Allergic rhinitis
- Food allergy
- Allergy to drugs

1819 – the first description of a hay fever-like syndrome

Today – 20 to 40% of populations in economically advanced countries

Allergy: vast, diverse medical fields

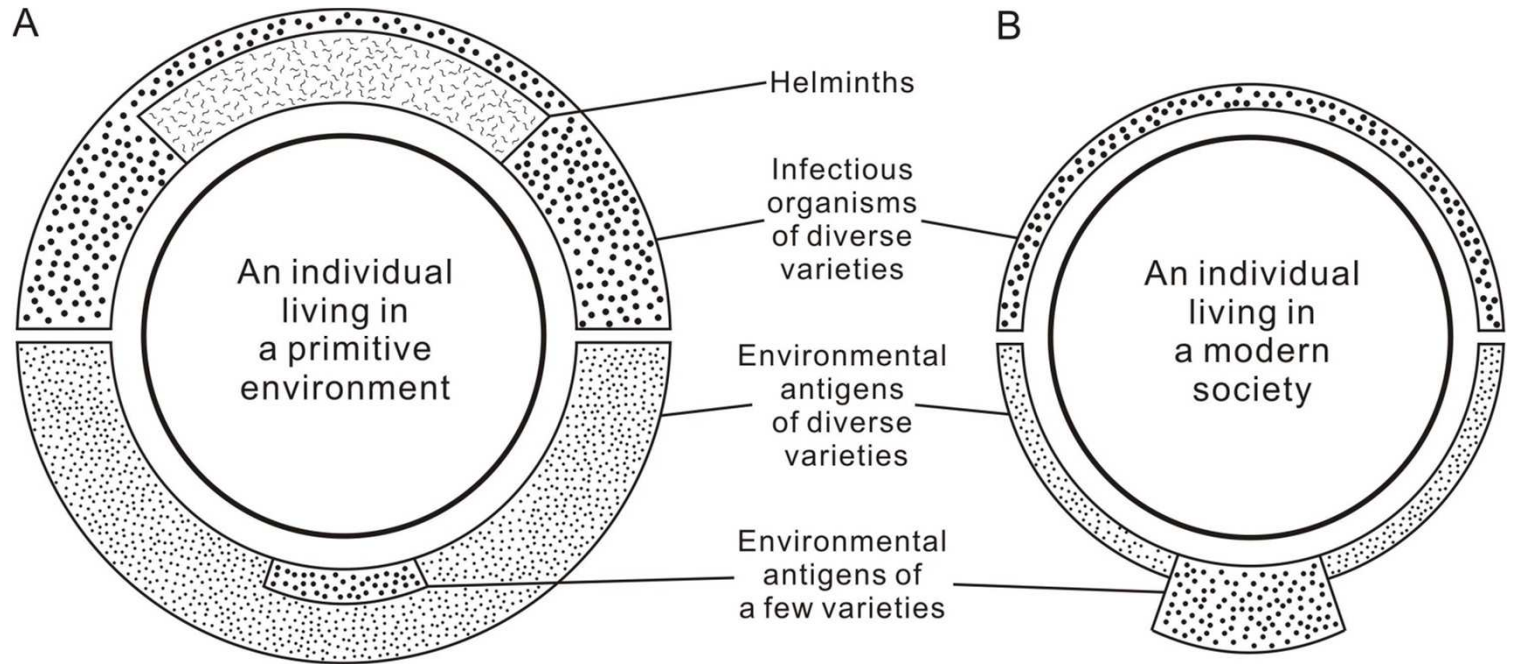
- Cared by doctors of different specialties
- Various societies, diverse journals
- Administered by NHLBI, NIAID, NIAMS in NIH, USA



Common drugs used for severe patients: corticosteroids

- High-dose corticosteroids have serious side effects.
- Some patients are still not controlled.

“Skewed Antigen Exposure” Theory

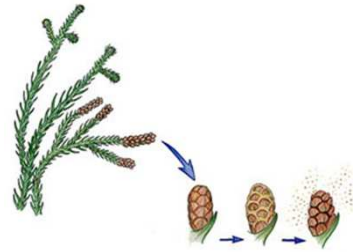


Cumulated environmental changes, skewed antigen exposure, and the increase of allergy.
Chang & Pan. Adv. Immunol. 98:39-83 (2008)

The most common allergens in our “artificial” world.



Dust mites



Pollens

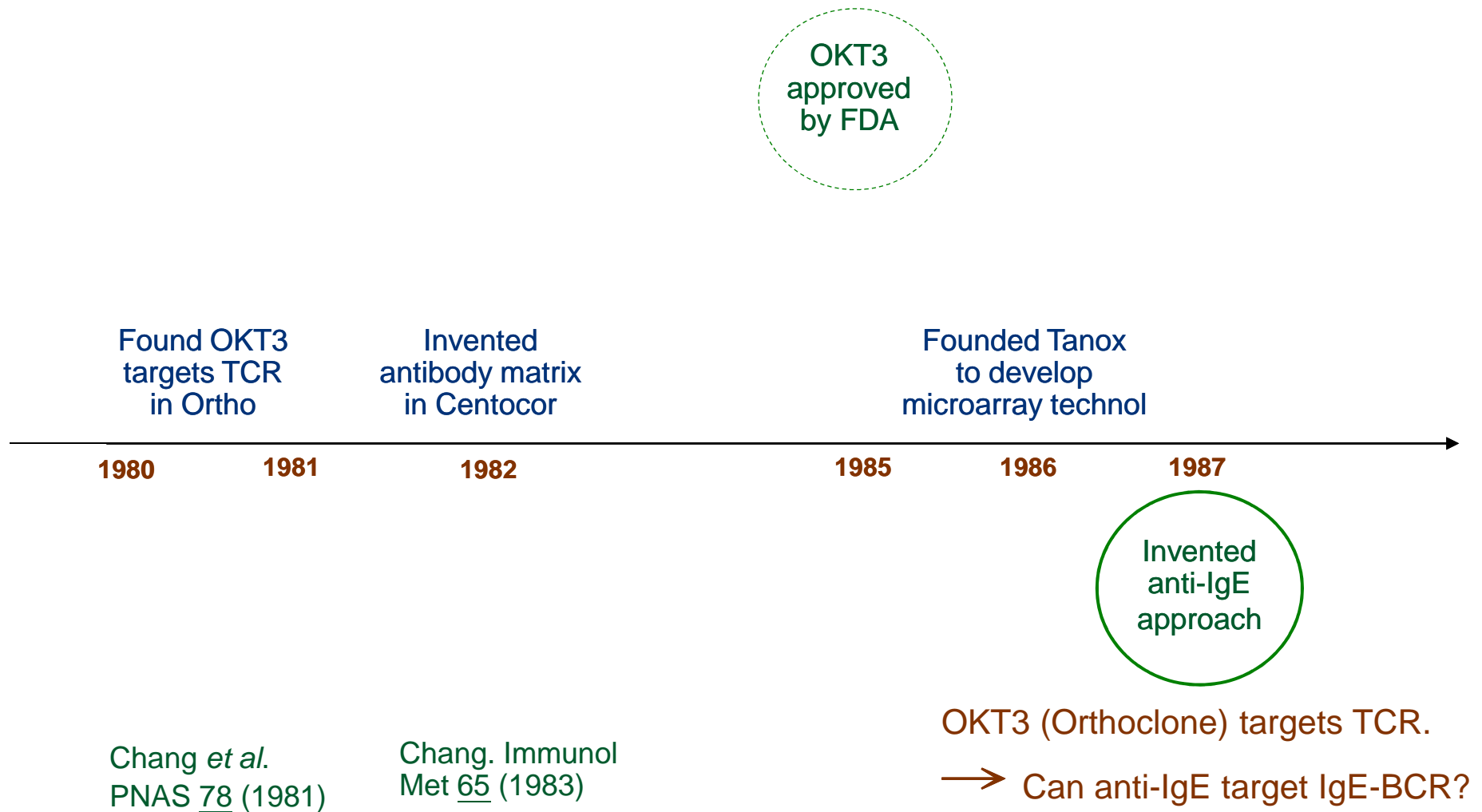


In “bio-deprived” indoor space, mites become the dominant antigen.

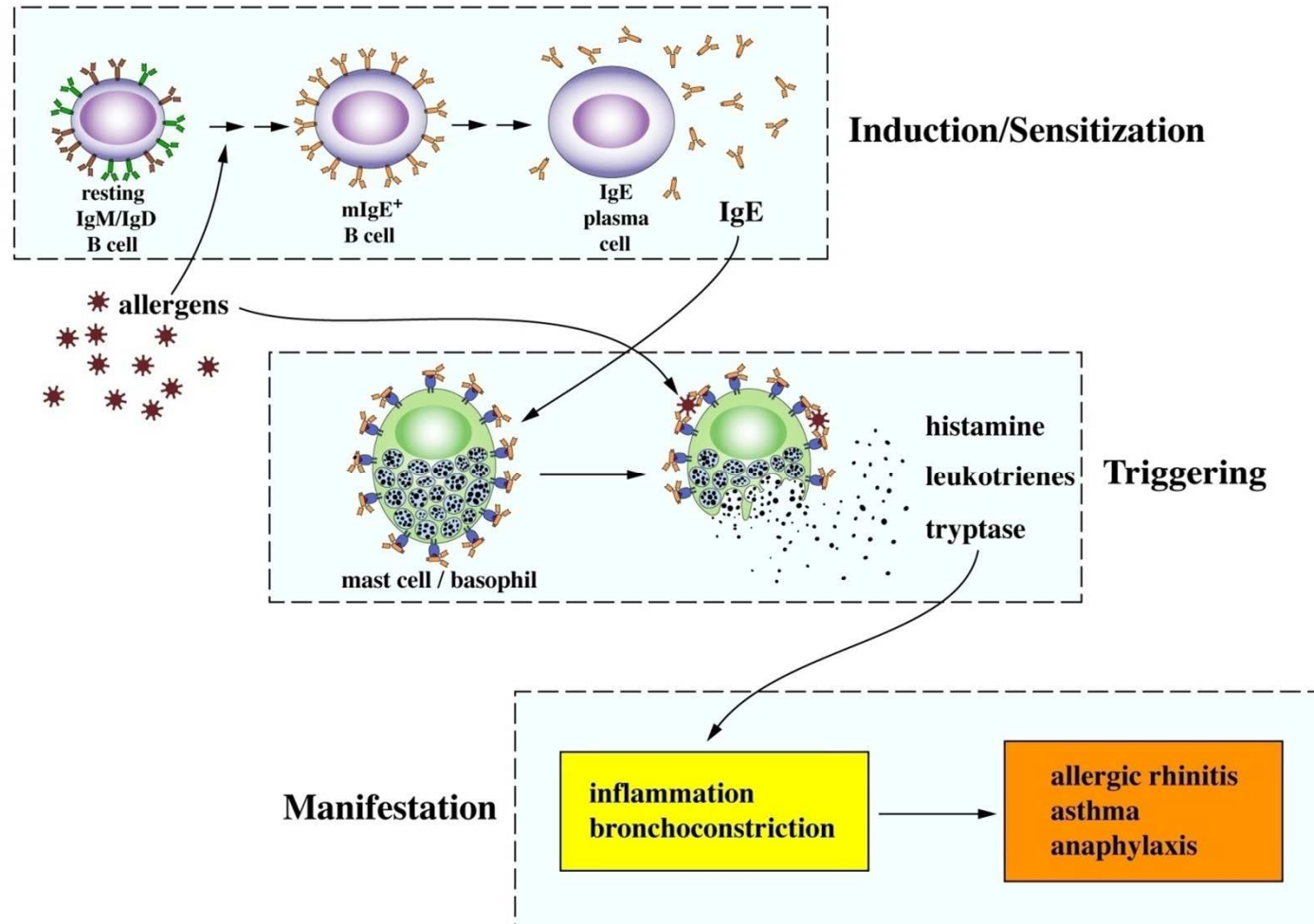


Sugi pollens are the dominant outdoor antigen in Japan.

Anti-IgE idea: inspiration from OKT3

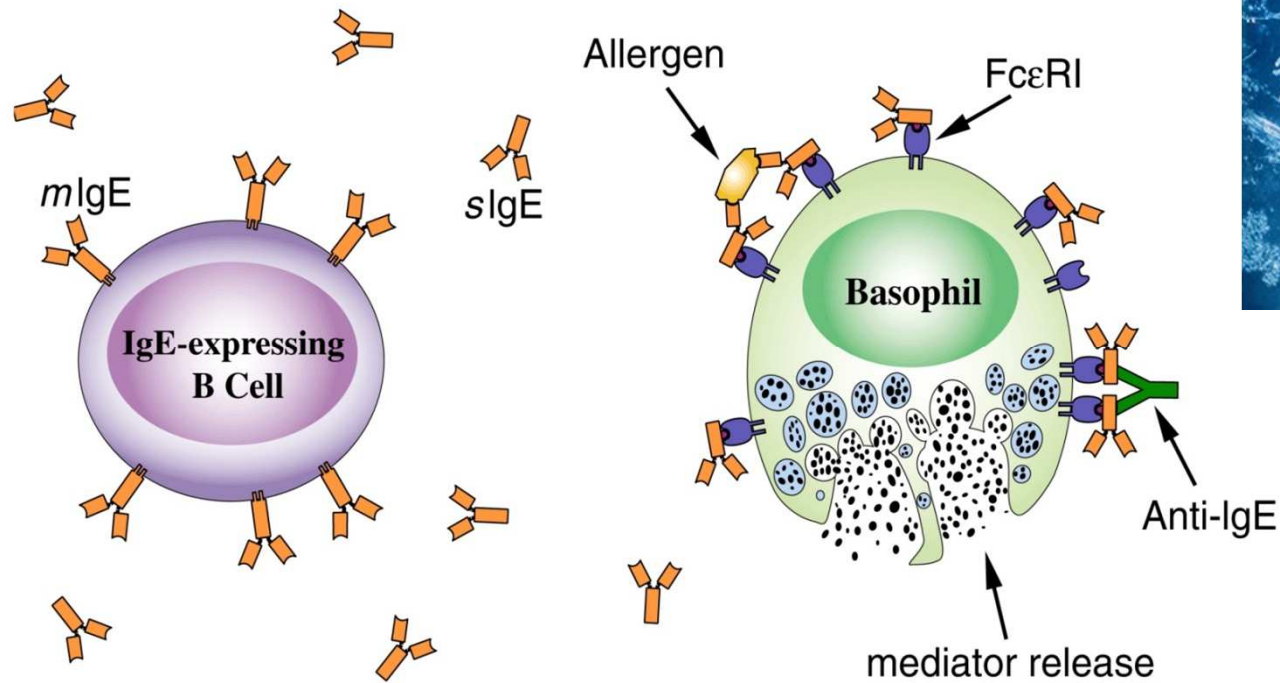


Major steps in IgE-mediated allergic pathway



Most current drugs work here.

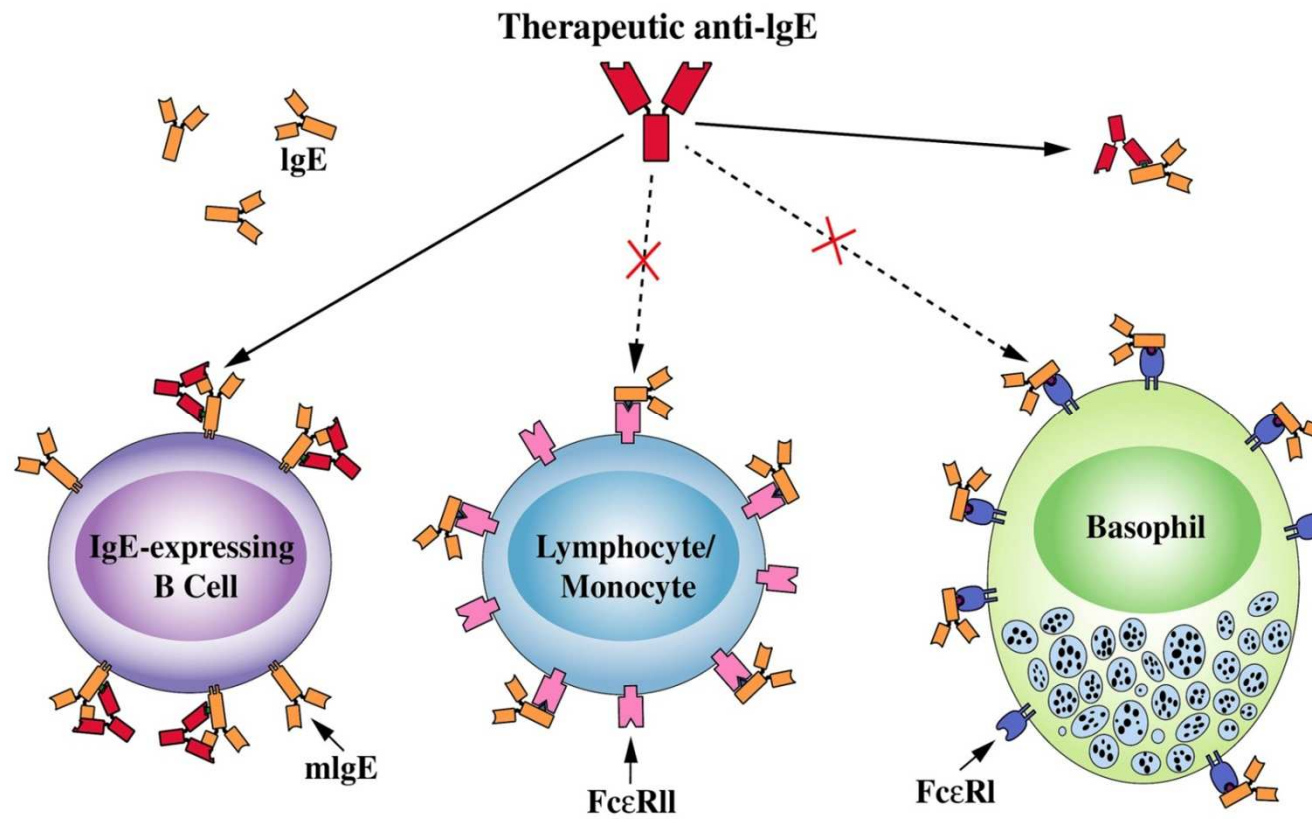
Our goal: to targets IgE and mIgE-B cells



An ordinary anti-IgE is a super sensitizer.

What was the prior art?

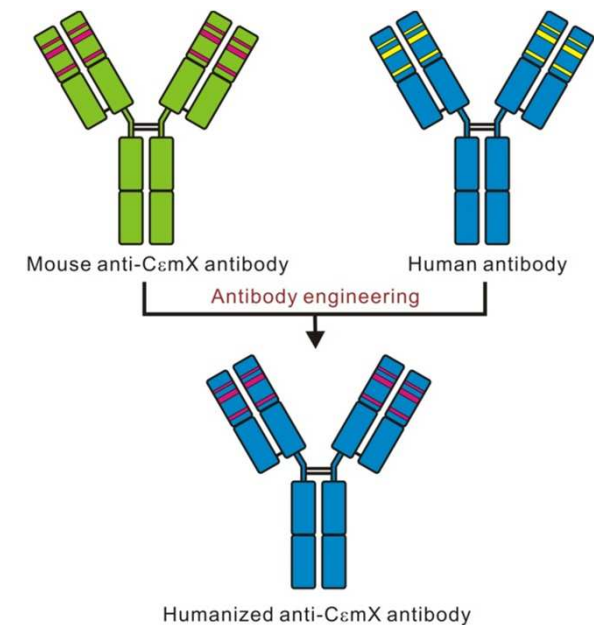
The binding specificities of a therapeutic anti-IgE



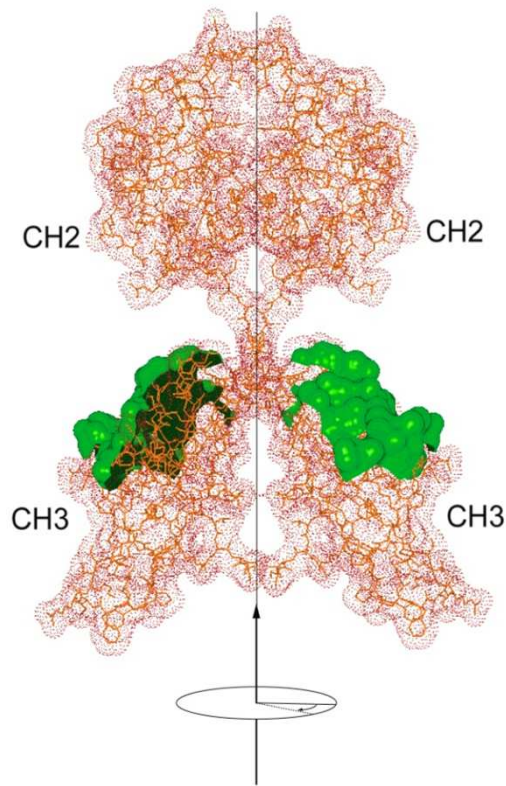
A billion-dollar idea!

Process for developing a therapeutic anti-IgE mAb

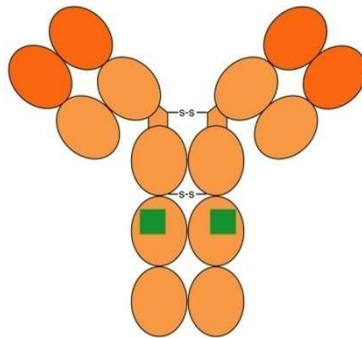
- Develop mouse antibodies with the desired specificities by serial screening –using hybridoma methodology
- Humanize the antibodies – using genetic engineering tools
- Develop the manufacturing process
 - expressed by CHO cells
 - in serum-free medium in 12,000L tanks
 - 3-5 g/L



Structural basis of the binding specificities of anti-IgE

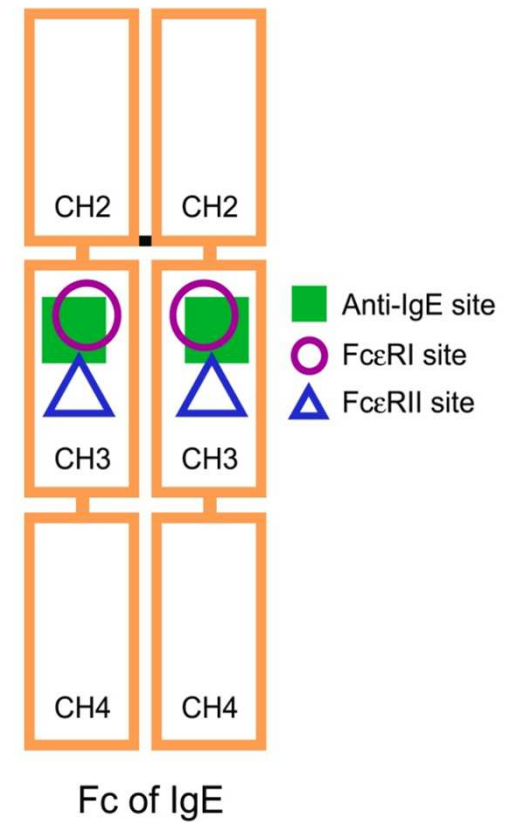


The binding site of anti-IgE on CH3 of IgE



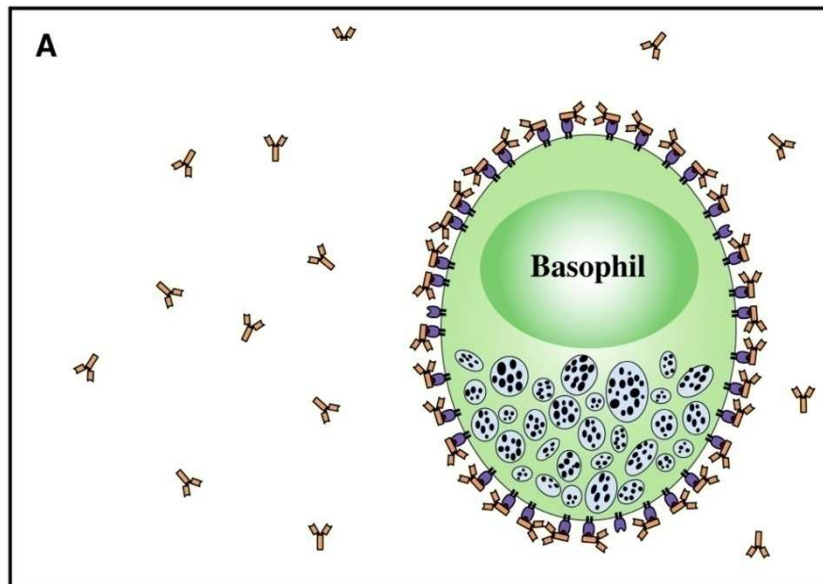
From Wright & Lim, Protein Eng 11 (1998)

The binding sites of FcεRI, FcεRII, and anti-IgE overlap.



Before and after anti-IgE treatment

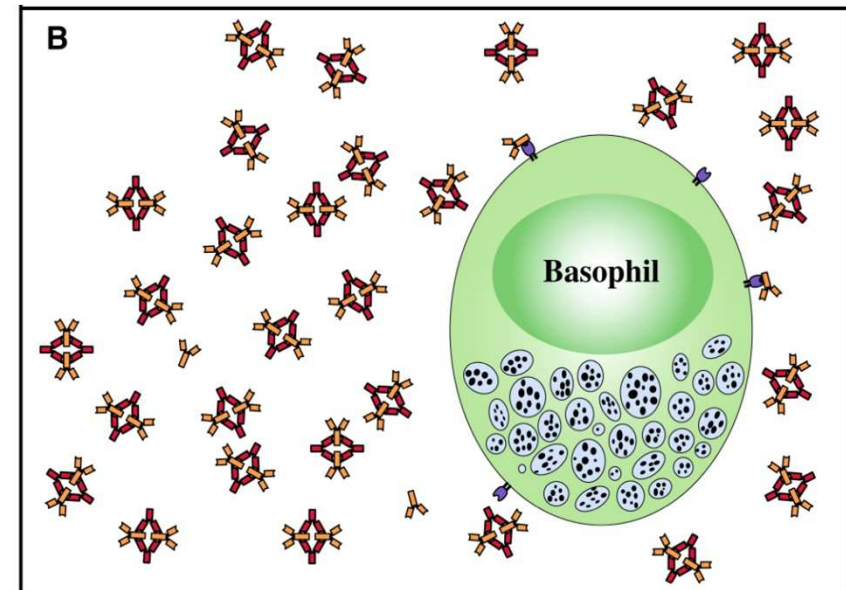
Before



Basophils cells are armed.

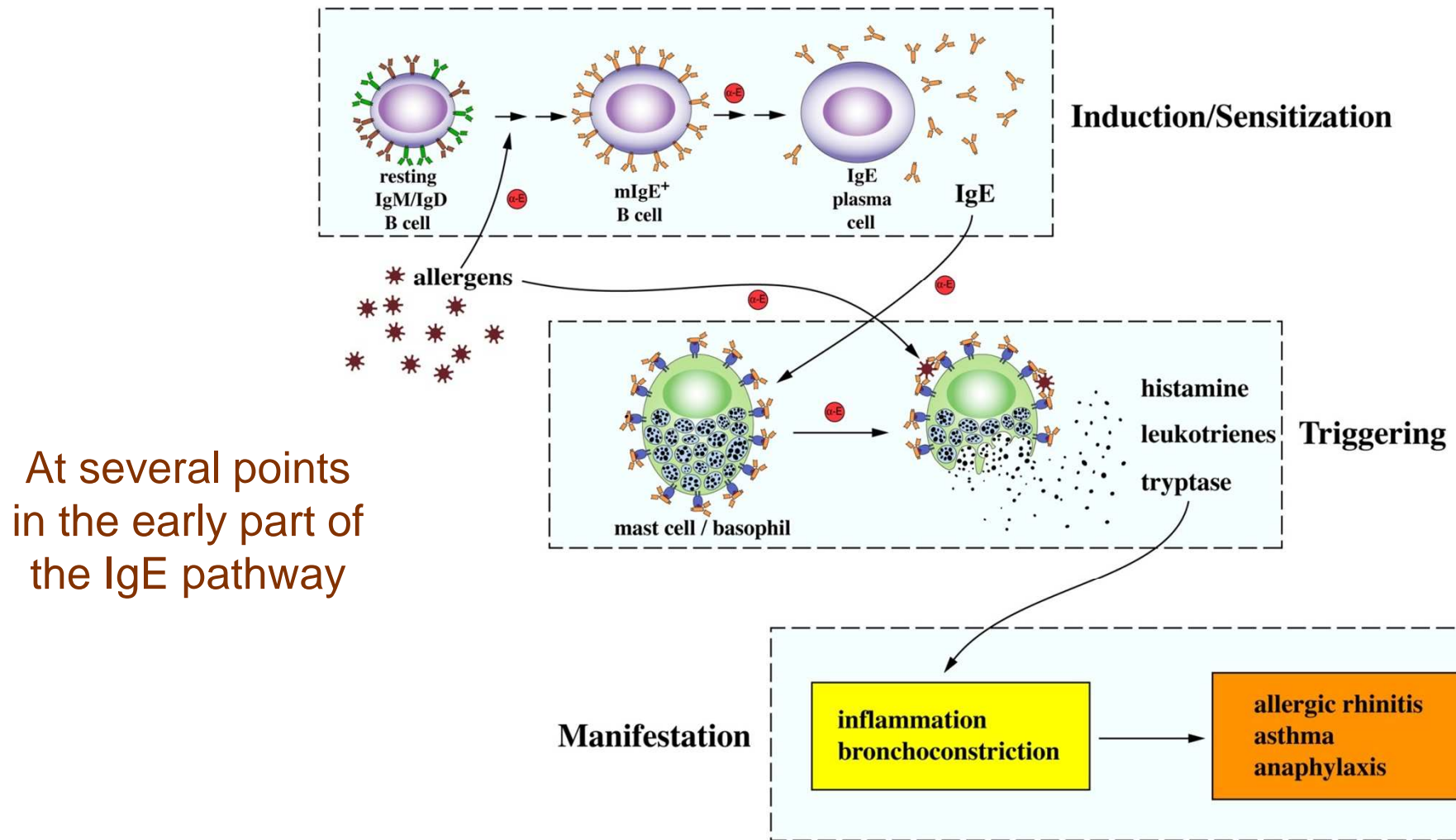
Chang Nature Biotechnol 18 (2000)
Hsu *et al*/ Int Immunopharmacol (2010)

After

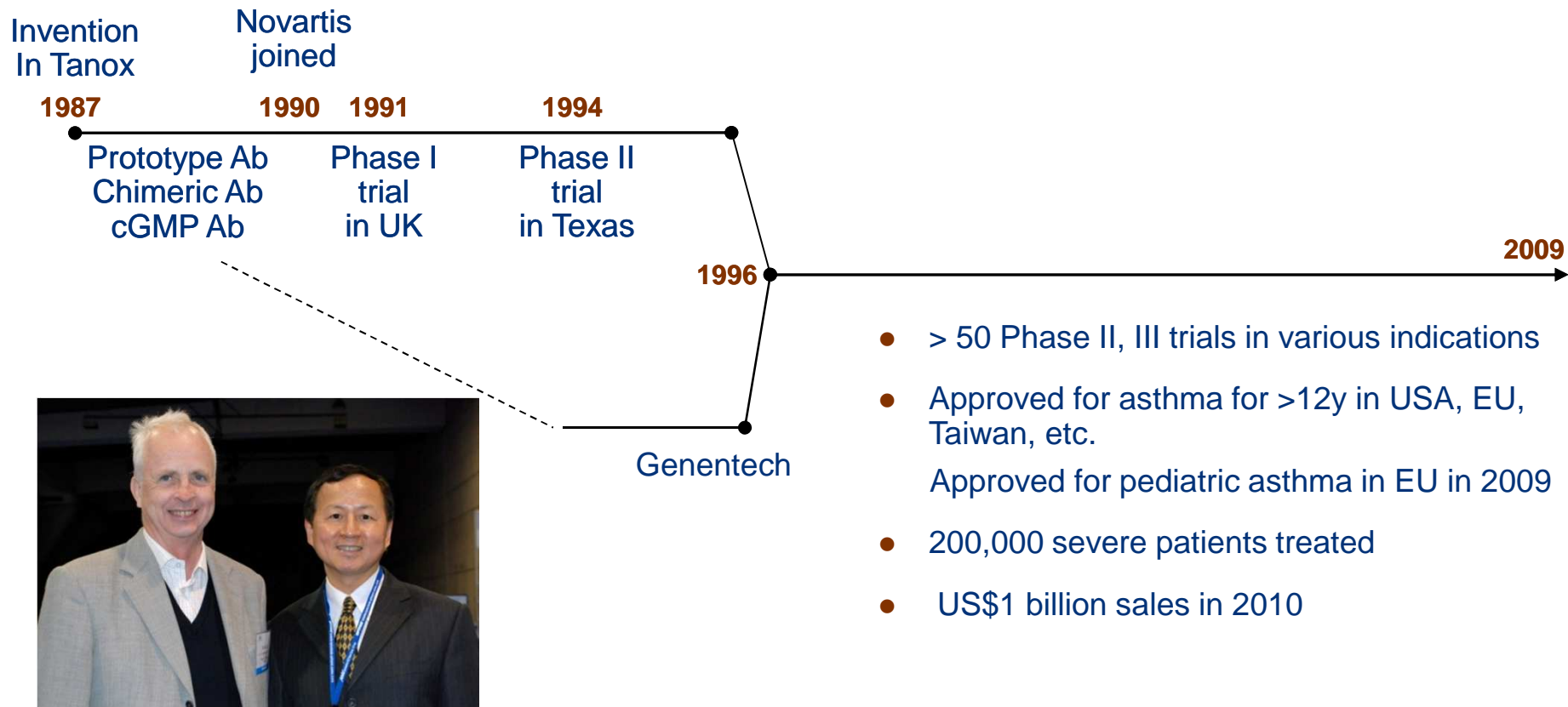


Antigens are mopped up.
Basophils are desensitized.

Multiple, immunoregulatory actions of anti-IgE



Anti-IgE program: it has taken 23 years. (It will take 5-10 more years.)



G. Johansson discovered IgE in 1967.
(In 2007 AAAAI meeting)

Anti-IgE: potentially a treatment platform

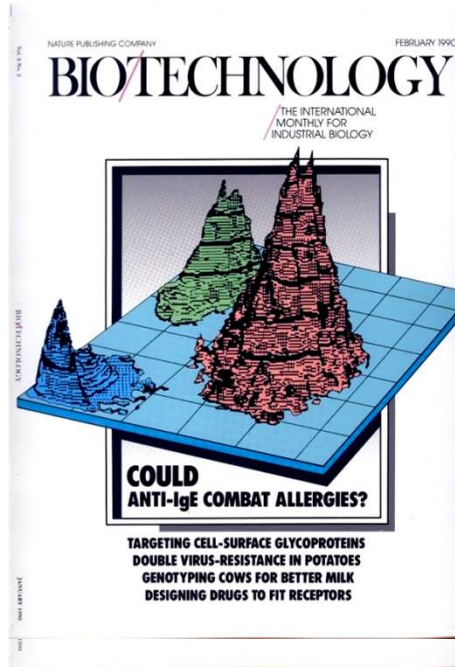
Disease	Efficacy	Status
Allergic asthma (>12y)	✓	approved
Allergic asthma (pediatric)	✓	approved in EU
Allergic rhinitis (seasonal)	✓	multiple phase III done
Allergic rhinitis (perennial)	✓	multiple phase III done
Peanut allergy	✓	one phase II done
Latex allergy	✓	one phase II done
Atopic dermatitis	positive	many case series
11 other allergic diseases	positive	case series

invention

1987



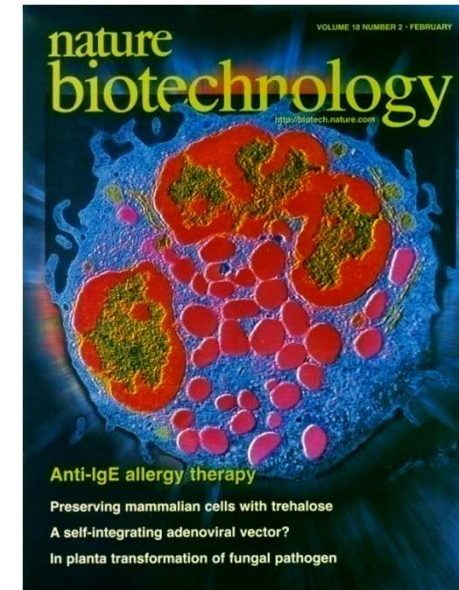
Feb. 1990



Leaders were skeptical of anti-IgE approach.

Whether IgE is involved in the pathogenesis of asthma was not clear.

Feb. 2000



Leaders voiced that anti-IgE is a promising approach.

It was confirmed that IgE is involved in the pathogenesis of asthma.

(same journal)

The evaluation by users of major asthma drugs

Data from WebMD <http://www.webmd.com/drugs/index-drugs.aspx>

39 Xolair users made evaluation

Drug	Efficacy	Satisfaction
Xolair	4.55	4.53
Singular	3.71	3.00
Prednisone	3.45	2.62
Albuterol	3.82	3.61
Advair	4.24	3.69
Symbicort	4.18	3.71

Full score 5

Note : the scores on ease to use not shown

Comments from patients using Xolair

WebMD <http://www.webmd.com/drugs/index-drugs.aspx>

- Thanks for making this product!!!
- I felt great taking it.
- A miracle drug (5 patients said this.)
- Xolair changed my life.
- If I had not been put on the Xolair could likely be dead by now.
- Xolair is the best Christmas present.
- The medication has been a God-send.
- This is magic medicine!
- It truly changed my life.



We need medicine in addition to omalizumab.

Anti-IgE

Approved

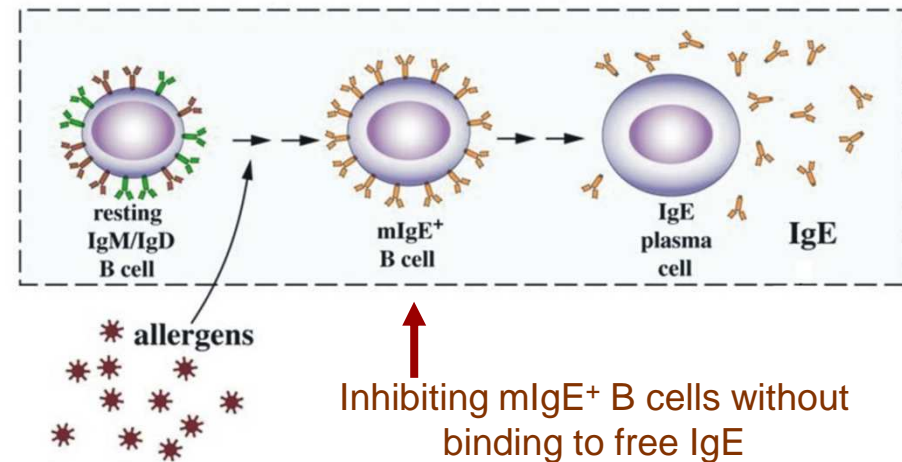
Omalizumab (Trade name Xolair)



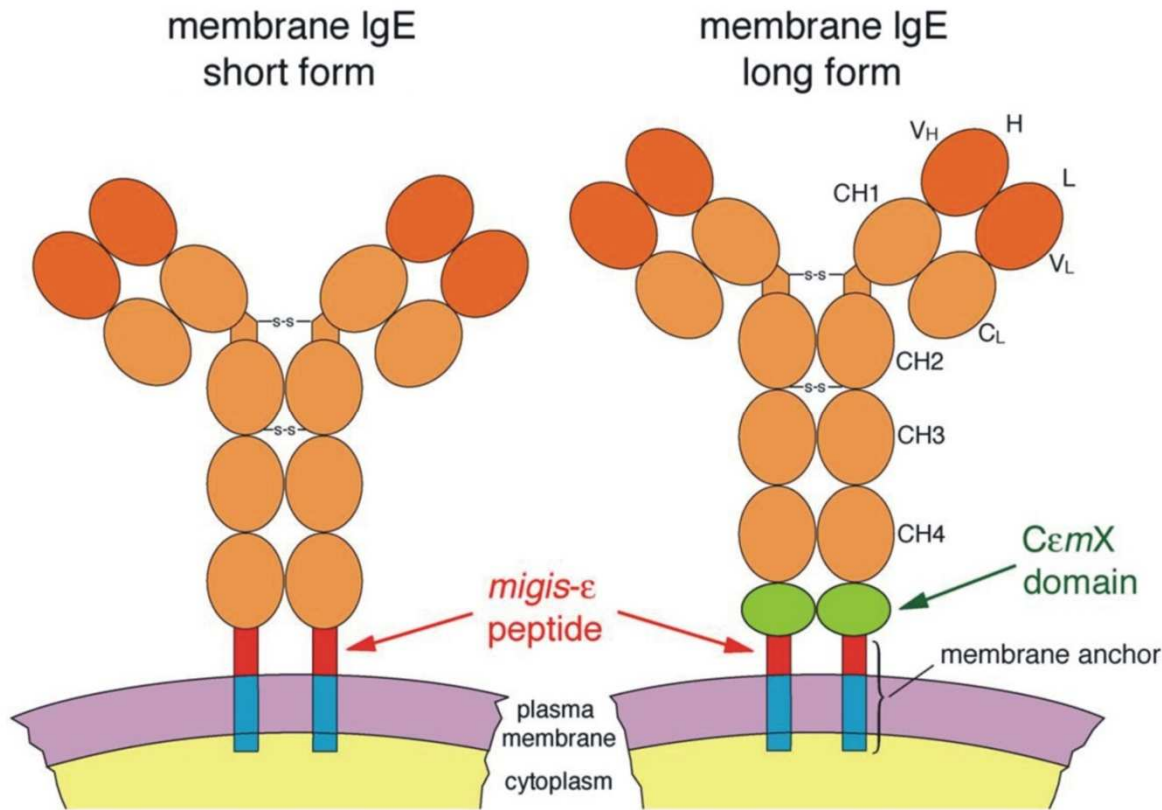
Anti-CεmX

In research

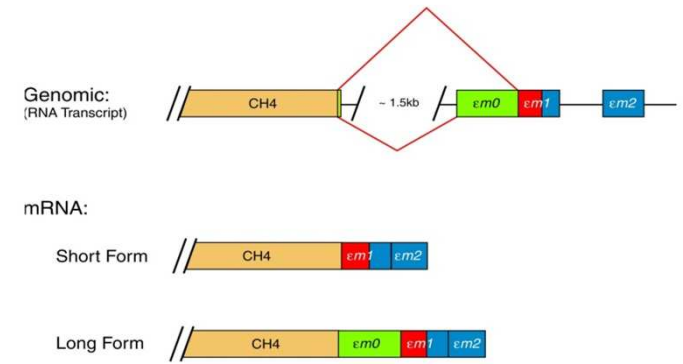
- For patients with IgE higher than 700 IU/ml
- To reduce the amount of antibodies
- To provide medicine to patients broadly



Human mIgE contains “C ϵ mX”.



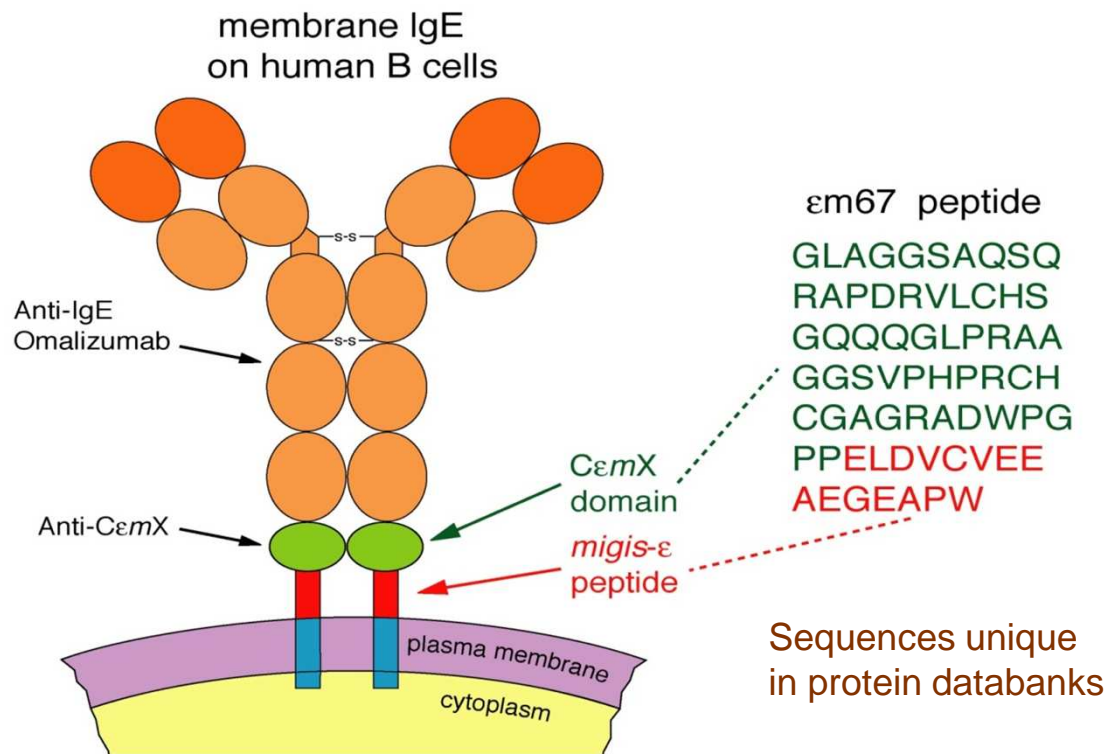
ϵ CH4 exon is spliced to membrane exons in two ways.



C ϵ mX: a 52 a.a. domain

Long form is 1000 times more than short form.

"CεmX" discovery offers new therapeutic strategies.



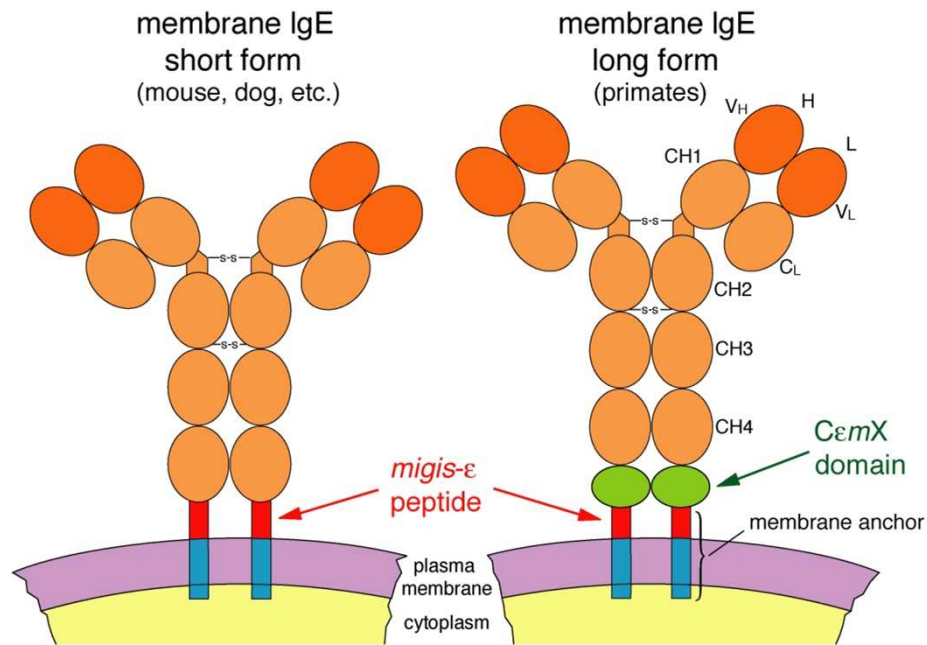
Approaches based on CεmX

- Anti-CεmX antibodies
- Vaccines based on CεmX

Alleles found on CεmX

- 16V and 16L

Human CεmX-harboring transgenic mice



Natural mIgE

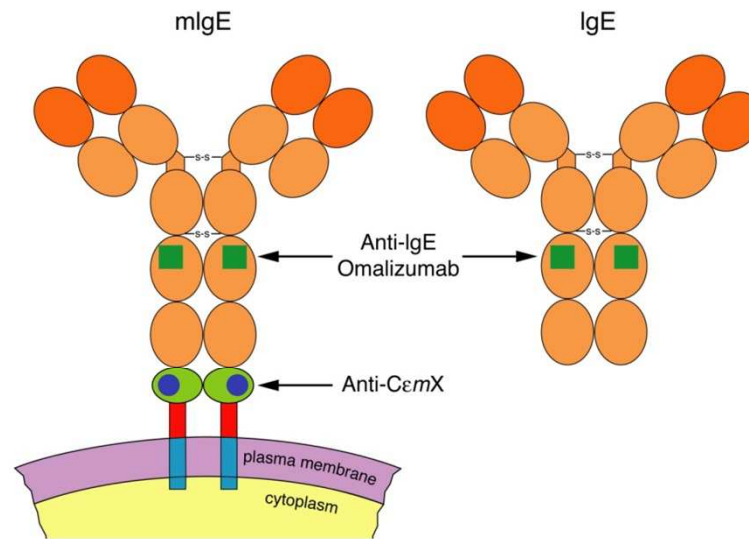


CεmX mouse

Anti-IgE helps severe patients.



Teresa Deng died of asthma in 1995.



With Xolair, many severe asthma patients can now live normal lives.