New Approaches to Immunotherapy

Harold S. Nelson, MD
Professor of Medicine
National Jewish Health and
University of Colorado School of Medicine,
Denver, Colorado, USA
Faculty Disclosure

Harold S. Nelson, MD

For the 12 months preceding this CME activity, I disclose the following types of financial relationships:

Honoraria received from:
• None

Consulted for:
• Fish and Richardson P.C., Forest Research Institute, Merck, Pharm-Olam International, Reigel, Sunovion

Held common stock in:
• None

Research, clinical trial, or drug study funds received from:
• Lincoln Diagnostics, NIH, URL Pharm

I will be discussing products that are investigational or not labeled for use under discussion.
Learning Objectives

Upon completion of this session the attendee should be informed regarding:

1) Alternative approaches to immunotherapy with currently available extracts;
2) Approaches to immunotherapy employing modified allergen extracts.
Increased Safety with Currently Available Extracts

- **Delayed absorption:**
  - Aluminum ✓
  - Tyrosine adsorption ✓
  - Encapsulation (liposomes)

- **Reduce levels of IgE**
  - Omalizumab ✓

- **Alternative routes**
  - Nasal
  - Oral (food allergy) ✓
  - Sublingual ✓
  - Epicutaneous ✓
  - Intralymphatic ✓

✓ Active study or current use
SLIT: What Are the Answered & Unanswered Questions?

- **Answered:**
  - Efficacy with monotherapy (Yes)
  - Optimal duration (3-4 years)
  - Prevention of new sensitization and progression to asthma. (Yes)
  - Persistent benefit after stopping (Yes)
  - Relative safety in subjects with allergic rhinitis and controlled asthma. (Yes)

- **Unanswered:**
  - Optimal dosing for allergens other than grass
  - Relative efficacy versus subcutaneous immunotherapy
  - Use of mixes of multiple unrelated allergens
  - Safety in poorly controlled asthma
Long-lasting Effects of sublingual Immunotherapy According to its Duration: A 15-year Prospective Study


- 78 patients were treated with house dust mite extract by SLIT with a cumulative dose 30X the SCIT dose.
- Initial treatment was for 3, 4 or 5 years.
- When group symptom scores rose above 50% of baseline they were retreated.
- Total duration of observation was 15 years.
A 15-year Prospective Study

- After stopping treatment relapse and retreatment occurred in 7 years in the 3-year group and 8 years in the 4-year and 5-year groups.
- The second course of SLIT produced more rapid improvement than the first in all three groups.
- Methacholine sensitivity and nasal eosinophils paralleled the clinical course.

Percentage of Nasal Eosinophils

- SLIT3
- SLIT4
- SLIT5
- CONTROLS

Nasal Eosinophils %

JACI 2010 126: 969-75
Percent of Patients with New Prick Skin Test Reactions

* Significant from this point onward
### Adverse Reactions to Grass SLIT
#### Summary of 7 Phase III Studies

<table>
<thead>
<tr>
<th></th>
<th>Adults (n=2096)</th>
<th>Children (n=598)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AIT</td>
<td>Placebo</td>
<td>AIT</td>
</tr>
<tr>
<td>Oral Pruritus</td>
<td>39%</td>
<td>5%</td>
<td>35%</td>
</tr>
<tr>
<td>Throat Irritation</td>
<td>21%</td>
<td>3%</td>
<td>25%</td>
</tr>
<tr>
<td>Ear Pruritus</td>
<td>14%</td>
<td>1%</td>
<td>8%</td>
</tr>
<tr>
<td>Mouth Edema</td>
<td>11%</td>
<td>&lt;1%</td>
<td>8%</td>
</tr>
<tr>
<td>Oral Paresthesias</td>
<td>8%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Any Drug-related</td>
<td>70%</td>
<td>23%</td>
<td>62%</td>
</tr>
</tbody>
</table>

Abstract EAACI June 2011
### Anaphylactic Reactions to SLIT

<table>
<thead>
<tr>
<th>Allergen</th>
<th>BU or Mnt</th>
<th>Symptoms</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple</td>
<td>BU</td>
<td>Pruritus, AE, wheezing, dizziness</td>
<td>Allergy 2006;61:1235</td>
</tr>
<tr>
<td>Latex</td>
<td>BU</td>
<td>Urt, asthma, “anaphylactic shock”</td>
<td>Allergy 2006;61:236</td>
</tr>
<tr>
<td>Multiple</td>
<td>Mnt</td>
<td>AE, chest pain, nausea, abd pain</td>
<td>Allergy 2007;62:567</td>
</tr>
<tr>
<td>HDM</td>
<td>Mnt3 yrs</td>
<td>Urt, wheezing</td>
<td>Allergy</td>
</tr>
<tr>
<td>6X dose</td>
<td></td>
<td>hypotension, syncope</td>
<td>2008;63:374</td>
</tr>
<tr>
<td>Grass (2)</td>
<td>1st dose</td>
<td>Includes hypotension</td>
<td>2009;64:963-4</td>
</tr>
</tbody>
</table>

No fatal or near-fatal reactions have been reported
SLIT: What Are the Answered & Unanswered Questions?

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  - Efficacy with monotherapy (Yes)
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- **Unanswered:**
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  - Relative efficacy versus subcutaneous immunotherapy
  - Use of mixes of multiple unrelated allergens
  - Safety in poorly controlled asthma
SLIT: Efficacy of Grass Tablets

- 628 adult subjects with grass SAR.
- Treated with placebo or 100 IR, 300 IR, or 500 IR 5-grass tablets beginning 4 months before season.
- The two highest doses significantly reduced symptoms 27% and 24%, the low dose was ineffective.

Didier JACI 2008
Dose-Response to Grass Pollen Extract

SLIT

N= 628 patients

100 IR ~ 8mcg Gp p 5, 300IR ~ 25mcg Gp p 5

Didier et al. JACI 2007;120:
Sublingual Immunotherapy: A Comprehensive Review

- 47 randomized studies with outcome data: 39 DBPC, remainder randomized open or double blind comparisons without placebo.
- Cumulative monthly dose in relation to investigators’ usual SCIT dose:
  - 1-5 X n = 24
  - 6-50 X n = 12
  - > 50 X n = 11
- All studies were with single allergens

L Cox, et al. JACI 2006
### SLIT: Dose-Response (X SCIT)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Duration</th>
<th>First year</th>
<th>First Year</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Symptoms</td>
<td>Medication</td>
<td>Symptoms</td>
<td>Medication</td>
</tr>
<tr>
<td>1-5 X</td>
<td>≤ 12 months</td>
<td>14</td>
<td>7</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 12 months</td>
<td>6</td>
<td>4</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6-50 X</td>
<td>≤ 12 months</td>
<td>7</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 12 months</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>&gt; 50 X</td>
<td>≤ 12 months</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&gt; 12 months</td>
<td>4</td>
<td>1</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>37</td>
<td>22</td>
<td>8</td>
<td>18</td>
</tr>
</tbody>
</table>

L Cox, et al. JACI 2006
Clinical, Functional and Immunologic Effects of Sublingual Immunotherapy in Birch Pollinosis: a 3-Year Randomized Controlled Study.


- Adults with rhinitis and asthma monosensitized to birch.

- Observed through one pollen season, then treated for 3.5 years and observed through four pollen seasons.
Methods/Results

- Randomized, but open trial with annual dose 102 mcg Bet v 1 (0.7-2.5 X SCIT dose)
- 79 enrolled, 17 control and 10 active dropped out (p < 0.02)
- Per protocol drop out due to new sensitizations: Control 10, active 3 (p < .05)
Effect of SLIT with Birch on Airway Symptoms

- Blue: SLIT
- Red: Control

Effect of SLIT on Nasal Eosinophils During Pollen Season

Clinical Efficacy of Sublingual and Subcutaneous Birch Pollen Allergen-Specific Immunotherapy: A Randomized, Placebo-Controlled, Double-Blind, Double-Dummy Study

MS Khinchi, et al. Allergy 2004;59:45-53

- Subcutaneous maintenance dose contained 3.28 µg Bet v 1 once monthly.
- Sublingual maintenance dose contained 49.2 µg Bet v 1 every other day (225 time SCIT dose).
- 5 cases of grade 3 or 4 systemic reactions in the SCIT group, two treated with adrenalin. No grade 3 or 4 reactions with SLIT.
### SLIT versus SCIT

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Symptoms</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>+ .02</td>
<td>+ 1.35</td>
</tr>
<tr>
<td>SLIT</td>
<td>- .36</td>
<td>+ .29</td>
</tr>
<tr>
<td>SCIT</td>
<td>- .75</td>
<td>No change</td>
</tr>
</tbody>
</table>

SLIT & SCIT significantly better than placebo, no difference between active treatments.

* Pollen counts higher second year

MS Khinchi, et al. Allergy 2004;59:45-53
SLIT vs SCIT Comparative Study
First Treatment Season
Mean Weekly Rhinoconjunctivitis Symptom and Medication Scores

The hatched areas indicate the daily birch pollen count. The rectangles indicate the defined pollen season.

Response to Sublingual Immunotherapy with Grass Pollen Extract: Monotherapy versus Combination with Multiallergen Extract

S M. Amar, RJ Harbeck, M Sills, LJ Silviera, H O’Brien, HS Nelson
National Jewish Health,
J Allergy Clin Immunol 2009;124:150-6
Study Design

- Single-center, randomized, double-blind, placebo-controlled.
- SLIT for 10 months, 56 subjects randomized to 3 arms
  - SLIT with timothy pollen extract alone (17 mcg Phl p 5 daily)
  - SLIT with same dose of timothy extract + 9 additional pollen extracts
  - SLIT placebo

## SLIT Arms

<table>
<thead>
<tr>
<th>MAT Group, Allergen Extract</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timothy</td>
<td>1.0 mL</td>
</tr>
<tr>
<td>Maple, Box-Elder</td>
<td>1.0 mL</td>
</tr>
<tr>
<td>Ash, White</td>
<td>1.0 mL</td>
</tr>
<tr>
<td>Juniper, Western</td>
<td>1.0 mL</td>
</tr>
<tr>
<td>Elm, American</td>
<td>1.0 mL</td>
</tr>
<tr>
<td>Cottonwood, Common</td>
<td>1.0 mL</td>
</tr>
<tr>
<td>Firebush (Kochia)</td>
<td>1.0 mL</td>
</tr>
<tr>
<td>Ragweed, Western</td>
<td>1.0 mL</td>
</tr>
<tr>
<td>Sagebrush, Common</td>
<td>1.0 mL</td>
</tr>
<tr>
<td>Russian Thistle</td>
<td>1.0 mL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TM Group, Allergen Extract</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timothy</td>
<td>1.0 mL</td>
</tr>
<tr>
<td>Diluent</td>
<td>9.0 mL</td>
</tr>
<tr>
<td>Caramelized Sugar</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Placebo Group</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diluent</td>
<td>10 mL</td>
</tr>
<tr>
<td>Caramelized Sugar</td>
<td></td>
</tr>
</tbody>
</table>

*Amount added to 10 ml vial for 1 month of treatment

*CMD : Timothy approximately 30x SCIT dose (17 mcg Phl p 5 q day), other allergens 15-20x SCIT dose

Multi-allergen Sublingual Immunotherapy: Results

Only 3 " of rain fell in Denver the first 6 months of 2008. Accordingly there was little grass pollen, few symptoms and no difference in symptom scores or medication use among the three treatment groups. There were, however, significant differences in several clinically relevant outcomes.

Mean $\Delta (2008-2007) \log_{10} NC$ score

Mean \( \Delta(2008-2007) \log_{10} tSPT \) score

Mean $\Delta (2008-2007) \log_{10} \text{IgG}_4$ level

The TM arm shows that SLIT is effective with 17 mcg Phl p 5 daily for 10 months.
The MAT SLIT results raise serious concerns regarding its effectiveness.
 Appropriately powered studies should be conducted to answer this question before multiallergen SLIT is introduced in allergy practice.

## Comparison of Subcutaneous & Sublingual Immunotherapy

<table>
<thead>
<tr>
<th>SCIT Has</th>
<th>SLIT Has</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identified effective doses</td>
<td>Greater safety and convenience</td>
</tr>
<tr>
<td>Greater efficacy</td>
<td></td>
</tr>
<tr>
<td>Studies with multiple allergen mixes</td>
<td></td>
</tr>
<tr>
<td>But</td>
<td>But</td>
</tr>
<tr>
<td>Inconvenient</td>
<td>Optimum dose not defined except for grass</td>
</tr>
<tr>
<td>More systemic reactions</td>
<td>Less effective (first year)</td>
</tr>
<tr>
<td></td>
<td>Multiple allergen mixes may be ineffective.</td>
</tr>
</tbody>
</table>
Grass Transcutaneous Immunotherapy in Children with Seasonal Rhinoconjunctivitis


- 15 children received grass transcutaneous immunotherapy and 15 placebo patches from February to April.
- Patches (grass pollen extract containing 11.25 mcg major allergen, 50% petrolleum jelly and <3% salicylic acid) were applied weekly for 12 weeks and removed after 24 hours.
Grass Transcutaneous Immunotherapy in Children with Seasonal Rhinocconjunctivitis

- There were no local or systemic reactions to the patches.
- Symptoms during the grass pollen season favored active treatment for:
  - Rhinitis (p = .009)
  - Nasal obstruction (p = .003)
  - Dyspnea (p = .03)
  - Ocular tearing (p < .05)
  - Antihistamine use (p < .02)

F Agostinis et al. Allergy 2010;66:410-1
**Grass Transcutaneous Immunotherapy**

**Green:** Grass pollen count  
**Orange:** Peak grass pollen season.  
**Red:** placebo  
**Yellow:** active treatment

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**Symptoms**

- **Total symptom score**
- **Pollen counts (m$^3$)**

**Anti-histamines**

- **Mean antihistamine intake per week**
- **Pollen counts (m$^3$)**

---

*Agostinis et al Allergy 2009; 60:L410-1*


- 132 grass-pollen allergic patients received epicutaneous therapy beginning 4 weeks before the pollen season.
- 6 weekly patches, remaining on 8 hours, contained 0, 10, 50 or 100 HEP of grass pollen extract.
- 100 HEP = 30 mcg Ph p 5.
- Followed through two pollen seasons without further treatment.
Mean VAS Symptom Scores

2008

- 32% N.S.

2009

- 24% N.S.

Total Side Effects by Treatment Group

Frequency of Side Effects by Patch Sequence

Epicutaneous Allergen-specific Immunotherapy

- High-dose epicutaneous immunotherapy significantly improved global rhinitis assessment the 2\textsuperscript{nd} year.
- Transient local reactions were common.
- 11 patients (8.3\%) stopped treatment because of a systemic reaction (placebo 1, 10 HEP 3, 50 HEP 3, & 100 HEP 4).

Intralymphatic Allergen Administration Renders Specific Immunotherapy Faster and Safer: A Randomized Controlled Trial


- Randomized, open label comparison of 3 years of subcutaneous injections (cumulative dose $4 \times 10^6$ SQ-U) or 3 intralymphatic injections at 4-week intervals (cumulative dose 3,000 SQ-U)
- Nasal tolerance was faster with IL injections (4 months versus 1 year) and persisted at 3 years.
- Reactions were fewer with IL injections.
- Other outcomes at three years were similar for the 2 approaches.
Intralymphatic vs. Subcutaneous

Cum. dose = 4'031'540 SQ-U

Cum. dose = 3'000 SQ-U

G Senti
PNAS
2008:105: 17908-17
Nasal Challenge: IL versus SC

Max. tolerated allergen conc. (log10)

Months

G Senti
PNAS
2008;105:
17908-17
Symptom Scores: IL versus SC

PNAS 2008;105:17908-12

Symptom Scores: IL versus SC

Hayfever
Nasal congestion
Nasal itching
Sneezing
Red eyes
Ocular itching
Asthma
Dry cough

Symptom score (VAS)

Years

IL
SC

PNAS 2008;105:17908-12
Increased Safety with Currently Available Extracts: Summary

- **Delayed absorption:**
  Allows more rapid escalation of dose with decreased systemic reactions

- **Reduce levels of IgE**
  Omalizumab - Reduces reactions to immunotherapy in patients with allergic rhinitis and asthma.

- **Alternative routes**
  - **Oral** - Investigated in food allergy
  - **Sublingual** - Established efficacy and safety but dose? Relative efficacy? Use of Mixes of allergens?
  - **Epi- or Trans-cutaneous** - Promising in initial studies with long-lasting effect.
  - **Intralymphatic** - 3-year response with 3 injections
Enhanced Safety and Efficacy with Modified Allergens

- **Chemical Treatment of Allergens:**
  - Allergoids √

- **Recombinant Technology**
  - Unmodified allergens √
  - Site-directed mutagenesis and deletion √
  - Peptides √
  - Fusion proteins.

- **Combined with Immune Stimulation**
  - ISS-ODN (CpG) √
  - Monophosphoryl Lipid A (MPL) √

√ Active study or current use
Efficacy of Recombinant Birch Pollen Vaccine for the Treatment of Birch-Allergic Rhinoconjunctivitis


- 3 vaccines were compared in 134 adults with birch pollen allergy:
  - Natural birch pollen extract
  - Naturally purified birch major allergen (nBet v 1)
  - Recombinant birch major allergen (rBet v 1)
- Received 12 weekly injections followed by monthly injections for 2 years with 15 mcg Bet v 1.
- Symptoms and medication use were significantly reduced in all active treatment groups without significant differences among them.
Austria, Denmark, France, Italy, Sweden

Birch Pollen 2004 (Grains/m³/24h)

4000 3500 3000 2500 2000 1500 1000 500 0

A

Pollen Counts and Symptom Scores 2004

Day number (=start of 2004 birch pollen season)

Birch pollen (0.0024)

rBet v1 (p=0.0002)

nBet v1 (p=0.0006) Placebo

4

Daily mean rhino-conjunctivitis score

Placebo

rBet v1 (p=0.0002)

nBet v1 (p=0.0006) Birch pollen (0.0024)

0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30

Day number (=start of 2004 birch pollen season)

B

Pauli G
JACI
2008;122:951-60
Clinical Effects of Immunotherapy with Genetically Modified Recombinant Birch Pollen Bet v 1 Derivatives.


- Recombinant Bet v 1-derived proteins were generated:
  - Bet v 1 trimer.
  - Two fragments representing the whole sequence of Bet v 1.

- Both had retained T-cell reactivity and markedly reduced reactivity with specific IgE.
Clinical Effects of Immunotherapy with Genetically Modified Recombinant Birch Pollen Bet v 1 Derivatives.


- A double-blind, placebo controlled study was conducted in 2001.
- Maintenance dose 80 µg protein (5 times effective subcutaneous dose)
- 84 subjects completed the study.
- There were some favorable outcomes, but symptoms/medication scores were not significantly improved over placebo.
Development and Preliminary Clinical Evaluation of a Peptide Immunotherapy Vaccine for Cat Allergy

M Worm---AB Kay, M Larche’. J Allergy Clin Immunol 2011;127:89-97

- Determined binding affinities of Fel d 1 peptides for 10 commonly expressed HLA-DR molecules.
- Functional immunodominant peptides were identified by means of peptide induced proliferation and cytokine secretion from PBMC of allergic donors.
- Histamine releasing activity was assessed to rule out reactivity with IgE.
Current Status of Peptide Allergen Extracts

Google for Circassia Ltd December 2011

- Ragweed (February 2010): Early skin response reduced 47%. (September 2010) Phase II with 275 subjects ongoing.
- House dust mites (November 2010): In 50 subjects, 4 doses decreased skin and ocular challenge response by 32-87%.
- Cat (13 June 2011): 202 subjects, 4 injections. Assessed in cat-exposure chamber. Optimal dose decreased symptoms 94% after 12 weeks and 133% after one year, when compared to placebo response. Phase III study in 2012.
- Grass (27 Sept. 2011): 50 subjects, 5 regimens of 4 injections, conjunctival challenge up to 30%, early skin tests up to 54%, late skin tests up to 19% above placebo. Chamber study with 280 subjects underway.
Immunostimulatory Sequences

- CpG motifs commonly found in bacterial and viral DNA, uncommon in vertebrates
- Stimulate TLR-9 of the innate immune system:
  - Macrophages: IFN-α & β, IL-6, IL-12, IL-18
  - NK cells: IFN-γ
- Bias adoptive immune response towards Th1
- Initial studies at Johns Hopkins encouraging.
Multicenter Study With Amb a 1 - CpG
Study Design

- **First preseason 6 weekly injections:**
  - Amb a 1-ISS 1.2 mg to 30 mg  \( n = 310 \)
  - Placebo  \( n = 152 \)

- **Second preseason 2 injections:**
  - Amb a 1-ISS/Amb a 1-ISS  \( n = 135 \)
  - Amb a 1-ISS/Placebo  \( n = 130 \)
  - Placebo/Placebo  \( n = 133 \)
The Effect of Amb a 1 ISS Conjugate on Peak Season TNSS: Change From Baseline

2004

Amb a 1-ISS  |  PLACEBO
---|---
21.2%  |  2.35
P=0.04  |  1.88

2005

Amb a 1-ISS / PLACEBO  |  Amb a 1-ISS / Amb a 1-ISS  |  PLACEBO / PLACEBO
---|---|---
28.5%  |  2.16  |  2.46
P=0.02  |  1.83  |  1.5
Ultrashort-specific Immunotherapy Successfully Treats Seasonal Allergic Rhinoconjunctivitis to Grass Pollen


- 1028 subjects were randomized to 4 injections of grass allergoid, tyrosine adsorbed with monophosphoryl lipid A (Grass MATA MPL) or placebo.
- Grass MATA MPL provided 13.4% benefit over placebo over all, 17.1% in subjects with severe symptoms, & 38.3% at sites with a higher burden of disease.
- 2.5% active withdrew due to AEs, mostly local.
Enhanced Safety and Efficacy with Modified Allergens

- Chemical Treatment of Allergens:
  - Allergoids - May reduce immunogenicity as well as allergenicity.

- Recombinant Technology
  - Unmodified allergens - No enhanced safety or efficacy.
  - Site-directed mutagenesis and deletion - Results to date disappointing.
  - Peptides – Preliminary data encouraging
  - Fusion proteins - no human studies

- Combined with Immune Stimulation
  - ISS-ODN (CpG) & Monophosphoryl Lipid A (MPL) - Results in large trials have been disappointing.
Future Directions in Immunotherapy: Conclusions

- Only subcutaneous and sublingual immunotherapy may be considered established.
- Omalizumab increases safety but is cost prohibitive for routine use.
- Intralymphatic and transcutaneous administration and peptide therapy show early promise.
- When approved in the US SLIT and modified extracts will be limited to the standardized allergens: grass, ragweed, cat and house dust mite.