

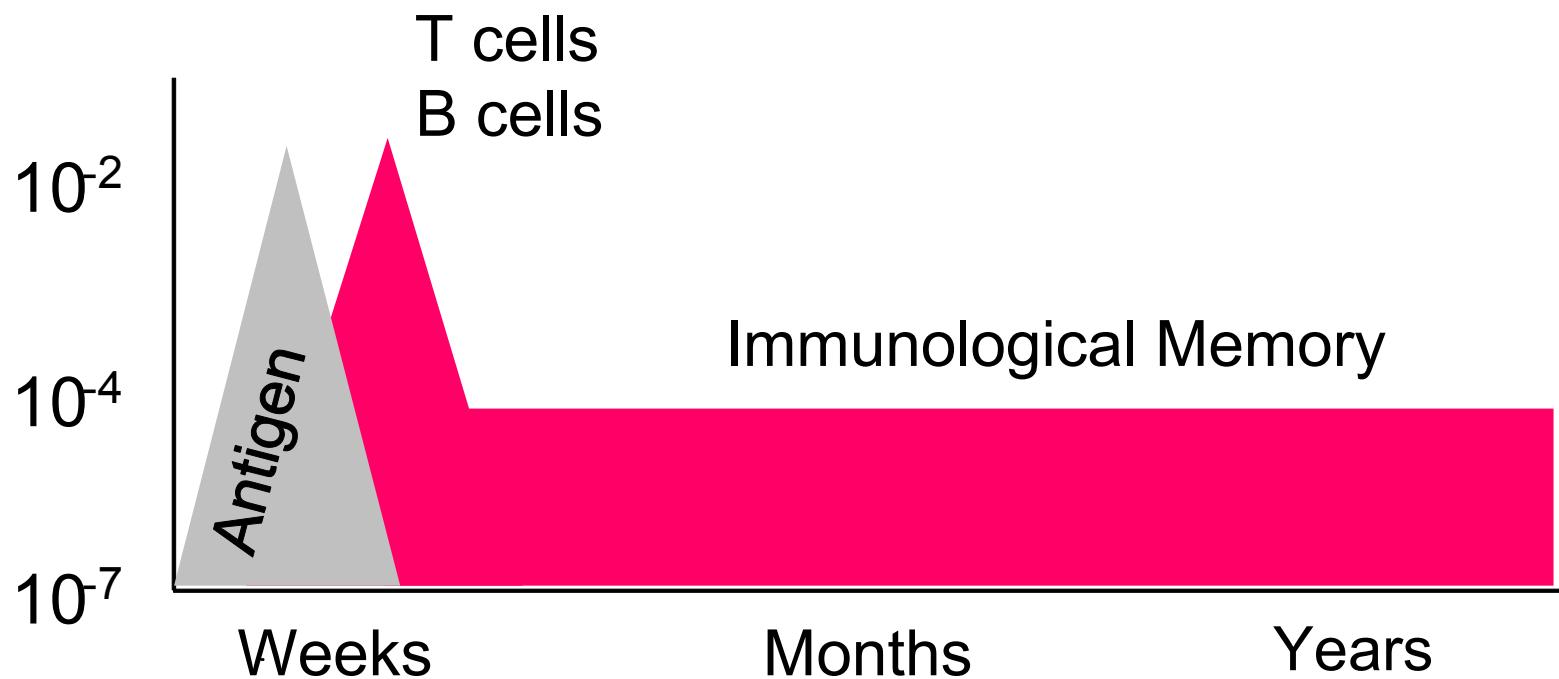


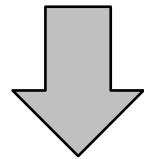
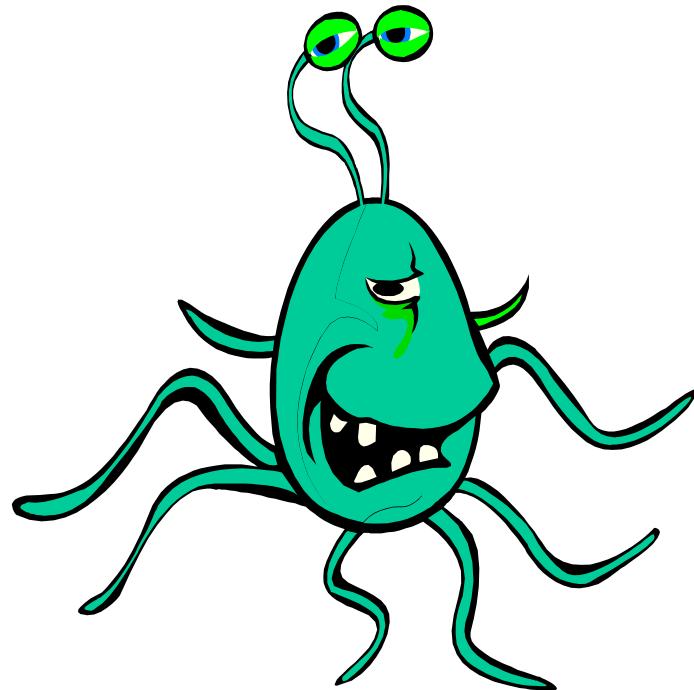
University Hospital
Zürich

New Routes for Allergen Immunotherapy

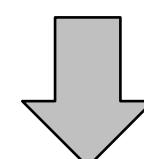
Thomas M. Kündig
Dermatology
Zurich University Hospital

Immunological Memory

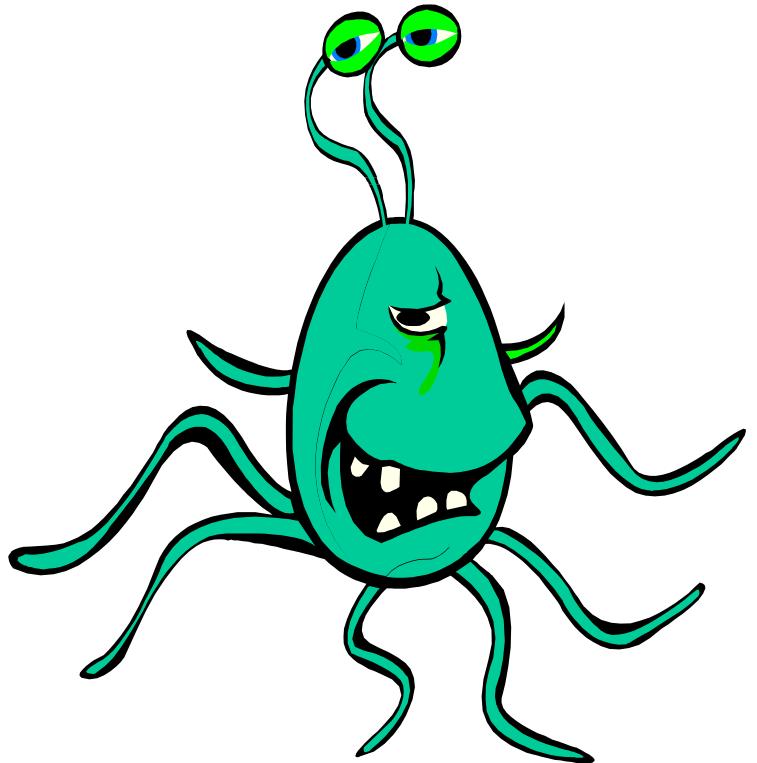




Weak
Memory

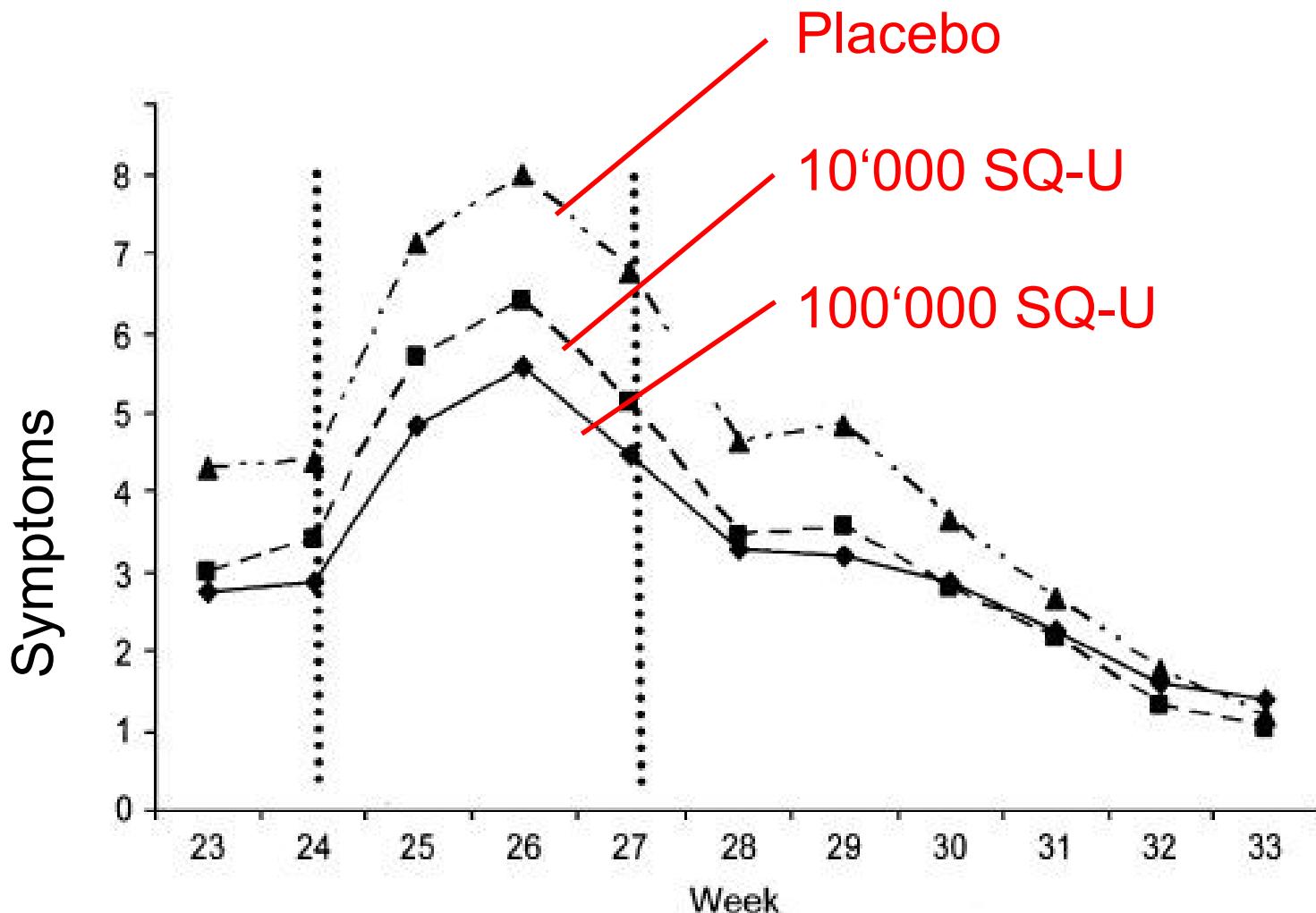


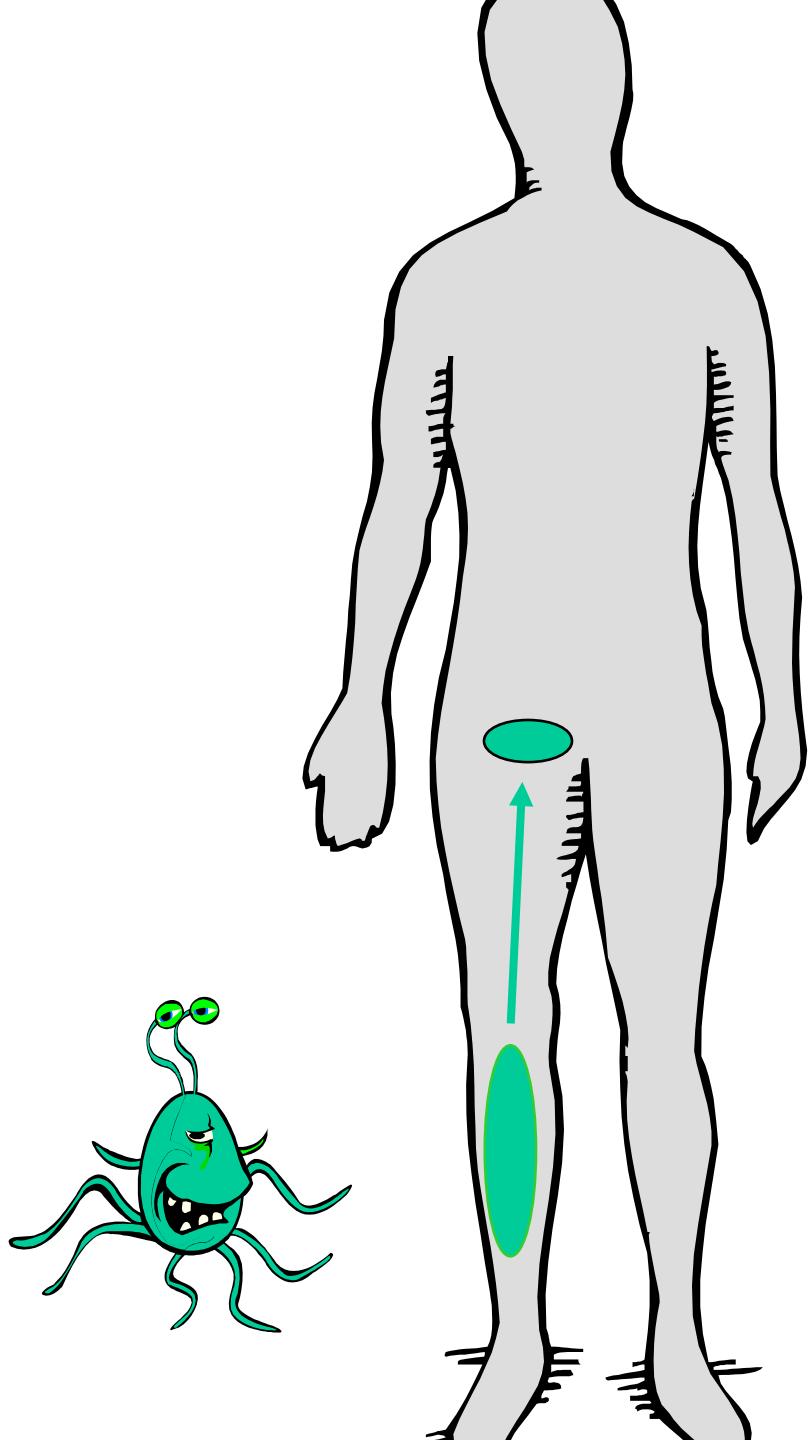
Strong
Memory



Dose +++

Dose Dependence

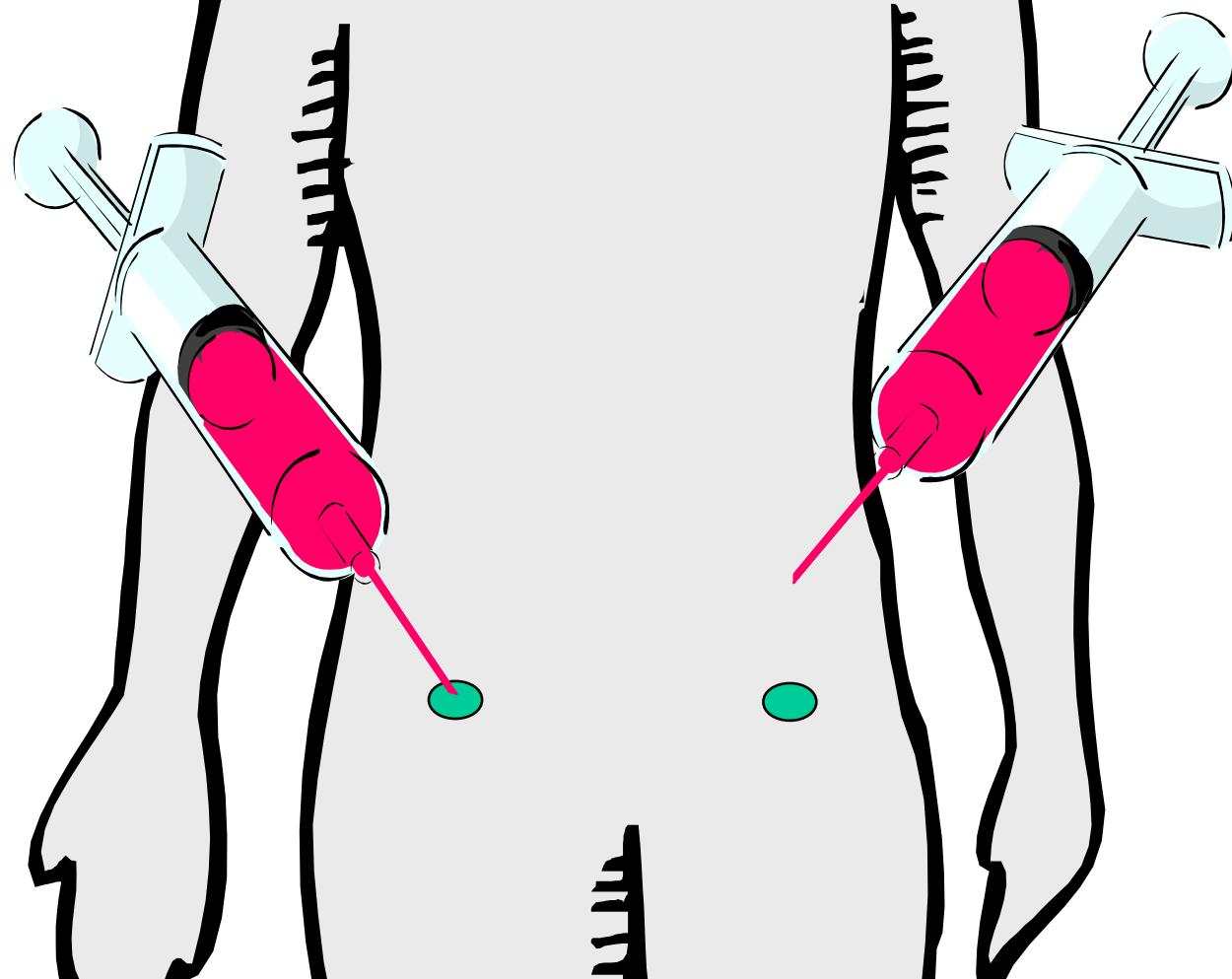




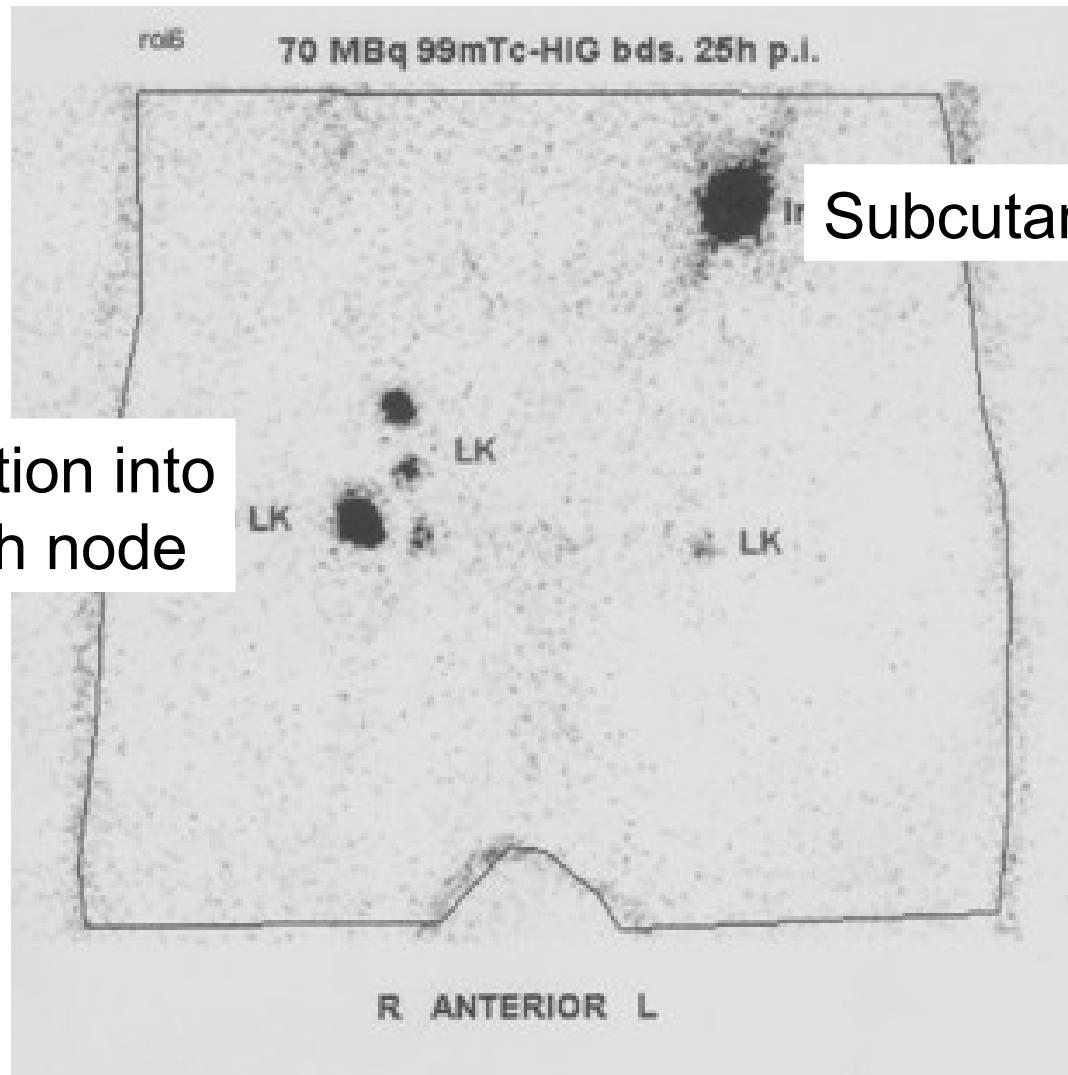
Spreading

into
lymph node

Subcutaneous

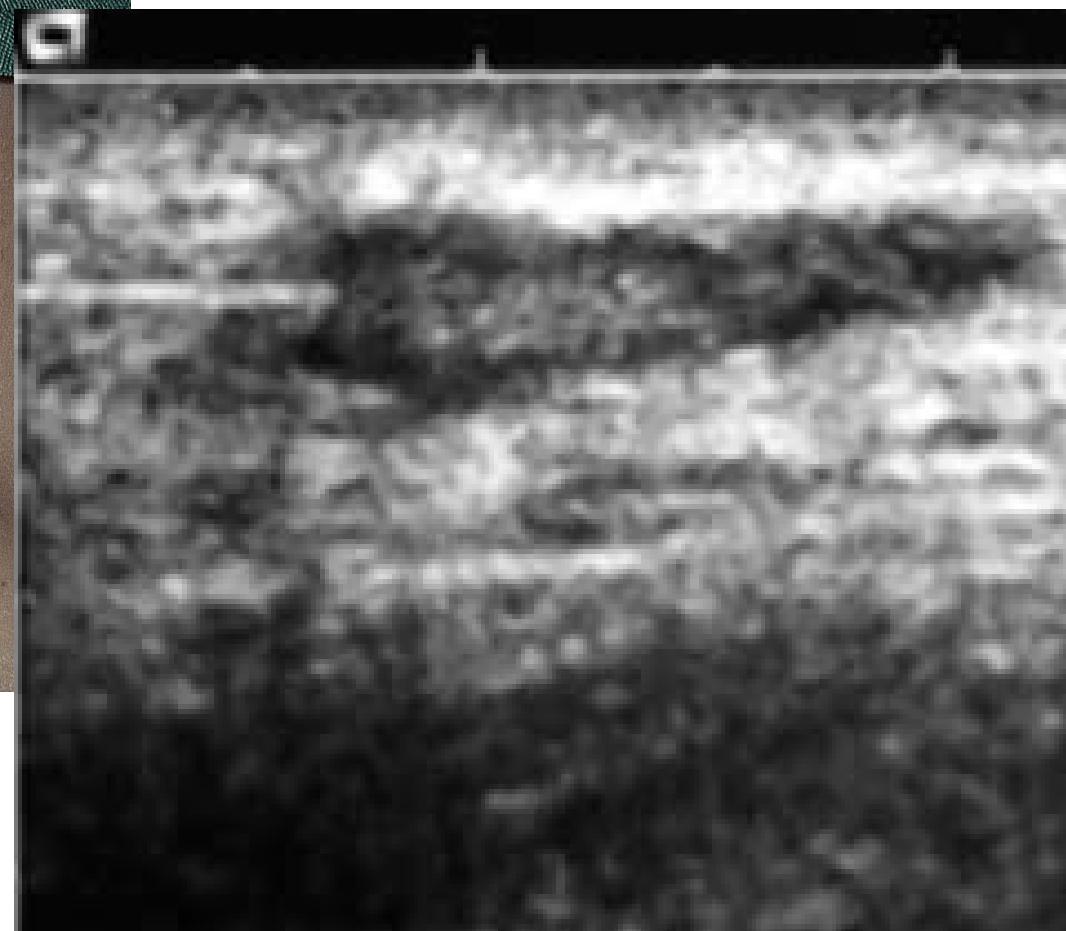
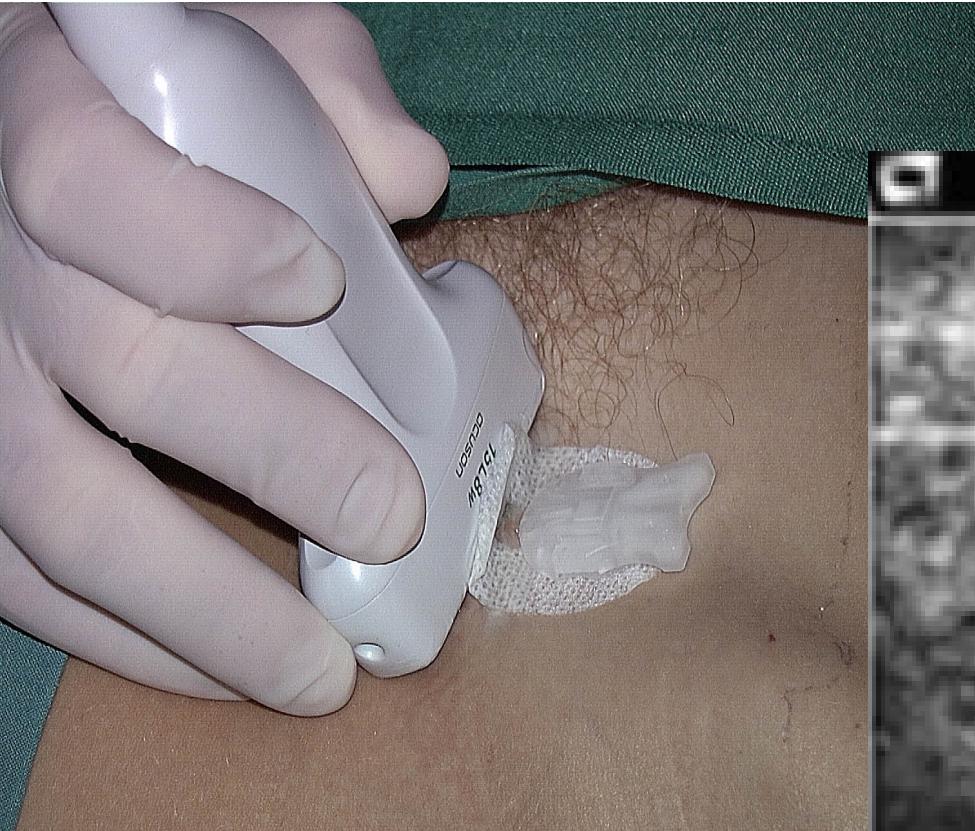


Distribution Allergen Extract (25h)



Senti et al.
Curr Opin Allergy
Clin Immunol 2009

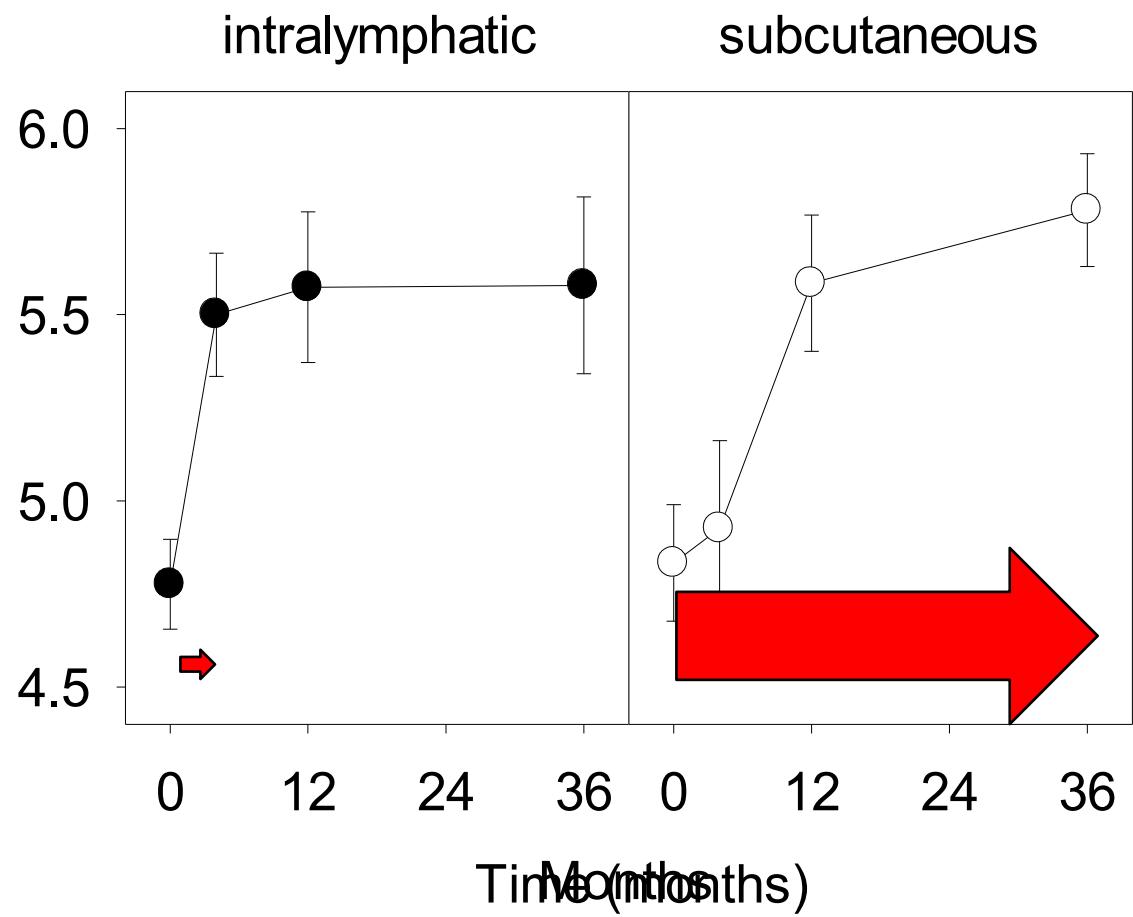
Intralymphatic Immunotherapy



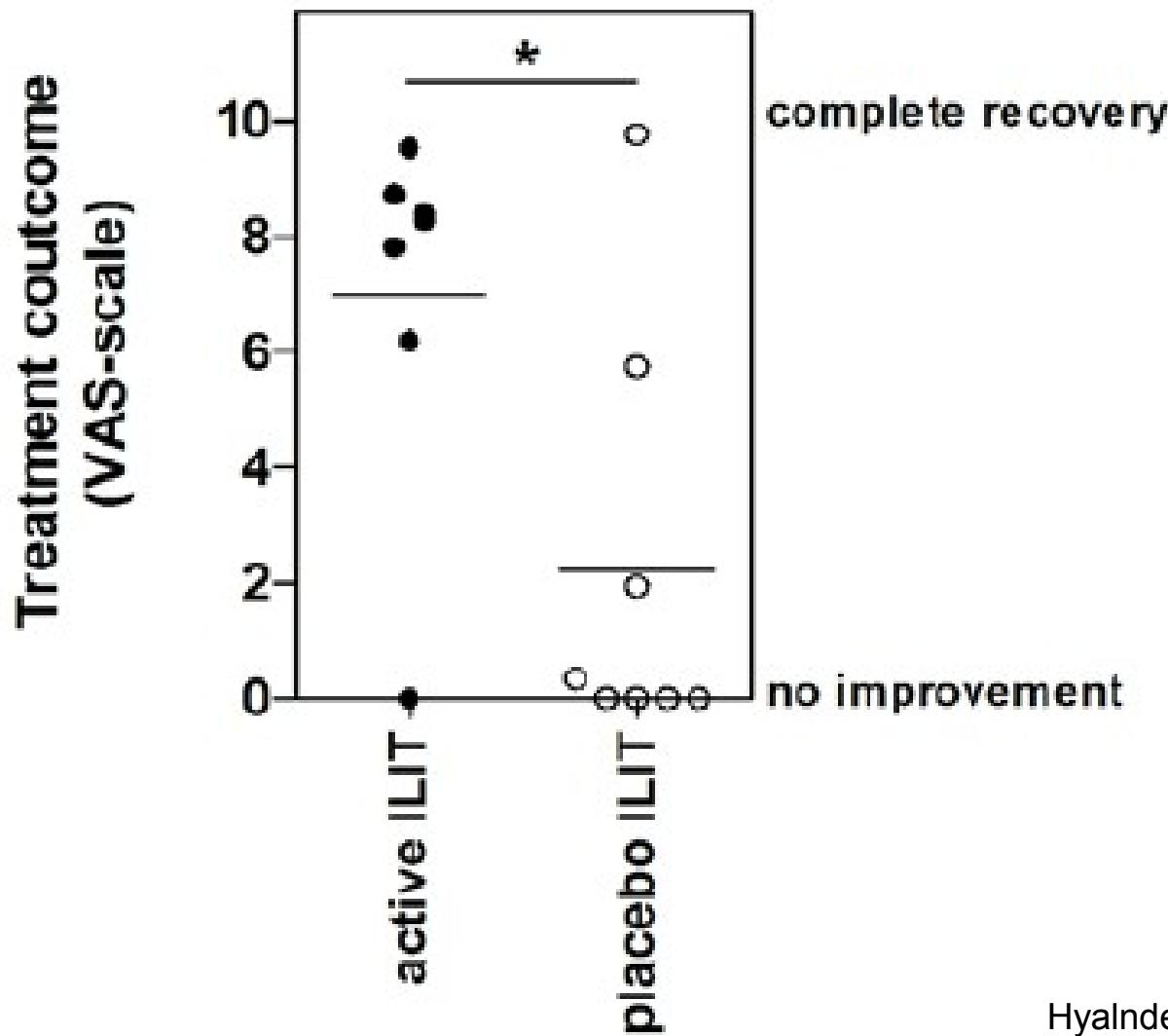
Intralymphatic Immunotherapy

3
Injections

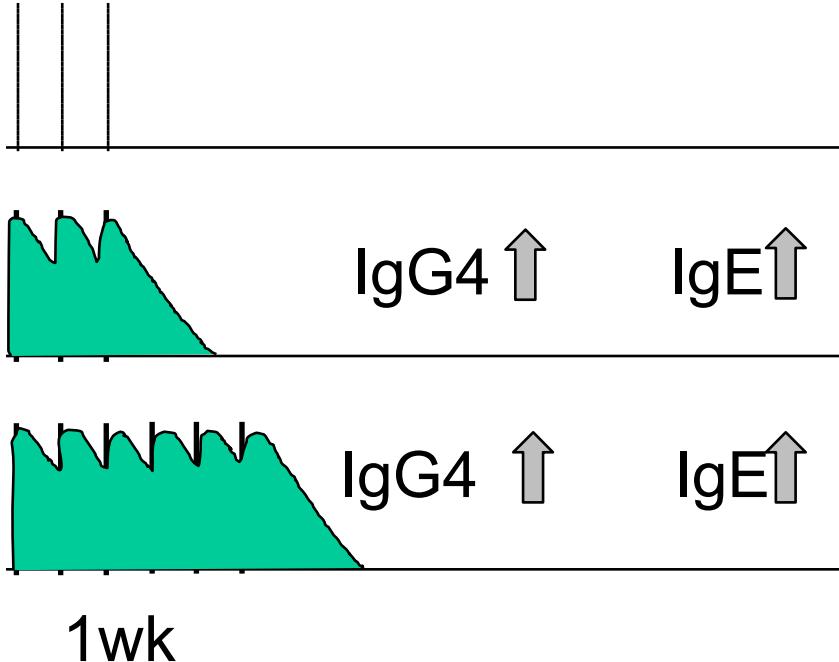
Maximum tol
concentratio



Intralymphatic Immunotherapy

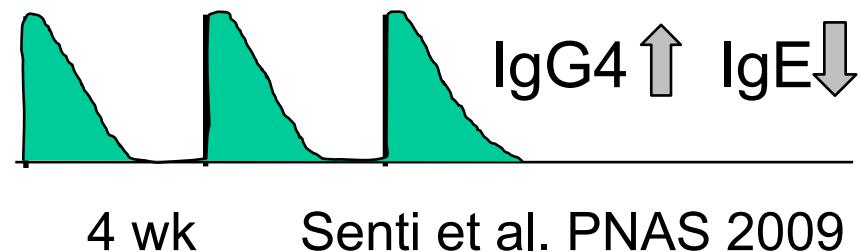


Malling et al.
(EAACI 2012)



Symptoms worse

Hylander et al.
(JACI 2013)



Symptoms improved

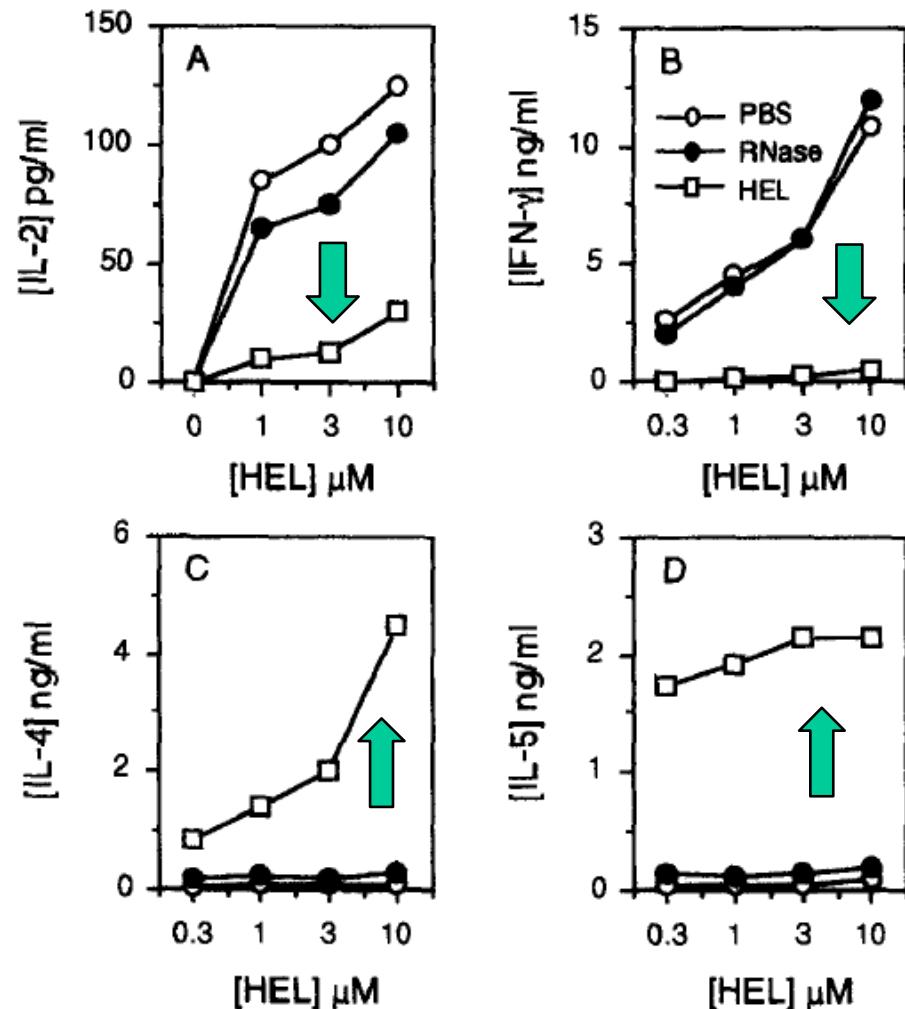
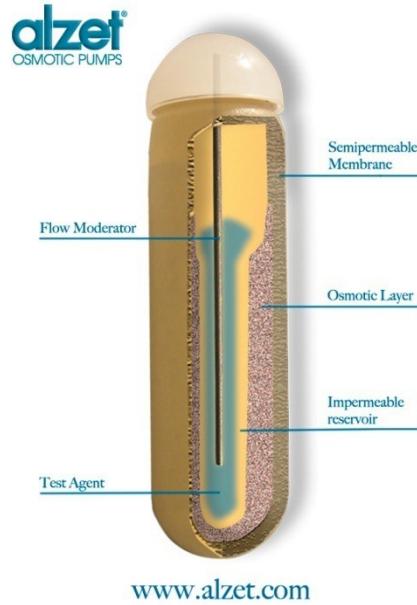
Table 2–5 Determinants of the Duration of Vaccine Antibody Responses in Healthy Individuals

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.

Selective Development of T Helper (Th)2 Cells Induced by Continuous Administration of Low Dose Soluble Proteins to Normal and β 2-Microglobulin-deficient BALB/c Mice

By Jean-Charles Guéry, Francesca Galbiati, Simona Smiroldo,
and Luciano Adorini

J Exp Med 1996



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

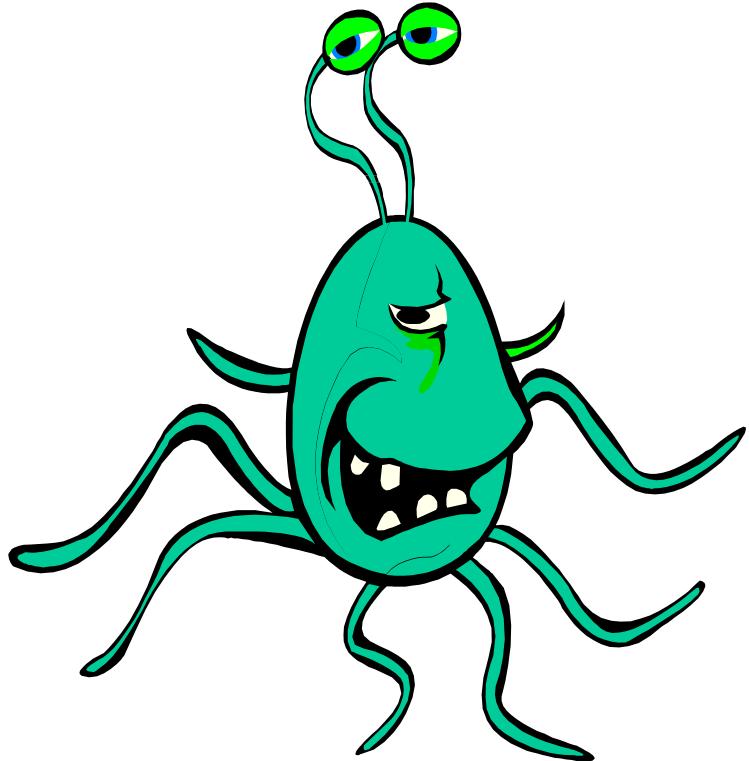
Malling, H; Blom, L; Poulsen, B; Poulsen, L; Witten, M

"Increasing the treatment dose cannot be advised since systemic reactions were seen in app. **10%** of the patients"

Table 2. Safety of intralymphatic and subcutaneous immunotherapy: Patients with adverse events

Adverse events	Subcutaneous	Intralymphatic
None	34	52
Mild (grade 1* and 2*)	18	6 ← 3%
Severe (grade 3*)	2	0
Anaphylactic (grade 4*)	0	0
Total	54	58

*Mueller grading of allergic reactions.



Bakterial DNA

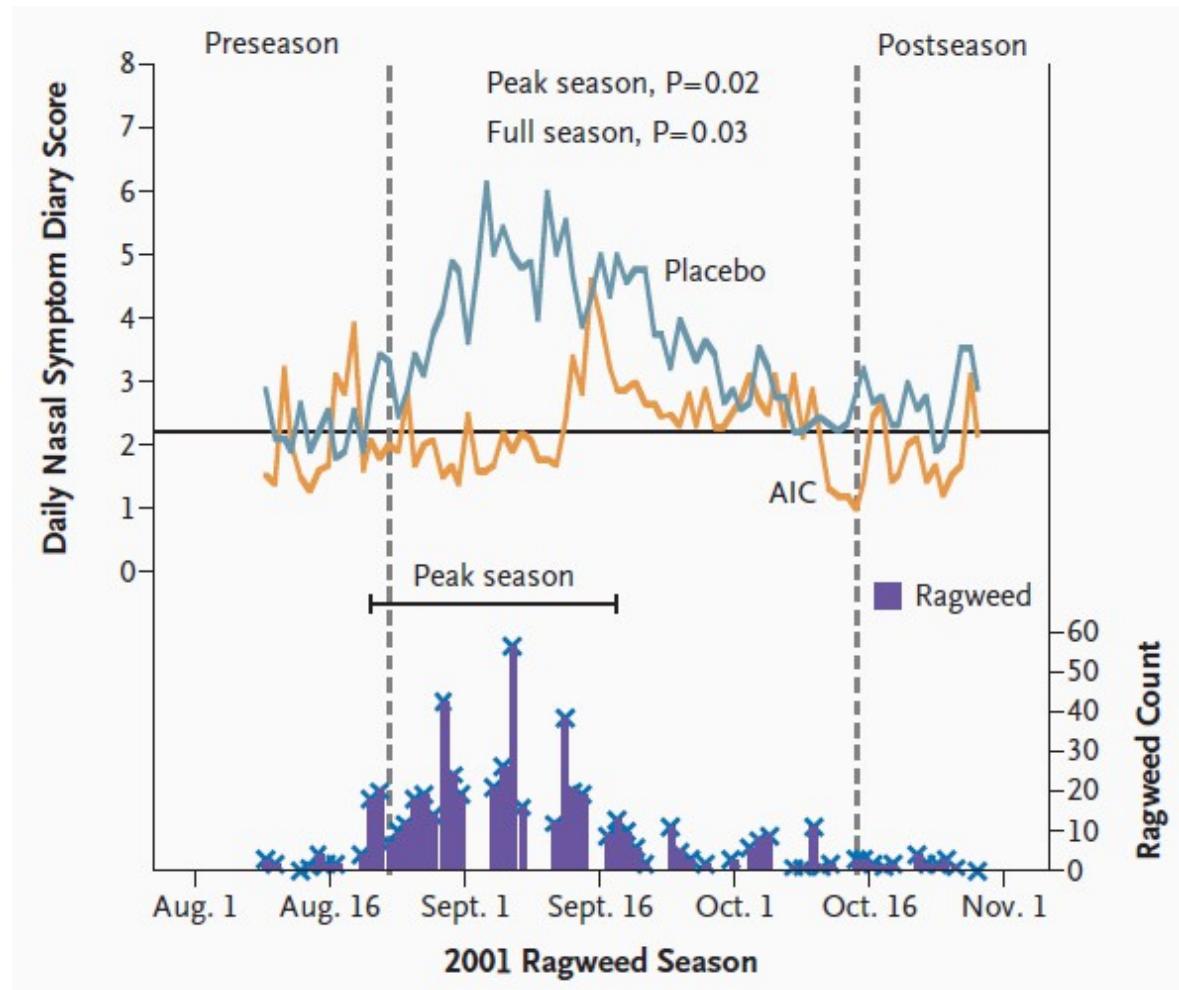
Viral RNA

LPS

.... PAMPS....

6 Injections

Allergen + CpG

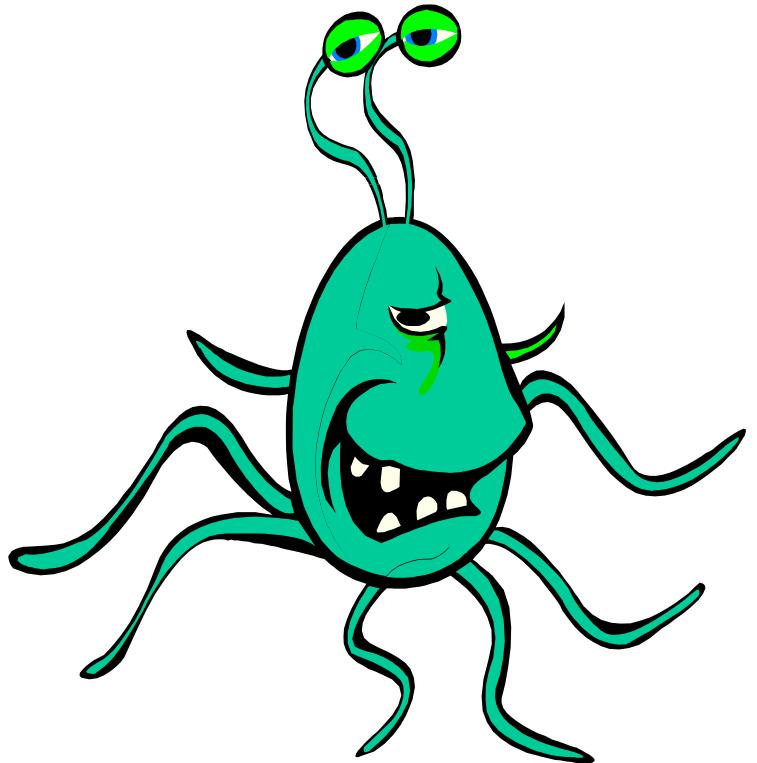


Allergen + MPL

Table 2. Overview of phase 3 clinical studies and post-marketing trials with Pollinex Quattro: study design and key results

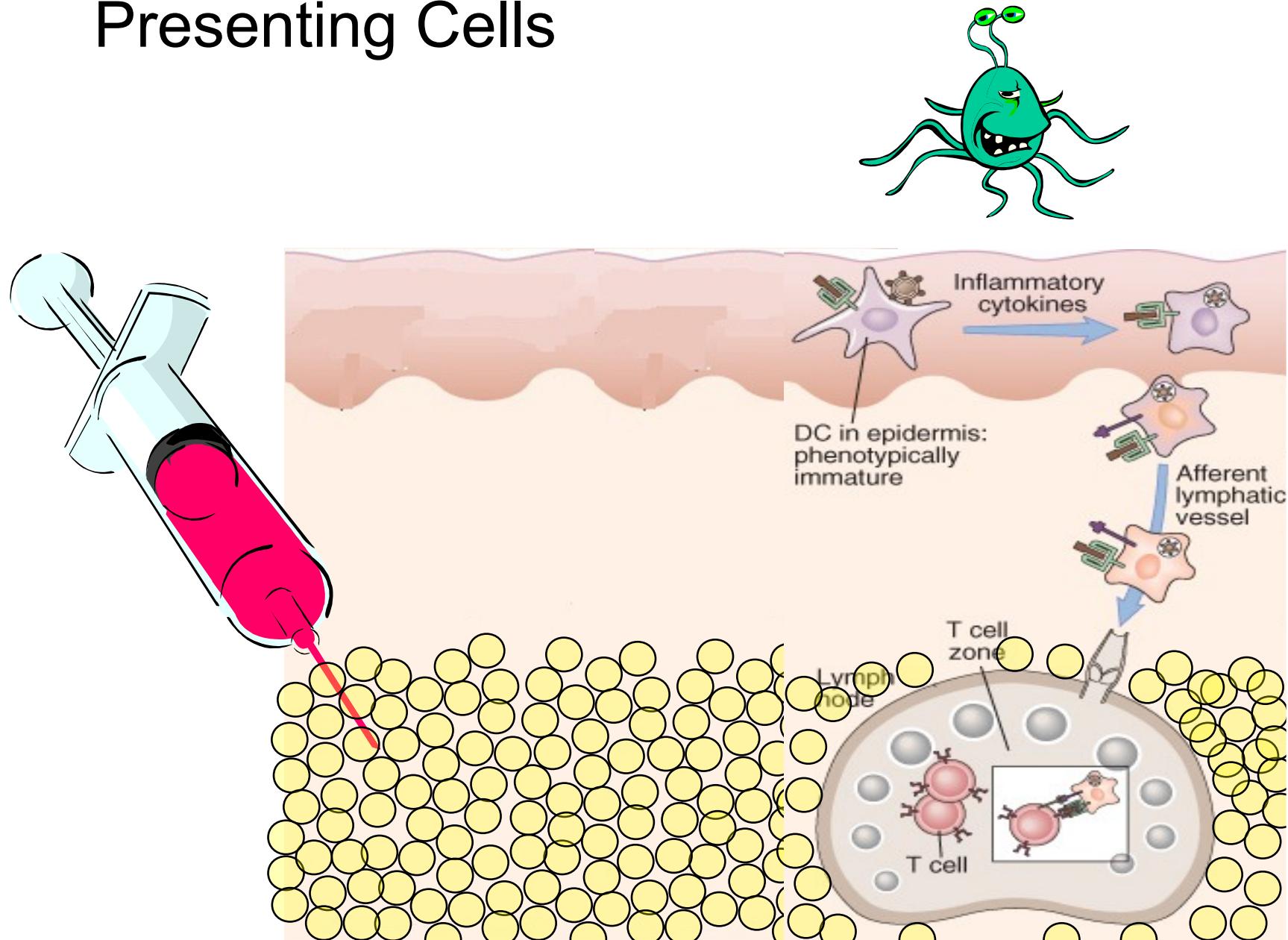
Study	Patients	Design	Major findings
Drachenberg 2001 ¹⁷	Adults with grass pollen AR/AA (n = 141)	Rand., db, placebo-contr.	CSMS ↓* Symptom score ↓* Skin reactivity (prick test) ↓* IgG ↑* No IgE increase
Drachenberg 2002 ¹⁸	Adults with tree pollen AR/AA (n = 84)	Rand., db, placebo-contr.	CSMS ↓* Skin reactivity (prick test) ↓* IgG ↑* IgE ↓*
DuBuske 2011 ²⁶	Adults with grass pollen AR/AC (n = 1028)	Rand., db, placebo-contr.	CSMS ↓* IgG ↑* No IgE increase
Drachenberg 2003 ²¹	Children and adolescents with grass/tree pollen AR/AA (n = 90)	Open-label	Symptom score ↓* Medication ↓* Skin reactivity (prick test) ↓* IgG ↑* IgE unchanged
Drachenberg 2002, ²⁷ Zielen 2007, ²⁸ Rosewich 2010 ²⁹	Adults, children and adolescents with grass/tree pollen AR/AA (n = 3144)	Open-label	Symptoms ↓* (signif. after 2nd year) Medication ↓*
Rabe 2011 ^{31,32}	Adults with grass/tree pollen AR/AA (n = 132)	Open extension	Quality of life score ↑* Medication ↓* Symptoms ↓*

AR, allergic rhinitis; AA, allergic asthma; AC, allergic conjunctivitis; db, double-blind; CSMS, combined symptom/medication score ↑ increase; ↓ decrease; *p < 0.05.

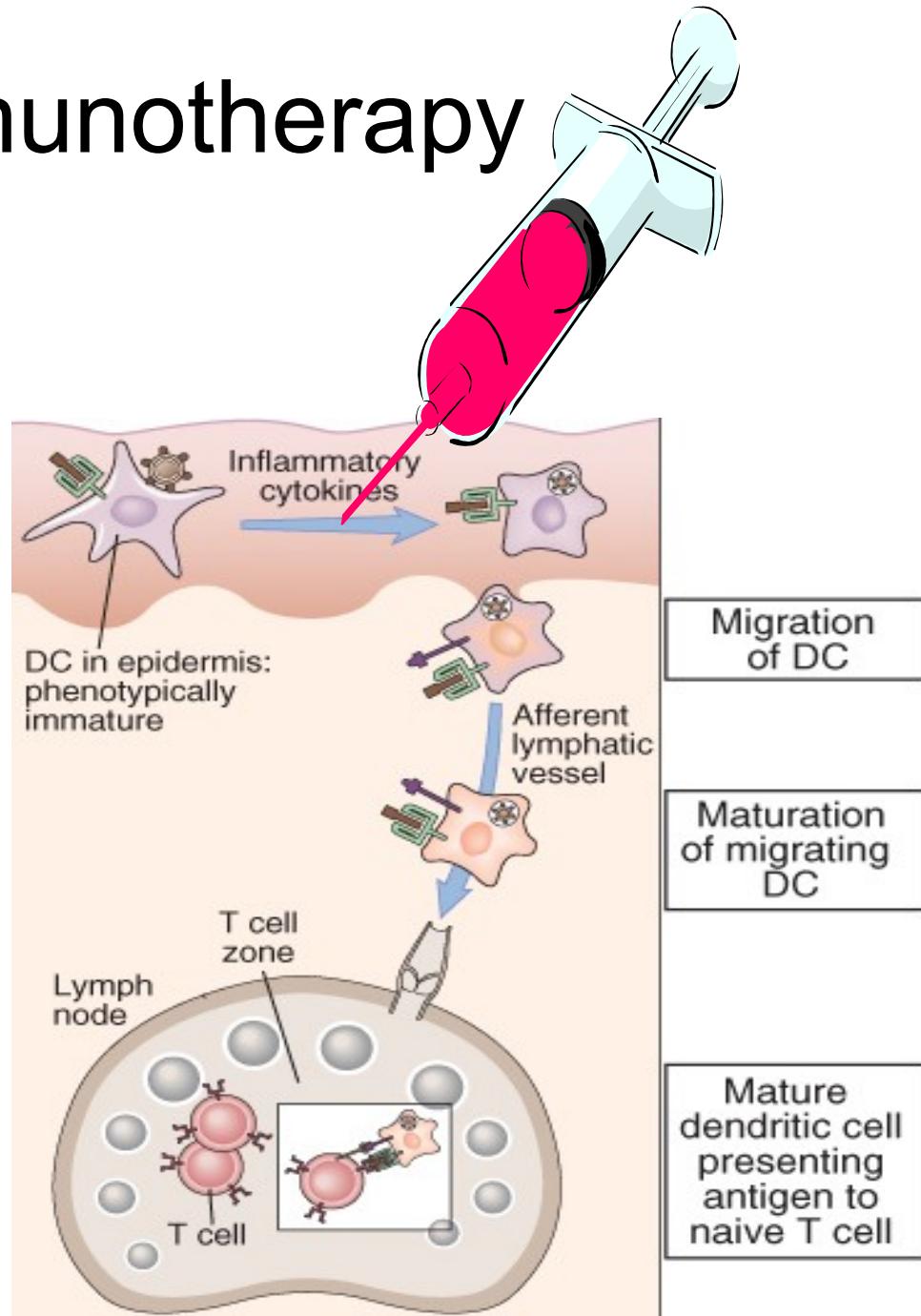


Route ?

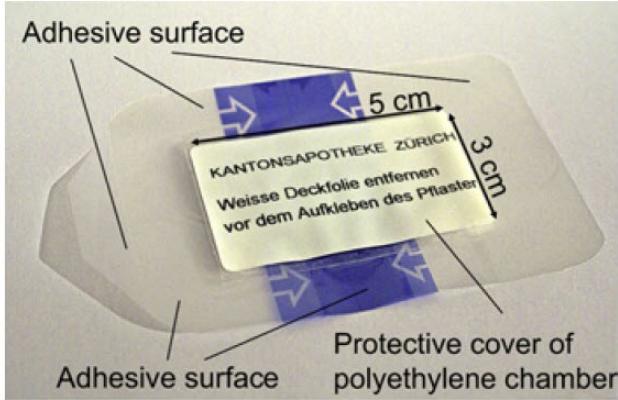
Density of Antigen Presenting Cells



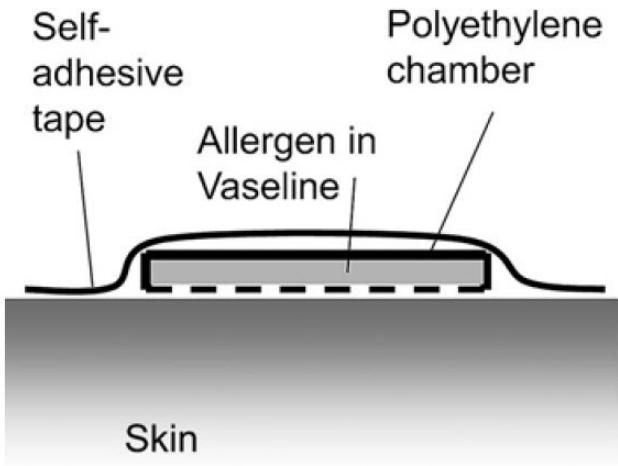
Epicutaneous Immunotherapy



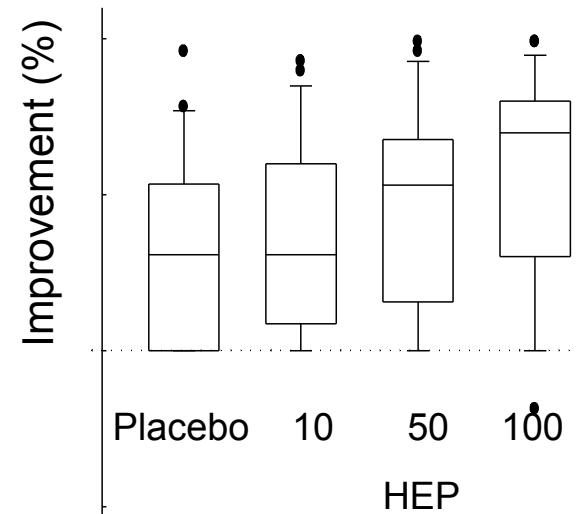
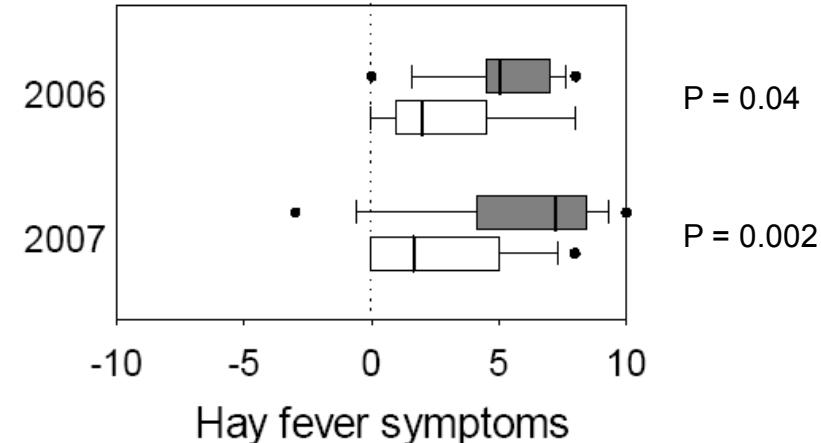
Epicutaneous Immunotherapy



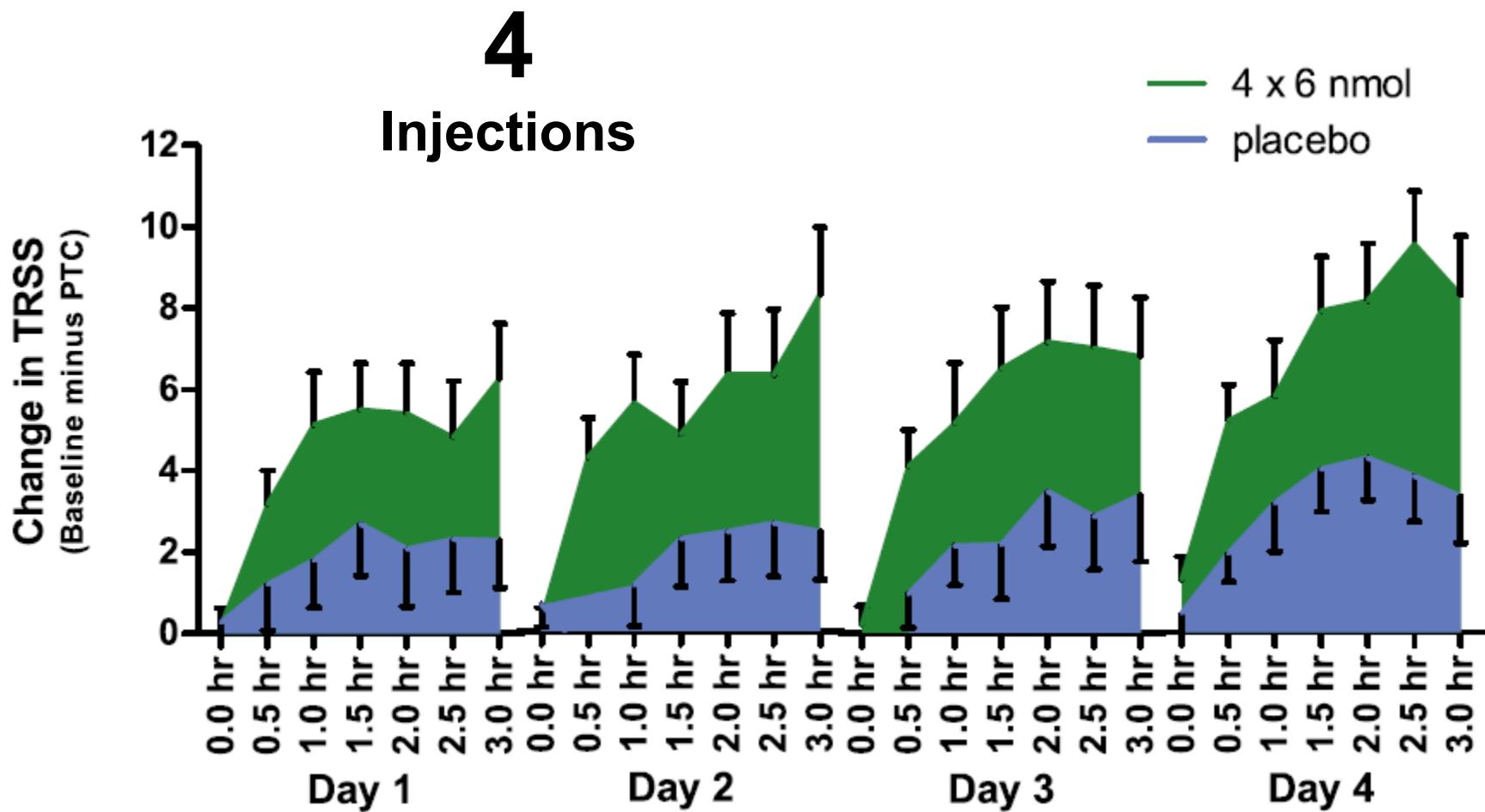
12
Patches



6
Patches

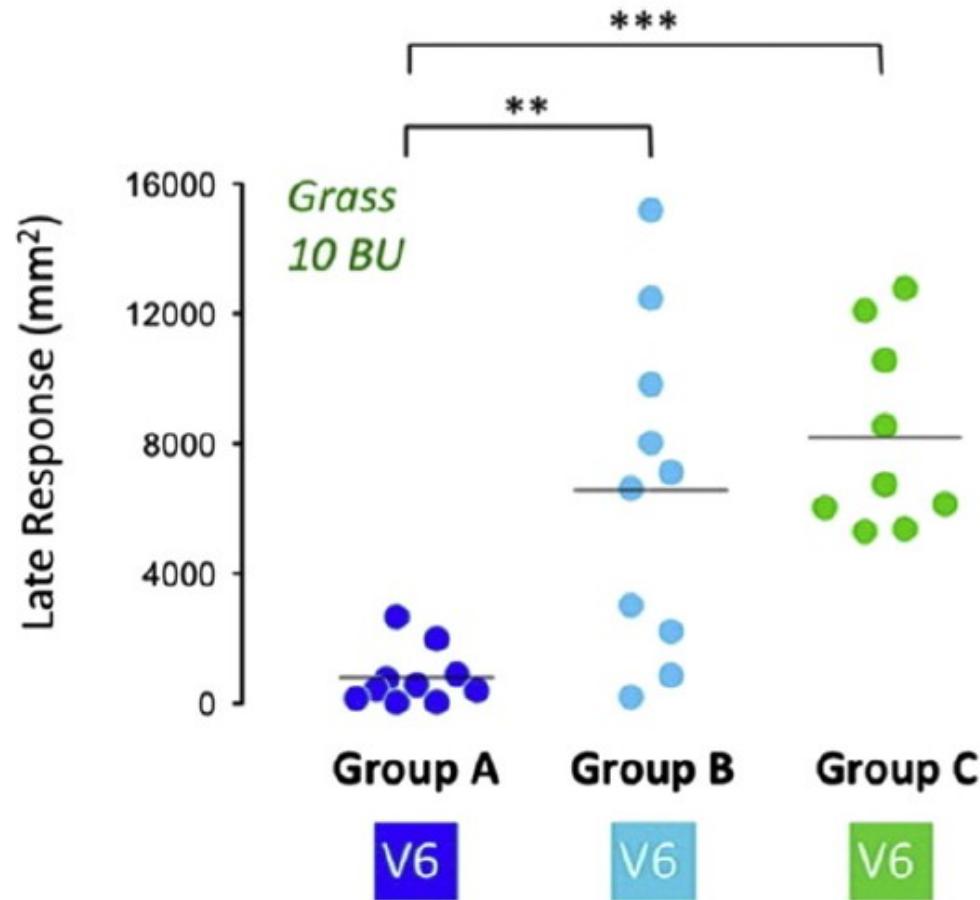


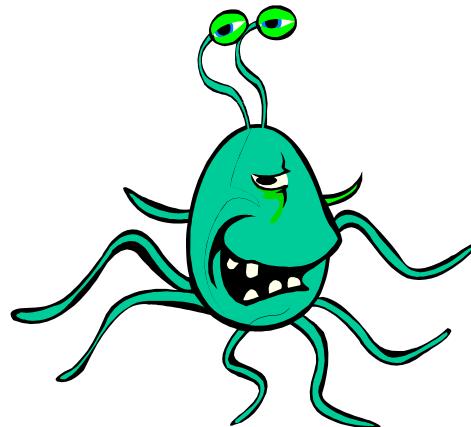
Intradermal Cat-PAD



Low Dose Intradermal Grasspollen

6
Injections





Dose

SIT

Distribution

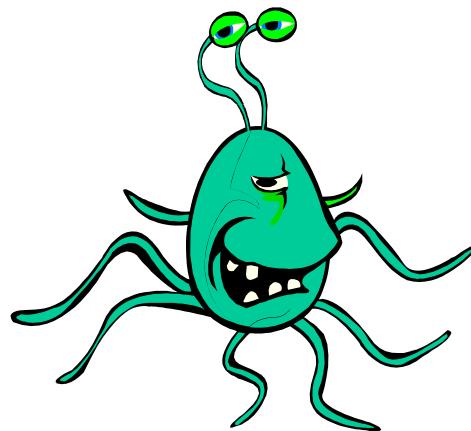
SIT

Adjuvant

SIT

Route

SCIT



Dose

SIT

Distribution

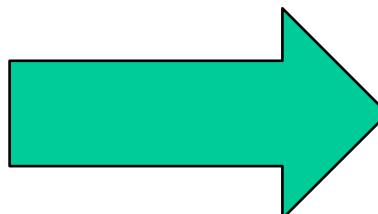
SIT

Adjuvant

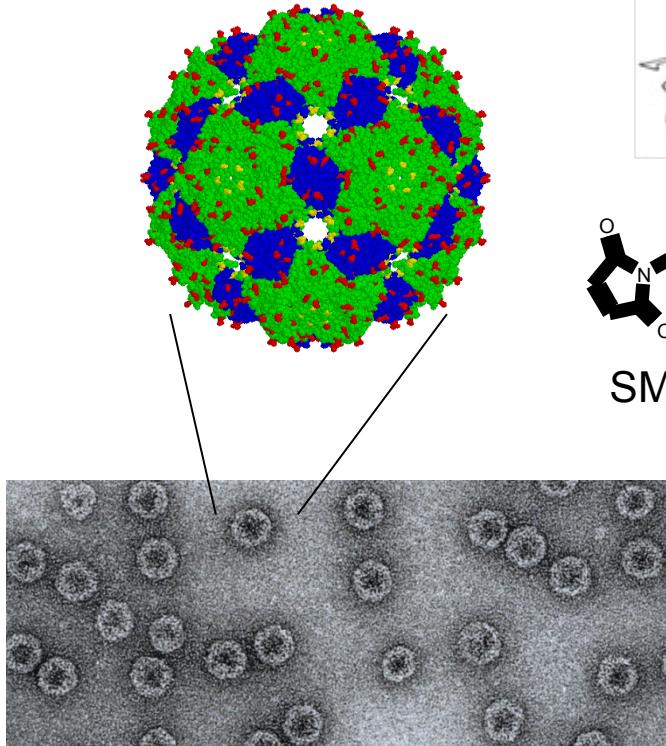
SIT

Route

SIT

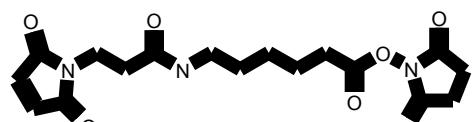
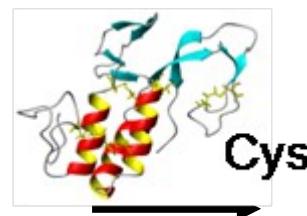


VLPs

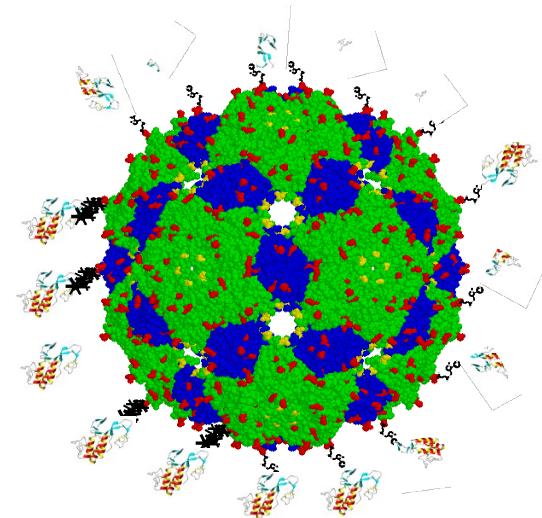


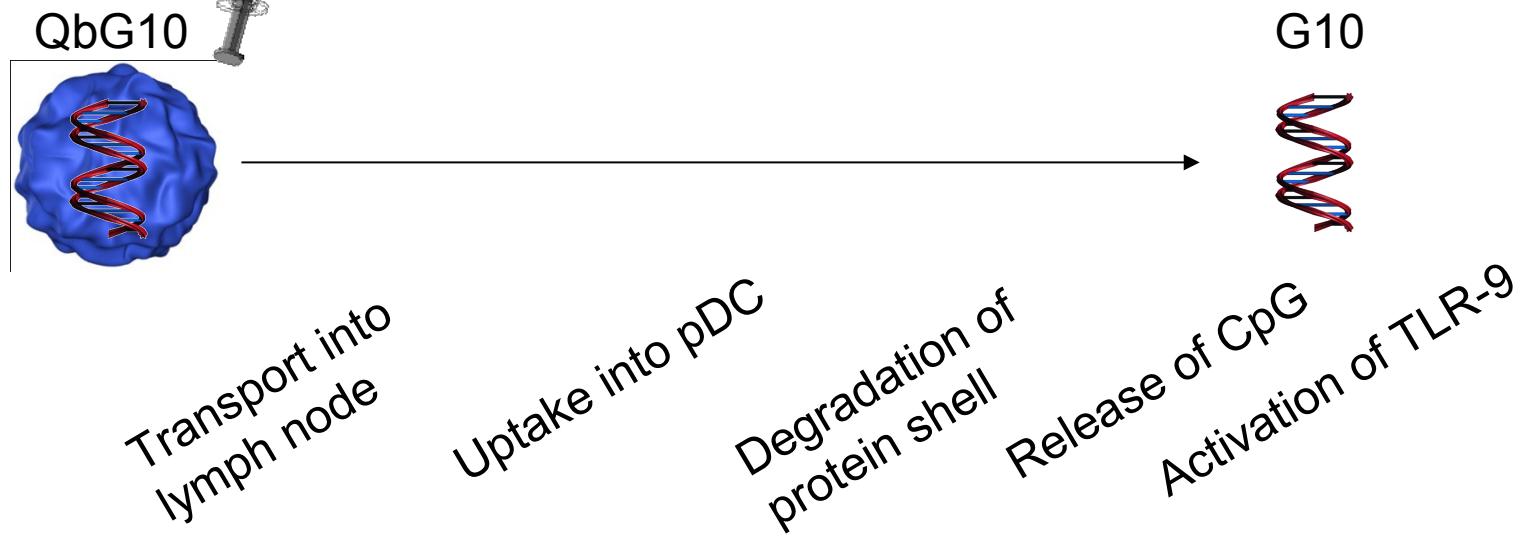
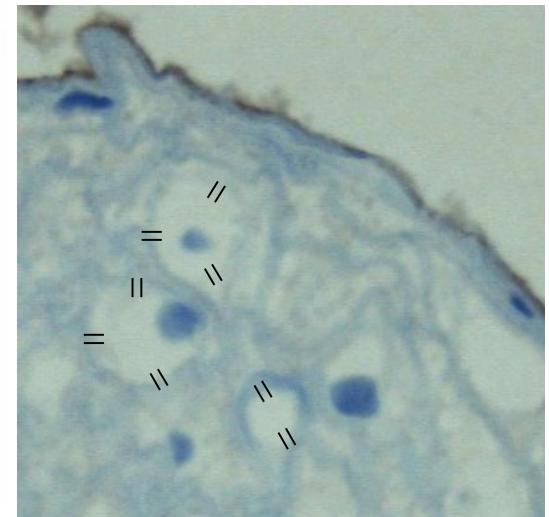
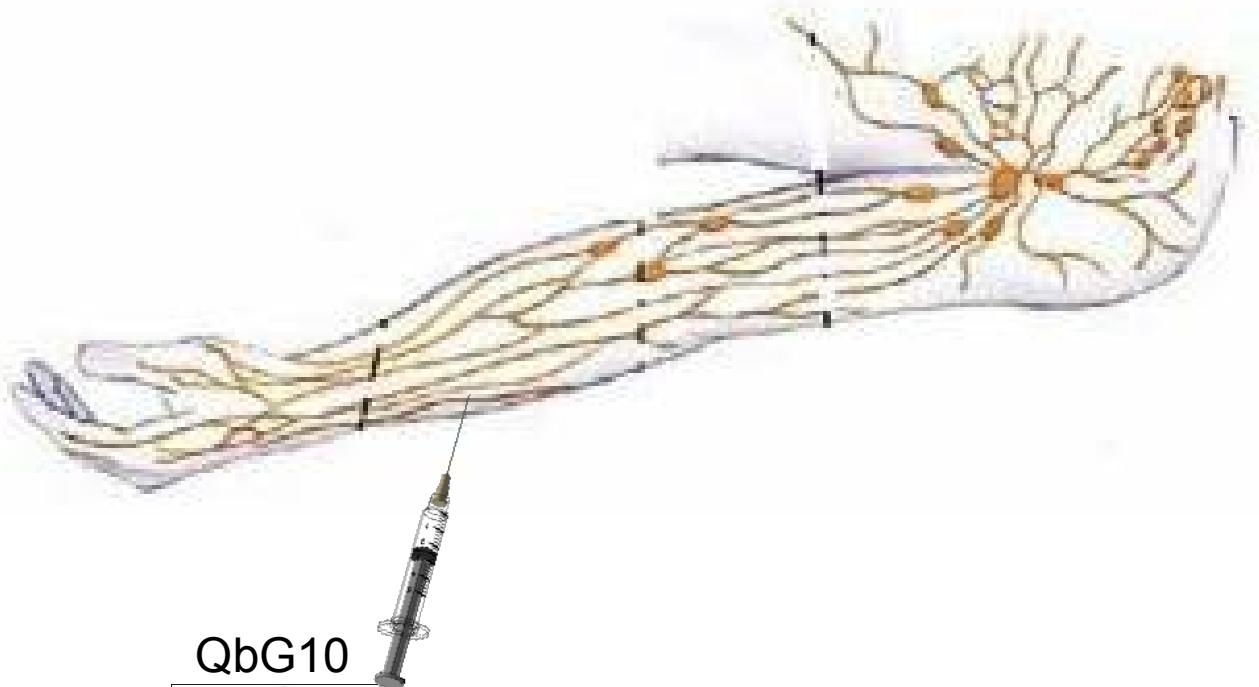
diameter = 30 nm

antigen



SMPH chemical linker

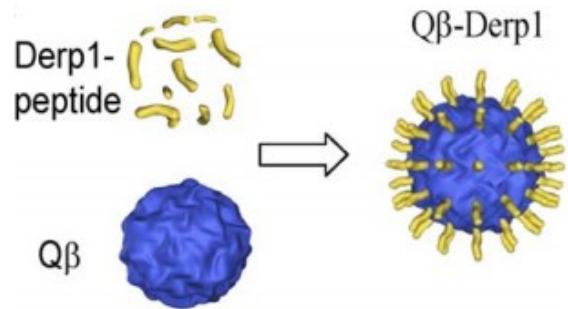




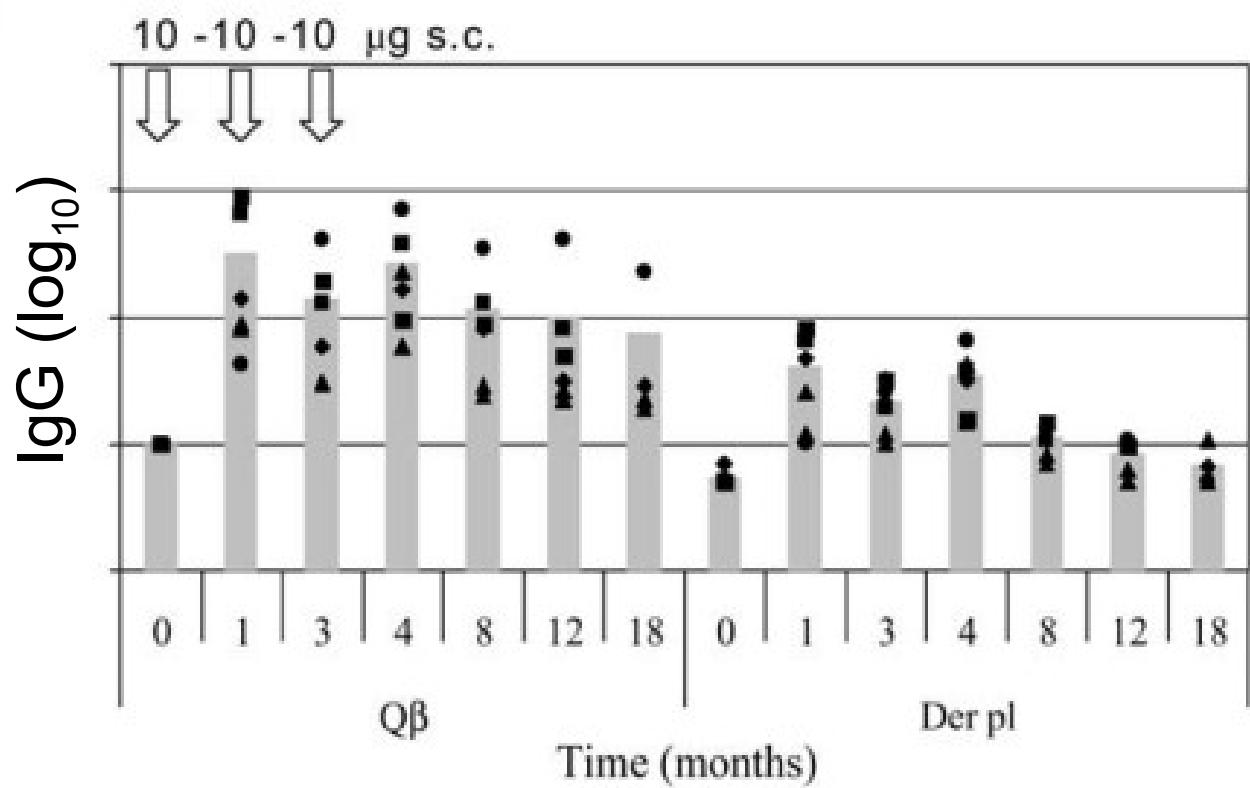
Antigen Organisation

Organization:	high	low	absent
Antibody response	+++	++	-
Induction of auto-antibodies	+++	-	-
T help Independent Type 1			

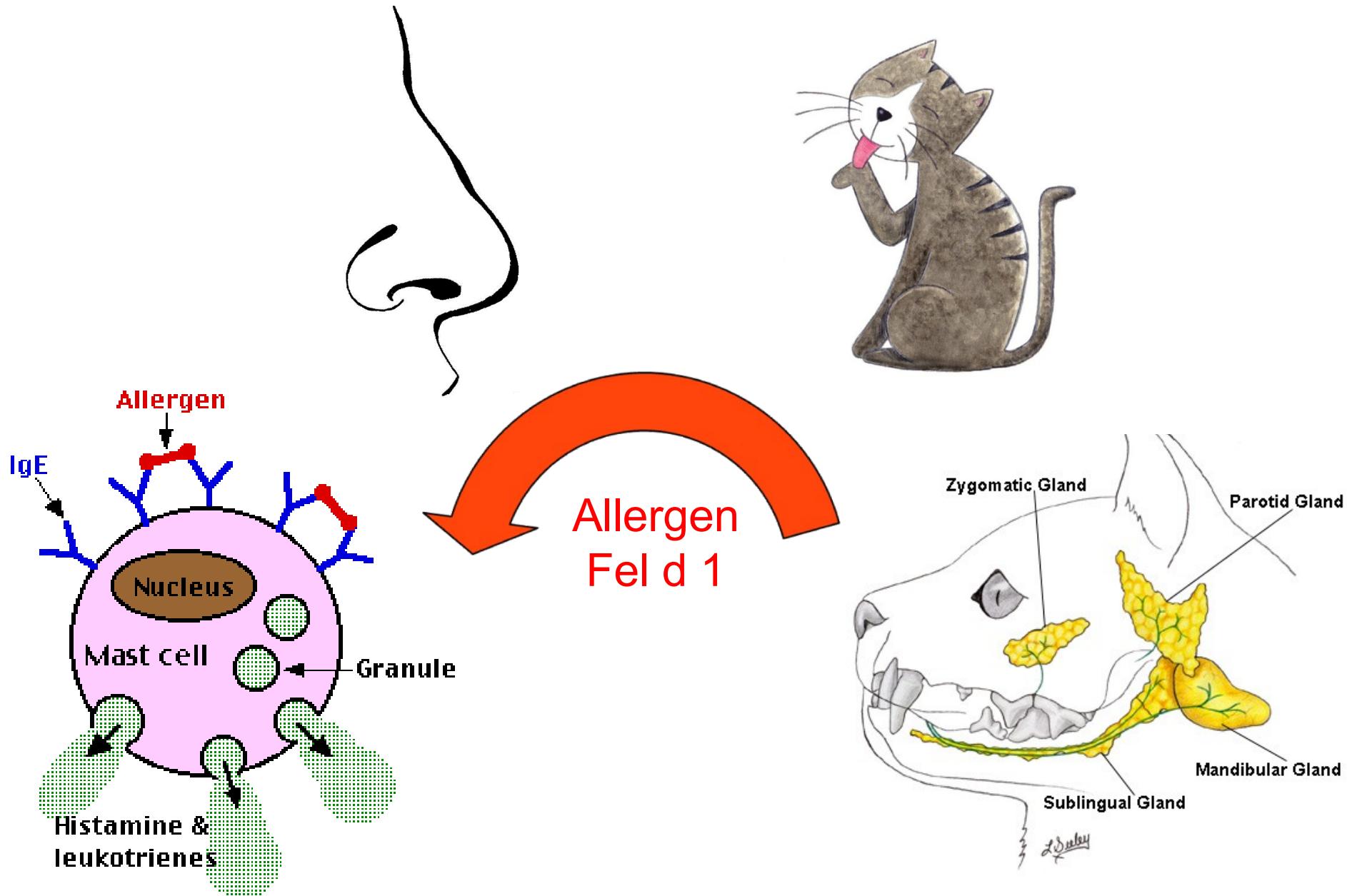
Virus Like Allergen: 1 Injection



1
Injection

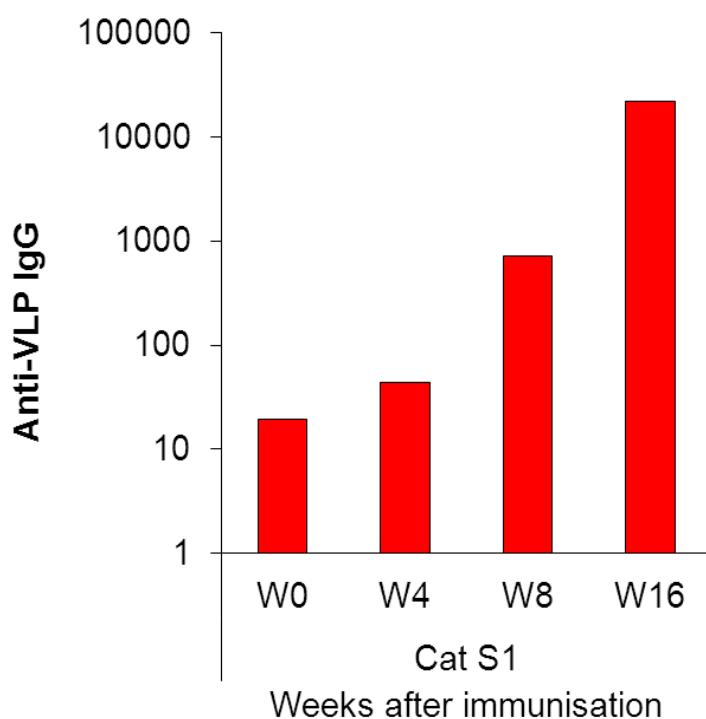




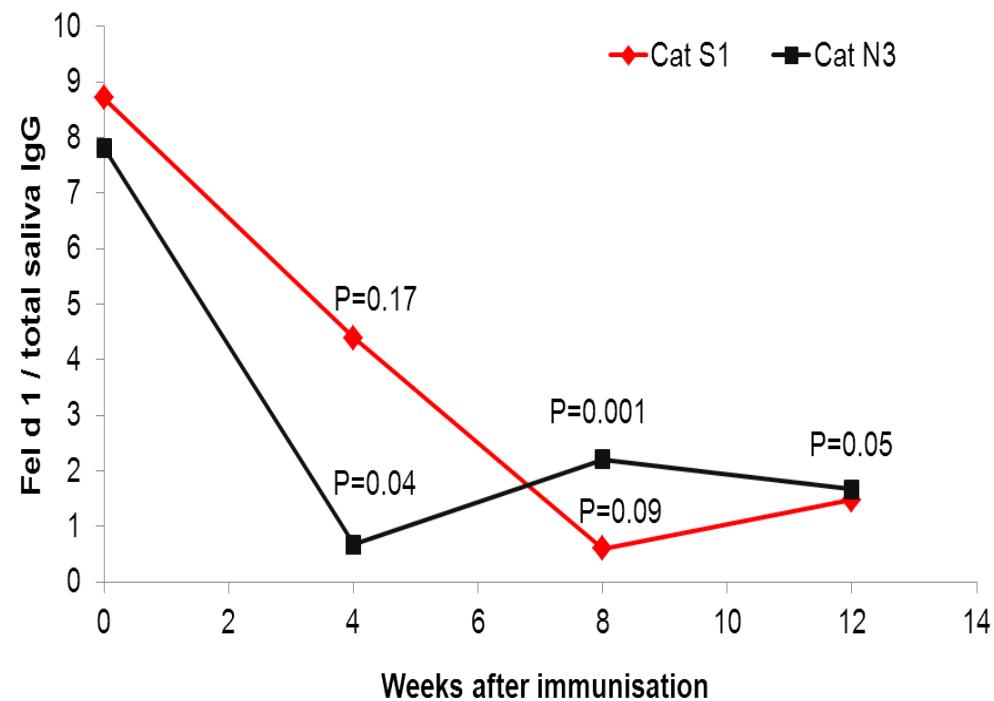


IPCIT: Zero Injections

IgG in saliva



Fel d 1 in saliva



Allergic patients

SLIT

ILIT

SCIT

EPIT

IPCIT

Rolf Zinkernagel

Gabriela Senti

Martin Bachmann

Lars French

Pal Johansen

Franziska Zabel

Antonia Fettelschoss

Deepa Mohanan

Ying Wäckerle-Men

Christine Tivig

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