Intralymphatic Immunotherapy ILIT

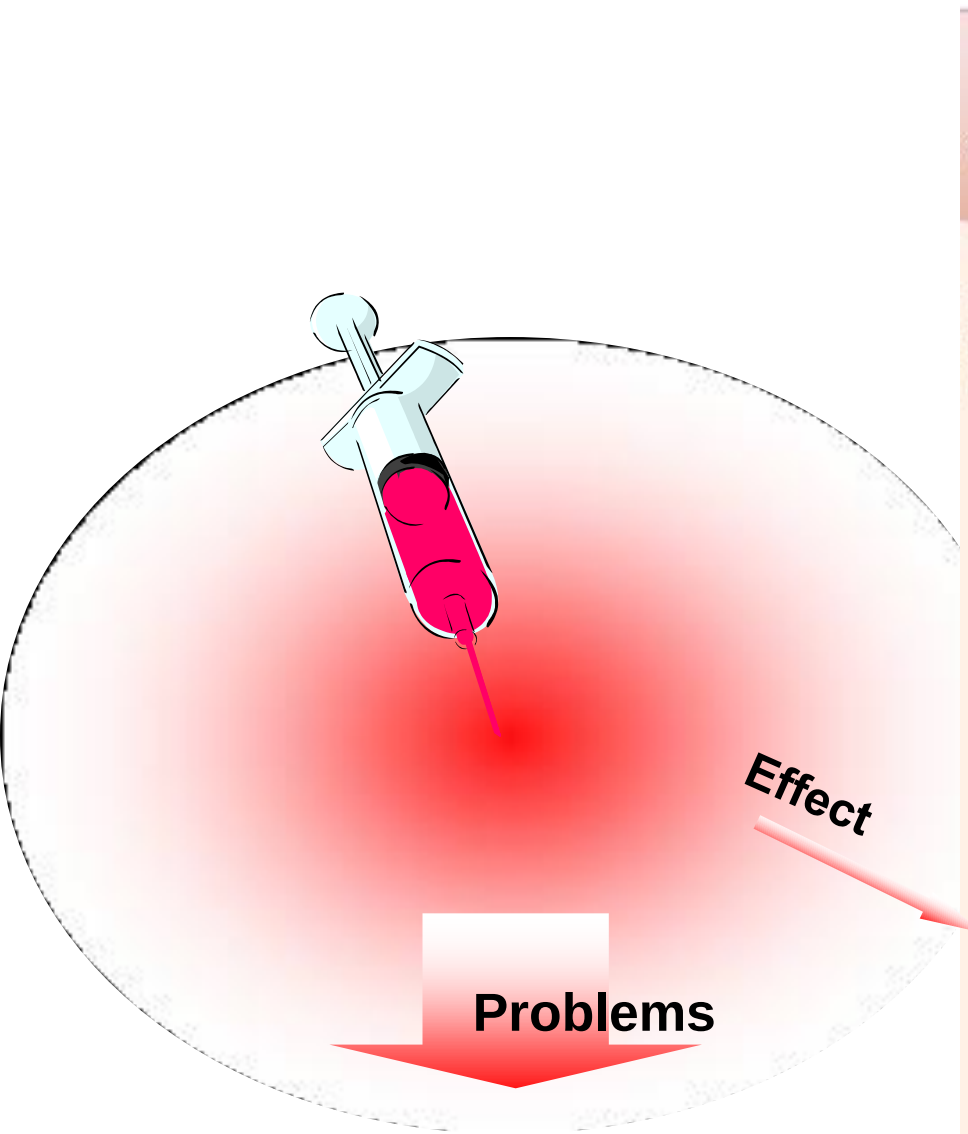
WAO Symposium on Immunotherapy & Biologics

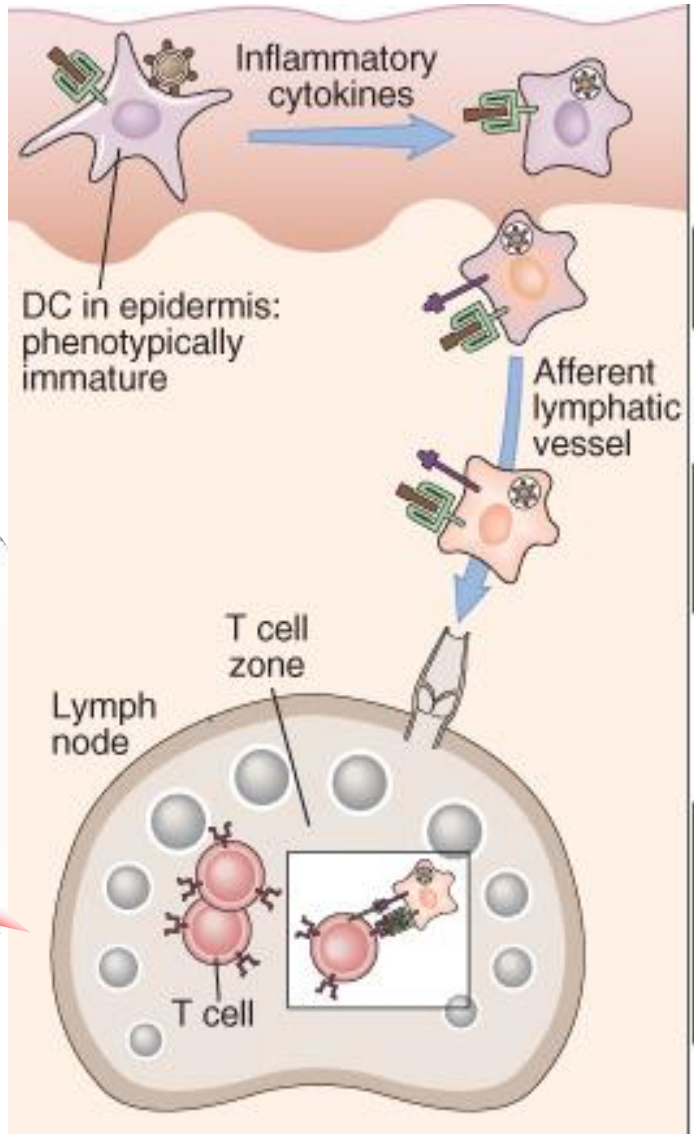
Chicago, IL, United States – 13-14 December 2013

A meeting of the World Allergy Organization

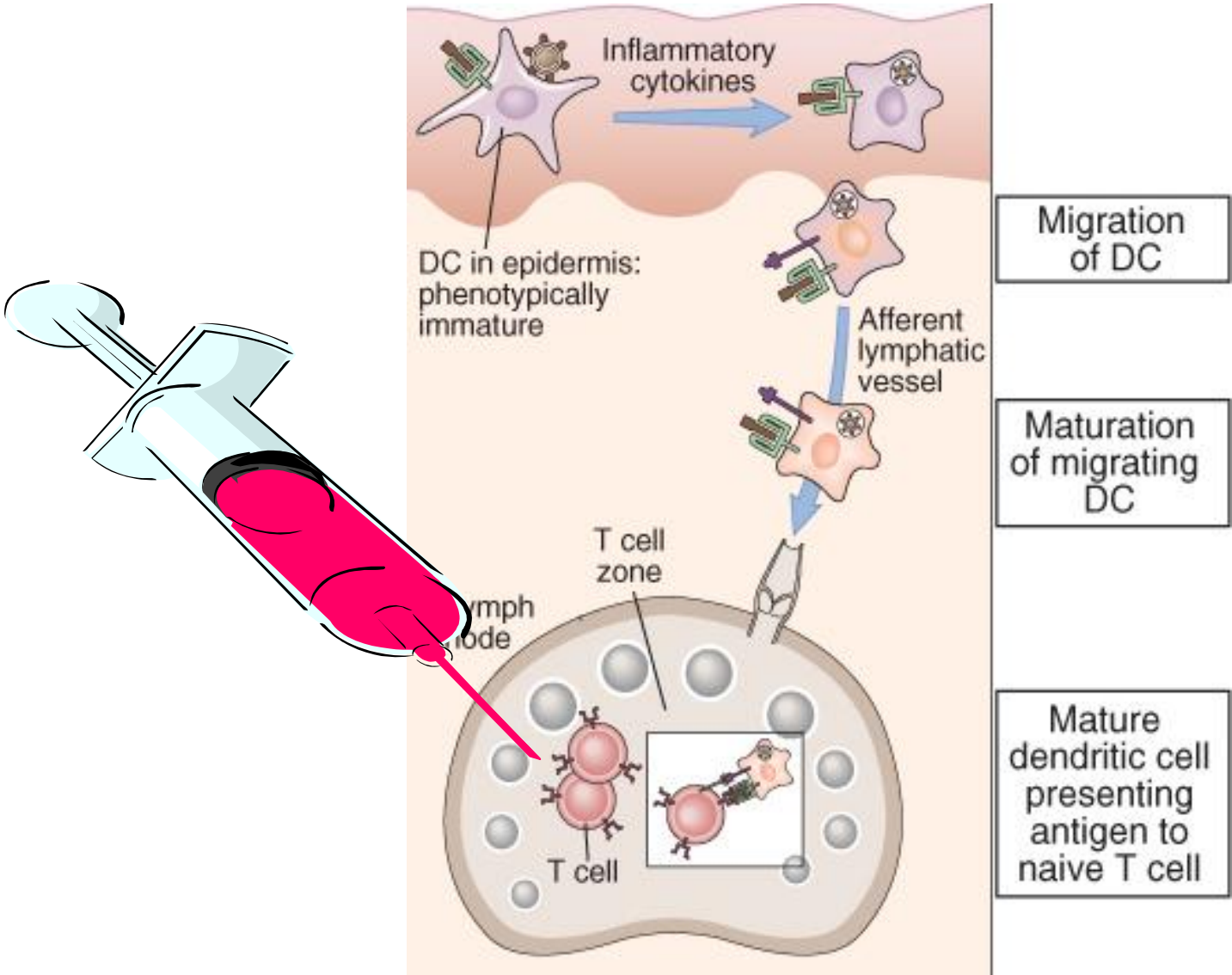
Gabriela Senti
Center for Clinical Research
University and University Hospital Zurich

Subcutaneous Immunotherapy

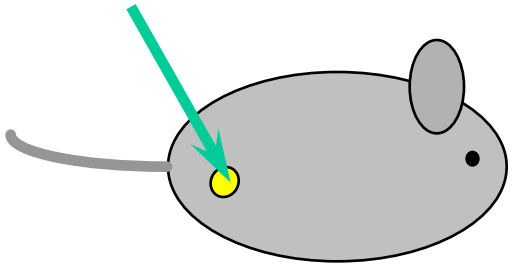




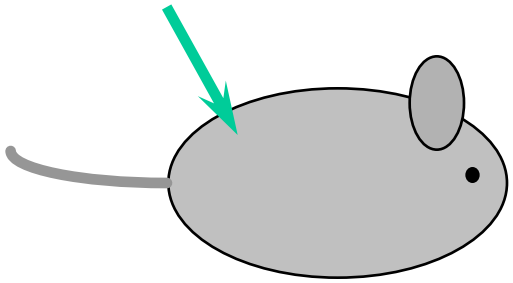
Intralymphatic Immunotherapy



Protein Vaccines



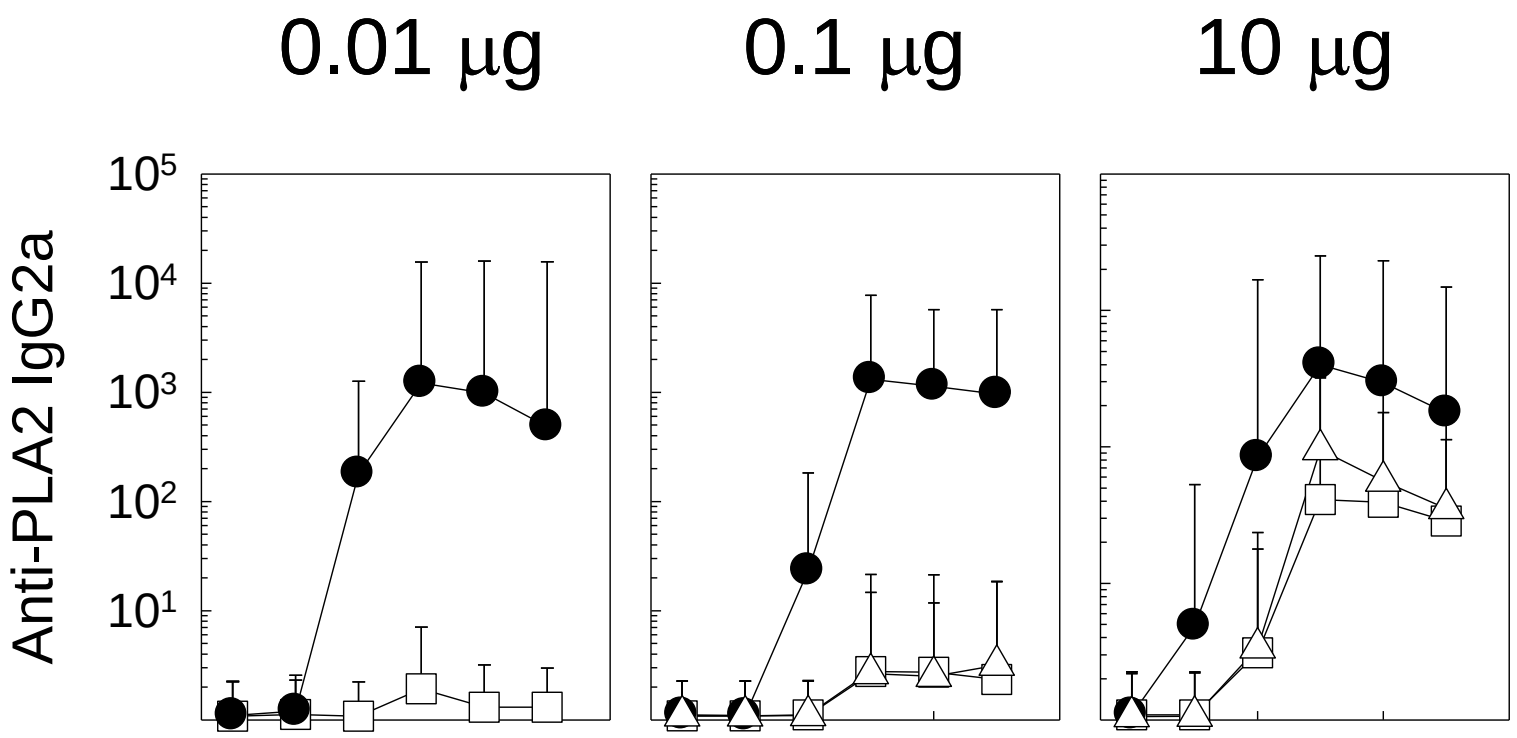
into lymph node



subcutaneous

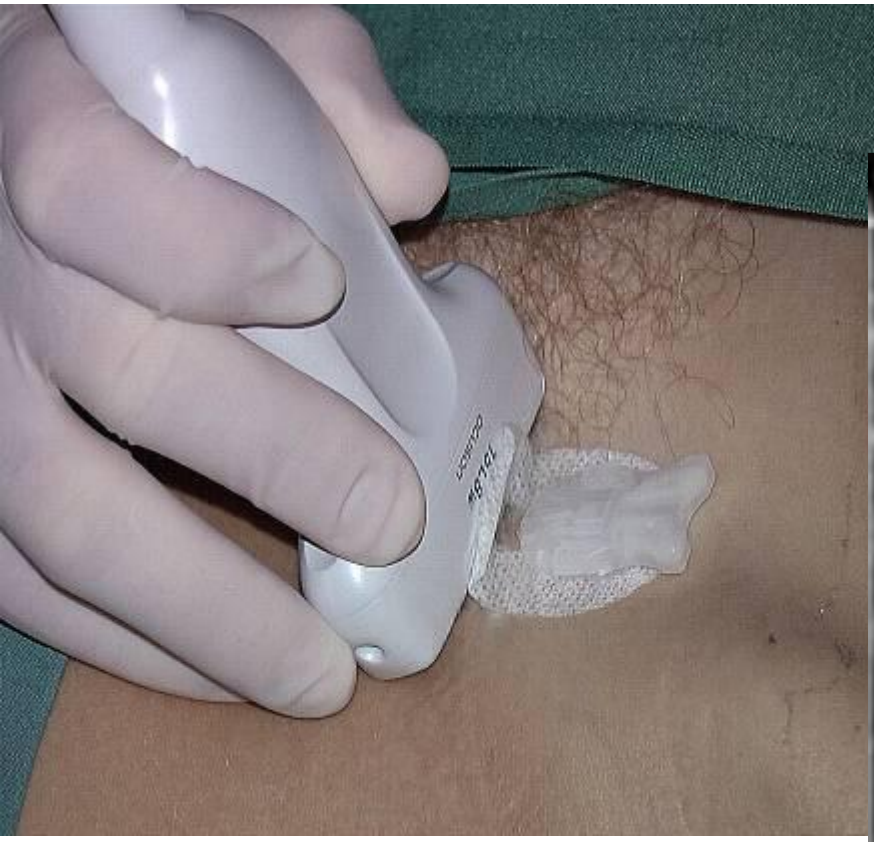
IgG ?

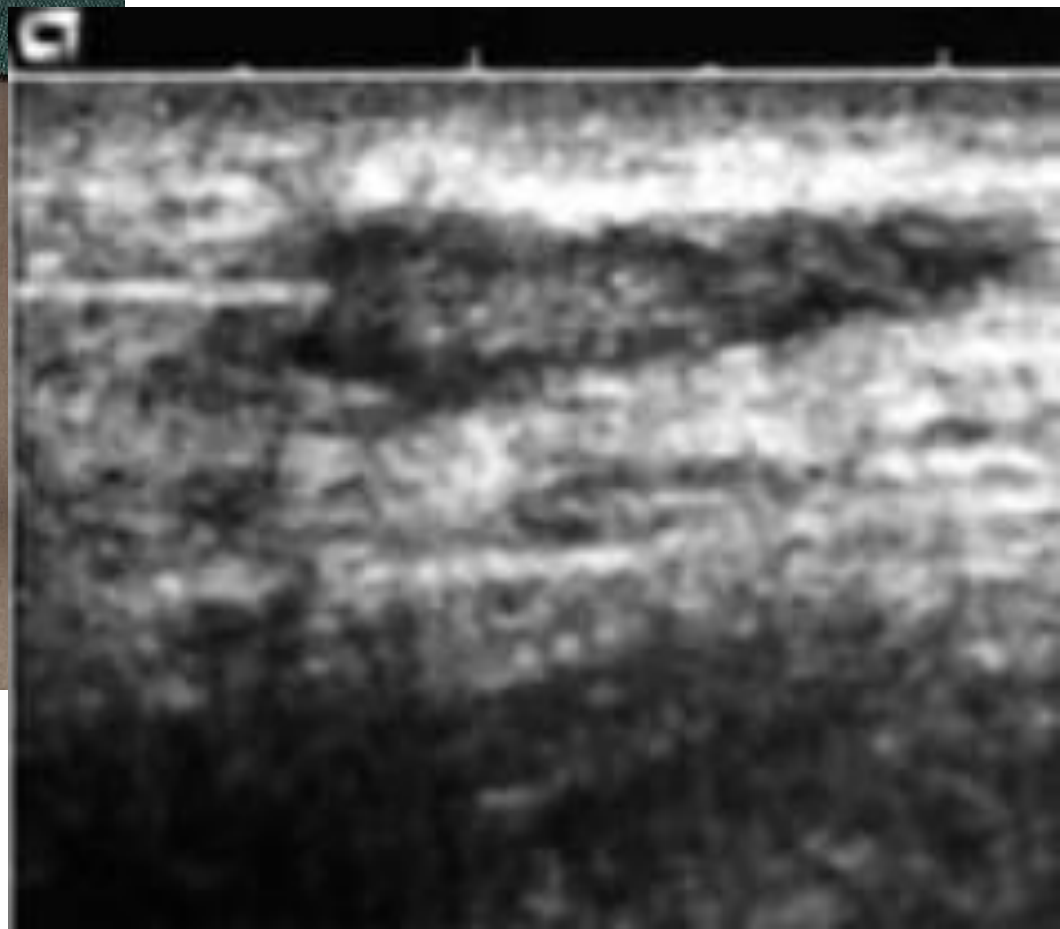
Allergen Administration Route



● intralymphatic (ILIT) □ subcutaneous (SCIT) Δ intraperitoneal

Injection into Lymph Nodes





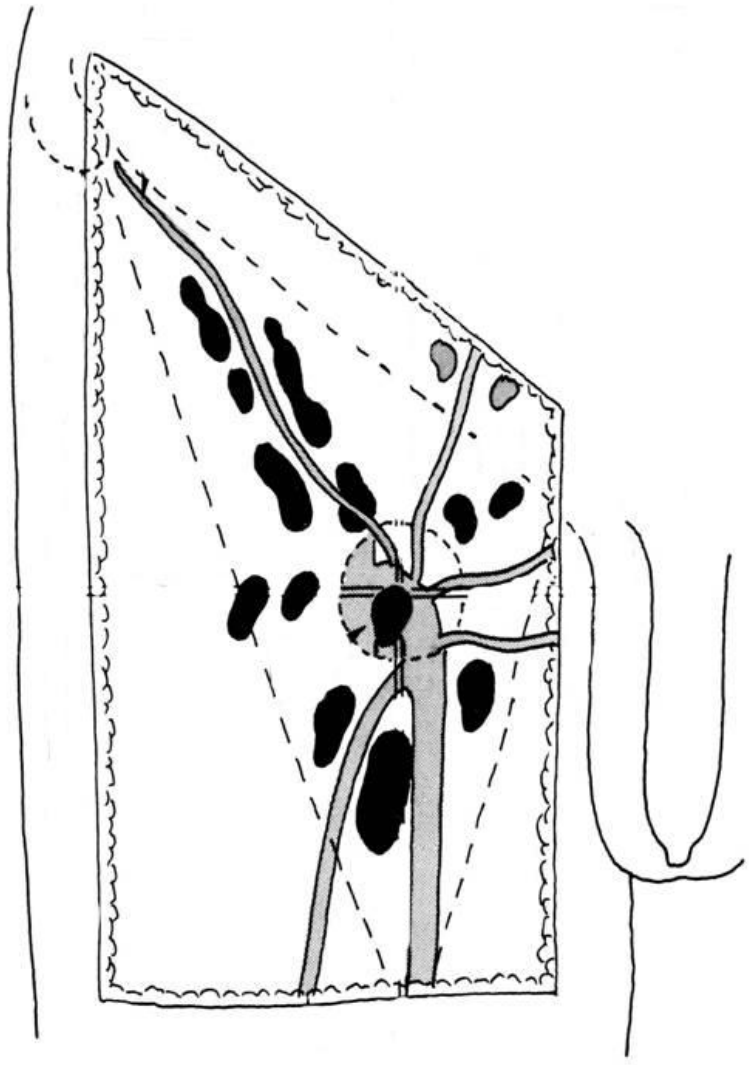
Inguinal Lymph Nodes

no large vessels

little movement

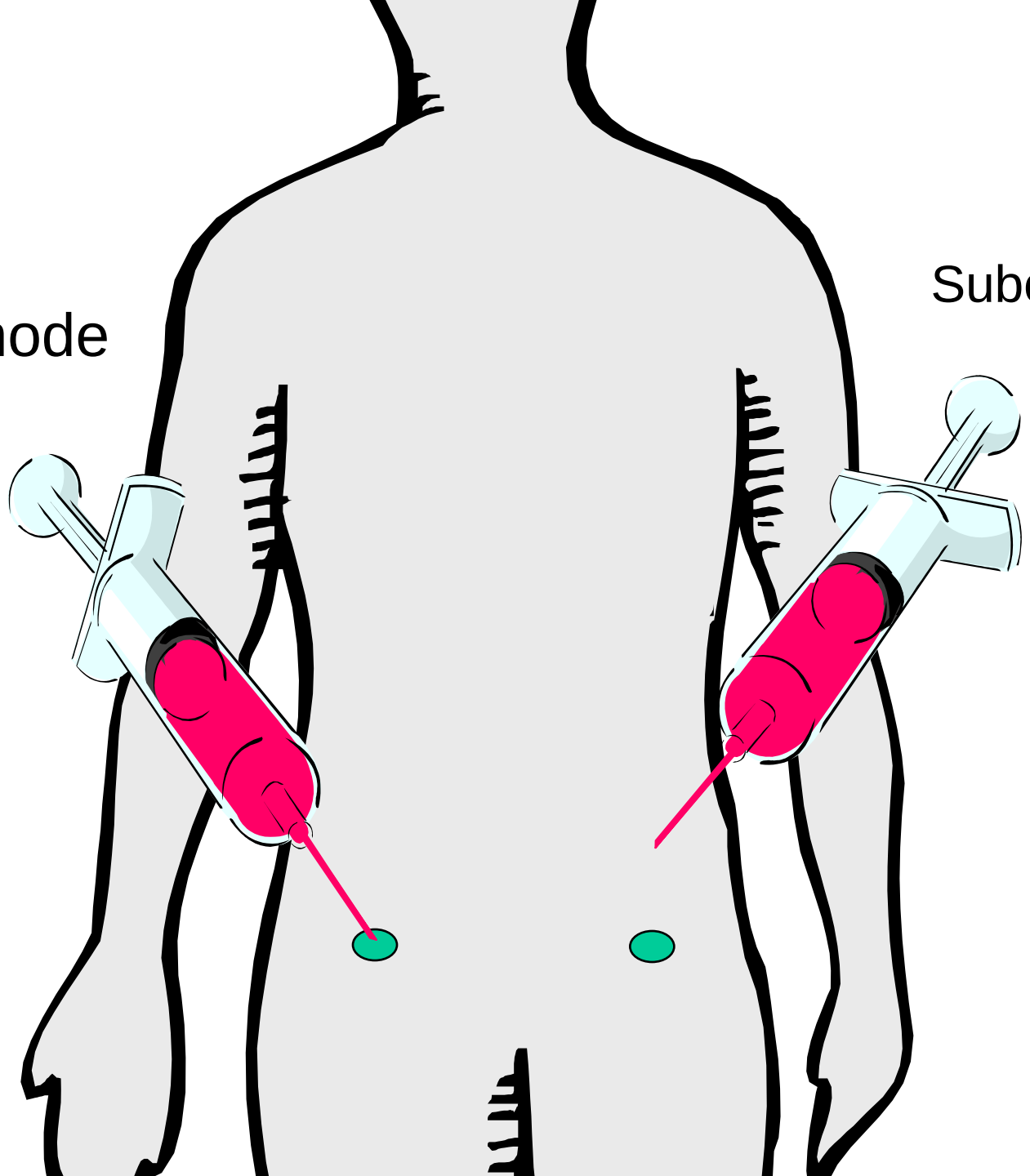
close to vessels

leg movement

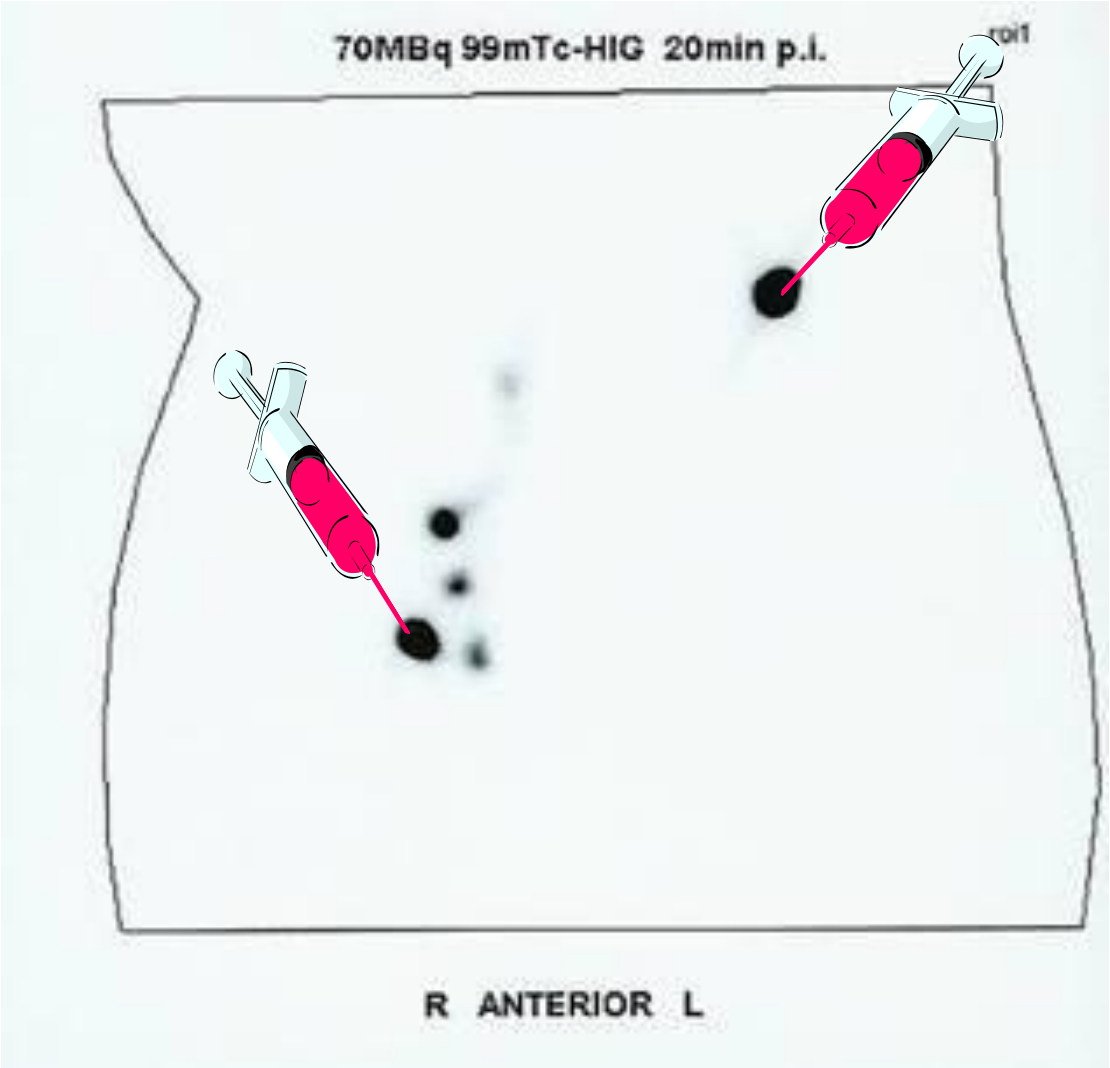


into
lymph node

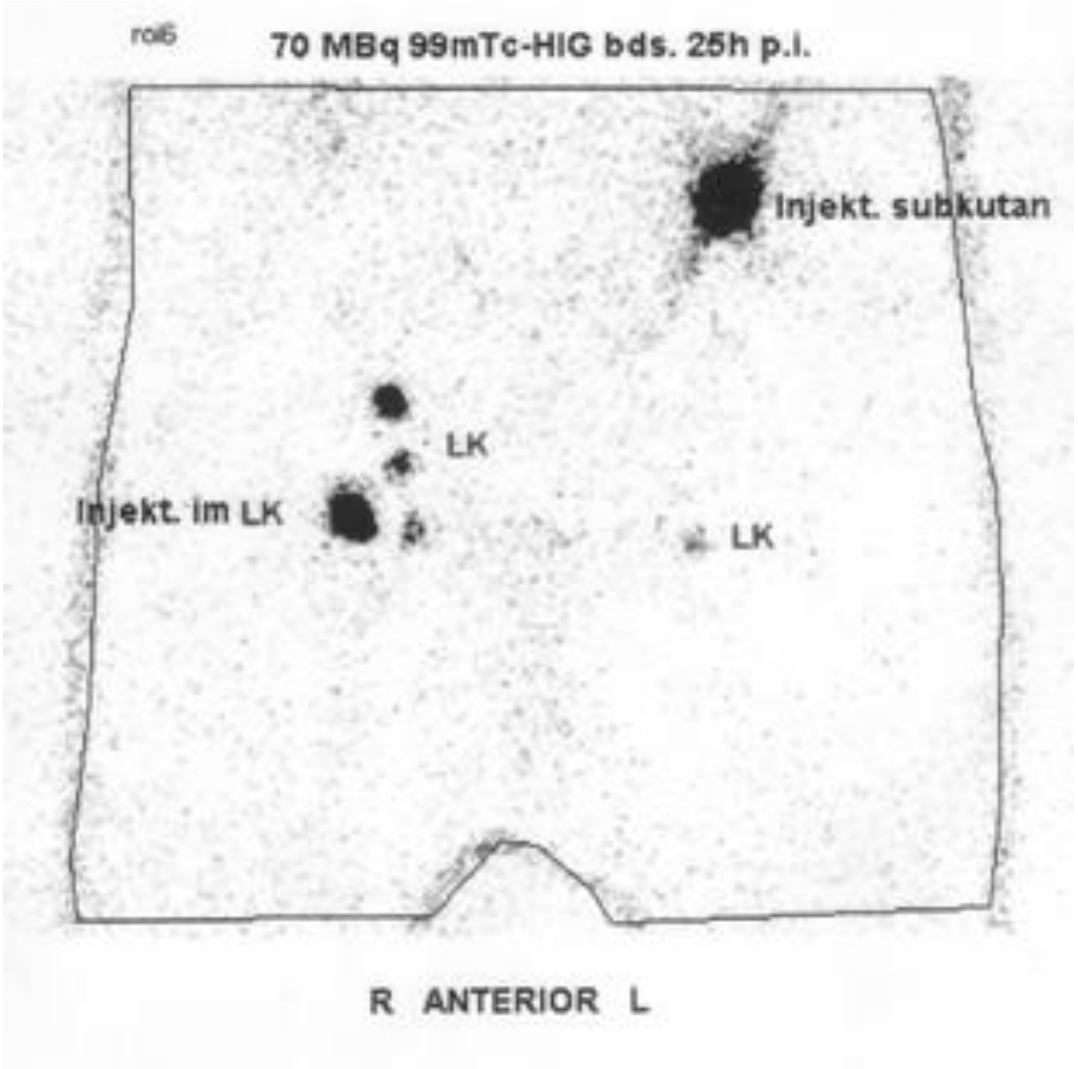
Subcutaneous



20 Min

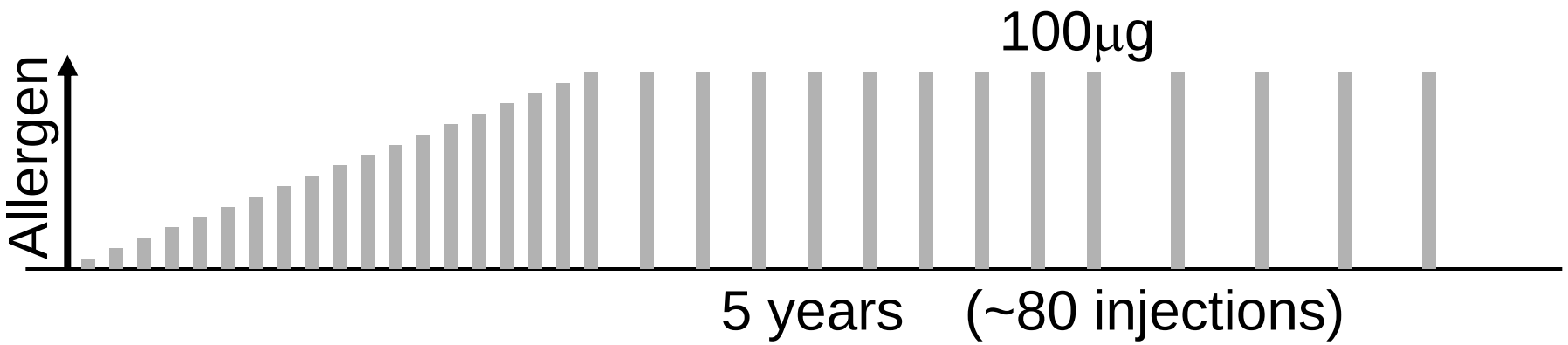


25 h



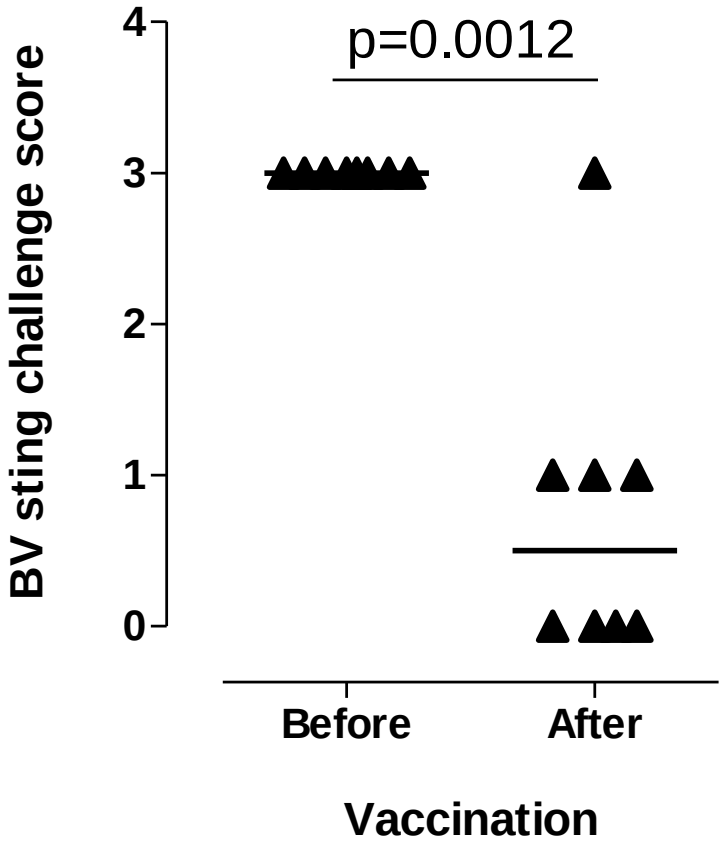
Senti et al.
Curr Opin Allergy
Clin Immunol 2009

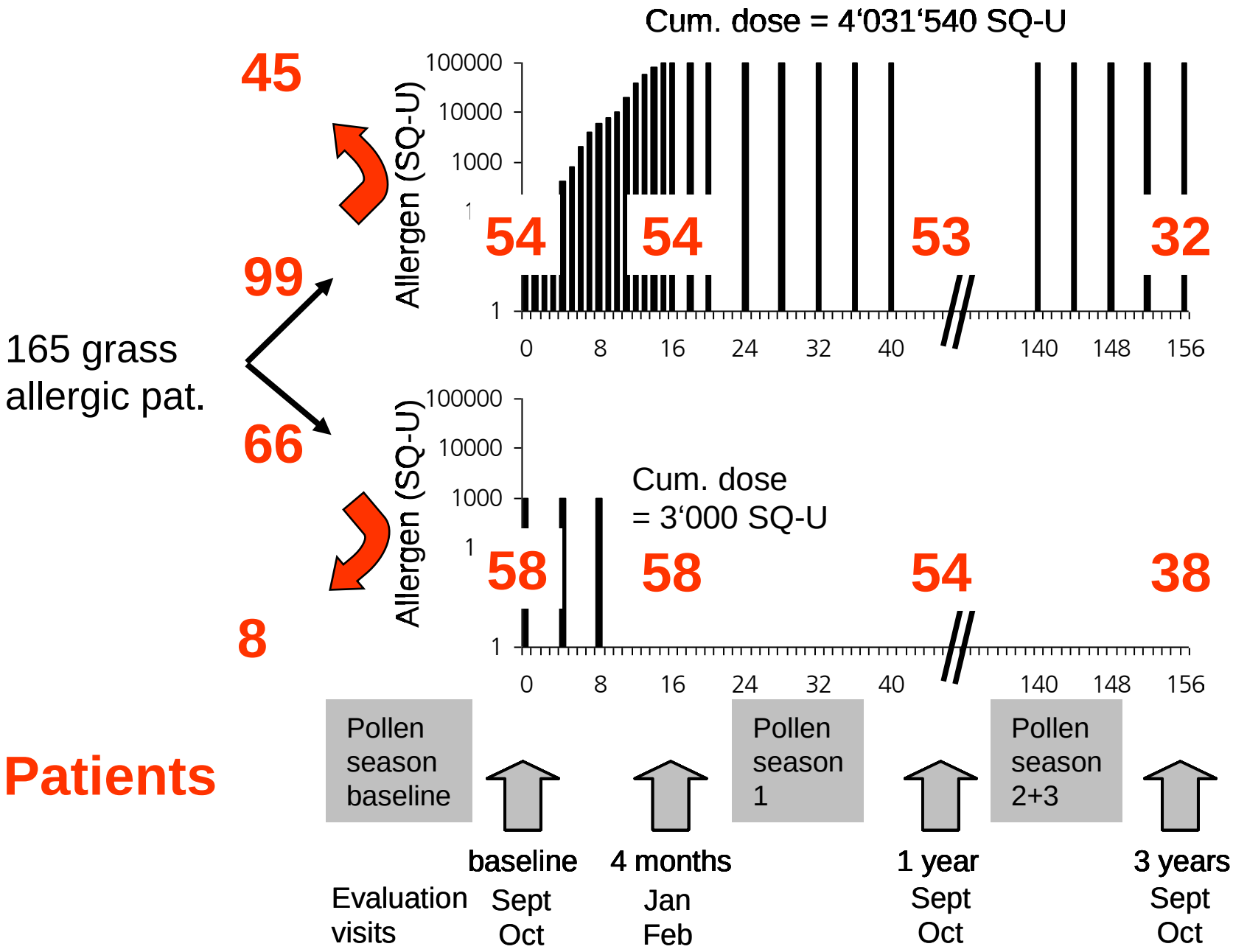
Clinical Trial ZU-BV-001



3 injections
2 wk intervals

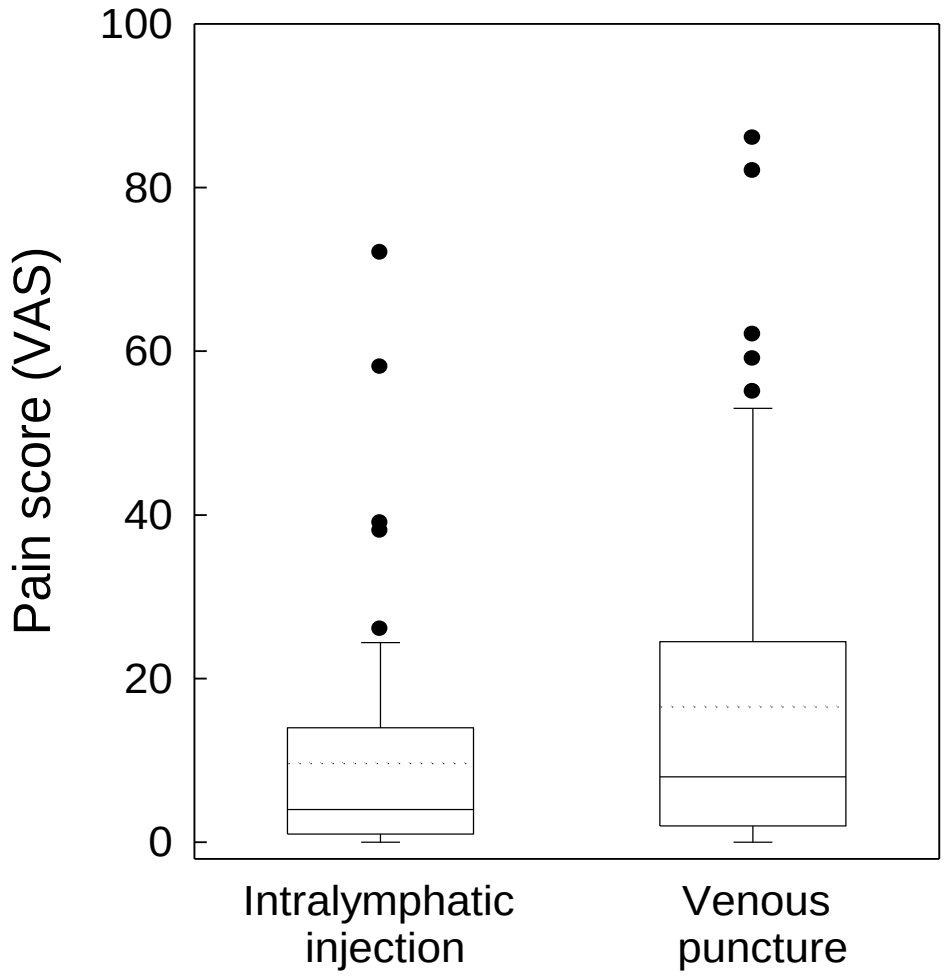
Sting Provocation



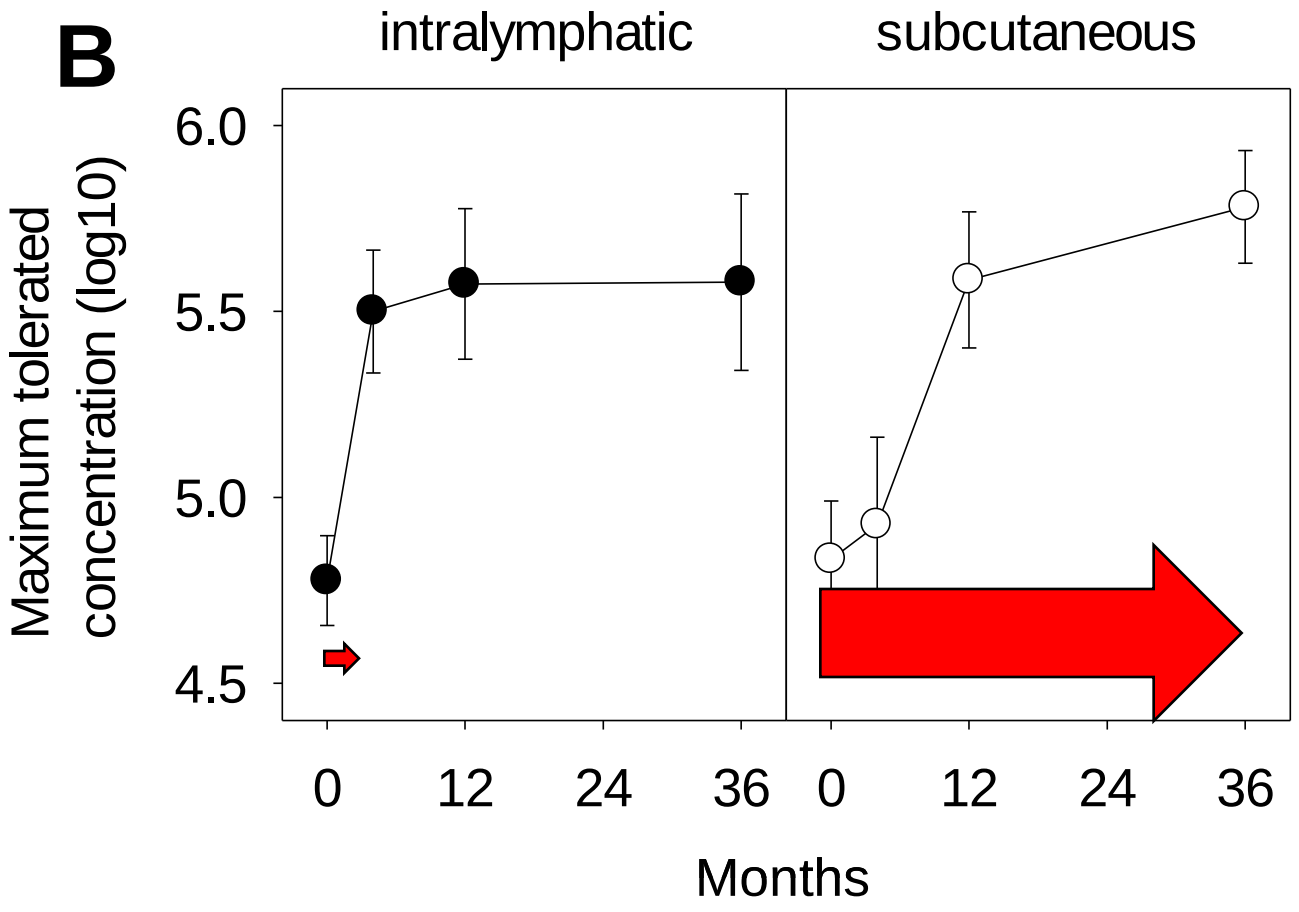


Senti et al. PNAS 2008

Pain?

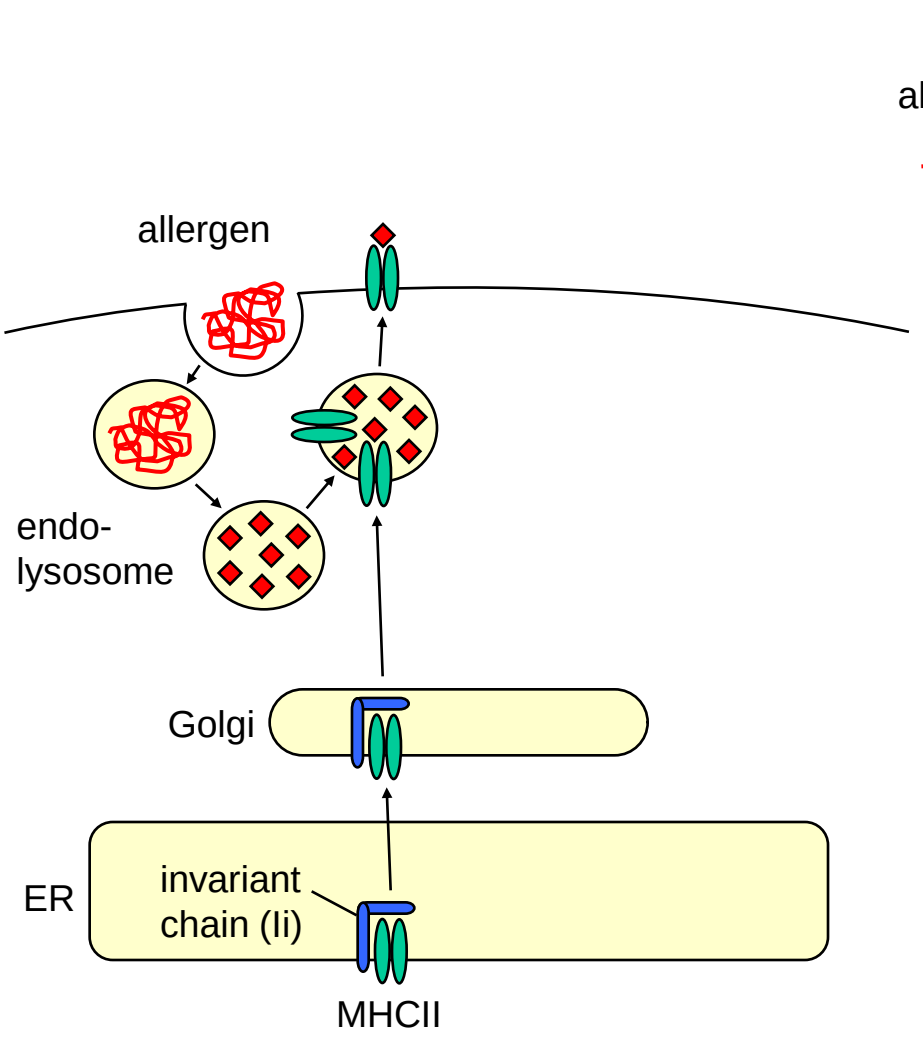

100
80
60
40
20
0
Pain score (VAS)
Intralymphatic injection
Venous puncture

Nasal Provocation Test

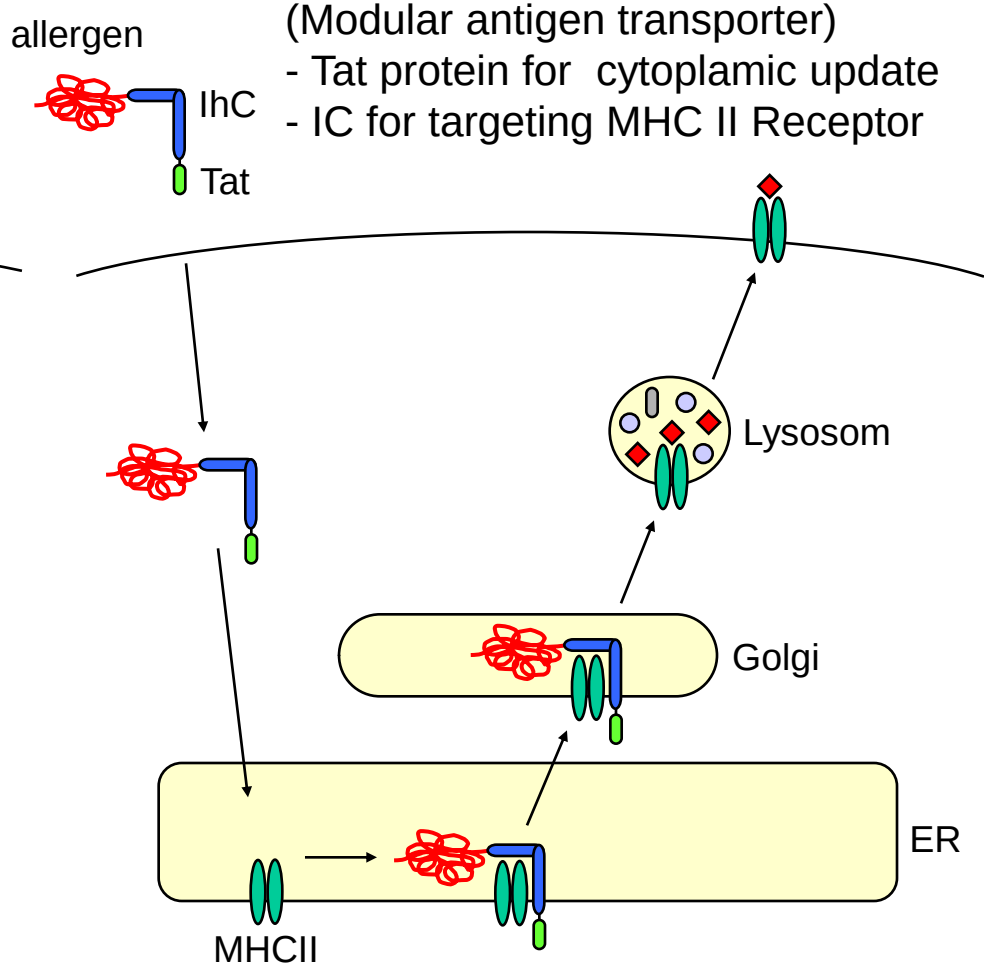


Senti et al. PNAS 2008

Antigen Presentation

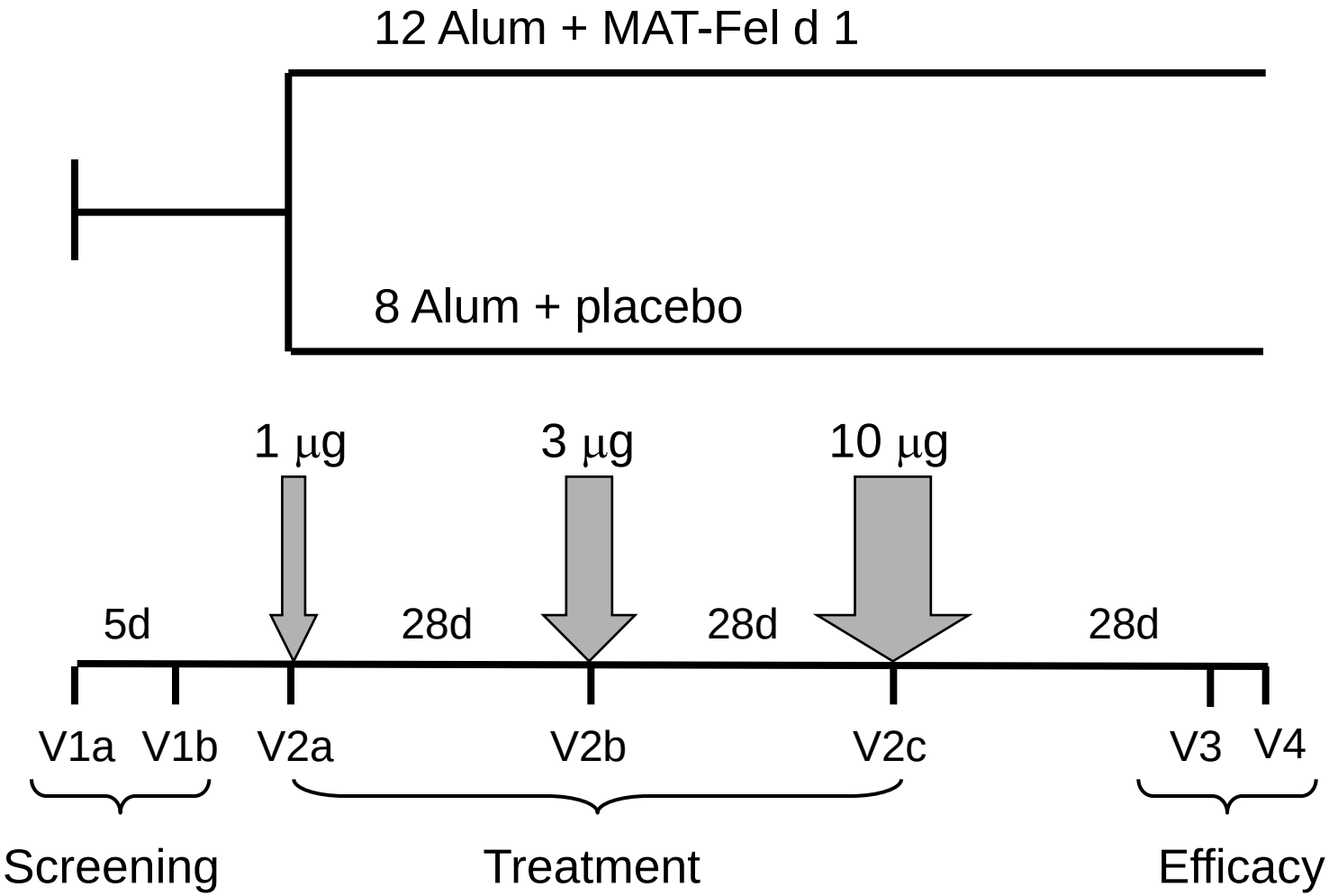


Molecular targeting : MAT Antigen
(Modular antigen transporter)
- Tat protein for cytoplamic update
- IC for targeting MHC II Receptor



Matinez-Gómez et al. Allergy 2009

IVN-CAT-001b



Senti et al. JACI 2012

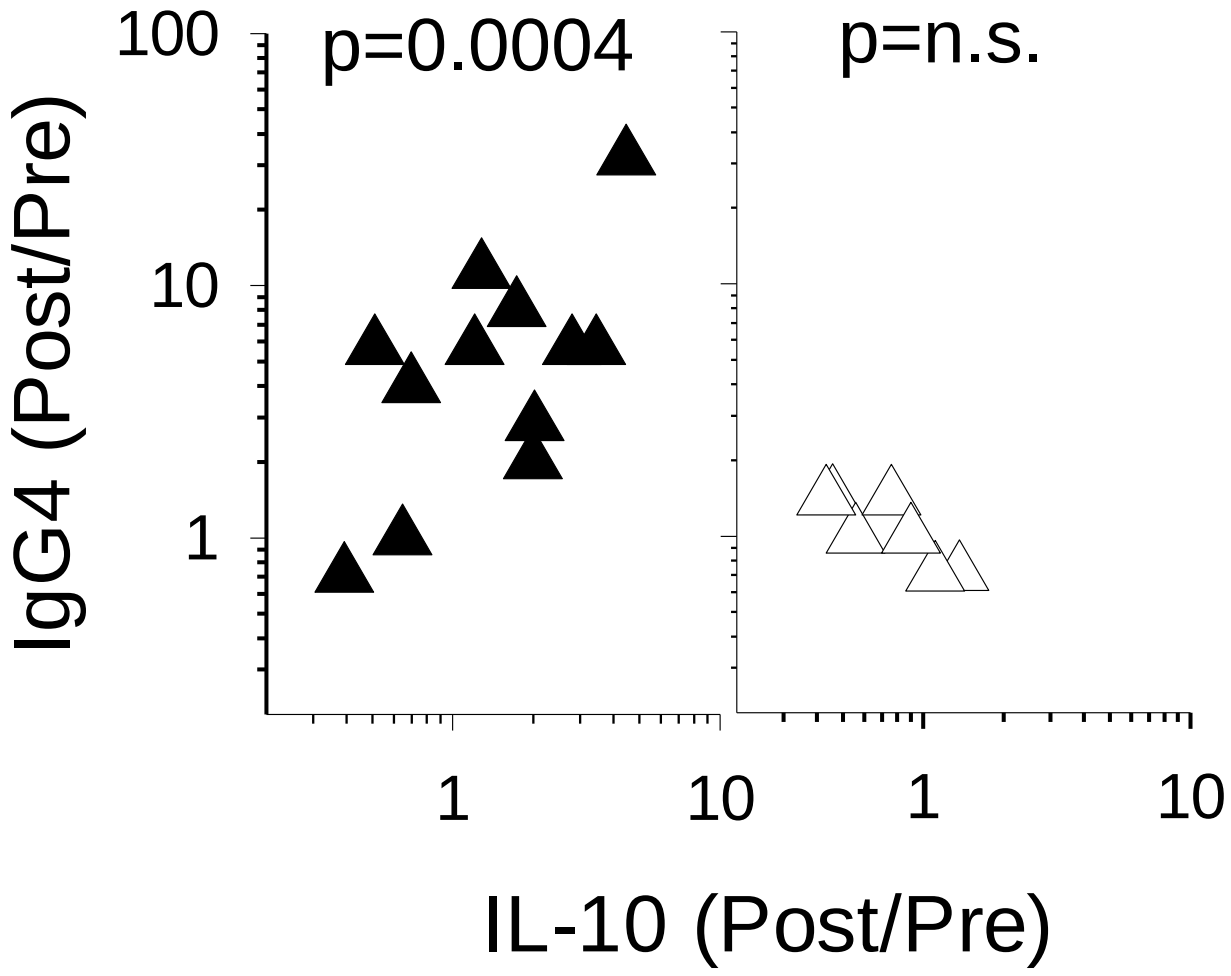
Adverse Events

No SAE

Possibly drug related AE	**Placebo**		**Verum**	
Severity	mild	moderate	mild	moderate
Local reactions				
temporary lymphnode swelling	2	1	3	1
Systemic reactions				
rhinorea	1	1	0	0
sneezing	1	1	0	0
pruritus	1	1	0	0
nausea	0	0	1	0
rash	0	0	0	1
dyspnoe	2	0	1	0
headache	1	1	0	0
cough	1	0	0	0
Total	**9**	**5**	**5**	**2**

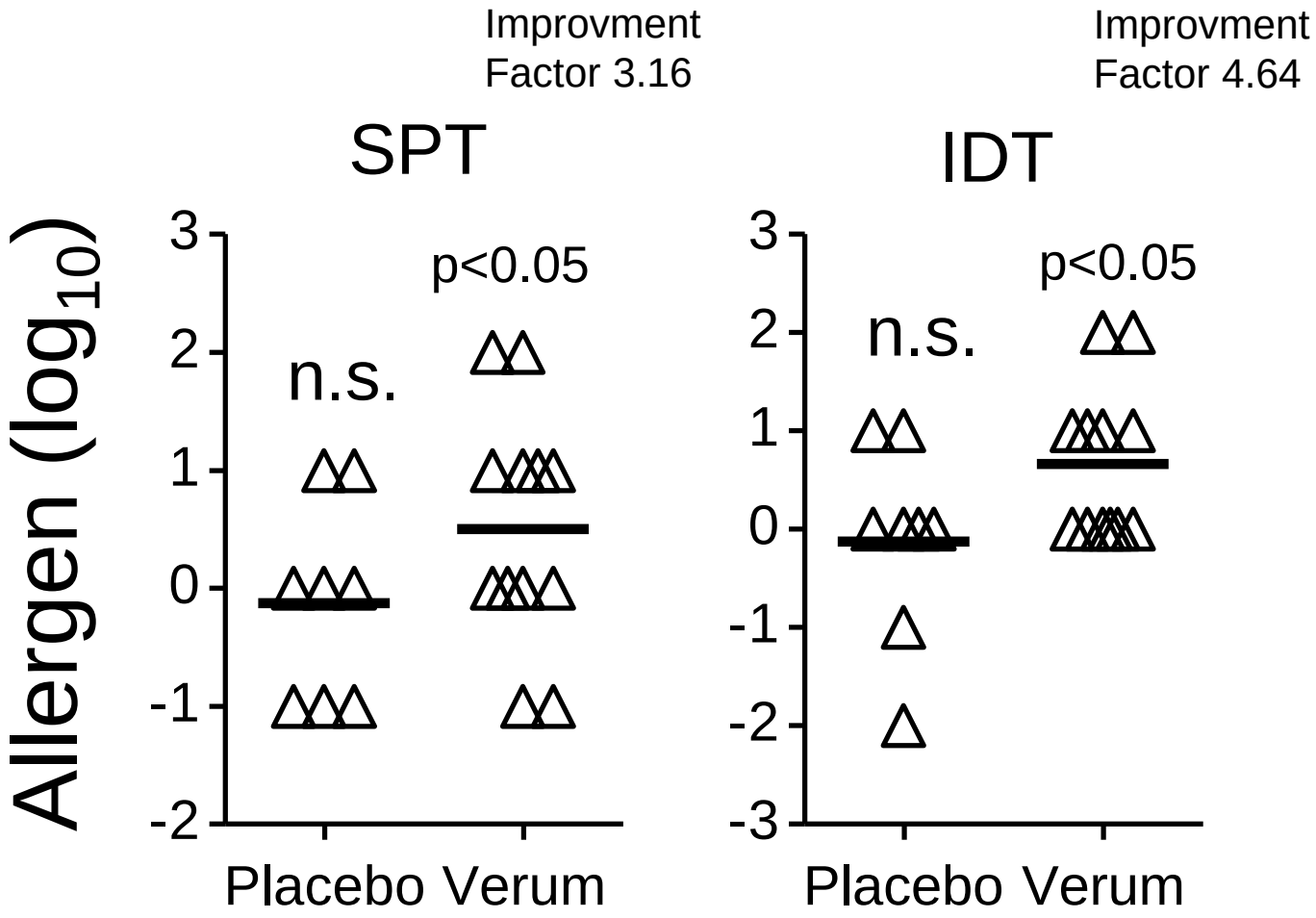
Senti et al. JACI 2012

IL-10 Correlates with IgG4



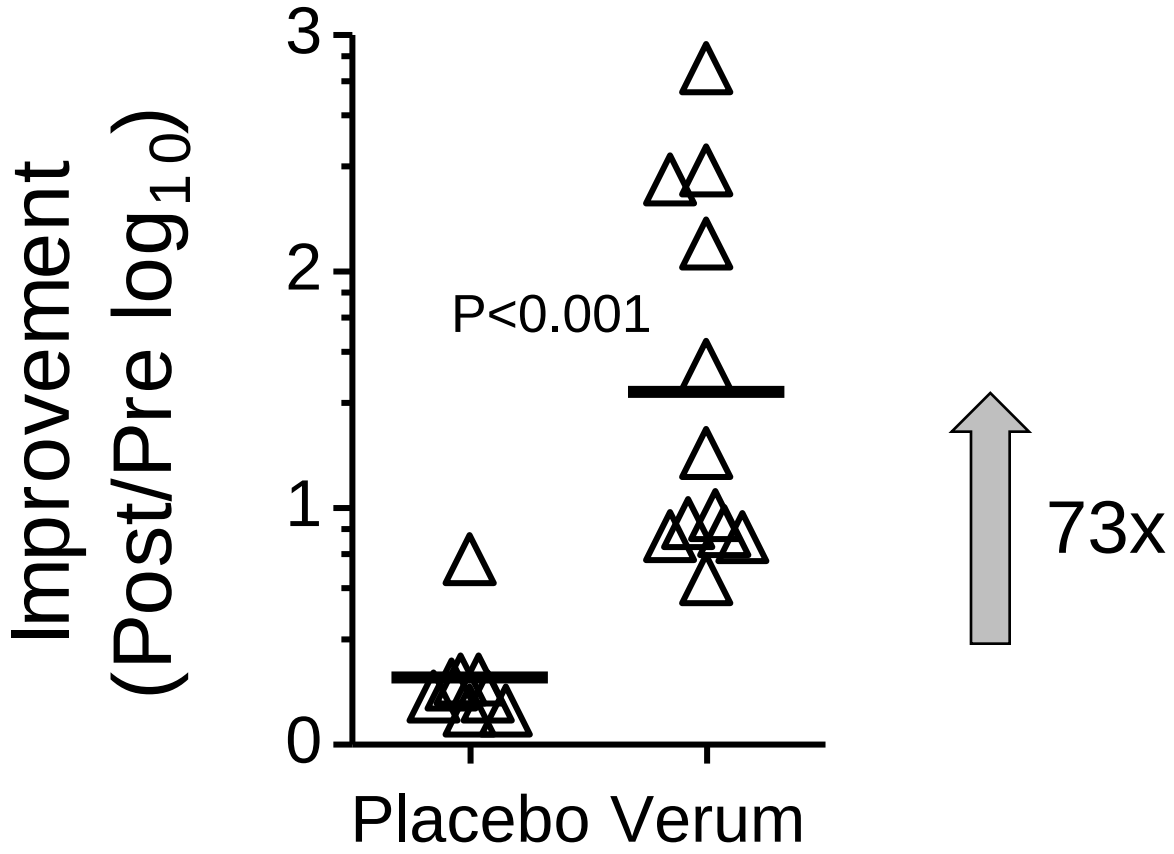
Senti et al. JACI 2012

Prick Test and Intradermal Test



Senti et al. JACI 2012

Nasal Tolerance



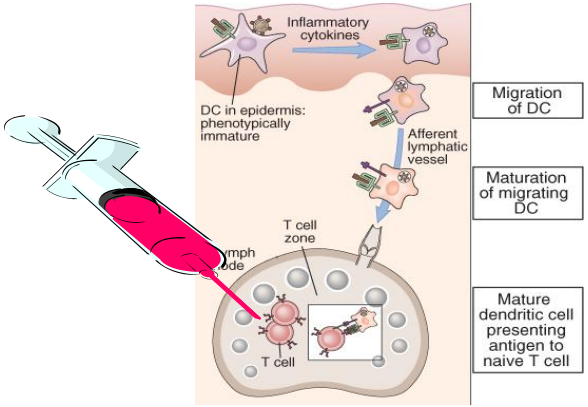
Senti et al. JACI 2012

More data will be published soon

From Kopenhagen → Low efficacy?
Weekly intervall too short?

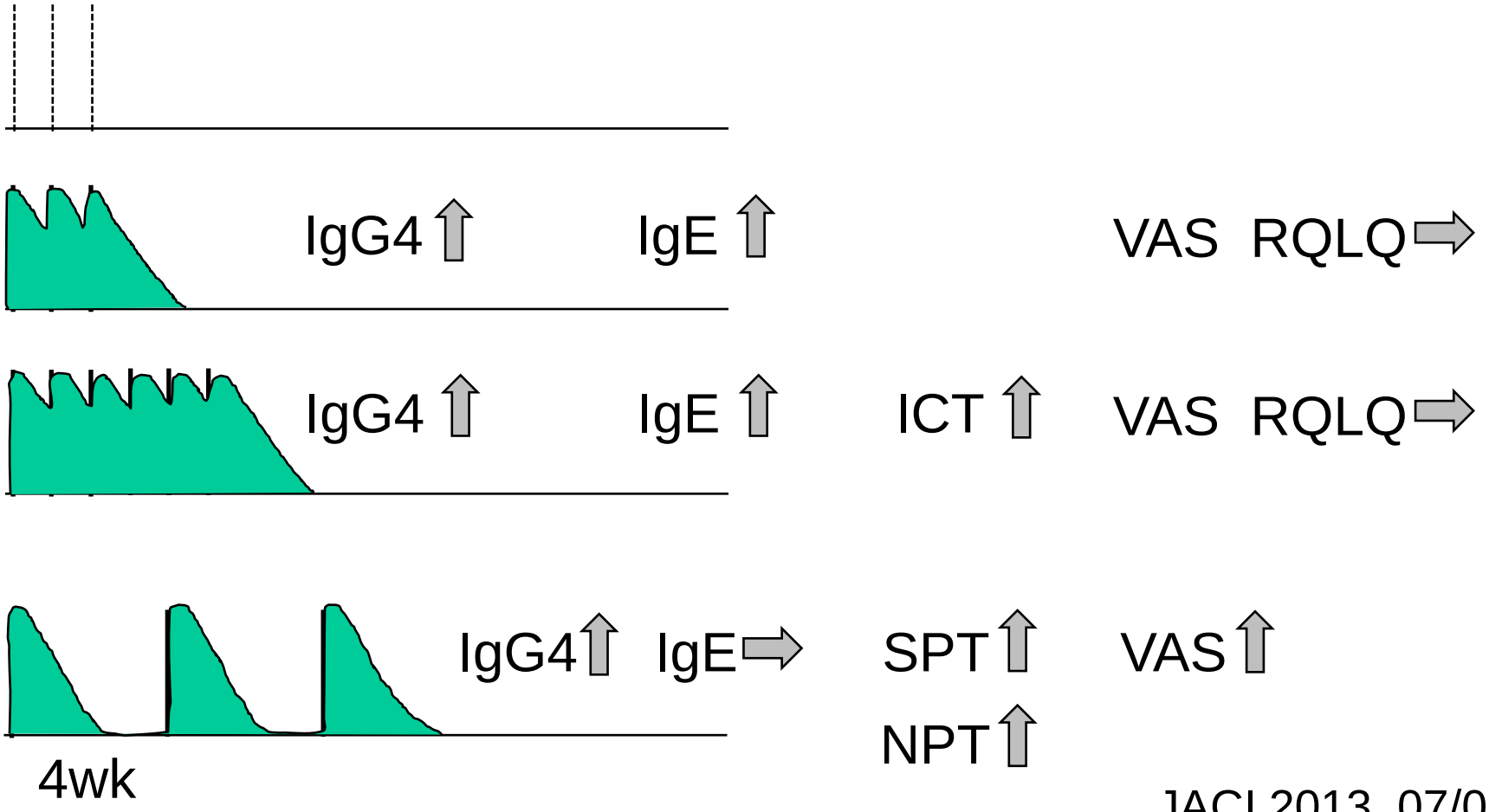
From Stockholm → Very positive results
We can relax again…

Interest from China → Drug Development
is not easy…

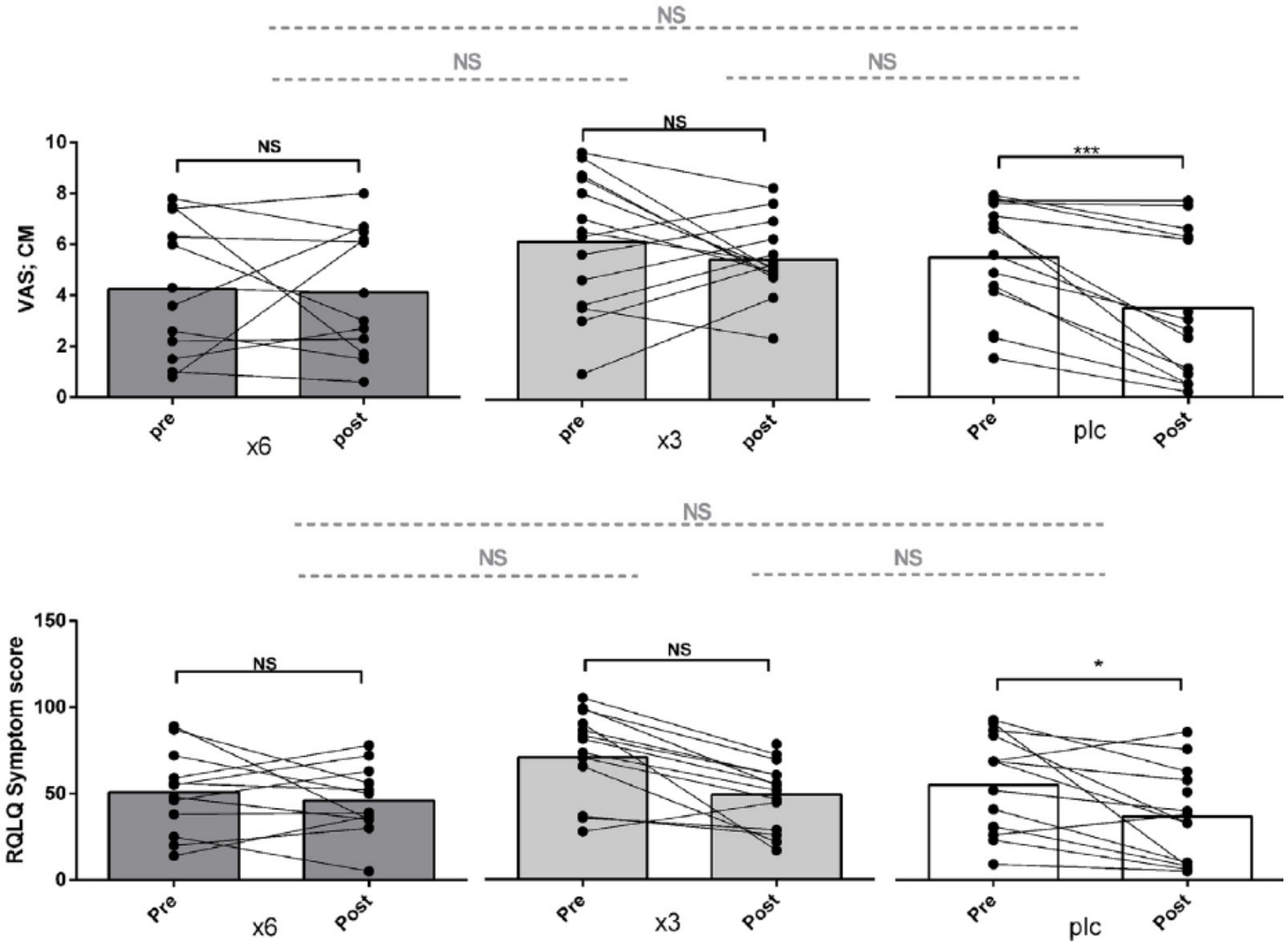


Is intralymphatic specific immunotherapy with grass pollen allergen ready for clinical use?

Malling, H; Blom, L; Poulsen, B; Poulsen, L; Witten, M



JACI 2013, 07/033



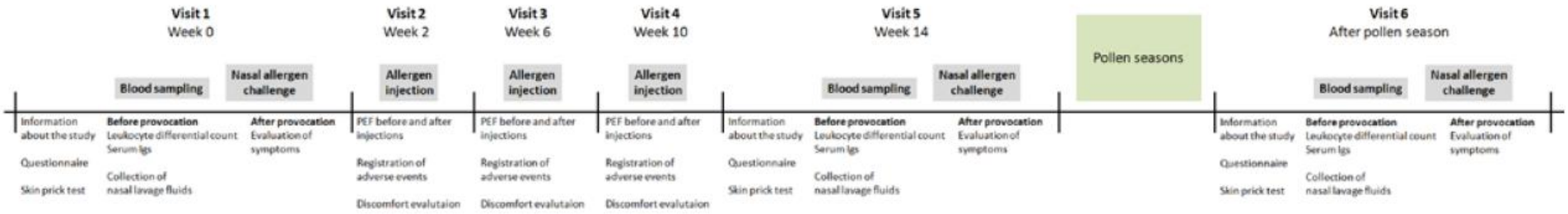
JACI 2013, 07/033

Table 2–5 Determinants of the Duration of Vaccine Antibody Responses in Healthy Individuals

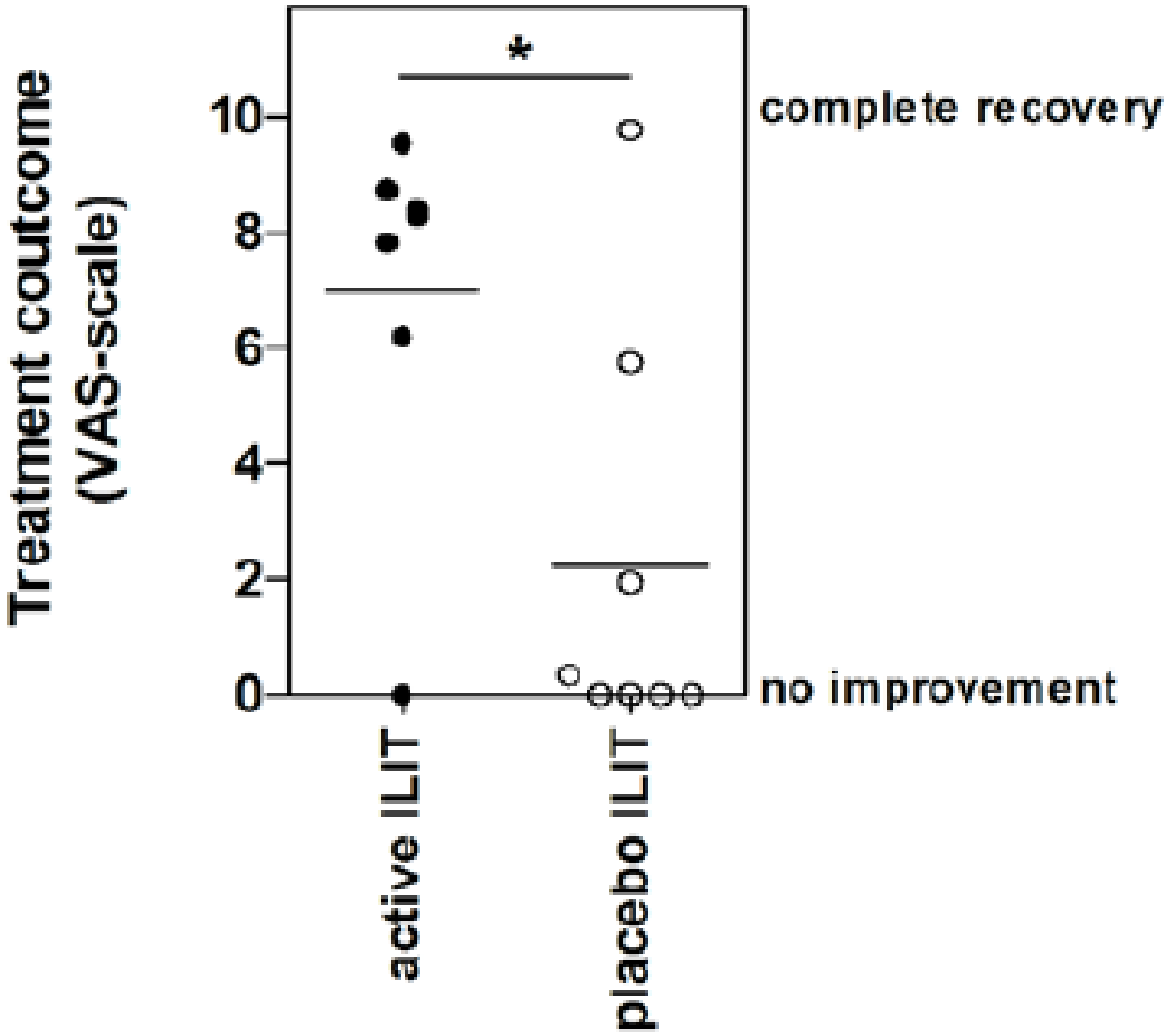
Determinants	Mechanisms (presumed)
Vaccine type	
Live vs inactivated	Live vaccines generally induce more sustained Ab responses, presumably through Ag persistence within the host.
Polysaccharide antigens	Failure to generate GCs limits the induction of memory responses and of high-affinity long-live plasma cells.
Vaccine schedule	
Interval between primary doses	A minimal interval of 3 weeks between primary doses allows development of successive waves of Ag-specific primary responses without interference.
Interval before boosting	A minimal interval of 4 months between priming and boosting allows affinity maturation of memory B cells, and thus higher secondary responses.

Intralymphatic allergen-specific immunotherapy: an effective and safe alternative treatment route for pollen-induced allergic rhinitis

Terese Hylander M.Sc.[1], Leith Latif MD[2], Ulla Petersson-Westin MD, PhD[2], Lars Olaf Cardell MD, PhD[1,2]



JACI 2013 Feb;131(2):412-20



JACI 2013 Feb;131(2):412-20

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.

JACI 2013 Feb;131(2):412-20

Clin. exp. Immunol. (1974) **17,** 329–338.

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.*

DISCOVER®
MAGAZINE

Health & Medicine | Mind & Brain | Technology | Space | Human Origins | Living World | Environment

Not Exactly Rocket Science

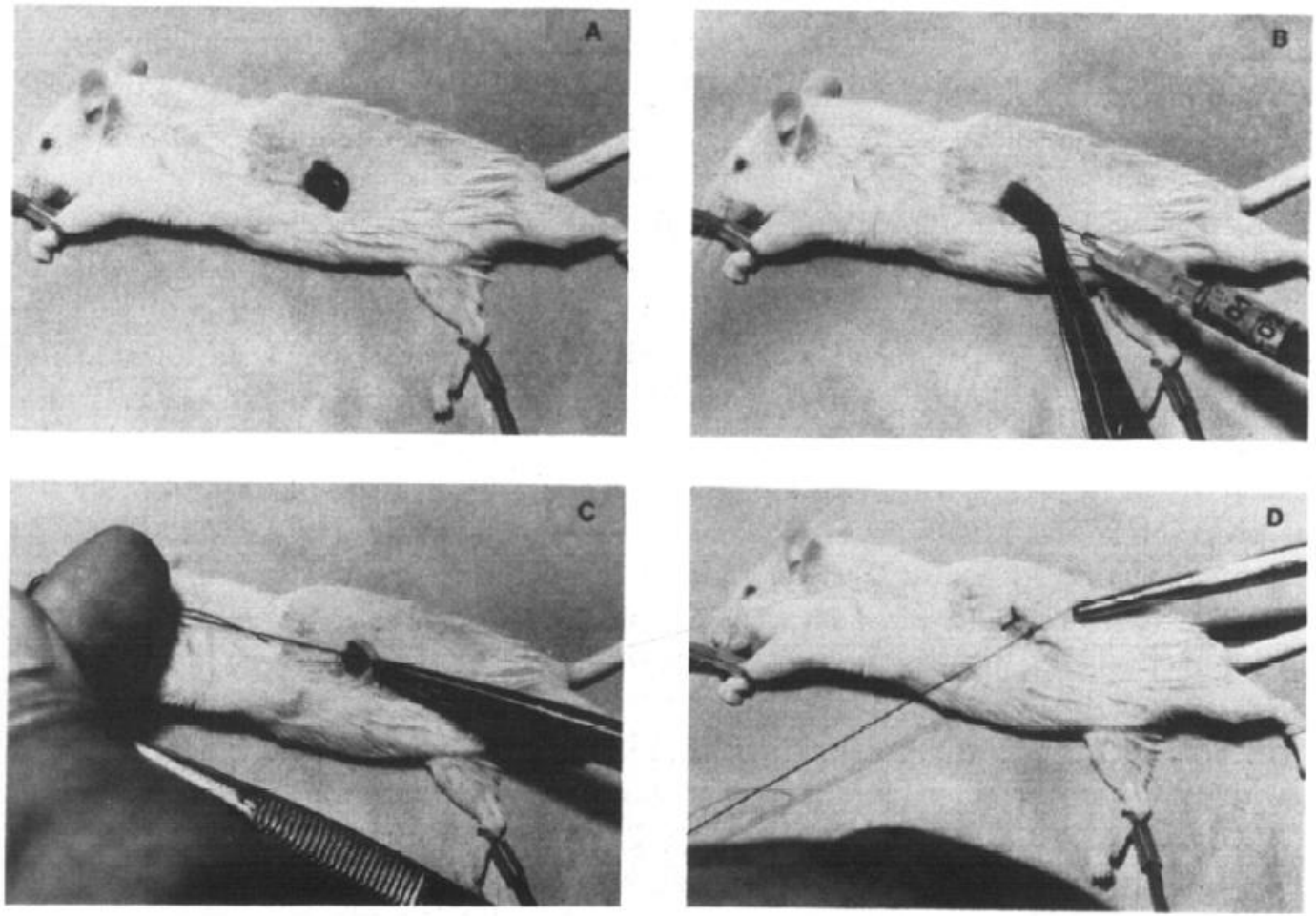
Lymph node injections provide safer, faster and easier relief against hay fever

Intrasplenic Primary Immunization for the Production of Monoclonal Antibodies

M. Spitz, L. Spitz, R. Thorpe and E. Eugui [1,*]

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)



Journal of Immunological Methods

Volume 188, Issue 1, 15 December 1995, Pages 43–49

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

Received 31 March 1995. Revised 7 June 1995. Accepted 1 August 1995. Available online 13 January 2000.

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

Juillard, GJF and Bubbers, JE, "Experimental Intralymphatic Immunotherapy (ILI) of Canine Allergic Disease". Federation Proceedings, Vol. 42, No. 3, March 1, 1983.

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”

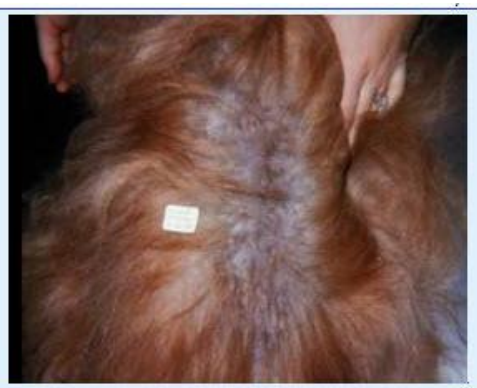


Fig. 1: Loss of hair before intralymphatic immunotherapy

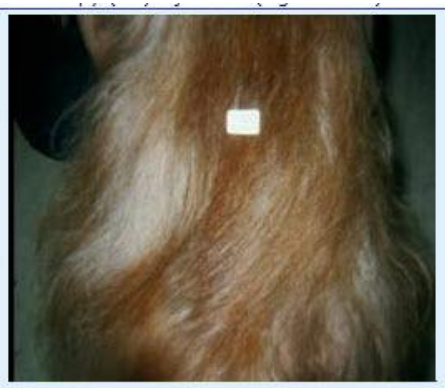
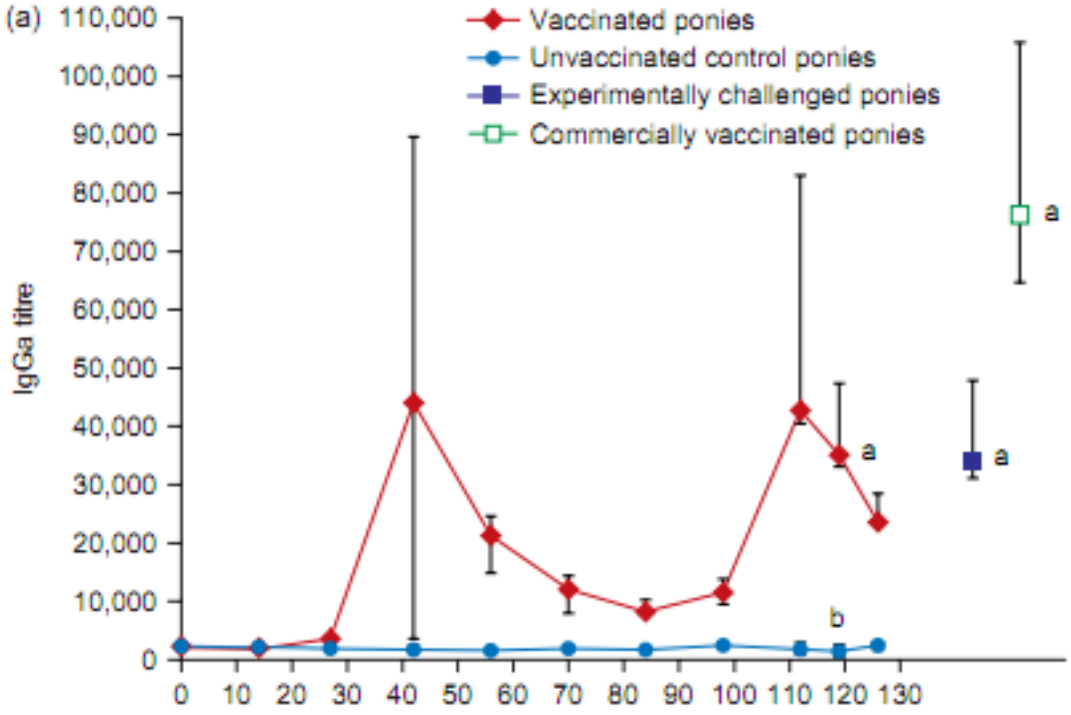


Fig. 2: Re-growth of hair after intralymphatic immunotherapy

Vet Dermatol 2011

Low-dose DNA vaccination into the submandibular lymph nodes in ponies

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



Protective mucosal immunity elicited by targeted iliac lymph node immunization with a subunit SIV envelope and core vaccine in macaques

THOMAS LEHNER[1], YUFEI WANG[1], MARTIN CRANAGE[2], LESLEY A. BERGMEIER[1], ELAINE MITCHELL[1], LOUISA TAO[1], GRAHAM HALL[2], MIKE DENNIS[2], NICOLA COOK[2], ROGER BROOKES[1], LINDA KLAVINSKIS[1], IAN JONES[3], CARL DOYLE[3] & ROBERT WARD[1]

[1]*Department of Immunology, United St. Thomas' Hospital,*
[2]*Centre for Applied Microbiology & Research, F*
[3]*Institute of Virology and Environmental Micro*
Correspondence shoul

Journal of Dairy Science

Volume 77, Issue 10, October 1994, Pages 2965–2974

Article

Effect of Whole *Staphylococcus aureus* and Mode of Immunization on Bovine Opsonizing Antibodies to Capsule[1]

A.J. Guidry, C.N. O'brien[2], S.P. Oliver[3], H.H. Dowlen[4], L.W. Douglass[2]

Milk Secretion and Mastitis Laboratory, Agricultural Research Service, Beltsville, MD 20705

Received 21 March 1994. Accepted 9 May 1994. Available online 30 May 2010.

"Antibodies of all four isotypes, IgG_1, IgG_2, IgA, and IgM, increased in dry secretions following immunization via lymph node."

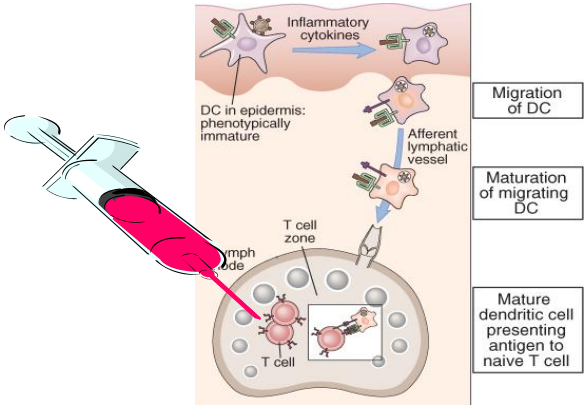
Conclusions ILIT vs SCIT

Low allergen doses ⇒ Improved safety

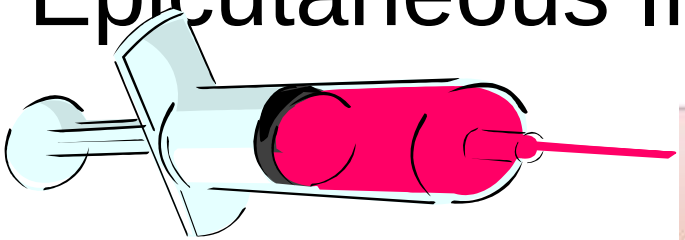
Enhanced immunogenicity ⇒ Fewer injections

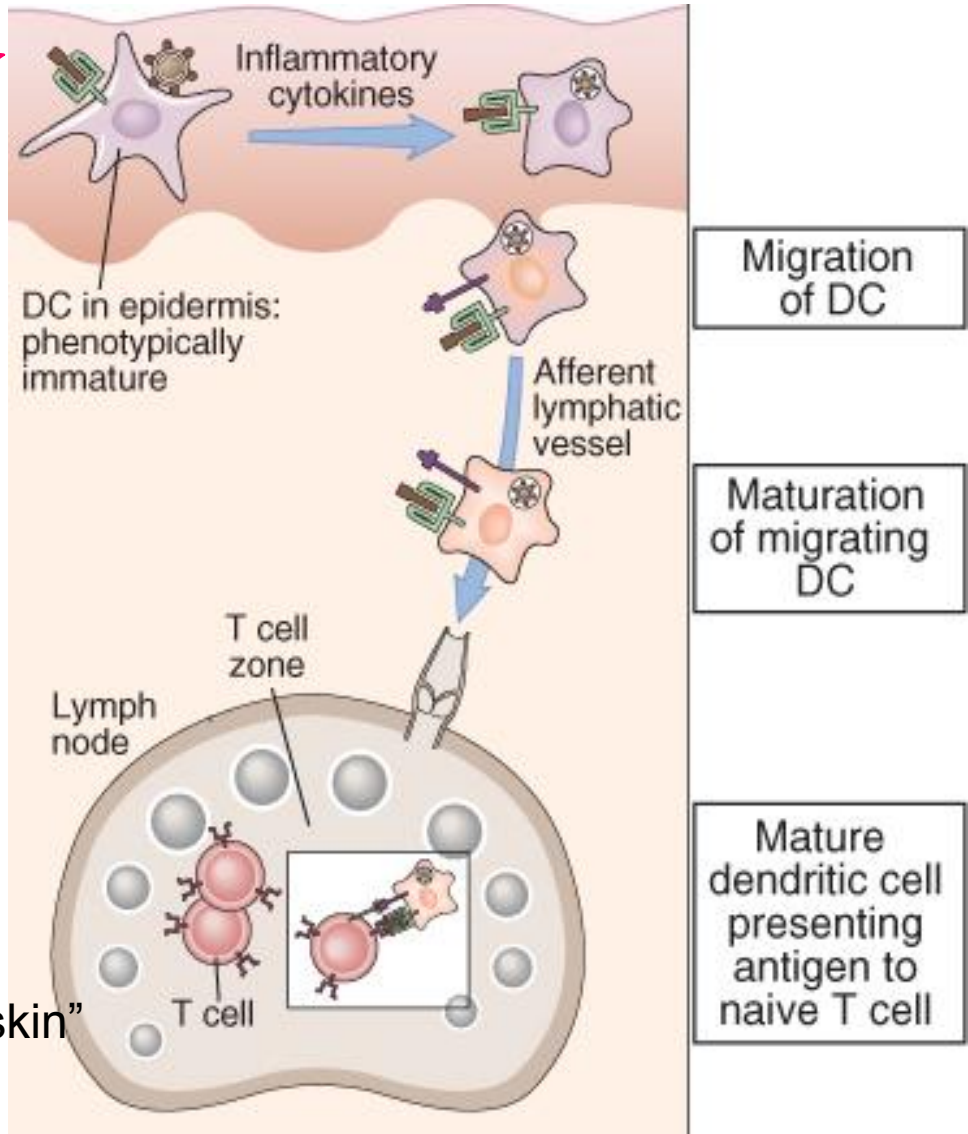
⇓

Practically painless ⇒ Enhanced compliance



Epicutaneous Immunotherapy

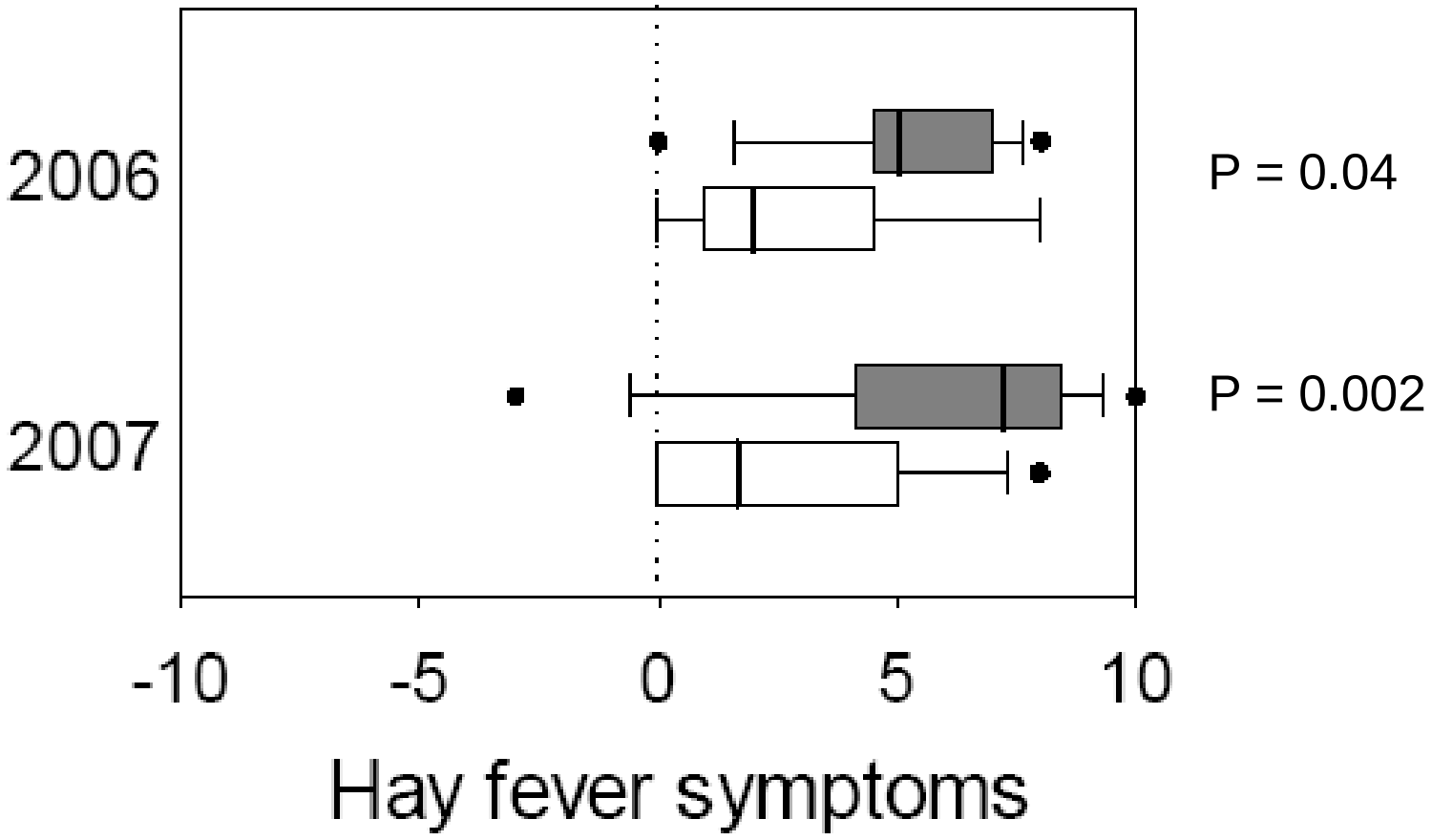




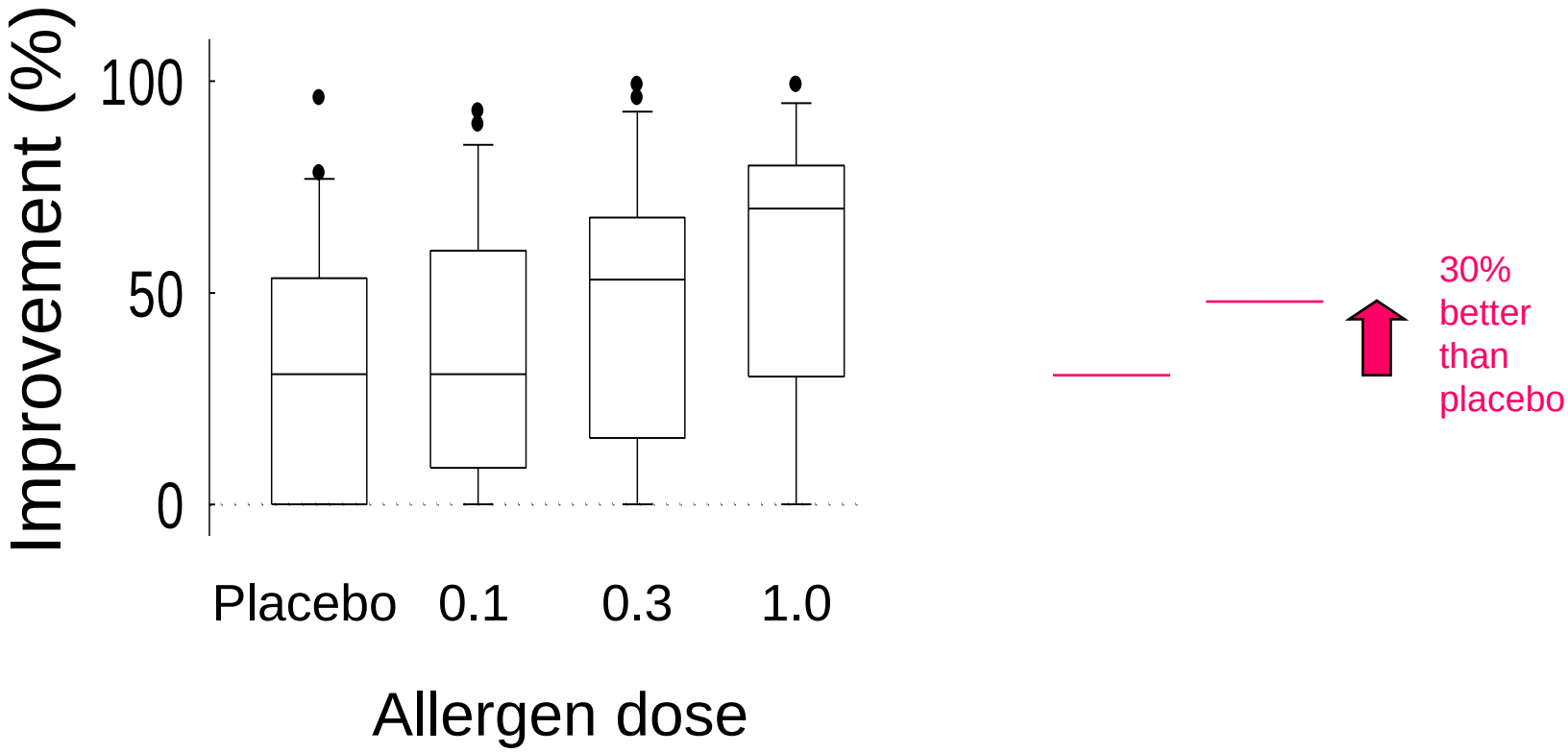
1911 “prophylactic hypodermic inoculation””

1929 “into the substance of the skin”

ZU-Skin-SIT 001



ZU-Skin-SIT 002



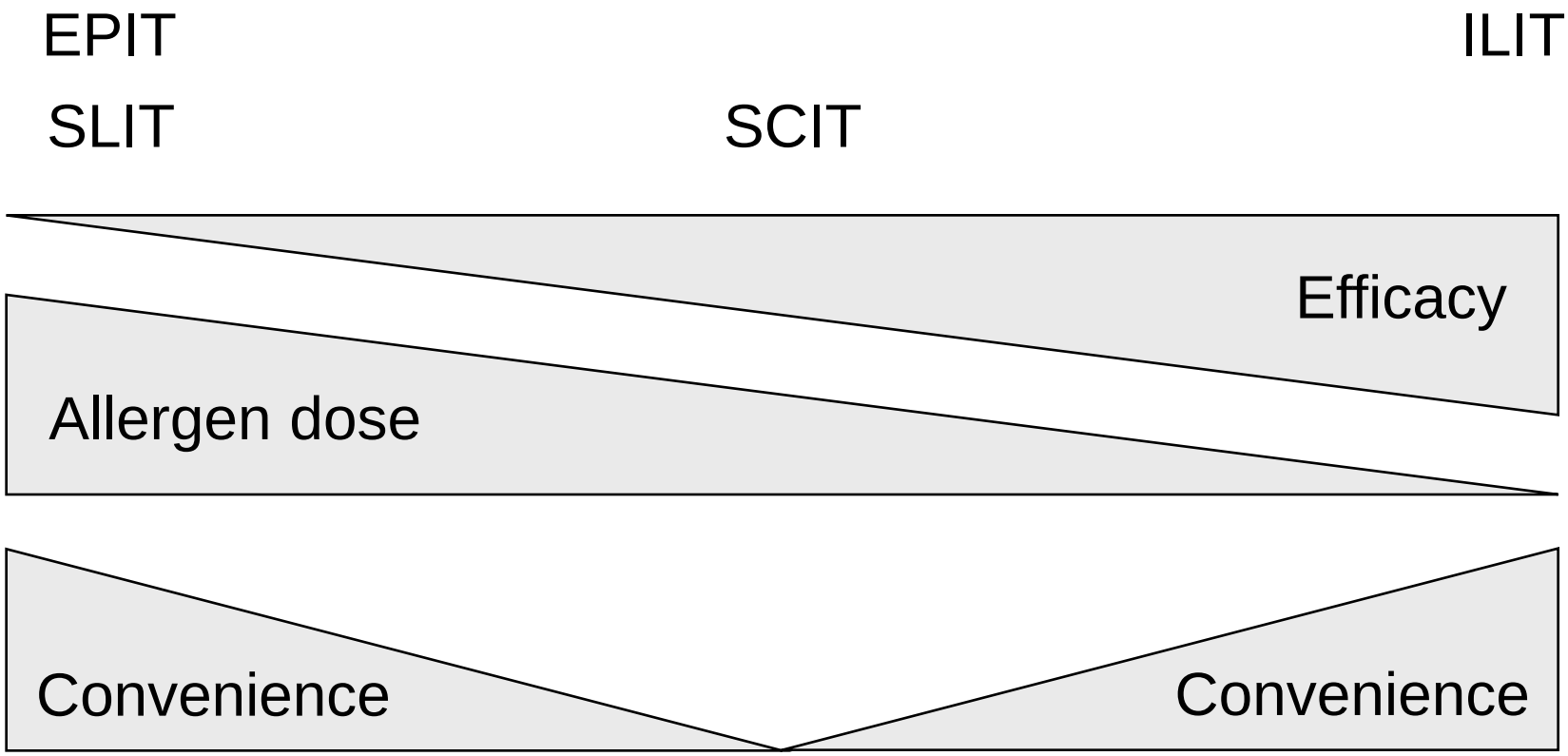
EPIT is «en vogue»

From Paris → DVB /VIASKIN
Preclinical Data

From Osaka → Dissolving Microneedles
Infectious Disease Data

From Salzburg → Generated micropores
using Laser Technologies
Preclinical Data

Summary


EPIT
ILIT
SLIT
SCIT
Efficacy
Allergen dose
Convenience
Convenience

Senti G, Crameri R, Kuster D, Johansen P, Martinez-Gomez JM, Graf N, Steiner M, Hothorn LA, Grönlund H, Tivig C, Zaleska A, Soyer O, van Hage M, Akdis CA, Akdis M, Rose H & Kündig TM. (2012)
Intralymphatic immunotherapy for cat allergy induces tolerance after only 3 injections.
JACI / The Journal of allergy and clinical immunology 129: 1290-1296.

Senti G, von Moos S, Tay F, Graf N, Sonderegger T, Johansen P & Kündig TM. (2012)
Epicutaneous allergen-specific immunotherapy ameliorates grass pollen-induced rhinoconjunctivitis: Adouble-blind, placebo-controlled dose escalation study.
JACI / The Journal of allergy and clinical immunology 129: 128-135.

Senti G, Graf N, Haug S, Ruedi N, von Moos S, Sonderegger T, Johansen P & Kündig TM. (2009)
Epicutaneous allergen administration as a novel method of allergen-specific immunotherapy.
JACI / The Journal of allergy and clinical immunology 124: 997-1002.

Senti G, Prinz Vavricka BM, Erdmann I, Diaz MI, Markus R, McCormack SJ, Simard JJ, Wüthrich B, Crameri R, Graf N, Johansen P & Kündig TM. (2008)
Intralymphatic allergen administration renders specific immunotherapy faster and safer: a randomized controlled trial.
PNAS / Proceedings of the National Academy of Sciences of the United States of America 105: 17908-17912.

More Senti & Kündig Stories will follow

You will hear about «Hypo Pet» soon