Mevsimsel Alerjik Rinitli Hastamda Alerjen immunoterapisinin geleceği

DOC. DR. F. MERVE TEPETAM

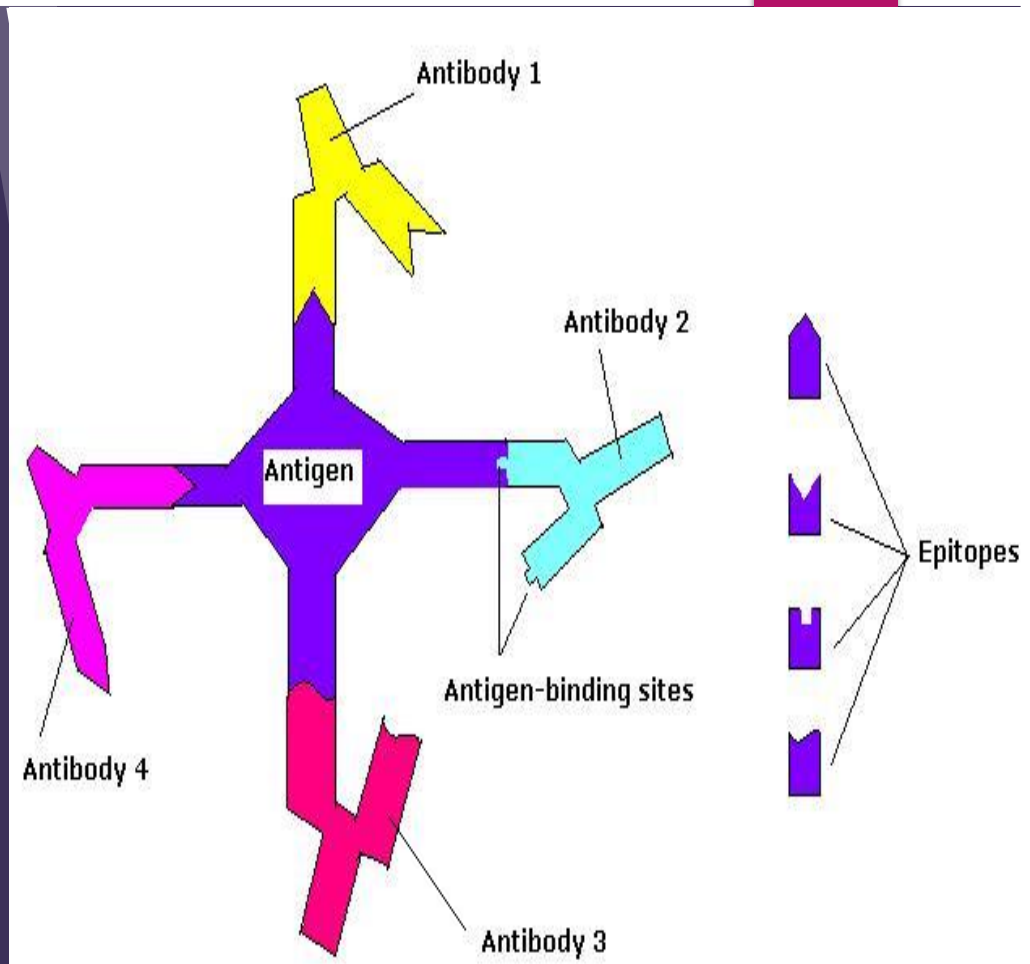
SAĞLIK BİLİMLERİ ÜNİVERSİTESİ

SÜREYYAPAŞA GÖĞÜS HASTALIKLARI VE GÖĞÜS CERRAHİSİ EAH

İMMUNOLOJİ VE ALLERJİ KLİNİĞİ

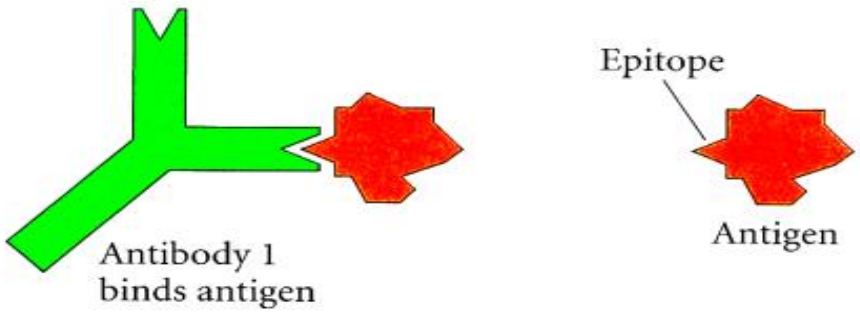
ALERJENİN YAPISI

- Allerjenin IGE sentezine neden olan özel a.a dizilimine sahip her bir bölgesine epitop veya alerjenik determinant denir
- Genel (pan alerjen) : Vital fonksiyonlar, patojen istilasından korunmak (PR)
- Major alerjen (Duyarlı kisilerin en az %50'si tarafından tanınan epitop)
- Minör alerjen (Duyarlı kisilerin daha az bir kısmı tarafından tanınan epitop)



. Bir alerjenin 3 boyutlu yapısı, şematik görünür

Temel Tanımlar – 2



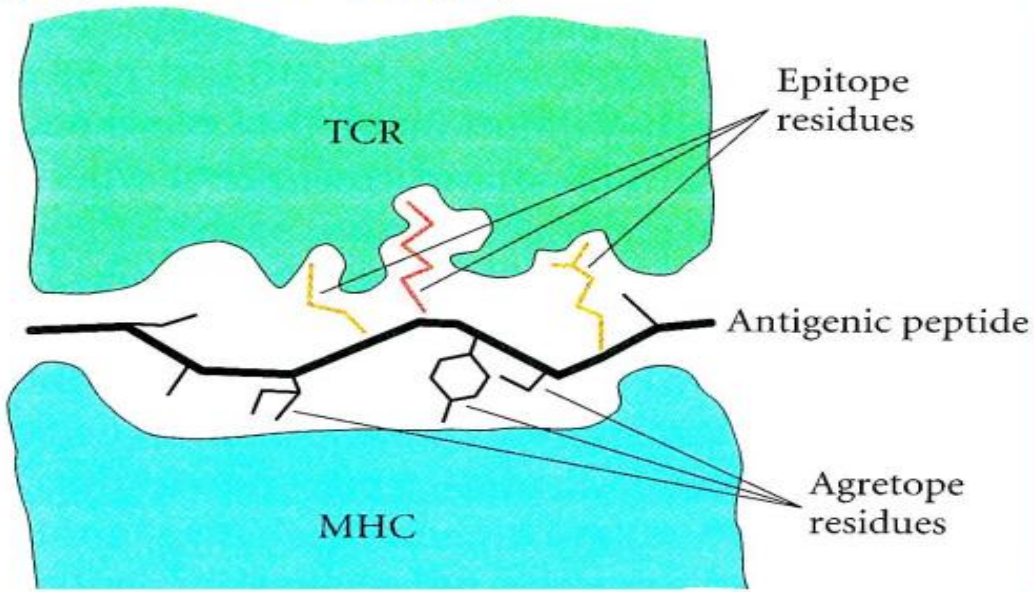
Epitop / Antijenik Determinant

Antijenin,

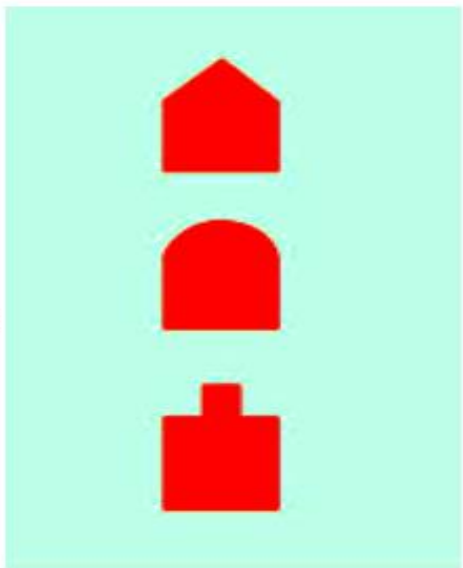
TCR / Ab bağlama bölgeleri ile

tanınabilen-bağlanabilen **kısmı / bölümü**dür

("T-hücre epitopu", "B-hücre epitopu")



Antijenik Determinantlar



B HÜCRE EPİTOPU

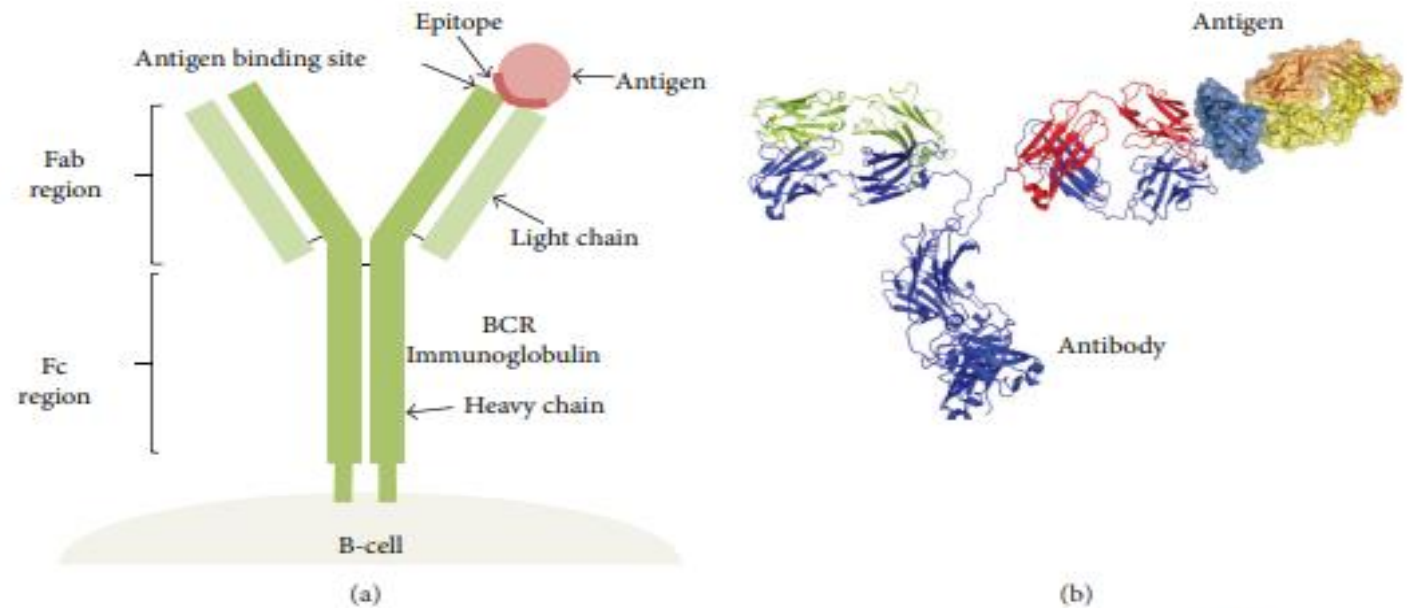
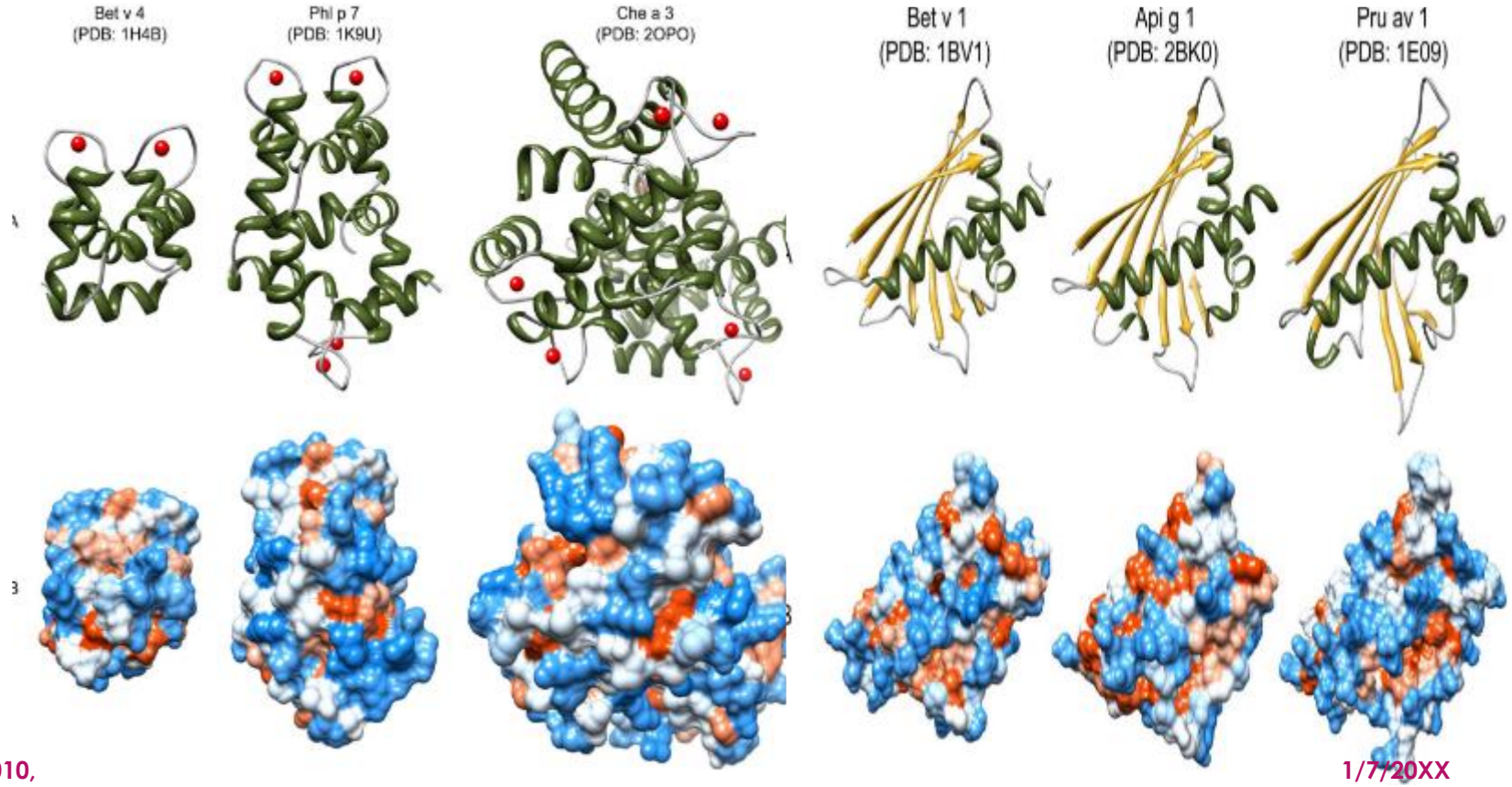


FIGURE 1: B-cell epitope recognition. B-cell epitopes are solvent-exposed portions of the antigen that bind to secreted and cell-bound immunoglobulins. (a) B-cell receptors encompass cell-bound immunoglobulins, consisting of two heavy chains and two light chains. The different chains and regions are annotated. (b) Molecular representation of the interaction between an antibody and the antigen. Antibodies are secreted immunoglobulins of known specificity.

SPESİFİK-ÇAPRAZ DUYARLILIK

- Spesifik duyarlılık,
  - Huş
  - Çayır
  - Akkazayağı
- Genel (çapraz duyarlılık) belirlenmesinde
  - Huş
  - Kereviz
  - Kiraz
- Bileşene bağlı tanı (Component Resolved Diagnosis :CRD)



Hauser et al. Allergy, Asthma & Clinical Immunology 2010,

Table 1 Members of panallergen families and of the Bet v 1 cluster

panallergen family	plant allergen source							
	pollen			food				product
	trees	grasses	weeds	fruits	vegetables	legumes	nuts/seeds	latex
profilins	Bet v 2 Car b 2 Cor a 2 Fra e 2 Ole e 2 Pho d 2	Cyn d 12 Lol p 12 Ory s 12 Phl p 12 Poa p 12 Zea m 12	Amb a 8 Art v 4 Che a 2 Hel a 2 Mer a 1 Par j 3	Act d 9 Ana c 1 Cit s 2 Cuc m 2 Fra a 4 Lit c 1 Mal d 4 Mus xp 1 Pru du 4 Pru av 4 Pru p 4 Pyr c 4	Api g 4 Cap a 2 Dau c 4 Lyc e 1	Gly m 3	Ara h 5 Cor a 2 Pru du 4	Hev b 8
polcalcins	Aln g 4 Bet v 3 Bet v 4 Fra e 3 Jun o 4 Ole e 3 Ole e 8 Syr v 3	Cyn d 7 Phl p 7	Amb a 9 Amb a 10 Art v 5 Che a 3					
nsLTPs	Ole e 7 Pla a 3		Amb a 6 Art v 3 Hel a 3 Par j 1 Par j 2 Par o 1	Act c 10 Act d 10 Cas s 8 Cit l 3 Cit s 3 Fra a 3 Mal d 3 Pru ar 3 Pru av 3 Pru d 3 Pru du 3 Pru p 3 Pyr c 3 Vit v 1	Api g 2 Aspa o 1 Bra o 3 Lac s 1 Lyc e 3 Zea m 14		Ara h 9 Cas s 8 Cor a 8 Jug r 3	Hev b 12
Bet v 1 cluster	Aln g 1 Bet v 1 Car b 1 Cas s 1 Cor a 1 Fag s 1 Que a 1			Act c 8 Act d 8 Ara h 8 Mal d 1 Pru ar 1 Pru av 1 Pru p 1 Pyr c 1	Api g 1 Dau c 1	Gly m 4 Vig r 1	Ara h 8 Cor a 1.04	

Currently known plant profilins, polcalcins, nsLTPs, and members of the Bet v 1 family of allergens http://www.allergen.org.

Çapraz reaktivite
alerji patolojisinde ve Allerjen İT'DE

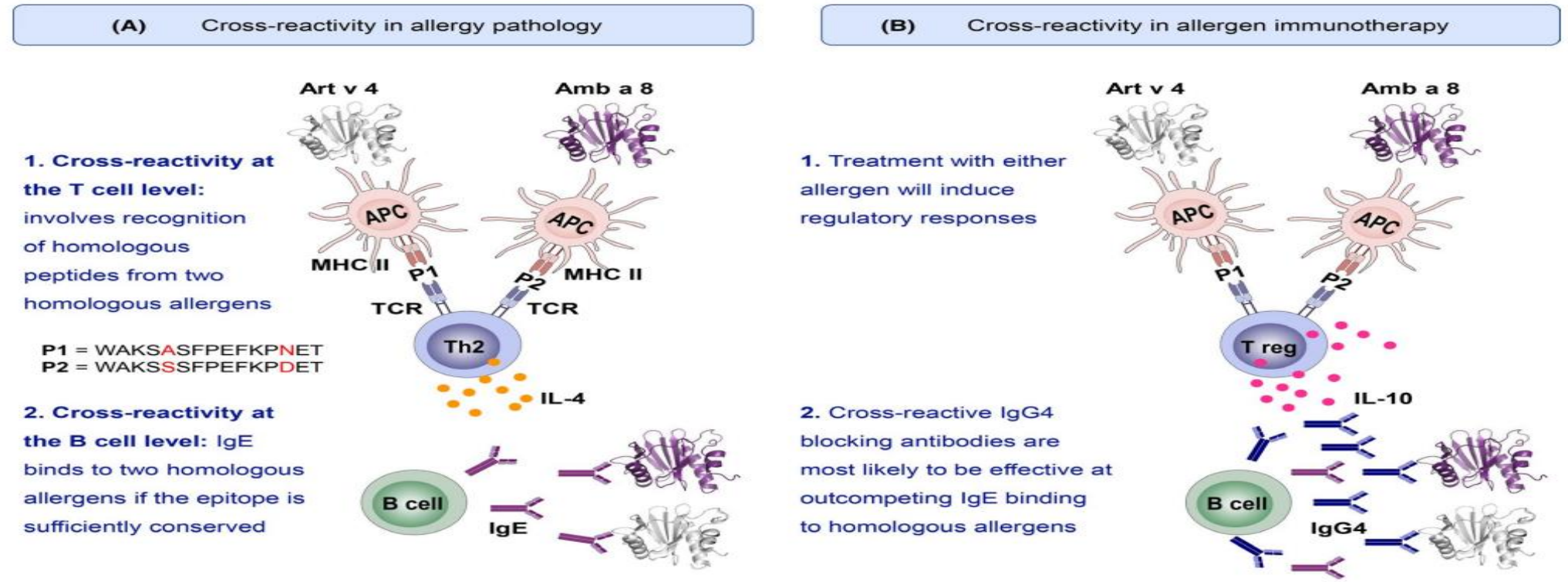


FIGURE 1 Schematic representation of mechanisms of cross-reactivity at the T (1) and B (2) cell level in allergy pathology (A) and allergen-specific immunotherapy (B). The two allergens images were created using the Protein Data Bank files of the X-ray crystal structures of two profilins: mugwort allergen Art v 4 (5EM0) and ragweed allergen Amb a 8 (5EM1), and the software PyMol. Molecules involved in APC-T cell interactions are indicated in A only: MHC II: major histocompatibility complex II; Peptides 1 and 2 (=P1 and P2): examples of possible peptides presented by the MHC II in the APC to the T cell; TCR: T-cell receptor

1/7/20XX

Allergy. 2020;75:9–11.

The Global Allergy and Asthma European Network (GA2 LEN)
Ortak protokolde bulunması önerilen solunum alerjenleri

Table 1 Standard prick test panel for inhalant allergens

Allergen/control	
Histamindihydrochloride 0,1 % (positive control)	
NaCl 0.9% (negative control)	
Hazel	*Corylus avellana*
Alder	*Alnus incana*
Birch	*Betula alba*
Plane	*Platanus vulgaris*
Cypress	*Cupressus sempervirens*
Grass mix	smooth meadow grass/*Poa pratensis*, cock's foot grass/*Dactilis glomerata*, perennial rye grass/*Lolium perenne*, timothy grass/*Phleum pratense*, meadow fescue/*Festuca pratensis*, meadow oat grass/*Helictotrichon pretense*
Olive	*Olea europaea*
Mugwort	*Artemisia vulgaris*
Ragweed	*Ambrosia artemisiifolia*
Alternaria	*Alternaria alternata (tenuis)*
Cladosporium	*Cladosporium herbarum*
Aspergillus	*Aspergillus fumigatus*
Parietaria	*Parietaria*
Cat	
Dog	
Dermatophagoides pteronyssinus	
Dermatophagoides farinae	
Blatella	*Blatella germanica*

Fındık Ağacı
Kızıl Ağaç
Huş Ağacı
Çınar Ağacı
Servi Ağacı

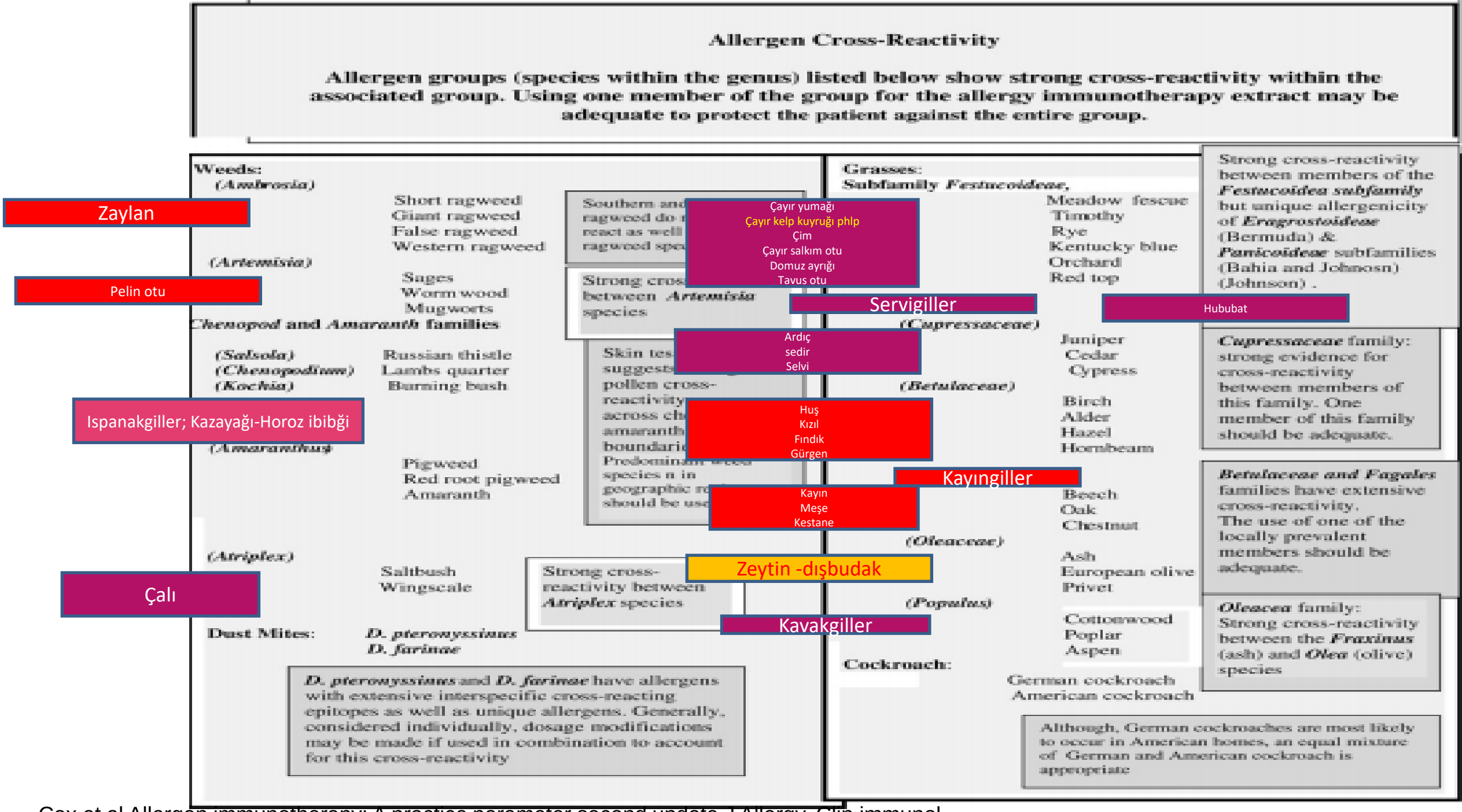
Paryeterya :
yapışkan çam
Wall pelitory

Ambrosia:
Arsız, zaylan
ragweed üzüm otu

Artemisia:
pelin otu, mugword

Etken	Alternatif isim	Major Alerjen	Çapraz	Mevsimi	Grubu
Der. Farinea	Ev Tozu Akarı	Derf1,Der f2			Akar
Der.Pteronyssinus	Ev tozu akarı	Derf1,Der f2			Akar
Lepidoglyphus Destructor	Depo Akarı	Lep d2			Akar
Bletella Germanica	Hamam böceği	Bla g2,Bla g4,Bla g5			
Olea Europaea	Zeytin	Ole e1	Phl p1 phl p5,phl 11	Nisan-ağustos	ağaç
Artemisia Vulgaris	Pelin Otu(Mugwort)	Art V1	Art v 6-Amb a1 Art v1-Amb a4 Art V3-Amb a6	Temmuz-ekim	Yabani ot
Parietaria Judaica	Yapışkan Çam(wall pelitory)	Par J2		Nisan-Ağustos	Yabani ot
Betula Verrucosa	Huş Ağacı	Bet V1	Kayın,meşe,kestane,Kızıl meşe PR-10 Elma,kiraz,kayısı,armut, şeftali,fındık,kereviz,havuç,maydanoz,patates	Mart-temmuz	ağaç
Dactiylis Glomerata	Domuz Ayrığı	Dac g1		Mart-Ağustos	grass
Lolium Perenne	İngiliz Çimi	Lol p5		Mart-Ağustos	grass
Poa Annua	Tavşan Bıyığı			Mart-Ağustos	grass
Phleum Pratense	Çayır Kelp Kuyruğu (timoty grass)	Phl p5,Phl p1		Mart-Ağustos	grass
Festuca pratensis	Çayır Yumağı	Fcı p5		Mart-Ağustos	grass
Ambrosia Artemisiifolia	Arsız Zaylan(ragweed,üzümotu)	Amb a5		Temmuz-Ekim	Yabani ot
Quercus Robur	Kızıl Meşe			Mart-temmuz	ağaç
Chenopodium Album	Akkazayağı			Nisan-ekim	Yabani ot
Secale Cereale	Çavdar			Nisan-Ağustos	tahıl
Alternaria Alternata		Alt a1			Dış mantar
Aspergillus Fumigatus					İç mantar
Cladospori					Dış mantar

25.07.2022



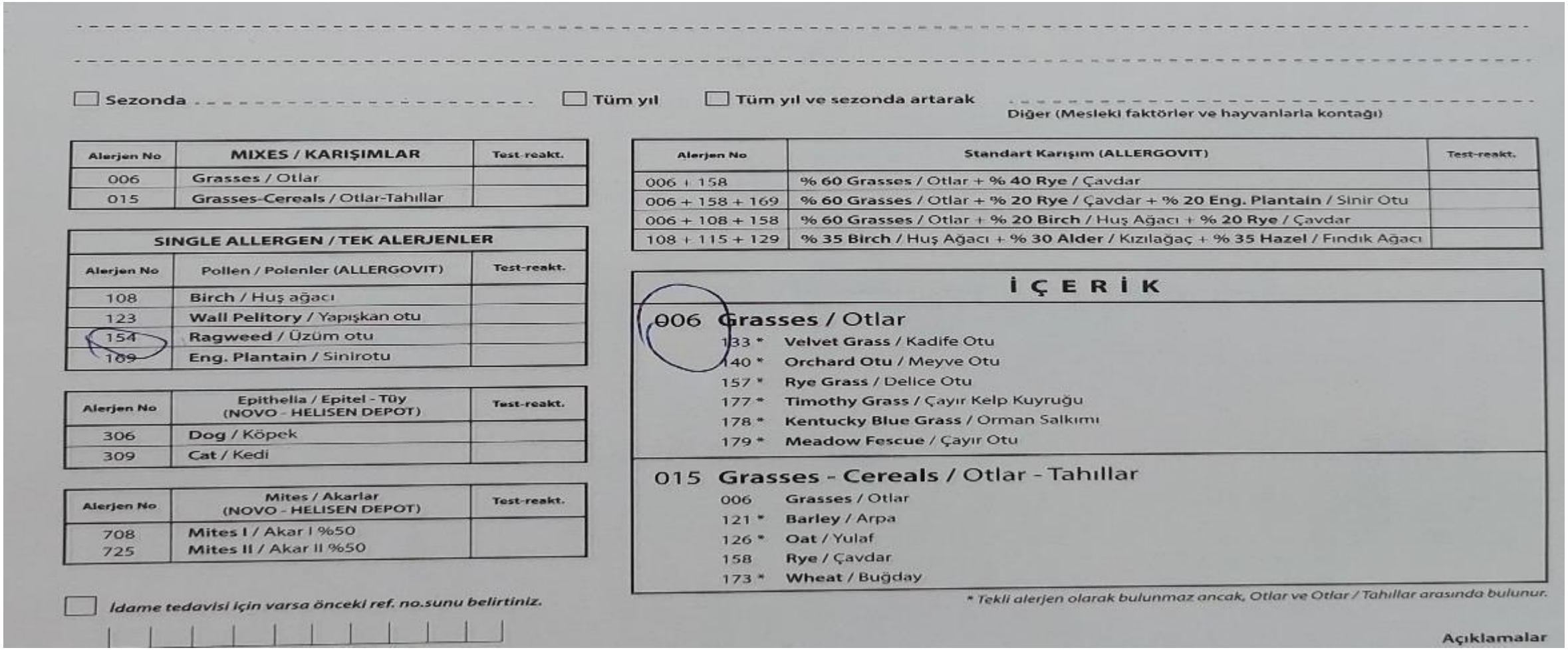
Cox et al Allergen immunotherapy: A practice parameter second update J Allergy. Clin.immunol

Başlıca polen aileleri, major allerjenler, pan-allerjenler ve çapraz reaksiyon

Polen ailesi	Major allerjen	Çapraz reaksiyon	Pan-allerjenler
Graminaceae Çayırgiller	Phl p 1, Phl p 5	Phl p 11 – Ole e 1	Phl p 12 (profilin) Phl p 7 (polcalsin)
Compositae Papatyagiller	Art v 1		
Ambrosia Ragweed;zaylan	Amb a 5	Amb a 1 – Art v 6 Amb a 4 – Art v 1 Amb a 6 – Art v 3	
Urticaceae Isırgan	Par j 2		
Plantaginaceae Sinirliotgiller	Pla l 1		
Fagales Kayıngiller: kayın, meşe, kestane	Bet v 1	PR-10 (besin)	Bet v 2 (profilin) Bet v 4 (polcalsin)
Oleaceae	Ole e 1	Ole e 1 - Phl p 11	
Cupressaceae	Cup a 1		

Eur Ann Allergy Clin Immunol. 2012;44(5):183-7

SCIT ‘DE KULLANDIĞIMIZ MEVCUT ALERJENLER



☐ Sezonda ☐ Tüm yıl ☐ Tüm yıl ve sezonda artarak

Diğer (Mesleki faktörler ve hayvanlarla kontağı)

Alerjen No	MIXES / KARIŞIMLAR	Test-reakt.
006	Grasses / Otlar	
015	Grasses-Cereals / Otlar-Tahıllar	

SINGLE ALLERGEN / TEK ALERJENLER

Alerjen No	Pollen / Polenler (ALLERGOVIT)	Test-reakt.
108	Birch / Huş ağacı	
123	Wall Pelitory / Yapışkan otu	
154	Ragweed / Üzüm otu	
169	Eng. Plantain / Sinirotu	

Alerjen No	Epithelia / Epitel - Tüy (NOVO - HELISEN DEPOT)	Test-reakt.
306	Dog / Köpek	
309	Cat / Kedi	

Alerjen No	Mites / Akarlar (NOVO - HELISEN DEPOT)	Test-reakt.
708	Mites I / Akar I %50	
725	Mites II / Akar II %50	

☐ *İdame tedavisi için varsa önceki ref. no.sunu belirtiniz.*

Alerjen No	Standart Karışım (ALLERGOVIT)	Test-reakt.
006 + 158	% 60 Grasses / Otlar + % 40 Rye / Çavdar	
006 + 158 + 169	% 60 Grasses / Otlar + % 20 Rye / Çavdar + % 20 Eng. Plantain / Sinir Otu	
006 + 108 + 158	% 60 Grasses / Otlar + % 20 Birch / Huş Ağacı + % 20 Rye / Çavdar	
108 + 115 + 129	% 35 Birch / Huş Ağacı + % 30 Alder / Kızılağaç + % 35 Hazel / Fındık Ağacı	

İ Ç E R İ K

006 Grasses / Otlar

133 * Velvet Grass / Kadife Otu
140 * Orchard Otu / Meyve Otu
157 * Rye Grass / Delice Otu
177 * Timothy Grass / Çayır Kelp Kuyruğu
178 * Kentucky Blue Grass / Orman Salkımı
179 * Meadow Fescue / Çayır Otu

015 Grasses - Cereals / Otlar - Tahıllar

006 Grasses / Otlar
121 * Barley / Arpa
126 * Oat / Yulaf
158 Rye / Çavdar
173 * Wheat / Buğday

** Tekli alerjen olarak bulunmaz ancak, Otlar ve Otlar / Tahıllar arasında bulunur.*

Açıklamalar

ALERJEN İMMUNOTERAPİ MEKANİZMA

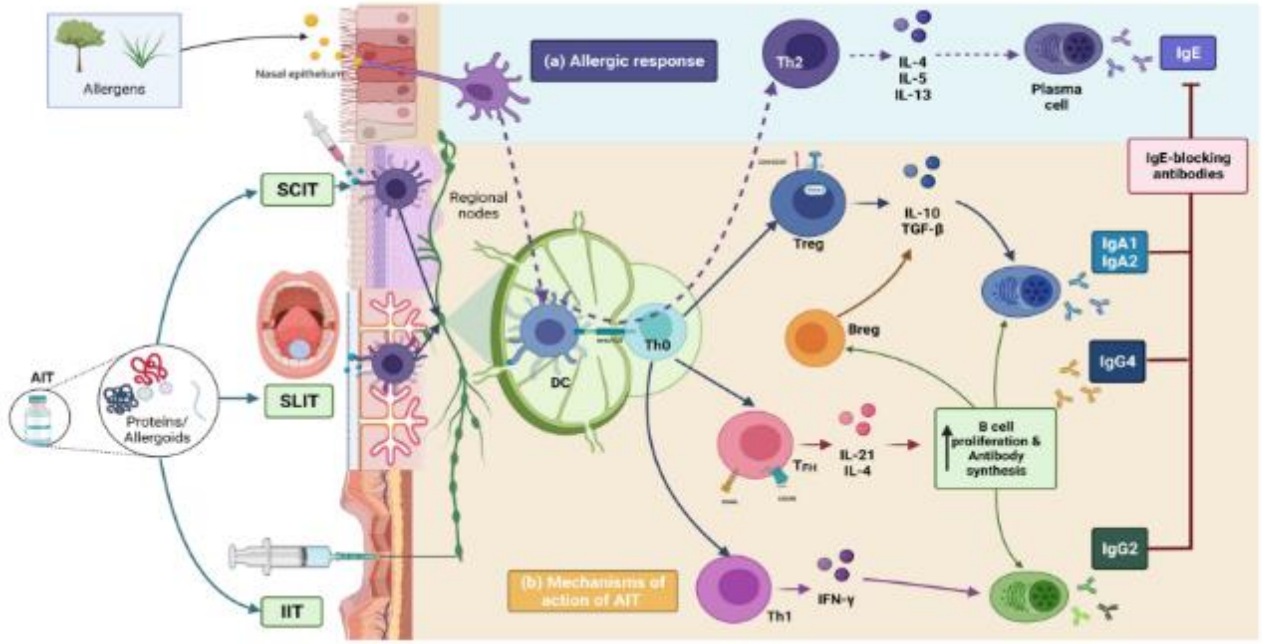


Figure 2. Mechanism of allergen-specific immunotherapy. (**a**) The allergic response begins with the allergen being endocytosed by the dendritic cells of the airway epithelium (DC). Subsequently, DC goes to local secondary lymphoid organs (lymph nodes) where the antigen presentation to Th0 happens. Th0 differentiate to Th2 and synthesize its interleukin profile to allow the production of IgE-type specific allergen antibodies. (**b**) Subcutaneous, sublingual, and intralymphatic immunotherapies (SCIT, SLIT, IIT) provides the antigen (peptide, recombinant, or protein complex) and induces T naive cells differentiation into different types, which synthesizes their interleukin profiles as Th1 (IFN-γ) or Treg Foxp3^{+} (IL-10 and TGF-β). TFH CXCR5^{+} (IL-21 and IL-4) profiles co-helping plasmatic cells to produce IgA1, IgA2, and IgG4 antibodies block against IgE-allergen specific.

AIT, GELECEK RİSKLERİN AZALTILMASI?

Alerjik astımda alerjen İmmunoterapi (AIT)

Semptom skorunu azaltır.

Subgrup

- Yaş:18 <ve 18> yararlı
- SCIT>SLIT
- 3yıl < ve> 3 yıl yararlı
- Hafif /orta astım :beklenen yarar (doğrulanmamış)
- Orta/ağır astım: olası yarar
- Ev tozu akarı, çayır poleni, kedi köpek : kanıtlanmış yarar
- Ağaç poleni: olası yarar, Mantar: yarar yok
- Monosensitize : kanıtlanmış yarar
- Polisensitize :olası yarar ((doğrulanmamış)
- Uzun süreli yarar: çalışma yok

İlaç skorunu azaltır

Subgrup

18 > doğrulanmış, 18<beklenen
SCIT doğrulanmış, SLIT beklenen
+
Yararlı
Beklenen yarar (doğrulanmamış)

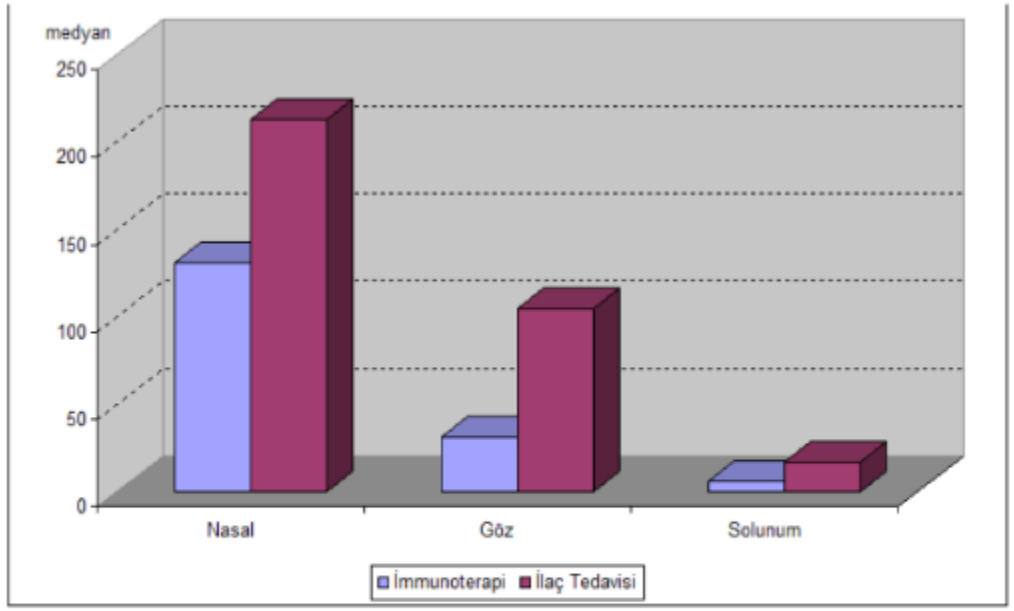
Ev tozu akarı, ağaç poleni: kanıtlanmış
Çayır poleni, mantar olası yarar
Monosensitize: olası yarar
Polisensitize: olası yarar
+

Astım kontrolü: kanıt yok
Atak: SCIT: kanıt yok, **SLIT azaltır**
FEV1 :kanıt yok
Alerjen Spesifik bronkoprovakasyon:
- **SCIT BHR'yi azaltır**
- SLIT: Değişiklik yok

Yaşam kalitesi: SCIT arttırır.
PEF:Açık bir fayda yok
FEF25-75:Faydalı
Nonspesifik Bronkoprovakasyon
Metakolinle BPT: etkili değil
Histaminle BPT :AIT lehine

Allergy. 2017;72:1825–1848.

Metakolin provakasyonu sonrası FEV1 değişimi SCIT kolunda azalıyor



Resim 1: Gruplara göre nasal, göz ve solunum semptom skoru ölçümleri

Tablo 2: Tedavi öncesi ve sonrasında Bronş Posprovakasyon sonrası FEV1 değişimlerinin karşılaştırılması.

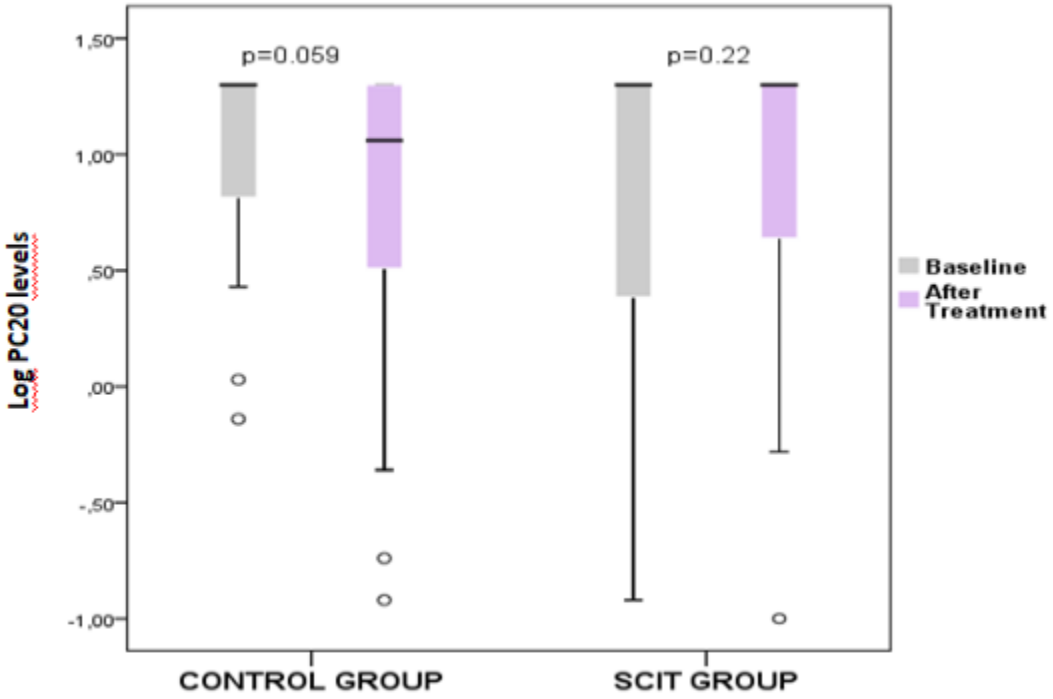
Bronş provakasyon sonu FEV1 değişimi	Gruplar		p
	İmmunoterapi (n=12)	İlaç Tedavisi (n=13)	
	Ort±SD (Medyan)	Ort±SD (Medyan)	
Tedavi öncesi	0,44±0,32 (0,40)	0,30±0,31 (0,20)	0,295
Tedav sonrası	0,29±0,45 (0,17)	0,28±0,29 (0,19)	0,936
Fark	0,15±0,41 (0,05)	0,026±0,20 (0)	0,354

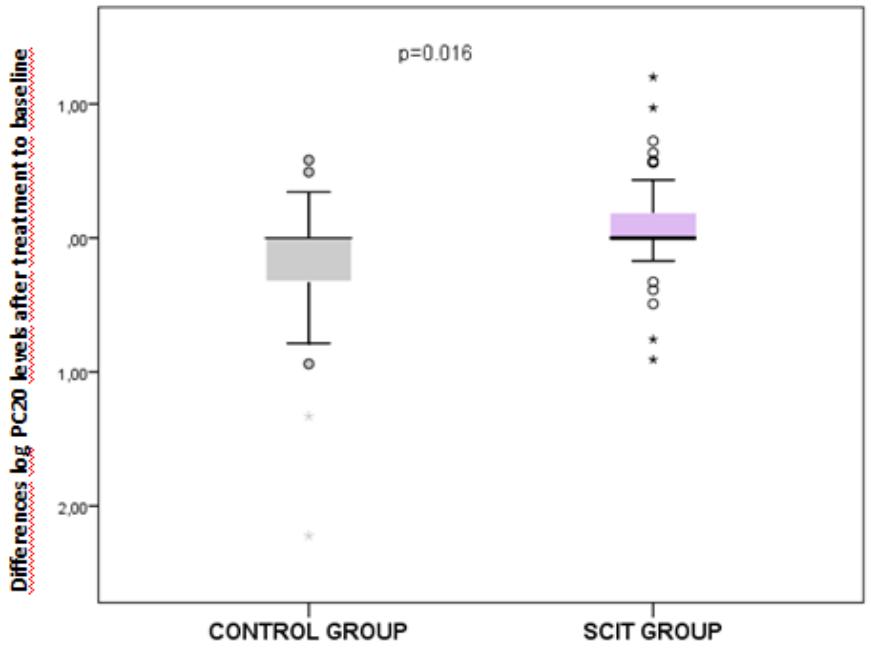
*Mann Whitney U Test

SCIT-BPT

	SCIT n=40			Control n=28		
	Baseline	**35 month⁺**	**p value**	**Baseline**	**30 month⁺**	**p value**
Symptom Score*	15.3	6.8	<0.001	10.6	8.9	0.061
Eosinophils (cell/mL)^	260	200	0.023	110	100	0.59
Eosinophils (%)*	4.1	3.4	0.057	2.8	2.6	0.72
PC20 (mg/mL)^	1.85	3.76	0.078	5.53	5.71	0.85
Log PC20 (mg/mL)*	0.84	0.91	0.22	1.02	0.81	0.059

SCIT log PC20'yi artırıyor





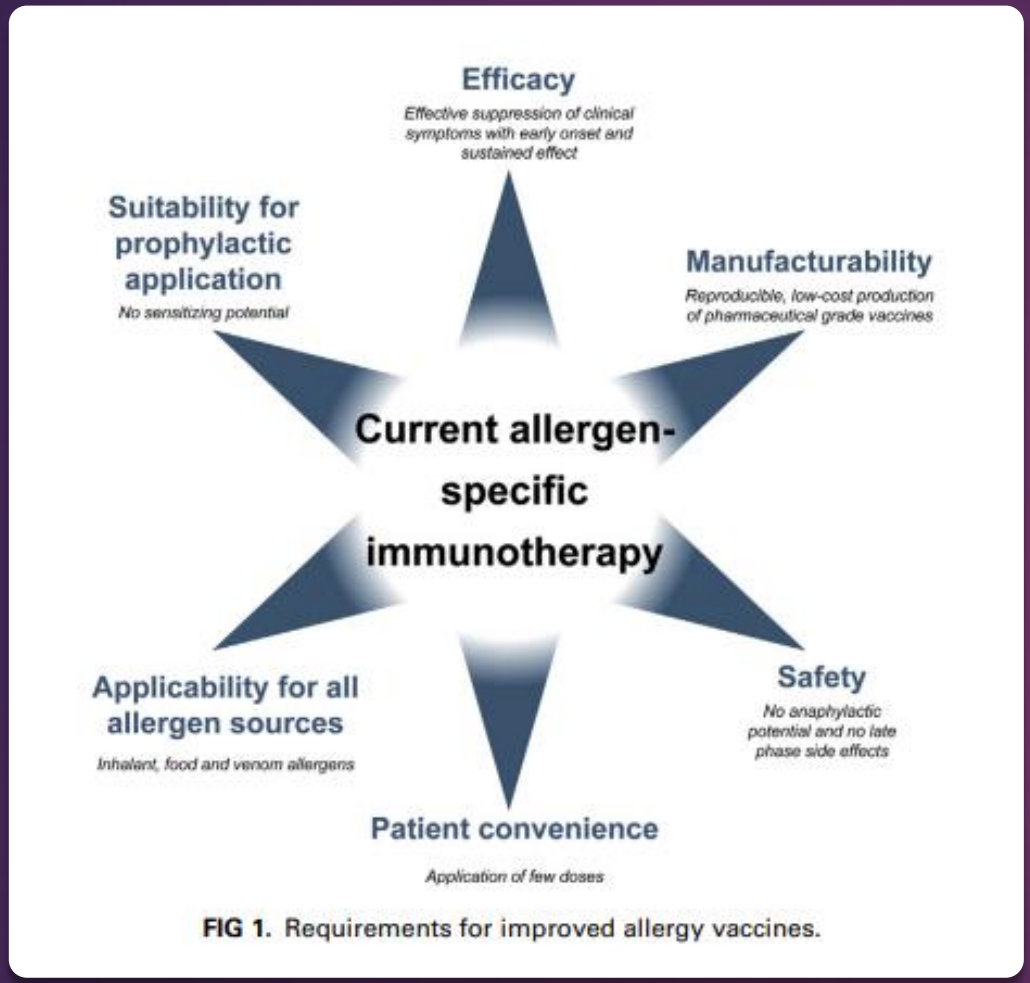


FIG 1. Requirements for improved allergy vaccines.

GELİŞTİRİLEN AŞILARDA İHTİYAÇLAR

TABLE 1 Some milestones in the development of AIT

1903	Pollen-specific antisera from immunized animals protect allergic patients from reactions	Dunbar[28]
1911	First desensitization with grass pollen extract	Noon[27]
1913	Vaccination by ragweed pollen extract	Clowes[29]
1921	Definition of components required for the development of an allergic reaction	Prausnitz and Küstner[30]
1927	First OIT attempt with pollen extract	Black[54]
1935	Suppression of allergen-specific skin reactivity by post-SCIT sera	Cooke et al[33]
1938	First AIT with Aluminum hydroxide-adsorbed allergen extracts	Sledge[38]
1940	Isolation and characterization of allergen-specific blocking IgG antibodies	Loveless et al[34]
1954	First double-blind, placebo-controlled AIT trial	Frankland and Augustin[58]
1966 1967	Discovery of IgE antibodies	Ishizaka et al[31] Johansson and Bennich[32]
1968	AIT long-term trial showing dose-effect of allergen mix and asthma reduction in children	Johnstone[59]
1964 1969 1977 1981	Modified allergen extracts with low allergenic activity (haptens, PEG modified, and allergoids)	Malley et al[39] Attallah and Sehon[40] Lee and Sehon[41] Marsh et al[42]
1976	Treatment of ragweed allergy by passive immunization with hyper gamma immunoglobulin	Rubinstein et al[35]
1981	AIT with allergoids	Norman et al[43]
1986	Low-dose SLIT for dust mite allergy	Scadding and Brostoff[55]
1996	First AIT with synthetic allergen-derived T-cell peptides	Norman et al[44] Simons et al[45]
1996	Plasmid DNA vaccination in mice	Raz et al[48] Hsu et al[49]
1999	Demonstration of long-term effects of AIT after discontinuation	Durham et al[61]
2002	Demonstration that AIT prevents the progression of allergic rhinitis to asthma	Möller et al[60]
2004	First AIT trial with recombinant hypoallergenic derivatives	Niederberger et al[62]
2005 2008	First AIT trials with recombinant wild-type allergens	Jutel et al[46] Pauli et al[47]
2006	AIT with Amb a 1 conjugated to a TLR 9 agonist	Creticos et al[51]
2012	Intralymphatic AIT with purified recombinant Fel d 1 hypoallergens	Senti et al[57]
2015 2016	First clinical safety and AIT studies with recombinant B-cell epitope-based grass pollen allergy vaccines	Niederberger et al[52] Zieglmayer et al[53]
2017	First clinical AIT study with a plasmid DNA vaccine	Su et al[50]
2017 2018	First clinical study with recombinant allergen-specific human IgG antibodies for passive immunization	Durham et al[37] Orengo et al[36]

SLIT

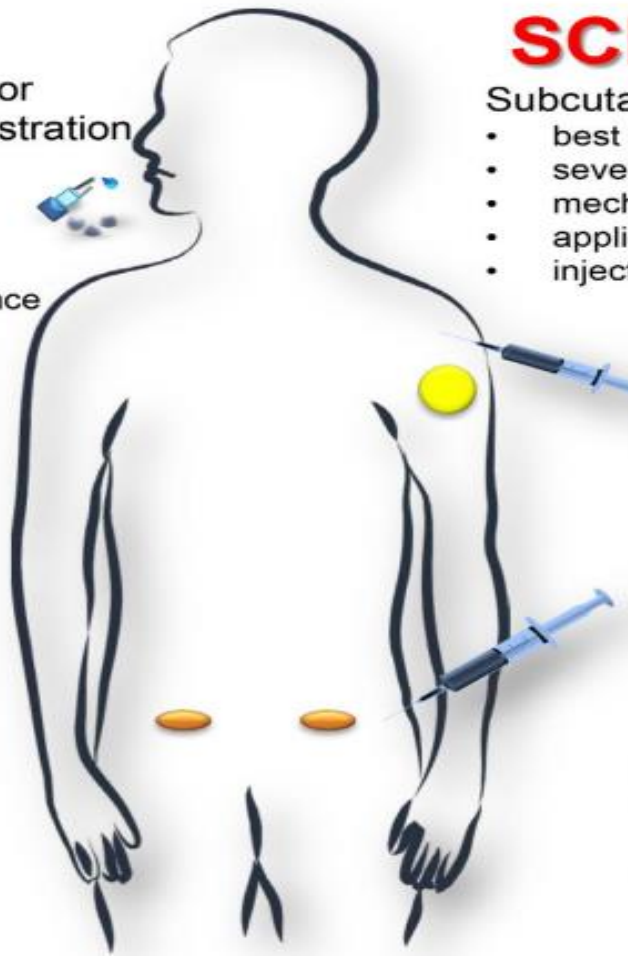
Sublingual application in form of drops or tablets under the tongue by self-administration

- clinical efficacy demonstrated in studies
- less effective than SCIT
- mechanisms are less well defined than for SCIT
- cumbersome treatment with low compliance
- applicable/available only for few allergen sources

OIT

Oral administration and swallowing

- effective only for few forms of food allergy but not for all other allergen sources
- high rate of side effects



SCIT

Subcutaneous injection

- best documented and effective AIT form
- severe side effects rare but possible
- mechanisms documented
- applicable for most allergen sources
- injection needed

EPIT

Epicutaneous administration on stripped skin

- experimental AIT form
- clinical efficacy not demonstrated

ILIT

Ultrasound-guided injection into subcutaneous lymphnodes

- experimental AIT form
- clinical efficacy partly shown
- ultrasound-guided injection needed
- advantage over SCIT not demonstrated

FIGURE 1 Routes for administration of AIT. Shown are different routes of administration for AIT and their features are mentioned

ALLERGOİD

Allergoids	Grass	Grazax ®	III	27% of reduction of drugs during the pollination season *vs.* placebo, and 31% reduction symptoms in median rhinoconjunctivitis symptom score.
		Allergovit®	II	6,000 TU of *Phleum pratense* reduce 26% of the TNSSS score.
				The accelerated high-doses escalation (10,000 TU/mL) is safe and tolerable in comparison to the standard escalation schedule (1,000 TU/mL).
				The comparison between the accelerated dose-escalation scheme group and the conventional dose escalation scheme group showed that TEAEs (intensity of treatment-emergent adverse effect) were similar between the 2 schemes, 43.4% of patients only reported mild TEAEs.
			III	Increased the levels of allergen-specific IgG2 and IgG4 and showed improvement of 48% in symptom medication score after the second year *vs*. placebo.
			III b	The 6-grass allergic AIT applied pre/intra/post-seasonal is safe. The symptom and medication score improved significantly 48.4% after the second year of treatment.
	Birch	Allergovit®Birch	II	Both dosages of 1,000 and 10,000 TU/mL induce IgG2 and IgG4 titers.
		Purethal®	IV	20,000 AUM of Purenthal induces an increase of 2–5 times of the levels of IgG and IgG4 for birch and Bet v 1 like to conventional AIT.

ALLERGOİD

- **Glutaraldehit veya formaldehit ile polimerizasyon** yoluyla kimyasal olarak modifiye edilmiş alerjenlerdir.
- Bu modifikasyon onlara daha **iyi immünojenisite özellikleri** verir, çünkü alerjenin polipeptit zincirindeki birincil amino gruplarıyla reaksiyona girerler.
- yüksek molekül ağırlıklı alerjenlerin molekül içi ve moleküller arası çapraz bağlı polimerler üretmesini sağlar
- İyi tanımlanmamış alerjen ekstratları içerir
- Mevcut standardizasyon prosedürlerinin çoğunun dayandığı IGE ve antikor epitoplarını kaybetmiştir. **IGE reaktivitesi azalır**
- **Kısa süre yüksek doz**

Allergoid ORAL LİYOFİLİZAT DİL ALTI tb (GRAZAX)

- Lizin gruplarının karbamilizasyonu
- Düşük molekül ağırlık
- Mukozadan emilen
- Monomeric allergoid of grup 5 Phleum pratense (Grazax® 75,000 standardized quality units)

ALLERGOİD TB -ÇALIŞMALAR

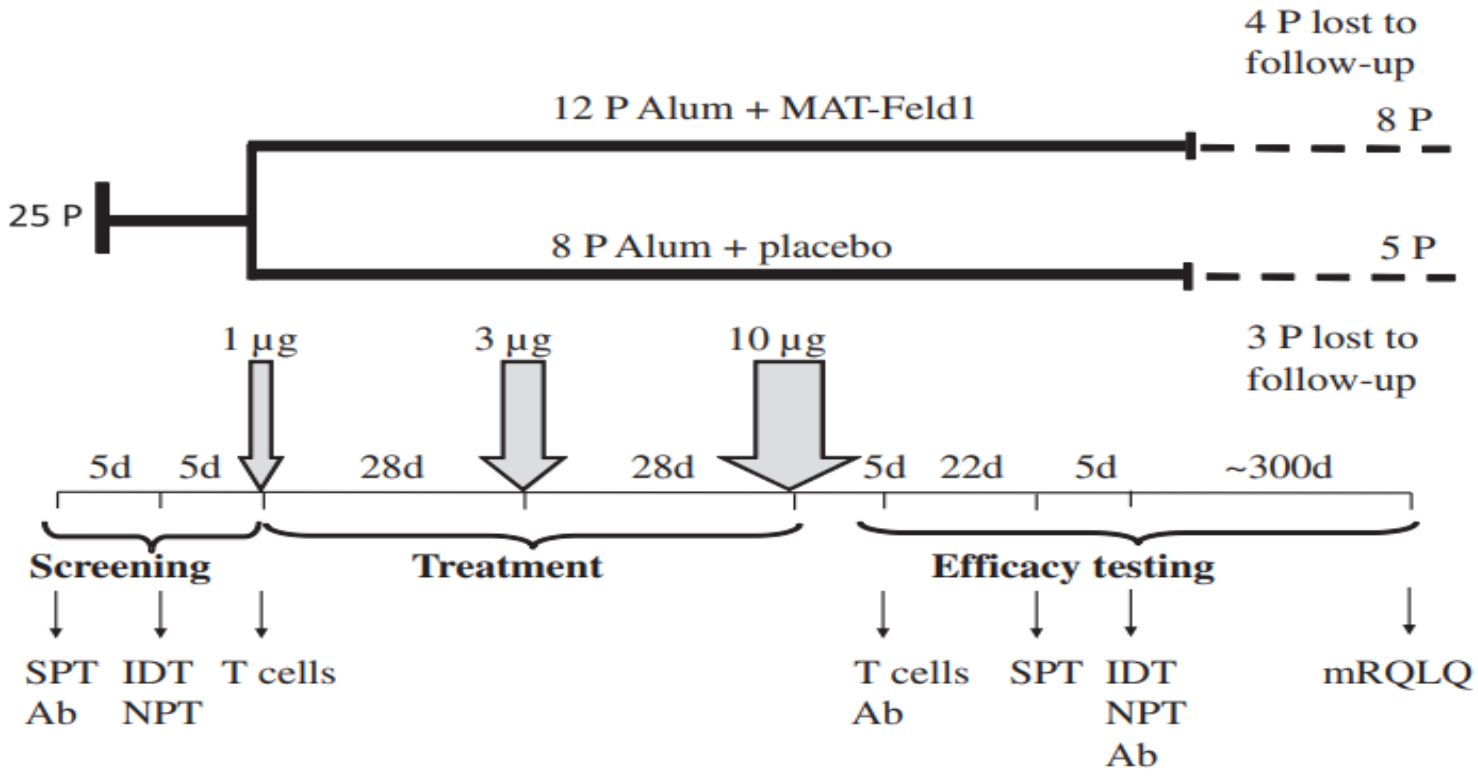
Appendix 4. Published trials of the treatment of grass pollen–induced allergic rhinoconjunctivitis.

Author	Method	Study participants				Outcomes	
						ve improve-n symptom	Relative improvement in medications score
V Bordignon (1994)	Double-blind, placebo-contr trial					*(p < 0.05)*	74.60% *(p < 0.001)*
C Caffarelli (2000)	Double-blind, placebo-contr trial					*(p < 0.01)*	n.s.
G Cavagni (1996)	Double-blind, placebo-contr trial					*(p < 0.01)*	22.63% *(p<0.05)*
C Lombardi (2001)	Open control trial					s: 17.27% *)* a: 60.47% *)*	Rhinitis: 55.55% *(p = 0.01)* Asthma: 68.43% *(p = 0.01)*
ML Pacor (1996)	Observational study	34		2 yrs	SLIT	*p<0.001*	n.s.
AG Palma-Carlos (2006)	Double-blind, placebo-controlled trial	17	16	2 yrs	SLIT vs. Placebo	*p<0.03*	*p<0.02*

Note: *n.s. = not specified*

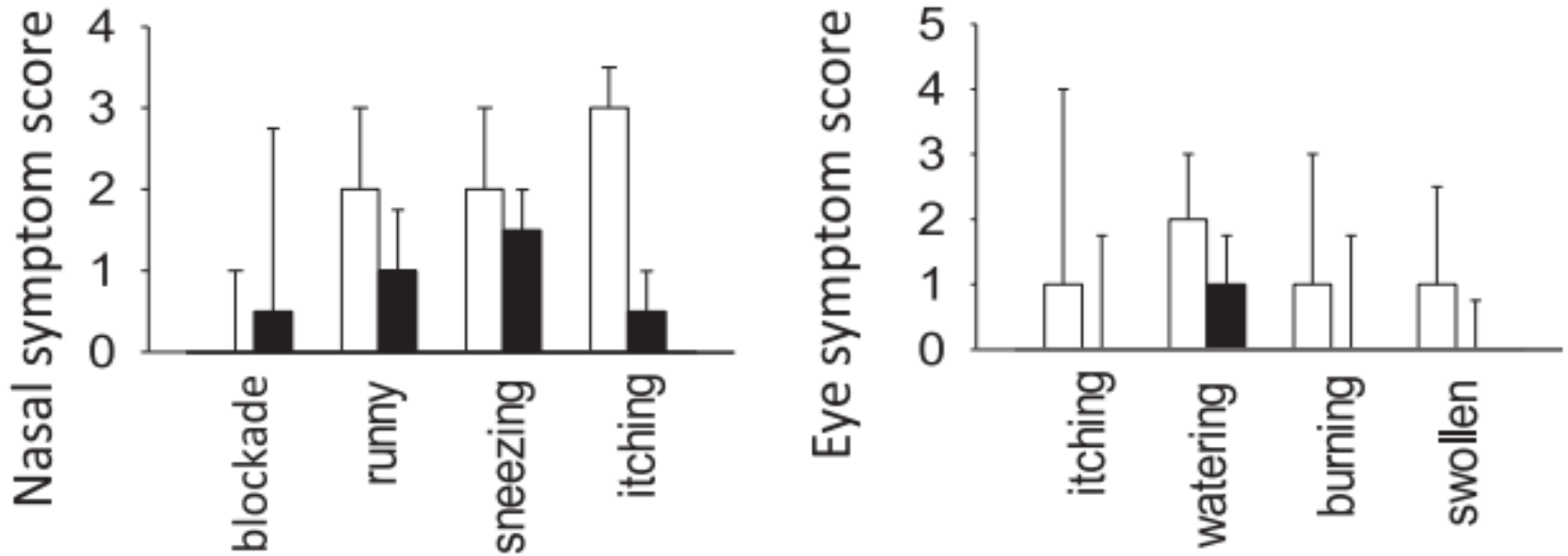
Alerjen spesifik IGE artar
Alerjen spesifik IGG 'de hafif ve geç (SLIT: 6 ay SCIT: 6 hafta) yükselme
UYUM? 3 yılın somunda %7
Maliyet 25tl/gün 3-4 dolar/gün

İntralenfatik (2012) modular antigen transporter (MAT)–Fel d 1



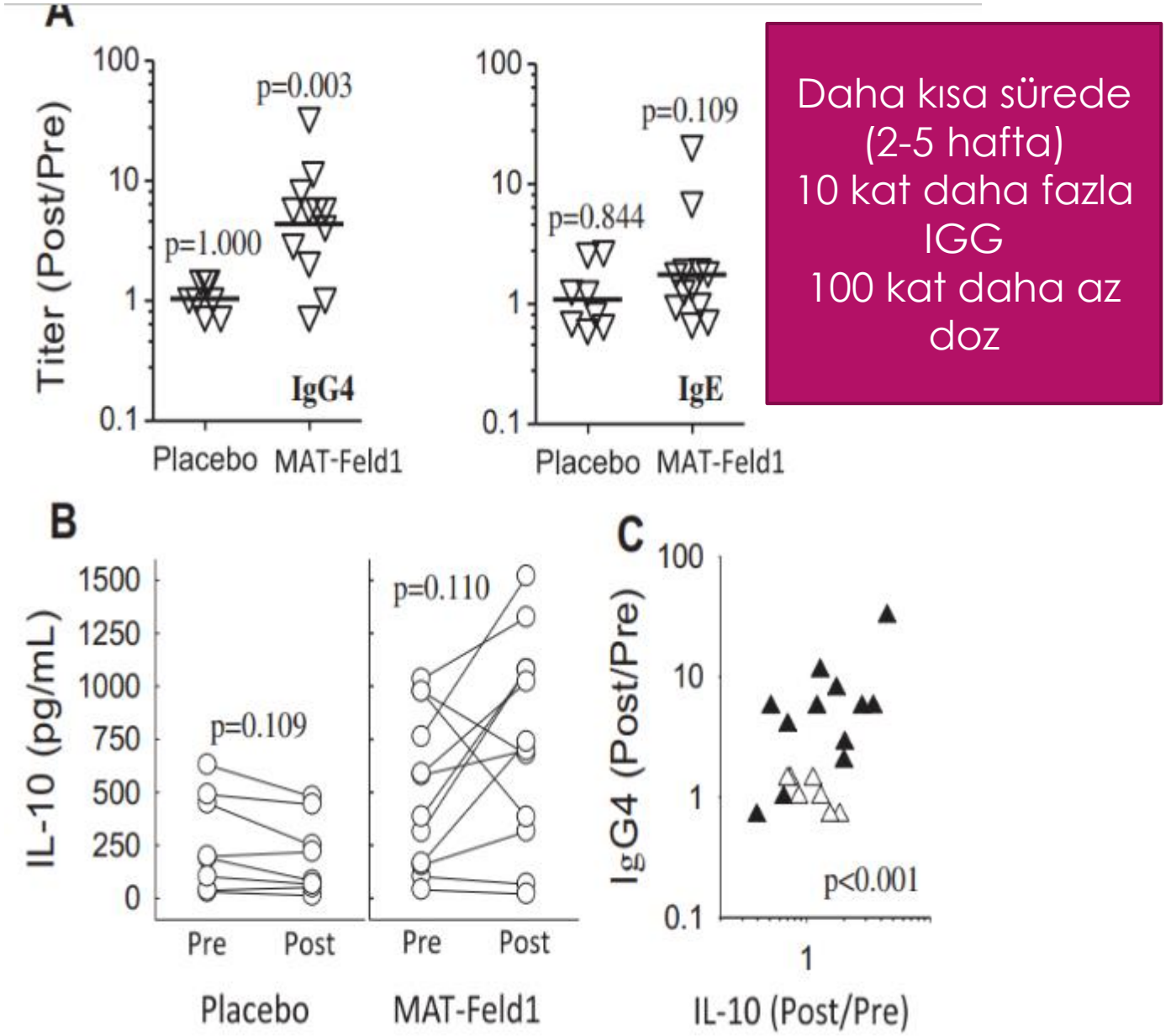
USG eşliğinde İnguinal bölgeye 25 gauge 1 ml hipodermik iğne 100uL

İntralenfatik IT klinik olarak etkin



J ALLERGY CLIN IMMUNOL MAY 2012

Intralenfatik IT tedaviden 5 hafta sonra immun tolerans oluşturmakta



Daha kısa sürede (2-5 hafta) 10 kat daha fazla IGG 100 kat daha az doz

Immunologic testing. A, Cat dander–specific IgG4 and IgE levels were analyzed at baseline (pre) and 5 weeks after final treatment (post). Changes (post/pre ratio) were analyzed by using a 2-sided exact Wilcoxon signed-rank test. B, Pretreatment and posttreatment production of IL-10 after in vitro restimulation of PBMCs with rFel d 1. The Welch t test was used to test the statistical significance between MAT–Fel d 1 and placebo treatment. C, Correlation between allergen-specific IgG4 titer changes with changes in IL-10 production for the combined MAT–Fel d 1–treated (solid triangles) and placebo-treated (open triangles) patients after Pearson correlation analysis (r 2 5 0.725)

J ALLERGY CLIN IMMUNOL MAY 2012

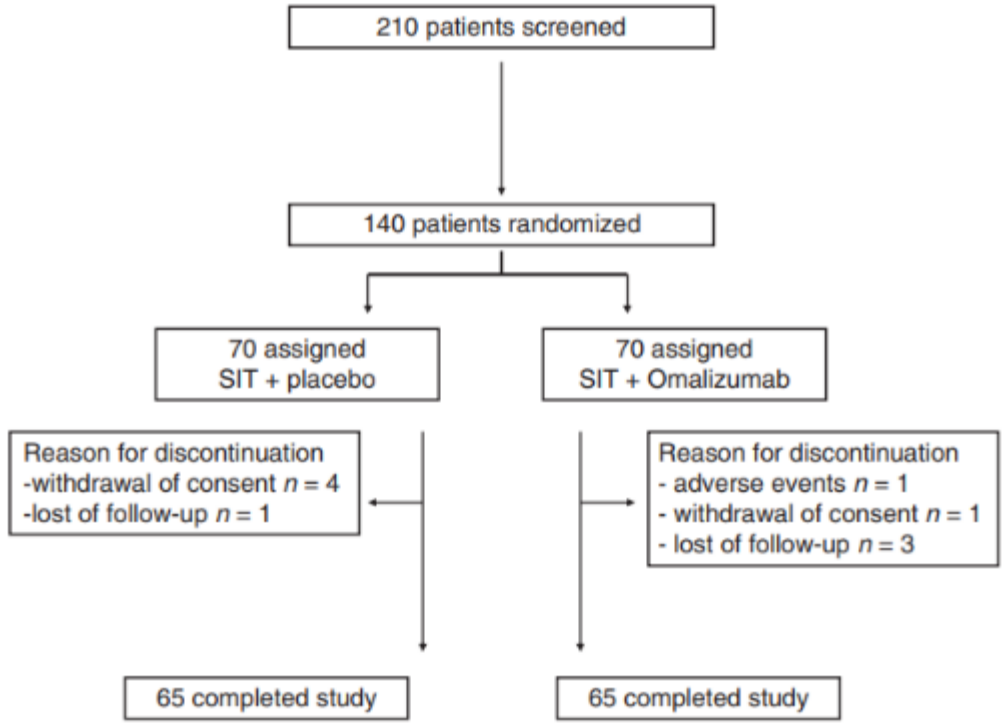
SCIT+OMALİZUMAB

Summary of allergoids, adjuvants, and recombinants used in allergen immunotherapy				
Type of molecule	Allergen	Brand	Clinical Phase	Efficacy
Subcutaneous/ Sublingual Immunotherapy	Xolair	Omalizumab	IV	Omalizumab plus AIT reduced symptoms by about 40% compared to AIT exclusive. Likewise, the combination improved the quality of life of patients with rhinoconjunctivitis and asthma.

Combination of omalizumab and specific immunotherapy is superior to immunotherapy in patients with seasonal allergic rhinoconjunctivitis and co-morbid seasonal allergic asthma

M. V. Kopp*, E. Hamelmann†, S. Zielen‡, W. Kamin§, K.-C. Bergmann¶, C. Sieder‖, S. Stenglein‖, S. Seyfried‖ and U. Wahn for the DUAL study group**

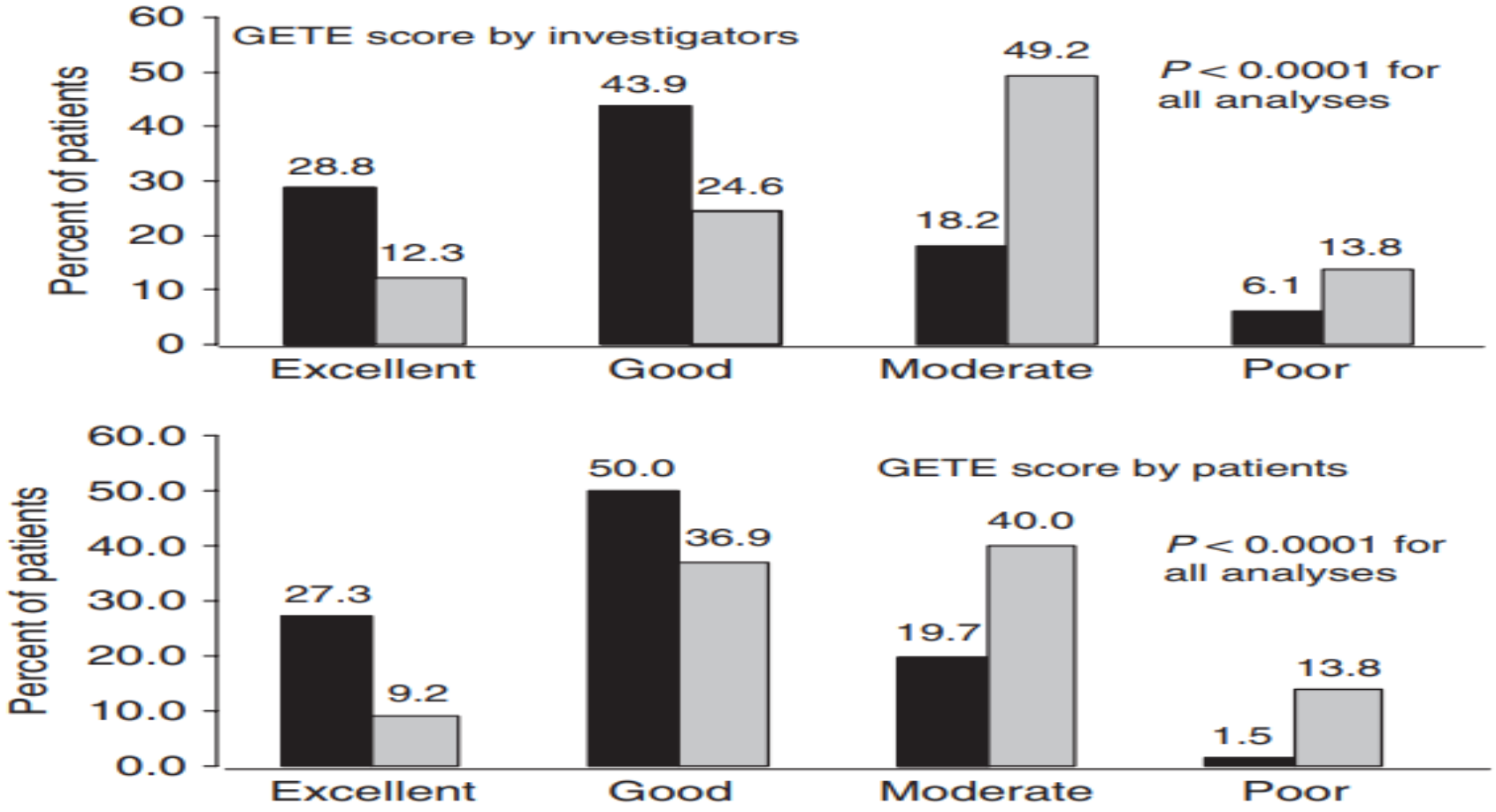
*Zentrum für Kinder- und Jugendmedizin, University of Freiburg, Germany, †Kinderklinik St Joseph Hospital, Ruhr-University of Bochum, Germany, ‡Klinik für Kinderheilkunde, University of Frankfurt, Germany, §Kinderklinik der Johannes Gutenberg-Universität Mainz, Germany, ¶Allergie-Zentrum-Charité, Berlin, Germany, ‖Novartis Pharma GmbH, Nuernberg, Germany and **Charité Virchow-Klinikum, Humboldt-University, Berlin, Germany



Sezonal A. Rinit ve sezonal kontrolsüz Astım(FEV1> %80)
Omalizumab/pl
Polen sezonundan 10 hafta önce
SCIT'den 2 hafta önce
Depigoid (grass)
Polen sezonundan 8 hafta önce
Rush İT
0,2-0,3ml 30 dk ara tek gün idame
4 haftada bir 0,5 ml
Toplam 16 hafta tedavi

Clinical and Experimental Allergy, 39, 271–279 c 2008

Astım responder oranı omalizumab kolunda daha fazla



Omalizumab kolunda Alerjik yan etki daha az

Ama istatiksel olarak anlamlı değil

Table 3. Adverse events in most frequently affected body systems (⩾5% in any group, safety population)

	Number of patients (%)	
	Depigoid+omalizumab	Depigoid+placebo
Patients studied, *n* (%)		
Total no. of patients with treatment	70	70
Total no. of patients with adverse events	36 (51.4)	38 (54.3)
Adverse events, *n* (%)		
General disorders and administration site conditions		
Local reaction	7 (10.0)	12 (17.1)
Application site reaction	2 (2.9)	4 (5.7)
Injection site pruritus	2 (2.9)	3 (4.3)
Injection site swelling	–	3 (4.3)
Infections and infestations		
Nasopharyngitis	8 (11.4)	9 (12.9)
Sinusitis	2 (2.9)	3 (4.3)
Respiratory, throracic and mediastinal disorders		
Cough	–	5 (7.1)
Nervous system disorders		
Headache	4 (5.7)	7 (10.0)

Table 2. Analysis of secondary efficacy variables (intention-to-treat population)

	Adjusted* mean					
Efficacy variable	Omalizumab	Placebo	Adjusted† treatment difference	95% confidence interval	*P*-value†	*P*-value*
Symptom severity	0.38	0.59	−0.21	[−0.35, −0.07]	0.0044	0.0157
Rescue medication	0.38	0.38	0	[−0.17, 0.17]	0.9807	0.2956
ACQ	1.63	1.96	−0.33	[−0.63, −0.03]	0.0295	0.0497
AQLQ	6.41	6.07	0.34	[0.04, 0.65]	0.0293	0.1093
RQLQ	1.80	2.11	−0.32	[−0.64, −0.01]	0.0537	0.0801

Omalizumab ile Semptom skoru (0-3;ortalama 0,5-1),
astım kontrolü ve yaşam kalitesi daha iyi

Kurtarıcı ilaç ihtiyacı farklı değil Antihist:1, nazal steroid: 3, sistemik steroid : 6
Salbutamol: 1, IKS: 3

YENİ İMMUNOTERAPİ MOLEKÜLLERİ

Antijenle fiziksel ya da kimyasal olarak reaksiyona girerek immun yanıtı arttıran moleküller

Table 1. Examples of new immunotherapy molecules.

Adjuvants	Hybrid Proteins	Recombinants
Aluminum	BTH2 (*Blomia tropicalis*)	MAT Fel d 1 (Cat)
Microcrystaline Tyrosine	DPx4 (*Dermatophagoides pteronyssinus*)	CatPAD (Cat)
Calcium Phosphate	MAVAC-BD-2 (*Blomia tropicalis* and *Dermatophagoides* sp.)	REGN1908 (Cat)
Toll-like Receptors		rBet v 1 FV (Birch)
Liposomes		rBet v 1 (Birch)
Virus Like Particles		BM32 (Grass)

TLR (TOLL LİKE RESEPTÖR)

Adjuvants	TLR	MPL®	I/II a	After ten weeks, patient groups that received SLIT with the highest MPL® developed the highest proportion of negative Grass allergen nasal challenge tests *vs.* placebo (47 and 44%, *vs.* 20%). Additionally, there were increased IgG levels and diminished IgE levels.
				Patients who completed the scheme recently (group 1), as well as those who completed it three years ago (group 2), had a reduction of five points in the weekly symptoms score. A great increase of IgG and IgG4 was observed in group 1, but the levels of group 2 were higher than placebo.
		AZD8848		Improved lung function in asthma patients. At 1 week after treatment, AZD8848 reduced the average late asthmatic response in FEV_1 by 27% compared to placebo. This effect lasted for four weeks after treatment.

TLR (Toll like reseptör)

Doğuştan gelen bağışıklığın temel bileşenleridir

istilacı patojenlere **(virüs bakteri mantar)karşı savunma**

Plazmanın içinde, hücre zarları ve hücre içi endozomlar,

Dendritik hücreler üzerindeki aktivasyon, adaptif bir bağışıklık

Alüminyum tuzları gibi geleneksel adjuvanların aksine, TLR agonistleri **net** bir anti-alerjik T lenfosit yanıtlarını destekleyen **immünomodülatör** profil.

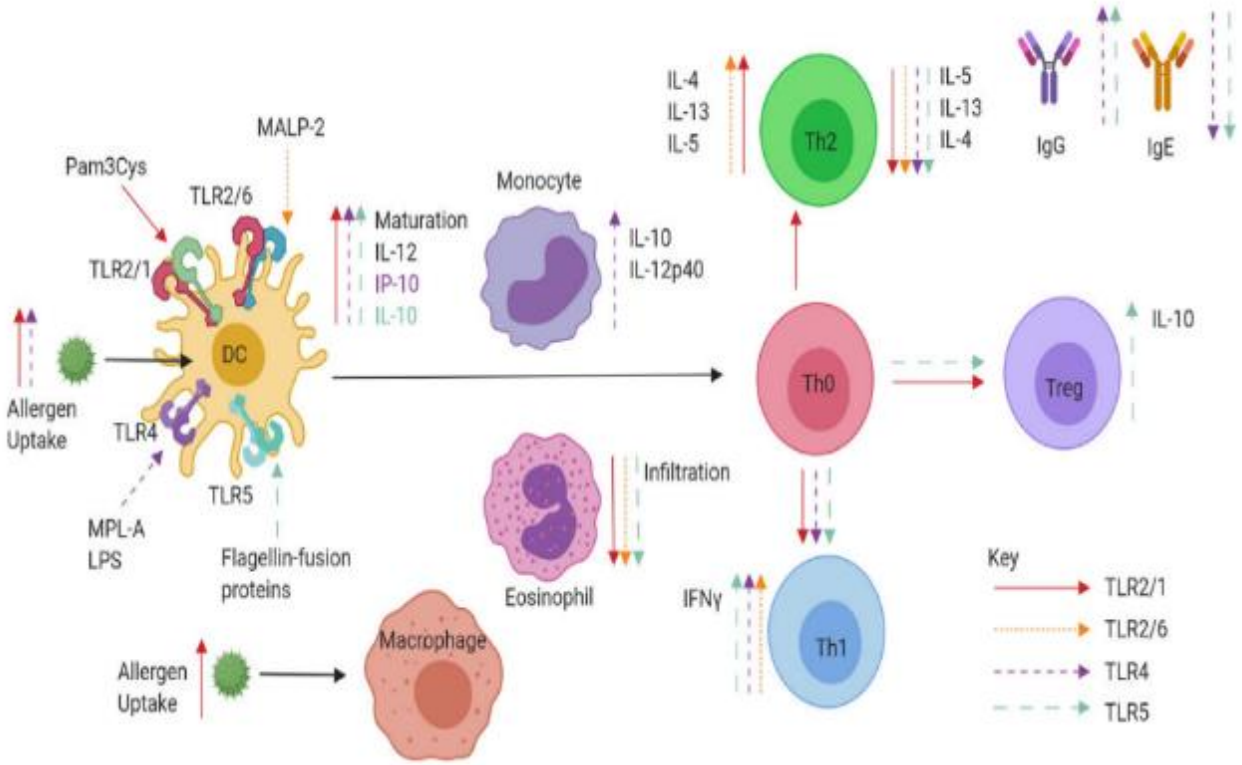


FIGURE 4 | Role of extracellular TLR agonists when administered in conjunction with allergen or conjugated to allergens in a fusion protein. TLR2/ (pink), TLR4 (purple), and TLR5 (blue) specific effects of tolerance induction. Ligand binding to TLRs on DCs can promote maturation, IL-10 and IL leading to priming of Naïve $CD4^+$ T helper cells. The promotion of IFNγ producing Th1 cells and IL-10 producing Tregs is observed, as well as incr decreases in IgE. Both decreases and increases in Th2 cell cytokine production are also observed.

TLR8/9 agonisti olan resquimod,palmiye polenine duyarlılaştırılmış A.R'li hastaların PMNL'de

- IFN-y (baskılayıcı) sentezini arttırır.

TLR2/6, Mycoplasma'dan türetilen bir lipopeptit tarafından uyarılabilir,

- Makrofaj Aktive Edici Lipopeptid olarak bilinir
- Th2 profilini azaltan
- BAL'da eozinofil sayısını azaltır
- Ancak Phleum bahanesine duyarlı hale getirilmiş faelerde T-reg hücreleri üzerinde etkisi yoktur

Bir fare alerji modelinde, füzyon proteinler rekombinant flagellin A (TLR5 agonisti) ve Bet v 1 (rFlaA:Betv1), rBet v 1'e kıyasla Th2 yanıtlarını azalttı ve alerjik duyarlılığı önlemiştir.

Monofosforillipid A (MPL), Salmonella hücre duvarının bir lipopolisakkariti olan bir TLR4 agonistidir.

- IFN-y ve IL-12 üretimini uyaran, ancak IL-5'i desteklemeyez
- Bir faz-I/IIa çalışmasında, MPL ve karışık çimen poleni ile tedavi edilen hastalarda düşük IgE seviyeleri ve düşük nazal reaktivite ile IgG'de bir artış geliştirdi.
- Benzer şekilde, Worm M. rolünü huş ağacı alerjisi ile değerlendirdi.ve MPL-huş uygulamasının
- **Bazofil aktivasyonunu Doğal alerjenlerle karşılaştırıldığında 100 kat daha fazla azalttığını gösterdi.**

MPL, grass duyarlı hastalarda **Pollinex Quattro allergoid** aşısına entegre edilmiştir.

- SCIT'in alternatif bir ultra kısa (dört mevsim öncesi enjeksiyonu) olan ,
- Semptomların azalmasının yanında **CD4+CD25+, Foxp3+ve IgG antikorları** artarken , IgE 'yi artırmaz;
- Kümülatif doz artırıldıktan sonra bile güvenliği tehlikeye atılmaz
- Pollinex'i bırakan hastalarda da benzer **Üç yıl sonra etkinlik devam etti**

MPL-Parietaria (üç yıl boyunca polen mevsiminden önce dört enjeksiyonluk bir şema) uygulanmış SCIT yolunun kullanılması, tedavinin kesilmesinden sonra beş yıla kadar klinik iyileşme göstermiş.

TLR9, bir rekombinant Chenopodium albümünü uyarmak için sitozin fosfat-guanozin (CpG) gibi TLR hücre içi agonistleri

- IL-10 ve IFN-y'yi arttırdı ve IL-4'ü azalttı.
- Sedire duyarlı hastalardan alınan B hücreleri, IL-5 ve IL-13 de azaltılmış

TLR'nin yeni agonistleri, **örneğinAZD8848-TLR7 ve bir faz-II'de astım hastalarında gelişmiş bir akciğer fonksiyonu gösterdi**

Bu bulgular TLR düzenlemesinin umut verici bir terapötik olabileceğini düşündürmektedir.

Doğal alerjen özlerinin dezavantajları

Çok sayıda tanımsız bileşen içerir, bunlardan bazıları alerjik immun yanıtı tetikleyebilir.

Önemli alerjenleri düşük miktarda içermesi veya içermemesi , kalitesiz

İstenmeyen materyaller veya alerjenlerle kontamine olabilir.

Hastanın duyarlılık profiline göre düzenlenemez, Yeni duyarlılıklara neden olabilir

Aşılar için uluslararası kalite standartlarına uymuyor

Farklı ürünler, firmalar arasında karşılaştırılamaz

Kesin olarak izlenmesine ve altta yatan mekanizmaların soruşturulmasına izin vermez.

Rekombinant alerjenlerin avantajları

Molekülleri tanımlanmış fizikokimyasal özellikleri temsil eder, karakteristik avantajları geliştirmek için immünolojik özellikler **modifiye** edilebilir.

Miktarlar, **kütle birimleri bazında kolayca kontrol** edilebilir

Potens ve oranlar her molekül için tam olarak ayarlanabilir

Saf molekülleri temsil

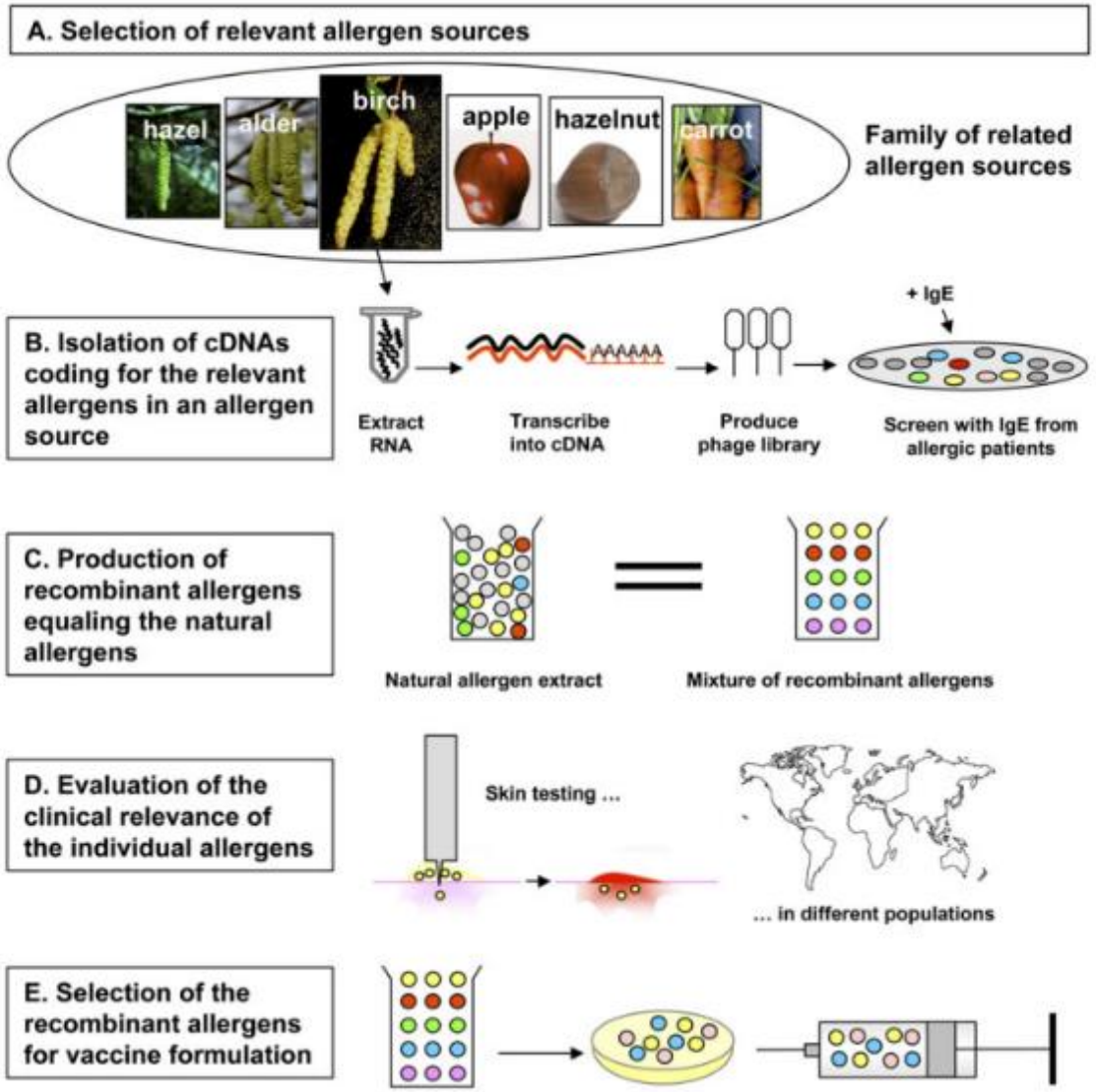
Aşılar hastaların duyarlılık profiline göre uluslararası kalite standartlarına uyar.

Ürünler, firmalar tutarlı ve tekrarlanabilir olması için tam olarak **karşılaştırılabilir**

Mekanizmaların hassas bir şekilde izlenmesine ve **araştırılmasına** izin verir

Uygun farklı tedavi stratejilerine **tekrarlanabilir şekilde modifiye edilebilir**.

J ALLERGY CLIN IMMUNOL
APRIL 2007



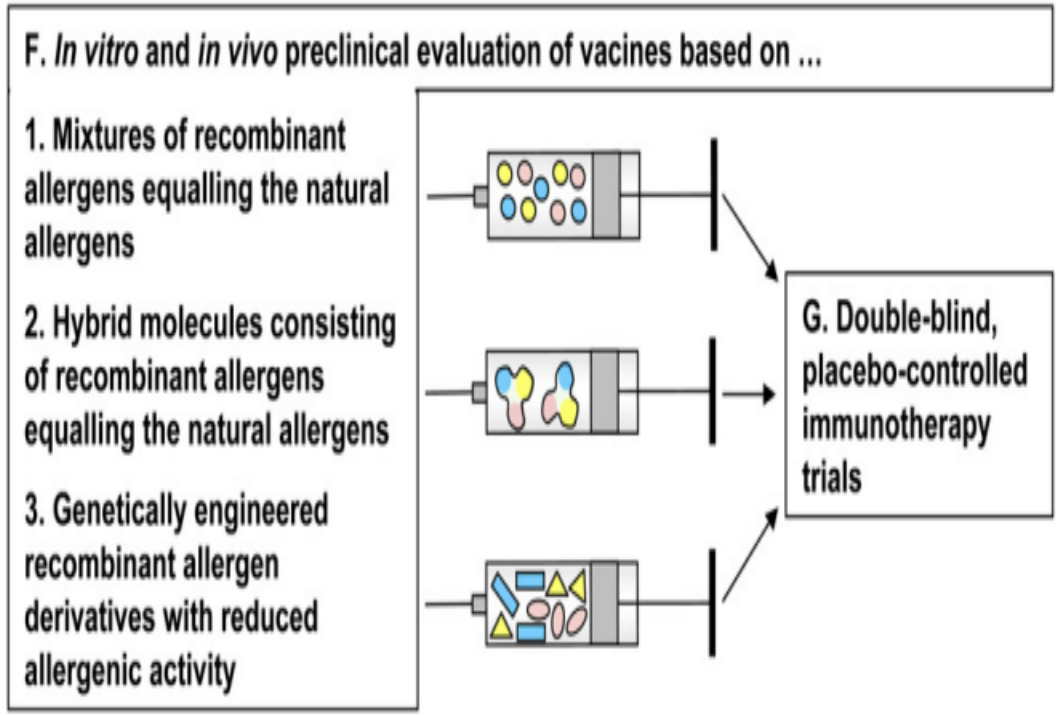
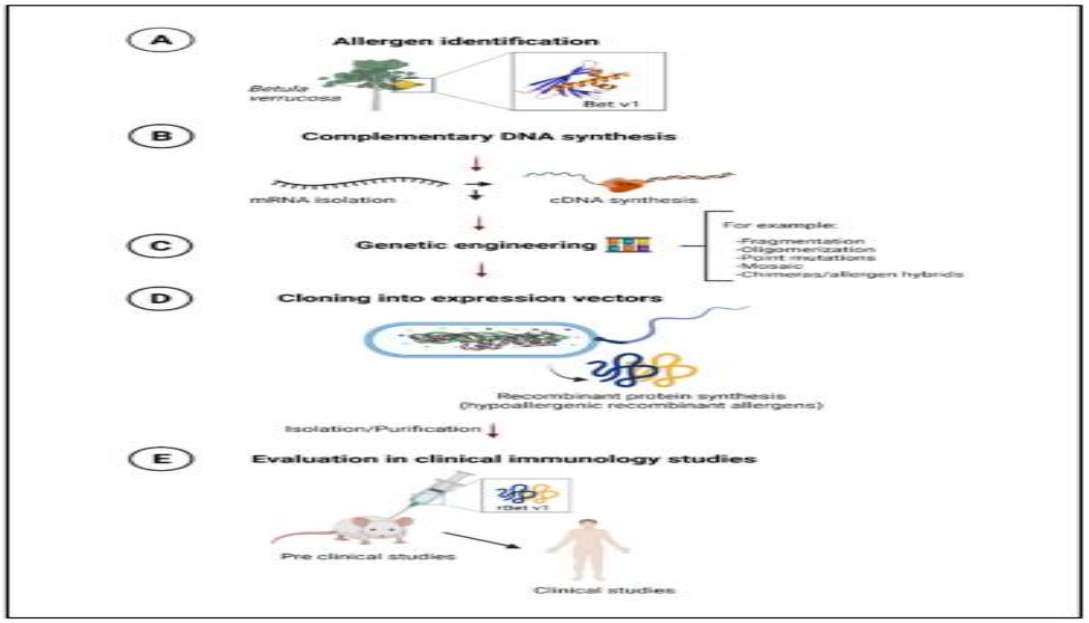


FIG 1. Steps toward recombinant allergen–based vaccines.

Rekombinant hipoalergen



Fragmentasyon
Oligomerizasyon
Mutasyon
Dizinin yeniden birleştrilmesi

IGE reaktivitesi az
T hücre aracılı geç reaksiyon?

Figure 3. Method for synthesizing recombinant allergens. **(A)** Identification of the amino acid sequence of the proteins associated with allergic symptoms (allergen); **(B)** Isolation of the messenger RNA through the use of the genetic code and creation of the successive complementary DNA (cDNA) with the reverse transcriptase enzyme constituting the specific gene for this protein; **(C)** Insertion of the cDNA sequence into the bacterial genetic material (*Escherichia coli*) and polymerization of the recombinant cDNA, **(D)** Insertion of the recombinant cDNA into the host microorganism with the subsequent synthesis of hypoallergenic recombinant allergens, **(E)** Evaluation in clinical-immunology studies.

Rekombinant alerjen İT

Recombinants	Birch		II	Induced the synthesis of IgG mainly of allergen-specific IgG1, IgG2, and IgG4 after treatment and subtle induction of allergen-specific IgA and IgM.
			II	Tablets of rBet v 1 (12.5-50 mcg) decreased 17% of the symptoms during the pollination season, through ASS.
			III	A maintenance dose of 80 mcg of rBet v 1 FV reduces the total symptom score around 80% in comparison to placebo.
	Grass		IIb	BM32 increases 25% the quality of life during the pollen season in the first year and 31% in the second year.
			II	BM32 induced grass pollen allergen-specific IgG antibodies and HBV-neutralizing response.

Rekombinant wild-hipoalerjenik alerjenler SCIT çalışmalar

TABLE II. Immunotherapy trials with recombinant allergen-based vaccines

Molecules	Allergen source	Treatment groups	No. of patients	Application	Adjuvant	Study design	Ref
Type I recombinant wild-type allergen							
rPhl p 1+rPhl p 2+ rPhl p 5a+rPhl p 5b+ rPhl p 6	Grass pollen	Allergen mix, placebo	n = 62	Subcutaneous	Alum	DBPC, randomized, single-center	25
rBet v 1	Birch pollen	rBet v 1, nBet v 1, birch pollen extract, placebo	n = 147	Subcutaneous	Alum	DBPC, randomized, multicenter	27
Type II recombinant hypoallergenic allergen derivatives							
rBet v 1 fragments rBet v 1 trimer	Birch pollen	rBet v 1 fragments, rBet v 1 trimer, placebo	n = 124	Subcutaneous	Alum	DBPC, randomized, multicenter	16, 2
rBet v 1-FV	Birch pollen	rBet v 1-FV reference group birch pollen extract	n = 51	Subcutaneous	Alum	Open, single-center	24

Alum, Aluminium hydroxide; *DBPC*, double-blind, placebo-controlled.

J ALLERGY CLIN IMMUNOL APRIL 2007

HİPOALERJENİK REKOMBİNANT BET V1 FRAGMANT TRİMER

- 124 hasta (%40 pl, %30 fragment, %30 trimer)
- Sezon öncesi
- Sekiz s.c. içeren enjeksiyon
- Artan dozlarda (1, 2, 4, 8, 10, 20, 40 ve 80 ug protein)
- Bir ila iki haftalık aralıklarla veya placebo
- Antikor kasım aralık ve tedavi 1 yıl sonrası ocak

Table 1. Analysis of the IgG1–4 subclass reactivity and IgA and IgM responsiveness to Bet v 1

Ab class/ subclass	Placebo		Fragments		Trimer	
	Before	After	Before	After	Before	After
IgG1	0.159	0.152	0.152	0.566	0.188	0.836
IgG2	0.046	0.044	0.054	0.265	0.058	0.319
IgG3	<0.040	<0.040	<0.040	<0.040	<0.040	<0.040
IgG4	0.042	0.039	0.031	0.269	0.033	0.476
IgA	0.224	0.222	0.262	0.345	0.314	0.435
IgM	0.219	0.211	0.151	0.142	0.216	0.301

Mean OD values corresponding to the amount of Bet v 1-specific Abs are given for the three groups (placebo, $n = 27$; fragments, $n = 18$; and trimer, $n = 21$) before and after treatment.

ÇAPRAZ REAKTİVİTE ÜZERİNE ETKİSİ

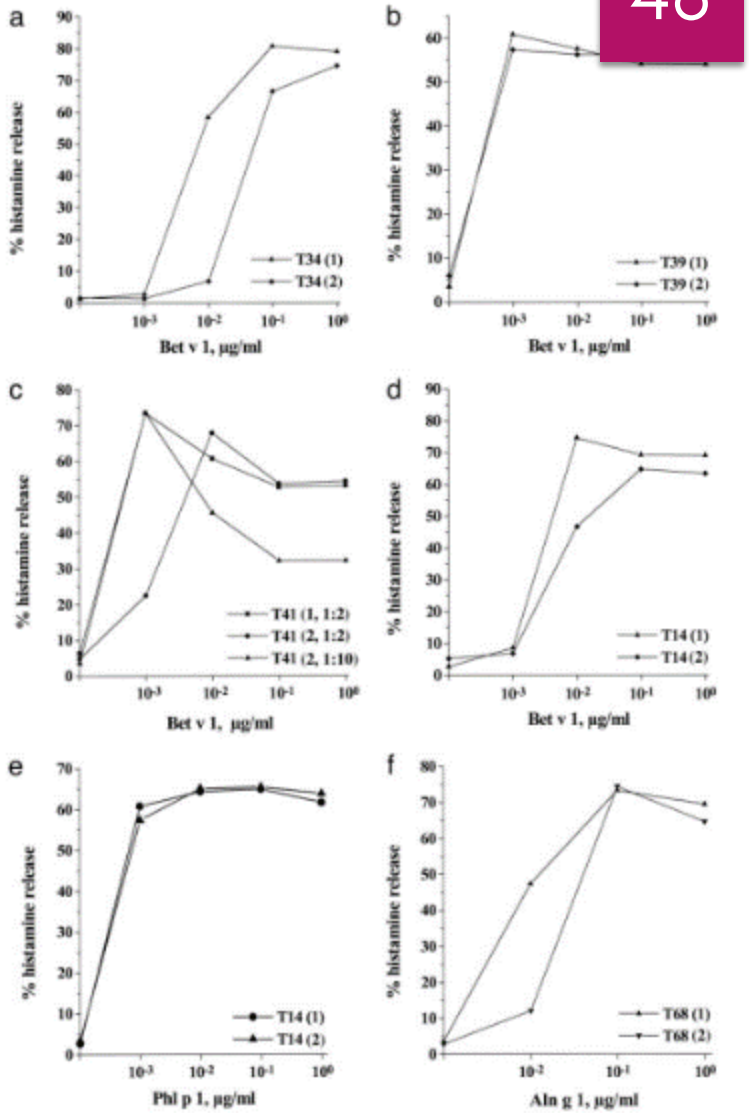
Table 2. Cross-reactivity of therapy-induced IgG1 Abs with major allergens

	Alder		Hazel		Celery		Carrot		Apple	
Group	Before	After	Before	After	Before	After	Before	After	Before	After
Placebo	0.125	0.121	0.086	0.082	0.048	0.043	0.087	0.084	0.087	0.081
Active treatment	0.067	0.439	0.056	0.312	0.048	0.140	0.066	0.127	0.050	0.191

Major allergens are as follows: alder pollen, Aln g 1; hazel pollen, Cor a I; celery, Api g 1; carrot, Dau c 1; and apple, Mal d 1. Results are given for patients showing improvement of their birch-pollen allergy-associated oral allergy syndrome ($n = 7$) vs. a randomly selected placebo group ($n = 7$). Mean OD values corresponding to the amount of allergen-specific Abs are given for the three groups before and after treatment.

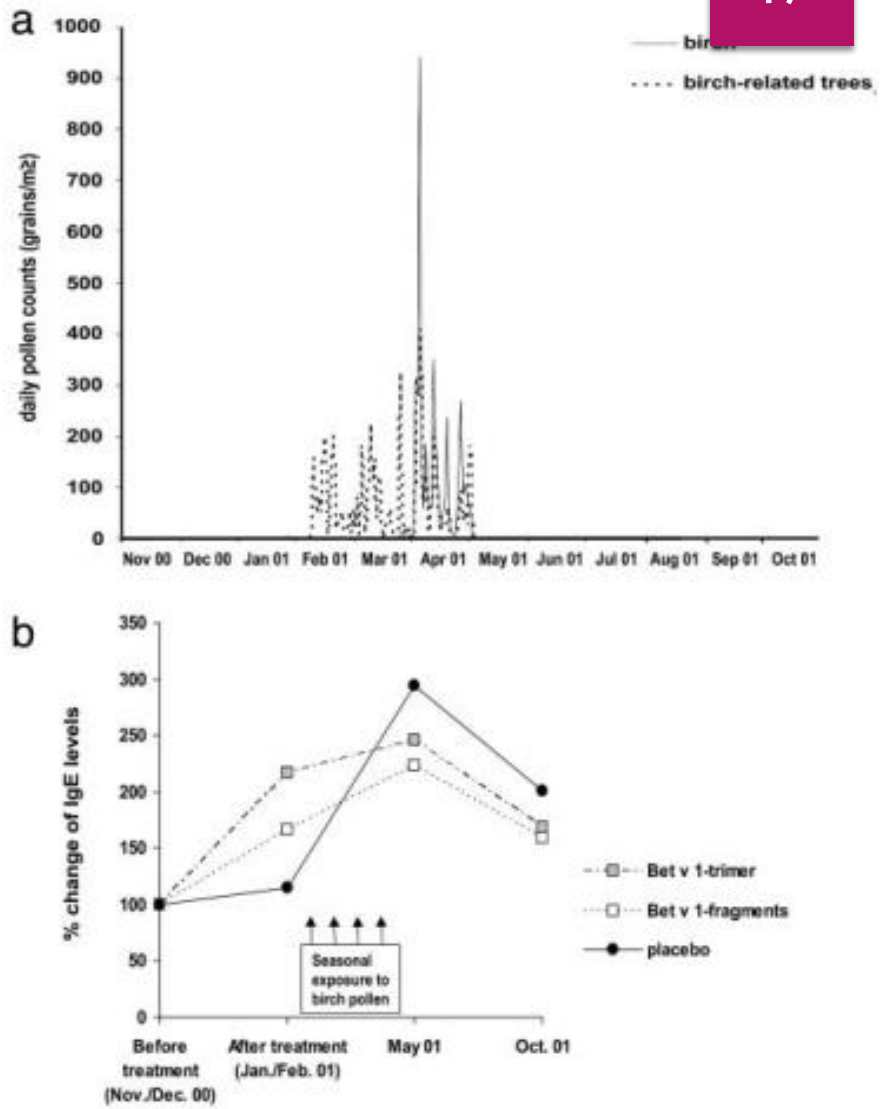
BAZOFİL HİSTAMİN SALINIM

▶Fig. 3. Therapy-induced Abs inhibit basophil histamine release in an allergen-specific manner. Basophils from birch pollen-allergic patients were exposed to different concentrations of rBet v 1, which were preincubated with sera from a trimer-treated (T34) (a) and placebo-treated (b) patient (T39) obtained before (1) and after (2) therapy. (c) Influence of preincubation of Bet v 1 with sera obtained from a trimer-treated patient (T41) before (1, 1:2 dilution) and after (2, 1:2 and 1:10 dilution) therapy on Bet v 1-specific histamine release. The effects of sera from a fragment-treated patient (T14) obtained before and after therapy on Bet v 1-induced (d) and Phl p 1-induced (e) histamine release are shown. The Bet v 1-cross-reactive allergen from alder pollen, Aln g 1, was preincubated with sera obtained from a fragment-treated patient (T68) (f) before (1) and after (2) therapy. The percentages of histamine release (y axis) for different allergen concentrations (x axis) are shown.



BET V1 SPESİFİK IGE

- Fig. 4. Reduction of IgE increases in vaccinated patients. (a) Exposure to birch pollen (solid line) and birch-related pollens (dotted line) (y axis: grains per m310) in Vienna between November 2000 and the end of October 2001. (b) Bet v 1-specific IgE levels. Percentages of alteration compared with the baseline before treatment (NovemberDecember 2000) in the three patient groups (placebo, n 27; fragments, n 18; trimer, n 21), after treatment (February 2001), after the birch pollen season (May 2001), and in October 2001 are given



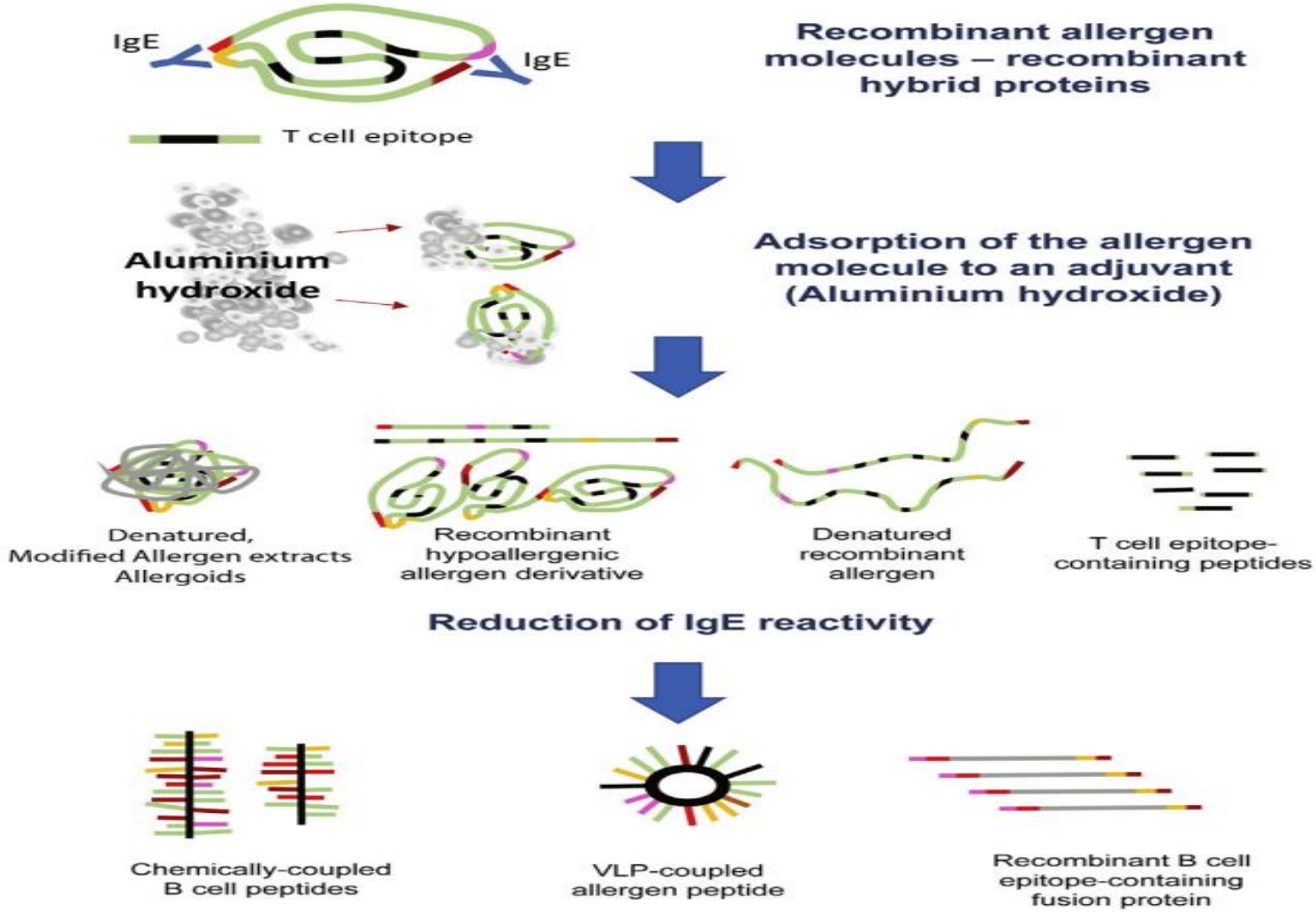


FIG 2. Steps toward improvement of allergy vaccines.

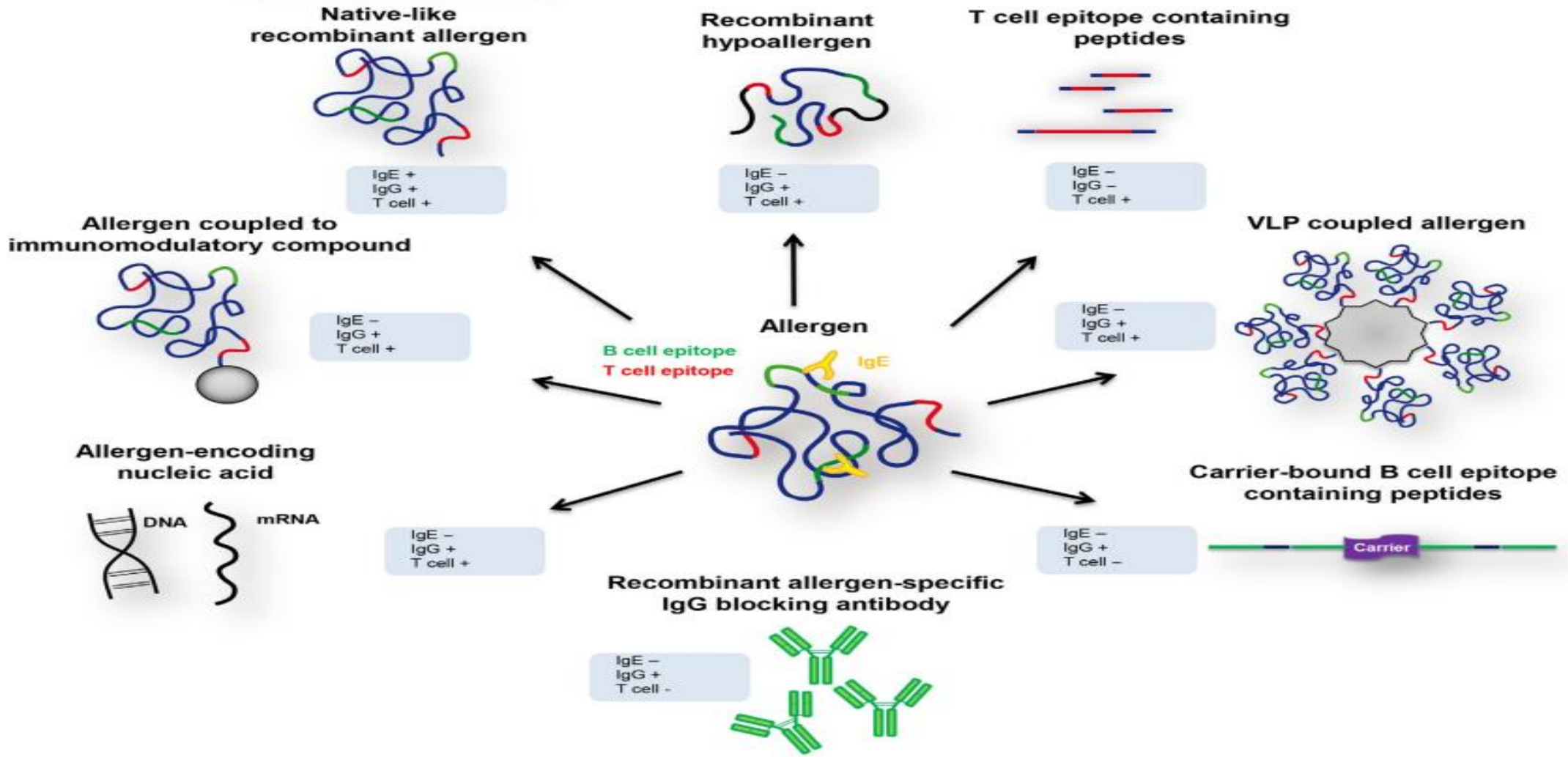
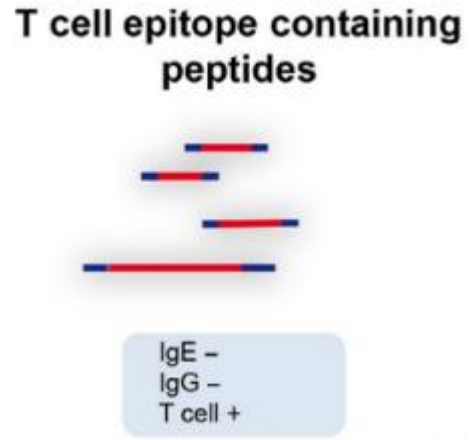


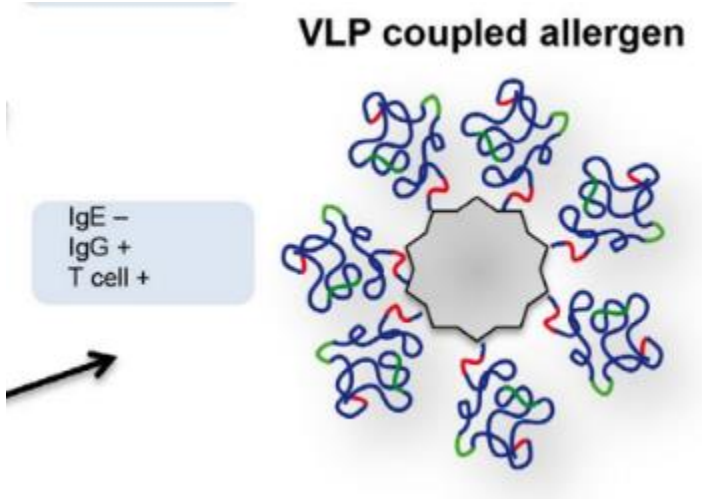
FIGURE 2 Molecular forms of AIT. Based on the knowledge of the DNA sequence and molecular structure of the disease-causing allergens different molecular AIT strategies have been developed. The different strategies comprise native-like recombinant allergens, recombinant hypoallergens, T-cell epitope-containing peptides, VLP-coupled allergens, carrier-bound B-cell epitope-containing peptides, recombinant allergen-specific IgG blocking antibodies, allergen-encoding nucleic acids, and allergens coupled to immunomodulatory compounds. The blue boxes inform about IgE- and T-cell reactivity of each component and its ability to IgG blocking antibody activity

T hücre epitop

- 1000'den fazla hastayı içeren bir faz III çalışmasında
- Büyük bir plasebo etkisi gözlendi ve
- Aktif tedavi plaseboya göre iyileşme elde edilmedi
- T hücresi epitopu içeren peptitler nispeten kısadır
- Alerjene özgü koruyucu IgG antikorlarını indükleyememiştir



VİRUS LİKE PARTİKÜL-ALLERJEN

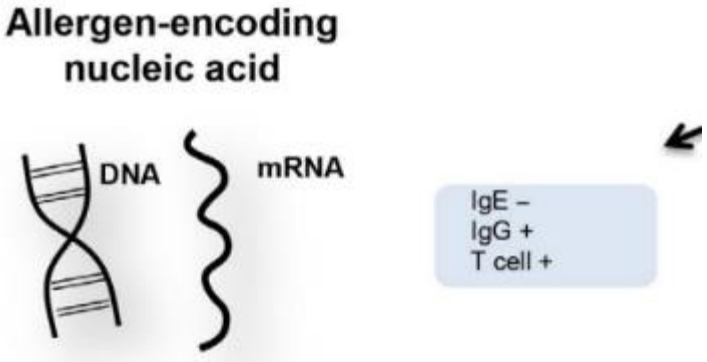


- **VLP epitopları saklayarak** alerjenik aktiviteyi azaltır.
- Büyük oligomerler mast ve bozofil hücrelerine zayıf bağlanır.
- İnsandan **Rhinovirüs** viral proteinler VP1, **hepatit B'**den PreS
- Alerjene spesifik IGG indüklenir
- Ayrıca virüse özgü antikorlar, **virüs nötralize edici aktiviteleri** bile vardı
- Birleştirmek zor tekrarlanabilir değil.
- **Virüs like nanopartikül (VLN)**: alerjen kodlayan cDNA, virüs kodlayan DNA'ya (Matrix proteini, p15MA)veya eksprese edilecek bir glikozil-fos phatidil inositol ankor alıcı dizisine kaynaştırılır.
  - **Preklinik Mugword polen alerji modelinde profilaktik** aşılamada başarılı
  - Klinik deneyim yok ancak bir çalışmada **alerjik olmayan denekler, alerjene özgü IgG'nin indüklendiğini gösterildi**

Allergy. 2021;76:131–149.

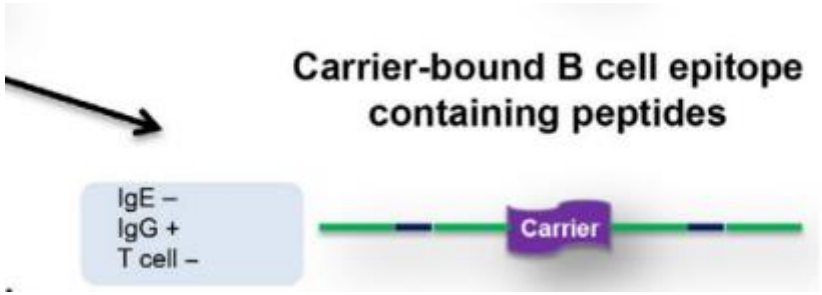
Alerjen kodlayan Nükleik Asit

- 20 yıl önce: alerjen kodlayan DNA
- Fare deneylerinde TH1 ve Alerjen spesifik IGG yi arttırmış
- **Kontrolsüz alerjen salınımı, alerjik yan etki fazla**
- Hipoalerjık DNA veya RNA
- Çalışma sonucunda immun yanıtı uyarıp uyarmadığı bilgisi yok



Allergy. 2021;76:131–149.

B hücre Epitop/BM32



- Taşıyıcıya bağlı B-hücresi epitopu içeren peptitler,
- Rekombinant hipoalerjenlerin daha ileri bir gelişimini temsil eder.
- Hepatit B'den türetilmiş **PreS proteinini** (alerjenik olmayan peptitlerin türetildiği bir taşıyıcı protein)
- **Alerjenlerin IgE bağlama bölgeleri kaynaşmıştır. Non IGE peptit**.
- Escherichia coli'de ekspresyon yoluyla rekombinant kaliteli tutarlı füzyon proteinleri
- **IGE aracılı ve T hücre aracılı reaksiyon azalır**
- **Devam ederek artan Spesifik IGG4 yanıtı**
- **Hepatit B den koruyucu**

Allergy. 2021;76:131–149.

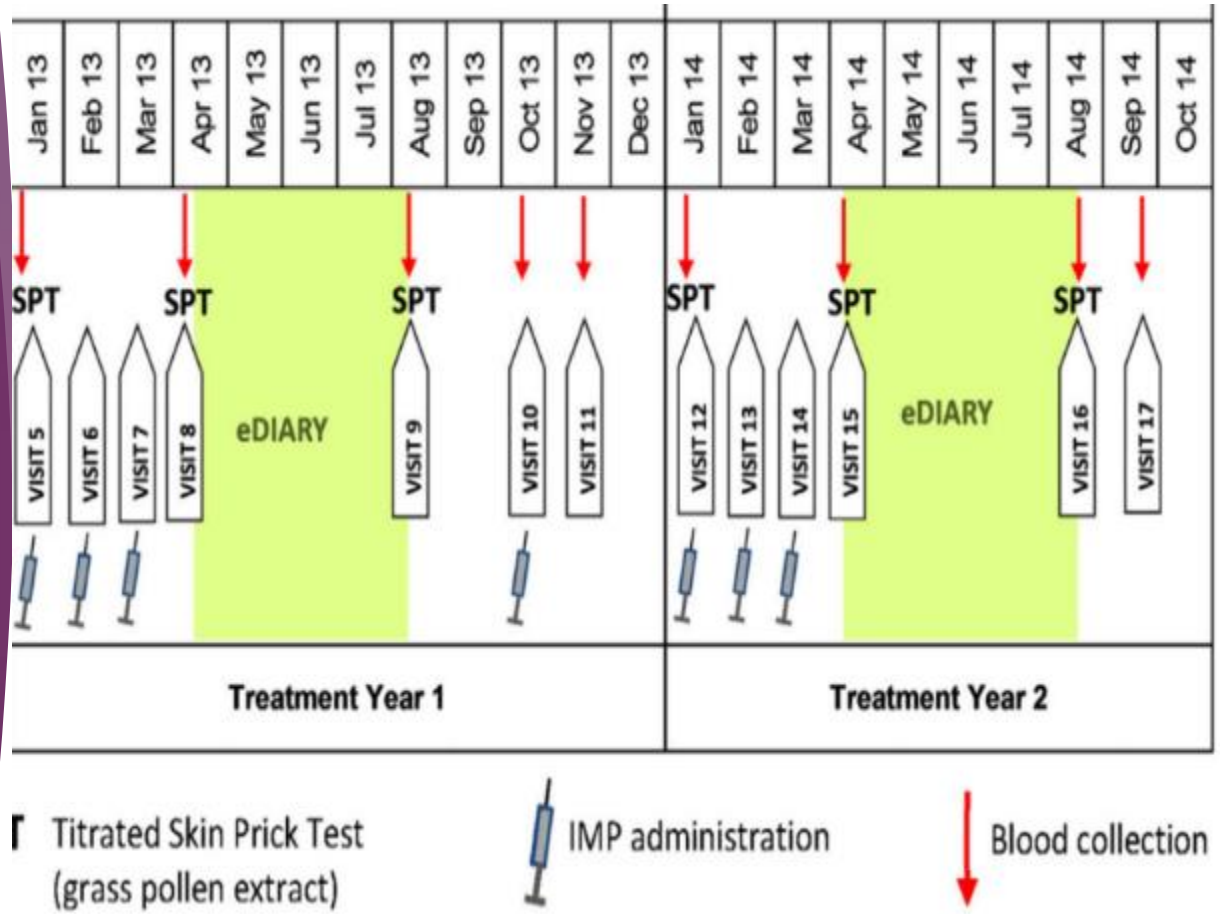
BM32 Çalışma

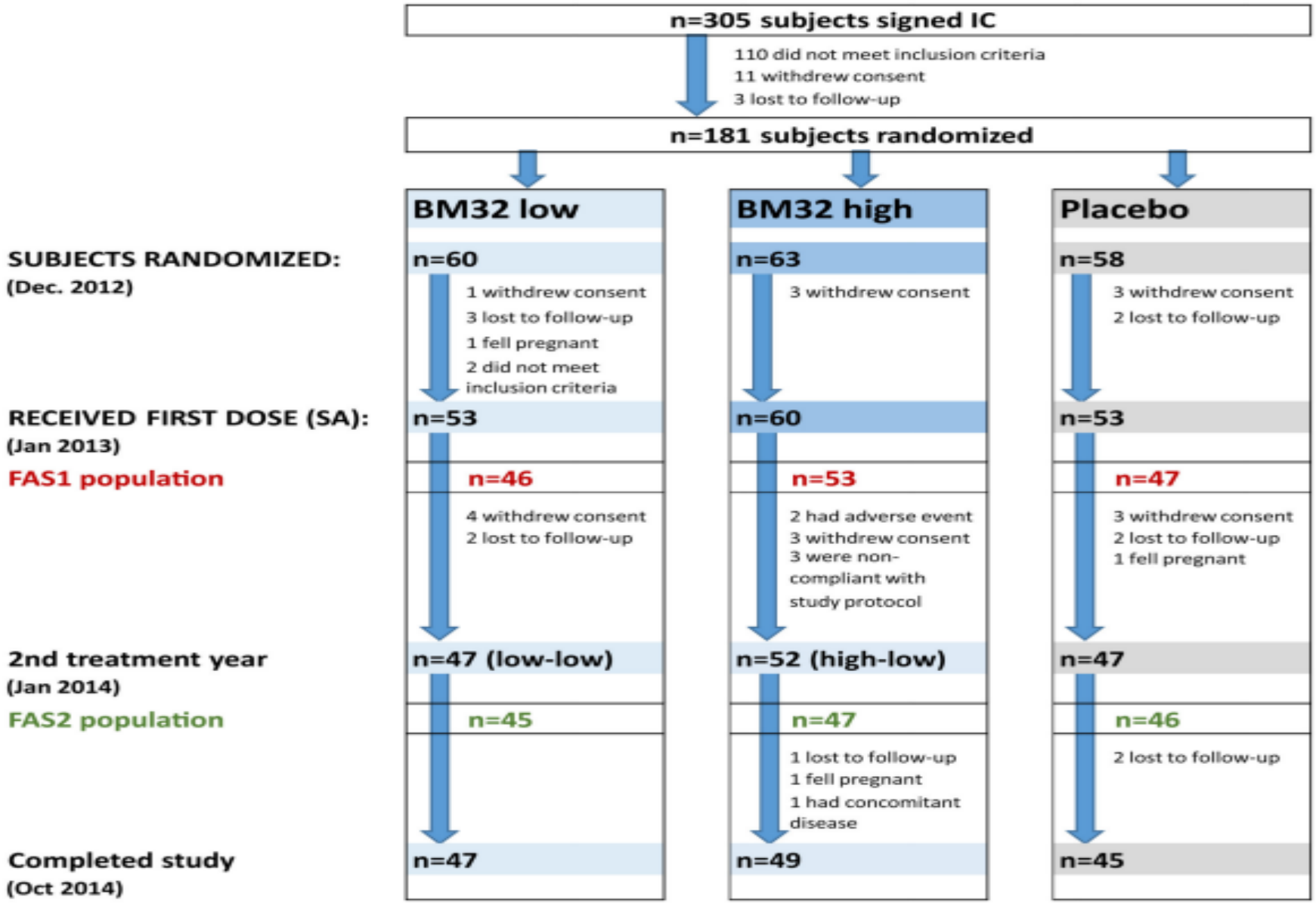
- Grass polen alerjenlerinden B hücre epitopları (Phlp 1, 2,5,6) Hipoalerjenik non IGE peptid

+

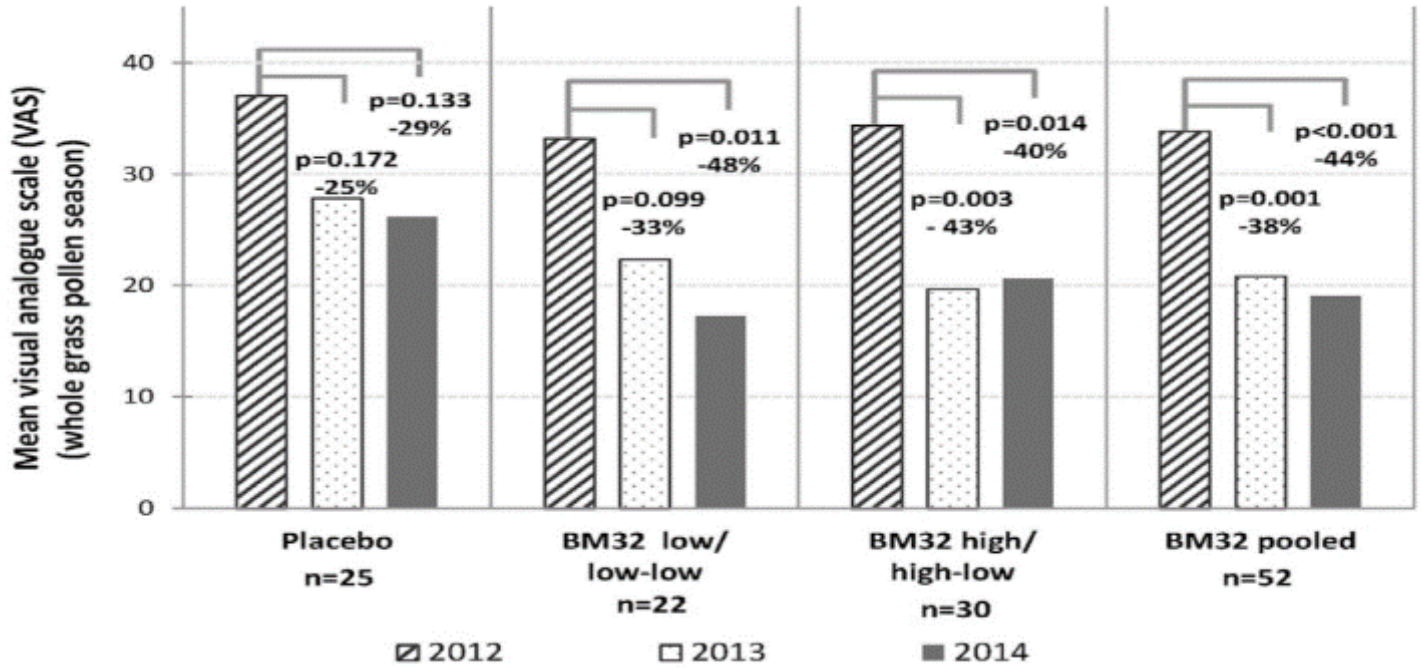
- Non alerjenik İmmunojenik taşıyıcı (Hepatit B virüs –Pre S)

Presezonal ocak-subat-mart 3 enjeksiyon
Ekim 1 enjeksiyon
Ertesi yıl ocak-subat-mart 3 enjeksiyon
Toplam 7 enjeksiyon
80ug/160ug/placebo

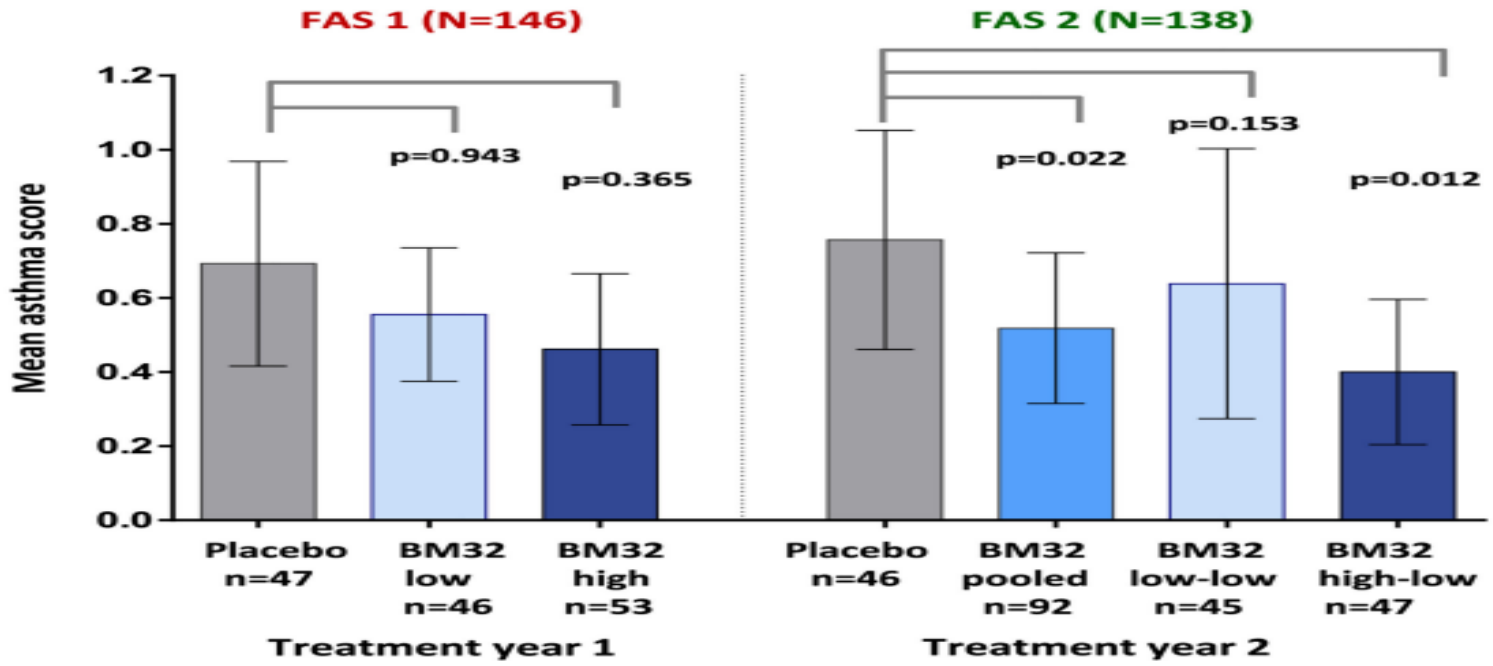


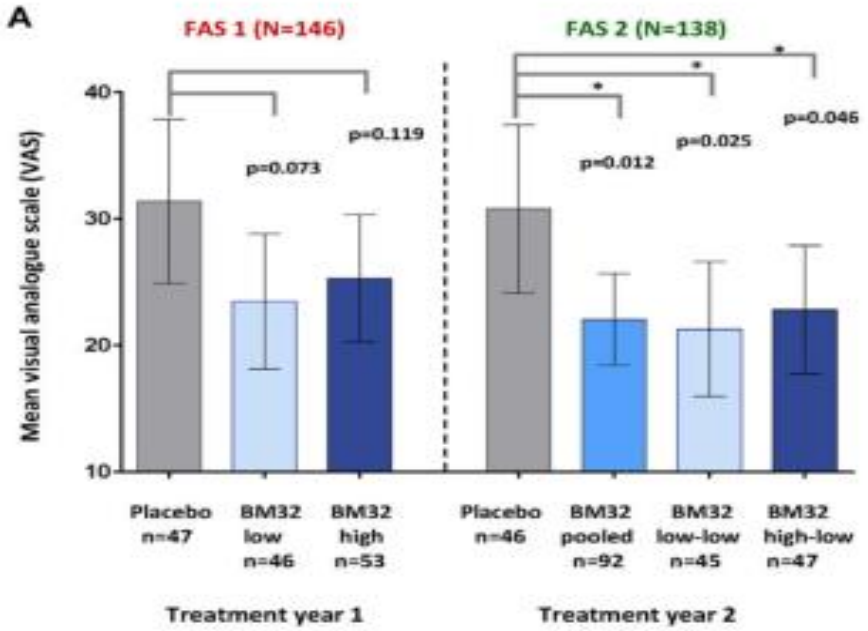

n=305 subjects signed IC
110 did not meet inclusion criteria
11 withdrew consent
3 lost to follow-up
n=181 subjects randomized
BM32 low
BM32 high
Placebo
SUBJECTS RANDOMIZED:
(Dec. 2012)
n=60
n=63
n=58
1 withdrew consent
3 lost to follow-up
1 fell pregnant
2 did not meet inclusion criteria
3 withdrew consent
3 withdrew consent
2 lost to follow-up
RECEIVED FIRST DOSE (SA):
(Jan 2013)
n=53
n=60
n=53
FAS1 population
n=46
n=53
n=47
4 withdrew consent
2 lost to follow-up
2 had adverse event
3 withdrew consent
3 were non-compliant with study protocol
3 withdrew consent
2 lost to follow-up
1 fell pregnant
2nd treatment year
(Jan 2014)
n=47 (low-low)
n=52 (high-low)
n=47
FAS2 population
n=45
n=47
n=46
1 lost to follow-up
1 fell pregnant
1 had concomitant disease
2 lost to follow-up
Completed study
(Oct 2014)
n=47
n=49
n=45

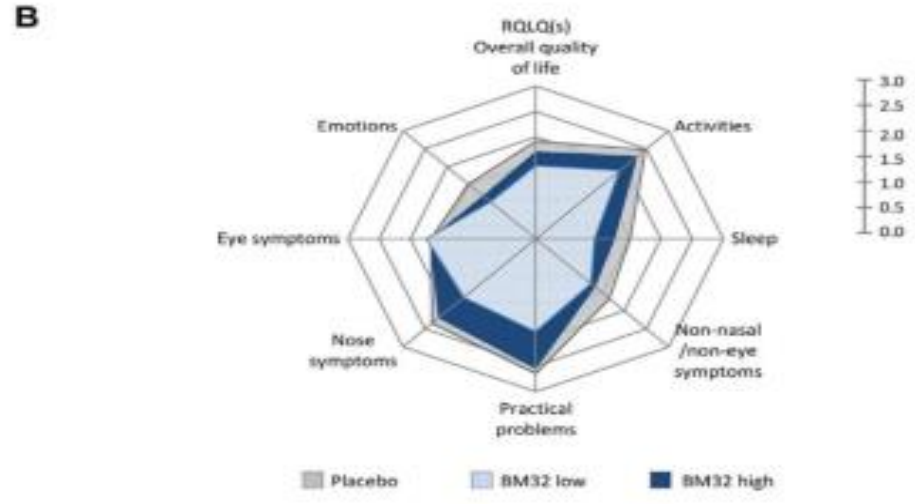
BM-32 Semptom skor



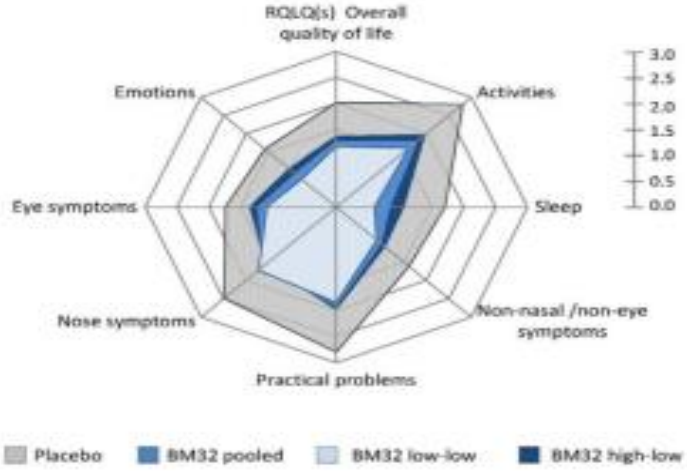
Astım skoruna etkisi
Öküsürük, nd, vizing (0-3)



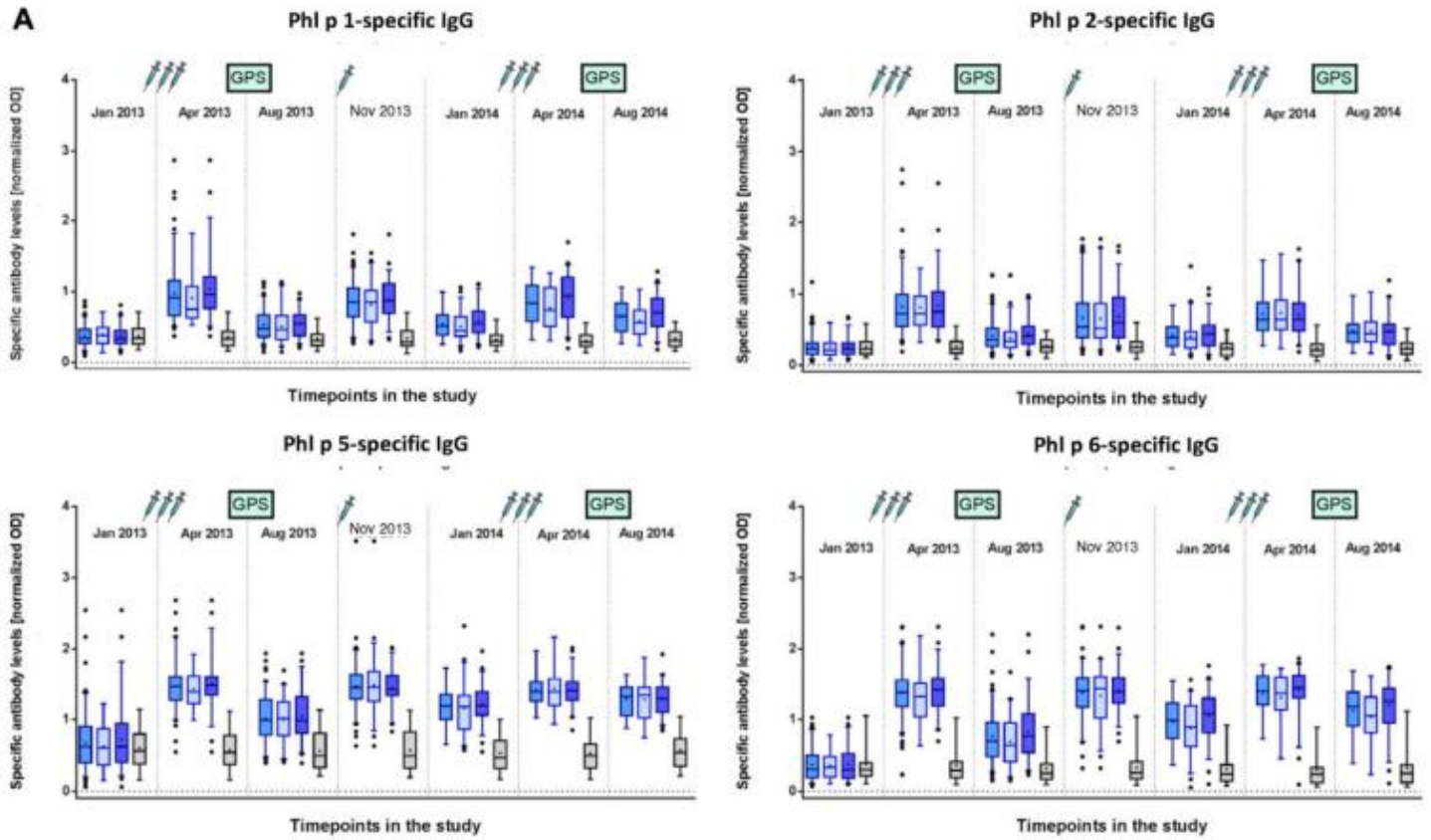




	RQLQ(s) Overall quality of life	Activities	Sleep	Non-nasal /non-eye symptoms	Practical problems	Nose symptoms	Eye symptoms	Emotions
p-value BM32 low vs. Placebo	0.130	0.112	0.182	0.389	0.033	0.031	0.772	0.151
p-value BM32 high vs. Placebo	0.727	0.681	0.532	0.417	0.726	0.980	0.681	0.375



	RQLQ(s) Overall quality of life	Activities	Sleep	Non-nasal /non-eye symptoms	Practical problems	Nose symptoms	Eye symptoms	Emotions
p-value BM32 low-low vs. Placebo	0.004	<0.001	0.001	0.057	0.057	0.024	0.187	0.006
p-value BM32 high-low vs. Placebo	0.032	0.022	0.062	0.153	0.093	0.002	0.438	0.069
p-value BM32 pooled vs. Placebo	0.004	0.001	0.001	0.054	0.038	0.002	0.232	0.009



SPESİFİK IG G ÜZERİNE ETKİSİ

Kovansiyonel AİT- BM 32 B hücre Epitop AİT

GPE AİT: 8 hasta 35 enjeksiyon

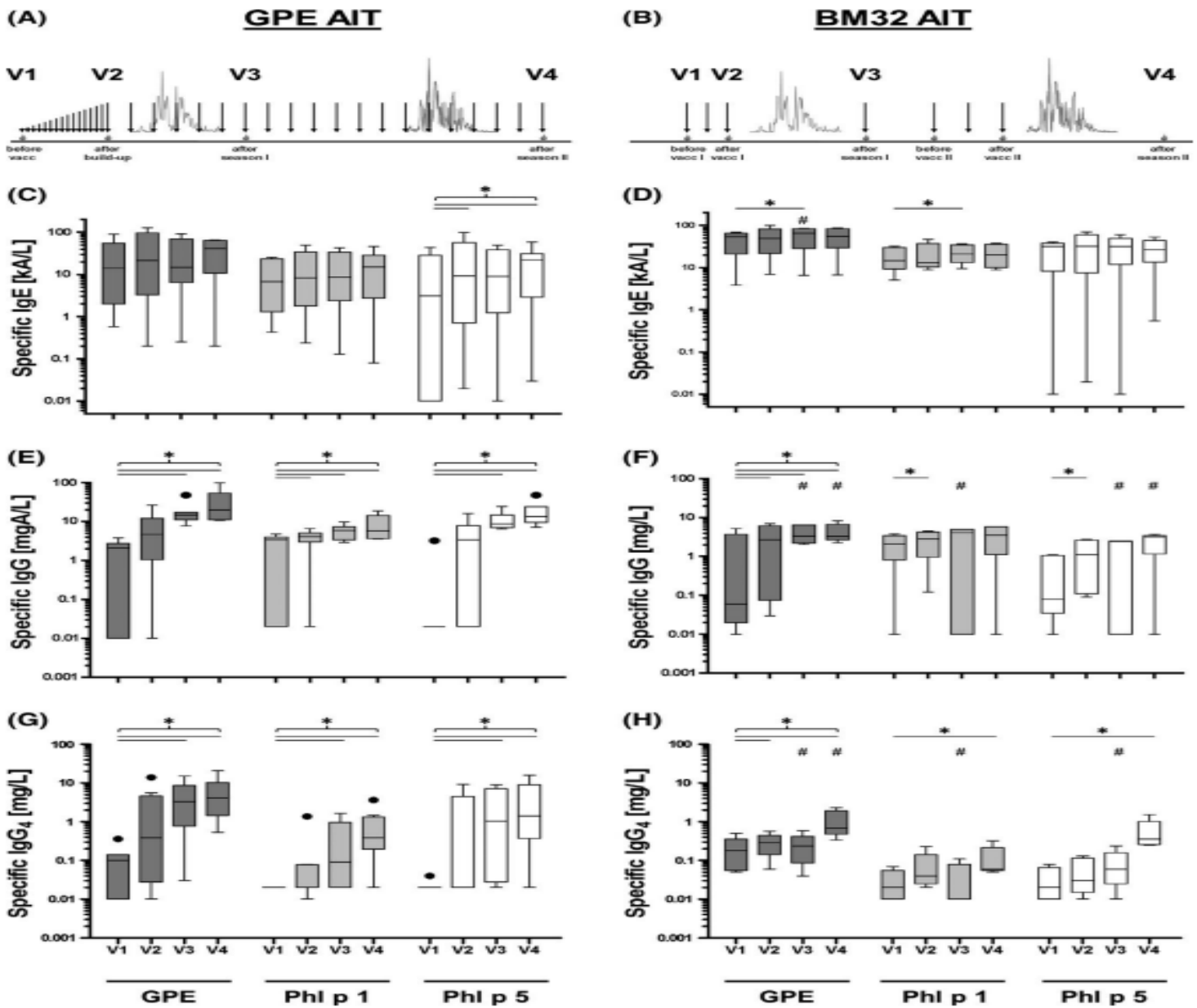
BM32 AİT: 5 hasta 7 enjeksiyon

GPE AİT: IGE 2-7 kat artma eğiliminde

Phlp 1,5, GPE spesifik IGG-G4 deki artış GPE'de daha fazla

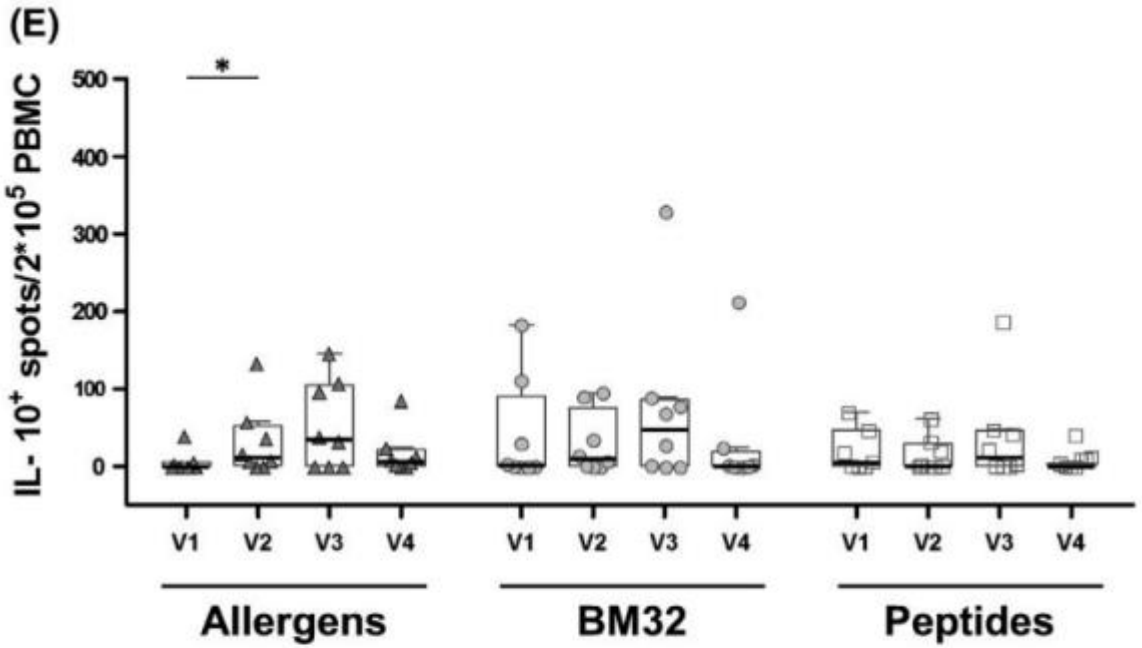
Php 2,6 PEPTİD (HİPOALERJENİK IGE PEPTİD) spesifik IGG BM32 de fazla

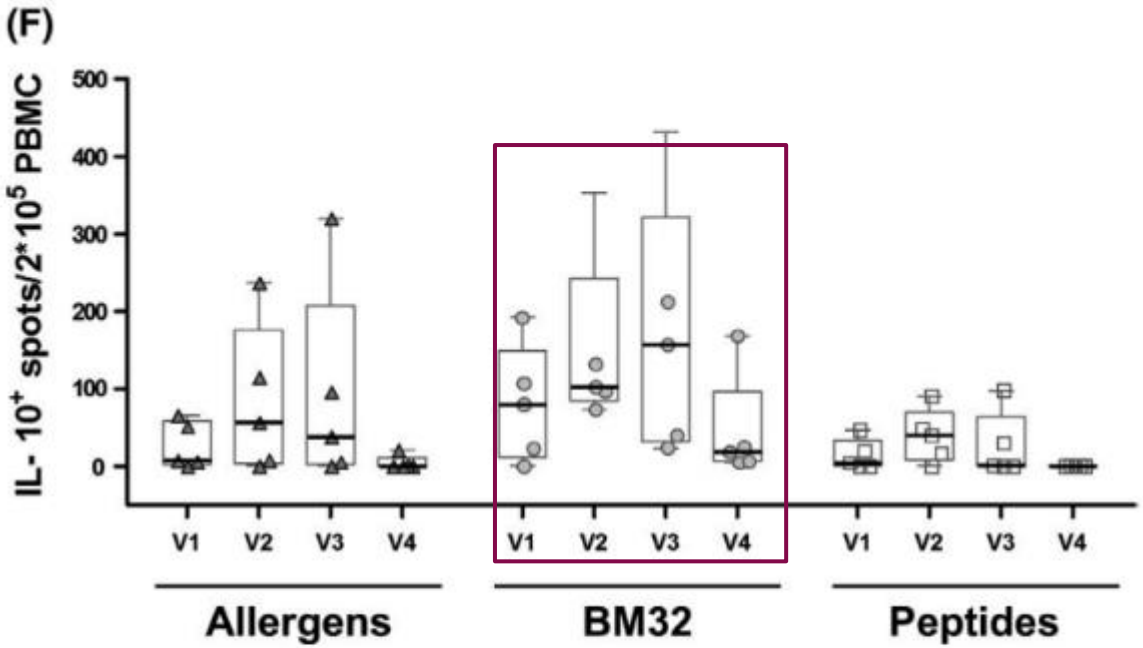
IGE bağlanan bölge hedef ?

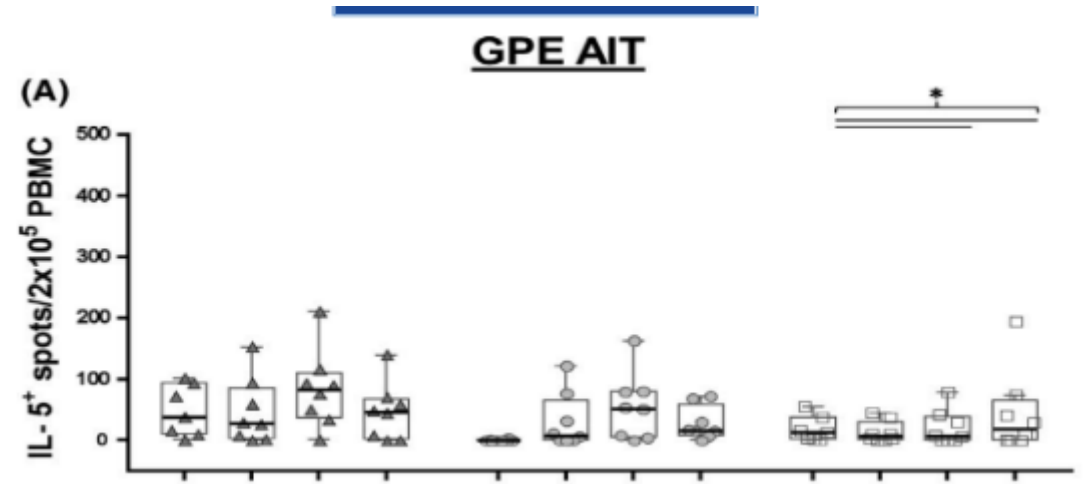


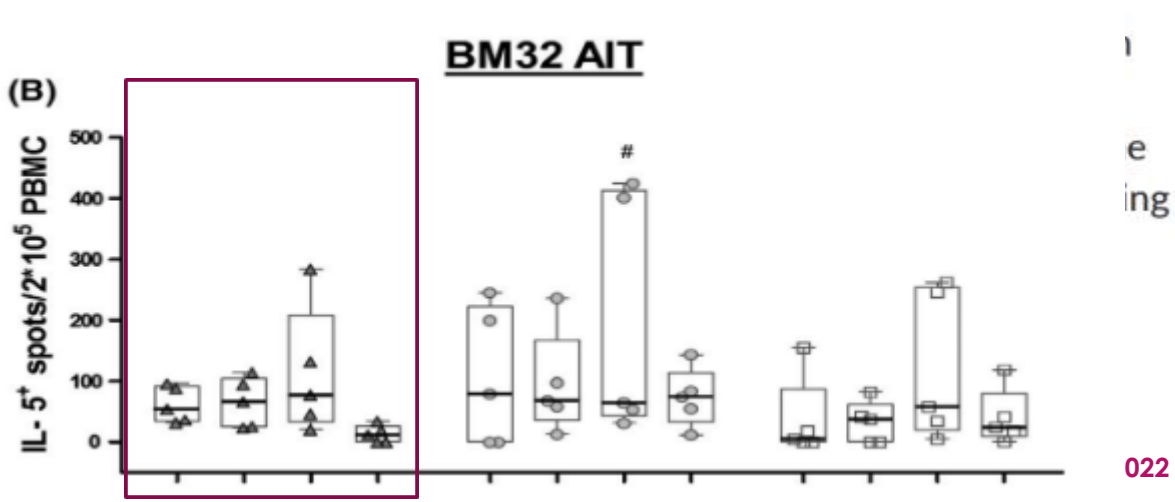
Allergy. 2019;00:1–4.

25.07.2022


(E)
IL- 10+ spots/2*10^5 PBMC
500
400
300
200
100
0
*
V1 V2 V3 V4 V1 V2 V3 V4 V1 V2 V3 V4
Allergens
BM32
Peptides


(F)
IL- 10+ spots/2*10^5 PBMC
500
400
300
200
100
0
V1 V2 V3 V4 V1 V2 V3 V4 V1 V2 V3 V4
Allergens
BM32
Peptides


GPE AIT
(A)
IL- 5+ spots/2x10^5 PBMC
500
400
300
200
100
0
*


BM32 AIT
(B)
IL- 5+ spots/2*10^5 PBMC
500
400
300
200
100
0
#

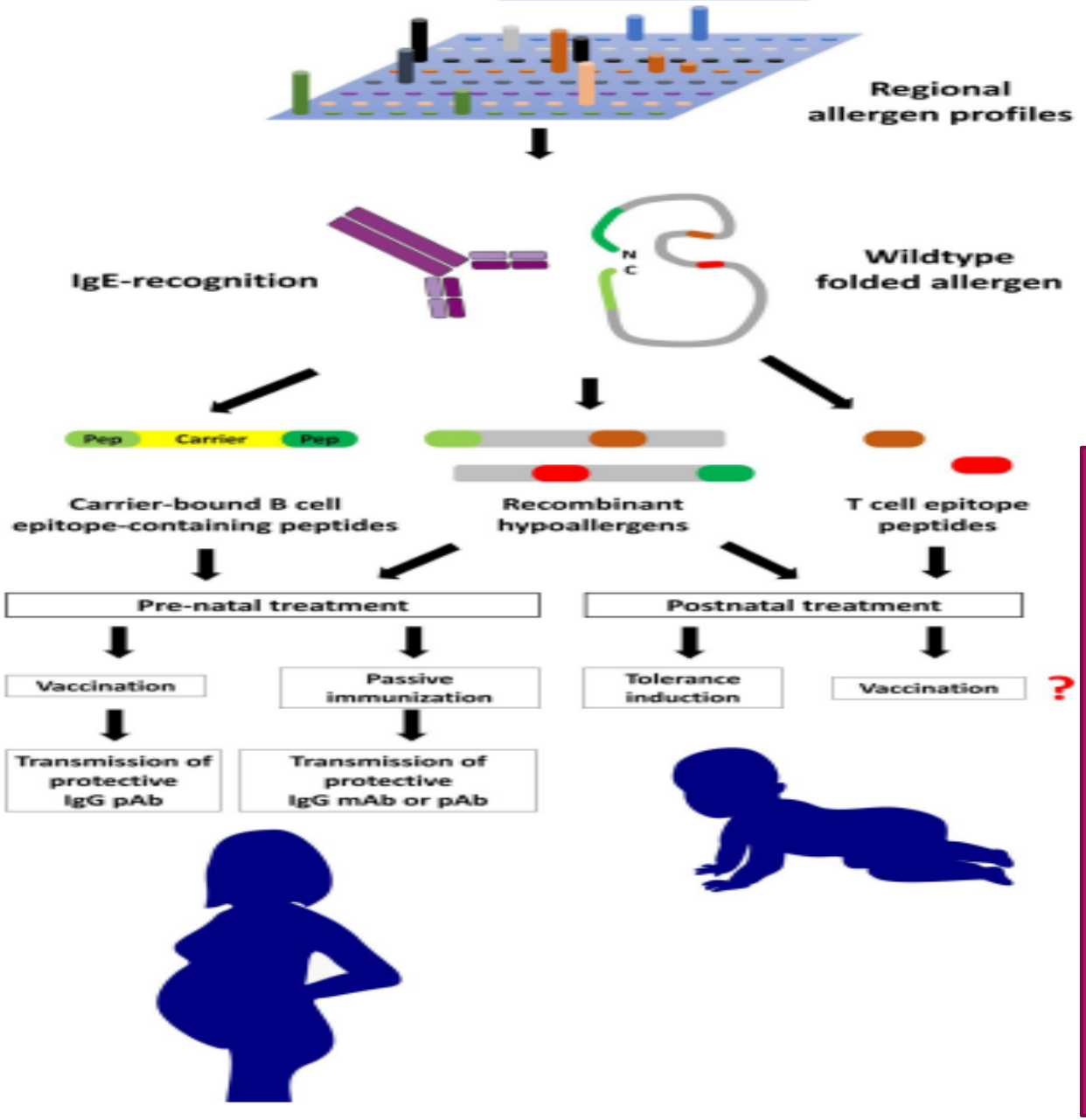
022

Pasif İmmunizasyon

- Dunbar; 1903: antisera
- Monoklonal IGA Antikor: Amb A1
- IGG antikor Betv1 (BAB1)
- IGE FAB – IGG Antikor Phlp-2,
- ICAM1 Spesifik IGG

- Tek duyarlılık
- Presezonal
- Yüksek titre

FIGURE 3 Toward allergen-specific prevention of allergy. Using chips containing micro-arrayed allergen molecules (top), it is possible to identify the clinically relevant allergen molecules for a given population. According to these profiles IgE- and T-cell epitopes of these allergens can be mapped and used for the development of molecular approaches for allergen-specific prevention (middle part). Carrier-bound B-cell epitope-based peptides and recombinant hypoallergens may be used for prenatal vaccination of mothers to transmit blocking antibodies to the off-spring or for early postnatal vaccination (Bottom). The administration of allergen-specific blocking antibodies by passive immunization of mothers may also be considered for primary prevention. T-cell epitope-containing peptides may be used for early postnatal tolerance induction



Primer önleme

En sık karşılaşılan alerjenlerle Gebelik erken dönem ve gebeliğin sonunda yüksek dozda

Tölerans indüksiyon:

Allerjen
+
hemopoetik kök hücre
Kord kanı
Oral alerjen
Oral t hücre epitopları

Allergy. 2021;76:131–149

Sonuç

FASTER SAFER IMMUNOTERAPI SEÇIMLERI GELICEK

Primer koruma: doğal ortamlarda yaşama