Mevsimsel alerjik rinitli hastamda alerjen immünoterapisinin dünü – bugünü

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11.06.2022,Sapanca

Alerjik rinit;

- Th2 inflamasyonun rol oynadığı, IgE aracılı gelişen kronik inflamatuar hastalık

Sıklığı;

- Erişkinlerde %20-30
- Çocuklarda %40 (1).

✓Yaşam kalitesini

✓Uyku kalitesini

✓Okul ve iş performansını olumsuz etkiler

- Sıklıkla astım eşlik eder

EAACI, 2018

Tedavi

İnflamasyonu ve semptomları önlemeye yönelik

- Alerjenden kaçınma

✓ Her zaman alerjenden kaçınmak mümkün değil

✓ Özellikle Güney Avrupa ülkelerinde çoklu allerji ve çapraz reaktivite fazla

✓ Polen mevsimleri uzun ve çeşitli polenler aynı mevsime denk geliyor

- Antihistaminik
- Steroid
- LR antagonistleri
- Dekonjestanlar
- **Alerjen spesifik İmmünoterapi**

Allergy 66 (2011) 713–724

Clin Exp Allergy. 2021;51:821–828

Allerjen spesifik immünoterapi (ASİT)

- Desensitizasyon
- Hiposensitizasyon
- Alerji aşısı

IgE aracılı hastalığı olan kişiye duyarlı olduğu bilinen alerjenin idame doza çıkana ve kişinin semptomları rahatlayana kadar giderek artan dozlarda verilmesi

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ASİT;

- Alerjenden kaçınma & İlaç tedavisine rağmen

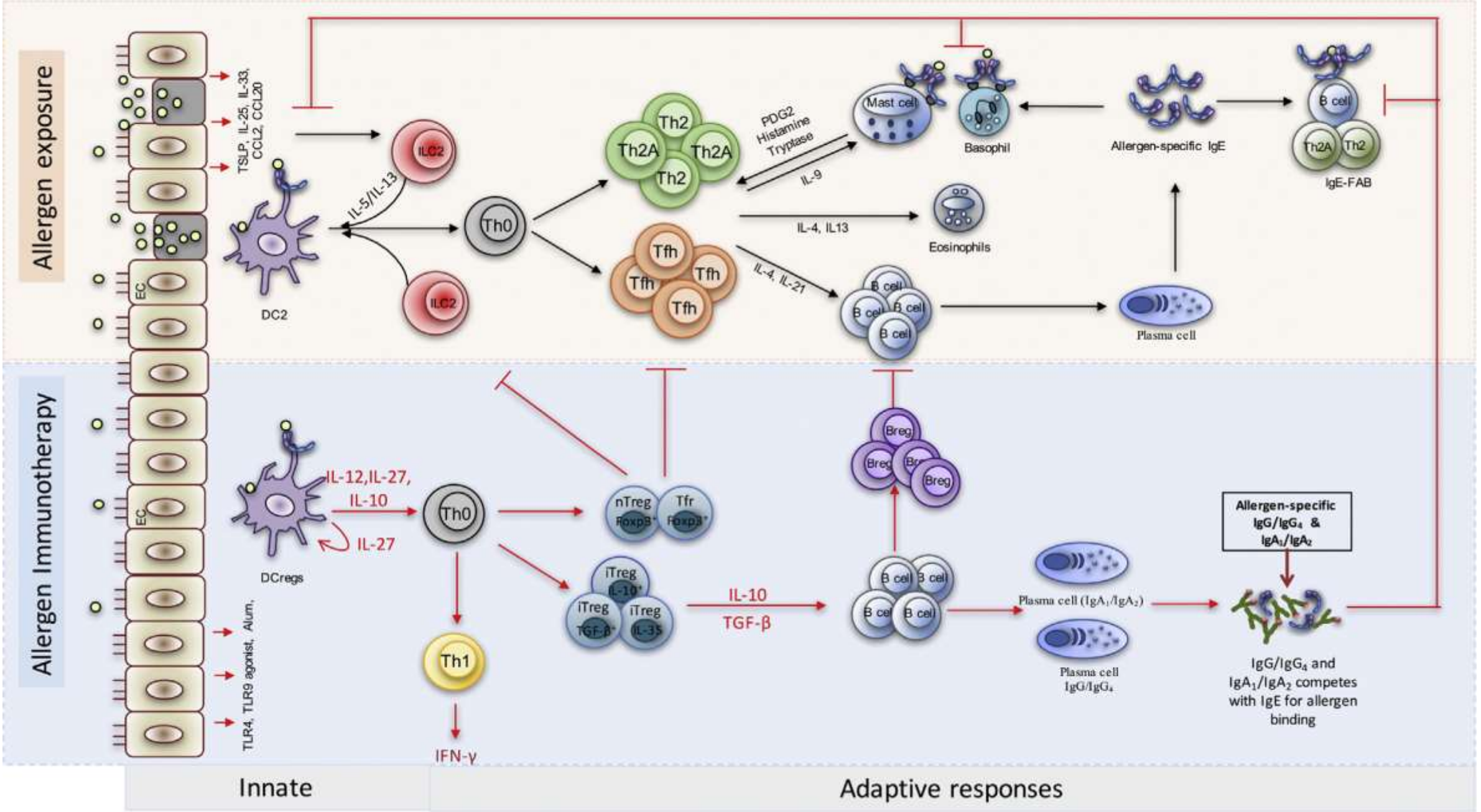
✓Semptomlar kontrol atına alınamıyorsa

✓İlaç yan etkileri ortaya çıktıysa

✓İlaçlar kesildiğinde semptomatik oluyorsa

✓Artık ilaç kullanmayı istemiyor, uzun süreli bir rahatlama istiyorsa

EAACI, 2018



J Allergy Clin Immunol
2017;140:1485-98.

Confucius der ki;

«Geleceği keşfetmek istiyorsan geçmişi öğrenmelisin»

Allergy. 2021;76:131–149

Received: 3 February 2020 | Revised: 25 February 2020 | Accepted: 15 March 2020

DOI: 10.1111/all.14300

REVIEW ARTICLE

Allergy WILEY

Past, present, and future of allergen immunotherapy vaccines

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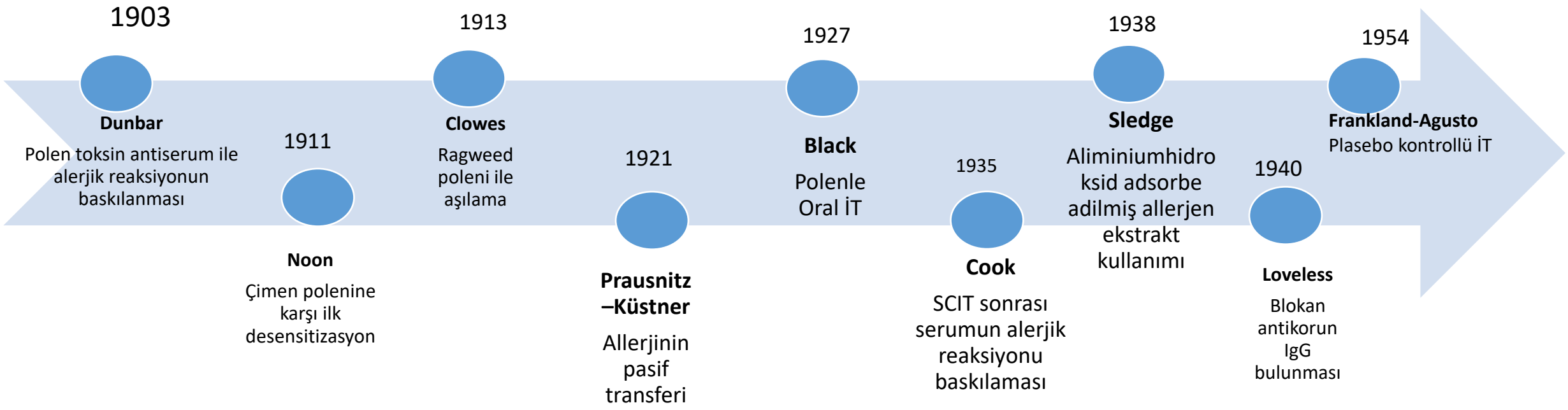
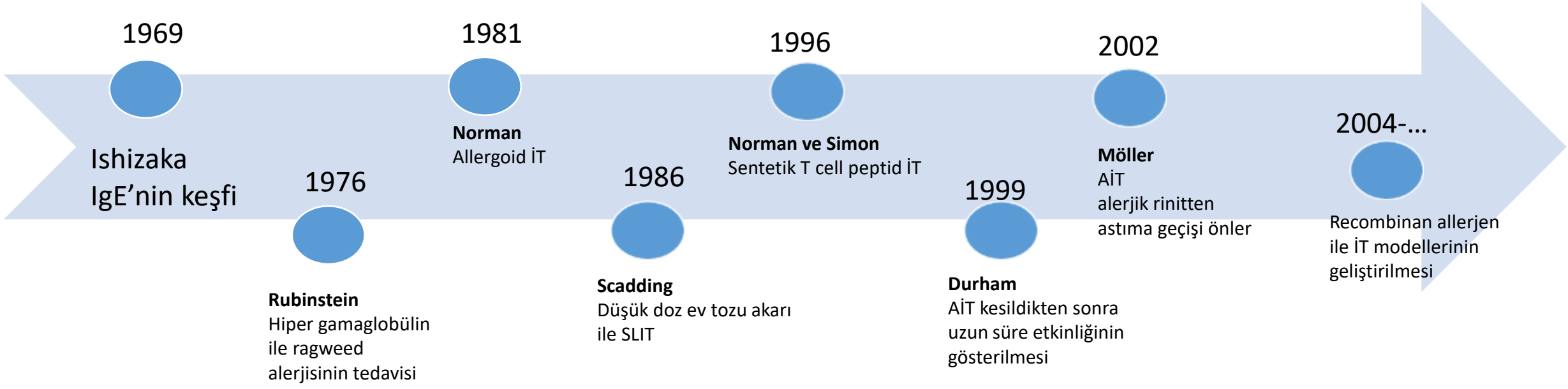
TABLE 1 Some milestones in the development of AIT

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]

İT tarihsel gelişimi




1969
Ishizaka
IgE'nin keşfi
1976
Rubinstein
Hiper gamaglobülin
ile ragweed
alerjisinin tedavisi
1981
Norman
Allergoid İT
1986
Scadding
Düşük doz ev tozu akarı
ile SLIT
1996
Norman ve Simon
Sentetik T cell peptid İT
1999
Durham
AİT kesildikten sonra
uzun süre etkinliğinin
gösterilmesi
2002
Möller
AİT
alerjik rinitten
astıma geçişi önler
2004-...
Recombinan allerjen
ile İT modellerinin
geliştirilmesi

Alerjen Spesifik İmmünoterapide kilometre taşları

- 1911 Leonard Noon polenlere karşı İT
- Polen=zehir
- Polenlere karşı hipersentivite ve immünolojik reaksiyon bilinmiyor
- Allerjen tanımlanmamış
- IgE henüz tanımlanmamış

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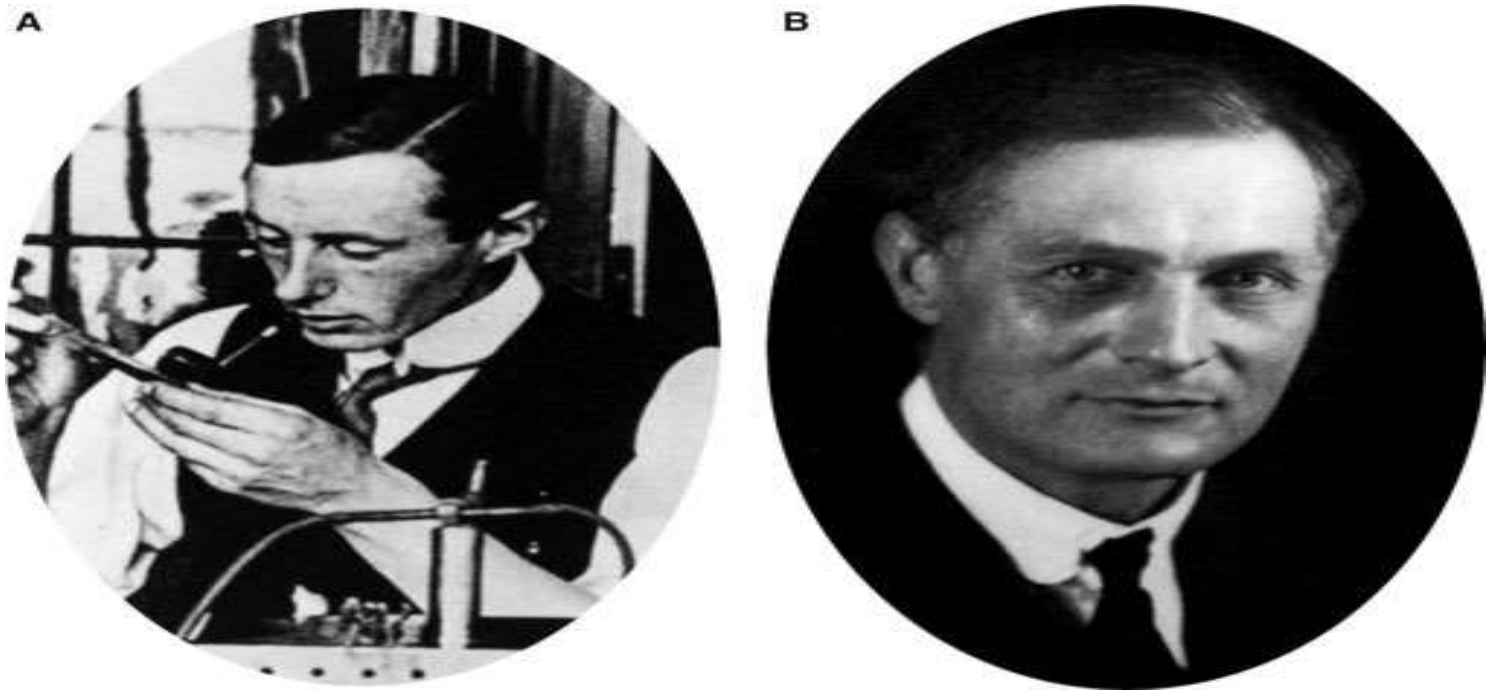


Leonhardt Noon (1878–1911) and (B) John Freeman (1877–1962), the pioneers of allergen-specific immunotherapy

bleeding, and then administer salines. In the other 14 cases so treated the condition of the patients permitted of the delay necessary for preparatory treatment and for the removal of all blood clots from the abdomen.

The crisis having passed, and when the case is first seen subsequent to the formation of a distinct and encapsulated hæmatocele, more conservative treatment is warranted. With rest in bed the majority of such cases undergo complete absorption, the only indication for operative interference being the possibility of secondary rupture of the hæmatocele demanding coeliotomy, or infection of the sac, which is best treated by vaginal incision and drainage. Against an entirely expectant line of treatment the element of time has to be considered, especially with hospital patients. Large hæmatoceles may take weeks to undergo complete absorption, which loss of time may be prevented by the safe proceeding of vaginal incision and drainage. Of my six cases so treated five were typical cases of retro-uterine hæmatoceles, and the patients left the hospital within three weeks from date of admission. In the remaining case of hæmatoma, abdominal section having shown that the blood was encapsulated in the broad ligament, the abdomen was closed and the case further treated by vaginal incision and drainage.

Dundee.

PROPHYLACTIC INOCULATION AGAINST HAY FEVER.

BY L. NOON, B.C. CANTAB., F.R.C.S. ENG.

(From the Laboratory of the Department for Therapeutic Inoculation, St. Mary's Hospital.)

HAY fever is a form of recurrent catarrh affecting certain individuals during the months of May, June, and July. It is caused by a soluble toxin found in the pollen of grasses. The patients present the idiosyncrasy of being sensitive to this toxin, which is innocuous to normal individuals. The idiosyncrasy may be detected during any season of the year by dropping a little of an extract of grass pollen into the eye of the suspected individual; a reaction, described more fully below, will be obtained in the case of a hay fever patient, but a normal man will show no effect.

Bostock (1819)[1] recognised the seasonal recurrence of hay fever as separating it from other forms of catarrh. Blackley (1873)[2] advanced much evidence in favour of the pollen theory of its causation, but we owe chiefly to Dunbar (1903)[3] the exhaustive scientific proof of this theory. Dunbar showed that not only all the mucous membranes but even the skin of hay fever patients is sensitive to pollen toxin in a way not shown by normal individuals. He also proved that the injection of the pollen toxin gives rise in animals to the production of an antitoxin having a specific power of neutralising this toxin. Further, in hay fever patients, he showed the occurrence of some of the reactions associated with the production of immunity:—namely, a specific precipitation of pollen extracts by the patient's serum, and the phenomenon of complement deviation, during the hay fever season, and persisting for a short time after this. Pollen toxin is, therefore, a body capable of giving rise to the production of antibodies in animals and even in hay

use of this remedy, but admittedly in exceptional cases; and where the conditions are not understood and the experience is not constantly repeated, one must hesitate to attribute the result to the cause cited. On general grounds a much more satisfactory result would be expected from the induction of an active immunity, and it seemed worth while to put this expectation to the test of experiment. The questions to be answered are as to what degree of immunity can be induced in hay fever patients by inoculations of pollen toxin, how these inoculations may best be regulated, and whether the affection can by this means be permanently cured.

With this end in view the experiments here described were undertaken in the past autumn, winter, and spring to study the reaction of hay fever patients towards inoculations of pollen toxin. The off season of the year, when the patients were not exposed to spontaneous inoculations, was favourable to this investigation, as the scheme of dosage was then not liable to be upset by spontaneous absorption of toxin from the air, laden with actively poisonous pollen grains. The plan of experiment was to obtain a numerical measure of the sensitiveness of the patients to the pollen toxin and to observe whether this was increased or decreased by subcutaneous inoculations of various quantities of pollen toxin. These observations can be conveniently carried out by the method described below, and it was found that, with well-regulated dosage, it was possible in every case to raise the patient's resistance, to a marked degree, within the lapse of a few months, while, on the other hand, ill-regulated dosage was at once made evident by a decrease in the resisting power.

The pollen extract used was prepared by Dunbar's method of extraction with distilled water, aided by freezing and thawing several times. The extracts were boiled for ten minutes after having been sealed in glass tubes; this treatment was not found to decrease their activity at all. The pollens tested were grass pollens of different species—*Phleum pratense*, *Poa trivialis*, *Holcus lanatus*, and *Agropyrum caninum*. These pollens were all found capable of exciting an energetic reaction when instilled into the conjunctival sac of hay fever patients. Timothy grass (*Phleum pratense*) was found to yield the most active extract, and this extract was consequently used throughout the rest of the experiments. One gramme of pollen was extracted with 50 c.c. of water. The activity of this extract may be judged from the fact that one drop of a five thousand-fold dilution is sufficient to excite a distinct reaction in the conjunctiva of the more sensitive patients.

In order to express the strengths of pollen extracts used in testing patients and the doses of pollen toxin given subcutaneously, a unit of pollen toxin has been arbitrarily chosen. This unit is the quantity of pollen toxin which can be extracted from the thousandth part of a milligramme of Phleum pollen, and it has the advantage that all the quantities used can be expressed in whole numbers. The strength of a pollen extract is given below in terms of the number of such units contained in a cubic centimetre of the extract. Extracts of other pollens have been standardised against the Phleum extract by comparative tests on the eyes of hay fever patients.

A measure of the patient's resistance during the experiments is obtained by observing the strength of pollen extract

Title page of Leonhard Noons original publication, Lancet 1911.

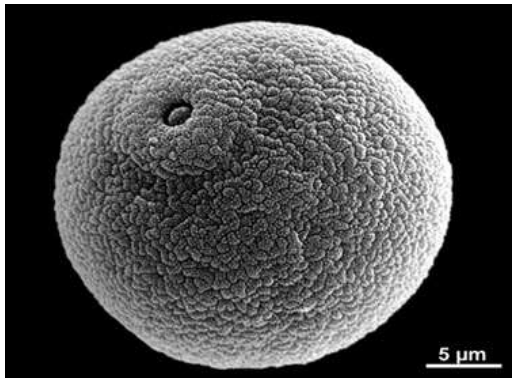
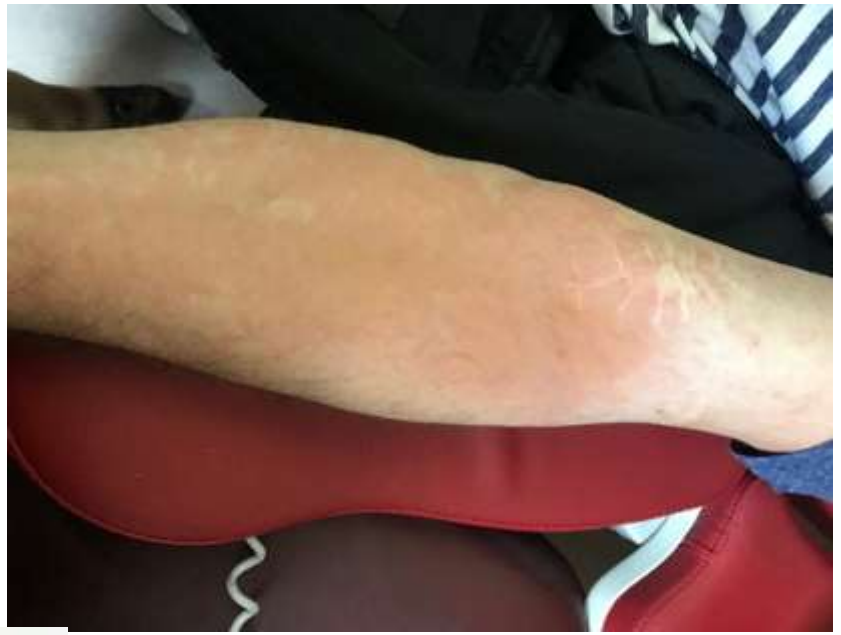
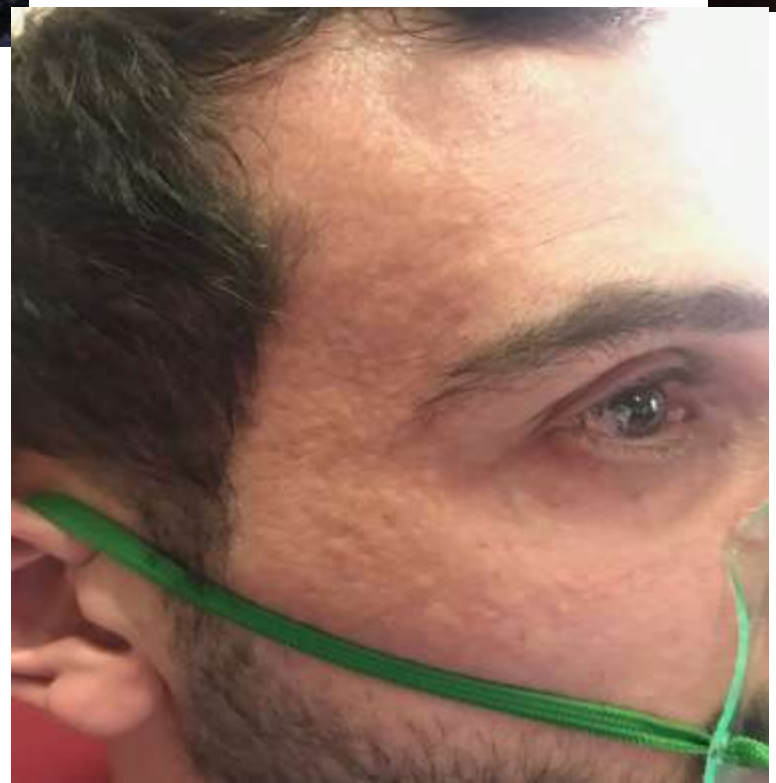


Figure 3 Scanning electron microscopy of a grass pollen grain –
Noons therapeutic agent (courtesy from Heidrun Behrendt, Munich).

- 1923 Prausznitz –Küstner reaksiyonu; antijen duyarlı olduğu düşünülen kişinin serumu sağlıklı kişiye enjekte edilir, ardından şüpheli antijen serum enjekte edilen kişiye verilerek 24-48 saat içinde enjeksiyon bölgesindeki şişlik ve kızarıklık değerlendirilir
- Reaksiyon pozitifse, serumu alınan kişide allerji olduğu saptanır
- Bu aynı zamanda IgE'nin pasif transfer edilebildiğinin de göstergesidir
- Henüz IgE tanımlanmamışken IgE'nin, alerjenin araştırılmasına temel olan önemli bir gelişme

«Alerjen İmmünoterapideki gelişmelere rağmen, yan etkiler önemli sorun»





AİT’de yan etkileri azaltmak için günümüzdeki yapısal çalışmalar

- Alüminium hidroksitle konjugasyonu
- PEG kullanımı
- Günümüzde hidrolize ekstraktlar

*Yine de grade IV şiddetli alerjik reaksiyonlar var

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Teknolojik iyileştirmeler

✓DNA plazmid aşıları
✓İmmünomodülatör DNA sekanslarının alerjenle konjugasyonu
*alerjenik aktiviteyi azaltmakta
*immünmodülatuar fonksiyonu arttırmakta
✓Taşıyıcı protein bağlayan alerjen derived-B cell epitop peptidleri
*yeni jenerasyon hipoalerjenik rekombinan aşılar
Rekombinan Alerjen molekülleri ile IT modelleri Betulacea (Bet v1) ve timothy grass için çalışılmıştır
✓Çimen poleni alerji aşısı BM32 hem nonalerjik hem de alerjen spesifik IgG üretiminde oldukça başarılı
*Booster IgE üretimine neden olmadığı için profilaktik aşılama için de uygun görünüyor

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Yan etkiyi azaltmak için ASİT uygulama yolları,

- SCIT
- SLIT (damla ya da tablet) %52 ile en sık tercih edilen uygulama
- Epikutan
- İntralenfatik

AİT yan etkileri azaltmak için uygulama yollarının farklılaştırılması

- Subkutan immünoterapi (SCIT) mekanizması en iyi bilinen yöntem

1911'den beri uygulanıyor

✓Frankland ve Agustin çift-kör plasebo kontrollü ASİT çalışması

*ASİT plasebo etkiye sahip, bu çalışma ile plasebo etkisinden öte objektif klinik yararlı etkisi gösterildi

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SLIT;

30 yıldır

- Etki mekanizması net değil
- Polen ve ev tozları için, allerjen çeşitliliği az
- Orta derecede blokan IgG antikor yapımı
- Yüksek miktarda alerjen spesifik IgE yapımı
- Yine de semptom kontrolünde etkili
- Plasebo etkisi?
- 3 yıllık hasta uyumu %7

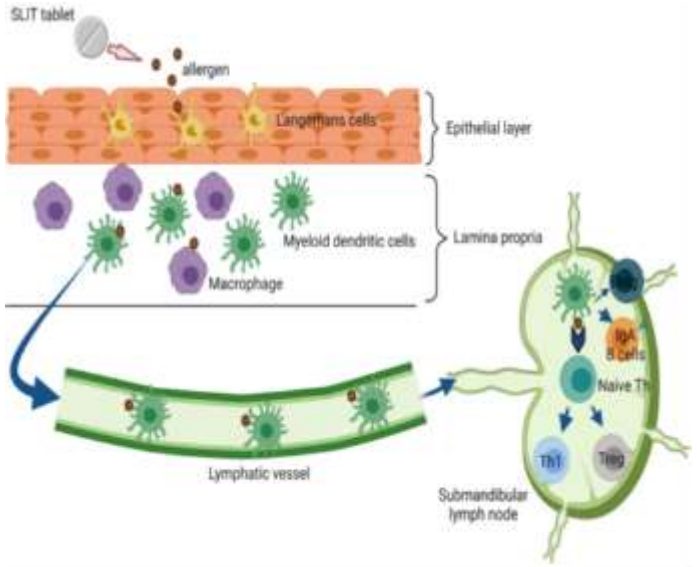
Yan etkiyi azaltmak için ASİT uygulama yolları

- ✓ Oral immünoterapi (OİT) 1927 ‘de besin alerjisi için
- ✓ SLIT 1986’da uygulama

Passalaque allergoid SLIT ile ilk randomize kontrollü çalışma

- ✓ Intralymphatic AIT

(ILIT) rekombinan alerjen deriveleri uygulama



SLIT

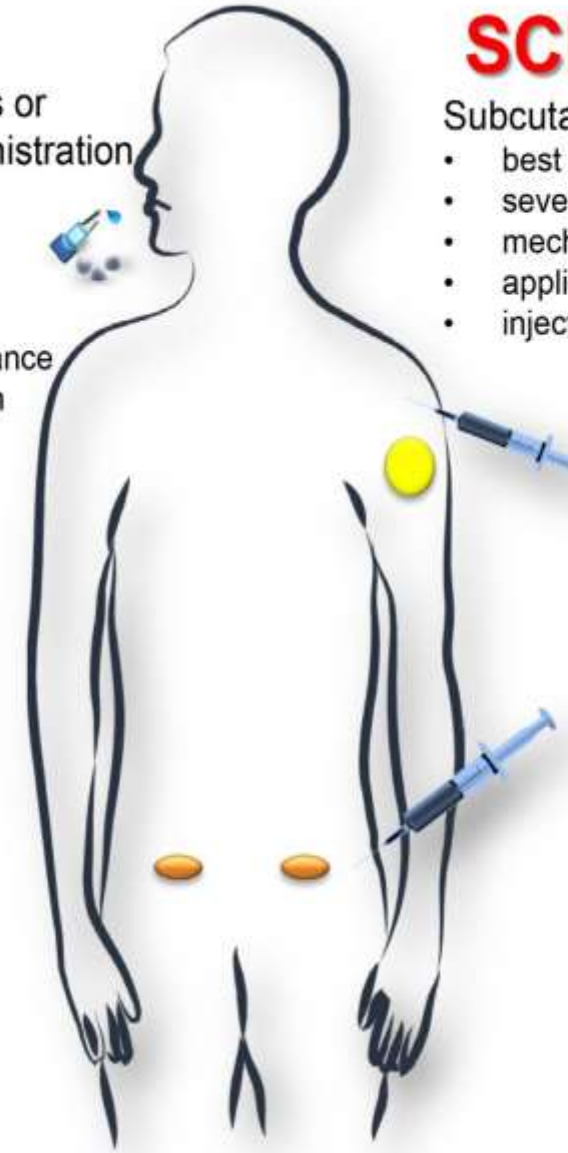
Sublingual application in form of drops or tablets under the tongue by self-administration

- 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

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ASIT bugün;

- Günümüzde halen immünoterapide kullanılan alerjen ekstreleri doğal kaynağından elde edilmekte
- Firmalar arasında farklar
- Saflık sorunu
- Üretim kazanlarının içeriğinin standart olmaması
- İçeriğinde farklı alerjen epitoplarının varlığı
- Her majör alerjene karşı blokan antikor gelişmemesi
- Farklı epitoplara karşı yeni duyarlılıkların oluşabilme riski

Geçmişte ve bugün allerjen standardizasyonu için kullanılan birimler

W/V	**Weight/volume**
Noon	**1/1000000 g Pollen**
PNU	**Protein nitrogen unit**
HEP	**Histamine equivalent prick**
IU	**International unit**
AU	**Allergy unit**
BAU	**Biological allergy unit**
BU	**Biological unit**
IR	**Index of reactivity**
TU	**Therapeutic unit**

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SONUÇ OLARAK
ASİT;

- Semptomları kontrol altına alır
- İlaç kullanımını azaltır
- Yaşam kalitesini arttırır
- Yeni gelişecek duyarlanmaları ,
- Astım gelişimini önler

Ancak halen ;

- Yan etki ve etkinlik
- Standardizasyon
- Aşı preparatlarına ulaşım sorunları mevcut
- Geliştirilmeye, iyileştirilmeye, standart çalışmalara ihtiyaç olan bir alan olsa da…

Mevsimsel alerjik rinitli hastalarımızda

- **Alerjen spesifik immünoterapi etkili bir tedavi yöntemidir**
- **SCIT ya da OIT şeklinde ülkemizde immünoterapi preparatlarına ulaşılabilir**