World Allergy Forum Symposium: New Insights Into Immunotherapy for Allergic Disorders

2009 AAAAI Annual Meeting
Tuesday, March 17, 2009
10:45 a.m. – 12:00 p.m.

Washington Convention Center
Room 146 AB, Street Level
Washington DC, USA

Moderators:
G. Walter Canonica, MD
Hugh A. Sampson, MD FAAAAI

Sublingual Immunotherapy for the Prevention and Management of Pediatric Asthma
Giovanni Passalacqua, MD

Modular Antigen Translocating (MAT) Molecules: A Novel Allergy Vaccine Strategy
Cezmi A. Akdis, MD FAAAAI

Effects of Allergen Immunotherapy and Omalizumab on Molecular and Cellular Mechanisms of Inflammation
Thomas B. Casale, MD FAAAAI

The World Allergy Organization (WAO) is an international organization of 77 regional and national allergy and clinical immunology societies. WAO’s mission is to be a global resource and advocate in the field of allergy, advancing excellence in clinical care, education, research and training through a worldwide alliance of allergy and clinical immunology societies.

WAO is an educational program of the World Allergy Organization.
“New Insights Into Immunotherapy for Allergic Disorders”

Program

Moderators:
G. Walter Canonica, MD
University of Genoa
Genoa, Italy

Hugh A. Sampson, MD FAAAAI
Mount Sinai School of Medicine
New York, NY USA

1. Welcome to the World Allergy Forum Symposium and Introduction to “New Insights Into Immunotherapy for Allergic Disorders”
G. Walter Canonica and Hugh Sampson

2. Sublingual Immunotherapy for the Prevention and Management of Pediatric Asthma
Giovanni Passalacqua, MD
University of Genoa
Genoa, Italy

3. Modular Antigen Translocating (MAT) Molecules: A Novel Allergy Vaccine Strategy
Cezmi A. Akdis, MD FAAAAI
Swiss Institute of Allergy and Asthma Research (SIAF)
University of Zurich
Davos, Switzerland

4. Effects of Allergen Immunotherapy and Omalizumab on Molecular and Cellular Mechanisms of Inflammation
Thomas B. Casale, MD FAAAAI
Creighton University School of Medicine
Omaha, NE USA

Upon completion of this session, participants should be able to:
Discuss the effects of sublingual immunotherapy for the treatment and prevention of pediatric asthma.
Evaluate novel immunotherapeutic strategies to attenuate allergic responses.
Describe the immunologic and gene expression programs during a pollen season and the effects of allergen-specific immunotherapy and omalizumab on these events.

2008-2009 World Allergy Form Advisory Board

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About the World Allergy Organization

World Allergy Organization (WAO)
The World Allergy Organization (WAO) is an international umbrella organization of 77 regional and national allergy and clinical immunology societies. By collaborating with member societies, WAO provides direct educational outreach programs, symposia and lectureships to WAO individual members around the globe.

The World Allergy Organization Mission
To be a global resource and advocate in the field of allergy, advancing excellence in clinical care through education, research and training as a world-wide alliance of allergy and clinical immunology societies.

Programs of the World Allergy Organization

GLORIA Global Resources in Allergy™

www.worldallergy.org/gloria
The GLORIA program promotes good practice in the management of allergic diseases through programs developed by panels of world experts. GLORIA educates medical professionals worldwide through regional and national presentations and local training initiatives. GLORIA educational modules promote the World Allergy Organization’s (WAO) mission – to optimize allergy care worldwide.

GLORIA Modules
Module 1: Allergic Rhinitis
Module 2: Allergic Conjunctivitis
Module 3: Allergic Emergencies
Module 4: Immunotherapy
Module 5: Treatment of Severe Asthma
Module 6: Food Allergy
Module 7: Angioedema
Module 8: Anaphylaxis
Module 9: Diagnosis of IgE Sensitization
Module 10: Chronic Rhinosinusitis and Nasal Polyposis
Module 11: Drug Allergy
Module 12: Urticaria

World Allergy Forum (WAF)

www.worldallergy.org/waf
WAF symposia are held at major international allergy meetings. Developed by international expert advisory panels, the symposia provide up-to-the-minute presentations on scientific and clinical developments in the field of allergic disease.

Emerging Societies Program

www.worldallergy.org/esp
WAO offers advice on initiating and developing allergy societies throughout the world. This proactive initiative aims to expand and improve the specialty of allergy by supporting colleagues working in the field of allergy worldwide. Through sharing practical experiences and alerting new societies to the criteria required for WAO membership, ESP creates relationships with future World Allergy Organization member societies, and educates WAO’s leadership about the challenges and opportunities faced by colleagues in developing countries.

WAO Seminars & Conferences

www.worldallergy.org/sc
The Seminars & Conferences program invites member societies to apply to host a WAO Invited Lecturer. Complementing WAO’s existing programs, Seminars & Conferences gives Member Societies the opportunity to bid for an international speaker to give a plenary lecture in the scientific program of the Society’s annual meeting, on a topic of the Society’s choice.

World Allergy Organization Journal

www.waojournal.org
World Allergy Organization Journal is the official publication of the World Allergy Organization. An international online-only journal, World Allergy Organization Journal underscores WAO’s commitment to raising awareness and advancing excellence in clinical care, education, research and training in the field of allergy.
**WAO Member Societies**

### National Member Societies

- Albanian Society of Allergology and Clinical Immunology
- American Academy of Allergy, Asthma and Immunology
- American College of Allergy, Asthma and Immunology
- Argentine Association of Allergy and Immunology
- Argentine Society of Allergy and Immunopathology
- Australasian Society of Clinical Immunology and Allergy
- Austrian Society of Allergology and Immunology
- Azerbaijani Society for Asthma, Allergy and Clinical Immunology
- Bangladesh Society of Allergy and Immunology
- Belgian Society of Allergology and Immunology
- Brazilian Society of Allergy and Immunopathology
- British Society for Allergy and Clinical Immunology
- Bulgarian National Society of Allergology
- Canadian Society of Allergy and Clinical Immunology
- Chilean Society of Allergy and Immunology
- China Allergology Society and Chinese Allergists
- (Chinese) Hong Kong Institute of Allergy
- Colombian Allergy, Asthma, and Immunology Association
- Croatian Society of Allergology and Clinical Immunology
- Cuban Society of Allergology
- Czech Society of Allergology and Clinical Immunology
- Danish Society for Allergology
- Egyptian Society of Allergy and Clinical Immunology
- Egyptian Society of Pediatric Allergy and Immunology
- Finnish Society of Allergology and Clinical Immunology
- French Society of Allergology and Clinical Immunology
- Georgian Association of Allergology and Clinical Immunology
- German Society for Allergology and Clinical Immunology
- Hellenic Society of Allergology and Clinical Immunology
- Hungarian Society of Allergology and Clinical Immunology
- Icelandic Society of Allergology and Immunology
- Indian College of Allergy, Asthma and Applied Immunology
- Indonesian Society for Allergy and Immunology
- Israel Association of Allergy and Clinical Immunology
- Italian Association of Territorial and Hospital Allergists
- Italian Society for Allergology and Clinical Immunology
- Japanese Society of Allergology
- Korean Academy of Allergy, Asthma and Clinical Immunology
- Latvian Association of Allergists
- Lebanese Society of Allergy and Immunology
- Malaysian Society of Allergy and Immunology
- Mexican College of Allergy, Asthma and Clinical Immunology
- Mexican College of Pediatricians Specialized in Allergy and Clinical Immunology
- Mongolian Society of Allergology
- Netherlands Society of Allergology
- Norwegian Society of Allergology and Immunopathology
- Panamanian Association of Allergology and Clinical Immunology
- Paraguayan Society of Immunology and Allergy
- Peruvian Society of Allergy and Immunology
- Philippine Society of Allergy, Asthma and Immunology
- Polish Society of Allergology
- Portuguese Society of Allergology and Clinical Immunology
- Romanian Society of Allergology and Clinical Immunology
- Russian Association of Allergology and Clinical Immunology
- Association of Allergy and Clinical Immunology for Serbia and Montenegro
- Singapore Society of Immunology, Allergy & Rheumatology
- Allergy Society of South Africa
- Spanish Society of Allergology and Clinical Immunology
- Swiss Society of Allergology and Immunology
- Allergy and Immunology Society of Thailand
- Turkish National Society of Allergy and Clinical Immunology
- Ukrainian Association of Allergologists and Clinical Immunologists
- Uruguayan Society of Allergology
- Venezuelan Society of Allergy and Immunology
- Vietnam Association of Allergy, Asthma and Clinical Immunology
- Zimbabwe Allergy Society

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- Ecuadorian Society of Allergology and Affiliated Sciences
- Ecuadorian Society of Allergy and Immunology
- Honduran Society of Allergy and Clinical Immunology
- Slovenian Association for Allergology and Clinical Immunology
- Allergy & Immunology Society of Sri Lanka
- Swedish Association for Allergology

### Regional Organizations

- Asia Pacific Association of Allergology and Clinical Immunology
- Commonwealth of Independent States (CIS Society)
- European Academy of Allergology and Clinical Immunology
- Latin American Society of Allergy and Immunology

### Affiliate Organizations

- International Association of Asthmology

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For WAO membership information please contact the Secretariat

World Allergy Organization (WAO)

555 East Wells Street, Suite 1100 • Milwaukee, WI 53202-3823 USA

Tel: +1 414 276 1791 • Fax: +1 414 276 3349
e-mail: info@worldallergy.org

Web site: www.worldallergy.org
Dear Colleagues,

It is our pleasure to welcome you to the 33rd World Allergy Forum symposium, New Insights into Immunotherapy for Allergic Disorders.

Immunotherapy is a topic of major interest to allergists worldwide; it is the only therapy for allergic disease that currently offers potentially long-term benefit and the possibility of prevention of disease progression. Immunotherapy is thus the focus of several collaborative initiatives between WAO and AAAAI at the present time; at the end of 2008, WAO and AAAAI representatives met to review the US experience with Sub-lingual Immunotherapy (SLIT) and to discuss the optimal methodology for future studies. In January 2009 AAAAI representative and WAO Board member, Tom Casale Co-Chaired a meeting of WAO member societies and other medical organizations to create a global Position Statement on SLIT, considering a wide range of important issues including efficacy, safety and patient selection. AAAAI is partnering with WAO in organizing the 2nd Immunotherapy Day, to be held at the World Allergy Congress in Buenos Aires, 6-10 December, 2009. WAO is most grateful to AAAAI for its continuing support in these global initiatives, and for including this World Allergy Forum symposium on immunotherapy in this year’s scientific program; the unrestricted educational grant from Novartis which has enabled us to invite an international panel of experts to speak on this important topic is gratefully acknowledged.

Gianni Passalacqua will start today’s program with a discussion on Sublingual Immunotherapy for the Prevention and Management of Pediatric Asthma. The current experience of SLIT in children with rhinoconjunctivitis and asthma will be presented, and information regarding the preventive effects of SLIT will be discussed.

In his presentation Modular Antigen Translocating (MAT) Molecules: A Novel Allergy Vaccine Strategy, Cezmi Akdis will describe the properties that would constitute a ‘perfect’ immunotherapy vaccine, and will introduce studies being conducted by his group that aim to improve the efficacy and safety of allergen-SIT.

Concluding the symposium, Tom Casale will speak on the Effects of Allergen Immunotherapy and Omalizumab on Molecular and Cellular Mechanisms of Inflammation, and will present a study that provides an in-depth view of a systemic allergic response triggered by inhaled allergens, and shows how immunotherapy works to counteract this response.

We hope you will enjoy this World Allergy Forum symposium, and look forward to your comments and questions!

With best regards,

G. Walter Canonica
President
World Allergy Organization

Hugh A. Sampson, MD FAAAAI
President
American Academy of Allergy, Asthma and Immunology
Abstract

Giovanni Passalacqua, G. Walter Canonica
Allergy and Respiratory Diseases, Dept of Internal Medicine,
University of Genoa, ITALY

The clinical efficacy of sublingual immunotherapy (SLIT) has recently been confirmed in several meta-analyses and large randomized controlled trials. The safety profile has also been confirmed to be satisfactory in both clinical trials and post-marketing surveys. Moreover, there is convincing evidence that the mechanisms of action of SLIT are partially similar to those of injection immunotherapy. In particular, SLIT is capable of inducing the production of IFN-γ from regulatory T cells, thus modifying the balance between Th1 and Th2 lymphocytes (1).

Concerning the clinical efficacy in pediatric patients, there are very few studies specifically designed to evaluate asthma symptoms. Nevertheless, the results of rhinoconjunctivitis studies in children, which also assessed asthma, were pooled together in a meta analysis. Despite the large heterogeneity of the trials considered, the analysis showed that SLIT was significantly more effective than placebo in reducing symptoms and asthma medications (2). Well designed and adequately powered trials in children are urgently needed to assess the magnitude of the effect of SLIT in pediatric asthma.

In respect to the prevention of asthma in children with rhinitis, a randomized open prospective study in children receiving SLIT or drugs only was published in 2004 (3). This trial demonstrated that SLIT can reduce significantly the onset of asthma over a 3-year period of observation. Another large prospective randomized open trial (4), involving more than 200 children treated with SLIT or drugs alone for 3 years, demonstrated that SLIT reduced significantly the onset of persistent asthma and the onset of new skin sensitizations. Finally, a long-term follow-up of children with mite allergy (5), showed that SLIT reduced the onset of asthma, and that this effect was maintained for 5 years after discontinuation.

References

What do we mean by “modifying the allergic disease”? 

- Change in the immune response to allergens
- Symptom reduction during natural exposure
- Effect on the natural progression, if any

What do we mean by “modifying the allergic disease”? 

- Change in the immune response to allergens
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Meta-analysis of the efficacy of sublingual immunotherapy in allergic asthma in pediatric patients, 3 to 16 years of age.

M Penagos, G Pasekicque, E Compeel, C Bona-Cagnoli, S Oroco, A Pedroza GW Cordoncisco

SYMPTOMS

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Before Treatment</th>
<th>After Treatment</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal congestion</td>
<td>3.4</td>
<td>2.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sneezing</td>
<td>3.1</td>
<td>2.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>3.0</td>
<td>2.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Itching</td>
<td>3.2</td>
<td>2.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Skin rash</td>
<td>3.1</td>
<td>2.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>3.0</td>
<td>2.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

** MEDICATIONS**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Before Treatment</th>
<th>After Treatment</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihistamines</td>
<td>2.7</td>
<td>1.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>2.4</td>
<td>1.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bronchodilators</td>
<td>2.2</td>
<td>1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Decongestants</td>
<td>2.0</td>
<td>1.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>1.8</td>
<td>1.0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
What do we mean by
"modifying the allergic disease"?

- Change in the immune response to allergens
- Symptom reduction during natural exposure
- Effect on the natural progression, if any
What do we mean by “modifying the allergic disease”?

What do we know about drugs?

NO DRUG IS CURRENTLY ABLE TO AFFECT THE PROGRESSION OF THE DISEASE

Long-Term inhaled Corticosteroids in Preschool Children at High Risk for Asthma
Guilbert T, NEJM 2000

Disease-modifying properties of SIT

Prevention of asthma onset (reduction of the risk of developing asthma)

Prevention of the onset of new sensitizations (skin tests)

(Prevention of the relapses – long-term effect)
Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study

Coseasonal SLIT reduces the development of asthma in children with allergic rhinitis. Novembre E. et al, JACI 2004

PREVENTIVE EFFECTS OF SUBLINGUAL IMMUNOTHERAPY IN CHILDHOOD. AN OPEN RANDOMIZED CONTROLLED STUDY

Maurizio Marogna MD, D. Tomasetti, A. Bernasconi, P. Colombo, Alessandro Massolo BS, A. Di Rienzo Businco, Giorio W Canonica MD, Giovanni Passalacqua MD and Salvatore Tripodi MD

1. Pneumology Unit, Cusino al Monte, Macchi Hospital Foundation, Varazze
2. Department of Animal Biology, University of Pavia, Pavia
3. Allergy & Respiratory Diseases, Department of Internal Medicine, Genoa University
4. Pediatric Allergy Unit, S. Pertini Hospital, Rome

AAA/2008, 101: 281
Randomized open controlled study of SLIT in real life: Clinical efficacy and more

NEW SKIN SENSITIZATIONS AFTER 3 YEARS

<table>
<thead>
<tr>
<th>SLIT 271 PTS</th>
<th>CONTROL 170 PTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.9%</td>
<td>38%</td>
</tr>
</tbody>
</table>

P < 0.001
Long-lasting effect of sublingual immunotherapy in children with asthma due to house dust mite: a ten-year prospective study

V. Di Rienzo, F. Marcucci, P. Puccinelli, S. Parmiani, F. Frati, L. Sensi, GW Canonica, G. Passalacqua

Rome, Milan, Perugia and Genoa

Clin Exp Allergy, 2003
Modular Antigen Translocating (MAT) Molecules: A Novel Allergy Vaccine Strategy

Cezmi A. Akdis, MD FAAAAI
Swiss Institute of Allergy and Asthma Research (SIAF)
University of Zurich
Davos, Switzerland

Abstract
Cezmi A. Akdis, Thomas Kündig, Claudio Rhyner, Mübcecel Akdis, Reto Crameri
Swiss Institute of Allergy and Asthma Research (SIAF),
University of Zurich, Obere Strasse 22, CH-7270 Davos, Switzerland.

Allergen-specific immunotherapy (SIT) has been used for almost a century as a desensitizing therapy for allergic diseases and represents the only curative and specific way of treatment. Administration of appropriate concentrations of allergen extracts has been shown to be reproducibly effective when patients are carefully selected. However, allergen-SIT faces several problems related to the allergen content of the extracts used, type of the adjuvant, route of application, long duration of treatment, side effects and limited efficacy. Intensive studies are being performed to improve efficacy and safety of allergen-SIT. Based on PTD (protein transduction domain) technology, we have engineered MAT (modular antigen translocation) molecules, aimed to enhance antigen presentation through intracellular targeting of the MHC II presentation pathway. MAT vaccines consist of a cloning cassette, which fuses Tat (transactivator of transcription) peptide to a truncated Ii (invariant chain), which is able to target antigens to the nascent MHC II molecules in the trans-Golgi compartment. To test the efficacy of intracellular targeting, we engineered arrays of MAT-fusions and compared the effects of recombinant allergens, Tat-conjugated allergens and MAT-conjugated allergens for the ability to stimulate T-cell proliferation and cytokine production in human PBMC (peripheral blood mononuclear cell) cultures derived from allergic individuals, and to elicit protective immune responses in mice. MAT-vaccines induced a strong proliferation of PBMCs at a low concentration and induced a Th2 to a Tregulatory/Th1 cell shift in the cytokine profile, reflecting those reported in successfully desensitized allergic individuals. In mouse models of allergy, we showed that MAT-vaccines are highly efficient in desensitizing mice and protect them from anaphylactic shock. The technology is applicable not only for the treatment of allergies, but also for the development of preventive vaccines in general.
Modular Allergen Translocation Vaccines

Cezmi A. Akdis
Swiss Institute of Allergy and Asthma Research (SIAF)

Problems in SIT

- Side effects: A little bit improved since 1993.
- Efficacy: Vom is fine, what about mouth, tree pollens, drugs?
- Dose: Incredibly, is it still a question?
- Time: Do you mean duration, why not a single dose? Why not once a year?
- Place: SLIT is now more than 80% in some countries.
- Intervals: Maybe one dose will be enough.
- Compliance: Includes all of the questions above and below.
- When to start: We believe in great decisions.
- When to stop: Some say never stop.
- To whom to start: If care is in the horizon, why not to everyone (PREVENTIVE VACCINES).
- Predictors for: start, stop, success. More and more studies.

Mechanisms of allergen-specific immunotherapy

- Early decrease in mast cell and basophil activity for degranulation and systemic anaphylaxis.
- T cell tolerance induction of T helper cells suppression of Th2 cells.
- Decrease in tissue mast cells and eosinophils and release of their mediators.

Relative change

- 1 2 3 years
Mechanisms of allergen-specific immunotherapy

which one will be the first APC to present the allergen to the T cell?

which one will be the first T cell to contact APC?
Immune tolerance to allergens in healthy immune response and successful SIT

What a perfect SIT vaccine should do?

a) induce tolerance in allergen-specific effector T cells, suppress IgE production and promote IgG4 or IgA isotype blocking antibody production

b) should not induce side effects

c) should be easily administered

d) should achieve clinical success in short time with few applications

e) there should exist early biological markers to assess clinical success before the onset of the treatment

Can we make them better?

Bypassing IgE, targeting T cells

Faxeb J 1999
Trends Immunology 2000
<table>
<thead>
<tr>
<th>Type of the vaccine/approach</th>
<th>Description and mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fusion of major allergens</td>
<td>Several major allergens (Api m 1, Api m2) are fused and expressed as a single recombinant protein. IgE binding is attenuated, T cell reactivity is preserved. Preventive effect on generation of IgE is demonstrated in mice.</td>
</tr>
<tr>
<td>Chimeric allergens</td>
<td>Fragments of major allergens (Api m 1, Api m2, Api m3) are fused and expressed as a single protein. IgE binding is attenuated, T cell reactivity is preserved. Preventive effect on generation of IgE is demonstrated in mice.</td>
</tr>
</tbody>
</table>

Kussebi et al. JACI, Karambo et al. Eur. J. Imm
Candidate vaccines for venom SIT

<table>
<thead>
<tr>
<th>1</th>
<th>99</th>
<th>63</th>
<th>219</th>
<th>349</th>
<th>40</th>
<th>134</th>
<th>87</th>
<th>231</th>
<th>1</th>
<th>43</th>
</tr>
</thead>
<tbody>
<tr>
<td>Api m 2-1</td>
<td>Api m 3</td>
<td>Api m 2-3</td>
<td>Api m 1-2</td>
<td>Api m 2-2</td>
<td>Api m 1-1</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Api m [1/2/3] |

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Api m (1/2) |

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Characteristics of both vaccines
1. T cell epitopes are fully preserved
2. IgE binding is almost deleted due to conformational change
3. Doses to induce basophil degranulation are 1000 x high
4. Skin test reactivity is deleted
5. IgE induction in mice is prevented

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single dose 7d before sensitization

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IgE

--- |

PC/LogE titre

--- |

0 7 14
cays after sensitization
Recombinant allergen fragments and trimers

- Monomer
- Fragments
- Trimer

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<table>
<thead>
<tr>
<th>Type of the vaccine/approach</th>
<th>Description and mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fragments of major allergens</td>
<td>Major allergen (Bet v 1) is divided to non-IgE binding fragments. IgE binding is attenuated.T cell reactivity is preserved. A multi-center clinical trial has been reported.</td>
</tr>
<tr>
<td>Polymers of major allergens</td>
<td>Major allergen (Bet v 1) is trimerized. Mast cell, basophil degranulation is attenuated, T cell reactivity is preserved. A multi-center clinical trial has been reported.</td>
</tr>
</tbody>
</table>

Vrtala et al JI, Niederberger et al. PNAS, Gafvelin et al. Int Arch Allergy Immunol

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Peptide immunotherapy

- T cell epitopes

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<table>
<thead>
<tr>
<th>Type of the vaccine/approach</th>
<th>Description and mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptides of major allergens</td>
<td>Non-IgE binding T cell epitope peptides (Fel d 1, Api m 1) have been used in cat and bee venom allergy.</td>
</tr>
<tr>
<td></td>
<td>Larche &amp; Kay Fel d 1</td>
</tr>
<tr>
<td></td>
<td>Norman et al. Fel d 1</td>
</tr>
<tr>
<td></td>
<td>Müller &amp; Aidis &amp; Blaser  Bee venom PLA</td>
</tr>
</tbody>
</table>

Summary of findings:
1. Targeting only T cells is sufficient to induce asthma
2. T cell tolerance by IL-10 is induced
3. Both Th1 and Th2 cytokines are decreased
4. Skin late phase response size and cellular infiltration decreased

<table>
<thead>
<tr>
<th>Type of the vaccine/approach</th>
<th>Description and mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixture of several major recombinant allergens</td>
<td>Clinical efficacy of a mixture of five recombinant grass pollen allergens (Phl p 1, Phl p 2, Phl p 5a, Phl p 5b, Phl p 6) in reducing symptoms and need for symptomatic medication in grass pollen allergic patients was demonstrated.</td>
</tr>
<tr>
<td></td>
<td>Jutel et al JACI 2005</td>
</tr>
</tbody>
</table>

Summary of findings:
1. Clinical success
2. One of the highest reported increase in specific IgG4
3. Patients, who did not have IgE against a certain component only developed IgG4

<table>
<thead>
<tr>
<th>Type of the vaccine/approach</th>
<th>Description and mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergens coupled to virus-like particles</td>
<td>Der p 1 peptides coupled to highly repetitive virus capsid-like recombinant particles induced high specific IgG titres. Kündig et al. JACI 2006</td>
</tr>
<tr>
<td>Combination of conventional SIT with anti IgE</td>
<td>Anti-IgE mAb pretreatment enhances the safety of SIT for allergic rhinitis. Its role on long term efficacy is still under investigation. Künker et al JACI 2007</td>
</tr>
<tr>
<td>Intralymphatic vaccination</td>
<td>Allergen-SIT vaccines administered directly into a lymph node are currently being investigated. The aim is to deliver high amounts of allergens into secondary lymphatic organs. Kündig et al. Eur J. Immunol 2005</td>
</tr>
<tr>
<td>Type of the vaccine/approach</td>
<td>Description and mechanism</td>
</tr>
<tr>
<td>------------------------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>GpG oligonucleotide-conjugated allergens</td>
<td>Major allergen (Amb a 1) is bound to a toll-like receptor 9-triggering CpG oligonucleotide. In this way allergen and innate immune response stimulating agent are expressed in one molecule.  Creticos et al. NEJM 2006</td>
</tr>
<tr>
<td>Monophosphoryl lipid A</td>
<td>Th2 to Th1 switch</td>
</tr>
</tbody>
</table>

Search for better adjuvants is very important
A number of mechanisms for the clinical effects of allergen-specific immunotherapy (SIT) and the monoclonal anti-IgE antibody, omalizumab, have been proposed. The effects of allergen-SIT include changes in both inflammatory mediators and cells. Mast cell and eosinophil numbers and mediator release decrease. Decreased levels of IL-4 and IL-5, potent drivers of the Th2 response, have been observed in both tissue and peripheral blood. Corresponding increases in IFN\(\gamma\), a Th1-profile cytokine, have also been observed in skin and nasal tissue after pollen SIT, although not in peripheral blood. Perhaps one of the most important changes involves the generation of Treg cells and the secretion of IL-10 and TGF-\(\beta\). These cytokines promote increased levels of serum-specific IgA and IgG4, and an eventual decline in serum-specific IgE. SIT appears to act, at least in part, through cytokine deviation by modulating the balance of Th1/Th2 cells towards a more Th1-like response.

The primary effects of omalizumab include a rapid decrease in free IgE levels in serum and the decreased expression of the high affinity IgE receptor. These effects lead to decreased mediator release and inflammation.

We found that all treatments were associated with significant changes in gene transcripts. For example, 457 transcripts were differentially expressed between omalizumab plus immunotherapy vs. placebo plus immunotherapy at study week 13. In addition, seasonal exposure to ragweed in the placebo treated group also resulted in a number of gene transcript changes.

Our studies indicate that immunotherapy results in gene expression changes representative of a diminished inflammatory response and a program of B and T cell differentiation towards a memory Th1-like response. A subset of genes related to the Th2 program was identified and appears to be regulated by seasonal exposure to allergen, and are unaffected by SIT.

The data provide an in depth view of a systemic allergic response triggered by inhaled allergens and show how immunotherapy works to counteract this response. These data show that the major effect of immunotherapy involves modulation of the inflammatory response and the differentiation of B and T cells to a memory phenotype. In addition to providing a better understanding of the nature of the allergic response, the immunotherapy and seasonally regulated genes discovered present opportunities for new targets of therapy. Finally this study provides evidence that biomarkers of peripheral blood immune responses are valuable tools for assessing disease onset, progression, and therapeutic efficacy.
Selected References:


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