

# **Novel Immunotherapies**

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## **Objectives**

- **Discuss the rationale behind using novel immunotherapy approaches for allergic diseases**
- **Examine the therapeutic effects of novel immunotherapy approaches on allergic diseases**

## **Abstract:**

**Allergen immunotherapy has been a treatment option for diseases such as allergic rhinitis, allergic asthma, and venom allergy for the last 100 years. During the first 75 years, conventional subcutaneous immunotherapy did not change much. However, the last 25 years has seen substantial growth in the development of alternatives to conventional subcutaneous immunotherapy. The addition of omalizumab, an anti-IgE mAb, to immunotherapy offers the potential for increased safety and efficacy. Activation of the innate immune system through Tolllike receptor agonists with and without specific allergens appears to improve the immunologic responses and clinical outcomes in patients with allergic diseases. The use of chemically altered allergens, allergoids, recombinant allergens, and relevant T-cell epitope peptides are all approaches that have yielded positive results. Finally, alternative modes of delivery hold promise, with sublingual immunotherapy rapidly approaching mainstream use in many countries. One thing is clear: the next century of immunotherapy will be vastly different from today's current standard of care.**

## ■ Talk outline

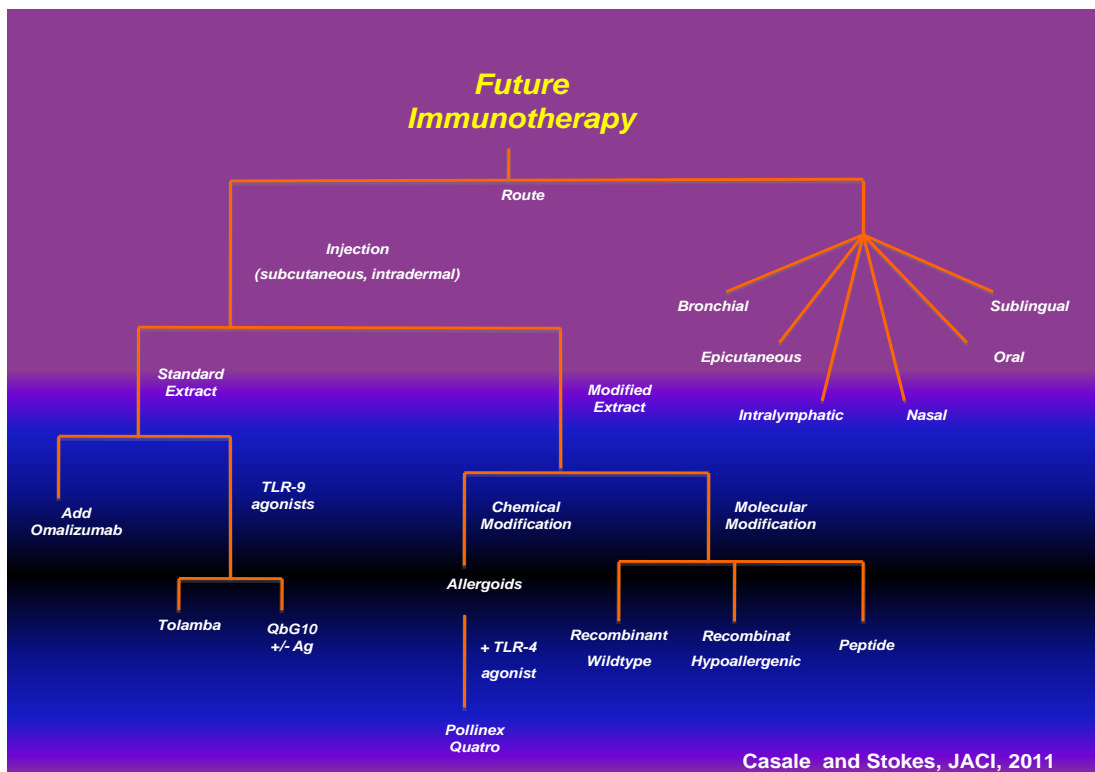
### ● The Goals Of Immunomodulation:

To Reprogram the immune system to ignore “insignificant” threats without compromising its ability to respond to real threats

For allergies, the immune system could be trained to ignore allergens like pollen and cat dander, but still fight bacterial pathogens (ITN)

To be able to stop treatment with persistent pathologic and clinical improvements.

To be Safe!



### ● The Advantages Of ILIT

#### ● Omalizumab Plus SCIT and SLIT

Added efficacy and safety

Don't know if can stop omalizumab and have continues efficacy and safety

#### ● Monophosphoryl Lipid A (MPL) TLR4 Agonist + Allergen

Ultra short-course vaccine used since 1970s for SAR from grass, tree or ragweed:

- Glutaraldehyde-modified Ag adsorbed onto L-tyrosine depot to enhance tolerability
- + MPL to improve efficacy
- 4 pre-seasonal injections:
  - Reduce Sxs and medication use
  - Elevate Ag-specific IgG
  - Blunt seasonal elevation of IgE
- US trials with positive results for grass and ragweed

-----Proof Of Concept study done with SLIT + grass



#### TLR 9

#### ISS (CpG, B-type) Allergy Immunotherapy plus Amb a1

**CYT003-QbG10, A-Type CpG**

CYT003-QbG10 + HDM for 10 weeks led to long-term improvements in asthma and rhinitis.

**Clinical Effects in 80 SAR Patients: Dose Escalating Study W/O Ag showed efficacy**

**QbG10 Adverse Events >3%**

**CYT003-QbG10 Conclusions:**

**Improved objective and patient reported outcome measures in allergic rhinitis and asthma**

**Has steroid sparing and anti-inflammatory effects**

**2/3 of QbG10 treated patients had their asthma "well controlled despite corticosteroid withdrawal**

**Acts through an allergen-independent mechanism of action and not through an adjuvant effect**

**Treatment was safe and well tolerated**



#### Depigoid Birch Pollen IT

- **Pros and Cons Of Recombinant Allergens**



***Pros:***

- **Ultrapure defined molecules**
- **Consistent pharmaceutical quality**
- **Dosage in mass units: absolute standardization**
- **Dose optimization and formulation**
- **Precise monitoring of clinical and laboratory outcomes**



***Cons:***

- **Stringent production requirements**
- **Selection of isoforms**
- **High development costs, limited market potential**

Chapman JACI 2000; Cromwell et al, JACI 2011

- **Specific immunotherapy with recombinant pollen allergens appears safe, well tolerated and effective**

- >30% decrease in symptom-medication scores**
- Optimal maintenance dose 10-15mcg allergen**
- Associated with ~2 log increase in Ag- specific IgG**
- Recombinant products include:**
  - Dust mite**
  - Cat**
  - Grass**
  - Ragweed**
  - Tree**

- **Recombinant Peptide Principles**

- **Identifies and uses T-cell epitopes**
  - **Binds to MHC class II on APCs to induce TRegs to blunt allergic response**

- Less safety issues
  - Lack of B cell epitopes in peptides avoids cross linking of mast cells avoiding need to dose escalate
- Broadly applicable across range of allergies
  - Allergens already identified
  - Standardized dosing; short course of immunotherapy over 3 months
- Clinical trial :Primary endpoint: change in TRSS in ITT Population progressively improved with added exposure
- Effects Of Cat Toleromune:
  - 1 Year Follow-up With No Further Treatment
- Effects of Toleromune Cat Administration On FEV<sub>1</sub> Over 8 hours In Asthmatics-----No effect
- Toleromune /Peptide Summary
  - Peptides manufactured synthetically allowing dose standardization
    - No dose escalation phase
    - Room temperature stable formulation
  - Safety profile looks good
  - Short Course of Immunotherapy over 3 months
    - Clinical Efficacy with 4 administrations
    - Effects lasting 1 year
- Allergens studied:
  - Cat, Ragweed, Mite and Grass in clinical trials
  - Birch epitopes defined
  - Dog and Alternaria in process

**Key Reference:**

**Casale TB, Stokes JR. Future forms of immunotherapy. J Allergy Clin Immunol. 2011 Jan;127(1):8-15; quiz 16-7. Epub 2010 Nov 20. Review. PubMed PMID: 21094518.**