# New Advances in Allergen Vaccines for Allergic Respiratory Diseases: Modified Allergens/DNA Adjuvants/Peptide Constructs/Recombinants

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## Disclosures

In the past 3 years, I have received research grants from: Stallergenes-Greer, Circassia, Merck.

I am a consultant to: ASIT, Allakos, Allergy Therapeutics, Biomay, and Stallergenes-Greer.

I am a section editor and author for UpToDate.

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## Part I

## Methods of Allergen Immunotherapy

- Classic Subcutaneous Immunotherapy (SCIT)
- Sublingual Immunotherapy (SLIT)
- T-cell-derived peptide immunotherapy
- SCIT modified w/ adjuvant approaches

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## Concept

Synthetic peptides comprised of T cell epitopes whose sequence is derived from known amino acid sequences of specific allergens can be utilized to our advantage to induce tolerance

Animal models and human studies demonstrate that short linear peptides can be designed which retain the ability to stimulate allergen-specific responses while being of insufficient length to crosslink IgE on the surface of mast cells and basophils

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## Early Work: Inducing T-cell Tolerance with Peptide Epitopes

O'Hehir RE, Yssel S, Verma J, et al. Clonal analysis of differential lymphokine production in peptide and super-antigen induced T cell anergy. Int Immunol 1991; 3:819-826.

Higgins JA, Lamb JR, Marsh SGE, et al. Peptide-induced non-responsiveness of HLA-DP restricted human T cells reactive with Dermatophagoides spp (house dust mite). J Allergy Clin Immunol 1992; 90:749-756.

Briner TJ, Kuo M-C, Keating KM, Rogers BL. Peripheral T-cell tolerance induced in naïve and primed mice by subcutaneous injection of peptides from the major cat allergen Fel d 1. Proc Natl Acad Sci 1993; 90:7608-12.

Wallner BP, Gefter ML. Immunotherapy with T-cell-reactive peptides derived from allergens. Allergy 1994; 49:302-308.

Counsell CM, Bond JF, Ohman JL, Greenstein JL, Garman RF. Definition of the human T cell epitopes of Fel d 1, the major allergen of the domestic cat. J Allergy Clin Immunol 1996; 98:884-894.

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## Clinical Studies Assessing 1st Generation T-cell-Tolerizing Peptides

Norman P, Ohman J, Long A, Creticos P, et al. Treatment of cat allergy with T-cell reactive peptides 1996. Am J Respir Crit Care Med; 154: 1623-28.

**Norman** PS, Nicodemus CF, Creticos PS, Wood RA, et al. Clinical and Immunologic Effects of Component Peptides in Allervax® Cat. Int. Arch Allergy Immunol. 1997; 113: 1-3.

**Creticos**, PS, Hebert, J, Philip, G, and the Allervax® Ragweed Study Group. Efficacy of Allervax® ragweed in the treatment of ragweed-induced allergy. J. Allergy Clin**.** Immunol**.** 99, No. 1, Part 2:S401(1631), 1997

**Creticos** PS. Peptide Downregulation of the Immune Response. Asthma and Allergic Diseases. Academic Press. Editors: Gianni Marone, K. Frank Austen, Stephen T. Holgate, A. Barry Kay, Lawrence M. Lichtenstein. 1998; Chapter 30: 407-415

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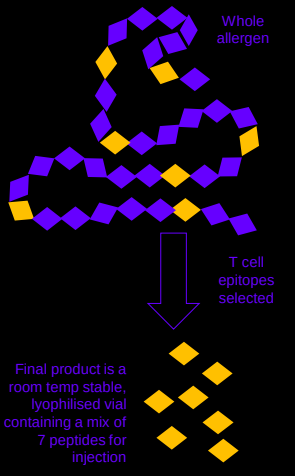
## Synthetic Peptide Immuno-Regulatory Epitopes (SPIREs) - a new class of immunotherapy [Circassia]

**T cell reactive peptides: linear stretches of amino acids within allergen sequence [mix of 7 small peptides (13-17 AA in length]**

- **peptides bind to MHC class II on antigen presenting cells to induce regulatory T cells**

- **Lack of B cell epitopes in peptides avoids cross-linking of mast cells**

**By obviating the tertiary structure that would otherwise result in recognition of IgE antibodies and increase the likelihood of an immediate type hypersensitivity reaction to an allergen injection, it is postulated that peptide therapy could afford a safer therapeutic approach**

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## Clinical Studies Assessing Cat-SPIRE

Alexander C, Tarzi M, Larche M, Kay AB. The effect of Fel d 1-derived T-cell peptides on upper and lower airway outcome measurements in cat-allergic subjects. Allergy 2005; 60:1269-74.

Worm M, Lee HH, Kleine-Tebbe J, Hafner RP, et al. Development and preliminary clinical evaluation of a peptide immunotherapy vaccine for cat allergy. J Allergy Clin Immunol 2011; 127 (1):89-97.

Patel D, Couroux P, Hickey P, et al. Fel d 1-derived peptide antigen desensitization shows a persistent treatment Effect 1 year after the start of dosing: A randomized, placebo-controlled study. J Allergy Clin Immunol 2013; 131(1): 103-109.

Worm M, Patel D, Creticos PS. Cat peptide desensitization for cat allergic rhinoconjunctivitis. Expert Opin Investig Drugs 2013; 22 (10):1347-1357.

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## DBPC Field Trial to Assess the Efficacy & Safety of Cat Peptide Immunotherapy (SPIRE) in Patients with ARC and/or Asthma

**Study Objective:**

- To evaluate the therapeutic efficacy/safety of treatment with ID administration of T cell epitope-defined peptides (derived from cat Fel d 1) in reducing the symptoms and use of allergy relief meds

**Study Design:**

- Randomized, double-blind, placebo-controlled clinical trial in cat-allergic subjects (12-65) who are exposed to cats on a regular basis in their home setting.
- history of moderate to severe rhinoconjunctivitis +/- GINA step 1-controlled asthma / + skin test reactivity to cat extract / + ImmunoCAP to cat dander / demonstrable symptoms during screening baseline
- Tx Regimens: Cat-PAD (4x6 nmol) 4 wks apart f/u by 4 PL injs (4 wks apart) / Cat-PAD (4x6 nmol) 4 wks apart f/u by a second course of Cat-PAD (4x6 nmol) 4 wks apart / Two courses of Placebo x 4 (4 wks apart)

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## DBPC Field Trial to Assess the Efficacy & Safety of Cat Peptide Immunotherapy (SPIRE) in Patients with ARC and/or Asthma

- **Study Results (Press Release: June 20, 2016):**

The study compared a four-dose course of Fel d 1 allergen peptides, two sequential courses (eight doses) and placebo. The primary endpoint measure was the mean Combined Score (combined total rhinoconjunctivitis symptom score [TRSS] and rescue medication use score); mean TRSS was a secondary endpoint measure. The study's endpoint outcomes were the difference between placebo and active groups one year after the start of dosing.

- **Efficacy Results**

- All groups had greatly improved Combined Score vs Baseline:

*CS reduction vs BL*: 4 x 6nmol = 58.2% / 8 x 6 nmol = 59.8% /PL = 58.5%

- All groups had greatly improved TRSS vs Baseline:

[4 x 6nmol]: 14.5 TRSS points decreased to 5.7 points (-61.0%); [8 x 6 nmol]: 14.2 decreased to 5.5 points (-61.1%); [placebo]: 14.5 decreased to 5.9 points (-59.5%)

- The Combined Score in the active treatment groups were not significantly different to placebo.

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## Phase IIb RDBPC Field Trial to Assess the Efficacy/Safety of HDM SPIRE in Subjects w/ HDM-induced Rhinoconjunctivitis

### Study Design

RDBPC multicenter trial / ages: 18-65 / hx of moderate-to-severe rhinoconjunctivitis skin test sensitivity to Df/Dpt / HDM-specific IgE ≥ 0.7 kU/l / <GINA 3 / FEV1 ≥80%

Treatment phase (4 arms): a single (12 nm) four-dose course of treatment administered over 12 weeks / two sequential courses (eight doses) / a high-dose (20 nm) course of four administrations, and placebo.

Primary endpoint: the difference in mean Combined Score (CS: combined total rhinoconjunctivitis symptom score and rescue medication use score) between the placebo and active groups one year after the start of dosing.

### Efficacy Results

The placebo group showed a substantial reduction in Combined Score from baseline (39.1%).

- The 4 x 12nmol regimen improved the Combined Score by 34.9% from baseline; (CS vs placebo p=0.26).
- The 4 x 20nmol regimen improved the Combined Score by 40.9% from baseline; (CS vs placebo p=0.65).
- The 8 x 12nmol regimen improved the Combined Score by 44.3% from baseline; (CS vs placebo p=0.14).

### Corporate Decision

Despite positive clinical findings in previous chamber studies, the inability of active treatment to demonstrate a therapeutic benefit as compared to placebo in this Phase IIb field study (as well as the disappointing results in the cat-SPIRE field study) has resulted in the company halting its allergy programs.

**Source: Circassia Press Release: April 18, 2017**

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## Continuous Overlapping Peptides [Anergis]

- Continuous overlapping peptides (COP) are long synthetic peptides (up to 80 amino acids) which reproduce fragments of the AA sequence of a selected major allergen (e.g., birch Bet v 1)

  -- the methodology reproduces the entire sequence of the naturally-occurring allergen in an attempt to achieve optimal immunogenicity by covering all T-cell epitopes

  -- the COP vaccine contains all linear epitopes, hence disrupting the 3-D structure that otherwise would lead to the conformational changes that are integral to eliciting the allergic reaction through IgE binding.

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## Pertinent Clinical Studies with COP


• Pellaton C, Perrin Y, Boudousquie C, et al. Novel birch pollen specific immunotherapy formulation based on contiguous overlapping peptides. Clin Transl Allergy 2013; 3:17.

• Spertini F, Perrin Y, Audran R, et al. Safety and immunogenicity of immunotherapy with Bet v 1-derived contiguous overlapping peptides. J Allergy Clin Immunol 2014; 134:239-40 e13.

• Spertini F, DellaCorte G, Kettner A, et al. Efficacy of 2 months of allergen-specific immunotherapy with Bet v 1-derived contiguous overlapping peptides in patients with allergic rhinoconjunctivitis: Results of a phase IIb study. J Allergy Clin Immunol 2016; 138:162-8.

• Hoffmann HJ, Valovirta E, Pfaar O, Moingeon P, Schmid JM, Skaarup SH, Cardell LO, Simonsen K, Larche M, Durham SR, Sorensen P. Novel approaches and perspectives in allergen immunotherapy. Allergy 2017;72(7):1022-34.

• Kettner A, DellaCorte G, de Blay F, Jacobsen L, Jutel M, Worm M, Charlon V, Simonsen K, Reymond C, Spertini F. Benefit of Bet v 1 contiguous overlapping peptide immunotherapy persists during first follow-up season. J Allergy Clin Immunol 2018; 142(2):678-80.


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## Benefit of Bet v 1 Contiguous Overlapping Peptide Immunotherapy Persists During First follow-up Season. Kettner A, et al. J Allergy Clin Immunol 2018; 142:678-80.

• **Study Design:**

- 2nd Year blinded follow-up of DBPC clinical trial (196/240 pts)

- Treatment: 5-injection subcutaneous regimen with Birch Bet v 1 COP (Bet v 1 COP 50µg; Bet v 1 COP 100µg; Placebo)

**Clinical Findings:**

• Primary endpoint (Combined RSMS) [mn change vs PL)

- Bet v 1 COP 50 µg: 21% (p=.03)
- Bet v 1 COP 100 µg: 18% (p=.07)

• Mini RCQOL: favorable improvement of 21% (p=.03); 20% (p=.05)

• Antibody Response: Bet v 1 $IgG_4$ increased 10- to 20-fold with initial Bet v 1 COP treatment; prior to the 2nd birch season, albeit a ↓ was observed, the $IgG_4$ level remained 2- to -3 fold elevated vs PL (p: <0.001)

• Conclusions: This work demonstrates sustained benefit over 2 birch seasons with a short 5-injection treatment regimen employing COP

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## Natural Allergen Peptide Fragments (ASIT Biotech)

- Product: Allergenic extract comprised of highly purified natural allergen fragments
  - technology results in extraction of soluble components from natural sources of allergen (e.g., lolium perenne)
  - steps in purification of protein ensure elimination of non-proteic components
  - standardized enzymatic hydrolysis of purified proteins results in highly purified natural allergen fragments (encompassing a broad panel of epitopes)

- Concept: the ASIT+™ technology platform provides an adjuvant-free formulation that can stimulate a rapid protective immune response in a short course dosing regimen (4 SQ injections over 3 wks) that optimizes long-term safety

- Platforms:

  gp-ASIT+™ (grass) – in Phase II/III
  hdm-ASIT+™ (house dust mite) – in Phase I
  other airborne allergens and food allergens in preclinical discovery/development

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## Recent Publications with Highly Purified Natural Fragments of LPP for grass-induced ARC

- Shamji MH, Ceuppens J, Bachert C et al. Lolium perenne peptides for the treatment of grass pollen allergy: A randomized double blind placebo-controlled clinical trial. J Allergy Clin Immunol 2018; 141(1):448-451.

  • This first-in-man study (BTT-004) in which a formulation of purified peptide fragments of rye grass [Lolium perenne peptides (LPP)] administered as 5 SQ injections of increasing doses of the LPP was well-tolerated and induced a clear immunological response.

  Albeit not powered for efficacy, subgroup analyses of patients that received a higher cumulative dose of LPP showed improvement in clinical outcomes (CPT; symptom scores) which together with ex-vivo data provide evidence for the advantage of the LPP peptides over whole allergens.

- Mösges R, Koch AF, Raskopf E, et al. Lolium perenne peptide immunotherapy is well tolerated and elicits a protective B-cell response in seasonal allergic rhinitis patients. Allergy 2018(June); 73(6): 1254-1262.

  • The phase 2A study (BTT-007) reports on the overall good safety and tolerability of doses up to 490µg, and provides confirmation of the first-in-man study data related to efficacy.

- Mösges R, Kasche EM, Raskopf E, et al. A randomized, double-blind, placebo-controlled, dose-finding trial with Lolium perenne peptide immunotherapy. Allergy. 2018(April); 73(4): 896-904.

  • The phase 2B dose-finding study (BTT-008) identifies 170µg as optimal target dose from a benefit/risk perspective based on CPT, with confirmation of efficacy and safety results of previous studies.

- Mösges R, Bachert C, Panzner P, et all. Short-course of grass allergen peptides immunotherapy over three weeks reduces seasonal symptoms in allergic rhinoconjunctivitis with/without Asthma: A randomized, multicenter, double-blind, placebo-controlled trial. Allergy 2018(Sept); 73(9): 1842-1850.

  • The phase 3 study (BTT-009) confirms overall safety and efficacy on the surrogate endpoint CPT, and also demonstrates the efficacy of the short-term treatment with the LPP peptides (gpASIT) administered as 8 injections over 3 weeks during the pollen season

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## Part II

## Methods of Allergen Immunotherapy

- Classic Subcutaneous Immunotherapy (SCIT)
- Sublingual Immunotherapy (SLIT)
- T-cell-derived peptide immunotherapy
- SCIT modified w/ immunostimulatory adjuvant (TLR-9; TLR-4)

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## Selected Clinical Trials with Adjuvant Vaccines

**TLR-9:** Immunostimulatory DNA (CpG Oligonucleotide Conjugated to Allergen) [Dynavax]

**MPL:** Bacteria-derived lipopolysaccharide (Monophosphoryl Lipid A) [Allergy Therapeutics]

**QbG10 Nanopoarticles:** CpG motif packaged in virus-like particles (VLPs) derived from bacteriophage [Cytos]

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## TLR-9 Vaccine Development Program (Dynavax)

**Cx Trials in Human Subjects with Immunostimulatory DNA [CpG Oligonucleotide Conjugated to Allergen]**

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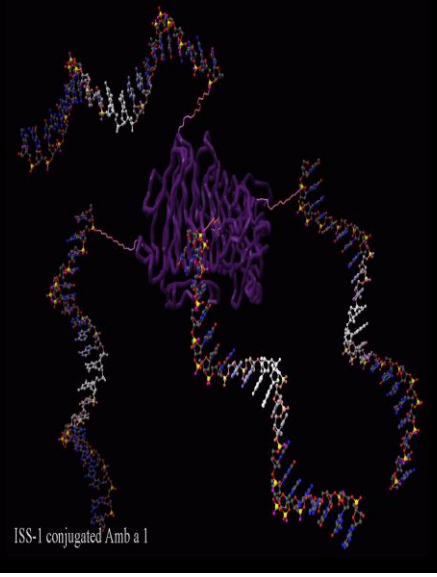
## Concept

### AIC (*Amb* a 1 Immunostimulatory Conjugate)

- **AIC consists of *Amb* a 1, the major allergen of ragweed pollen, that is first highly purified and then conjugated with a specific immunostimulatory CpG oligonucleotide (Dynavax 1018 CpG oligonucleotide).**
- **CpG oligonucleotide acts through the TLR-9 receptor on a variety of cells to redirect an untoward Th2-driven allergic diathesis and restore immunologic balance.**

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## NIH-ITN Phase II Clinical Trial to Evaluate Safety/ Efficacy/Immunologic Mechanisms of RW-TLR-9 Agonist Vaccine in Ragweed-induced Seasonal Allergic Rhinitis

- **Study Design:**
  - Randomized DBPC Clinical Trial (n=25)
- **Treatment Phase:**
  - 6 AIC injections advanced weekly as tolerated [.06/0.3/1.2/3.0/6.0/12.0µg AIC]
- **Challenge Phase:**
  [Nasal Scraping/Lavage/Allergen Provocation]
  - Pretreatment/2-weeks/2-months post 6-injection AIC regimen
- **Cx and Immunologic Assessments at Defined Points:**
  - Symptom diaries/Visual Analog Scale/QOL
  - Antibody and T cell assays

Creticos, et al. NEJM 2006; 355:1445-55

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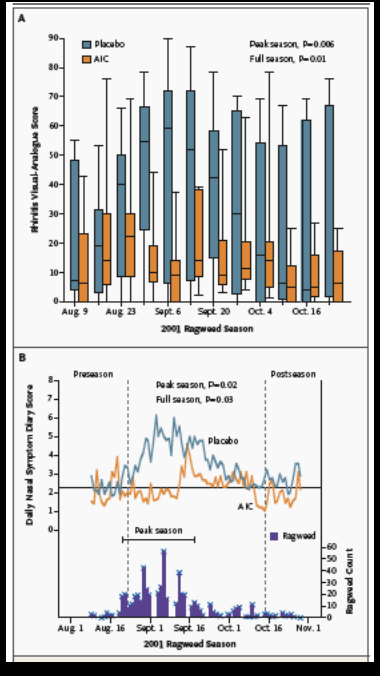


### Initial Ragweed Season

**Rhinitis Visual Analog Score**

- The mean peak-season VAS in the AIC group was 3-fold lower than that in the placebo group [13.2 vs 40.8; p=0.006]

**Rhinitis Daily Nasal Symptom Diary Score**

- The mean peak-season NSDS in the AIC group was 55% lower than that observed in the placebo group [1.8 vs 4.0; p=0.02]

Creticos, et al. NEJM 2006; 355:1445-55

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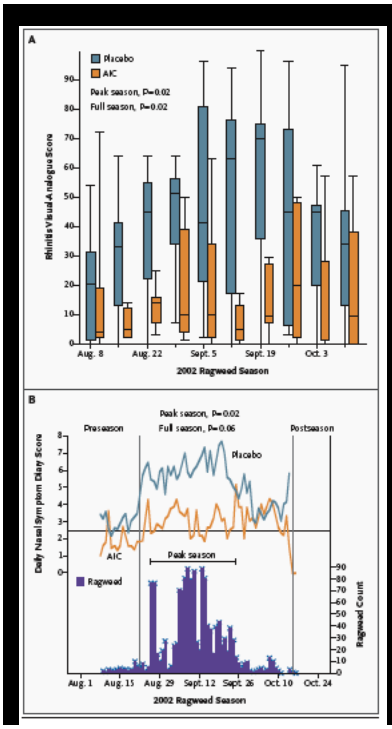


## Follow-up Ragweed Season

### Rhinitis Visual Analog Score

- The mean peak-season VAS in the AIC group was again ~ 1/3 of that reported in the placebo group [13.9 vs 49.4; p=0.02]

### Rhinitis Daily Nasal Symptom Diary Score

- The mean peak-season NSDS was reduced by 53% in the AIC group as compared with the placebo group [2.8 vs 5.9; p=0.02]

Creticos, et al. NEJM 2006; 355:1445-55

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## Summary of Ragweed AIC Findings

- Was well tolerated and safely administered in a brief 6-injection, once-weekly regimen
- Patients demonstrated significant improvement in clinical endpoints when compared to placebo [VAS/Nasal Symptom Complex Score/QOL]
- AIC induced only a modest and transient rise in Amb a 1 and RW-specific IgG antibody with no detectable functional IgG activity (FAP assay)
- AIC blunted the initial seasonal rise in Amb a 1 and RW-specific IgE and clearly suppressed the seasonal rise in RW-IgE in the subsequent allergy season
- Induced long-term clinical tolerance with comparable control observed during the follow-up RW-season

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## TLR-4 Vaccine Development Program (Allergy Therapeutics)

**Compound: Allergoid-Specific Adjuvant Construct**

Native Allergens [Grass/Ragweed/Birch] modified in 3 ways:

**a)** gluteraldehyde-modified (allergoid)
- allergenic epitopes modified to reduce allergenicity but preserve immunogenicity

b) tyrosine-absorbed
- slow-release kinetics

c) MPL adjuvant incorporated

- immunostimulatory adjuvant derived from detoxified LPS originating from the gram negative bacterium *Salmonella Minnesota* (Monophosphoryl Lipid A) [TLR-4 adjuvant]

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## Ultrashort-specific Immunotherapy Successfully Treats Seasonal Allergic Rhinoconjunctivitis to Grass Pollen

DeBuske, Frew, Horak, et al 2011; Allergy Asthma Proc; 32: 239-247

**Study Design:**

- Randomized, DBPC, parallel-group clinical trial
  n = 1028 grass allergic adults
- Treatment: 4 ~ weekly injections (300/800/2000/2000 SU) of either Grass MATA-MPL (modified grass allergen + tyrosine absorbate + MPL adjuvant) or placebo

**Entry Criteria:**

- history of rhinoconjunctivitis in previous grass season
- + skin prick test to *Phleum pratense* (≥5mm wheal)
- + serum allergen-specific IgE [≥ Class II (0.71 U/mL; ImmunoCap)]

**Outcomes:**

- Significant improvement in primary outcome (Mean Combined Symptom Medication Score) during the 4 peak pollen weeks [13.4% vs PL (p= 0.0038)]
- Increase in grass-specific IgG to tx (6.5-fold median rise) (p: <0.001)

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## Nanoparticle-based Immune Modulation

**Compound: CYT003-QbG10** (Cytos)

- *Nanoparticle-based Immunomodulator technology*

- CpG Oligonucleotide (G10; A-type unmethylated CpG motif) packaged into virus-like particles (VLPs) derived from bacteriophage (Qbeta)

- The nanoparticle construct protects the CpG-ODN from degradation by DNAses and allows efficient drainage to regional lymph nodes where the TLR-ligand can enhance activation of resident APCs (eg. pDC) through interaction of the CpG ligand with its receptor (eg. TLR-9)

- The VLPs are non-infectious, harbor no replicative genetic material, and thereby do not integrate into the host's cell genome.

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## Initial Clinical trials with Nanopeptide VLPs [Cytos]

**Use of A-type CpG Oligonucleotides as an Adjuvant in Allergen-specific Immunotherapy in Humans: a Phase I/II Clinical Trial.** Senti, Johansen, Haug, et al. Cx Et Experimental Allergy 2009; 39: 562-70

- Design: Single center; open-label (n=20 HDM allergic adults w/ PAR + asthma)

- Tx: bacteriophage Qb capsid VLPs (QbG10) admixed w/ std HDM (Allergopharma) [SQ injs. x3 (escalated cluster) vs fixed phase regimen (6 SQ injs. at 1-2 wk intervals)]

- Results: a) CPT: 10-100 fold increased tolerance; b) RCSS (med): ↓ by 86% at 2 wks post-tx ($p<.0001$) and maintained x 48 wks ($p< .001$); c) Asthma score reduced to symptom-free at 12/34/48 wks ($p< .0001/<.0007/<.0001$)

**Assessment of Clinical Efficacy of CYT003-QbG10 in Patients with Allergic Rhinoconjunctivitis: a Phase IIb Study.** Klimek, Willers, Hammann-Haenni et al; Cx Exp Allg 2011; 41:1305-12

- Design: RDBPC (n=299 HDM allergic adults w/ perennial allergic rhinoconjunctivitis)

- Tx: bacteriophage Qb capsid VLPs (QbG10) *w/out co-admin of allergen* [6 weekly SQ injs. [a) 0.5 mg VLP construct; b) 1 mg VLP construct; c) Placebo]

- Results: a) CPT: median 10-fold increased tolerance in 1 mg group ; b) RCSS: benefit in high-dose group vs PL [0.31 vs 0.52 ($p=0.04$)]; c) + MiniRQLQ ($p=.02$); d) 6/16 pts dcont'd 2° TRAEs

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**CYT003, a TLR9 Agonist, in Persistent Allergic Asthma – a Randomized PL-controlled Phase 2b Study.** Casale TB et al. Allergy 2015;70:1160-68

**Study Design:**

365 patients with persistent moderate-to-severe asthma not sufficiently controlled with inhaled corticosteroids +/- LABAs were randomized in a PL-controlled study design

Tx Regimen: 7 SQ doses of the TLR-9 agonist (A-type CpG G10) encapsulated into VLPs (.3, 1.0, or 2.0 mg) or PL as add-on therapy to conventional controller medication.

**Clinical Results:**

All treatment groups, including placebo, demonstrated clinical improvement in the ACQ score at the end of the treatment phase

- no significant difference observed between [CYT003-QbG10] and PL at Week 12 [LSMeans diff: 0.3 mg: -0.027 (95%CI: -0.259 to 0.204); 1 mg: 0.097 (-0.131 to 0.325); 2 mg: 0.081 (-0.148 to -0.315)]

- No sig. diffs in secondary outcomes (▲ in FEV1; Mini Asthma QOL; safety)

- Due to lack of efficacy, the study was terminated at the end of the Tx phase

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## Part III
## Methods Of Allergen Immunotherapy

- Classic Subcutaneous Immunotherapy (SCIT)
- SCIT modified w/ adjuvant approaches
- Synthetic Peptide Immuno-Regulatory Epitopes
- Sublingual Immunotherapy (SLIT)
- Intralymphatic Immunotherapy (ILIT)
- Recombinant vaccines
- Epicutaneous Immunotherapy (EPIT)

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## Selected Studies of Recombinant Allergen-Specific Immunotherapy


Klimek L, Bachert C, Doemer C, et al. Specific immunotherapy with recombinant birch pollen allergen rBet v 1-FV is clinically efficacious. Allergy Clin Immunol Int 2005; 1-15.

Jutel M. Jaeger L, Suck R, et al. Allergen-specific immunotherapy with recombinant grass pollen allergens. J Allergy Clin Immunol 2005; 116: 608-13.

Pauli G, Larsen TH, Rak S, et al. Efficacy of recombinant birch pollen vaccine for the treatment of birch-allergic rhinoconjunctivitis. J Allergy Clin Immunol 2008; 122: 951-990.

Winther L, Poulsen LK, Robin B, et al. Safety and tolerability of recombinant Bet v 1 (rBet v 1) tablets in sublingual immunotherapy (SLIT). J Allergy Clin Immunol 2009; 123:S215.

Valenta R, Linhart B, Swoboda I, Niederberger V. Recombinant allergens for allergen-specific immunotherapy: 10 years anniversary of immunotherapy with Recombinant allergens. Allergy 2011: 66: 775-783 (Review).


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## Biomay

### Compound: Recombinant B-cell Epitope Vaccine

- peptide carrier *fusion vaccine* that contains linear peptides which are parts of B-cell epitopes
  - -- these peptides are fused to an immunogenic carrier element and utilizing recombinant technology are expressed as fusion proteins
- The peptide carrier fusion vaccine is capable of inducing allergen-specific IgG that is then directed against parts of the IgE epitope and blocks the binding of IgE

### Current Work:

- Ongoing Phase IIb 2-Year clinical study with a grass recombinant vaccine (√ clinicaltrials.gov)
- Pre-clinical development of a peptide carrier fusion vaccine for birch

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## Mechanisms, Safety, and Efficacy of a B cell Epitope-based Vaccine for Immunotherapy of Grass Pollen Allergy Zieglmayer et al; EBioMedicine 2016

**Study Design: RDBPC (Vienna Challenge Chamber) clinical trial**

• n=71 grass-allergic patients randomized to one of 3 doses [10µg, 20µg, 40µg] of BM32 fusion protein (Timothy-derived peptides (Phl p 1/2/5/6) and hepatitis B surface protein domain preS as a carrier) or matching PL

-- Tx Phase: 3 SQ injections of BM32 dose at 3-4 wk intervals

-- VCC: at baseline and at 3-4 wks post last tx dose

• **Results:**

-- TNSS (in VCC) [primary endpoint]: sig ↓ in 20µg [-1.41 (p=.03); %RD: 24%] and 40µg [-1.34 (p=.003); %RD: 20%] vs PL (-10%)

-- TOSS and SPT showed a dose-dependent decrease

-- BM32 induced a marked increase in the allergen-specific $IgG_4$ response (p<.0001); but not in allergen-specific IgE

-- addn of tx-induced IgG signif suppressed T cell activation

-- tx well-tolerated: No Grade 2-4 syst rxs; Gr 1 rxs were LP (AR:7/AC:1/Cut (3)

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## Safety & Efficacy of Recombinant B-cell Epitope-based Vaccine in Grass-allergic Patients Niederberger et al; J Allergy Clin Immunol 2018

• Study Design: RDBPC multicenter trial conducted over 2 grass seasons

• n=181 grass-allergic patients followed over a baseline season

- Tx Yr 1: randomized to 3 pre-seasonal injections of BM32 [low dose (80µg); high dose (180µg)] or PL; followed by a booster in autumn

- Tx Yr 2: all BM32 pts received 3 pre-seasonal injections of low dose BM32 (60µg) whereas, PL patients cont'd on placebo

• Results:

- Primary Endpoint (CSMS): did not reach stat signif

- Secondary Endpoints:
  - BM32-treated patients showed improvement in symptom medication scores, VAS, QoL score, and asthma symptom scores
  - Tx resulted in the induction of allergen-specific IgG without an increase in IgE (and a reduction in seasonally-induced IgE in Yr 2)

- Safety: in Yr 1: more Grade 2 Rxs [EAACI criteria] observed in active treatment group; in Yr 2: essentially no difference in reactions between groups.

• Conclusions: The B-cell epitope vaccine demonstrated improvement in grass-associated clinical symptoms and was well-tolerated over the 2 year course of treatment

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## Part IV

## Methods of Allergen Immunotherapy

- Classic Subcutaneous Immunotherapy (SCIT)
- Sublingual Immunotherapy (SLIT)
- T-cell-derived peptide immunotherapy
- SCIT modified w/ adjuvant approaches
- Allergoids / Polymerized Allergens
- Combination Therapy: AIT w/ Biologic

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## Anti-TSLP + Allergen-specific Immunotherapy to Cat

Compound: anti-TSLP (thymic stromal lymphopoietin) antibody
[Amgen; MedImmune]

- TSLP is a cytokine capable of both initiating and maintaining allergic sensitization to antigens

- Hypothesis: blocking TSLP during administration of cat IT may induce immune changes that lead to tolerance

Current Status: ITN-sponsored clinical trial of anti-TSLP (CatNip) underway to evaluate benefit of investigational drug to enhance the disease-modifying properties of immunotherapy in cat-allergic patients (not living with cats)

Study design: a-TSLP admin q 4wks at 700 mg IV (1 day prior to IT through week 24; then on same day as IT inj x 2 yrs) [4 arms]

Primary outcome: TNSS after cat nasal allergen challenge (@ 104 wks)
Secondary: PST Δ / EPR (IDST) / LPR (IDST) / PNIF (as compared to TNSS)

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## Part VI
## Methods Of Allergen Immunotherapy

- Classic Subcutaneous Immunotherapy (SCIT)
- SCIT modified w/ adjuvant approaches
- Synthetic Peptide Immuno-Regulatory Epitopes
- Sublingual Immunotherapy (SLIT)
- Intralymphatic Immunotherapy (ILIT)
- Epicutaneous Immunotherapy (EPIT)
- Recombinant vaccines

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## Selected Studies of Intralymphatic Immunotherapy (ILIT)


Senti G, Prinz Vavricka BM, Erdmann I, Diaz MI, Markus R, McCormack SJ et al. Intralymphatic allergen administration renders specific immunotherapy faster and safer: a randomized controlled trial. Proc Natl Acad Sci (USA) 2008 ;105:17908–17912.

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## Part VII
## Methods Of Allergen Immunotherapy

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- Epicutaneous Immunotherapy (EPIT)

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## Selected Studies of Epicutaneous Immunotherapy


Senti G, Graf N, Haug S, Ruedi N, von Moos S, Sonderegger T et al. Epicutaneous allergen administration as a novel method of allergen-specific immunotherapy. J Allergy Clin Immunol 2009; 124: 997-1002.

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Senti G, von Moos S, Tay F, et al. Epicutaneous allergen-specific immunotherapy ameliorates grass pollen-induced rhinoconjunctivitis: a double-blind, placebo-controlled dose escalation study. J Allergy Clin Immunol 2012; 129: 128.

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**Thank You**

That's All, Folks!

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