Intralymphatic Immunotherapy ILIT
Subcutaneous Immunotherapy

- DC in epidermis: phenotypically immature
- Inflammatory cytokines
- Afferent lymphatic vessel
- Migration of DC
- Maturation of migrating DC
- Mature dendritic cell presenting antigen to naive T cell

Effect

Problems
Intralymphatic Immunotherapy
Protein Vaccines

subcutaneous into lymph node

IgG ?
Allergen Administration Route

0.01 µg  0.1 µg  10 µg

Anti-PLA2 IgG2a

0.01 µg  0.1 µg  10 µg

Anti-PLA2 IgE

- intralymphatic (ILIT)
- subcutaneous (SCIT)
- intraperitoneal

- intralymphatic (ILIT)
- subcutaneous (SCIT)
- Δ intraperitoneal
Injection into Lymph Nodes
Inguinal Lymph Nodes

- no large vessels
- little movement
- close to vessels
- leg movement
into lymph node

Subcutaneous
20 Min
25 h
Clinical Trial ZU-BV-001

Allergen (80 injections)

- 100 µg
- 10 µg

5 years (~80 injections)

3 injections
2 wk intervals
Sting Provocation

Before

After

p=0.0012

Vaccination

BV sting challenge score
165 grass allergic pat.

Patients

- 45
- 58
- 54
- 10000
- 100000
- 0 8 16 24 32 40 140 148 156
- Allergen (SQ-U)
- Cum. dose
- = 3'000 SQ-U

- 99
- 54
- 53
- 148 156
- Allergen (SQ-U)
- Cum. dose = 4'031'540 SQ-U

- 66
- 32
- 148 156
- Allergen (SQ-U)
- Cum. dose = 4'031'540 SQ-U

- 8
- 38
- 148 156
- Allergen (SQ-U)
- Cum. dose = 4'031'540 SQ-U

Screened for eligibility
n=172
Randomized
n=154
Allocated to Intralymphatic SIT
n=66
Baseline
n=58

- Evaluation visits
- Pollen season baseline
- Pollen season 1
- Pollen season 2+3

- baseline
- 4 months
- 1 year
- 3 years

- Sept
- Oct
- Jan
- Feb

Senti et al. PNAS 2008
Pain?

![Box plot comparing pain scores (VAS) for Intralymphatic injection and Venous puncture.](chart.png)
Nasal Provocation Test

Maximum tolerated concentration (log10)

Months

0 12 24 36

intralymphatic

subcutaneous

4.5 5.0 5.5 6.0

B

Senti et al. PNAS 2008
Antigen Presentation

Molecular targeting: MAT Antigen (Modular antigen transporter)
- Tat protein for cytoplasmic update
- IC for targeting MHC II Receptor
IVN-CAT-001b

12 Alum + MAT-Fel d 1

8 Alum + placebo

Screening

Treatment

Efficacy

V1a V1b V2a V2b V2c V3 V4

5d 28d 28d 28d

1 μg 3 μg 10 μg
## Adverse Events

No SAE

<table>
<thead>
<tr>
<th>Possibly drug related AE</th>
<th>Severity</th>
<th>Placebo</th>
<th>Verum</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Local reactions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>temporary lymphnode swelling</td>
<td>mild</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>moderate</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Systemic reactions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rhinorea</td>
<td>mild</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>moderate</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>sneezing</td>
<td>mild</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>moderate</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>pruritus</td>
<td>mild</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>moderate</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>nausea</td>
<td>mild</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>moderate</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>rash</td>
<td>mild</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>moderate</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>dyspnoe</td>
<td>mild</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>moderate</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>headache</td>
<td>mild</td>
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<td>0</td>
</tr>
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<td></td>
<td>moderate</td>
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<td>0</td>
</tr>
<tr>
<td>cough</td>
<td>mild</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>moderate</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>9</td>
<td>5</td>
</tr>
</tbody>
</table>

Senti et al. JACI 2012
IL-10 Correlates with IgG4

\[ p=0.0004 \quad p=n.s. \]

Senti et al. JACI 2012
Prick Test and Intradermal Test

**SPT**

![Graph showing SPT results with placebo and verum groups.]

- Placebo: n.s.
- Verum: Improvement Factor 3.16

**IDT**

![Graph showing IDT results with placebo and verum groups.]

- Placebo: n.s.
- Verum: Improvement Factor 4.64

Allergen (log$_{10}$) vs. Placebo and Verum

Senti et al. JACI 2012
Nasal Tolerance

NPT
Placebo
Verum

Treatment group
Improvement
(Post/Pre log_{10})

P<0.001
Senti et al. JACI 2012
More data will be published soon

From Kopenhagen
Low efficacy?
Weekly intervall too short?

From Stockholm
Very positive results
We can relax again…

Interest from China
Drug Development is not easy…
Is intralymphatic specific immunotherapy with grass pollen allergen ready for clinical use?
Malling, H; Blom, L; Poulsen, B; Poulsen, L; Witten, M
<table>
<thead>
<tr>
<th>Determinants</th>
<th>Mechanisms (presumed)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vaccine type</strong></td>
<td></td>
</tr>
<tr>
<td>Live vs inactivated</td>
<td>Live vaccines generally induce more sustained Ab responses, presumably through Ag persistence within the host.</td>
</tr>
<tr>
<td>Polysaccharide antigens</td>
<td>Failure to generate GCs limits the induction of memory responses and of high-affinity long-live plasma cells.</td>
</tr>
<tr>
<td><strong>Vaccine schedule</strong></td>
<td></td>
</tr>
<tr>
<td>Interval between primary doses</td>
<td>A minimal interval of 3 weeks between primary doses allows development of successive waves of Ag-specific primary responses without interference.</td>
</tr>
<tr>
<td>Interval before boosting</td>
<td>A minimal interval of 4 months between priming and boosting allows affinity maturation of memory B cells, and thus higher secondary responses.</td>
</tr>
</tbody>
</table>
Intralymphatic allergen-specific immunotherapy: an effective and safe alternative treatment route for pollen-induced allergic rhinitis

Terese Hylander M.Sc.¹, Leith Latif MD², Ulla Petersson-Westin MD, PhD², Lars Olaf Cardell MD, PhD¹.²
Capsule summary

Intralymphatic allergen-specific immunotherapy is safe and effective for treatment of allergic rhinitis. The therapy reduces allergic symptoms upon challenge and during pollen season, decreases nasal inflammatory responses and enhances activation of peripheral T lymphocytes.

Clinical implications: In this study, intralymphatic allergen-specific immunotherapy is further highlighted as a safe and effective administration route for the treatment of patients with pollen-induced allergic rhinitis.
STUDIES ON THE CONTROL OF ANTIBODY SYNTHESIS

VI. EFFECT OF ANTIGEN DOSE AND TIME AFTER IMMUNIZATION ON ANTIBODY AFFINITY AND HETEROGENEITY IN THE MOUSE

YOUNG TAI KIM AND G. W. SISKIND

The Division of Allergy and Immunology, Department of Medicine, Cornell University Medical College, New York, New York 10021, U.S.A.
Lymph node injections provide safer, faster and easier relief against hay fever
Intrasplenic Primary Immunization for the Production of Monoclonal Antibodies

M. Spitz, L. Spitz, R. Thorpe and E. Eugui

National Institute for Biological Standards and Control, Holly Hill, Hampstead, London NW3 6RB, and
* Clinical Research Centre, Watford Road, Harrow, Middlesex HA1 3UJ, U.K.

(Received 19 September 1983, accepted 30 December 1983)
Research report

Mouse ear spleen grafts: a model for intrasplenic immunization with minute amounts of antigen

Fabíola Cardillo, a, José Mengel b, Sérgio B. Garcia c, Fernando Q. Cunha a

a Department of Pharmacology, Faculty of Medicine of Ribeirão Preto, University of São Paulo, USP, Ribeirão Preto 14049-900, São Paulo, Brazil

b Department of Immunology, Institute of Biological Sciences, University of São Paulo, 05508-900 São Paulo, Brazil

c The Department of Morphology, Faculty of Medicine of Ribeirão Preto, University of São Paulo, USP, Ribeirão Preto 14049-900, São Paulo, Brazil

Intralymphatic immunotherapy for allergic diseases was pioneered at UCLA and publicly disclosed in 1983 at the Federation of American Societies for Experimental Biology

Intralymphatic Injection of Immunogenic Material in Afferant Lymphatic Vessel: A Method of Choice
by Guy Juillard, M.D., Professor

After thousands of intralymphatic injections of immunogenic material in dogs and mostly in humans the safety of this method was so stunning that we applied it to the treatment of allergic diseases which had resisted other modalities of allergens administration.

The legacy left to the scientific community for thought is threefold:

- A method of choice, safe, effective for treatment of allergic diseases.
- A method which should be resurrected for immunotherapy of cancer, as the vaccines can now be much more effective with adjunction of dendritic cells and even cytokines (e.g. gmcsf) to the irradiated tumor cells.
- An observation worth of attention: the protection against viral infections (possibly including HIV), by relatively safe and inexpensive administration of agents which boost the immune system in a non specific way: if intralymphatic injections of irradiated tumor cells can do it, why not other ways (cytokine, cytokine patches, etc.), however we think that the direct stimulation of lymphnodes may be unique in achieving a boost of the immune system capable of protecting against all viruses.

I. Allergic Diseases
Practicability and safety of intralymphatic allergenspecific immunotherapy in dogs with atopic dermatitis.

Hatzmann K, Mueller RS.

3 low dose i.ln. vs. 30 high dose s.c.

“intralymphatic allergen-specific immunotherapy is an interesting and safe alternative to subcutaneous administration. A more prominent decrease of pruritus score, CADESI (Canine Atopic Dermatitis Extent and Severity Index) and total score was noted in the trial group”
Low-dose DNA vaccination into the submandibular lymph nodes in ponies

G. A. Landolt, S. B. Hussey, K. Kreutzer, A. Quintana, D. P. Lunn

Veterinary Record | August 21, 2010
Protective mucosal immunity elicited by targeted iliac lymph node immunization with a subunit SIV envelope and core vaccine in macaques

THOMAS LEHNER¹, YUFEI WANG¹, MARTIN CRANAGE², LESLEY A. BERGMEIER¹,
ELAINE MITCHELL¹, LOUISA TAO¹, GRAHAM HALL², MIKE DENNIS², NICOLA COOK¹,
ROGER BROOKES¹, LINDA KLAVINSKIS¹, IAN JONES¹, CARL DOYLE³ & ROBERT WARD¹

¹Department of Immunology, United
St. Thomas' Hospital,
²Centre for Applied Microbiology & Research,
³Institute of Virology and Environmental Microbiology
Correspondence should
“Antibodies of all four isotypes, IgG₁, IgG₂, IgA, and IgM, increased in dry secretions following immunization via lymph node.”
Conclusions ILIT vs SCIT

- Low allergen doses $\rightarrow$ Improved safety
- Enhanced immunogenicity $\rightarrow$ Fewer injections
- Practically painless $\rightarrow$ Enhanced compliance
Epicutaneous Immunotherapy

1911 “prophylactic hypodermic inoculation”
1929 “into the substance of the skin”
ZU-Skin-SIT 001

![Box plot showing hay fever symptoms in 2006 and 2007 with P-values: P = 0.04 and P = 0.002.](image)
ZU-Skin-SIT 002

Improvement (%)

Placebo 0.1 0.3 1.0

Allergen dose

30% better than placebo
EPIT is «en vogue»

From Paris ➔ DVB /VIASKIN Preclinical Data

From Osaka ➔ Dissolving Microneedles Infectious Disease Data

From Salzburg ➔ Generated micropores using Laser Technologies Preclinical Data


More Senti & Kündig Stories will follow
You will hear about «Hypo Pet» soon