Novel Approaches to Immunotherapy

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Disclosure Statement

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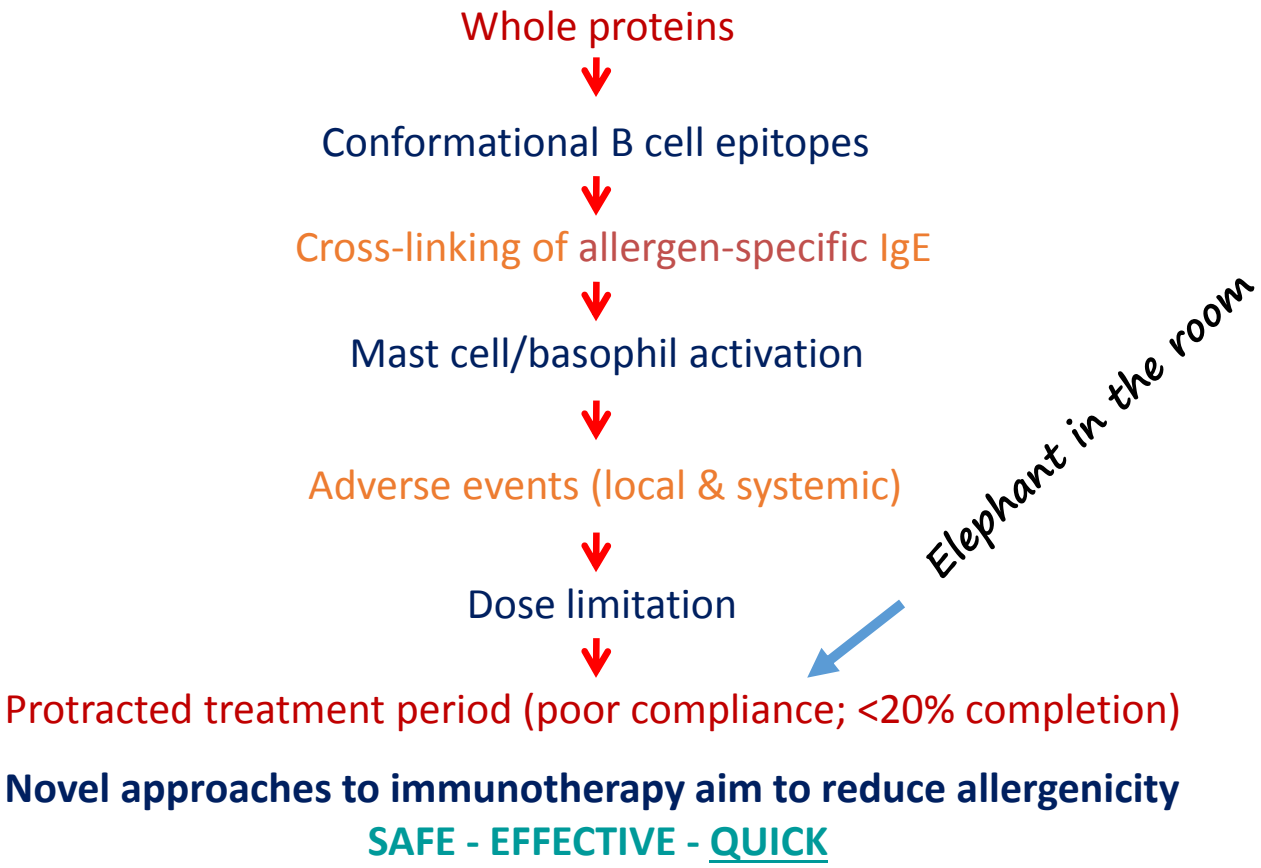
In relation to this presentation, I declare the following, real or perceived conflicts of interest:

- - Circassia Pharmaceuticals plc- Intellectual property rights
- - Circassia Pharmaceuticals plc- Consulting fee
- - Circassia Pharmaceuticals plc- co-Founder/Ownership interest
- - Adiga Life Sciences – Consulting
- - Abbott – Consulting (spouse)
- - Abbott – Honoraria (spouse)

- - Canadian Institutes for Health Research: operating grants
- - NIAID: U19 cooperative agreement U19AI100266
- - Immune Tolerance Network: subcontract
- - Scleroderma Society of Ontario: PhD Studentship
- - Adiga Life Sciences: research contracts
- - Canada Research Chair: salary award
- - McMaster University/GlaxoSmithKline: endowed Chair
- - Canada Foundation for Innovation: infrastructure award
- - AllerGen Network of Centres of Excellence; operating grants

Factors that limit the effectiveness of current immunotherapy approaches



Novel approaches to immunotherapy aim to reduce allergenicity

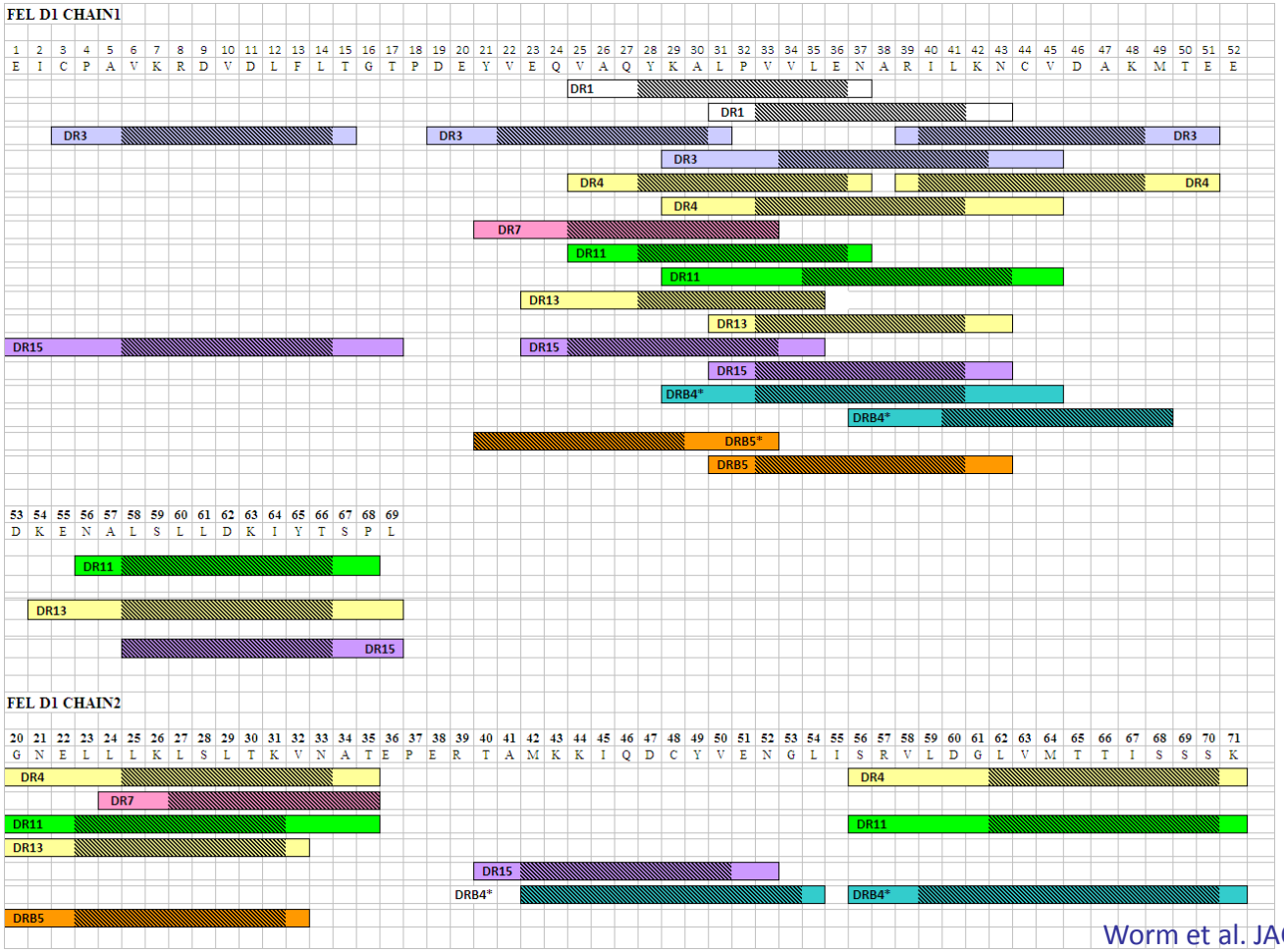
SAFE - EFFECTIVE - QUICK

Synthetic Peptide Immuno-Regulatory Epitopes (SPIRE)

- Short, synthetic sequences of amino acids representing immunodominant T cell epitopes
- Chemically defined, standardized
- Reduced secondary/tertiary structure
- Markedly reduced capacity to cross-link IgE on effector cells
- Modulation of allergen-specific T cell responses, induction of immuno-regulation
- Short treatment course
- No dose escalation
- Improved safety
- Enduring efficacy

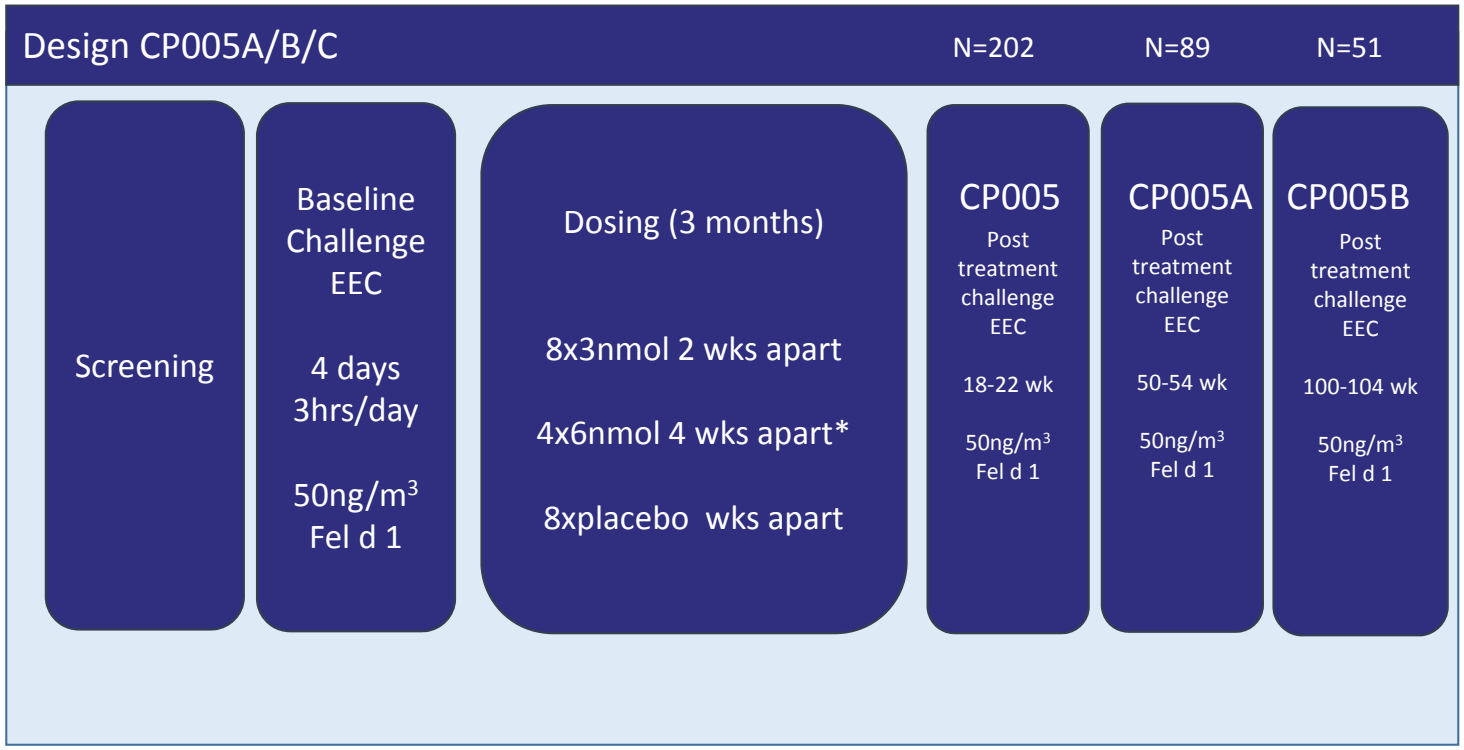
Cat

MHC class II restriction map of Fel d 1: defining epitopes for therapy



Worm et al. JACI 2011

Cat: Study Design CP005



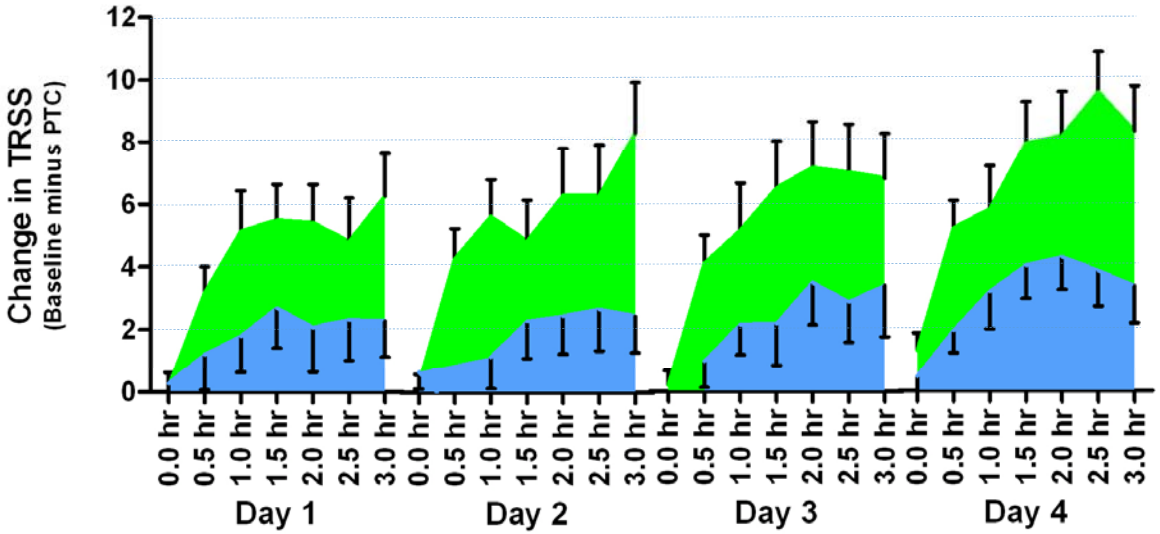
* infill placebo to maintain blind

Total Rhinoconjunctivitis Symptom Scores (TRSS) measured on 4 nasal and 4 ocular symptoms

- Patient **self-rated symptom scores** used as primary measure of efficacy
- Symptoms scored on a 4 point scale
  - 0: absent
  - 1: mild, barely noticeable
  - 2: moderate, annoying / troublesome
  - 3: severe, incapacitating
- Ocular symptoms scored on scale 0-3 for itchy eyes, watery eyes, red eyes, sore eyes
- Nasal symptoms scored on scale of 0-3 for running nose, sneezing, blocked nose, itchy nose
- TRSS score of 8 could be 8 “mild / barely noticeable scores”
- TRSS score of 12 could be 4 “mild / barely noticeable” and 4 “moderate / annoying” scores

CP005/5A efficacy and treatment duration study: Phase IIb

Randomized, double-blind, placebo-controlled parallel group trial with Environmental Exposure Chamber (EEC)



50-54wk follow-up

9 months after last dose

Marked treatment effect evident on day 1 which increases with time

Peak change in TRSS on fourth day almost 6 TRSS points

Median change in TRSS between 8 x 3nmol and 4 x 6nmol almost identical at 18-22wks

Patel et al., JACI 2013

Fel d 1–derived peptide antigen desensitization shows a persistent treatment effect 1 year after the start of dosing: A randomized, placebo-controlled study

Deepen Patel, MD,[a]* Peter Couroux, MD,[a]* Pascal Hickey, PhD,[b] Anne Marie Salapatek, PhD,[a]‡ Paul Laidler, PhD,[c] Mark Larché, PhD,[d] and Roderick P. Hafner, PhD[c] *Mississauga and Hamilton, Ontario, Canada, and Oxford, United Kingdom*

JACI 2013

TRSS: Total Rhinitis Symptom Score (nasal and ocular symptoms)

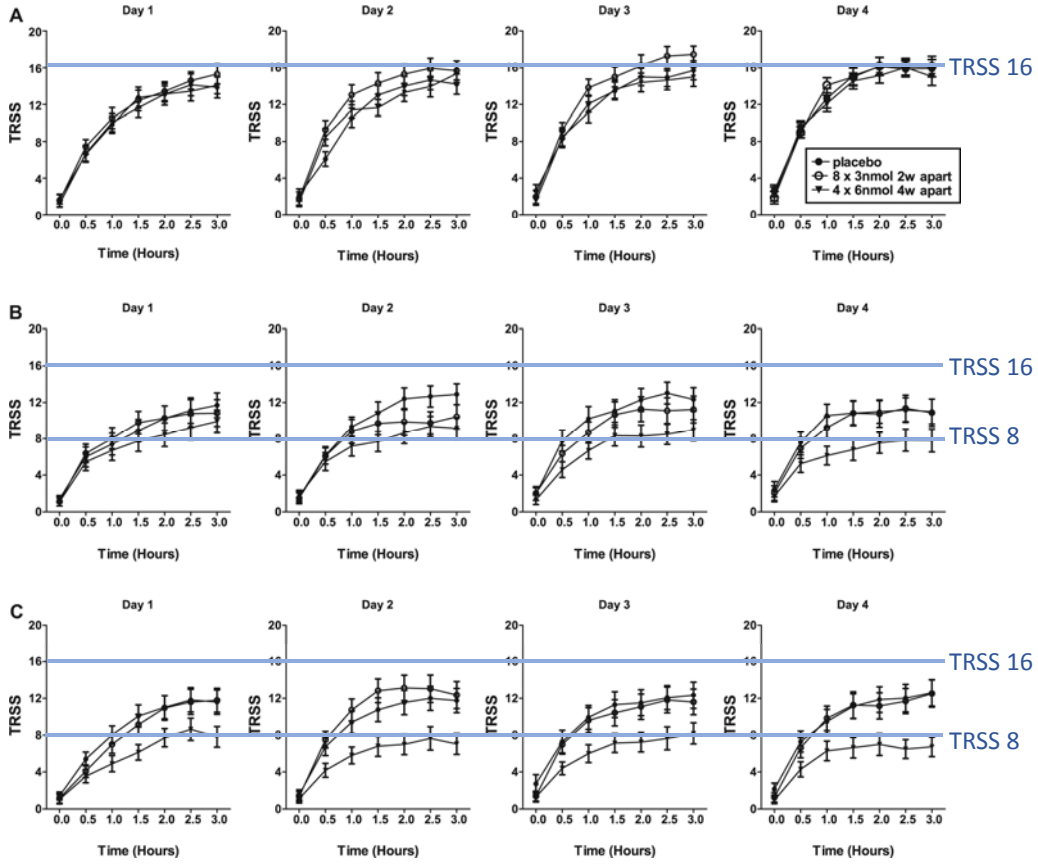
BL

18-22wk

n=202

50-54wk

n=89

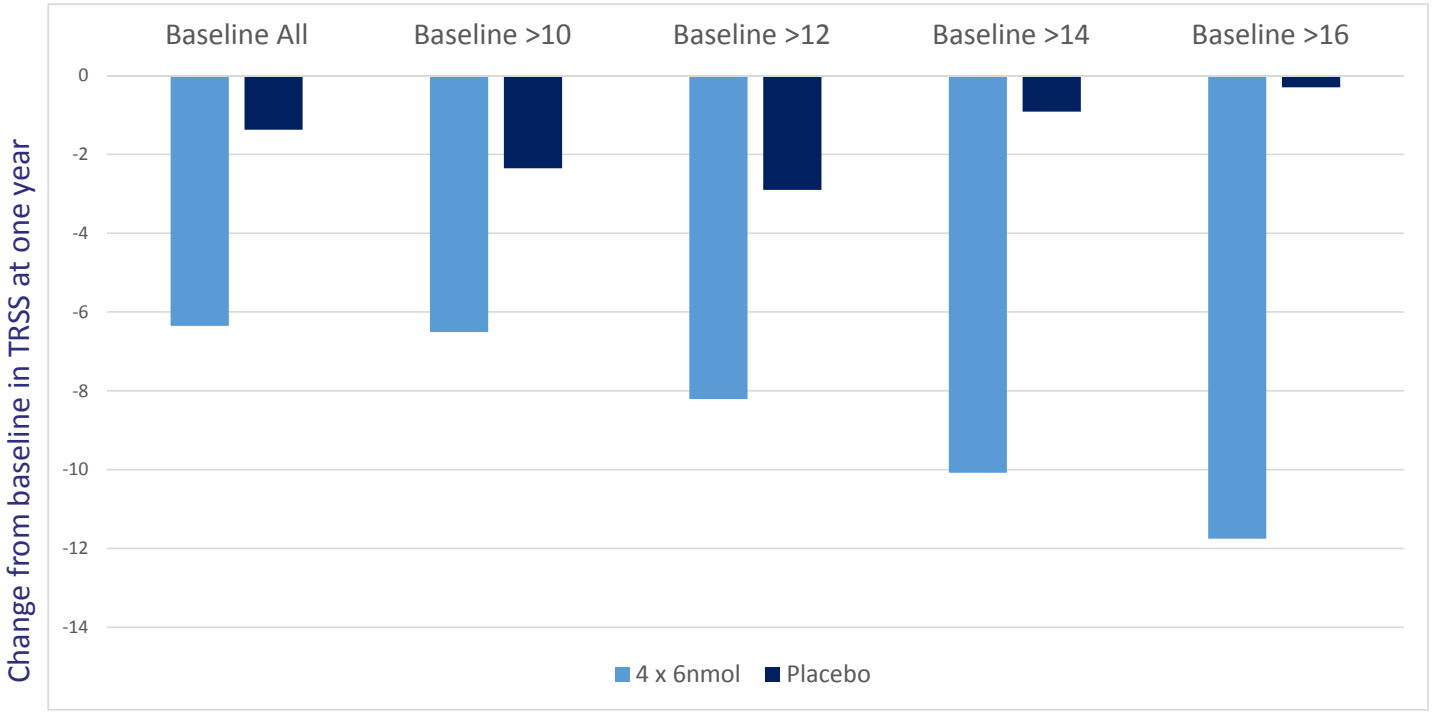


EEC chamber

TRSS (24 point scale)

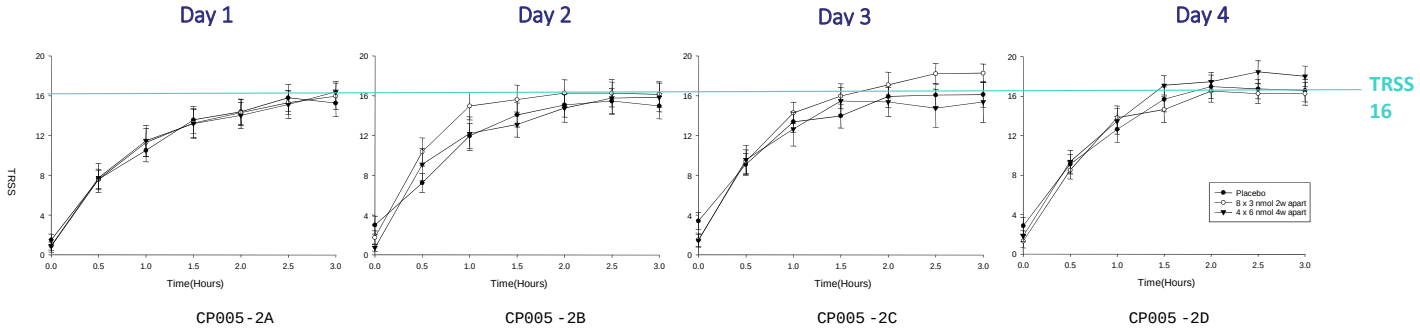
Adverse events indistinguishable from placebo

Treatment effect larger in more symptomatic subjects

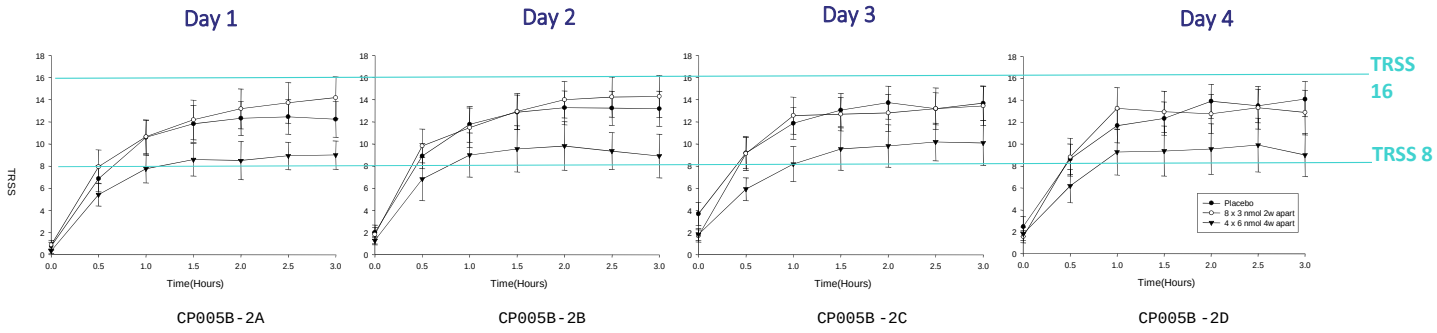


TRSS scores for subjects at two year follow up

Baseline Challenge



Post Treatment Challenge at 100-104w



CATALYST – Double blind placebo controlled Phase III study ongoing

- 1,182 adult & adolescent subjects
  - More than 1,100 subjects already randomized
- Two Cat-SPIRE active treatment arms, evaluating effect of one and two courses of treatment
- Primary endpoint change in Combined Score (Symptoms + Medication Use) measured one year after start of treatment
- Includes patients with GINA 1 asthma
- Exploratory endpoints include evaluating changes in asthma control in asthmatic subjects and the numbers of subjects developing asthma during the course of the study to provide a baseline for potential future follow-up.
- Aim to recruit all subjects by December 2014; results Spring 2016

House Dust Mite

Population Description

Key Inclusion Criteria

- Male or female, aged 18-65 years.
- A minimum 1-year documented history of rhinoconjunctivitis on exposure to HDM.
- Positive skin prick test to whole *Der p* allergen at least 3 mm larger than negative control
- ***Minimum qualifying symptom scores were a TRSS of 10 (out of a possible 24) on at least one time point on Days 2 & 3 of baseline challenge***

Key Exclusion Criteria

- Subjects with asthma or an FEV_1 < 80 % of predicted.
- Allergen or peptide immunotherapy during the last 12 months or any history of HDM immunotherapy.
- Symptoms of a clinically relevant illness, in the Investigator's opinion, within 6 weeks prior to the Screening Visit.

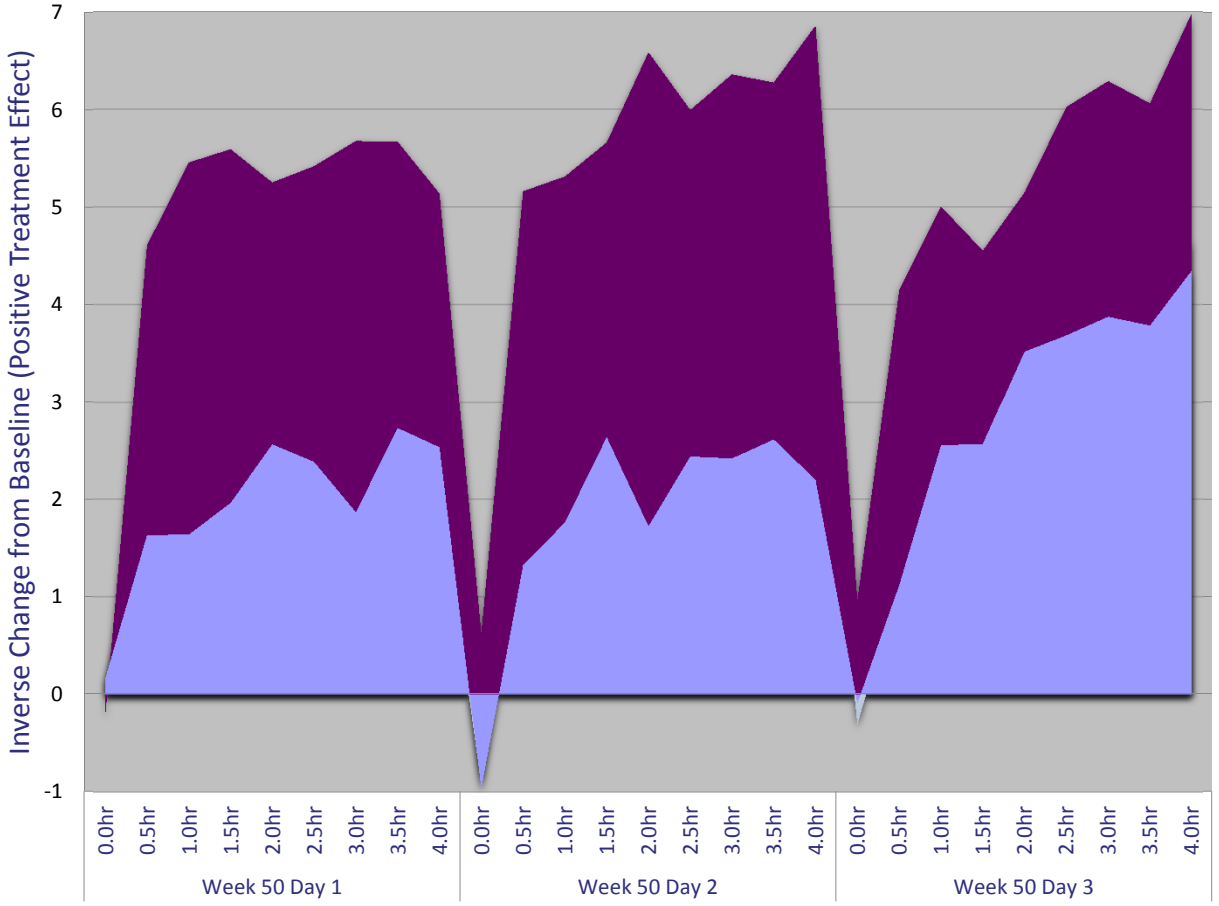
Study TH002 Efficacy Endpoints

Co-Primary Endpoints:

- Mean TRSS, comprising:
  - Severity of 4 nasal and 4 non-nasal symptoms
  - At the 1 to 4 hour time points, inclusive
  - During Days 2 and 3 of EEC Challenge
  - In active treatment groups compared to placebo
  - 19 and 49-50 weeks after completion of Baseline Challenge

- The analysis at 19 weeks was added as a co-primary during the study when the number of withdrawals was greater than expected
  - Withdrawals equal across all groups including placebo
  - Withdrawals not due to Adverse Reactions

TH002: House Dust Mite
4x12 nmol versus placebo at 50 weeks



- Primary endpoint on days 2 and 3 only
- Treatment effect larger if day 1 included

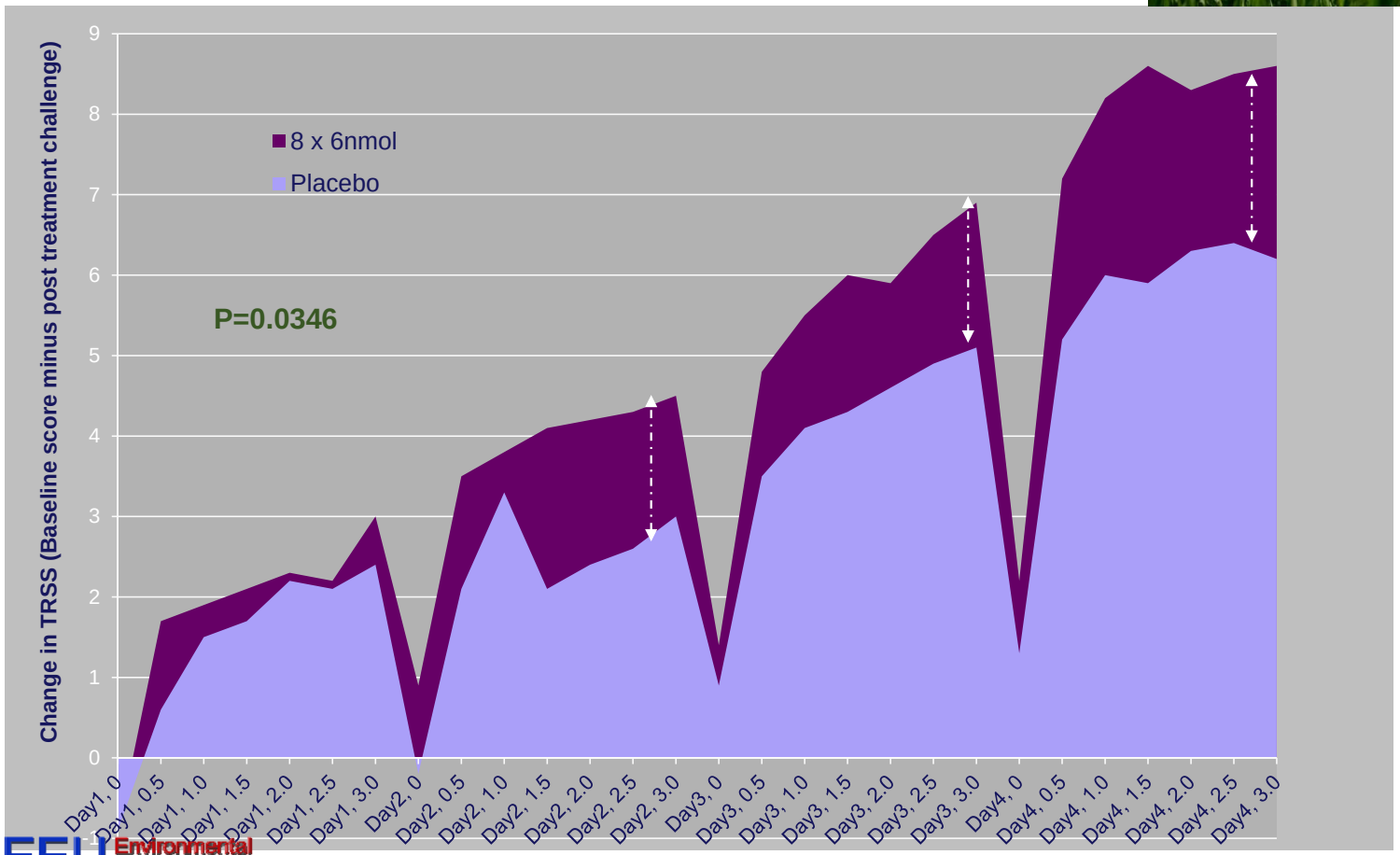
p =0.02

4x12nmol

Placebo

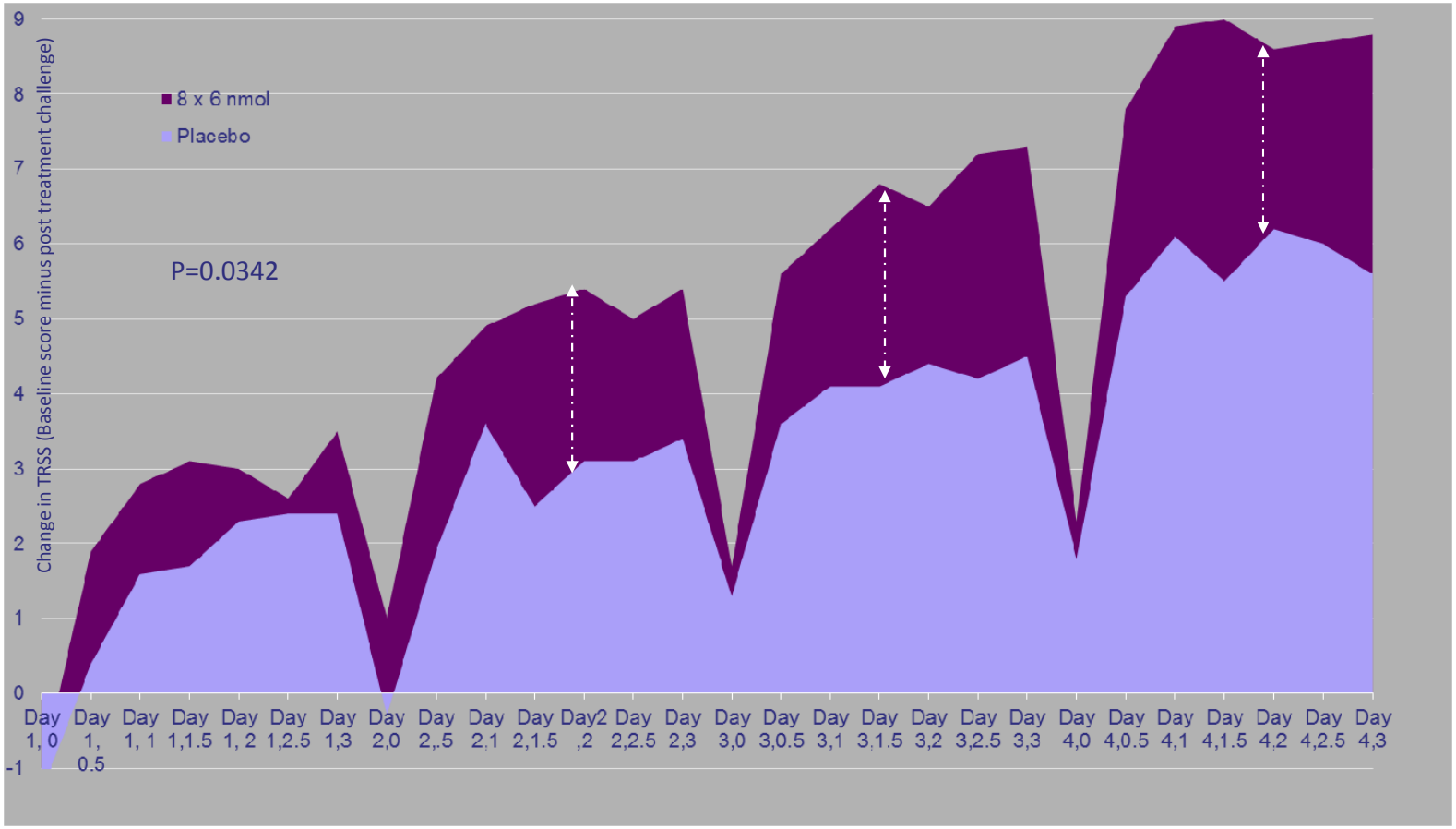
Grass Pollen

TG002: Grass Pollen
8x6nmol vs. placebo at 24-28wks
Subjects with mean baseline TRSS ≥8



EEU Environmental Exposure Unit

TG002: Grass Pollen
8x6nmol vs. placebo at 24-28wks
Subjects with mean baseline TRSS ≥12



Anergis

Allergen-specific T-cell tolerance induction with allergen-derived long synthetic peptides: Results of a phase I trial

Jean-Marc Fellrath, MD,[a] Alexander Kettner, PhD,[a,b] Nathalie Dufour,[a] Christian Frigerio, MD,[a] Dominique Schneeberger, MD,[a] Annette Leimgruber, MD,[a] Gampietro Corradin, PhD,[b] and François Spertini, MD[a] *Lausanne and Epalinges, Switzerland*

JACI 2003

Bee Venom allergic n=9 active n=7 placebo

Active treatment: 3 x long synthetic peptides (LSP)

Day 0: injections at 30 min intervals - 0.1ug, 1.0, 10, 20, 40, 80, 100ug

Day 4, 7, 14, 42, 70: 100ug maintenance dose*

Placebo treatment: ALK diluent

3/9 treated subjects experienced upper trunk flushing and pruritis 2-3 hrs after peptide dosing, two subjects had palm pruritis at Day 70 injection

*two subjects received maintenance doses of 300ug up to Day 42. One was withdrawn due to AE and the other returned to 100ug for Day 70

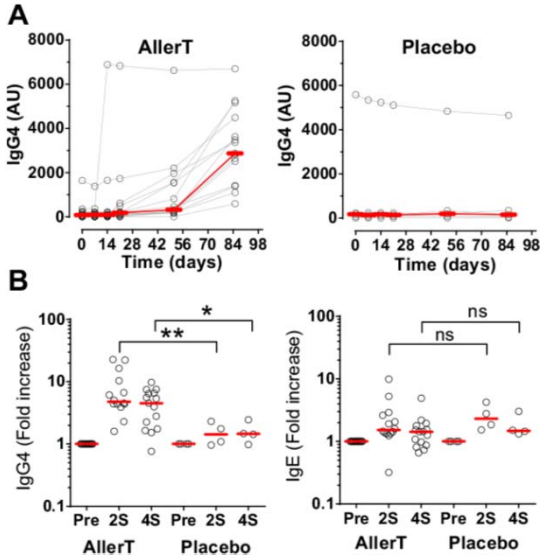
AN003

Safety: “a few mild and reversible delayed systemic reactions occurred”

Nasal Provocation: no change

Specific antibody responses: sustained 4.5-fold increase in specific IgG4 over baseline

Mini-RQLQ: Total Score and Rhino-Conjunctivitis Symptom Score 31% and 35% lower than placebo (statistical trend)
Asthma Score 65% lower than placebo (statistical trend)

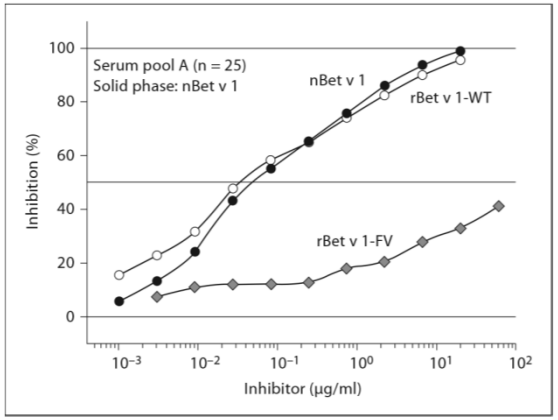


Allergopharma

Bet v 1 folding variant

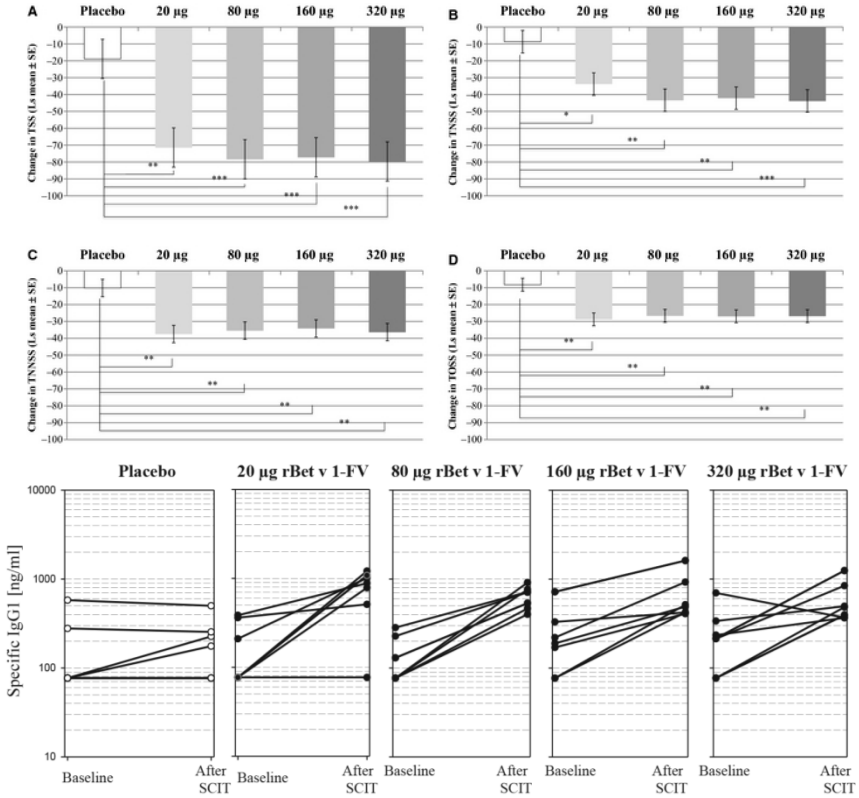
Characterization of a Hypoallergenic Recombinant Bet v 1 Variant as a Candidate for Allergen-Specific Immunotherapy

H. Kahlert[a] R. Suck[a] B. Weber[a] A. Nandy[a] M. Wald[a] W. Keller[b]
O. Cromwell[a] H. Fiebig[a]



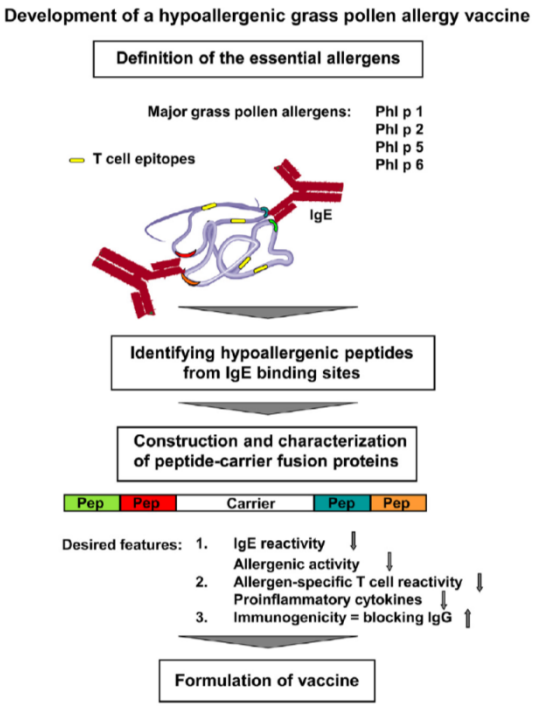
Double-blind, placebo-controlled, dose-ranging study of new recombinant hypoallergenic Bet v 1 in an environmental exposure chamber

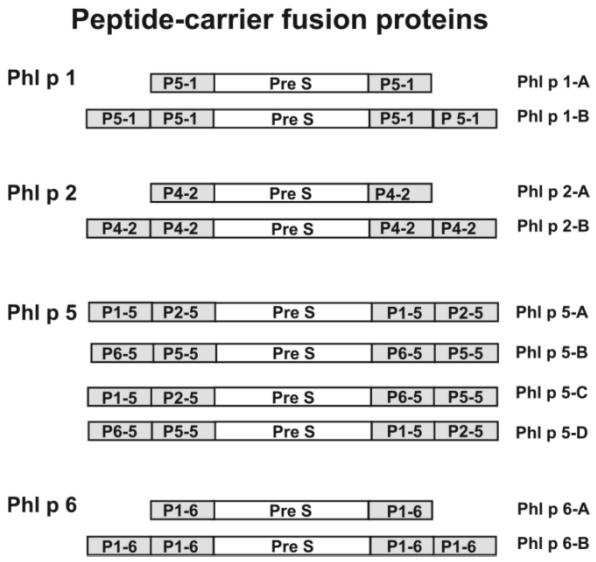
W. Meyer[1], A. Narkus[1], A. M. Salapatek[2] & D. Häfner[1]



Volume 68, Issue 6, pages 724-731, 27 APR 2013 DOI: 10.1111/all.12148
http://onlinelibrary.wiley.com/doi/10.1111/all.12148/full#all12148-fig-0002

Biomay/Valenta BM32





Focke-Tejkl et al., J Allergy Clin Immunol 2014 in press, courtesy of Rudolf Valenta

IgG blocking antibodies: not the whole story

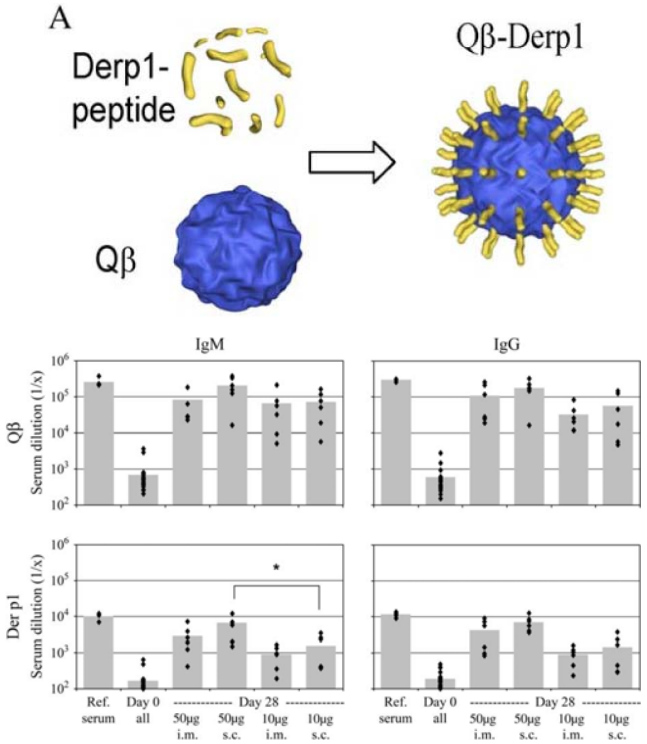
OIT is associated with increases in serum allergen-specific IgG/G_4

However, severe and unpredictable reactions can occur without warning, suggesting that mechanisms in addition to “blocking antibody” may have a role in protection

Cytos

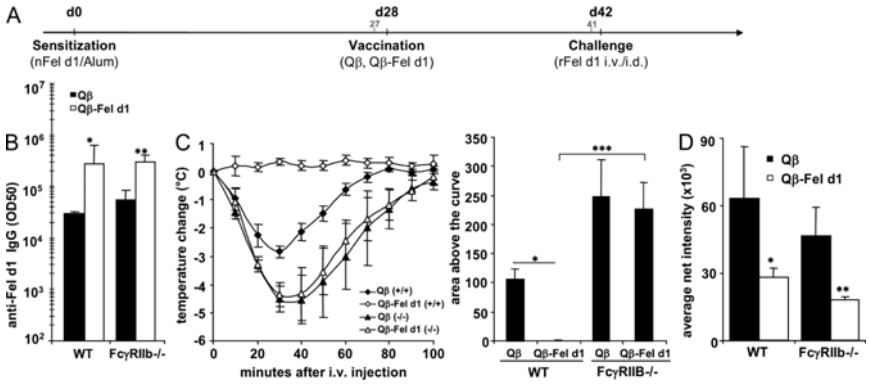
Der p 1 peptide on virus-like particles is safe and highly immunogenic in healthy adults

Thomas M. Kündig, MD,[a] Gabriela Senti, MD,[a] Gabriel Schnetzler, MD,[a] Charles Wolf, MD,[a] Bettina M. Prinz Vavricka, MD,[a] Alma Fulurija, PhD,[b] Frank Hennecke, PhD,[b] Katja Sladko,[b] Gary T. Jennings, PhD,[b] and Martin F. Bachmann, PhD[b] *Zurich and Zurich-Schlieren, Switzerland*



Displaying Fel d1 on virus-like particles prevents reactogenicity despite greatly enhanced immunogenicity: a novel therapy for cat allergy

Nicole Schmitz, Klaus Dietmeier, Monika Bauer, Melanie Maudrich, Stefan Utzinger, Simone Muntwiler, Philippe Saudan, and Martin F. Bachmann

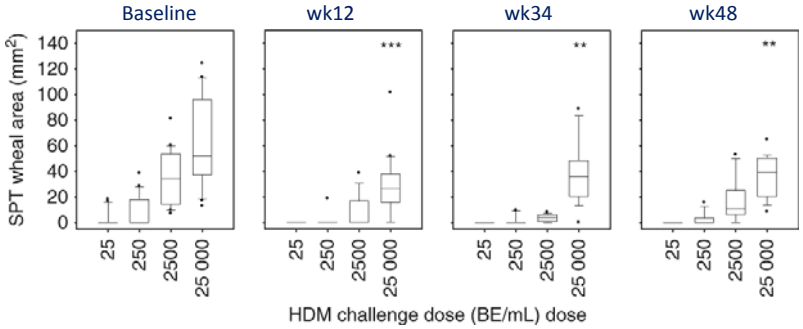


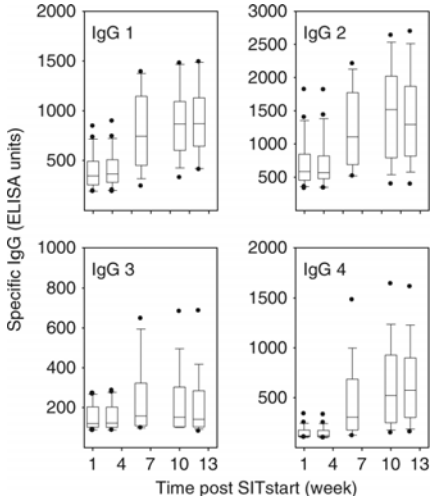
ORIGINAL ARTICLE Clinical Allergy

Use of A-type CpG oligodeoxynucleotides as an adjuvant in allergen-specific immunotherapy in humans: a phase I/IIa clinical trial

G. Senti*,†, P. Johansen*, S. Haug*, C. Bull*, C. Gottschaller*, P. Müller‡, T. Pfister‡, P. Maurer‡, M. F. Bachmann‡, N. Graf† and T. M. Kündig*

10wk open-label HDM immunotherapy + 300ug QbG10 in 21 subjects





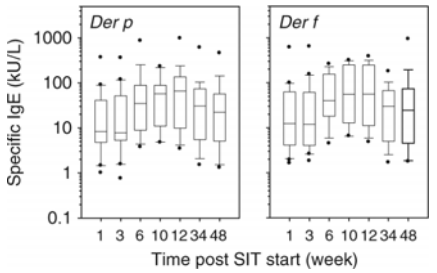


Table 2. Conjunctival provocation test

Time point (weeks)	Number of patients reacting in CPT with threshold concentration (BE/mL): 2.5	25	250	2500	25 000*
0	1	11	7	1	0
12	0	0	0	2	17
34	0	0	1	9	9
48	0	0	1	3	15

Table 3. Recorded symptoms of rhinoconjunctivitis (RcSDL) and asthma (AsSDL) in daily life as well as recorded scores for the daily-life consequences of rhinitis (CoR) and asthma (CoA): median (minimum and maximum)

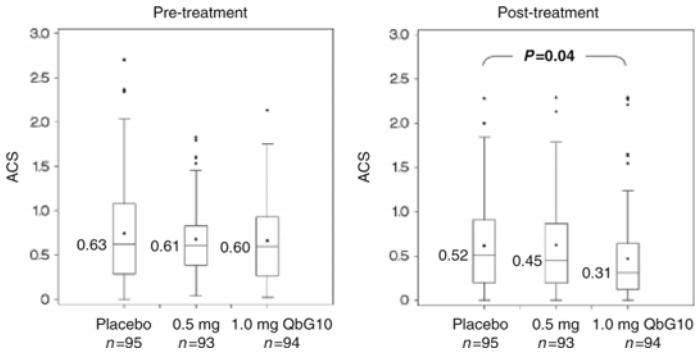
	Time of measurement: Baseline	12 weeks	34 weeks	48 weeks
RcSDL	10.5 (5–17)	1.5 (0–7)	3 (0–12)	2 (0–8)
AsSDL	2 (0–6)	0 (0–3)	0 (0–3)	0 (0–3)
CoR	3 (1–4)	0 (0–3)	1 (0–2)	0 (0–2)
CoA	3 (0–4)	0 (0–4)	0 (0–4)	0 (0–3)

Assessment of clinical efficacy of CYT003-QbG10 in patients with allergic rhinoconjunctivitis: a phase IIb study

L. Klimek[1], J. Willers[2], A. Hammann-Haenni[2], O. Pfaar[1], H. Stocker[2], P. Mueller[2], W. A. Renner[2] and M. F. Bachmann[2]

[1]Zentrum fuer Rhinologie & Allergologie, Wiesbaden, Germany and [2]Cytos Biotechnology AG, Schlieren, Switzerland

n=299
6 x weekly s.c. QbG10
1) Placebo
2) 0.5mg QbG10
3) 1mg QbG10



ACS post therapy significant vs placebo but NOT difference in deltas

Table 3. Conjunctival provocation test (CPT)

	Treatment group	N	logCPT Mean	logCPT SD	P-value vs. Placebo
Pre-treatment	Placebo	95	2.27	0.75	
	0.5 mg QbG10	93	2.24	2.00	0.84
	1 mg QbG10	94	2.26	0.84	0.95
Post-treatment	Placebo	95	2.66	1.19	
	0.5 mg QbG10	93	2.68	1.17	0.95
	1 mg QbG10	94	3.02	1.12	0.032

The table shows the allergen concentration (expressed as logCPT) necessary to induce an ocular irritation score of 2 or more. *P*-values based on Mann–Whitney test.

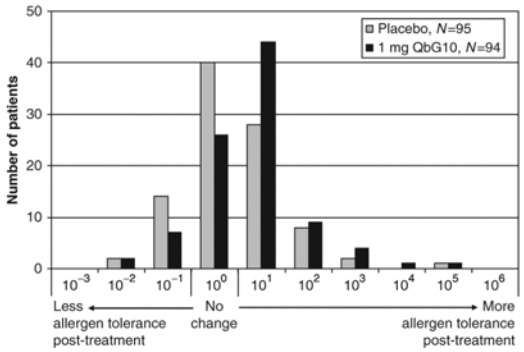


Table 2. Mini rhinoconjunctivitis quality of life questionnaire (MiniRQLQ)

	Treatment group	N	MiniRQLQ Score (points) Median	25–75%	Min–Max	P-value vs. Placebo
Pre-treatment	Placebo	95	1.64	1.00–2.29	0.07–4.93	
	0.5 mg QbG10	92	1.66	1.07–2.32	0.00–3.79	0.86
	1 mg QbG10	94	1.57	1.00–2.21	0.14–5.00	0.37
During treatment (day 14)	Placebo	94	1.32	0.57–1.93	0.00–4.64	
	0.5 mg QbG10	93	1.14	0.57–1.71	0.00–3.86	0.38
	1 mg QbG10	94	1.25	0.64–1.79	0.00–4.23	0.60
During treatment (day 28)	Placebo	95	0.93	0.43–1.86	0.00–4.86	
	0.5 mg QbG10	93	0.93	0.43–1.64	0.00–3.57	0.45
	1 mg QbG10	94	0.86	0.50–1.71	0.00–4.29	0.55
Post-treatment (day 49)	Placebo	95	1.21	0.57–1.71	0.00–4.64	
	0.5 mg QbG10	92	0.79	0.39–1.46	0.00–4.50	0.0498
	1 mg QbG10	94	0.71	0.43–1.50	0.00–4.29	0.02

Stats refer to “disease scores” vs placebo NOT difference in deltas

Follow up: “slight difference” at 6 months, nothing at 12 months

Primary Outcome: Average Combined Symptom & Medication Score (ACS)
Symptoms: 7 field RC scores (0-3) which was averaged to give Daily Symptom Score (0-3)
Medication: no drug (0), nasal/ocular anti-histamine (1), oral anti-histamine (2), topical steroid (3)
ACS calculated each day as arithmetic mean of average Daily Symptom Score and the Medication Score

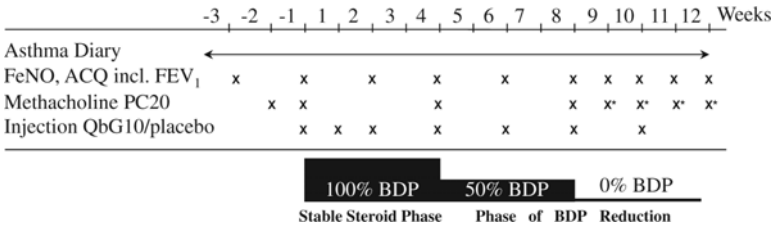
35 sites
Estonia (5), Latvia (3), Lithuania (4), Germany (9), Romania (10), Greece (4)
Competitive recruitment between sites
93% subjects HDM monoallergic

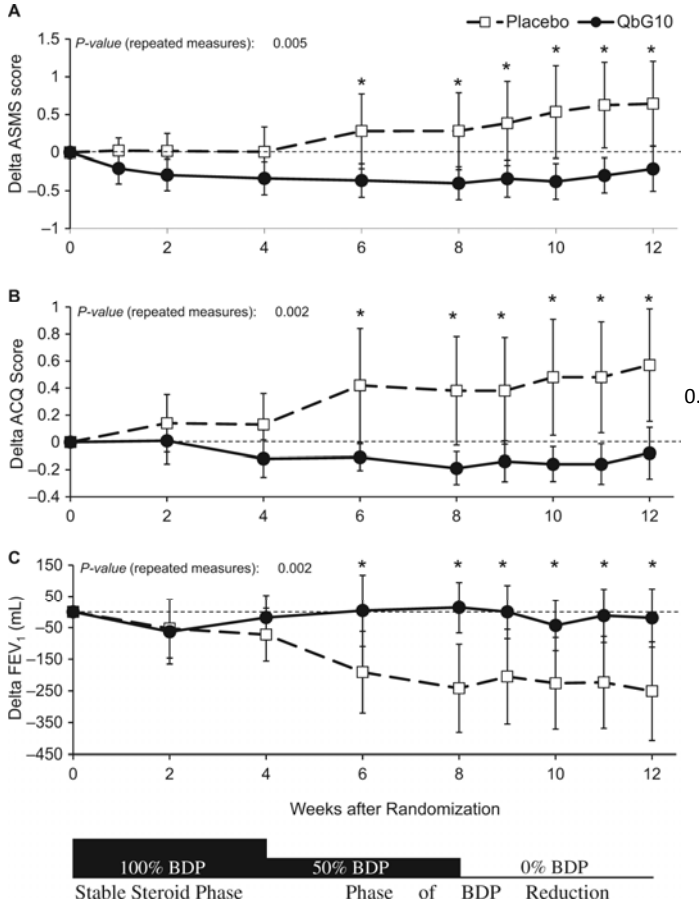
The novel TLR-9 agonist QbG10 shows clinical efficacy in persistent allergic asthma

5 sites in Germany

Kai-Michael Beeh, MD,[a] Frank Kanniess, MD,[b]* Frank Wagner, MD,[c] Cordula Schilder, MD,[d] Ingomar Naudts, MD,[e] Anya Hammann-Haenni, PhD,[f] Joerg Willers, PhD,[f] Hans Stocker, PhD,[f] Philipp Mueller, MD,[f] Martin F. Bachmann, PhD,[f] and Wolfgang A. Renner, PhD[f] *Wiesbaden, Lübeck, Berlin, Eisenach, and Rodgau, Germany, and Schlieren, Switzerland*

63 subjects GINA step 3/4 asthma
1) 7 x 0.9mg QbG10 (n=33)
2) Placebo (n=30)
Asthma stabilization phase followed by withdrawal

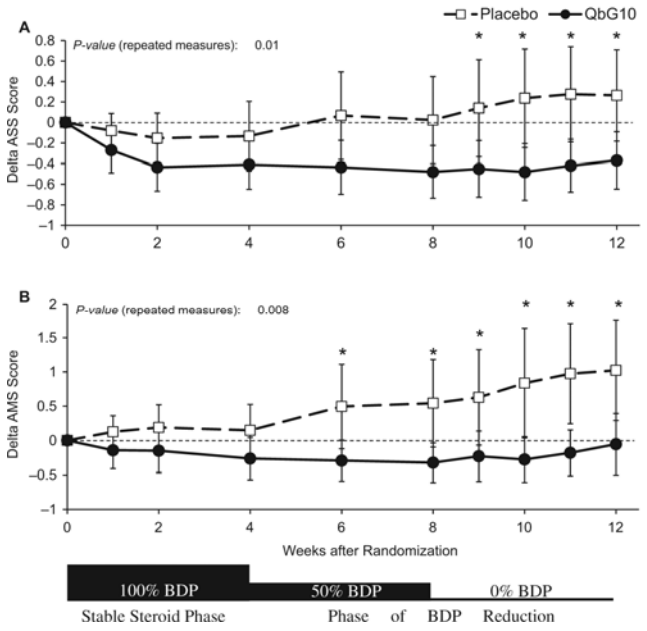




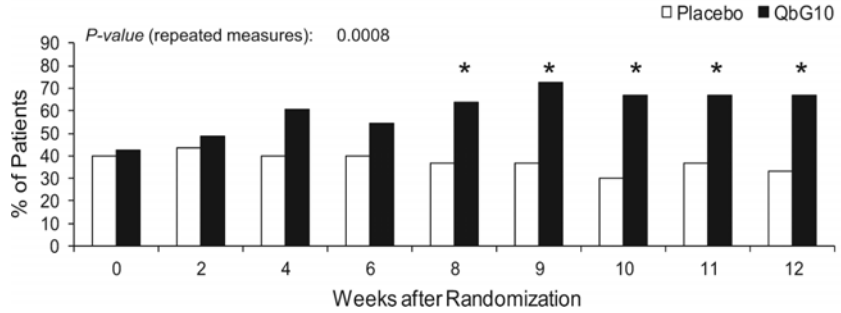
0.64

Publication states that the study was powered on F_{ENO} an "exploratory" outcome. The primary efficacy outcome is not explicitly stated in the publication nor on clinicaltrials.gov. The F_{ENO} outcome failed to reach statistical significance.

Symptom and Medication Scores broken out



Asthma Control



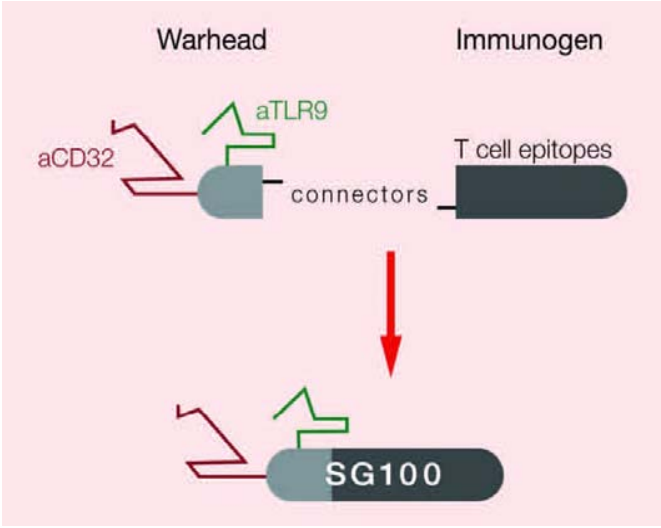
Blood eosinophilia significantly reduced
No change in PC_{20}
No change total IgE and IgG

S-TARget

S-TIR platform: Specific T cell Immunity Remodeler

Modular vaccines that target T cell epitopes to pDC

SG100 is the first product under development for house dust mite allergy



T cell epitopes engineered by shuffling to reduce allergenicity

Rationale

pDC are known to express large quantities of type I IFNs upon exposure to viruses and CpG

Type I IFNs are known to drive Th1 responses and suppress Th2 responses by down-regulating GATA-3

pDC from allergic individuals have significantly reduced type I IFN production in response to CpG

Signaling through FcεRI reduces type I IFN production in response to CpG

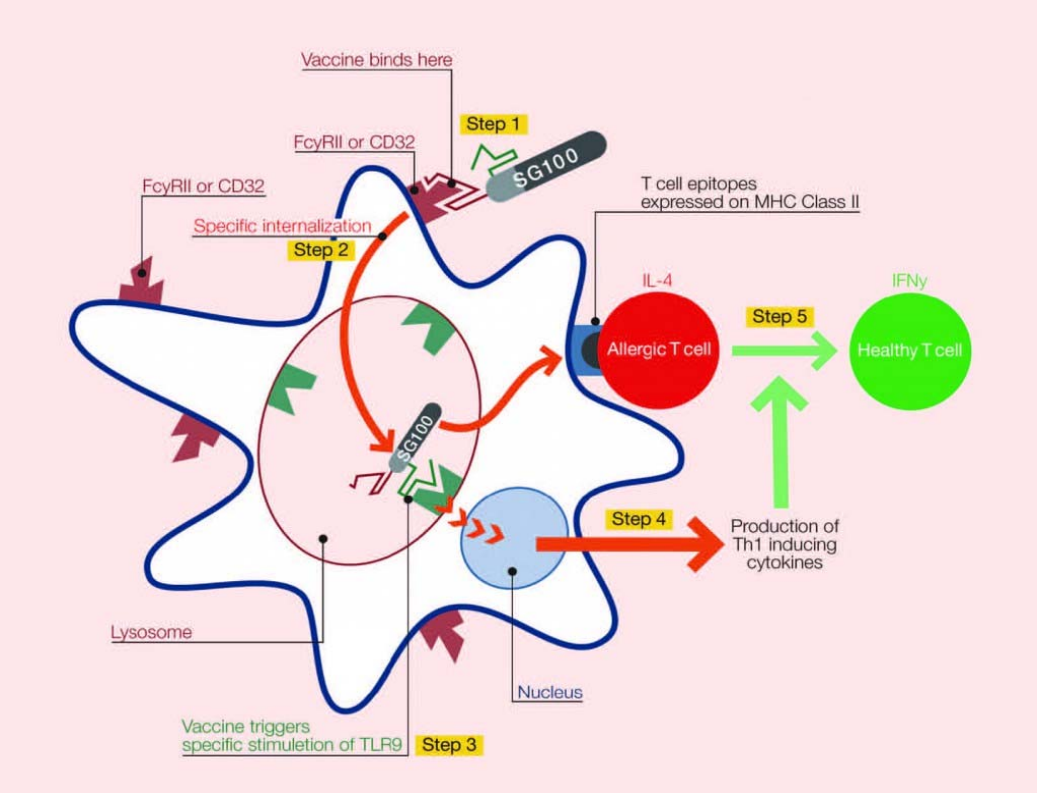
SCIT results in a 5-fold increase in type I IFN production in response to CpG

CpG has shown promise in the treatment of allergic diseases but has not been delivered in a targeted fashion i.e. directly to pDC

Recent studies have suggested that CpG works better as an adjuvant when antigen is delivered at the same time as both need to be present in the lysosome for optimal immune responses

Uptake of antigens via Fc receptors is known to deliver antigen to the lysosome and antibody-Fc-mediated antigen uptake is 100-1000 times more efficient than non-specific uptake

Proposed mechanism of action



CpG is conjugated via 3’ linkage rather than 5’

5’ linkage (used in Tolamba) significantly reduces immunostimulatory capacity

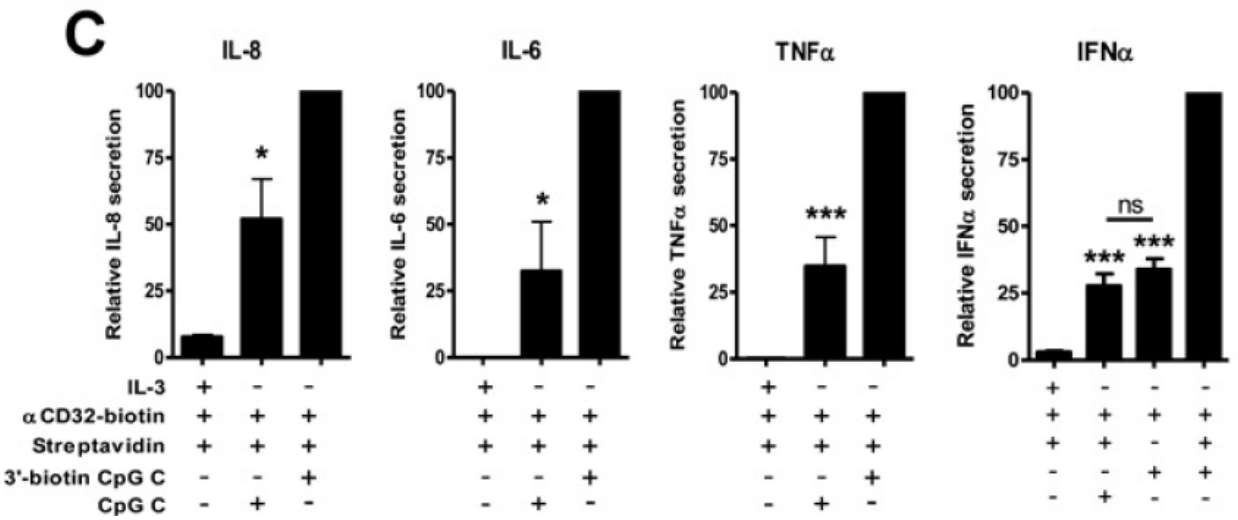
Contents lists available at SciVerse ScienceDirect

Immunobiology

journal homepage: www.elsevier.de/imbio

Targeted delivery of CpG ODN to CD32 on human and monkey plasmacytoid dendritic cells augments IFNα secretion

Jurjen Tel[a], Niels Beenhakker[c], Gerrit Koopman[c], Bert't Hart[c], Geert C. Mudde[d,*], I. Jolanda M. de Vries[a,b]



Targeting CpG through CD32 results in a 4-fold increase in type I IFN from pDC (also associated with significantly enhanced TNFa, IL-6, IL-8)

S-TARget future plans

SG100 works in cyno model which will be used for pre-clinical POC

Expect to enter Phase 1 in 2015

Selecta Biosciences

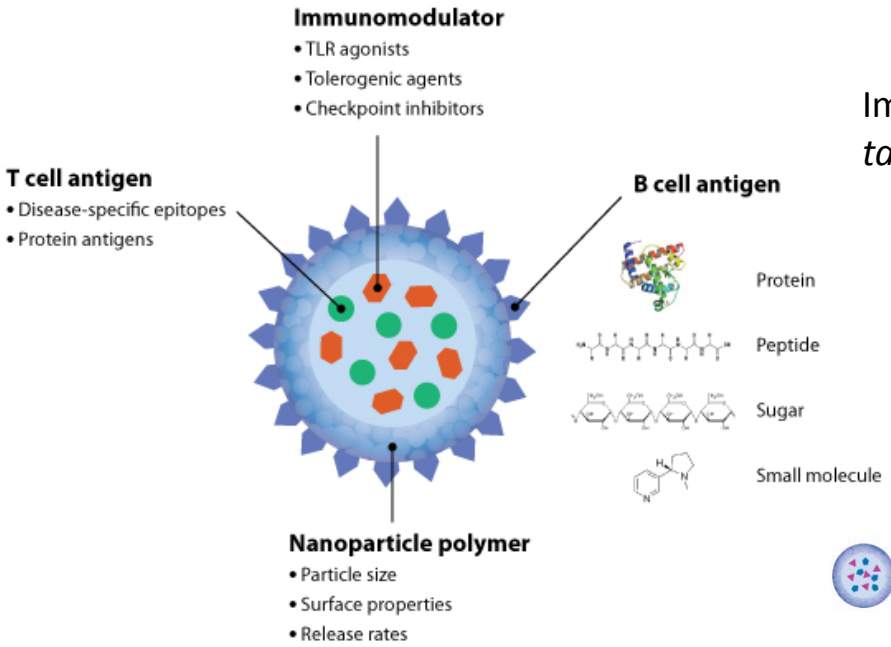
MIT/Harvard spin out

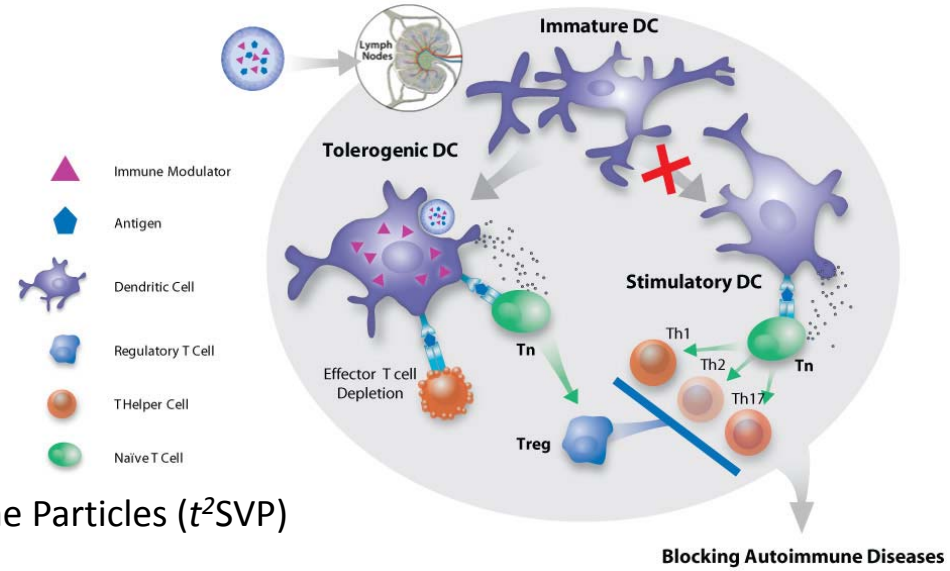
Founders:
Robert Langer (drug delivery),
Omid Farokhzad (nanoparticle development),
Ulrich von Andrian (immunology)

Self-assembling nanoparticles (NP) formulated for optimized molecular targeting, immune evasion and drug delivery

"maximal targeting, maximal stealth"

Immune activation
targeted Synthetic Vaccine Particles (*t*SVP)





Immune tolerance
targeted tolerogenic Synthetic Vaccine Particles (t^2SVP)

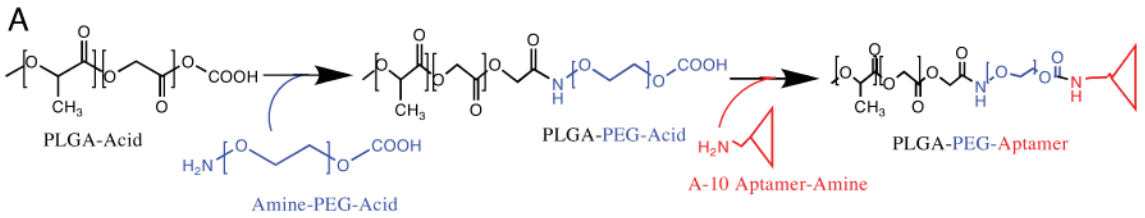
Poly(D,L-lactide-co-glycolide) (PLGA) – polyethylene glycol (PEG) – targeting moiety

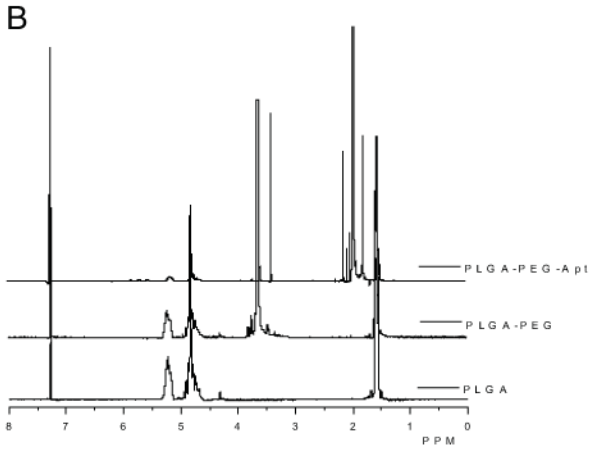
peptide (RGD motif)
protein
sugar
monoclonal antibody
RNA

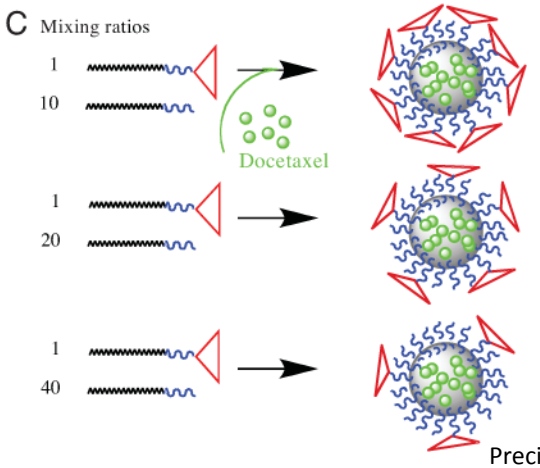
Increasing viscosity of PLGA regulates cargo release

Changing the length of the PEG regulates NP size

Optimization of targeting moiety optimizes NP targeting







Precipitation by addition of water induces “self-assembly” cargo is added at precipitation stage

Conclusions

- Evidence in phase 2b for efficacy with T cell peptides (SPIRE) across different allergens
- (unpublished) efficacy for B cell epitope peptides in grass pollen allergy
- Evidence for efficacy with VLP +/- allergen
- Evidence for efficacy with hypoallergenic allergen (rBet v 1-FV)
- Positive surrogate immunological markers with “long peptides”
- Several other adjuvanted strategies under development

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