Mechanismen der allergenspezifischen Immuntherapie

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http://www.allergy-research-program.at/cms/
Allergen-specific immunotherapy:

Administration of gradually increasing quantities of allergen vaccines to an allergic subject, reaching a dose which is effective in ameliorating the symptoms associated with subsequent exposure to the causative allergen.

WHO Position Paper, 1998

Noon L. Prophylactic inoculation against hayfever.
Lancet 1, 1572-1573, 1911
First evidence that allergen-specific immunotherapy is a vaccination

William Dunbar (1863-1922)
Allergen-specific immunotherapy induces allergen-specific protective IgG antibodies
The „blocking antibody concept“

1. Serum of an allergic patient taken before (A-serum) and after (P-serum) specific immunotherapy
2. Preincubation of sera with allergen extract
3. Injection into the skin of a non-allergic individual

Cooke et al., 1935
Recombinant allergen–based monitoring of antibody responses during injection grass pollen immunotherapy and after 5 years of discontinuation

E. Gadermaier¹, J. Staikuniene², S. Scheiblhofer³, J. Thalhamer³, M. Kundi⁴, K. Westritschnig¹, I. Swoboda¹⁵, S. Flicker¹ & R. Valenta¹⁵

¹Division of Immunopathology, Department of Pathophysiology and Allergy Research, Center for Pathophysiology, Infectiology and Immunology, Medical University of Vienna, Vienna General Hospital, Vienna, Austria; ²Department of Pulmonology and Immunology, Lithuanian University of Health Sciences, Kaunas, Lithuania; ³Division of Allergy and Immunology, Department of Molecular Biology, University of Salzburg, Salzburg, Austria; ⁴Institute of Environmental Health, Center for Public Health, Medical University of Vienna, Vienna, Austria; ⁵Christian Doppler Laboratory for Allergy Research, Division of Immunopathology, Department of Pathophysiology and Allergy Research, Center for Pathophysiology, Infectiology and Immunology, Medical University of Vienna, Vienna General Hospital, Vienna, Austria

Allergen-specific IgG are also present in nasal fluids

Allergen-specific nasal IgG antibodies induced by vaccination with genetically modified allergens are associated with reduced nasal allergen sensitivity

Renaissance of the Blocking Antibody Concept in Type I Allergy

Sabine Flicker  Rudolf Valenta

Loveless MH. Immunological studies of pollinosis. I. The presence of two antibodies related to the same pollen antigen in the serum of treated hay-fever patients. J. Immunol. 38, 25-50, 1940
Effects of blocking allergen-specific antibodies on basophil degranulation

Conversion of grass pollen allergen-specific human IgE into a protective IgG₁ antibody

Sabine Flicker¹, Peter Steinberger¹, Lars Norderhaug², Wolfgang R. Sperr², Yasamin Majlesi², Peter Valent², Dietrich Kraft¹ and Rudolf Valenta¹
Mechanism 1: Allergen-specific IgG induced by SCIT inhibit specific IgE-mediated mast cell and basophil degranulation.
Why is the induction of allergen-specific IgG not always correlated with clinical improvement?
Only allergen-specific IgG which compete with IgE have beneficial effects

Allergen extracts lacking or containing low amounts of certain allergens do not induce sufficient levels of allergen specific blocking antibodies.

Mothes N, et al., Clin Exp Allergy 2003; 33:1198-1208
Certain allergens are poorly immunogenic and therefore fail to induce sufficient levels of IgG

A hybrid molecule resembling the epitope spectrum of grass pollen for allergy vaccination

Birgit Linhart, PhD,* Arnulf Hartl, PhD,b Beatrice Jahn-Schmid, PhD,* Petra Verdino, PhD,c Walter Keller, PhD,* Maria-Theresa Krauth, MD,§ Peter Valent, MD,§ Friedrich Horak, MD,* Ursula Wiedemann, MD,* Josef Thalhamer, PhD,b Christof Ebner, MD,* Dietrich Kraft, MD,* and Rudolf Valenta, MD* Vienna, Salzburg, and Graz, Austria

(J Allergy Clin Immunol 2005;115:1010-6.)
Certain forms of immunotherapy rather sensitize the patients than induce allergen-specific IgG

Sublingual immunotherapy with once-daily grass allergen tablets: A randomized controlled trial in seasonal allergic rhinoconjunctivitis

Stephen R. Durham, MD, a William H. Yang, MD, b Martin R. Pedersen, MSc-Pharm, c Niels Johansen, MSc-Chem Eng, d and Sabina Rak, MD e London, United Kingdom, Ottawa, Ontario, Canada, Hørsholm, Denmark, and Göteborg, Sweden
Advantages of SIT with rBet v 1 over SIT with birch pollen extract

Rhinitis, sinusitis, and upper airway disease

Efficacy of recombinant birch pollen vaccine for the treatment of birch-allergic rhinoconjunctivitis

Gabrielle Pauli, MD, a, * Tina H. Larsen, MD, b, * Sabina Rak, MD, c Friedrich Horak, MD, d Elide Pastorello, MD, e Rudolph Valenta, MD, f Ashok Purohit, MD, a Monica Arvidsson, PhD, c Alexander Kavina, MD, d Jan W. Schroeder, MD, e Nadine Mothes, PhD, f Susanne Spitzauer, MD, g Armelle Montagut, PhD, h Sylvie Galvain, DPharm, i Michel Melac, MD, i Claude André, MD, j Lars K. Poulsen, MD, b and Hans-Jorgen Malling, MD b Strasbourg, Meylan, and Antony, France, Copenhagen, Denmark, Gothenburg, Sweden, Vienna, Austria, and Milan, Italy

(J Allergy Clin Immunol 2008; 122: 951-60.)
rBet v 1 induces higher birch pollen-specific IgG than birch pollen extract

Stronger reduction of cutaneous sensitivity to birch pollen under rBet v 1 treatment compared to treatment with birch pollen extract

Monitoring of IT with recombinant allergens

Monitoring of the immunological efficacy of IT

Measurement of specific IgG

Major allergens: Phl p 1, Phl p 5, Bet v 1, Ole e 1, Par j 2
Patient 6

SCIT (Grass)

<table>
<thead>
<tr>
<th>Time</th>
<th>IgE</th>
<th>Grass</th>
<th>IgG&lt;sub&gt;1&lt;/sub&gt;</th>
<th>IgG&lt;sub&gt;4&lt;/sub&gt;</th>
<th>Egg</th>
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</thead>
<tbody>
<tr>
<td>t1(5.1.2010)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t2(20.4.2010)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t3(27.7.2010)</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Bet v 1
Allergen-specific IgG antibodies induced by SIT cause a reduction of allergen-specific IgE binding on ISAC

Lupinek, Methods 2014, 43:1202-16.
Monitoring Allergen Immunotherapy Effects by Microarray

Christian Lupinek, MD
Eva Wollmann, MD
Rudolf Valenta, MD

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Division of Immunopathology, Department of Pathophysiology and Allergy Research, Center for Pathophysiology, Infectiology and Immunology, Medical University of Vienna, Waehringer Guertel 18-20, 30, 1090, Vienna, Austria
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Development of allergen-specific IgG is associated with reduced boosts of allergen-specific IgE during the pollen season.

Vaccination with genetically engineered allergens prevents progression of allergic disease


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% change of IgE levels

before treatment (Nov/Dec 00) after treatment (Jan/Feb 01) May 01 Oct 01

- Bet v 1-Trimer
- Bet v 1-Fragments
- Placebo

seasonal pollen exposure

PNAS | October 5, 2004 | vol. 101 | suppl. 2 | 14677–14682
Immunotherapy with CpG-conjugated Amb a 1 induces allergen-specific IgG which is associated with reduced seasonal boosts of IgE production.

**The New England Journal of Medicine**

**ORIGINAL ARTICLE**

**Immunotherapy with a Ragweed–Toll-Like Receptor 9 Agonist Vaccine for Allergic Rhinitis**

Peter S. Creticos, M.D., John T. Schroeder, Ph.D., Robert G. Hamilton, Ph. Susan L. Balcer-Whaley, M.P.H., Arouna P. Khattignavong, M.D., Robert Lindblad, M.D., Henry Li, M.D., Ph.D., Robert Coffman, Ph.D., Vicki Seyfert, Ph.D., Joseph J. Eiden, M.D., Ph.D., David Broide, M.B., Ch.B., and the Immune Tolerance Network Group

![Graph showing the effect of treatment and seasonal boosts of IgE production.](image-url)
Mechanism 3: Allergen-specific IgG inhibit IgE-facilitated allergen presentation to T cells, T cell activation and secretion of pro-inflammatory cytokines.
SCIT with natural allergen extracts induces allergen-specific IgG which inhibits IgE-facilitated allergen presentation to T cells, specific T cell activation and production of pro-inflammatory cytokines.
Mechanism 3: Allergen-specific IgG inhibit IgE-facilitated allergen presentation to T cells, T cell activation and secretion of pro-inflammatory cytokines

Prof. Dr. Rudolf Valenta
The three mechanisms of action of immunotherapy

Unwanted and side effects of allergen-specific immunotherapy

IgE-mediated unwanted effects

- Effector cell degranulation
- Priming and/or boosting of IgE response

IgE-dependent

- Allergen
- Mast cell
- FcεRI
- IgE
- Effector cell degranulation

IgE-independent

- Allergen
- IgE
- B cell
- T cell epitopes
- MHC II
- TCR
- IL-4, IL-5, IL-13

T cell-mediated side effects

SIT

Evidence for IgE-independent, T cell-mediated side effects. Non-IgE-reactive T cell epitope-containing peptides of the major cat allergen Fel d 1

Immunoglobulin E-independent Major Histocompatibility Complex-restricted T Cell Peptide Epitope-induced Late Asthmatic Reactions

By Brigitte M. Haselden, A. Barry Kay, and Mark Larché

Allergen-Derived T Cell Peptide-Induced Late Asthmatic Reactions Precede the Induction of Antigen-Specific Hyporesponsiveness in Atopic Allergic Asthmatic Subjects

William L. G. Oldfield, A. Barry Kay and Mark Larché

J Immunol 2001;167;1734-1739
Clinical effects of immunotherapy with genetically modified recombinant birch pollen Bet v 1 derivatives


*Service de Pneumologie, Hôpitaux Universitaires de Strasbourg, Strasbourg, France; †Department of Otorhinolaryngology, Medical University of Vienna, Vienna, Austria; ‡Department of Medicine, Clinical Immunology and Allergy Unit, Karolinska Institutet and University Hospital, Stockholm, Sweden; §Department of Medicine, Unit of Respiratory Medicine, Karolinska Institutet and University Hospital, Stockholm, Sweden; ‡Allergopharma Joachim Ganzer KG, Reinbek, Germany and †Christian Doppler Laboratory for Allergy Research, Division of Immunopathology, Department of Pathophysiology, Medical University of Vienna, Vienna, Austria

Evidence for IgE-independent, T cell-mediated side effects. Recombinant hypoallergenic derivatives of the major birch pollen allergen Bet v 1

Table 3. Nature and frequency of local and systemic adverse events

<table>
<thead>
<tr>
<th></th>
<th>Bet v 1 fragments</th>
<th>Bet v 1 trimer</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects (n)</td>
<td>38</td>
<td>37</td>
<td>49</td>
<td>124</td>
</tr>
<tr>
<td>Grade 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swelling 5–10 cm</td>
<td>47/14</td>
<td>78/20</td>
<td>40/14</td>
<td>163</td>
</tr>
<tr>
<td>Swelling &gt;10 cm</td>
<td>2/2</td>
<td>23/8</td>
<td>7/5</td>
<td>32</td>
</tr>
<tr>
<td>Grade 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>16/12</td>
<td>11/7</td>
<td>9/5</td>
<td>36</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>49/22</td>
<td>35/14</td>
<td>30/11</td>
<td>114</td>
</tr>
<tr>
<td>Cough</td>
<td>24/8</td>
<td>12/4</td>
<td>3/3</td>
<td>39</td>
</tr>
<tr>
<td>Wheezing</td>
<td>9/4</td>
<td>6/2</td>
<td>1/1</td>
<td>16</td>
</tr>
<tr>
<td>General urticaria</td>
<td>9/8</td>
<td>6/6</td>
<td>0/0</td>
<td>15</td>
</tr>
<tr>
<td>General itching</td>
<td>4/4</td>
<td>4/3</td>
<td>2/1</td>
<td>10</td>
</tr>
<tr>
<td>General erythema</td>
<td>0/0</td>
<td>2/1</td>
<td>0/0</td>
<td>2</td>
</tr>
<tr>
<td>Grade 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>9/7</td>
<td>4/3</td>
<td>0/0</td>
<td>13</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>3/2</td>
<td>1/1</td>
<td>0/0</td>
<td>4</td>
</tr>
<tr>
<td>Circulatory dysregulation</td>
<td>1/1</td>
<td>0/0</td>
<td>0/0</td>
<td>1</td>
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<tr>
<td>Gastrointestinal reaction</td>
<td>0/0</td>
<td>1/1</td>
<td>0/0</td>
<td>1</td>
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</tbody>
</table>
Synthetic allergy vaccines in clinical trials
Circassia ToleroMune Technology

Allergy

<table>
<thead>
<tr>
<th>Product</th>
<th>Research</th>
<th>Pre-Clinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Market</th>
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<tbody>
<tr>
<td>Cat</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>House Dust</td>
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<tr>
<td>Mite</td>
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<td></td>
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<tr>
<td>Grass</td>
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<td></td>
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<tr>
<td>Ragweed</td>
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</tbody>
</table>

T cell epitope peptides

- IgE
- T cell
- IgG-inducing
# Failure of the T cell epitope peptide approach

## Top-line efficacy results

### Primary endpoint

<table>
<thead>
<tr>
<th>ITT population</th>
<th>Placebo (n=414)</th>
<th>4 x 6 nmol (n=417)</th>
<th>8 x 6 nmol (n=414)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Combined Score (baseline)</td>
<td>2.53 pts</td>
<td>2.49 pts</td>
<td>2.49 pts</td>
</tr>
<tr>
<td>Mean Combined Score (52-54 weeks)</td>
<td>1.05 pts</td>
<td>1.04 pts</td>
<td>1.00 pts</td>
</tr>
<tr>
<td>Combined Score reduction from baseline</td>
<td><strong>58.5%</strong></td>
<td><strong>58.2%</strong></td>
<td><strong>59.8%</strong></td>
</tr>
<tr>
<td>LS mean difference vs placebo (52-54 weeks)</td>
<td>-</td>
<td>-0.01 pts (-0.7%)</td>
<td>-0.05 pts (-4.7%)</td>
</tr>
<tr>
<td>P value vs placebo</td>
<td>-</td>
<td>0.914</td>
<td>0.439</td>
</tr>
</tbody>
</table>

- Primary endpoint: combined TRSS (0-24 scale) and rescue medication use (RMS) score (0-3 scale)
  - Combined Score (0-6 scale) = (TRSS / 8) + (RMS)
Towards the most “hypoallergenic vaccine approach”

Genetically Engineered and Synthetic Allergen Derivatives: Candidates for Vaccination against Type I Allergy

Rudolf Valenta¹*, Susanne Vrtala¹,
Margit Focke-Tejkl¹,
Agnes Bugajska-Schretter², Tanja Ball¹,
Anna Twardosz¹, Susanne Spitzauer²,
Hans Grönlund³ and Dietrich Kraft¹

¹ Dept. of General and Experimental Pathology,
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³ Pharmacia and Upjohn Diagnostics AB,
S-75182 Uppsala, Sweden

Fig. 8 Synthetic Peptides or Recombinant Allergen Fragments Containing Portions of the IgE Epitopes. Peptides without IgE binding capacity (parts of IgE epitopes) representing surface-exposed portions of an allergen may be used to focus blocking antibodies to IgE epitopes.

Fig. 9 Vaccination with Hypoallergenic Allergen Derivatives Induces Synthesis of Blocking IgG Antibodies. Allergens hidden by IgG antibodies cannot be recognized by IgE.
Development of a recombinant B cell epitope-based grass pollen allergy vaccine

http://www.youtube.com/watch?v=61YFrPEU904
Mechanisms, safety and efficacy of a B cell epitope-based vaccine for immunotherapy of grass pollen allergy

Petra Zieglmayer\textsuperscript{a}, Margarete Focke-Tejkl\textsuperscript{b}, René Schmutz\textsuperscript{a}, Patrick Lemell\textsuperscript{a}, René Ziegelmayer\textsuperscript{a}, Milena Weber\textsuperscript{b}, Renata Kiss\textsuperscript{b}, Katharina Blatt\textsuperscript{c}, Peter Valent\textsuperscript{c}, Frank Stolz\textsuperscript{d}, Hans Huber\textsuperscript{d}, Angela Neubauer\textsuperscript{d}, Anette Knoll\textsuperscript{e}, Friedrich Horak\textsuperscript{a}, Rainer Henning\textsuperscript{d}, Rudolf Valenta\textsuperscript{b}, *

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\textsuperscript{b} Division of Immunopathology, Department of Pathophysiology and Allergy Research, Center for Pathophysiology, Infectiology and Immunology, Medical University of Vienna, Vienna, Austria
\textsuperscript{c} Department of Internal Medicine I, Division of Hematology & Hemostaseology, Medical University of Vienna, Vienna, Austria
\textsuperscript{d} BIOMAY AG, Vienna, Austria
\textsuperscript{e} SynteractHCR, Munich, Germany
Towards prevention of allergy by vaccination and tolerance induction

Prof. Dr. Rudolf Valenta
The three mechanisms of action of BM32

The BM32 team

Christian Doppler Laboratory for Allergy Research Medical University of Vienna, Austria

Biomay AG Vienna - Austria

Dept. of ENT, Medical University of Vienna, Austria

Div. of Hematology and Hemostaseology, Dept. of Internal Med. I Medical University of Vienna, Austria

Vienna Challenge Chamber (VCC), Vienna, Austria
Thank you for your attention!
Rudolf Valenta

http://www.allergy-research-program.at/cms/