İMMÜN SİSTEMİN YAŞLANMASI
ve
AŞILARA YANIT

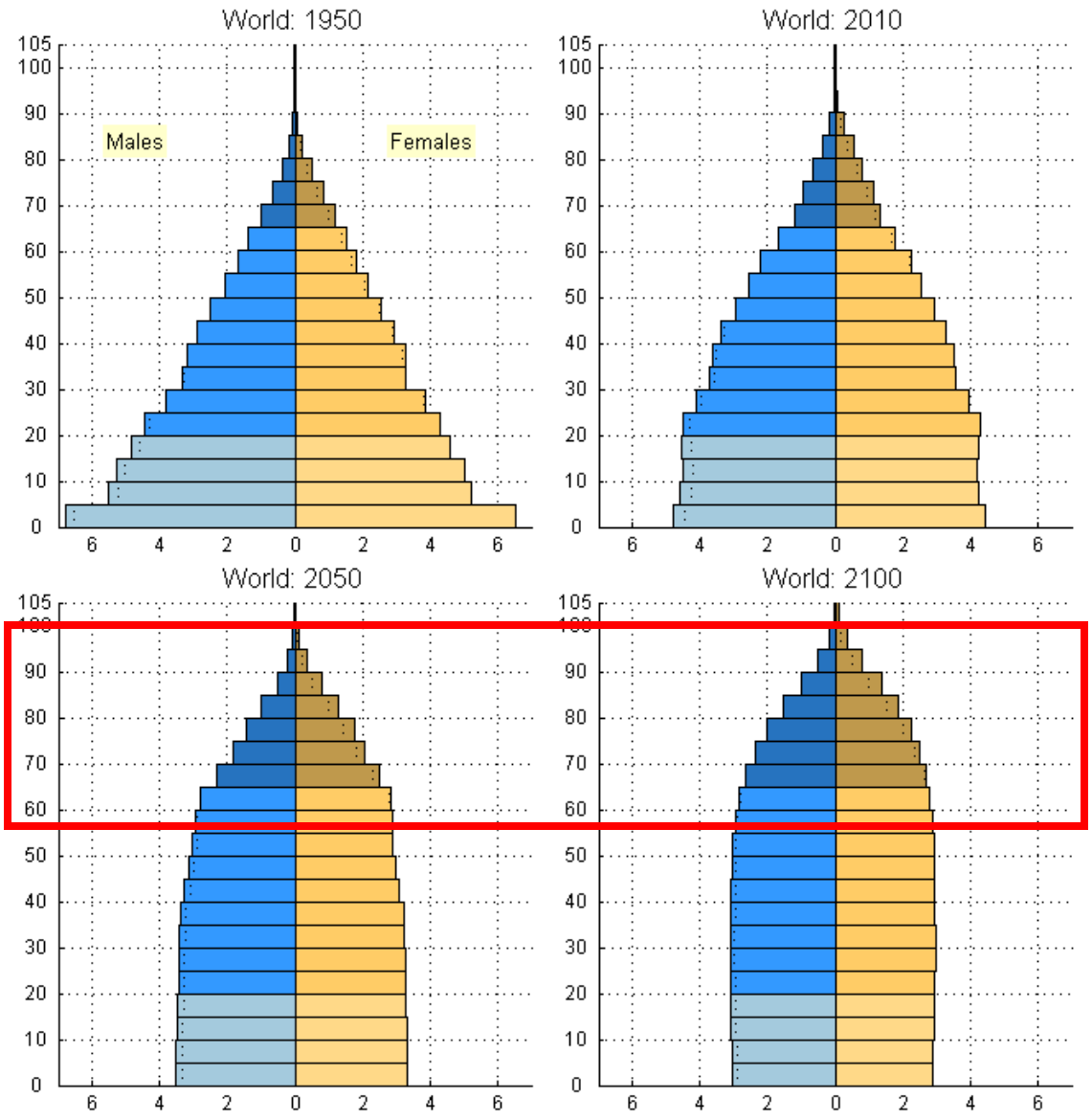
Selim BADUR
İstanbul Tıp Fakültesi
Viroloji ve Temel İmmünoloji Bilim Dalı
Ulusal Influenza Referans Laboratuarı

Dünya Nüfusu Artıyor

Dünyada Yoksulluk Artıyor

Dünya Yaşlanıyor

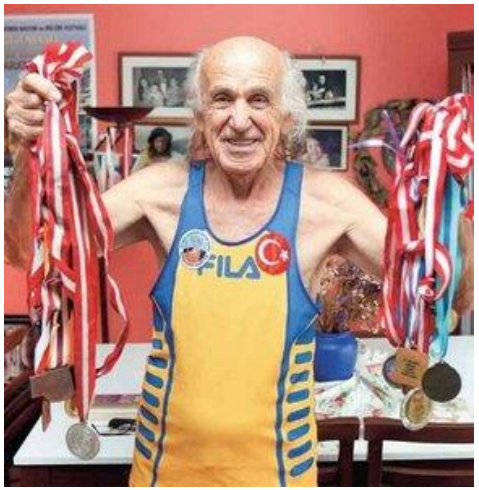
Dünya Nüfusunun Yaş Dilimlerine Göre Dağılımı

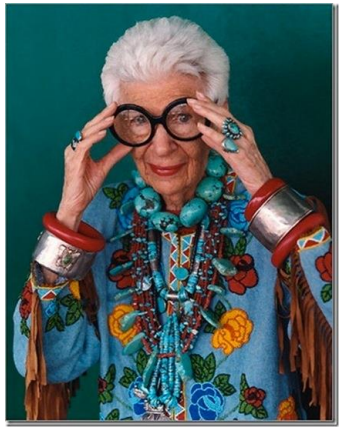


Source: United Nations, Department of Economic and Social Affairs, Population Division (2011): World Population Prospects: The 2010 Revision. New York

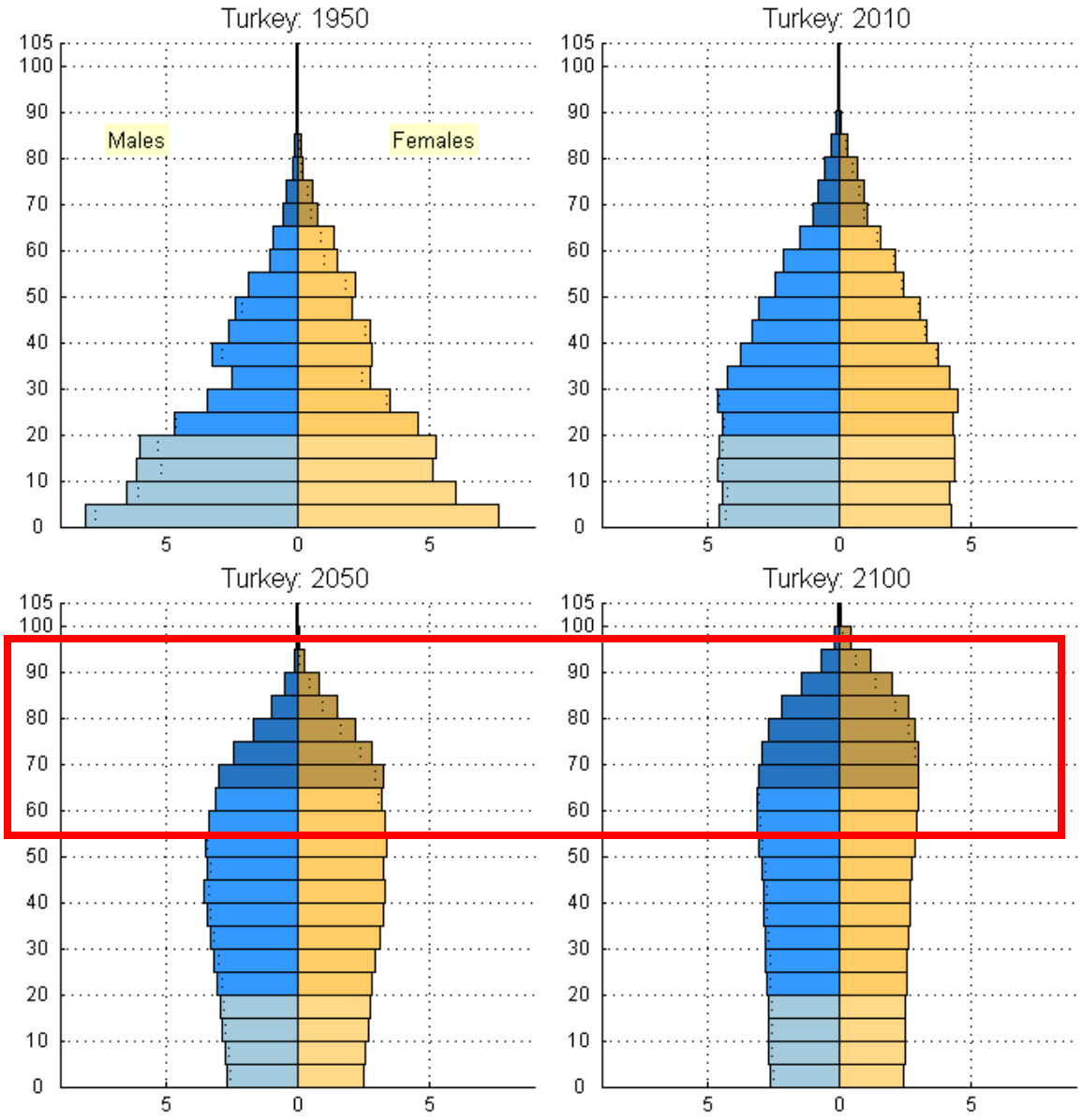
Fauja SINGH

Safter KARTOĞLU



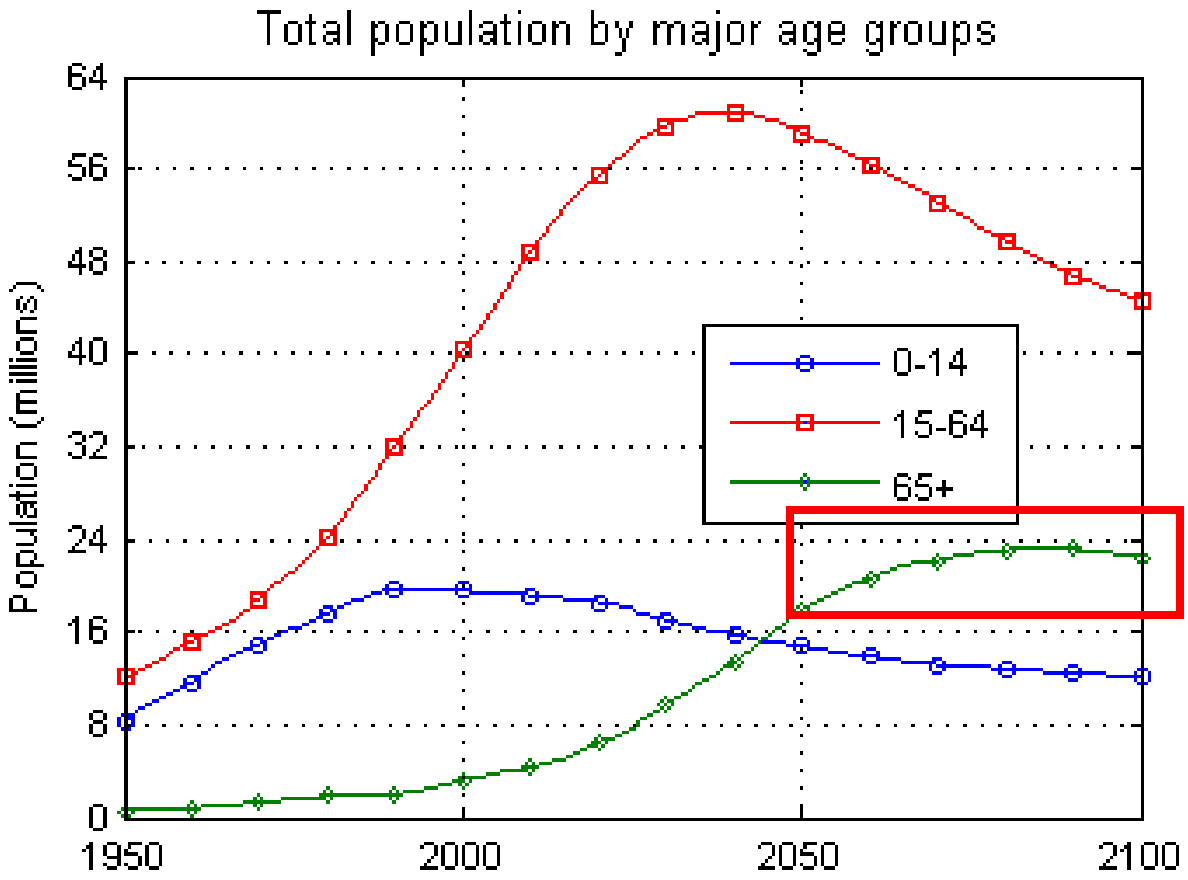


Türkiye'de Nüfusun Yaş Dilimlerine Göre Dağılımı



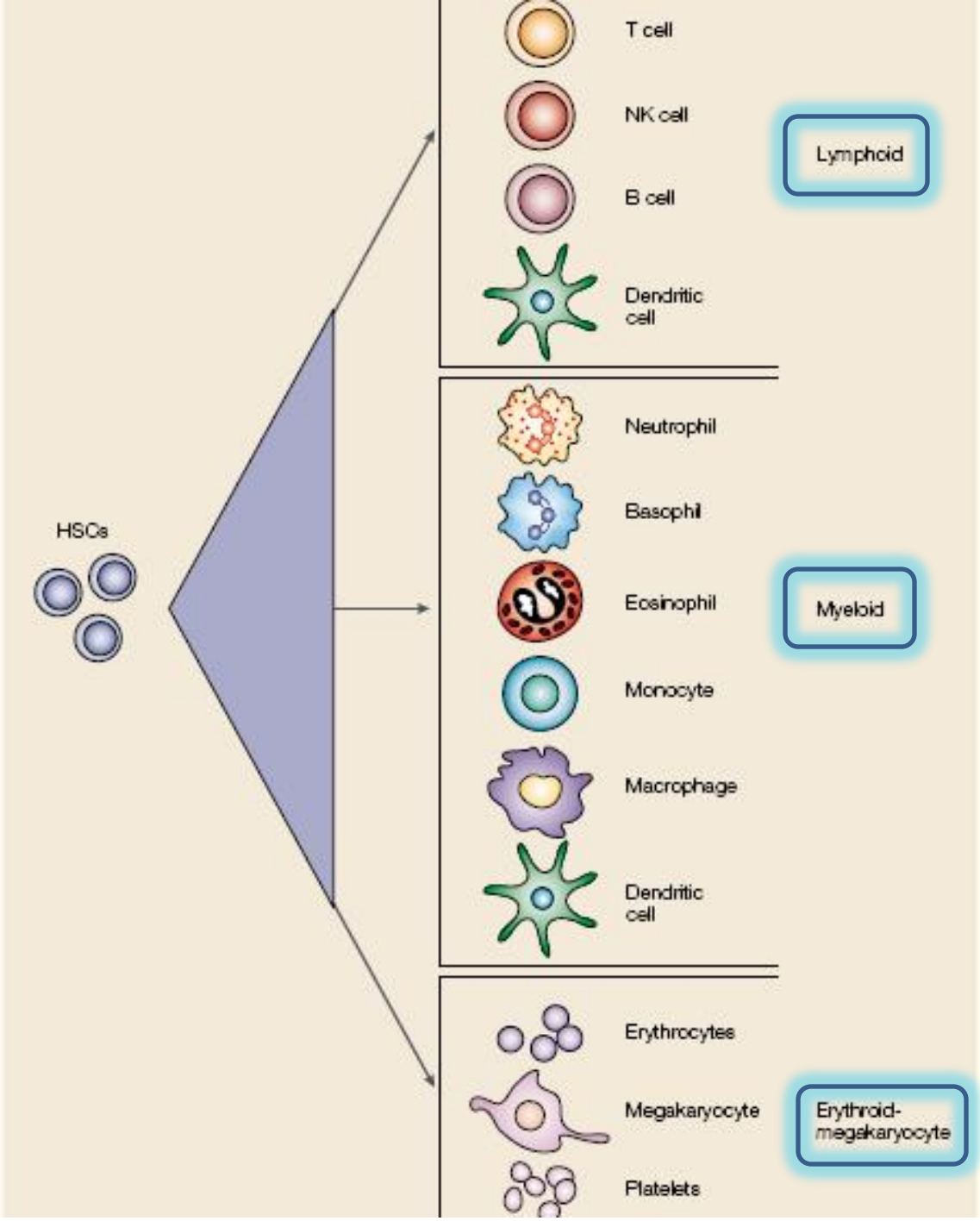
Source: United Nations, Department of Economic and Social Affairs, Population Division (2011): World Population Prospects: The 2010 Revision. New York

Türkiye için nüfusun yıllara göre tahmini dağılımı



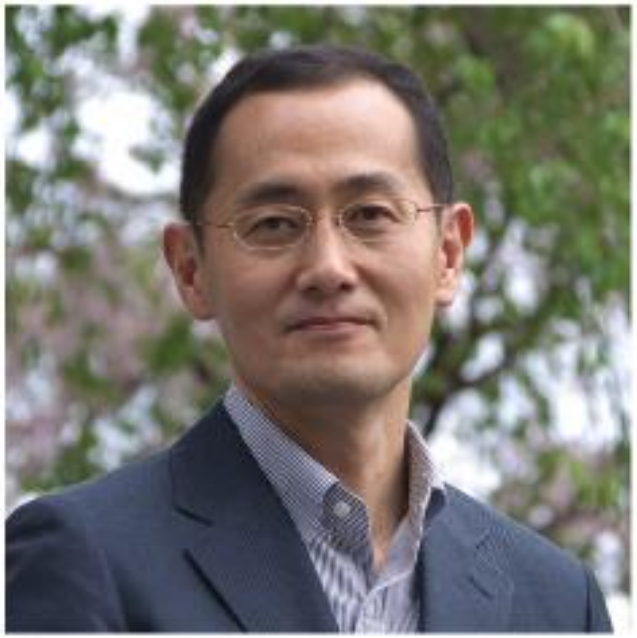
Kaynak: United Nations, Department of Economic and Social Affairs, Population Division (2011): World Population Prospects: The 2010 Revision. New York


BRAD PITT CATE BLANCHETT
The Curious Case Of
BENJAMIN BUTTON
CHRISTMAS DAY



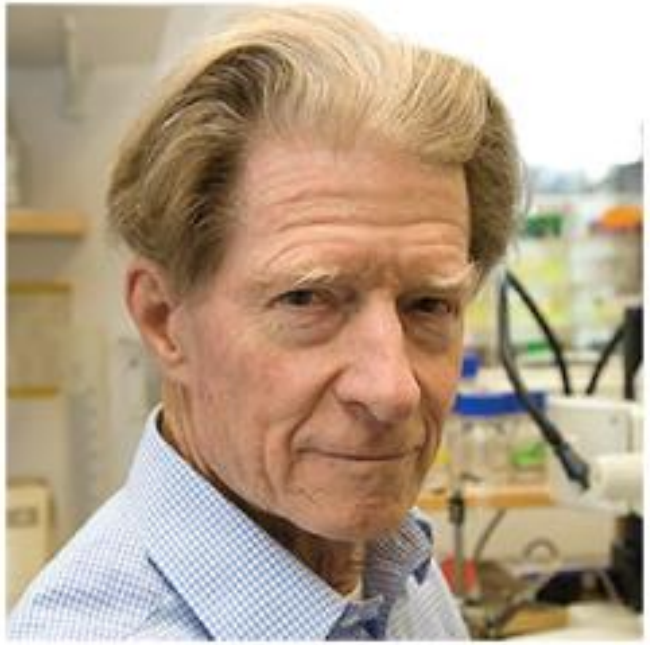
Nature Rev Immunol 2002;2: 127

2012 Nobel Prize in Physiology or Medicine

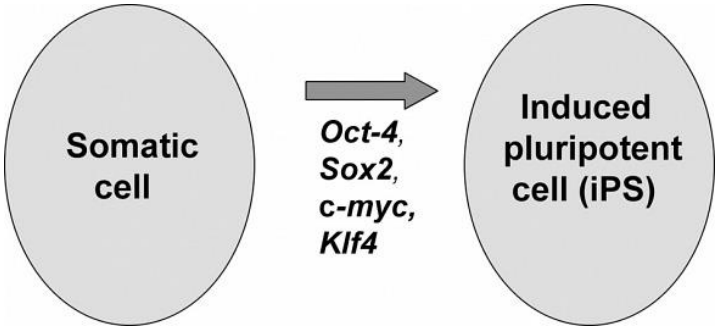


Shinya Yamanaka
University of Kyoto, Japan

Photo Credit:
Center for iPS cell Research and Application, Kyoto University



John B. Gurdon
Gurdon Institute in Cambridge, UK



Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors

Kazutoshi Takahashi,[1] Koji Tanabe,[1] Mari Ohnuki,[1] Megumi Narita,[1,2] Tomoko Ichisaka,[1,2] Kiichiro Tomoda,[3] and Shinya Yamanaka[1,2,3,4,*]

Successful reprogramming of differentiated human somatic cells into a pluripotent state would allow creation of patient- and disease-specific stem cells. We previously reported generation of induced pluripotent stem (iPS) cells, capable of germline transmission, from mouse somatic cells by transduction of four defined transcription factors. Here, we demonstrate the generation of iPS cells from adult human dermal fibroblasts with the same four factors: Oct3/4, Sox2, Klf4, and c-Myc. Human iPS cells were similar to human embryonic stem (ES) cells in morphology, proliferation, surface antigens, gene expression, epigenetic status of pluripotent cell-specific genes, and telomerase activity. Furthermore, these cells could differentiate into cell types of the three germ layers in vitro and in teratomas. These findings demonstrate that iPS cells can be generated from adult human fibroblasts.

Cell 2007;131: 861

Rapamycin slows aging in mice

John E. Wilkinson[1], Lisa Burmeister[2], Susan V. Brooks[3], Chi-Chao Chan[4], Sabrina Friedline[2], David E. Harrison[5], James F. Hejtmancik[6], Nancy Nadon[7], Randy Strong[8], Lauren K. Wood[3], Maria A. Woodward[9], and Richard A. Miller[2]

Rapamycin increases lifespan in mice, but whether this represents merely inhibition of lethal neoplastic diseases, or an overall slowing in multiple aspects of aging is currently unclear. We report here that many forms of age-dependent change, including alterations in heart, liver, adrenal glands, endometrium, and tendon, as well as age-dependent decline in spontaneous activity, occur more slowly in rapamycin-treated mice, suggesting strongly that rapamycin retards multiple aspects of aging in mice, in addition to any beneficial effects it may have on neoplastic disease.

Aging Cell 2012,11: 675

Forever young: SIRT3 a shield against mitochondrial meltdown, aging, and neurodegeneration

Brad Kincaid and Ella Bossy-Wetzel*

and antioxidant defenses. As a result, the mitochondrial energy metabolism increases. In addition, SIRT3 prevents apoptosis by lowering reactive oxygen species and inhibiting components of the mitochondrial permeability transition pore. Mitochondrial deficits associated with aging and neurodegeneration might therefore be slowed or even prevented by SIRT3 activation. In addition, upregulating SIRT3 activity by dietary supplementation of sirtuin activating compounds might promote the beneficial effects of this enzyme. The goal

Front Aging Neurosci 2013;5: 1

Yaşlılarda Enfeksiyon Sorunu

- Daha sık, daha ağır
- Farklılıklar gösterir:
  - Klinik seyir
  - Laboratuar bulguları
  - Epidemiyolojik özellikler
  - Tedavi şemaları
  - Enfeksiyon kontrolü
- Pnömoni, grip ve bakteriyemi komplikasyonları yaşlılarda belli başlı 10 major ölüm nedenlerinden
- Yaşlanma enfeksiyonlar için risk faktörü; enfeksiyonlar da yaşlanmayı hızlandırıyor!
  - Patojenlerin direkt doku hasarına yol açması
  - Inflamasyonun yıkıcı etkisi!
  - Latent / kronik enfeksiyonların yaşlanmayı hızlandırması

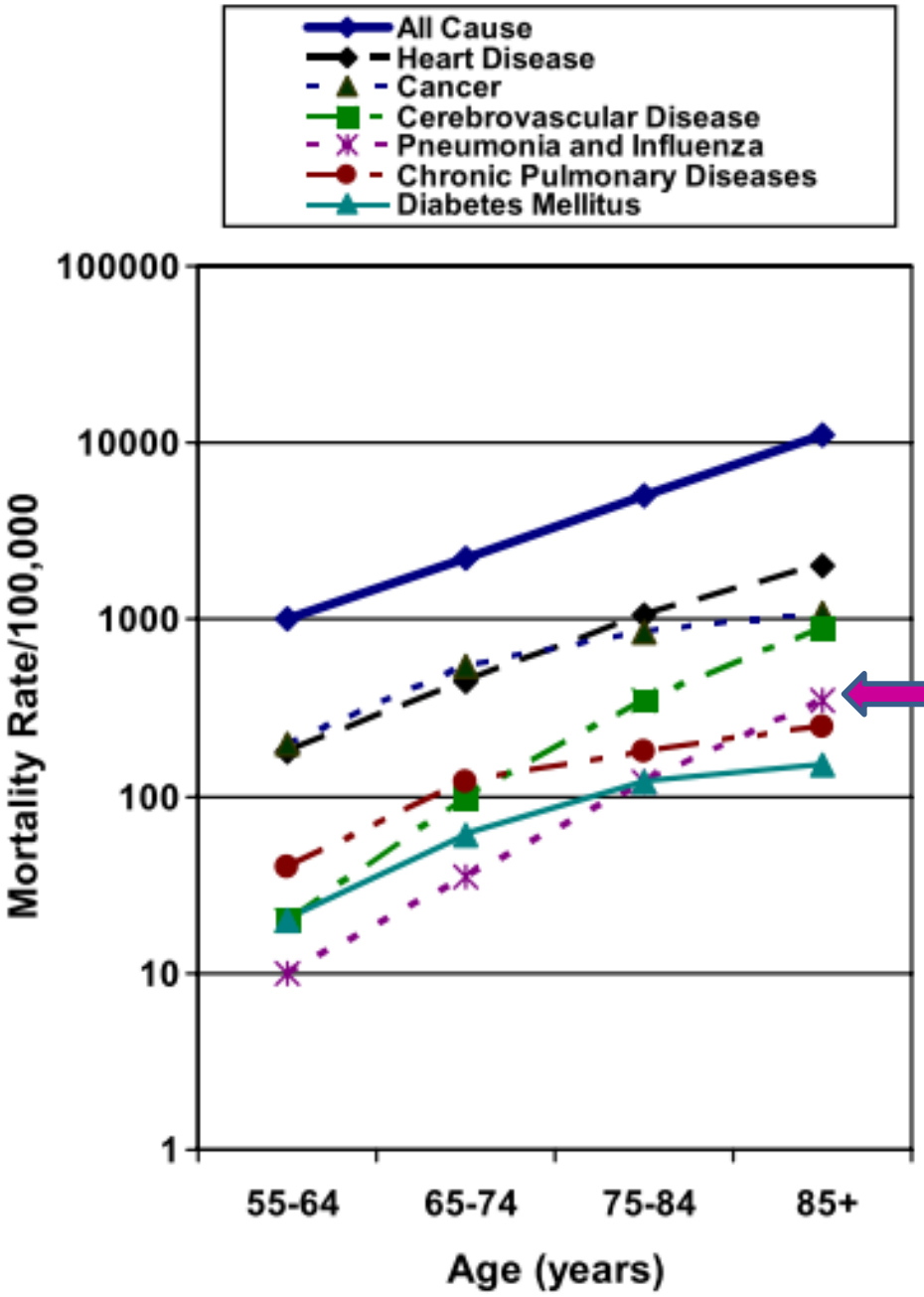
Enfeksiyonlara Duyarlık Artmıştır

* Yaşa bağlı olarak immün sistemde aksaklıklar enfeksiyona duyarlığı arttırır: "*immunosenescence*"
* Çelişkili bulgular olsa da…genel görüş:
  - İmmün sistem zayıflamıştır
  - İmmünokompetan hücrelerde sorun kalitatif…
* İki farklı yaklaşım:
  - Genel anlamda savunma sistemin zayıflaması
  - Savunmanın bazı parametrelerinin aksaması

  (İmmün sistemin hızlı çoğalan hücrelerindeki telomer kısalması ile ilintili)

* Hümoral / hücresel yanıttaki zayıflamaya iki kanıt:
  - Tbc reaktivasyonu
  - Grip aşısının etkinliğinde azalma

Yaşlanma ve İmmün Sistem: Grip Aşısı Örneği

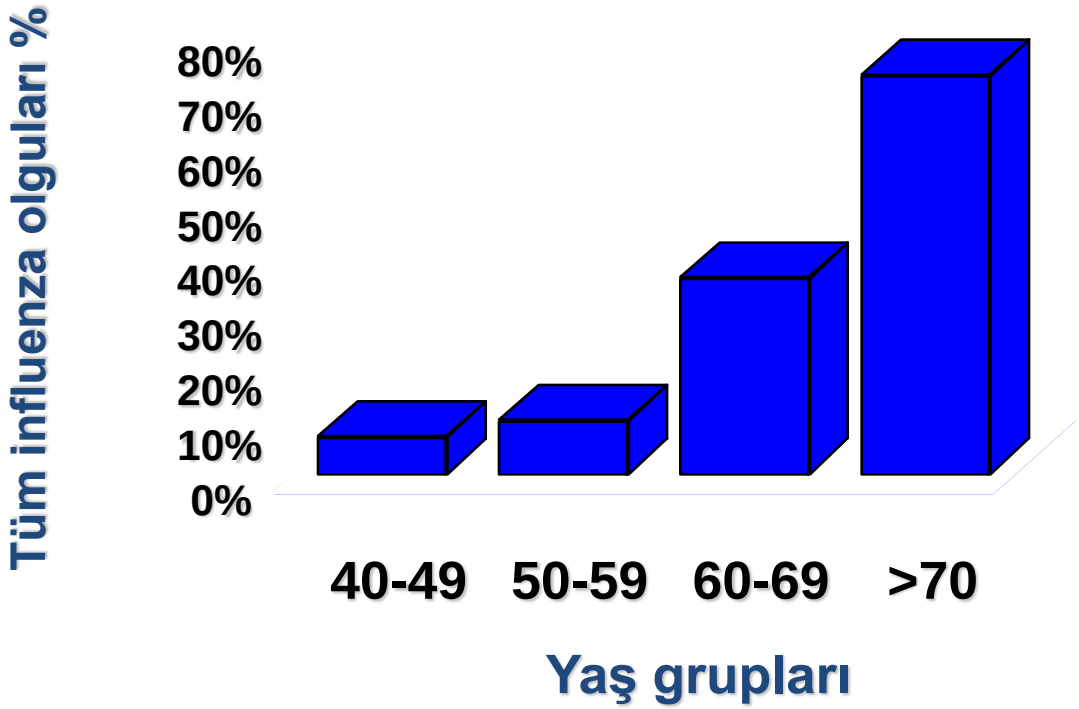


Pnömoni ve Grip

Table 2. Current recommendations for vaccines in the elderly (age ≥ 65 years).

Vaccine	Recommended frequency	Studies in elderly	Evidence of efficacy in the elderly
Pneumococcal (PPV)	Once at age ≥65 years	+	+/−
Influenza	1 dose annually	+	+/−
Tetanus, diphtheria	1 dose Td every 10 years	+	+
Herpes Zoster	Once at age ≥60 years	+	+
Hepatitis B	High-risk[a,b]	+	+
Measles, mumps, rubella	High-risk[a,b]	−	NA
Hepatitis A	High-risk[a,b]	+	NA
Meningococcal	High-risk[1,2]	+	NA
Japanese encephalitis	Travel[b]	+/−	NA
Typhoid (polysaccharide)	Travel[b]	−	NA
Typhoid (oral, live)	Travel[b]	−	NA
Polio	Travel[b]	−	NA
Yellow fever	Travel[b]	−	NA
Rabies	Travel[b]	+/−	NA
Cholera	Travel[b,c]	−	NA
Tick-borne encephalitis	Travel[b,c]	+	+

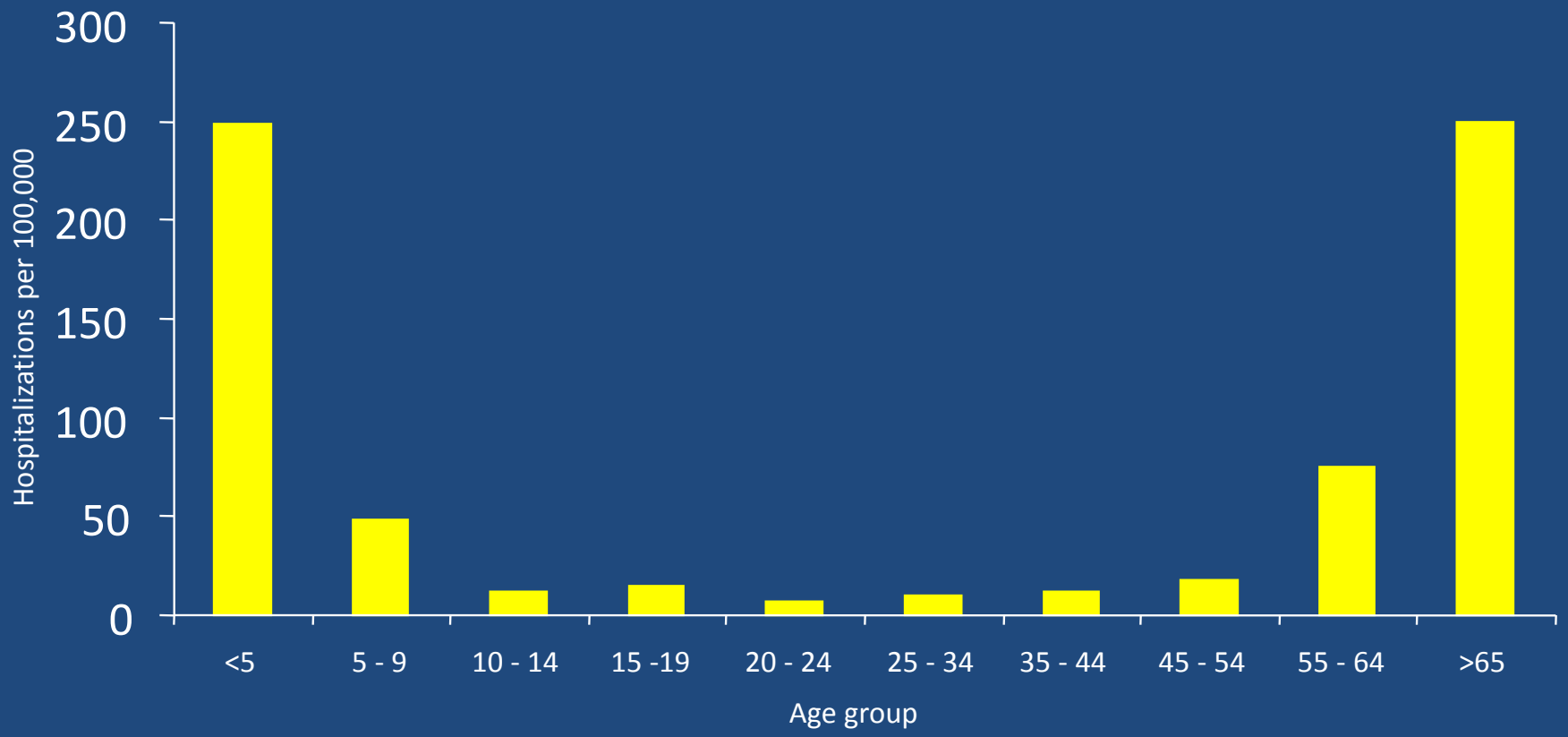
GRİP yaşlılar için Neden önemlidir ?



Epidemilerde hastaların yaş gruplarına göre dağılımı

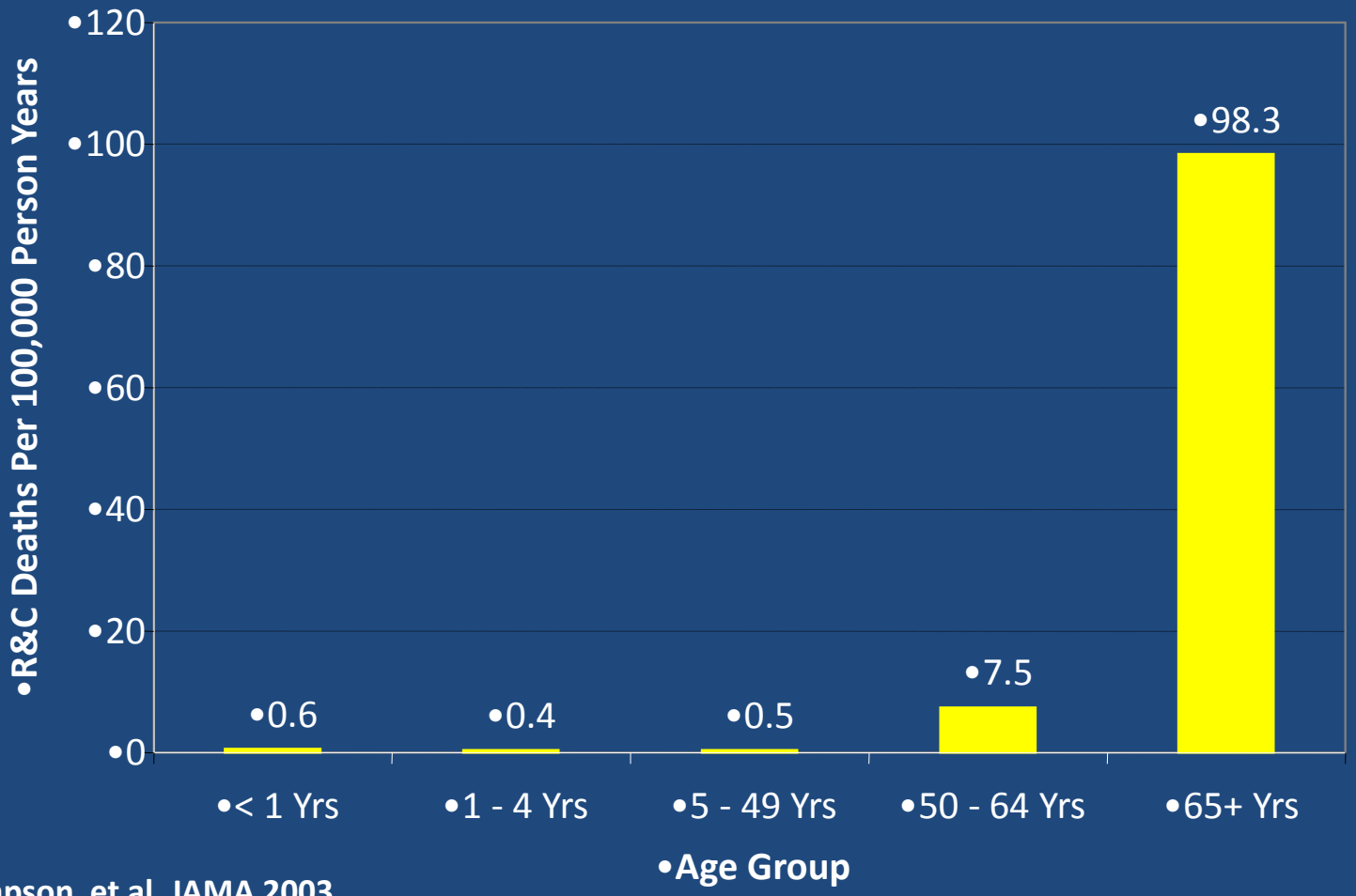
Betts FR, Douglas RG. Principles and practice of infectious diseases, 3rd ed., 1990;39:1306-25

Yaşlara Göre Gribe Bağlı Hastane Yatışları



Terebuh, Uyeki, Fukuda. PIDJ 2003;22:S231

Yaşlara Göre Gribe Bağlı ölümler



*Thompson, et al. JAMA 2003

**Respiratory & Circulatory

From bench to bedside and back: the SENIEUR Protocol and the efficacy of influenza vaccination in the elderly

Piotr Trzonkowski · Jolanta Myśliwska · Graham Pawelec · Andrzej Myśliwski

Table 1. SENIEUR protocol: inclusion and exclusion criteria for admission to immunogeriatic studies[a].

Inclusion criteria
1. Men and women 65 years of age or older
2. Community dwelling
3. Stable chronic non–immunologically mediated conditions (e.g. osteoarthritis, hypertension)
4. Normal range of reference laboratory for complete blood count and differential, thyroid-stimulating hormone, serum vitamin B_{12}, folate, vitamin E, aspartate aminotransferase/serum glutamate-oxaloacetate transaminase and alanine aminotransferase/serum glutamic pyruvate transaminase, albumin, fasting blood glucose, blood urea nitrogen and serum creatinine
Exclusion criteria
1. History or clinically apparent immunologically mediated chronic conditions (e.g. rheumatoid arthritis, lupus erythematosus)
2. Immunodeficiency
3. Severe respiratory disease requiring supplemental oxygen
4. Psychiatric disorder, untreated or not in remission
5. Infection within 2 weeks of immunization
6. Inflammatory processes such as known chronic infections, inflammatory bowel disease or Westergren sedimentation rate (>50 mm/h for men, >60 mm/h for women)
7. All malignancies (excluding nonmelanotic skin cancer) and lymphoproliferative disorders diagnosed or treated actively during the past 5 years
8. Arteriosclerotic event during the 2 weeks before enrollment (e.g. medically documented myocardial infarction, stroke, recanalization of the femoral arteries, claudication, or transient ischemic attack)
9. Cardiac insufficiency, if heart failure present (New York Heart Association functional class III or IV)
10. Poorly controlled hypertension (systolic blood pressure ≥180 mmHg, diastolic blood pressure ≥100 mmHg)
11. Renal Insufficiency (serum creatinine ≥2.0 or blood urea nitrogen ≥40)
12. Elevated or low glucose (fasting ≥140 or <70; nonfasting >200)
13. Cognitive impairment: score of <23 on the Folstein Mini-Mental State Examination.
14. Depression or mood alteration: score of ≥6 on the Geriatric Depression Scale (ref)
15. Malnutrition as defined by clinical judgment and by decreased serum albumin (<3.2 g/l) or hypercholesterolemia (<160 mg/dl), or low total lymphocyte count (<1500/ml^3).
16. Anemia (Hct <30% or low serum vitamin B_{12}, folate or vitamin E level)
17. History of or current alcoholism or consuming >2 oz of ethyl alcohol/d; current drug abuse; currently smoking ≥10 cigarettes./d.
18. Medication exclusions include prednisone >5 mg/d (or equal), colchicines, imuran, methotrexate, azathioprine, cyclophosphamide, cyclosporine, or interferons.

Biogerontol 2009;10: 83

Trends Immunol 2009;30: 351

Influenza Vaccination and Reduction in Hospitalizations for Cardiac Disease and Stroke among the Elderly

Kristin L. Nichol, M.D., M.P.H., M.B.A., James Nordin, M.D., M.P.H., John Mullooly, Ph.D., Richard Lask, M.D., Kelly Fillbrandt, B.S., and Marika Iwane, Ph.D.

CONCLUSIONS

In the elderly, vaccination against influenza is associated with reductions in the risk of hospitalization for heart disease, cerebrovascular disease, and pneumonia or influenza as well as the risk of death from all causes during influenza seasons. These findings highlight the benefits of vaccination and support efforts to increase the rates of vaccination among the elderly.

N Engl J Med 2003;348: 1322

Decline in influenza-associated mortality among Dutch elderly following the introduction of a nationwide vaccination program

Angelique G.S.C. Jansen[a,b], Elisabeth A.M. Sanders[b], Kristin L. Nichol[c], Anton M. van Loon[d], Arno W. Hoes[a], Eelko Hak[a,b,*]

With a retrospective nationwide cohort study in the Netherlands over 1992–2003, using mortality and viral surveillance data, the aim was to assess by means of rate difference methods the influenza-associated mortality in the elderly before and after the introduction of a nationwide influenza vaccination program in 1996 (vaccination coverage raised from below 50 to 80%). The average annual influenza-associated mortality declined in the years before and after the introduction from 131 to 105 per 100,000 persons (relative risk 0.80). The decline was largest in the age group 65–69 years (relative risk 0.54) and less in those aged 75 years and older. Validation by Serfling-type regression analysis revealed similar results. In conclusion, routine influenza vaccination among Dutch elderly was associated with a significant decrease in influenza-associated mortality, notably in those aged 65–69 years.

Vaccine 2008;26: 5567

Impact of Influenza Vaccination on Seasonal Mortality in the US Elderly Population

Lone Simonsen, PhD; Thomas A. Reichert, MD, PhD; Cecile Viboud, PhD; William C. Blackwelde
Robert J. Taylor, PhD; Mark A. Miller, MD

Conclusions: We attribute the decline in influenza-related mortality among people aged 65 to 74 years in the decade after the 1968 pandemic to the acquisition of immunity to the emerging A(H3N2) virus. We could not correlate increasing vaccination coverage after 1980 with declining mortality rates in any age group. Because fewer than 10% of all winter deaths were attributable to influenza in any season, we conclude that observational studies substantially overestimate vaccination benefit.

Arch Intern Med 2005;165: 265

Influenza-related mortality in the Italian elderly: No decline associated with increasing vaccination coverage

Caterina Rizzo[a,*], Cécile Viboud[b], Emanuele Montomoli[c], Lone Simonsen[d], Mark A. Miller[b]

distribution primarily targeted for the elderly. These findings suggest that either the vaccine failed to protect the elderly against mortality (possibly due to immune senescence), and/or the vaccination efforts did not adequately target the frailest elderly. As in the US, our study challenges current strategies to best protect the elderly against mortality, warranting the need for better controlled trials with alternative vaccination strategies.

Vaccine 2006;24: 6468

Vaccines for preventing influenza in the elderly (Review)

Jefferson T, Di Pietrantonj C, Al-Ansary LA, Ferroni E, Thorning S, Thomas RE

THE COCHRANE COLLABORATION®

Cochrane re-arranged: Support for policies to vaccinate elderly people against influenza☆

Walter E.P. Beyer[a], Janet McElhaney[b], Derek J. Smith[c,d,a], Arnold S. Monto[e], Jonathan S. Nguyen-Van-Tam[f], Albert D.M.E. Osterhaus[a,*]

A B S T R A C T

The 2010 Cochrane review on efficacy, effectiveness and safety of influenza vaccination in the elderly by Jefferson et al. covering dozens of clinical studies over a period of four decades, confirmed vaccine safety, but found no convincing evidence for vaccine effectiveness (VE) against disease thus challenging the ongoing efforts to vaccinate the elderly.

However, the Cochrane review analyzed and presented the data in a way that may itself have hampered the desired separation of real vaccine benefits from inevitable 'background noise'. The data are arranged in more than one hundred stand-alone meta-analyses, according to various vaccine types, study designs, populations, and outcome case definitions, and then further subdivided according to virus circulation and antigenic match. In this way, general vaccine effects could not be separated from an abundance of environmental and operational, non vaccine-related variation. Furthermore, expected impacts of changing virus circulation and antigenic drift on VE could not be demonstrated.

We re-arranged the very same data according to a biological and conceptual framework based on the basic sequence of events throughout the 'patient journey' (exposure, infection, clinical outcome, observation) and using broad outcome definitions and simple frequency distributions of VE values. This approach produced meaningful predictions for VE against influenza-related fatal and non-fatal complications (average ~30% with large dispersion), typical influenza-like illness (~40%), disease with confirmed virus infection (~50%), and biological vaccine efficacy against infection (~60%), under conditions of virus circulation. We could also demonstrate a VE average around zero in the absence of virus circulation, and decreasing VE values with decreasing virus circulation and increasing antigenic drift.

We regard these findings as substantial evidence for the ability of influenza vaccine to reduce the risk of influenza infection and influenza-related disease and death in the elderly.

Vaccine, 2013

Table 1. Vaccines and their efficacy in elderly persons.

Disease	Vaccine type	Vaccine efficacy in elderly persons, %
Influenza		
A/H1N1	Inactivated virus, subunit, adjuvanted subunit, and virosome	55 (32)[a]
A/H3N2	Inactivated virus, subunit, adjuvanted subunit, and virosome	58 (46)[a]
B	Inactivated virus, subunit, adjuvanted subunit, and virosome	41 (29)[a]
Hepatitis		
A	Inactivated virus	63[b]
A	Virosome	65 (97)[c]
B	Subunit	33[b]
Herpes zoster	Live attenuated virus	64 (18)[d]
Pertussis	Toxoid and acellular components	>81[e]
Pneumonia	Nonconjugated polysaccharide	50–70[f]
Poliomyelitis	Inactivated virus	99[g]
Tetanus and diphtheria	Toxoid	99 and 84[h]
Tickborne encephalitis	Inactivated virus	70[i]
Yellow fever	Live attenuated virus	100

I-MOVE

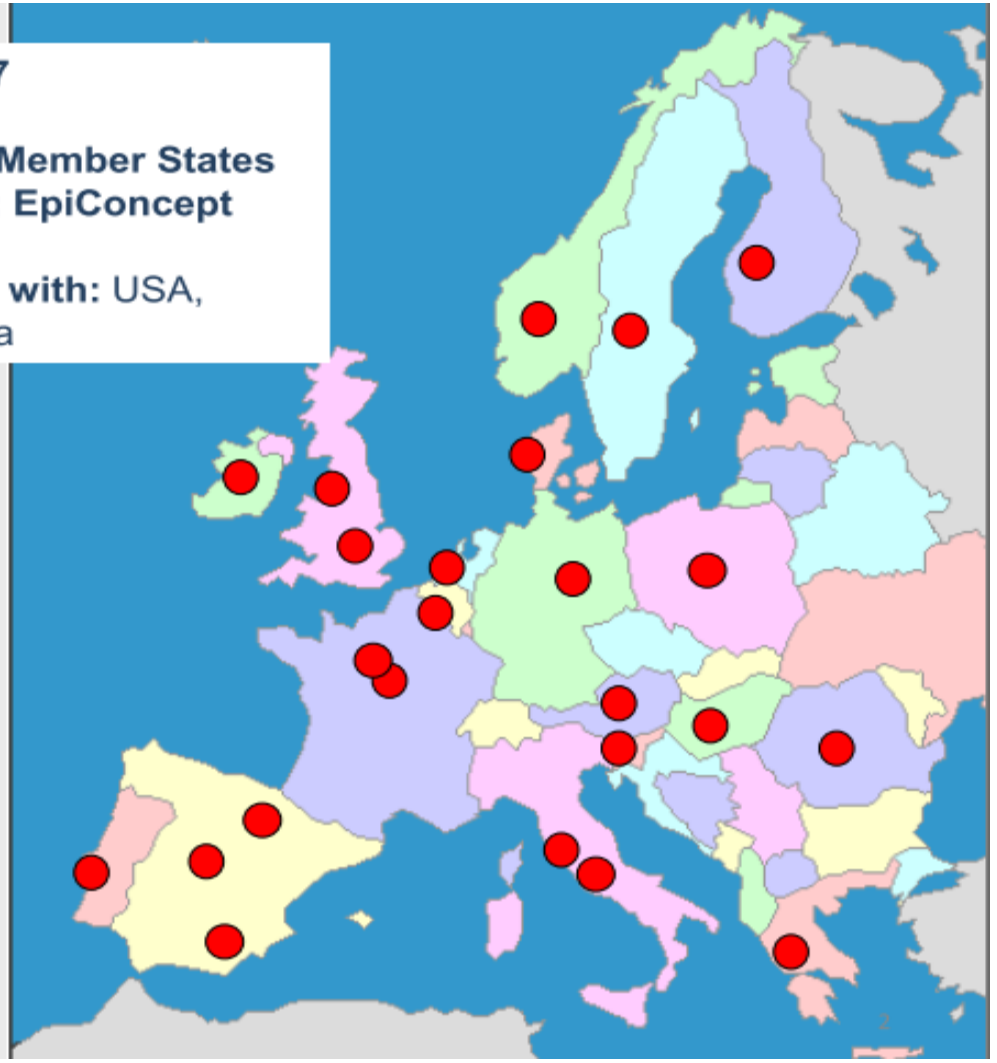
(The Influenza Monitoring Vaccine Effectiveness in EUROPE; ECDC)

- ECDC
  - EISN
- Health Prot
  Dublin, Irela
- Instituto de
- Institut de V
- National Ce
  Budapest, H
- National Ins
  Developme
  Immunolog
- National Institute for Pubic Health and the Environment (RIVM), Bilthoven, The Nertherlands
- Norvegian Institute of Public Health, Oslo, Norway
- National Public Health Institute, Helsinki, Finland
- Robert Koch Institute, Berlin, Germany
- Scientific Institute of Public Health, Brussels, Belgium
- Smittskiddsinstitutet, Stockholm, Sweden
- Statens Serum Institut, Copenhagen, Denmark
- Scottish Centre for Infection and Environmental Health (CIEH)
- Istituto Superiore Di Sanita, Rome, Italy
- Slovenia, National Institute of Health
- Greece, National Institute of Health
- Royal College of General practitioners Brimingham Research Unit, UK
- Insituto Nacional de Saude Dr. Ricardo Jorge, Lisboa, Portugal.

I-MOVE: since 2007

- **ECDC**
- **20 EU & EEA Member States**
- **Coordination: EpiConcept**

- **Collaboration with:** USA, Canada, Australia



Early estimates of seasonal influenza vaccine effectiveness in Europe among target groups for vaccination: results from the I-MOVE multicentre case–control study, 2011/12

E Kissling (e.kissling@epiconcept.fr)[1], M Valenciano[1], I-MOVE case–control studies team[2]

TABLE 4

Pooled crude (n=530) and adjusted (n=521) 2011/12 seasonal influenza vaccine effectiveness against laboratory-confirmed A(H3) influenza in target groups for vaccination at study sites in seven European Union countries, week 48/2011–week 7/2012

Crude versus adjusted	Cases/controls	Vaccinated cases/controls	Vaccine effectiveness (%)	95% confidence intervals
Crude[a]	206/324	54/123	42.9	10.3 to 63.6
Adjusted model [b,c]			43.0	-0.4 to 67.7

[a] Study site included in the model as fixed effect.

[b] Model adjusted for presence of at least one chronic disease, sex, at least one hospitalisation for chronic disease in the previous 12 months, age group, practitioners' visits in the previous 12 months (0-1, 2-4 and ≥5 visits) and week of symptom onset.

[c] Onset week 49 dropped due to no cases (nine records dropped).

2010-2011 influenza seasonal vaccine, preliminary mid-season effectiveness estimates: reason for concern, confounding or are we following the right track?

I Puig-Barberà (puig_ioa@gva.es)[1]

Eurosurveillance 2012

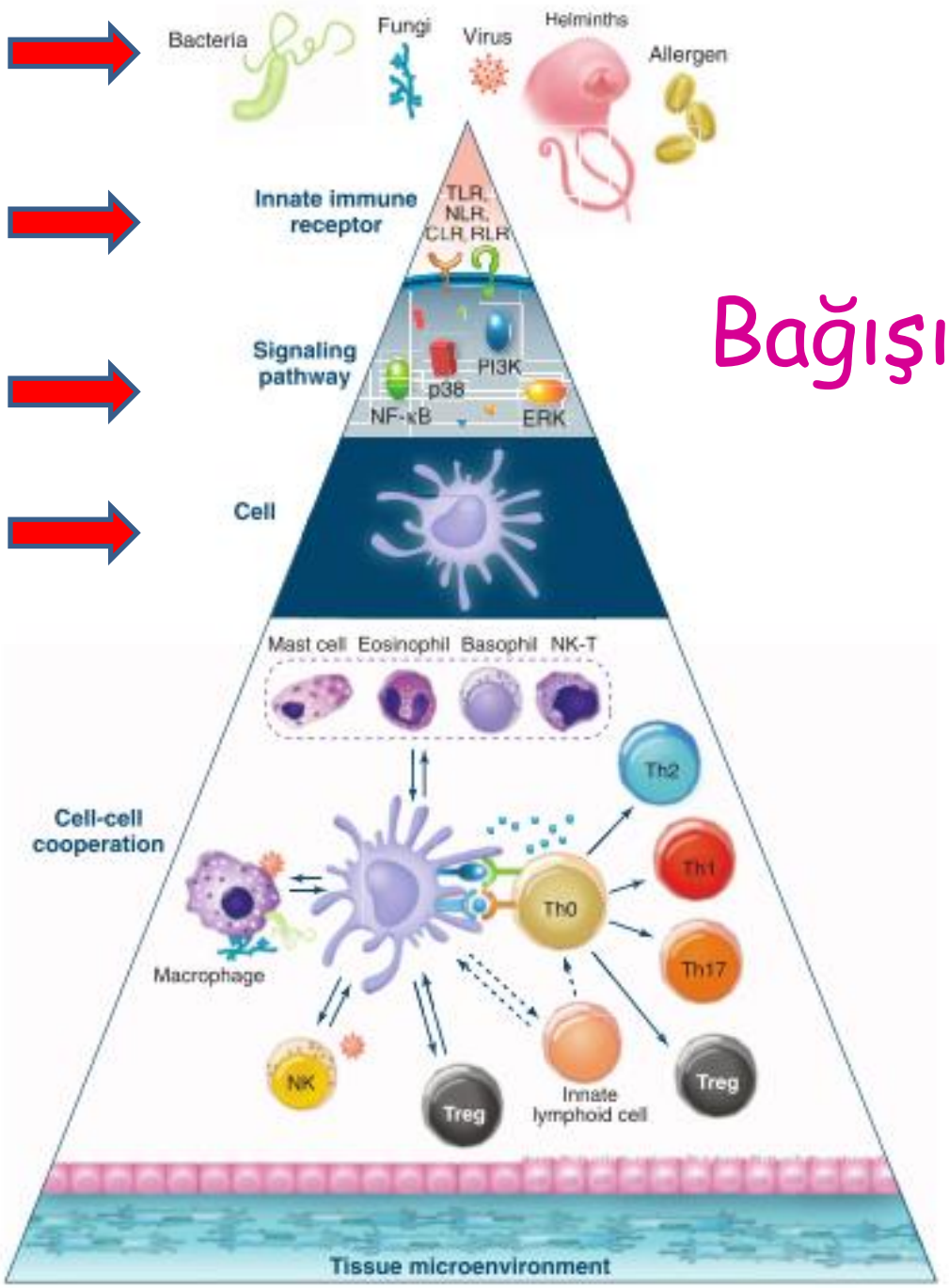
Yabancı Mikroorganizma

Reseptör

Sinyal iletisi

Hücre

Hücreler arası ilişki

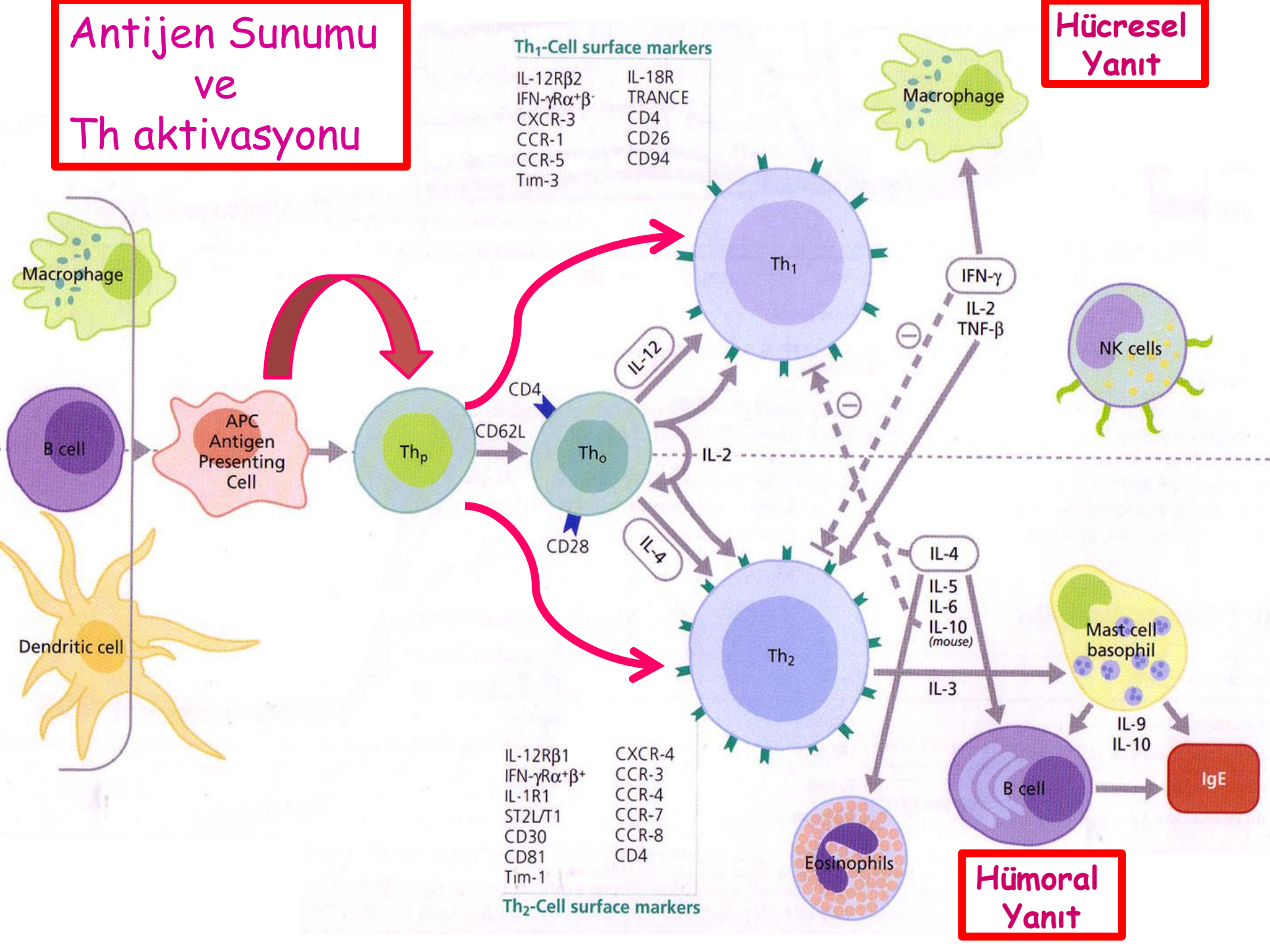


Bağışık Yanıt

Science 2012;337: 431

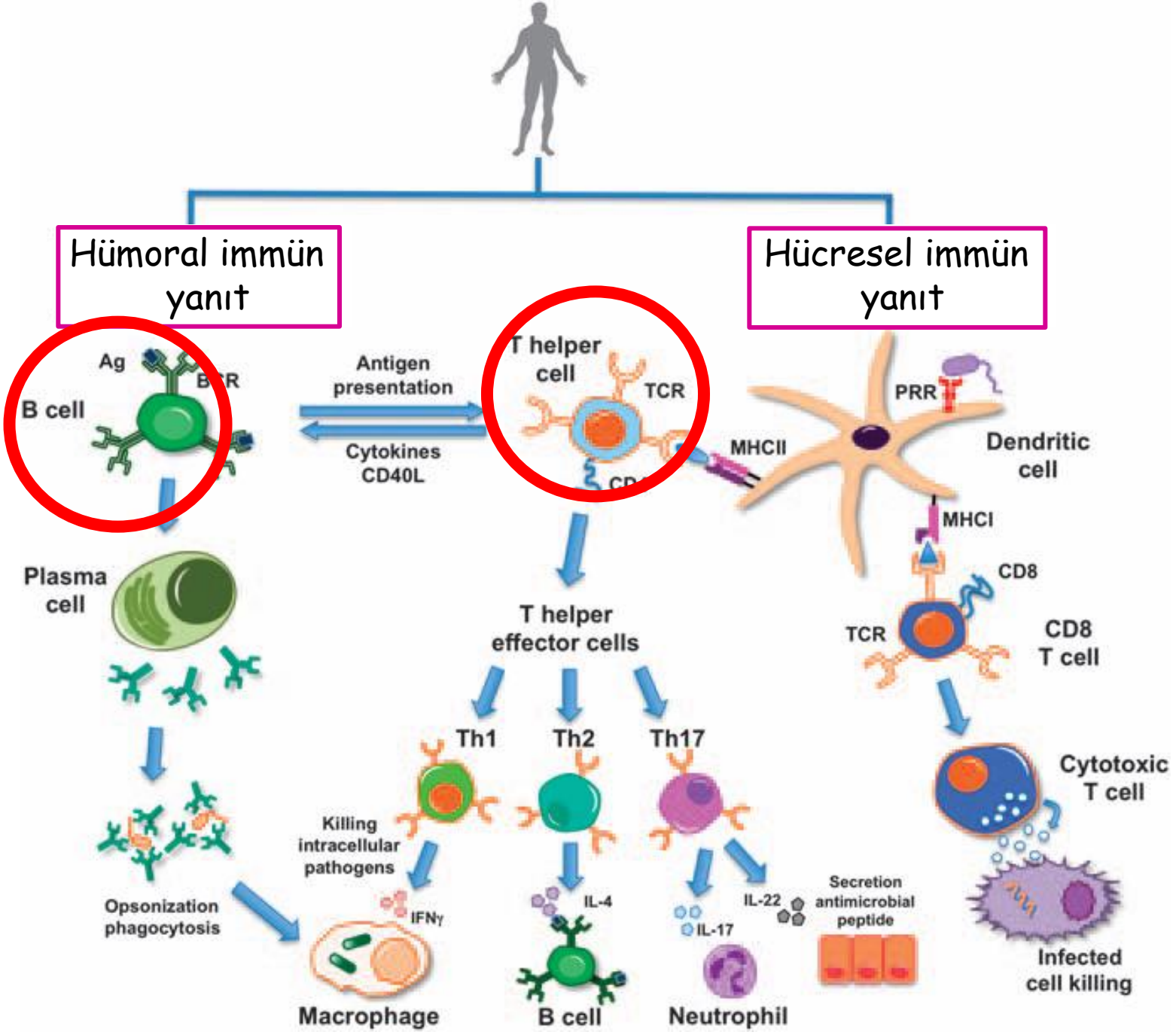
Antijen Sunumu ve Th aktivasyonu

Hücresel Yanıt



Hümoral Yanıt


BU ALEMDE İKİ BÜYÜK VAR
BEŞİKTAŞ ve 70'LİK RAKI



Immunol Cell Biol 2011;89: 332

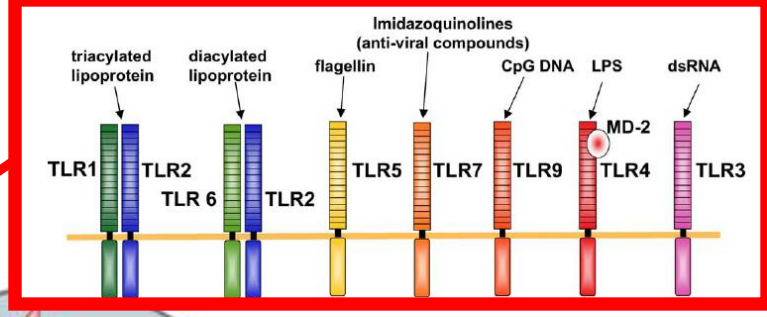
Edinsel bağışıklık karşılaştığı yabancı maddelere karşı konağı
Üç aşamada savunur:

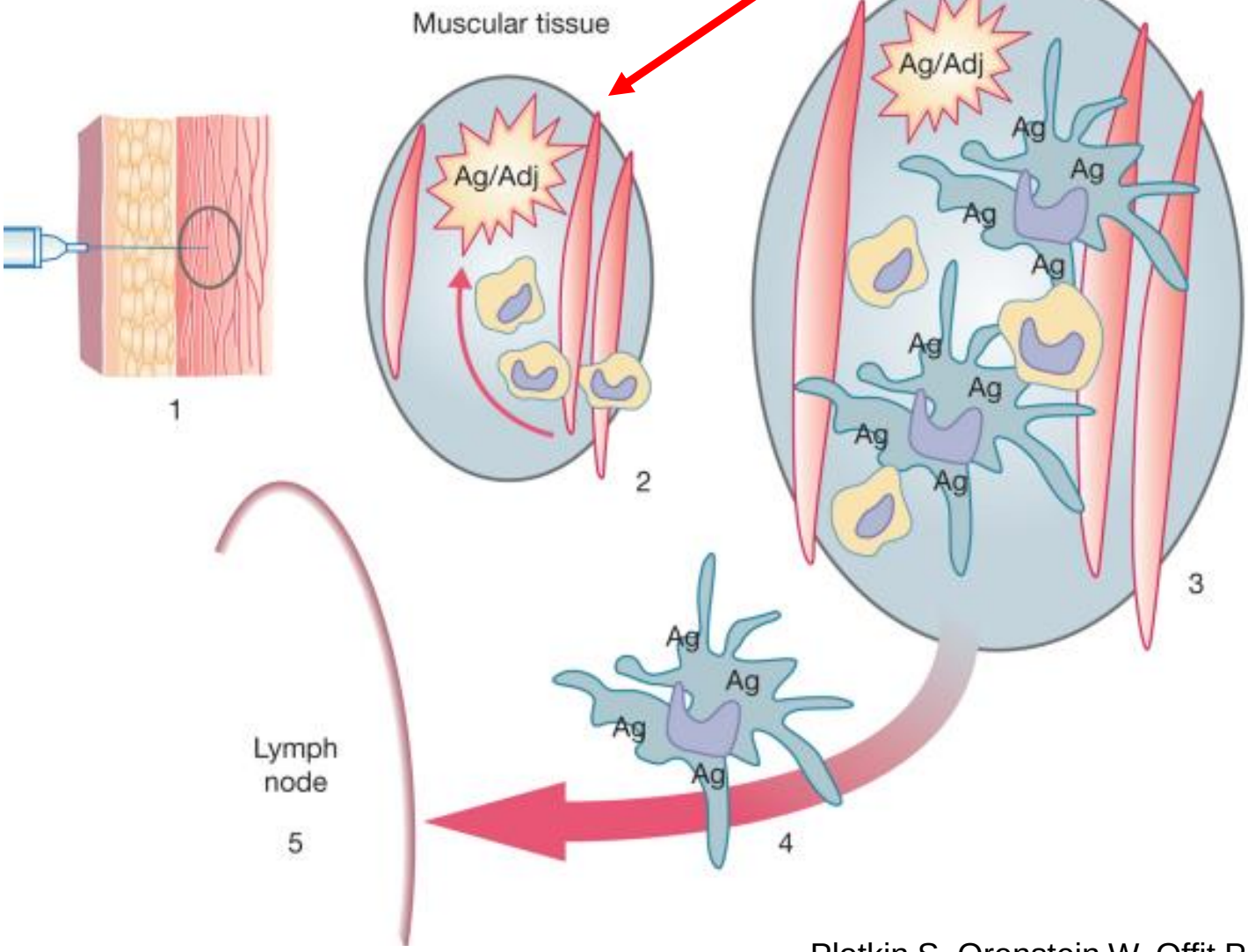
A- Yabancı olduğunu algılar

B- Bunlara karşı savunmayı sağlar

C- Bir daha unutmamak üzere belleğine kaydeder

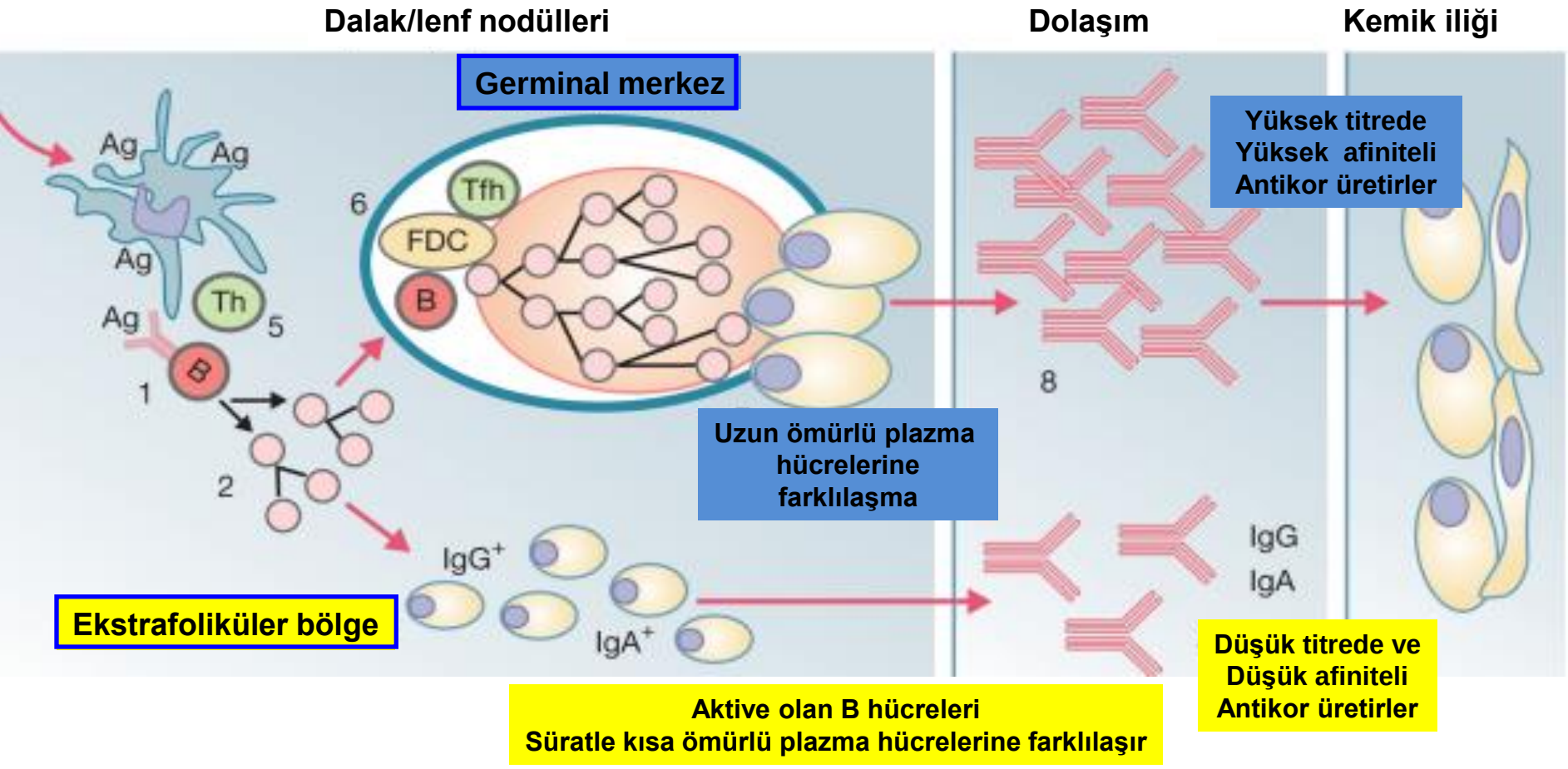
Aşıya yanıt başlıyor...

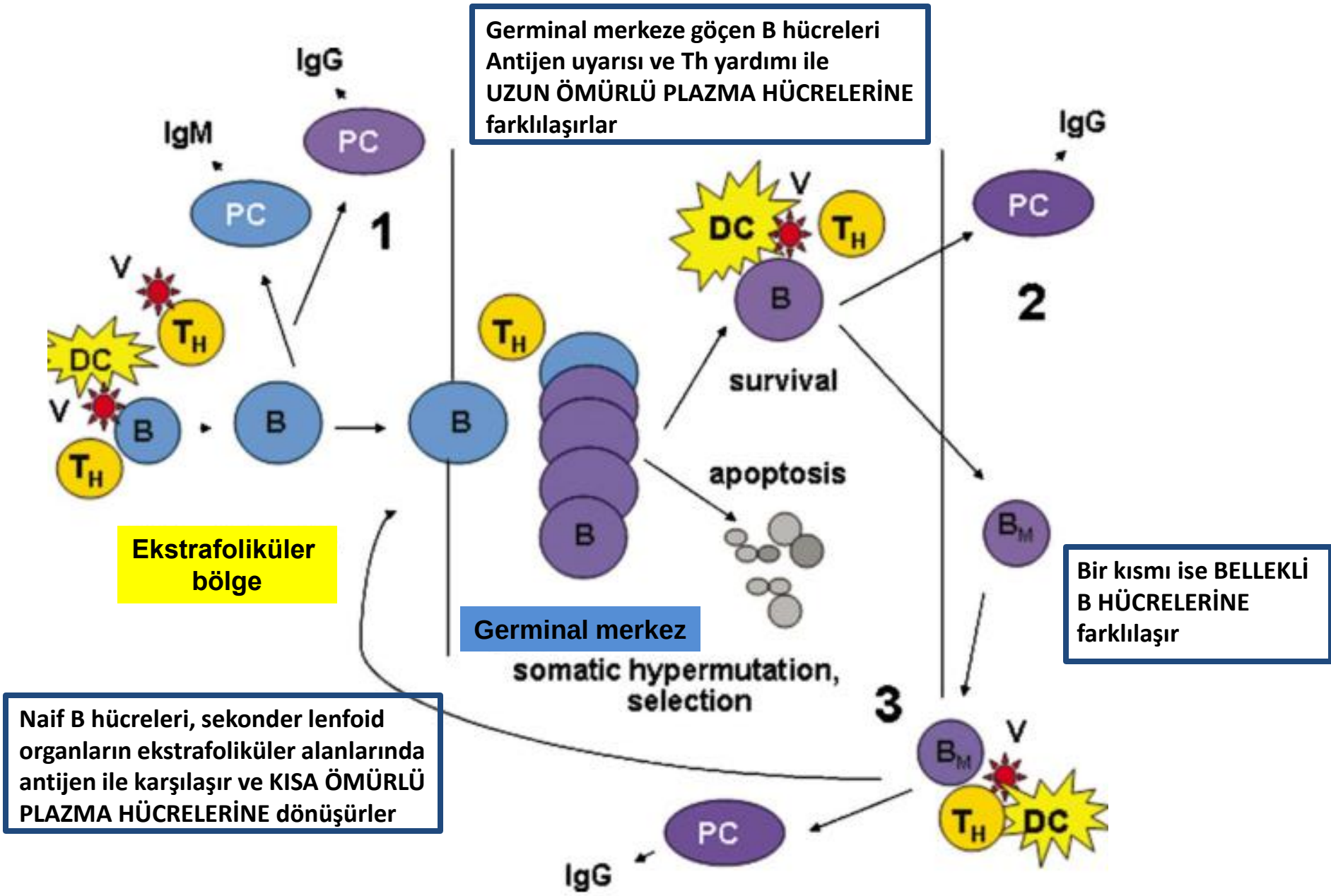




Plotkin S, Orenstein W, Offit P: Vaccines, 15 Edt, 2008

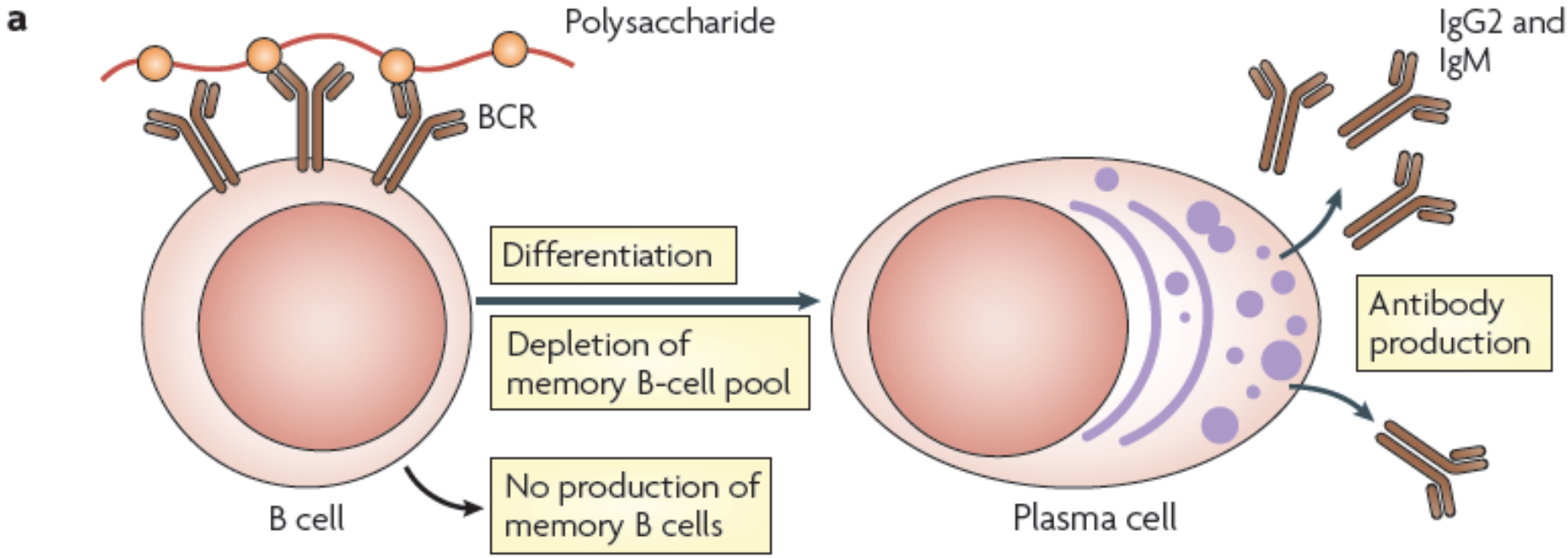
Protein antijenlerine karşı ekstrafoliküler ve germinal merkezde yanıt (TD)





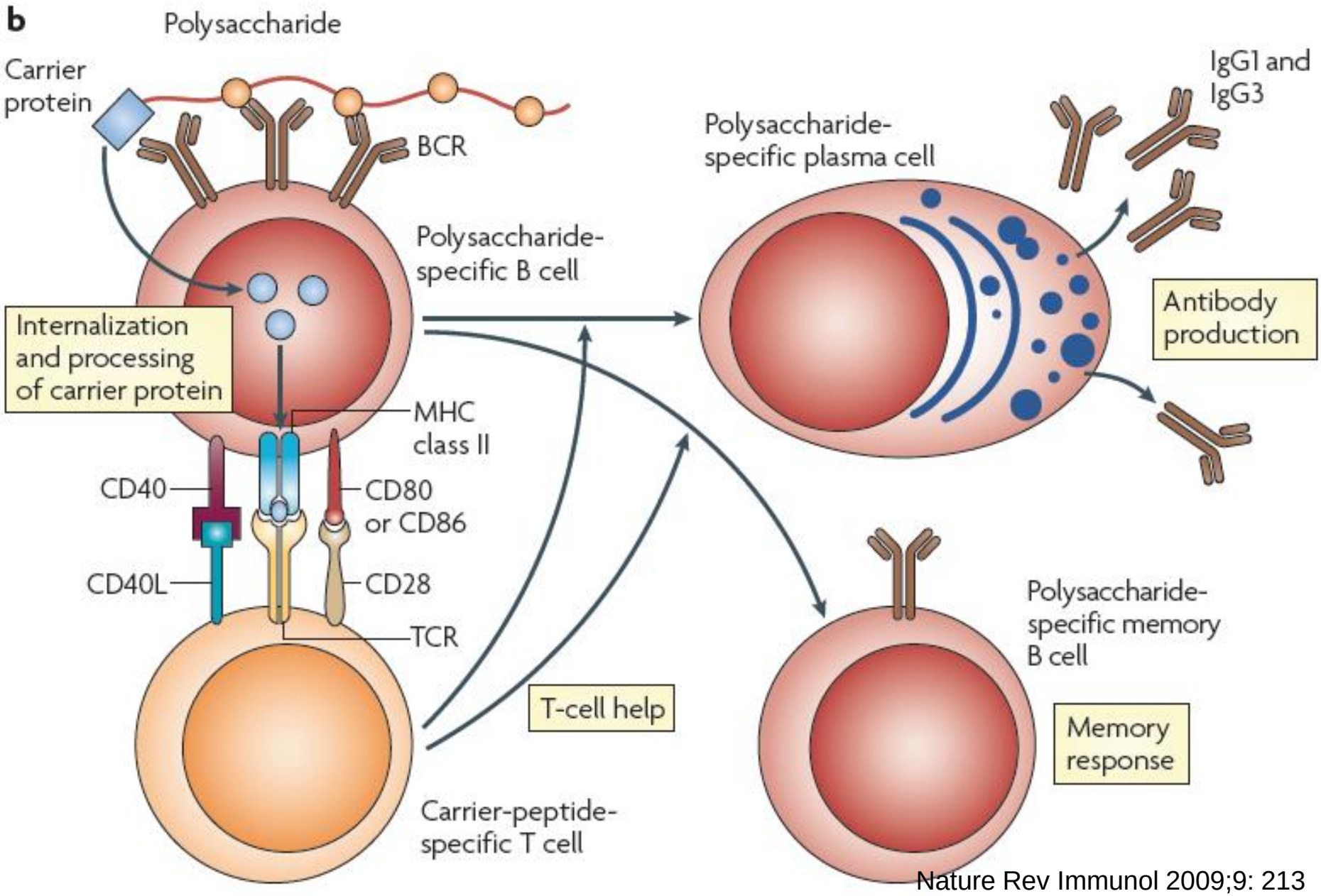
Ann Rev Immunol 2004;22: 711

Polisakkarit antijenlerine karşı ekstrafoliküler B hücre yanıtı



Nature Rev Immunol 2009;9: 213

Protein-Polisakkarid konjüge aşılarına karşı B hücre yanıtı



Nature Rev Immunol 2009;9: 213

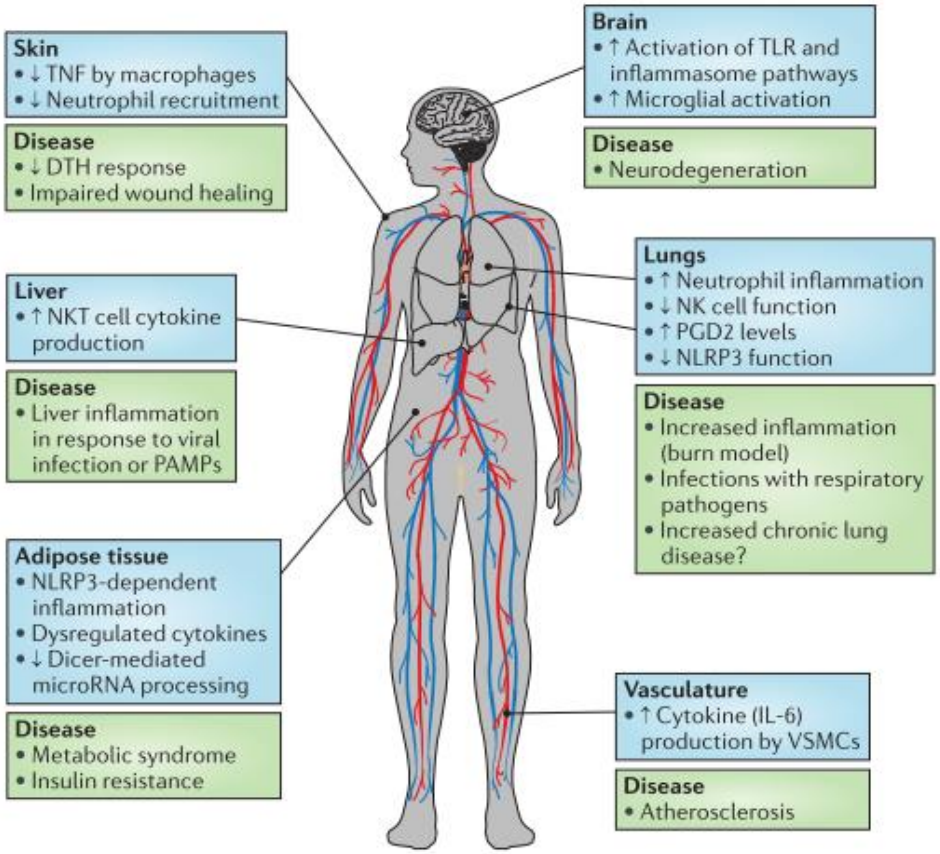
YAŞ TESTİ

Bu iki nesne arasındaki bağlantıyı biliyorsan üzgünüm ama...

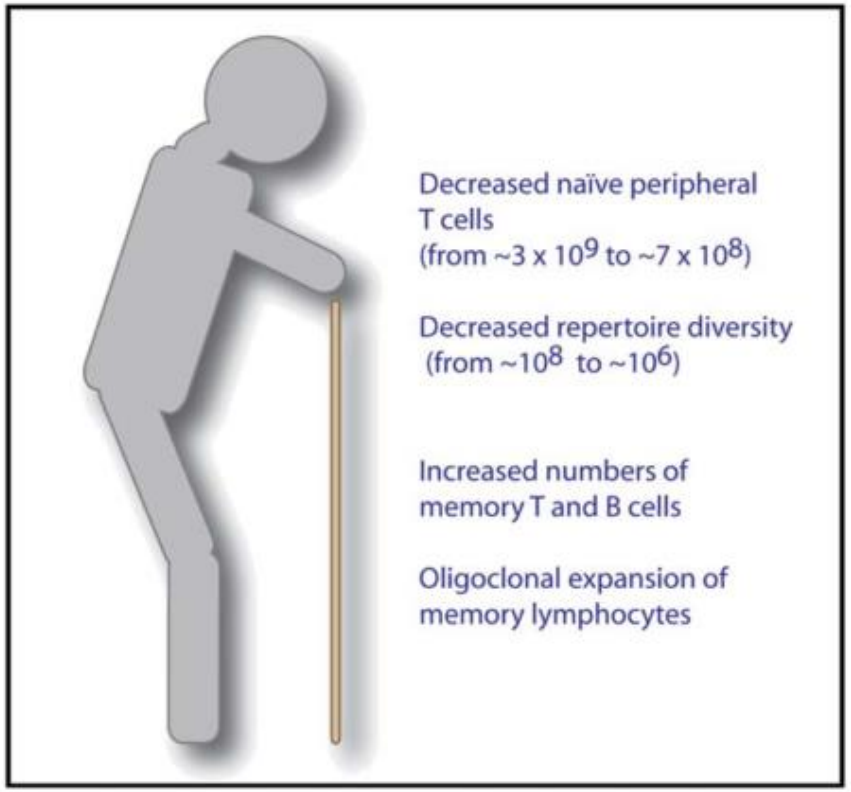
YAŞLISIN

Yaşlanma ve Hastalıklar Nedeniyle Ortaya Çıkan:

Doğal Bağışıklık ile İlgili Değişiklikler



Edinsel Bağışıklık ile İlgili Değişiklikler



Nature Rev Immunol 2013;doi:10.1038/nri3547

Immunity 2006;24: 495

Yaşlanma ile İmmün Sistemde Gözlenen Farklılaşmalar

- Hücrelerin kaynağında sorun var
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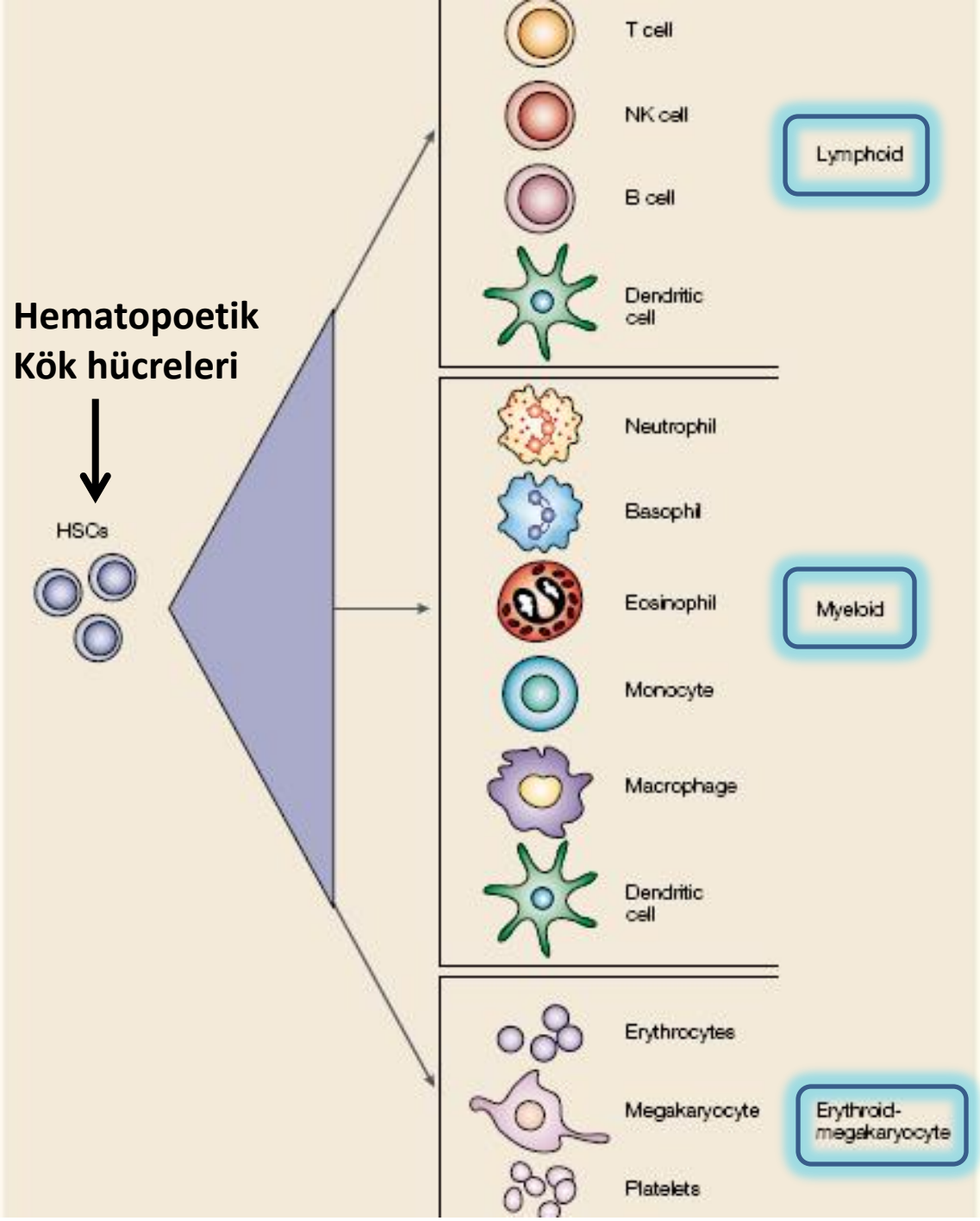
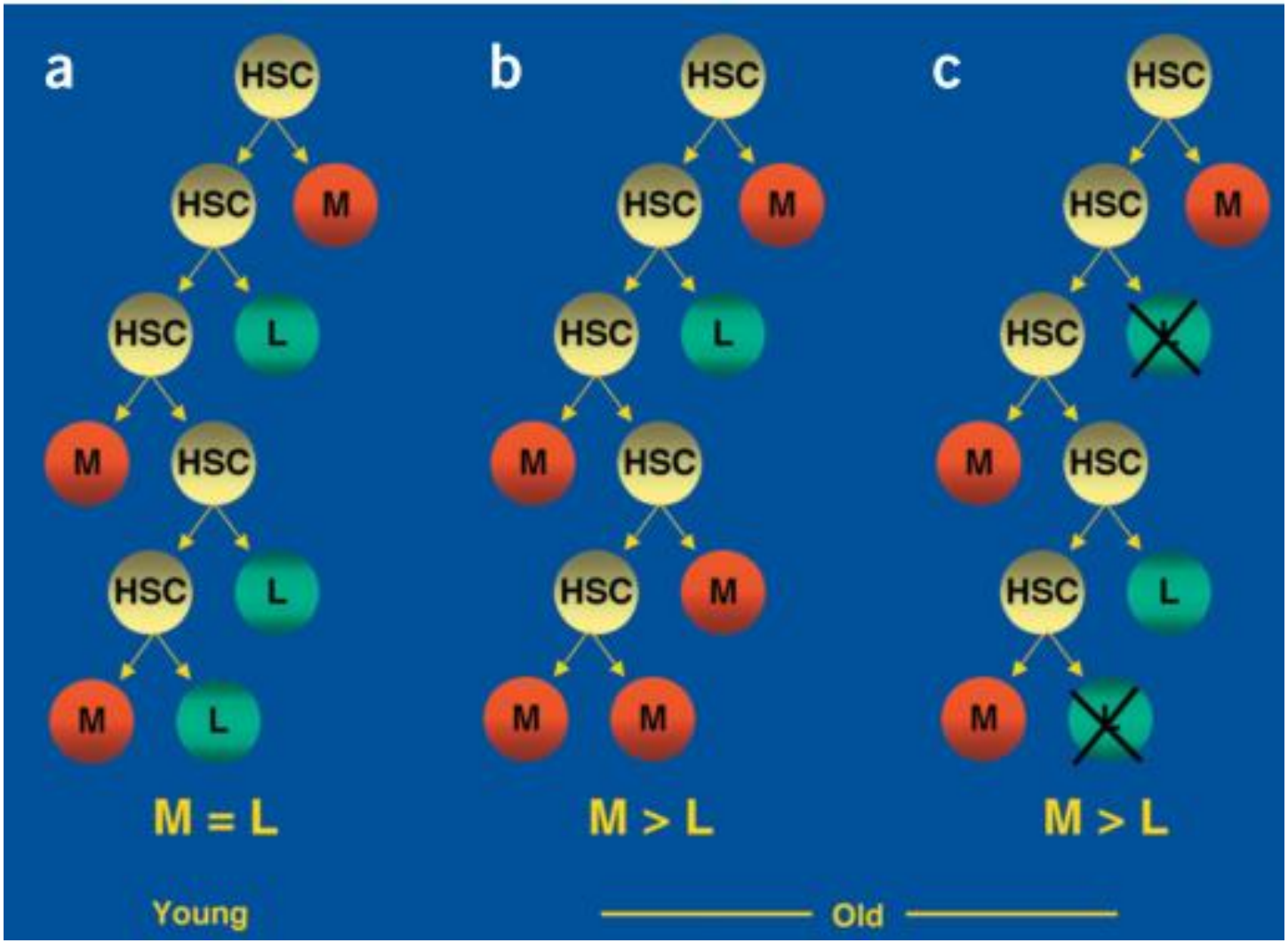
- Sitokin paterninde farklılaşma
- Antijen sunumunda zayıflama
- T lenfositlerinde farklılaşma
- B lenfositlerinde farklılaşma



Nature Rev Immunol 2002;2: 127

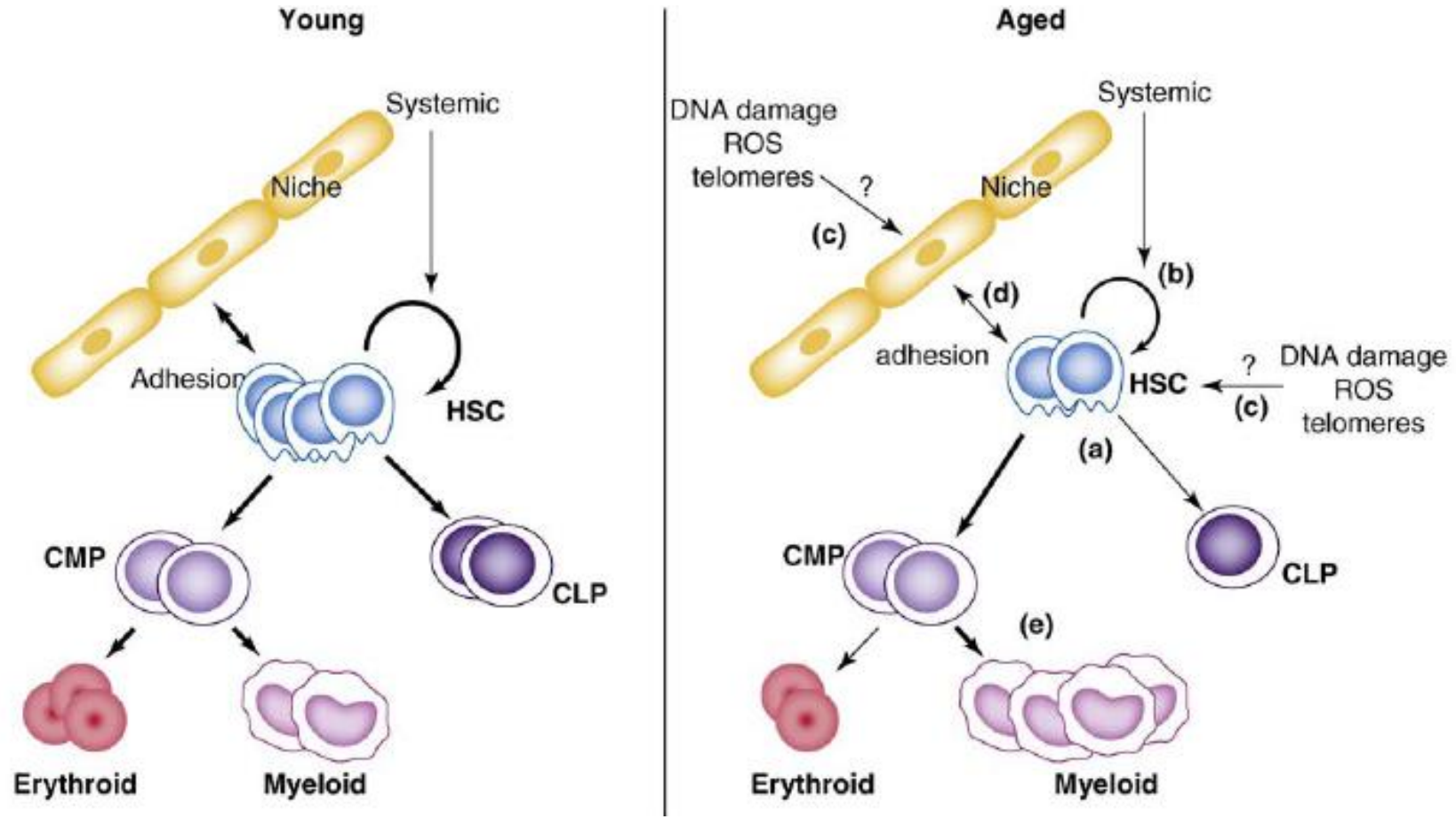
Farede kemik iliği içeriği



Nature Immunol 2004;5: 133

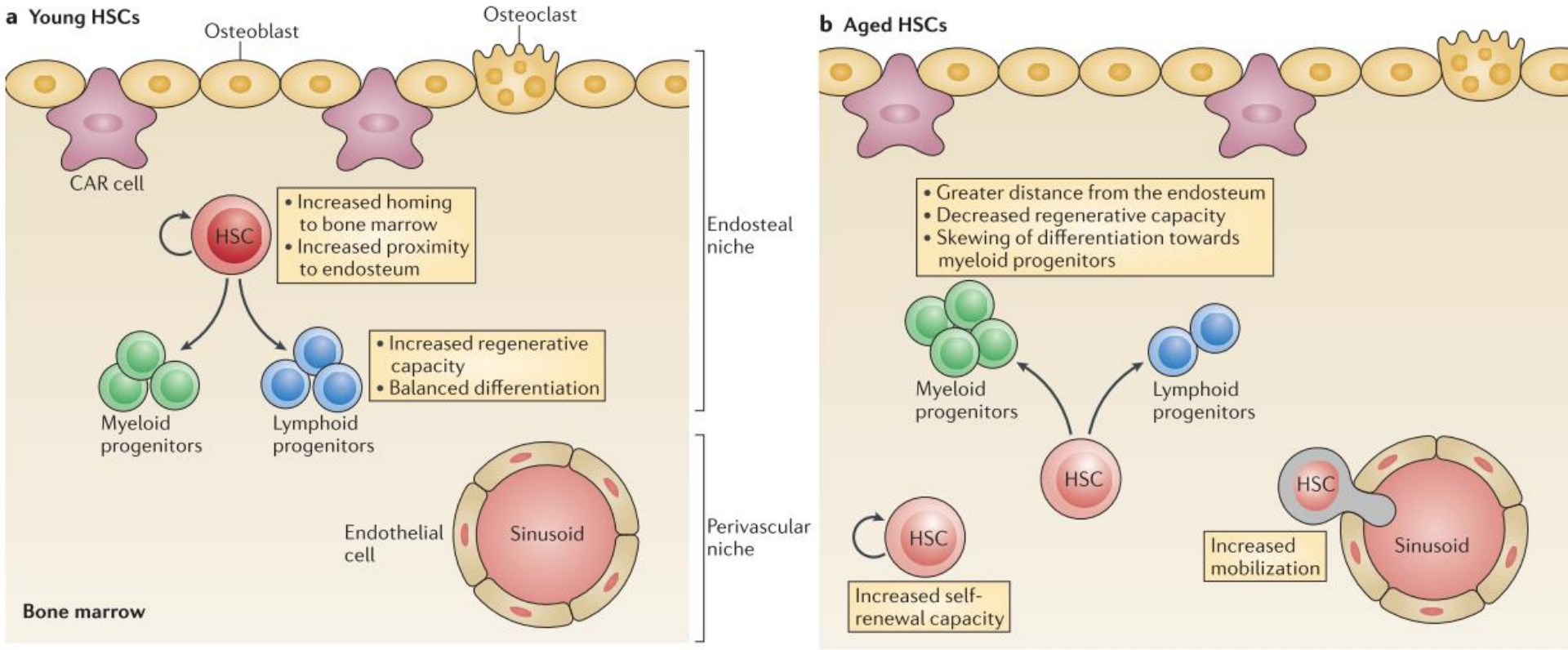
Aging in the lympho-hematopoietic stem cell compartment

Hartmut Geiger[1,2] and K. Lenhard Rudolph[3]

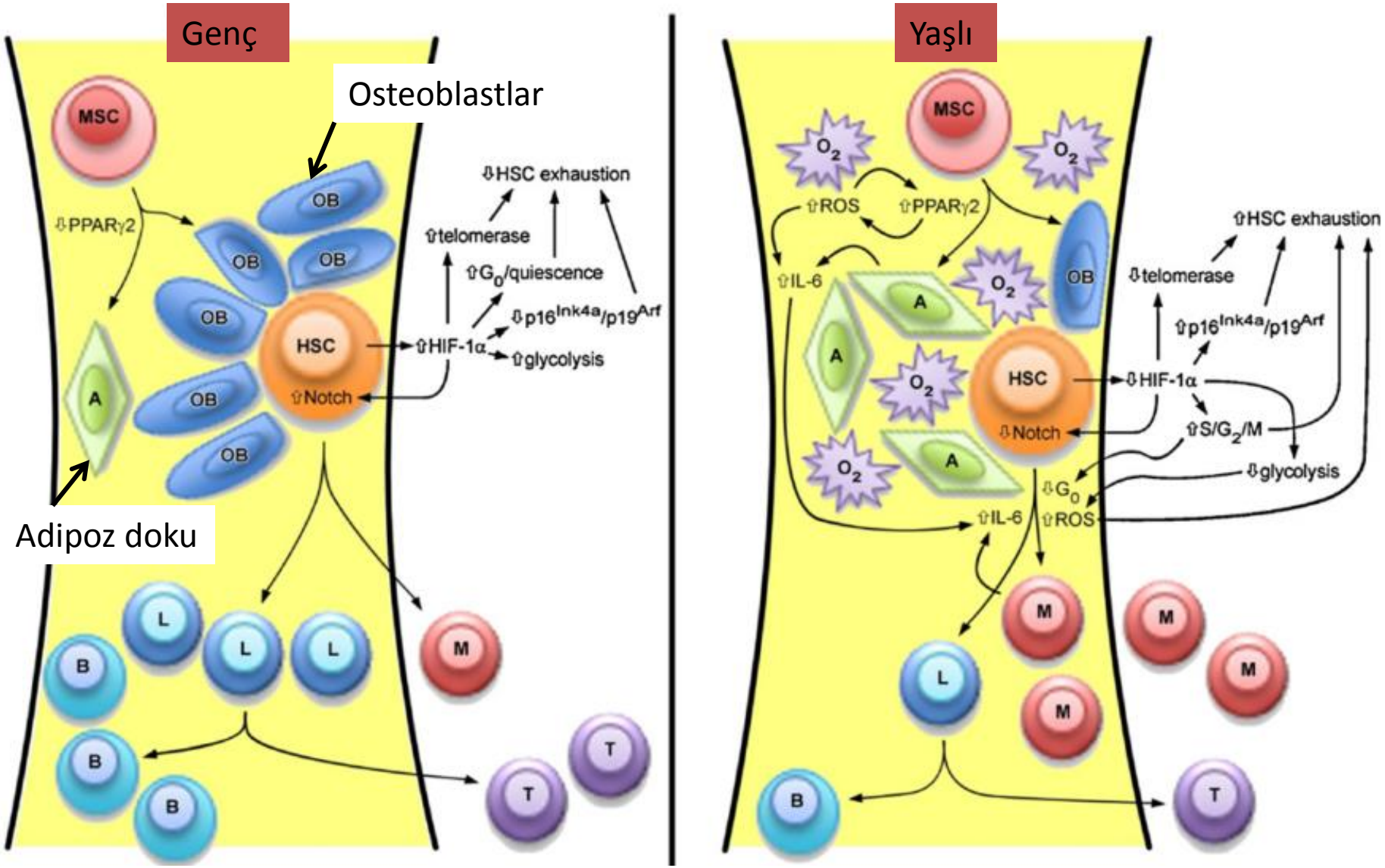


Trends Immunol 2009;30: 360

Yaşlanma ile HSC'lerde Fenotipik ve İşlevsel Farklılaşmalar

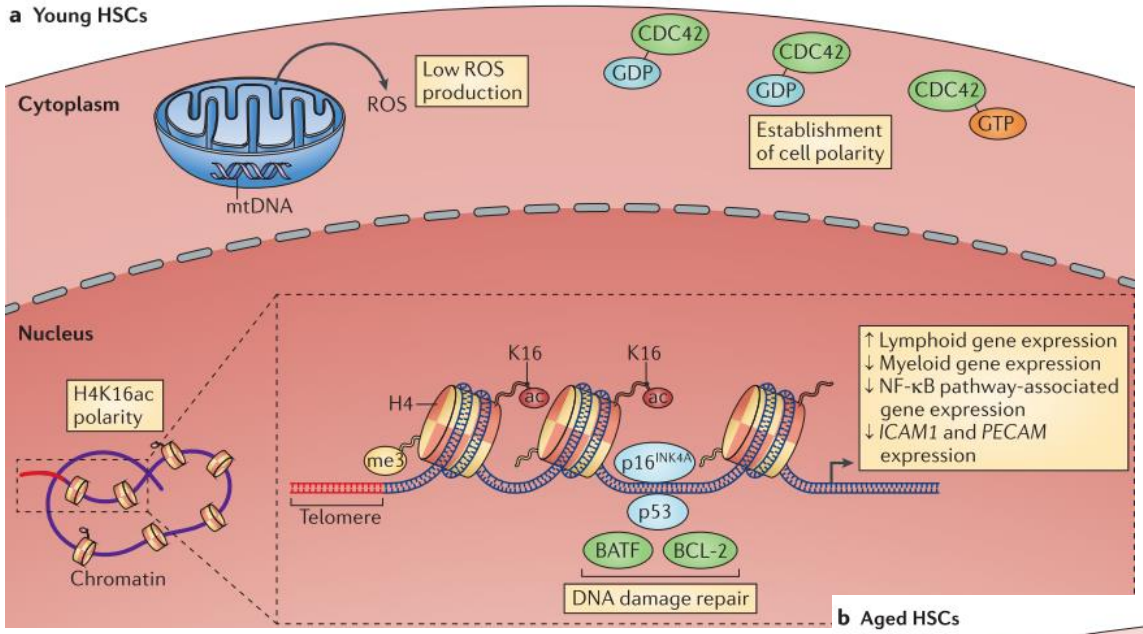


Nature Rev Immunol 2013;13. 376



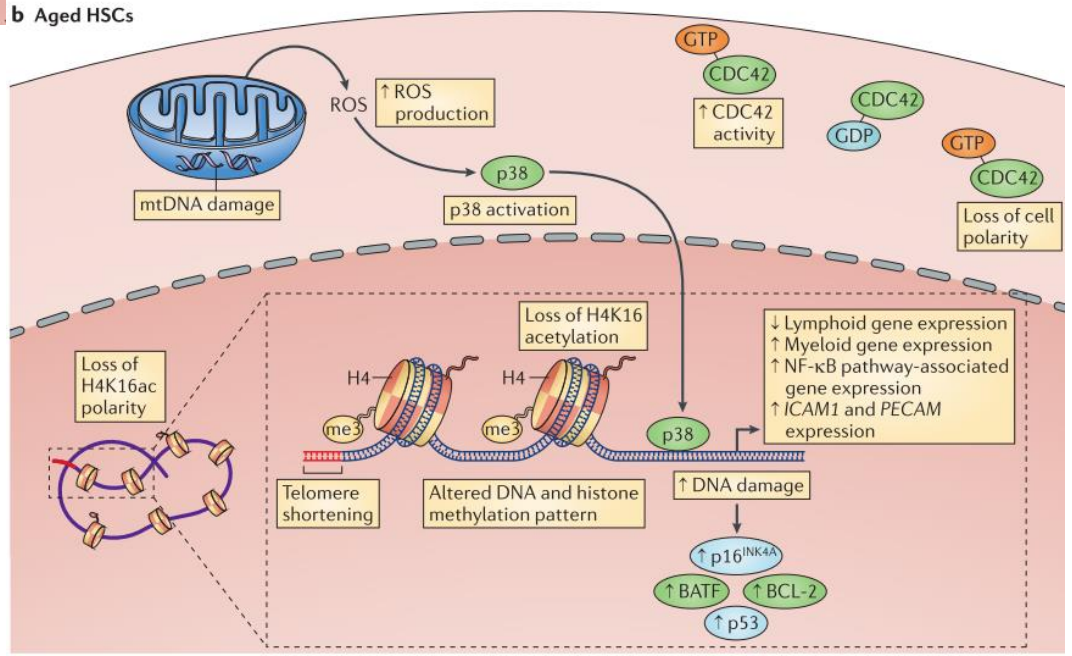
Sem Immunol 2012;24: 309

Yaşlanmada HSC' lerde Gözlenen Hücre İçi Mekanizmalar



- Mitokondrilerden ROS üretimi
- CDC42 ile hücre polarizasyonu
- HSC-DNA' ların onarım mekanizması

CDC42= «cell division control proteini 42»



Nature Rev Immunol 2013;13. 376

Yaşlanma ile İmmün Sistemde Gözlenen Farklılaşmalar

- Hücrelerin kaynağında sorun var
- Reseptör ekspresyonunda değişim
- Sitokin paterninde farklılaşma
- Antijen sunumunda zayıflama
- T lenfositlerinde farklılaşma
- B lenfositlerinde farklılaşma

Age-Associated Decrease in TLR Function in Primary Human Dendritic Cells Predicts Influenza Vaccine Response

Alexander Panda,[*,1] Feng Qian,[†,1] Subhasis Mohanty,[*] David van Duin,[*,2] Frances K. Newman,[‡] Lin Zhang,[†] Shu Chen,[§] Virginia Towle,[§] Robert B. Belshe,[‡] Erol Fikrig,[*,¶] Heather G. Allore,[§] Ruth R. Montgomery,[†,1] and Albert C. Shaw[*,1]

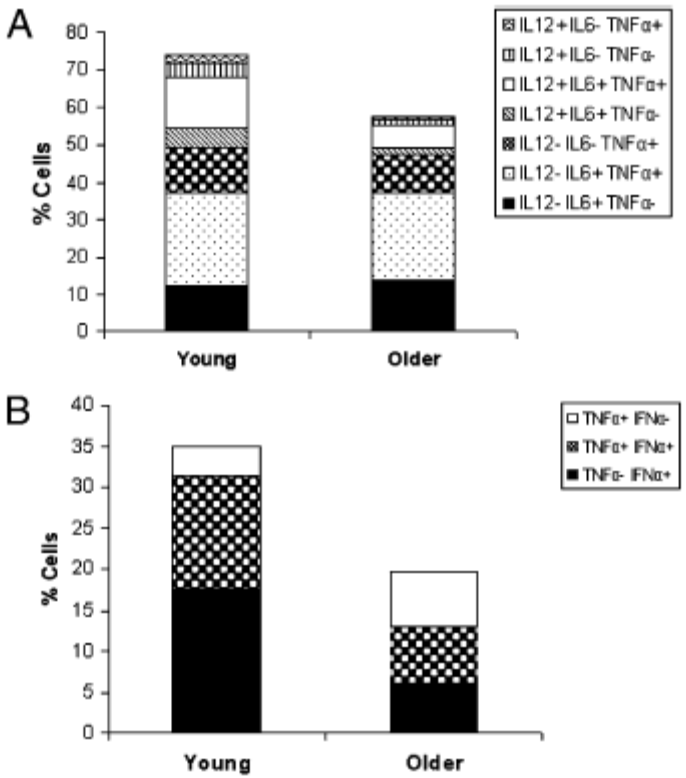


FIGURE 3. Boolean gating of DC subpopulations. *A*, The frequency of mDCs expressing each of the seven possible combinations of IL-6, TNF-α, and IL-12 (p40) after stimulation with the TLR7/8 ligand R848. *B*, The frequency of pDCs expressing each of the three possible combinations of IFN-α and TNF-α after stimulation with R848.

J Immunol 2010;184: 2518

Dysregulation of TLR3 Impairs the Innate Immune Response to West Nile Virus in the Elderly[▽]

Kok-Fai Kong, Karine Delroux, Xiaomei Wang, Feng Qian, Alvaro Arjona, Stephen E. Malawista, Erol Fikrig, and Ruth R. Montgomery*

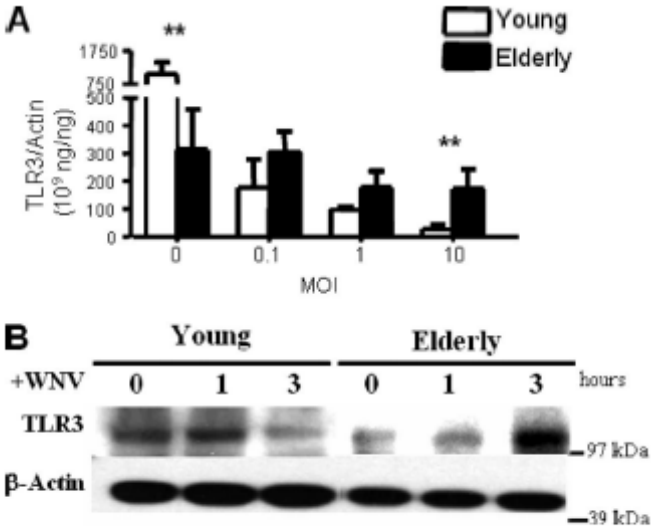
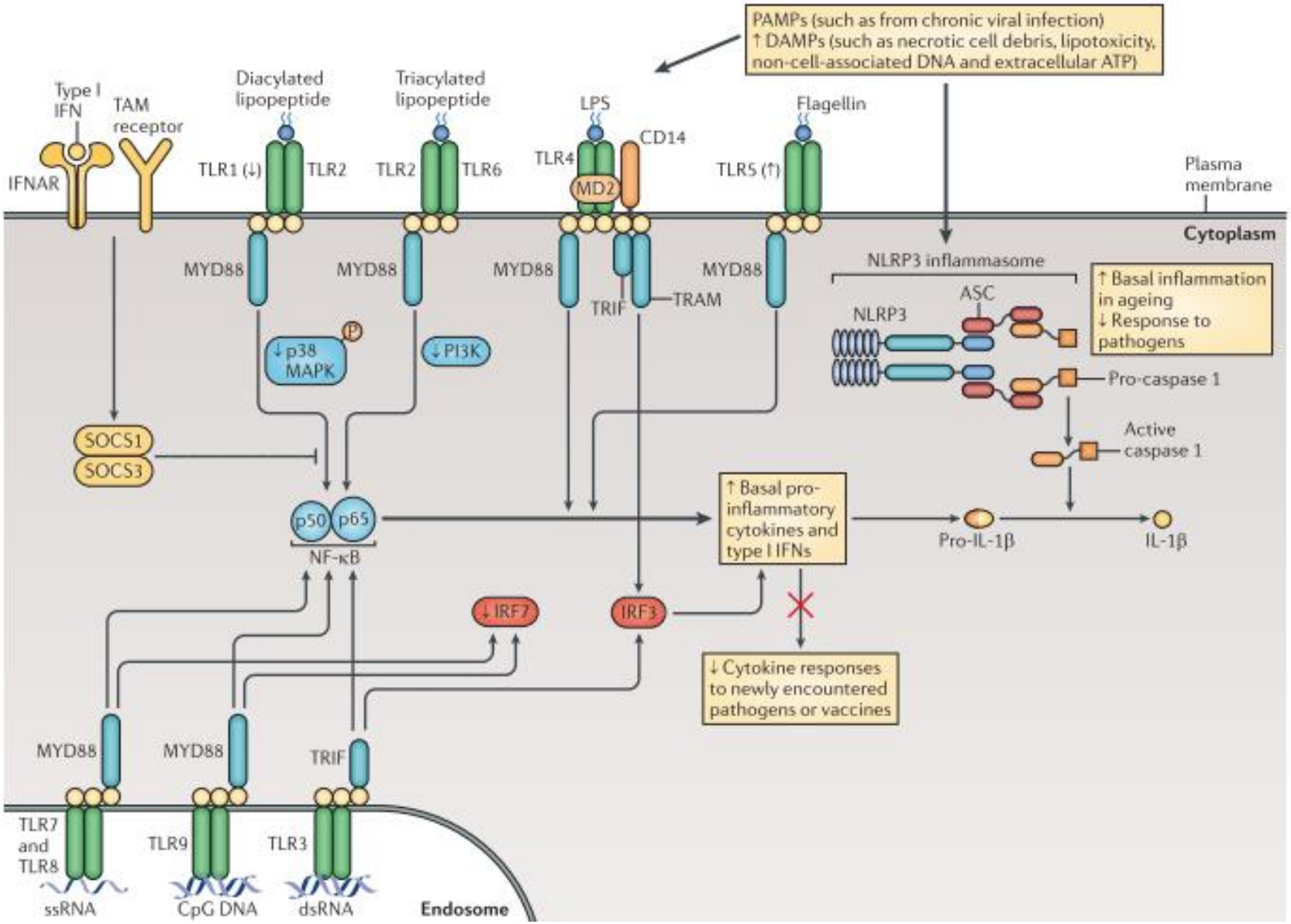


FIG. 1. TLR3 levels are reduced by WNV infection in macrophages from young but not elderly donors. (A) Primary macrophages from healthy young and older individuals were infected with WNV (MOI, 0.0, 0.1, 1.0 and 10.0) and incubated for 1 h (young, $n = 7$; elderly, $n = 8$; data shown are the means ± the standard errors of the means; **, ANOVA, $P < 0.05$). (B) Primary macrophages from healthy young and older individuals were infected with WNV (MOI, 1) for 0, 1, and 3 h. Total proteins were harvested, and the protein level of TLR3 was detected via immunoblotting. β-Actin was used as a control to ensure equal loading. Data are representative of three subjects in each cohort.

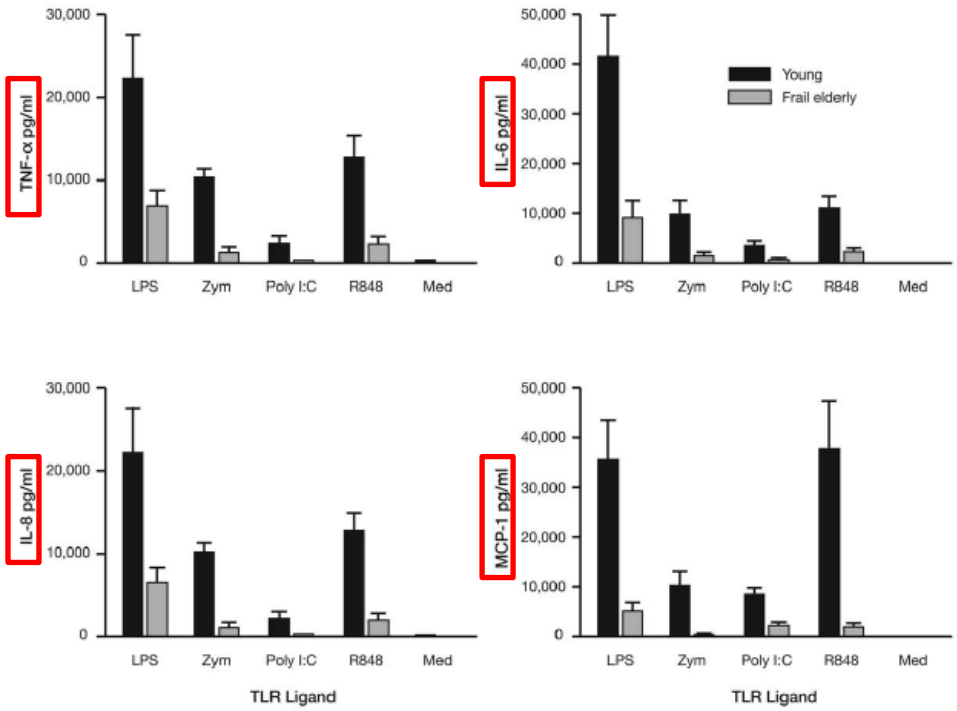
J Virol 2008;82: 7613

Yaşlanma ile Doğal Bağışıklığın PRR sinyal İletisindeki Farklılaşmalar



Nature Rev Immunol 2013;doi:10.1038/nri3547

Farklı uyaranlara yanıt olarak Monositlerin proinflamatuar sitokin üretimi



* Doğal bağışıklığın hücrelerinde hem sayısal, hem işlevsel azalma
* TNF, IL-1 gibi sitokin üretimi azalıyor
* Bu sitokinler, diğer sitokinlerin üretimi için gerekli
* IL-7 üretimi, lenfosit olgunlaşması için gerekli
* Proinflamatuar sitokinler ve kemokinler, edinsel yanıtı etkiler

Immun Ageing 2007;4: 9

Yaşlanma ile İmmün Sistemde Gözlenen Farklılaşmalar

- Hücrelerin kaynağında sorun var
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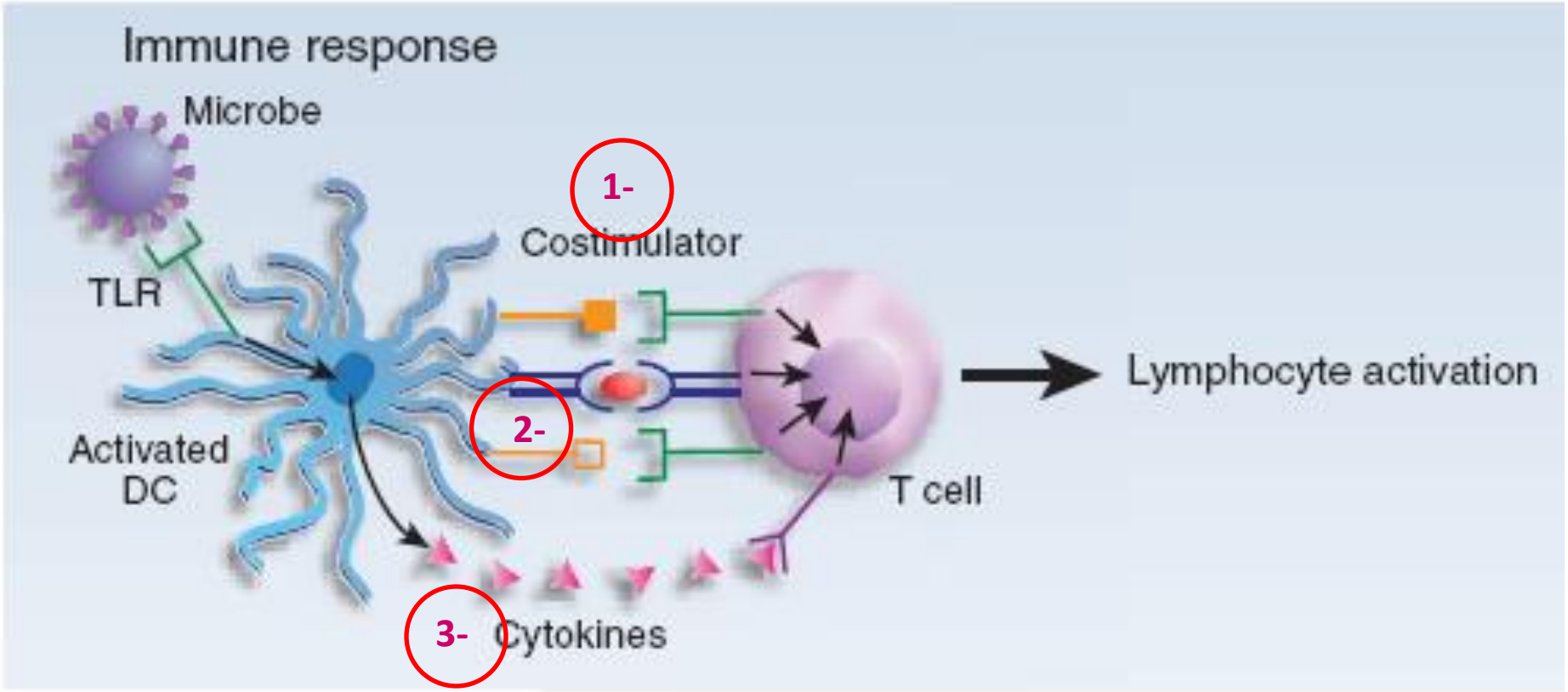
- Sitokin paterninde farklılaşma
- Antijen sunumunda zayıflama
- T lenfositlerinde farklılaşma
- B lenfositlerinde farklılaşma

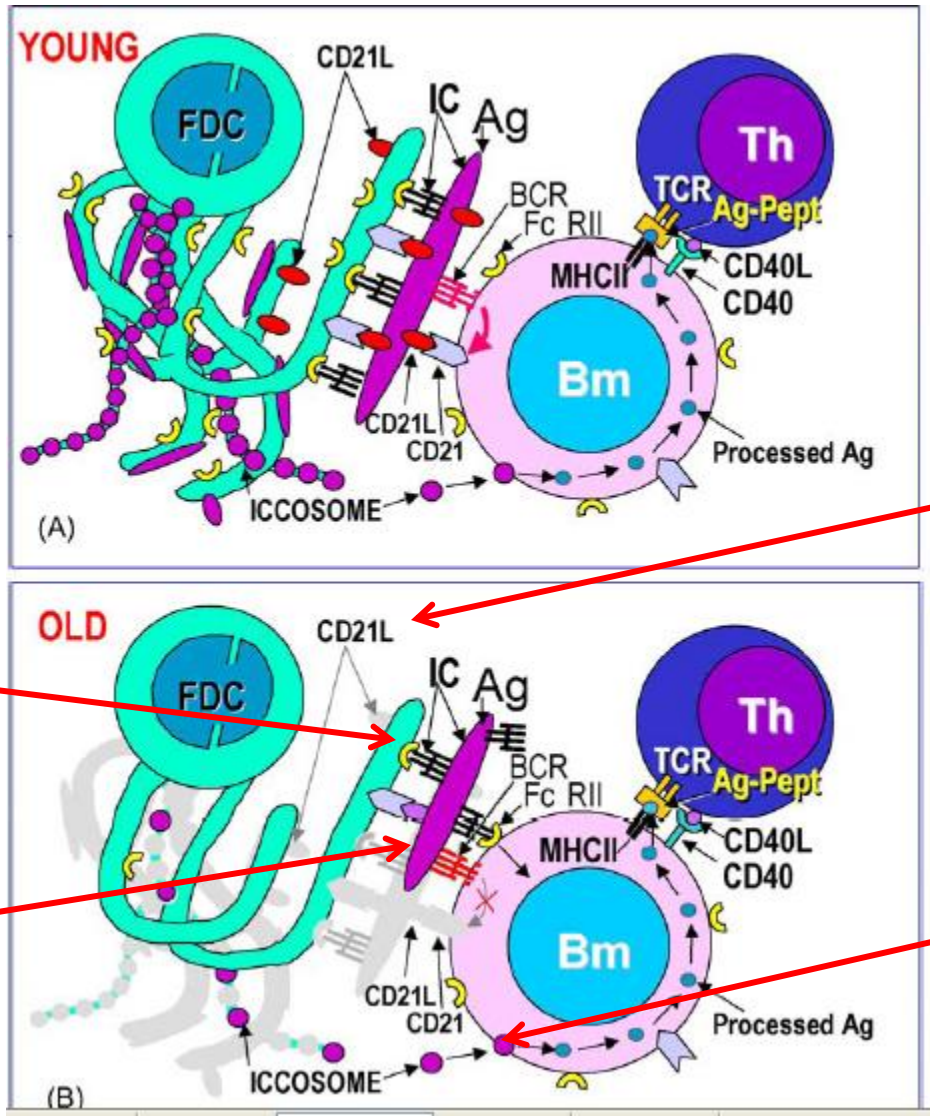
DH' lerin antijen sunuşu



Nature Immunol 2005;6: 227

Follicular dendritic cells in aging, a "bottle-neck" in the humoral immune response

Yüksel Aydar [a], Péter Balogh [a], John G. Tew [b], Andras K. Szakal [a,*]



CD21L üzerinden gerçekleşecek kostimülasyon azalmıştır

FcγRII reseptörlerinin azalmış olması nedeniyle antijen sunumu zayıflamıştır

Antijenin işlenmesi zayıflamıştır

Ikkozom sayısı azaldığı için B lerden T lere sunulan antijen sayısı azalmıştır

Ageing Res Rev 2004;3: 15

Yaşlanma ile İmmün Sistemde Gözlenen Farklılaşmalar

- Hücrelerin kaynağında sorun var
- Reseptör ekspresyonunda değişim
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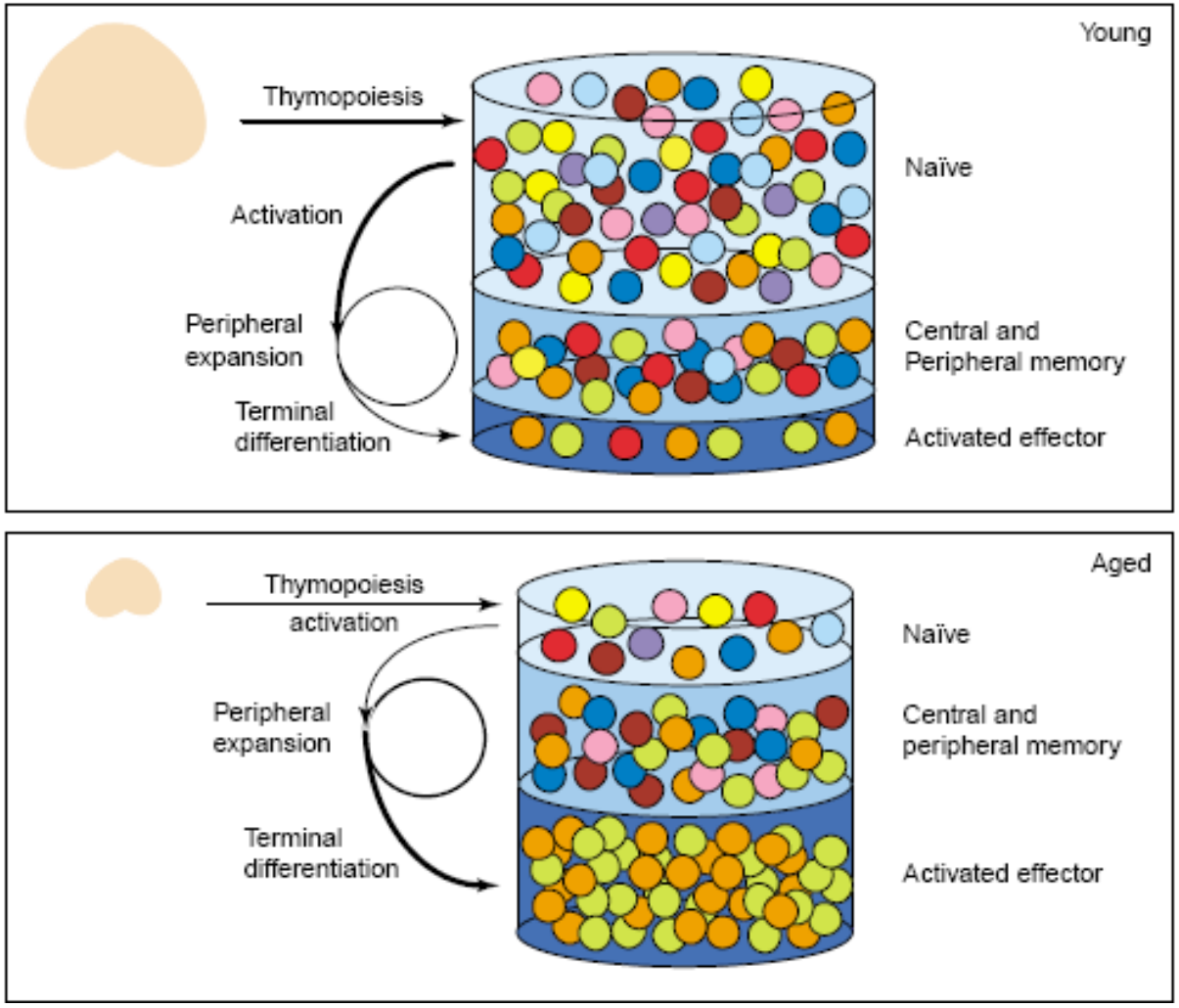
- Antijen sunumunda zayıflama
- T lenfositlerinde farklılaşma
- B lenfositlerinde farklılaşma

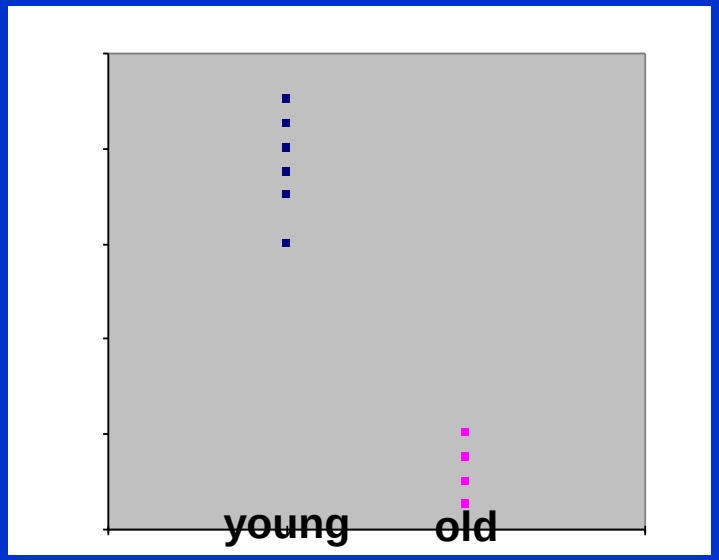
A)- Yaşlanma sırasında periferdeki T hücre havuzunun yapısı değişiyor



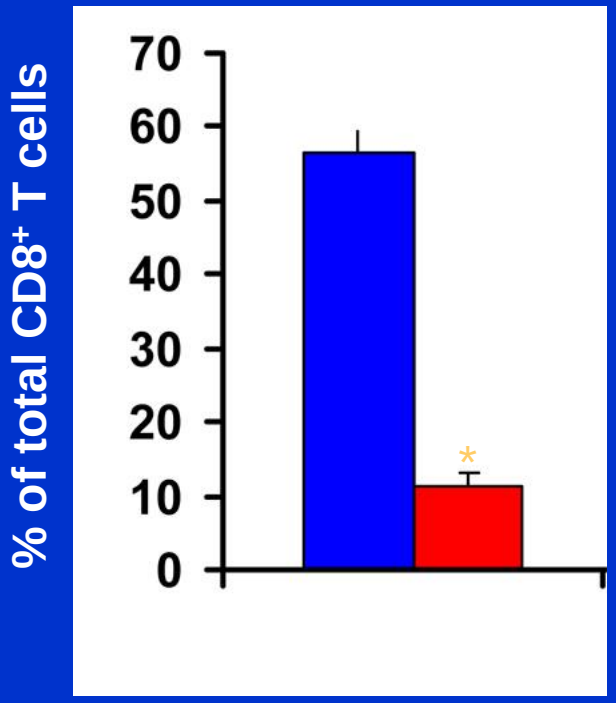
Curr Opin Immunol 2004;16: 151

Yaşlılarda Naif T hücreleri Azalmakta

Lymph node tissue



Peripheral blood



young; < 30 years

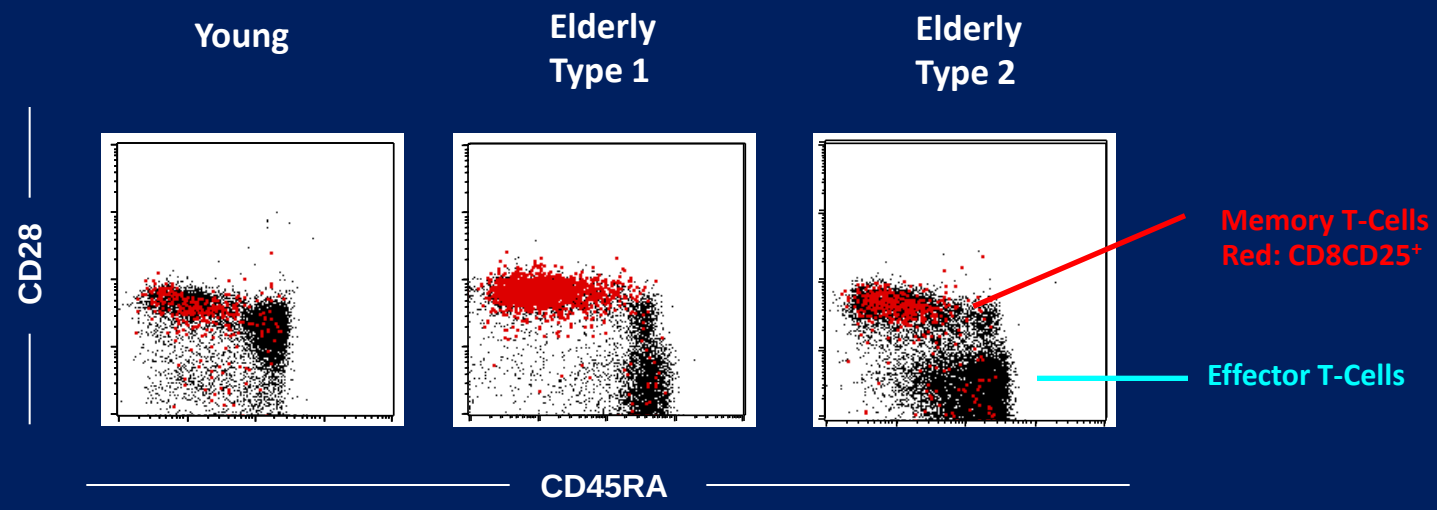
old; > 65 years

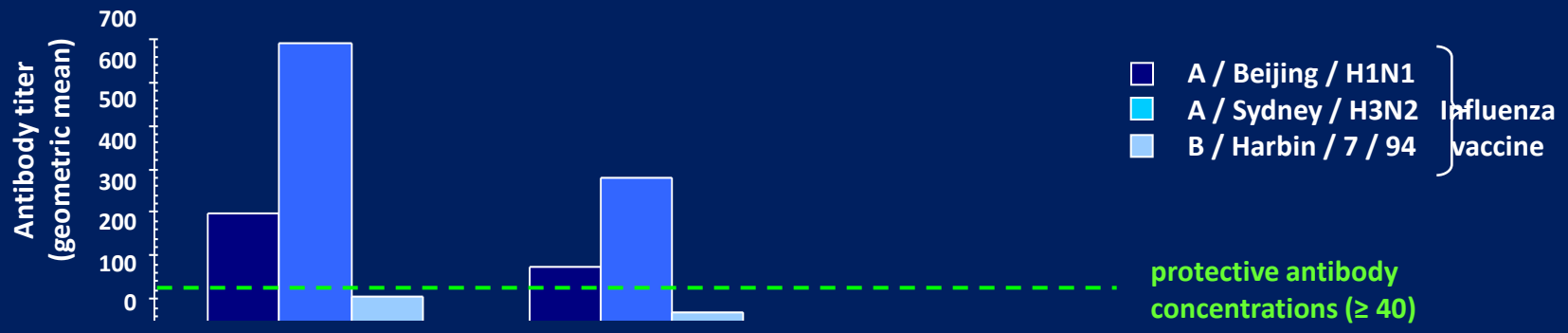
P < 0.001

*$CD8^+CD45RA^+CD28^+$

Lazuardi et al. *Immunology* (2005)

Yaşlılarda Bellek / Efektör T hücrelerin Oranı Değişir

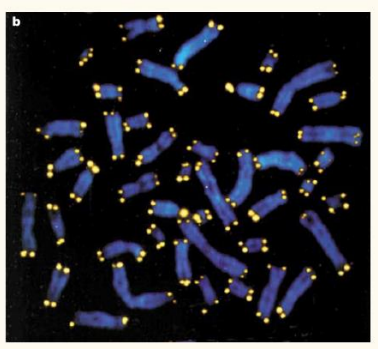


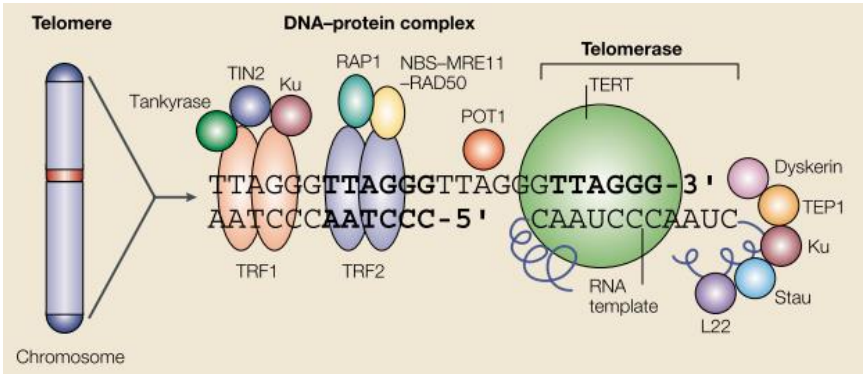


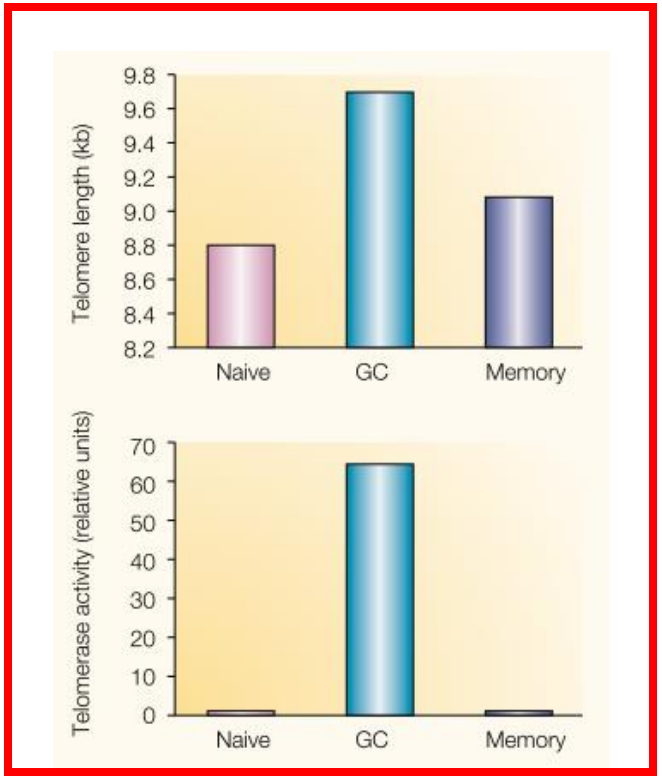
Herndler-Brandstetter et al. *J Immunol* (2005)

B)- Telomerler, immün sistem hücrelerinde de kısalmakta!

* Erişkinde her yıl 19-54 bp'lik kısalma
* Lenfositlerde her 20-50 yılda 1 kb'lık kısalma



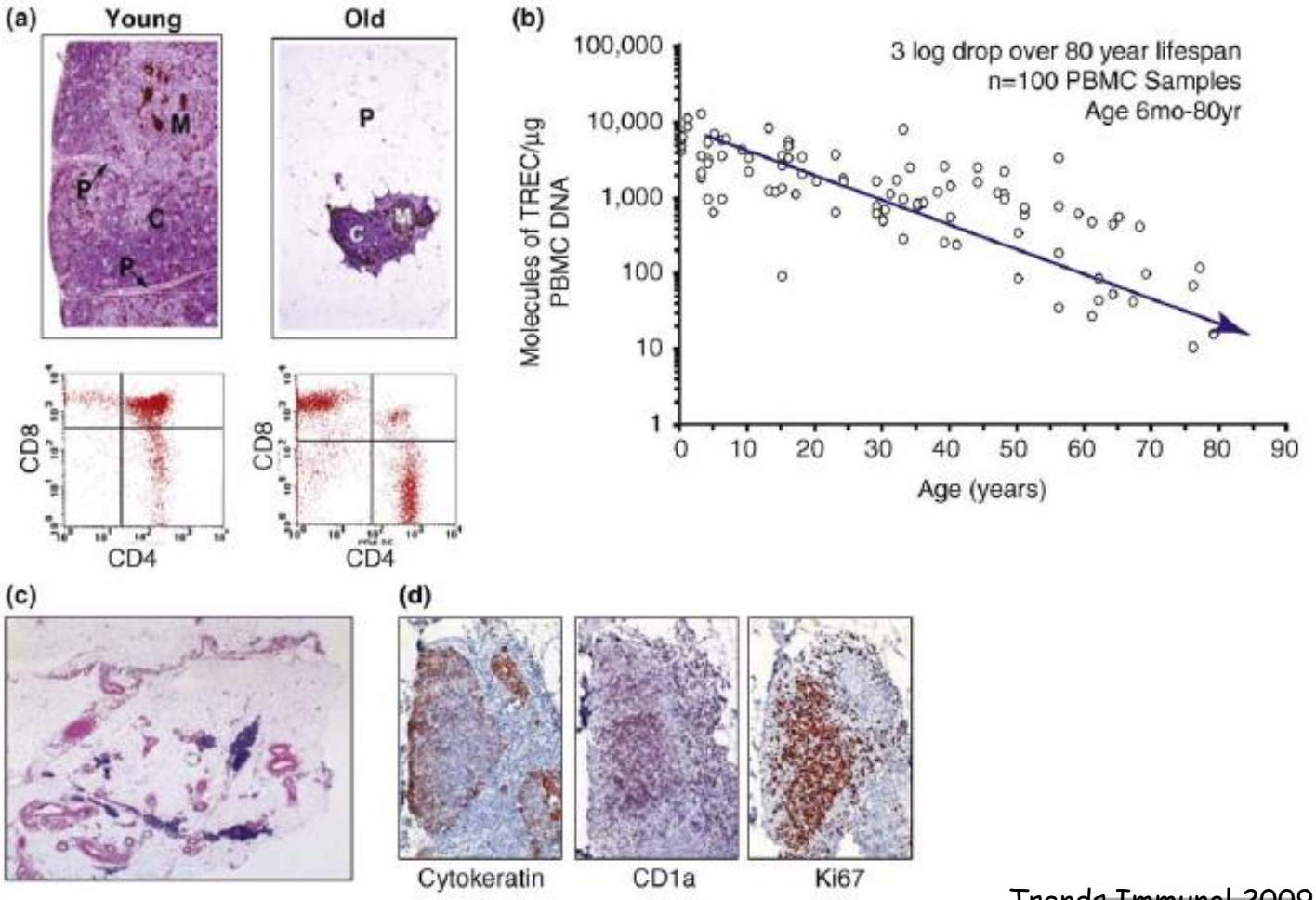




C)-

Thymic involution and immune reconstitution

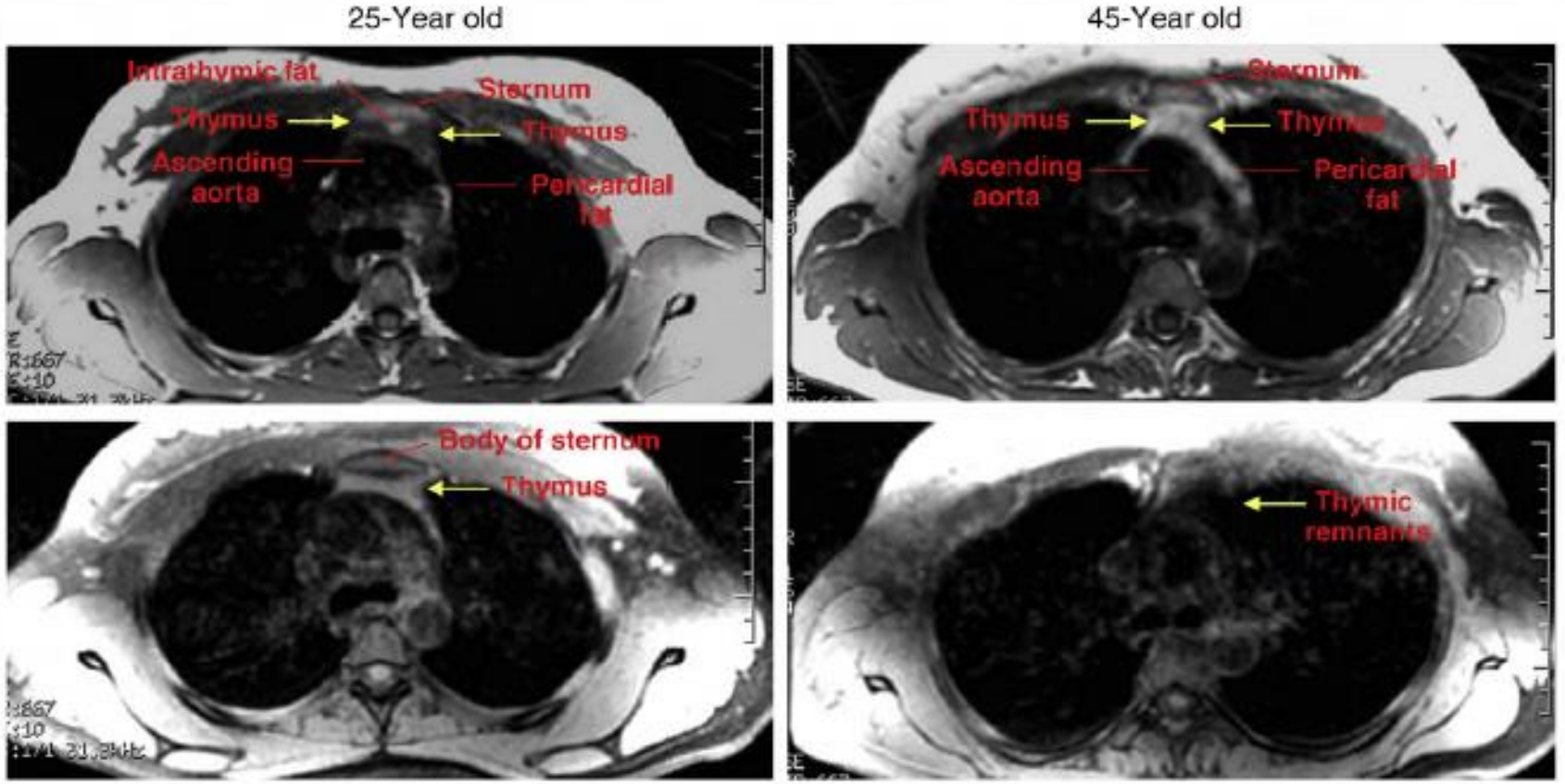
Heather E. Lynch[1], Gabrielle L. Goldberg[2], Ann Chidgey[3], Marcel R.M. Van den Brink[2], Richard Boyd[3] and Gregory D. Sempowski[1]



Trends Immunol 2009;30: 366

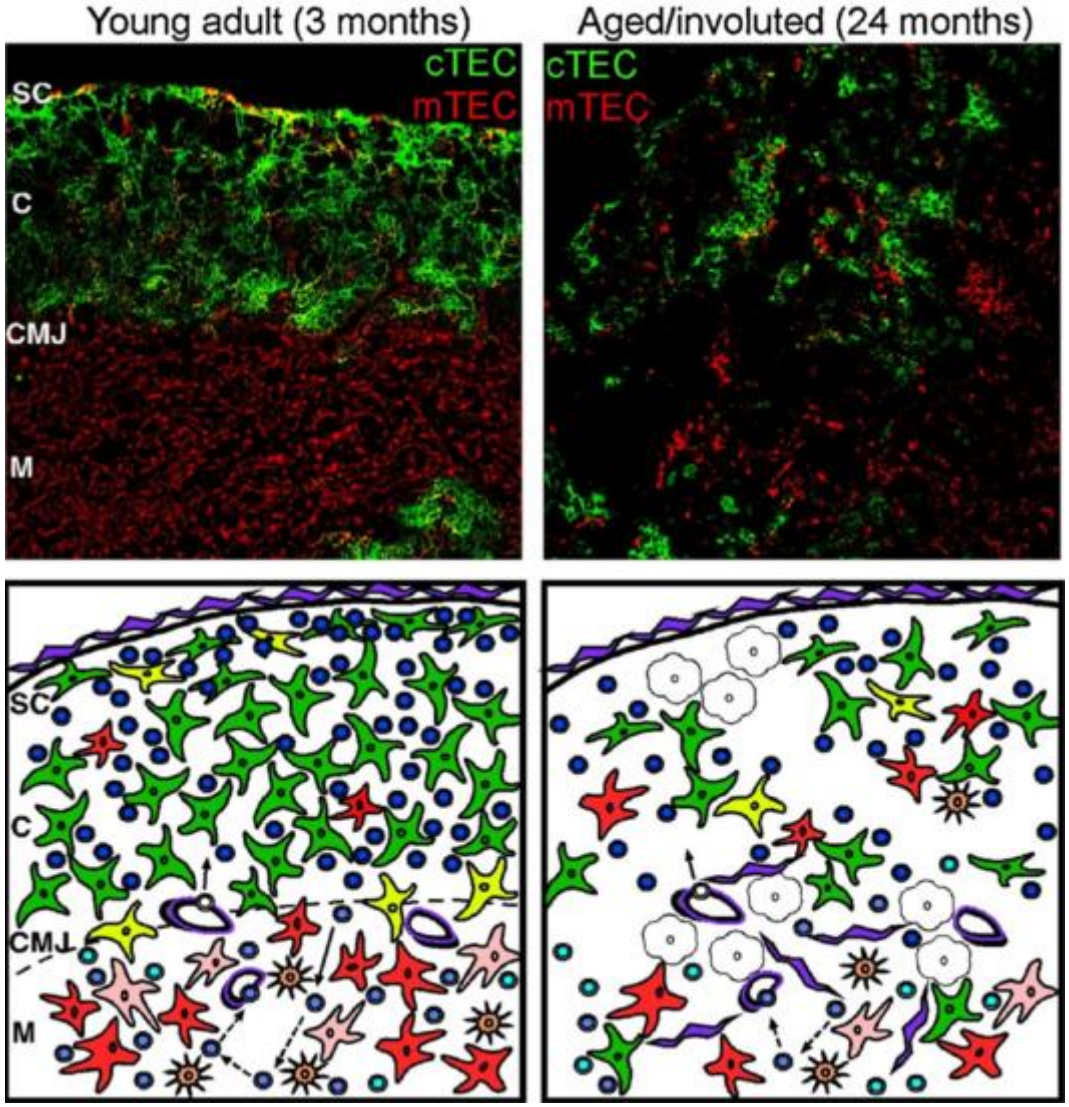
Thymic fatness and approaches to enhance thymopoietic fitness in aging

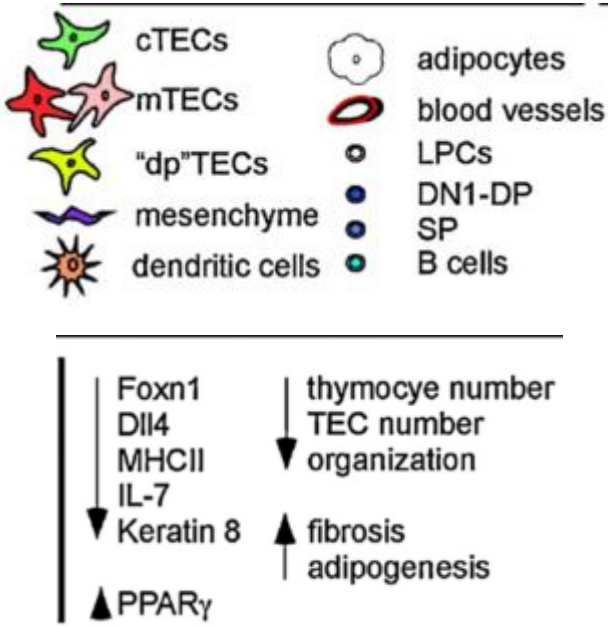
Vishwa Deep Dixit



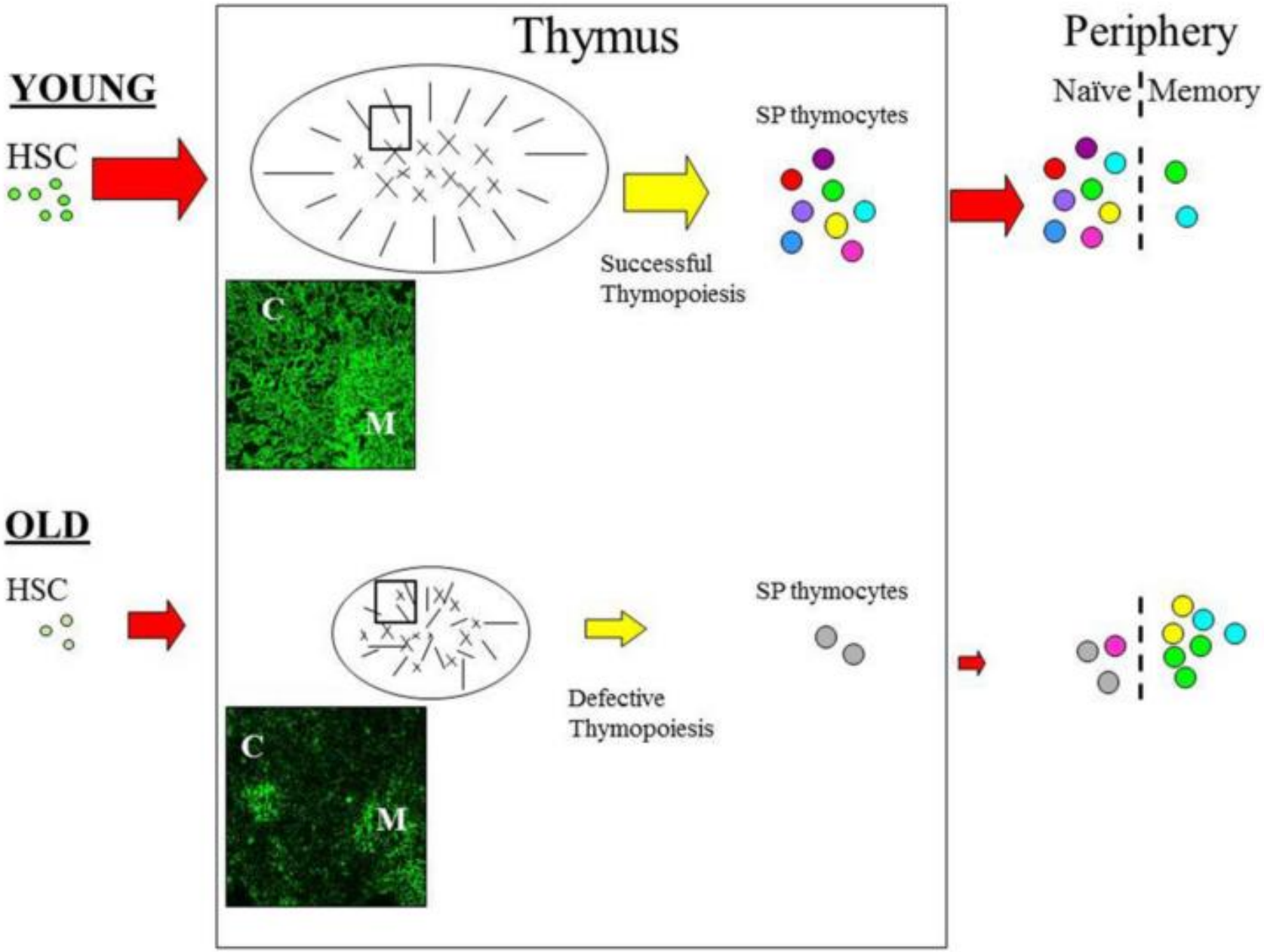
Curr Opinion Immunol 2010;22: 521

Genç ve yaşlı timusun organizasyonu





Sem Immunol 2012;24: 309



Frontiers Immunol 2013;4: 316

D)-

The Influence of Age on T Cell Generation and TCR Diversity[1]

Keith Naylor,* Guangjin Li,[2†] Abbe N. Vallejo,[2*] Won-Woo Lee,† Kerstin Koetz,* Ewa Bryl,* Jacek Witkowski,* James Fulbright,* Cornelia M. Weyand,*† and Jörg J. Goronzy[3*†]

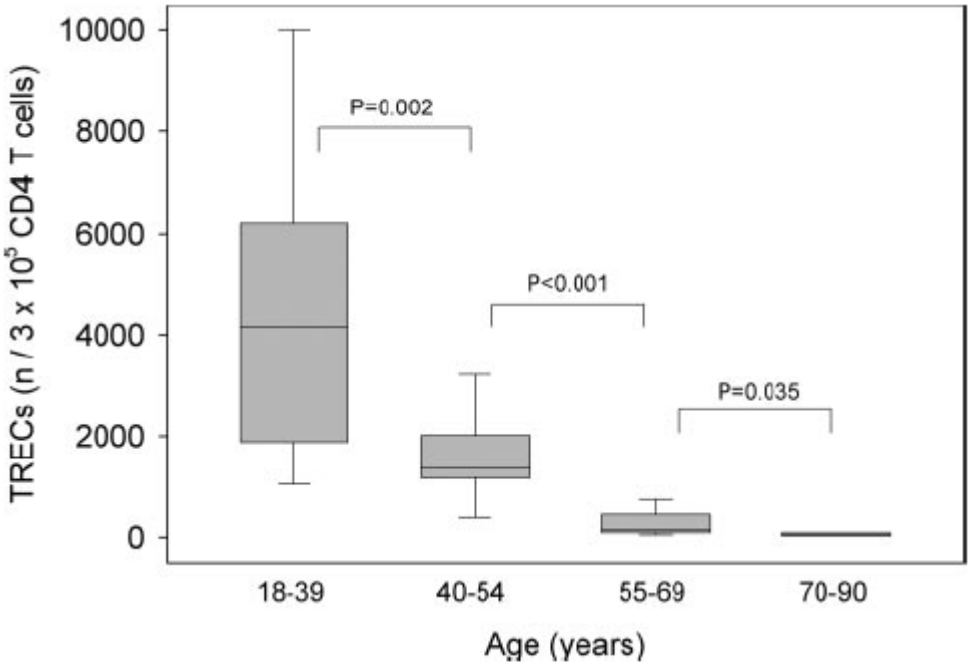
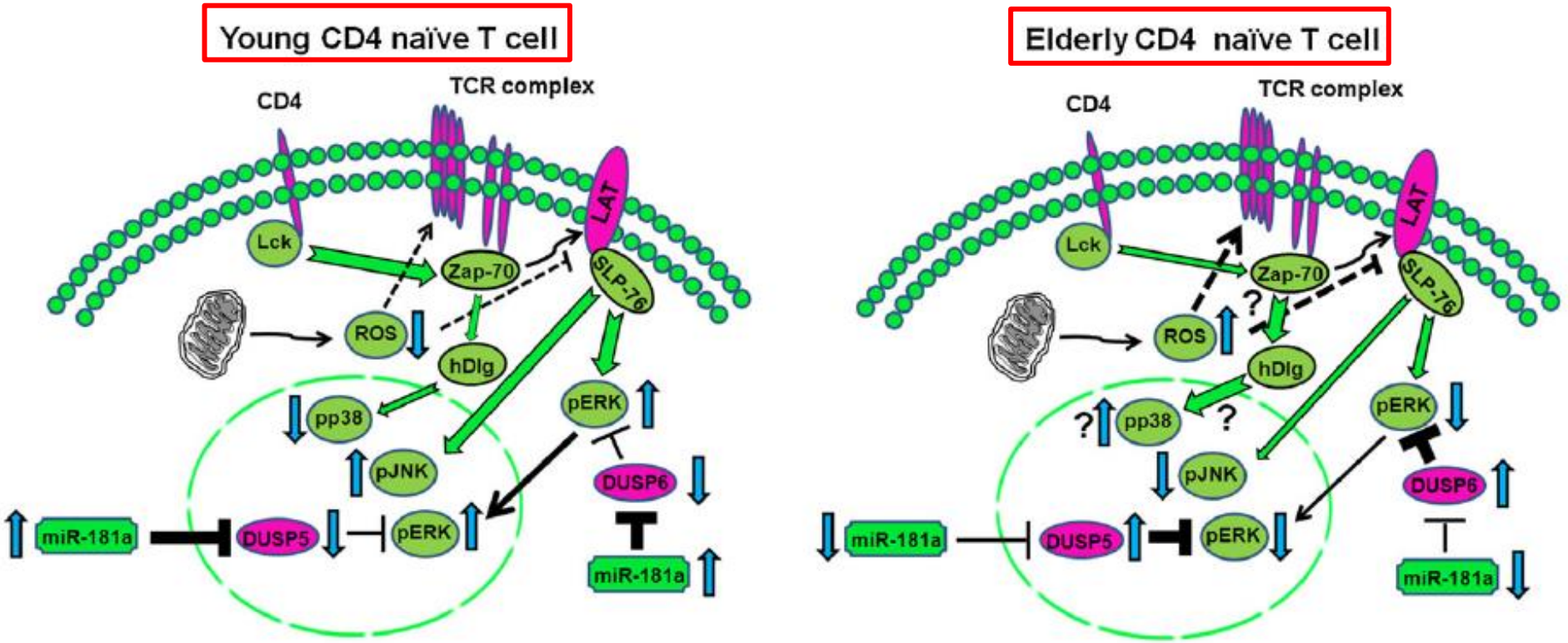


FIGURE 1. Age-dependent decline in thymic output. CD4 T cells were purified from healthy individuals aged 18–88 years, and the number of TREC was quantified. Results are shown as box plots for different age strata, displaying medians, 25th and 75th percentiles as boxes, and 10th and 90th percentiles as whiskers. TREC concentrations were very low after the age of 55 years, suggesting that thymic output after this age is minimal at best.

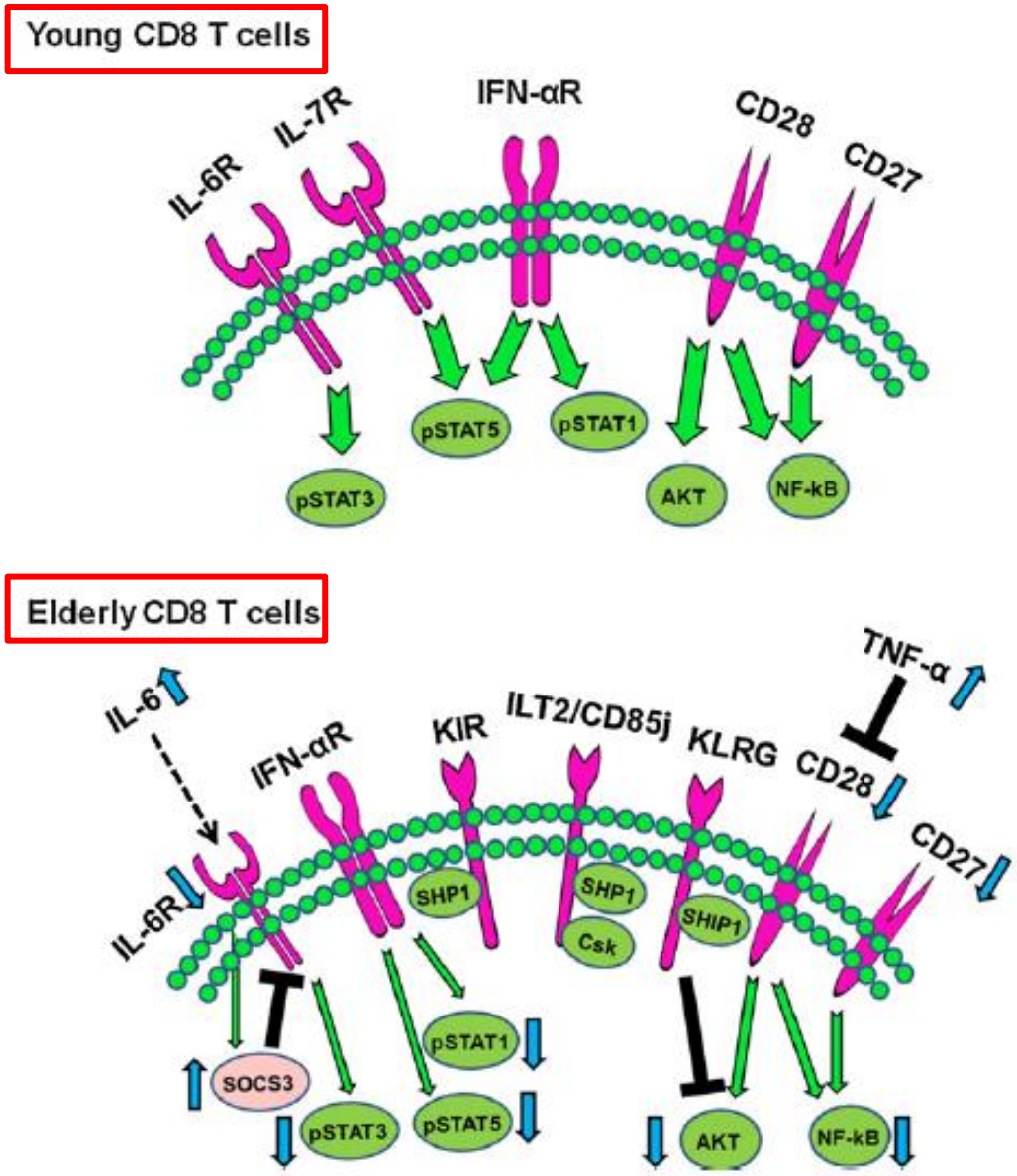
J Immunol 2005;174: 7446

T Hücrelerin Farklılaşma ve Yaşlanma Süreçlerinde THR sinyal İleti Yolakları-1



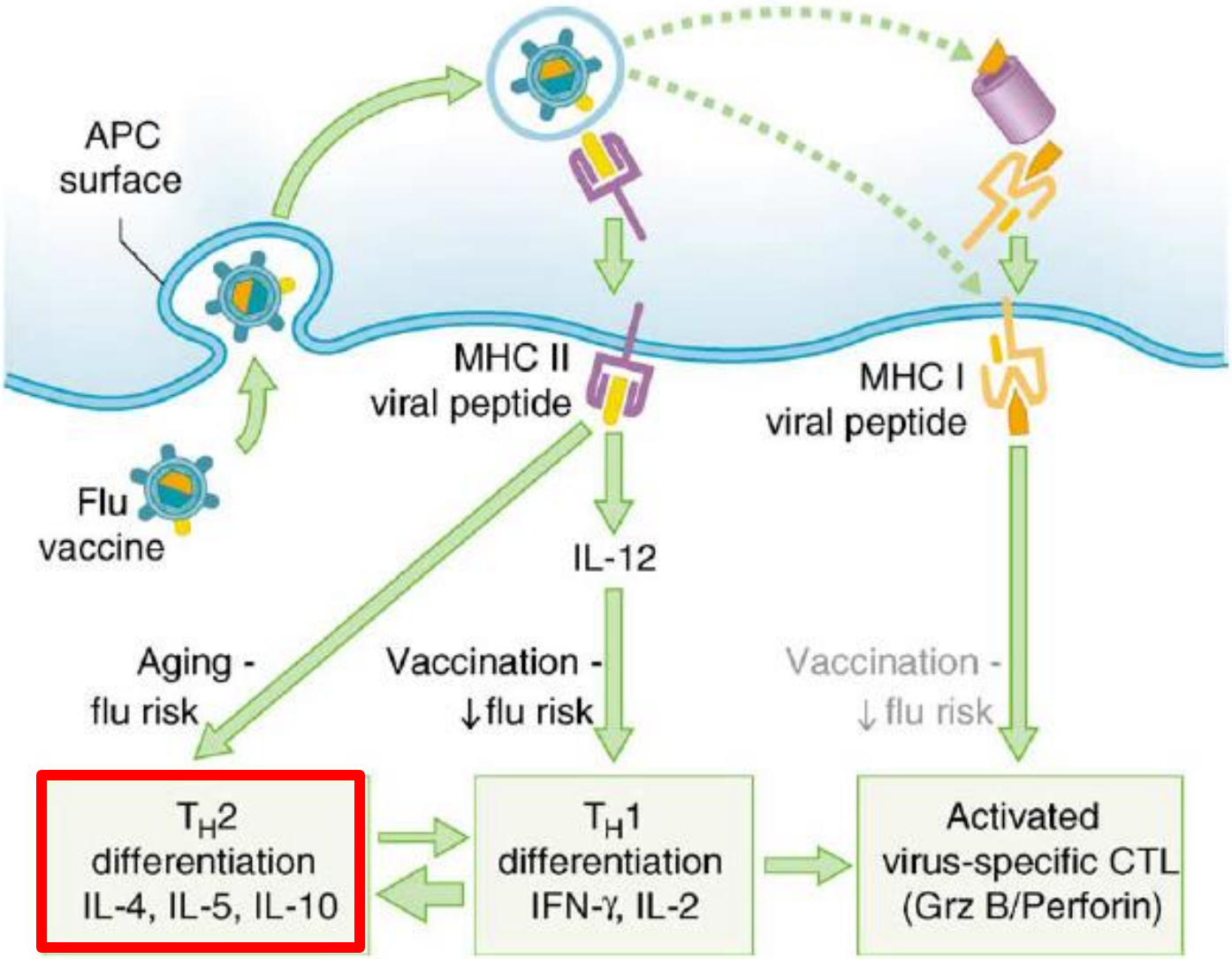
Sem Immunol 2012;24: 365

CD8 T Hücrelerinde Yaşlanma ile Reseptör ve Sinyalizasyon Moleküllerindeki Farklılaşma



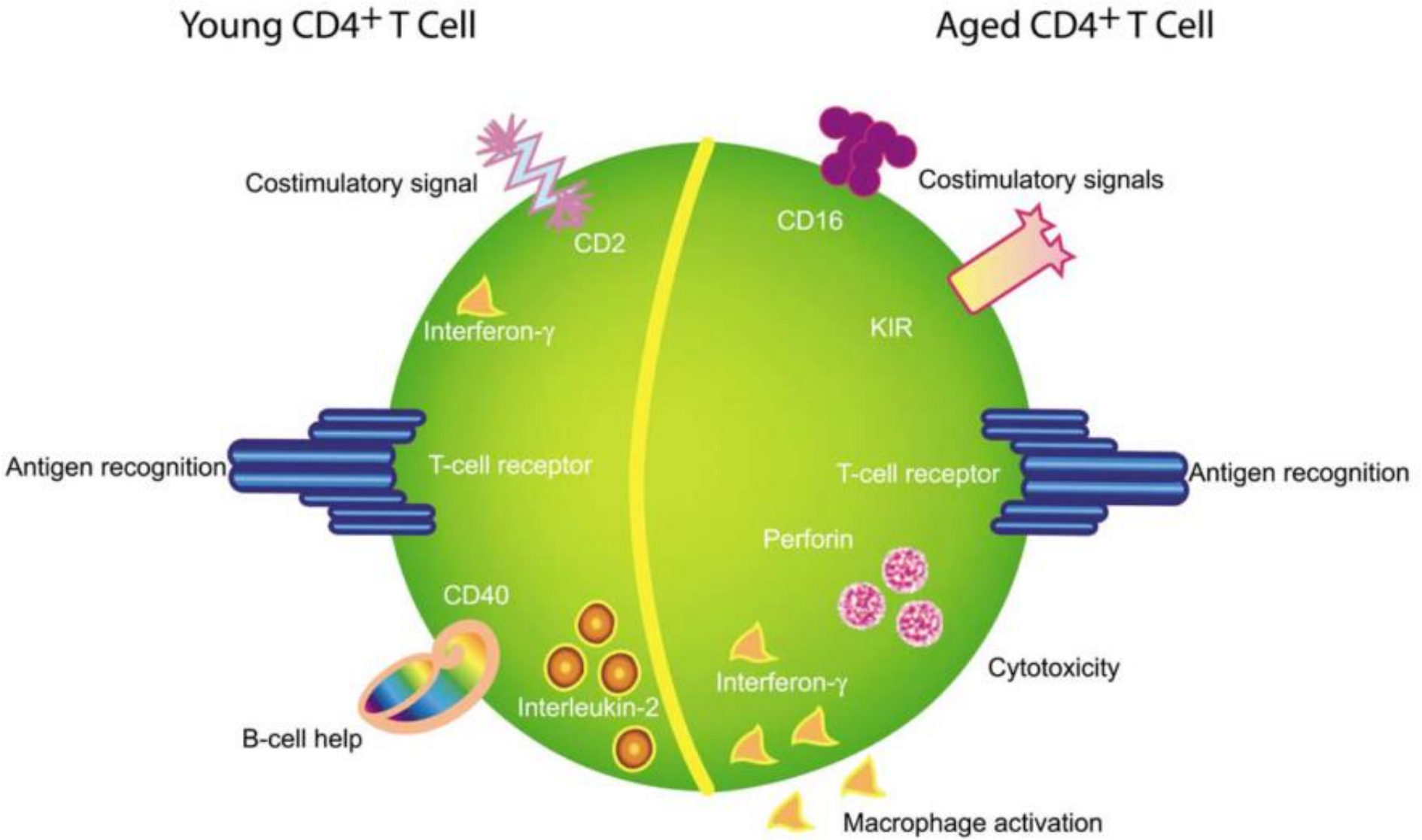
Sem Immunol 2012;24: 365

E)- Yaşlanma ile Th hücrelerinin farklılaşması Th-2 yönüne kayıyor: CTL cevabı zayıflıyor



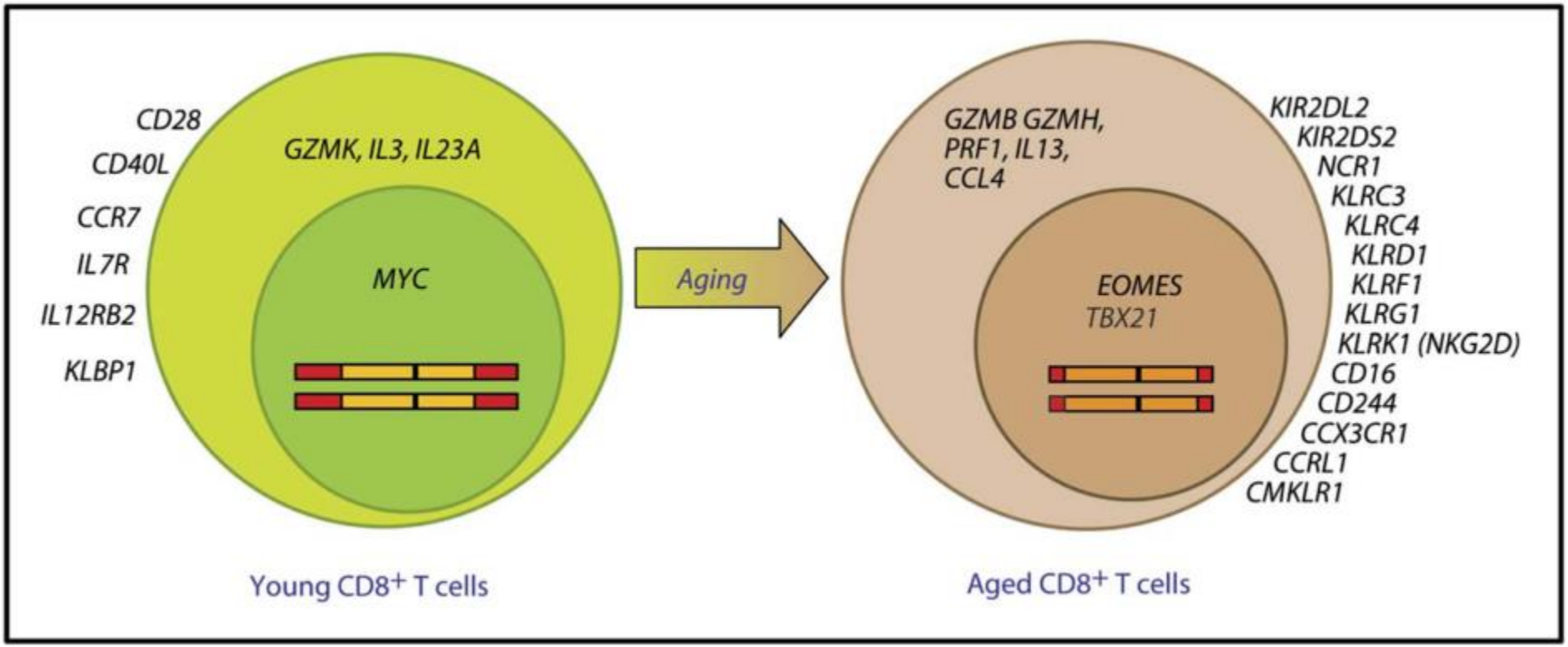
Vaccine 2005;23S1: S1/S1

F)- Yüzey reseptörlerinde farklılaşma: CD4



Exper Gerontol 2003;38: 833

Yüzey reseptörlerinde farklılaşma: CD8



Immunity 2006;24: 495

G)- CD8' de işlevsel zayıflama

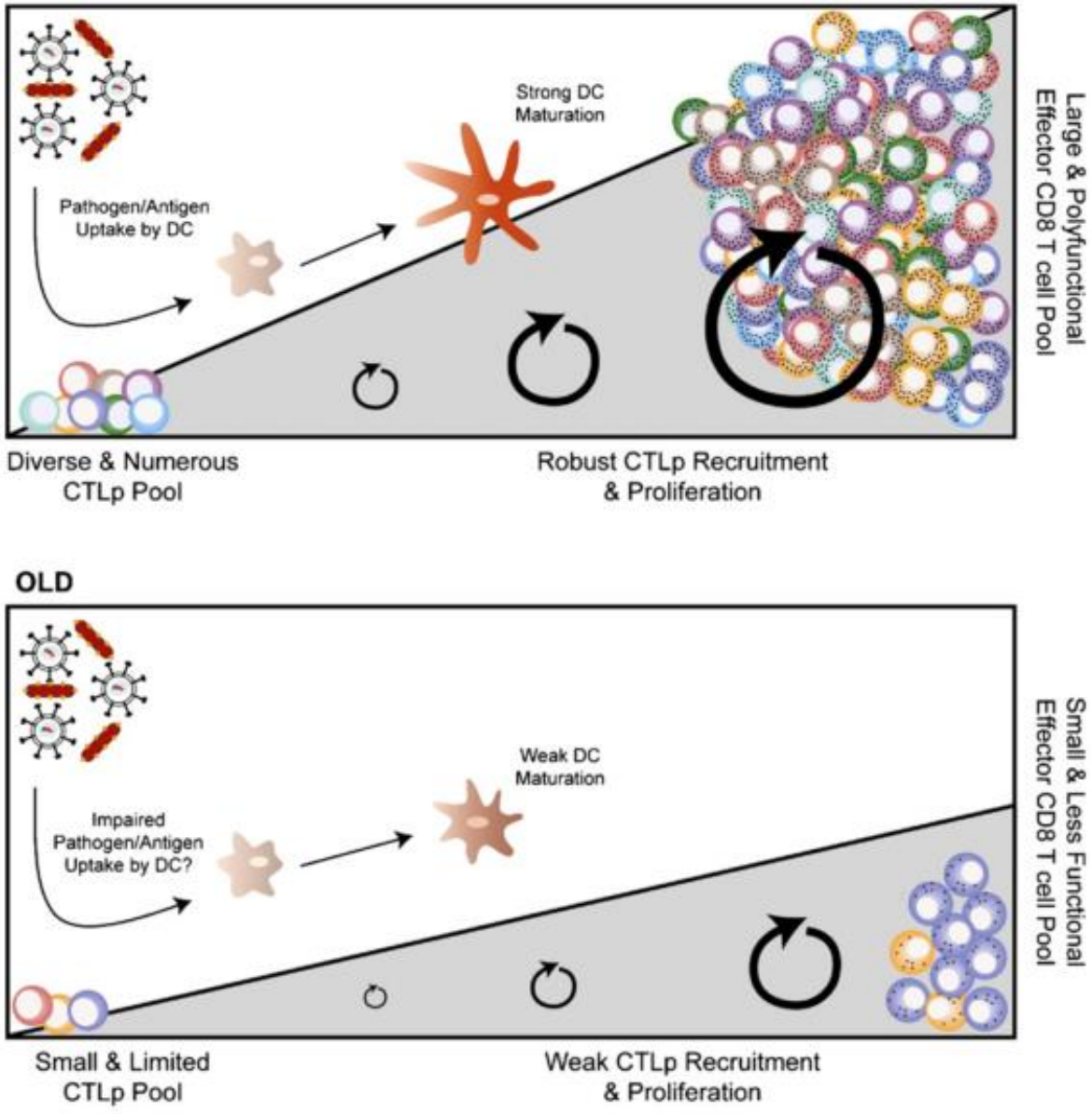


Table 1
Age-related impaired CD8 T cell effector functions.

Age-related effector CD8 defects
Proliferative capacity
Magnitude of primary response to infection/vaccination
Up-regulation of activation markers
Polyfunctional production of multiple effector proteins
Quantity of effector proteins produced
Target cell lysis

Sem Immunol 2012;24: 356

Yaşlanma ile T lenfositlerinde gözlenen farklılaşmalar

- Naif T hücre sayısı azalıyor
- İşlevsel özellikleri zayıflıyor
  - Kısalan telomer bölgesi
  - THR repertuarında kısıtlılık
  - Aksayan THR sinyalizsyonu
  - Azalan IL-2 üretimi
  - Kostimülatör molekül CD28 ekspresyonu azalıyor
  - Membran lipid oranı değişiyor ve immünolojik sinaps bozuluyor
  - CD40L (CD154) ekspresyonu bozuluyor ve B hücreleri ile etkileşim aksıyor

Yaşlanma ile İmmün Sistemde Gözlenen Farklılaşmalar

- Hücrelerin kaynağında sorun var
- Reseptör ekspresyonunda değişim
- Sitokin paterninde farklılaşma
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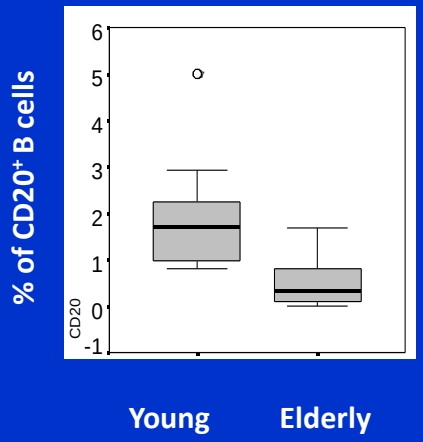
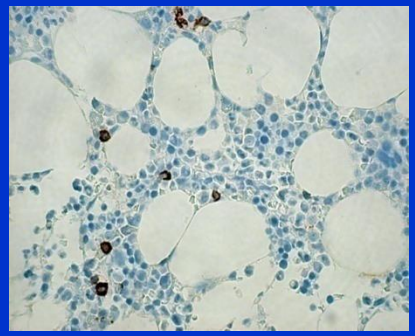
- T lenfositlerinde farklılaşma
- B lenfositlerinde farklılaşma

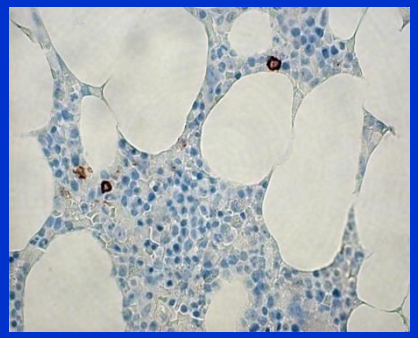
Kemik İliğinde Olgun Naif B hücrelerinin Yaşa Bağlı Olarak Azalmaları

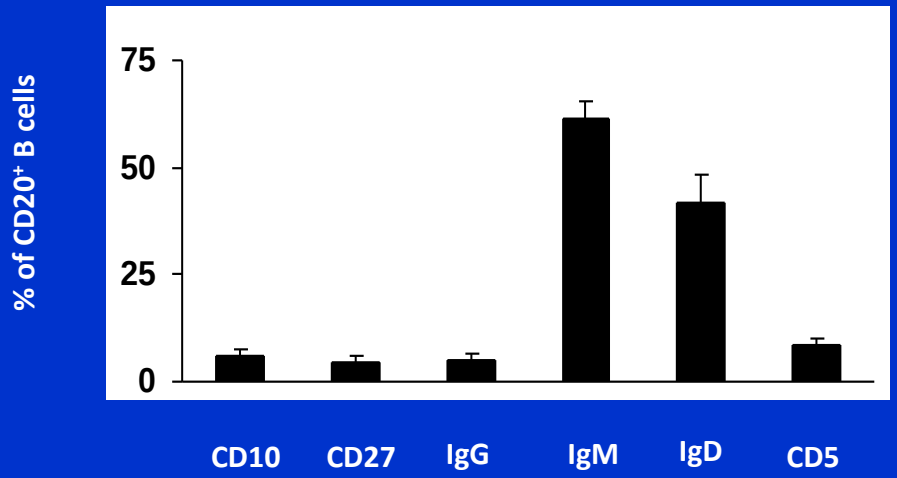


Young

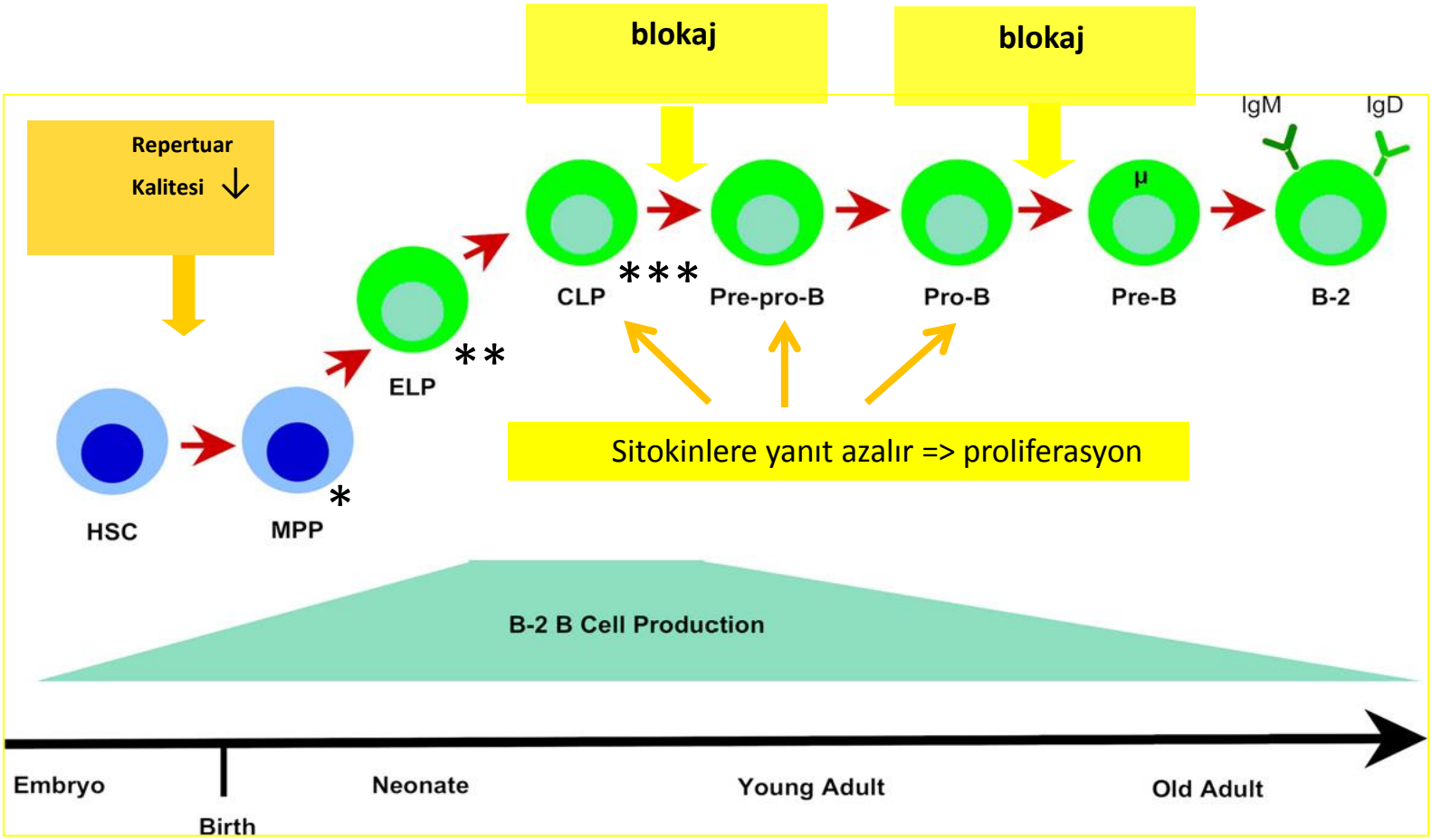


Elderly





A)- Pro-B' den Pre-B hücrelere olgunlaşma süreci kesintiye uğruyor

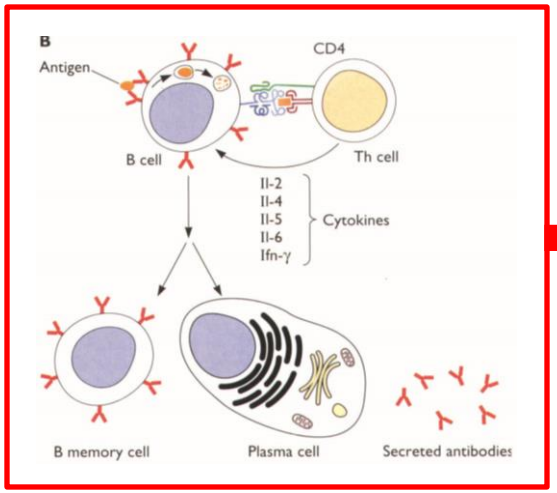


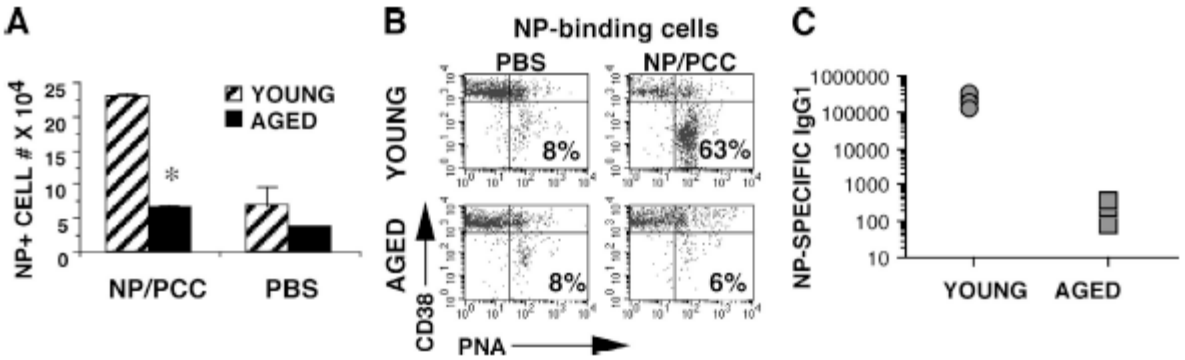
* multipotential progenitor
** early lymphoid progenitor
*** common lymphoid progenitor

Exp Gerontol 2007;42: 391

B)- **Age-related Defects in CD4 T Cell Cognate Helper Function Lead to Reductions in Humoral Responses**

Sheri M. Eaton, Eve M. Burns, Kimberly Kusser, Troy D. Randall, and Laura Haynes





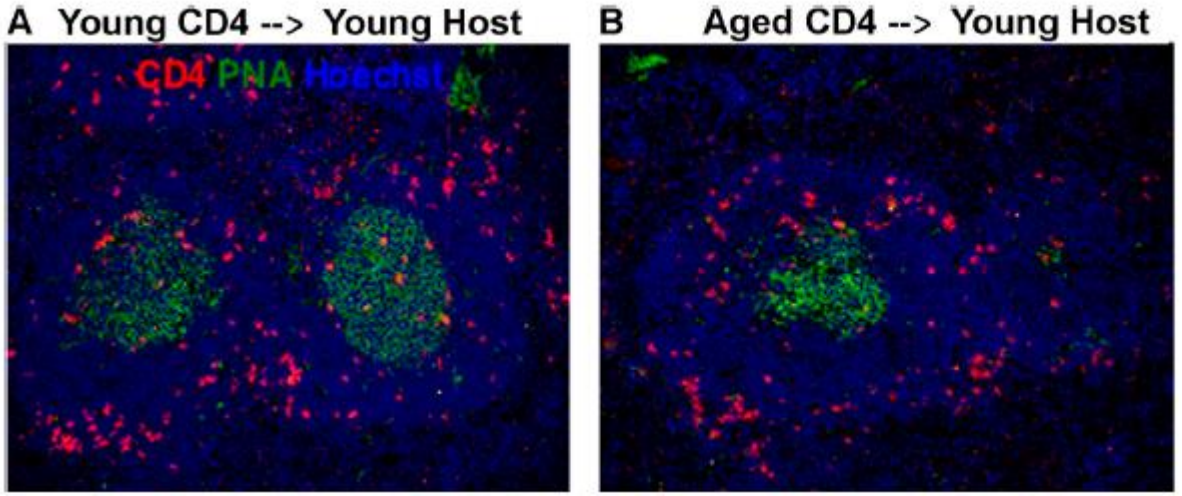
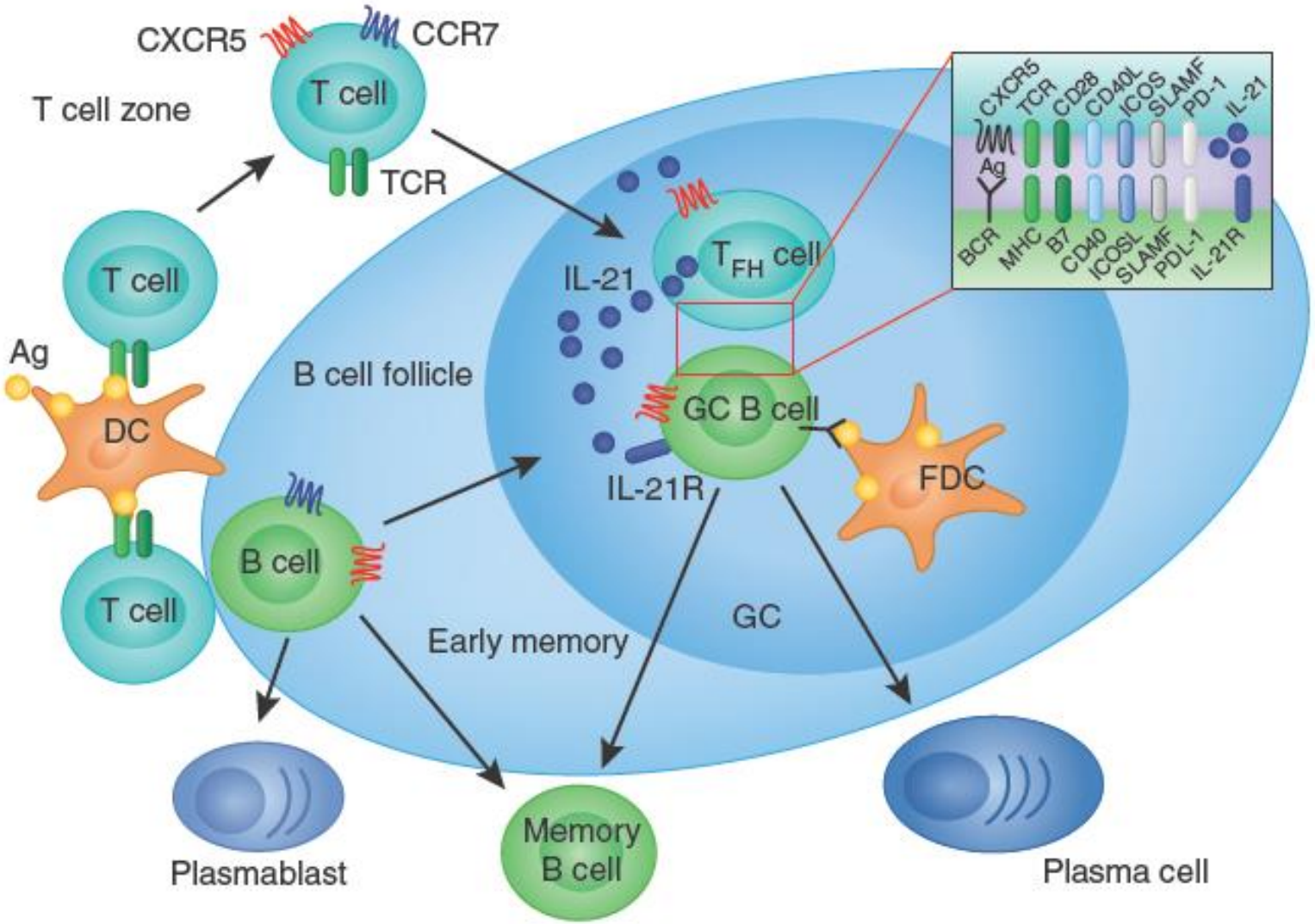


Figure 4. Young and aged Tg CD4 T cells migrate similarly in young hosts after immunization. On day 14 after immunization with NP-PCC/alum and transfer of young and aged donor T cells into young CD4KO hosts, the migration of donor cells into follicles was examined by fluorescence microscopy. Frozen sections were cut from spleens of young hosts receiving (A) young or (B) aged donor Tg CD4 T cells and stained with anti-CD4 (red), PNA (green), and Hoechst (blue).

J Exp Med 2004;12: 1613

C)- B lenfositlerinin fDH' lerce uyarılması yaşlılarda %70 oranında zayıflıyor



Nature Immunol 2011;12: 472

D)-

Lack of Antibody Production Following Immunization in Old Age: Association with $CD8^+CD28^-$ T Cell Clonal Expansions and an Imbalance in the Production of Th1 and Th2 Cytokines[1]

Maria Saurwein-Teissl,* Thomas L. Lung,* Florentine Marx,* Claudio Gschösser,* Esther Asch,* Imrich Blasko,* Walther Parson,† Günther Böck,‡ Diether Schönitzer,§ Emanuelle Trannoy,¶ Beatrix Grubeck-Loebenstein[2]*

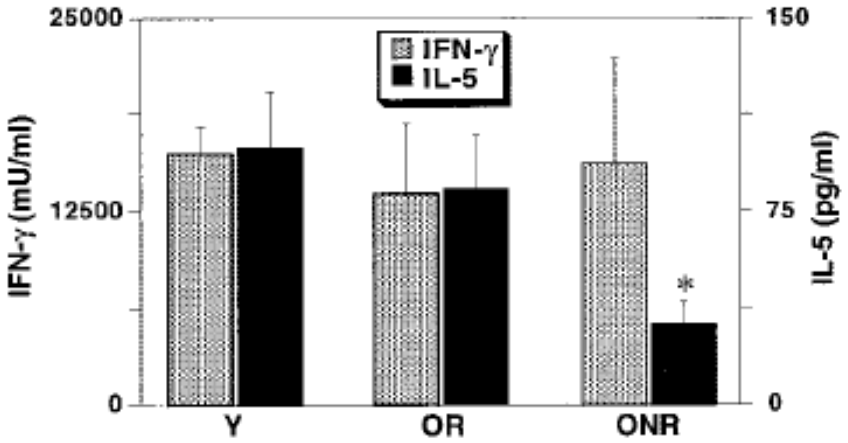


FIGURE 5. $CD4^+$ cells from elderly persons who fail to produce protective Abs following influenza vaccination have a decreased production of IL-5. Purified $CD4^+$ cells were seeded together with irradiated autologous PBMC and stimulated with PHA. Supernatants for the analysis of IFN-γ and IL-5 by ELISA were collected after 6 days of culture. Bars represent means ± SEM ($n = 6$ in the Y, $n = 14$ in the OR, and $n = 13$ in the ONR group); *, $p < 0.05$ vs Y and vs OR.

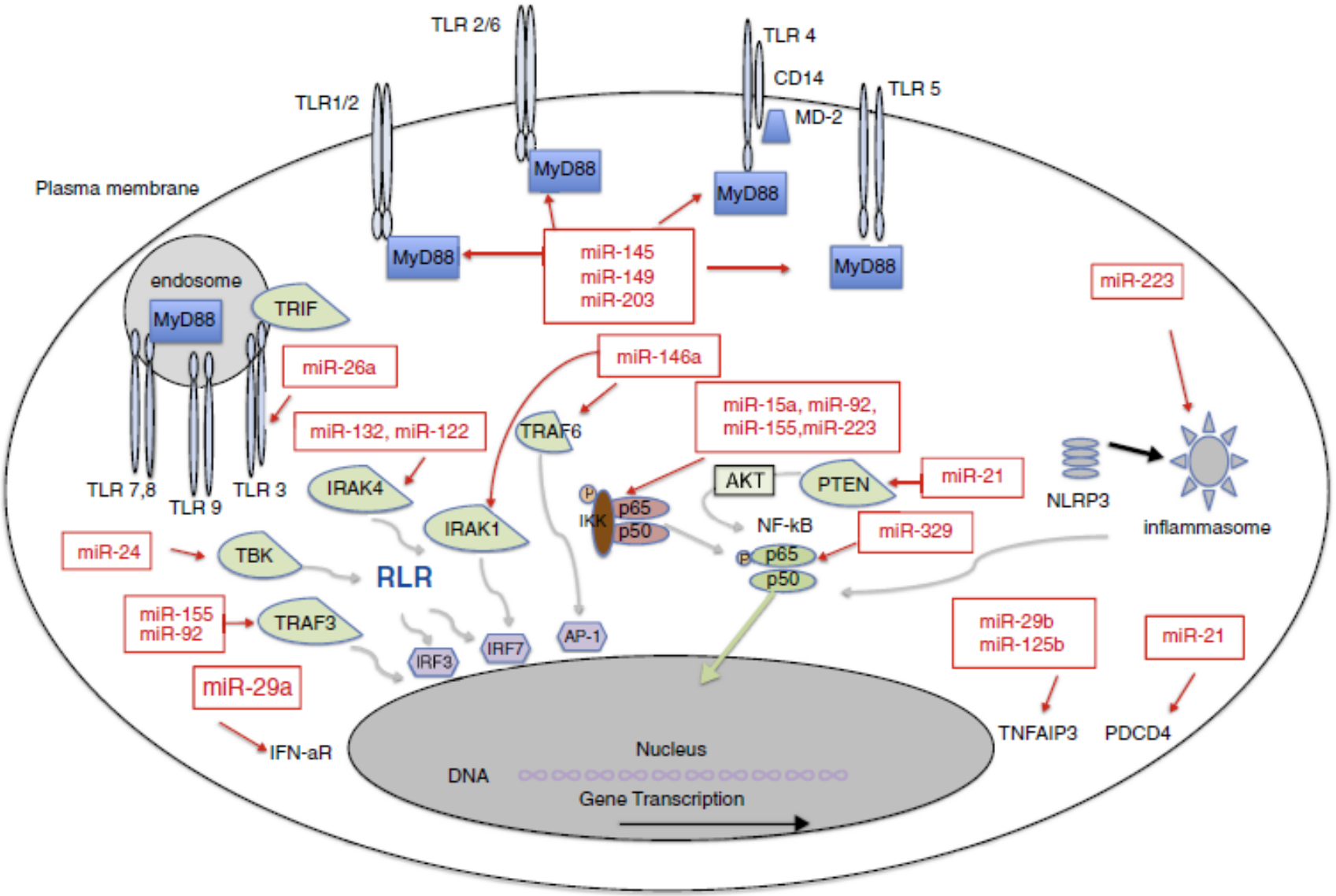
J Immunol 2002;168: 5893

Yaşlanma ile B lenfositlerinde gözlenen farklılaşmalar

- IL-7 azaldığından bu sitokine yanıt aksıyor
- Th'lerden yardım azaldığından aktivasyonu aksıyor
- Ig genlerindeki V-DJ rekombinasyonu azalıyor
- Hafif zinicirde lamda5 ekspresyonu azalıyor
- Transkripsiyon faktörlerinde (E12, E47) aktivite azalmasına bağlı olarak ağır zincir ekspresyonu azalıyor
- Th1 yanıtı yerini Th2 ye bıraktıkça, Otoantikor üretimi artıyor

Effect of aging on microRNAs and regulation of pathogen recognition receptors

Fabiola Olivieri[1,2], Antonio Domenico Procopio[1,2] and Ruth R Montgomery[3]



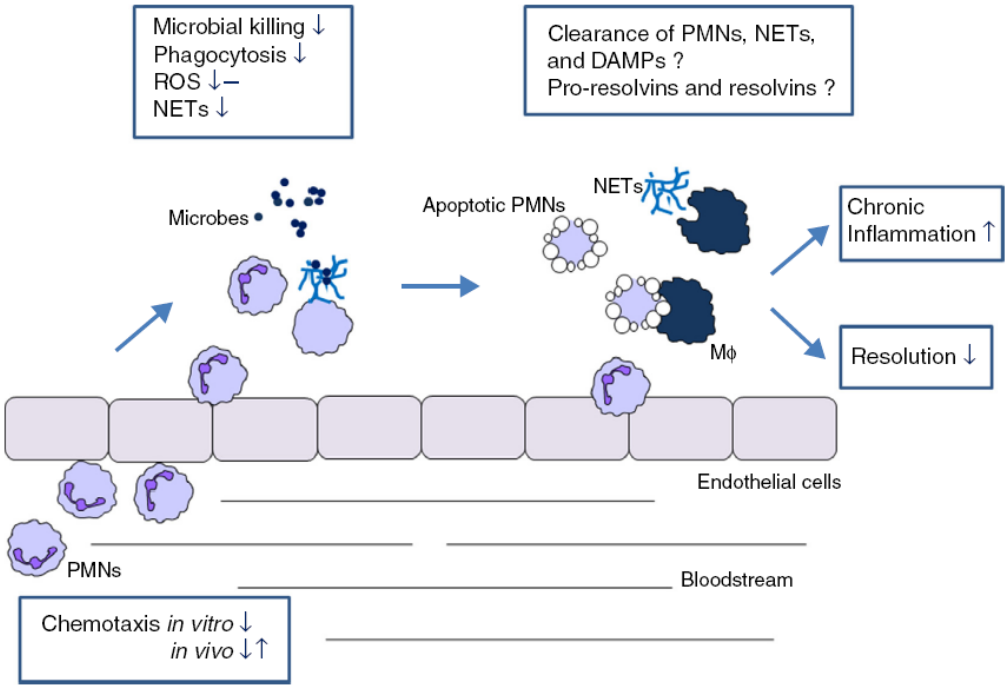
Curr Opinion Immunol 2014;29: 29

Expanding roles of neutrophils in aging hosts

Ching Wen Tseng[1,2] and George Y Liu[1,2]

Changes of neutrophil-related functionsin aged hosts

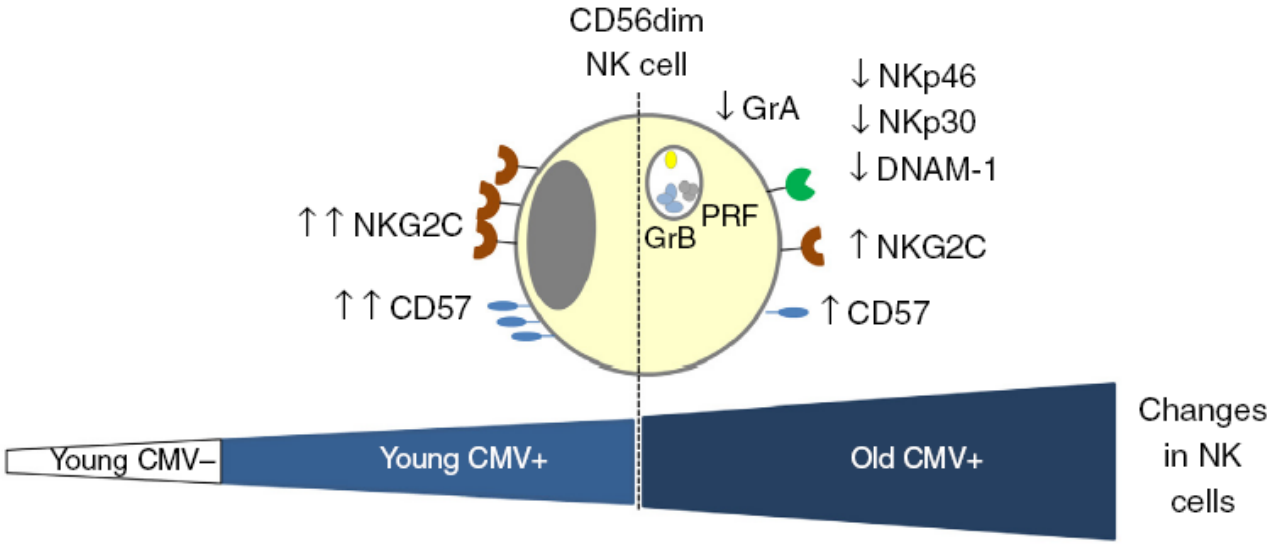
	Changes
Neutrophil number	↔
Neutrophil chemotaxis	
In vitro	↓
In vivo	↓, –, or ↑
Neutrophil antimicrobial functions	
Phagocytosis	↓
ROS	↓ or ↔
Elastase	Variable
NETs	↓
Clearance of dead neutrophils	Unknown
Clearance of DAMPs or NETs	Unknown
Pro-resolvins, resolvins, or protectins	Unknown
Cytokines	
Pro-inflammatory	↓ or ↔
Anti-inflammatory	↑
Existence of neutrophil types/subsets	
Pro-inflammatory/promoting tissue injury	[14••,36•,50••]
Anti-inflammatory/protective against tissue injury	[19•]



Curr Opinion Immunol 2014;29: 643

Shaping of NK cell subsets by aging

Rafael Solana[1], Carmen Campos[1], Alejandra Pera[1] and Raquel Tarazona[2]



	NK cell subsets				Phenotype*				Cytotoxic molecules and function*			
	$CD56^{bright}$ CD16–	$CD56^{bright}$ CD16+	$CD56^{dim}$ CD16+	CD56– CD16+	CD57	NKG2C	NCR	DNAM-1	Granzymes (Gr) A	Granzymes (Gr) B	Perforin (PRF)	CTX (per cell)
CMV[1]	=	=	=	=	↑↑	↑↑	?	?	=	=	=	?
AGE[2]	↓	↓	= or ↑	↑	↑	= or ↑	↓	↓	↓	=	=	↓

*Referred to CD56dim CD16+ NK cell subset; [1] Young CMV+ *versus* young CMV– individuals; [2] Elderly CMV+ *versus* young CMV+ individuals

Curr Opinion Immunol 2014;29: 56

Effects of polymorphisms in immunity-related genes on the immune system and successful aging

Qingwei Ruan[1,3], Feng Qian[2,3] and Zhuowei Yu[1]

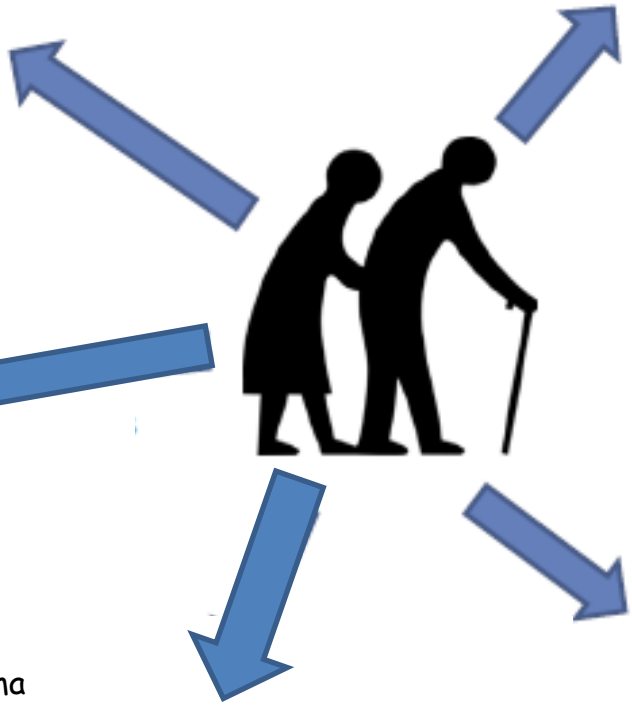
Immune system genes associated with successful aging

Gene name	Polymorphism/haplotype	Ref SNP	Effects
HLA I	A9; A30		Increased; decreased in Han Chinese
	A31*19, B7, Cw7		Increased in healthy elderly Italians
	B*15, C*07, C*15		Negative associated with longevity in Indians; B*15 decreased in Greeks
	B16		Increased in healthy elderly Greeks
HLA II	DRB1*18		Increased in male Sicilian centenarians
	DRB1*11		Increased in Dutch and Mexico healthy female elderly; French familial nonagenarians
	DRB1*07		Increased in healthy elderly Greeks
	DRB1*13		Increased in French centenarians
	DRB1*15		Increased in Sardinian centenarians
	DRB1*11 and DRB1*16 related haplotypes		Increased in healthy elderly Bulgarians and Romanians
KIR	2DL5, 2DS3		Associated with longevity in Irish population
	2DL2; 2DL3, 2DS1		Increased; decreased in healthy elderly Bulgarians
	A1B1, A1B3, A1B4; A1B10		Increased; decreased in healthy elderly Bulgarians
IL-6	−174C/G	rs1800795	−174C allele increased in Italian male centenarians
TNF-A	−308A/G	rs1800629	−308a allele decreased in centenarians
IFN-γ	874T/A	rs61923114	874A allele increased in female Italian centenarians
IL-10	−1082A/G	rs1800896	G allele increased in male Italian centenarians
TLR1	743A/G; 1805T/G	rs4833095; rs5743618	a higher accumulation of the genotype 743AA/1805GG in the old German individuals
TLR4	896A/G	rs4986790	896G increase in male Sicilian centenarians
CCR5	Delta 32	rs333	Increased in centenarians; decrease in PC,MI patients
RANTES	−403G/A; −int 1.1C/T	rs2107538; rs2280789	Haplotype −403G- −int 1.1C was over-represented in elderly female while −403A- −int 1.1T in male elderly
C RP	−717A/G; 1444C/T; 1846G/A	rs2794521; rs1130864	Haplotype ACA increased in nonagenarians of 4-year follow-up survival

Curr Opinion Immunol 2014;29: 49

Makrofajlarda değişim
. Fenotipin CD14dim/CD16bright e dönüşümü
. IFN üretiminde azalma
. NO/H2O2 üretiminde azalma
. Büyüme faktörlerine yanıtın zayıflaması

Diğer değişimler
. Telomeraz aktivitesinde azalma
. Replikasyonun azalması
. Pro-infşamatuar sitokin düzeyinde zayıflama
. Tümör insidansında artış
. Enfeksiyonlara duyuarlıkta artış
. Otoimmün reaksiyonlarda artış



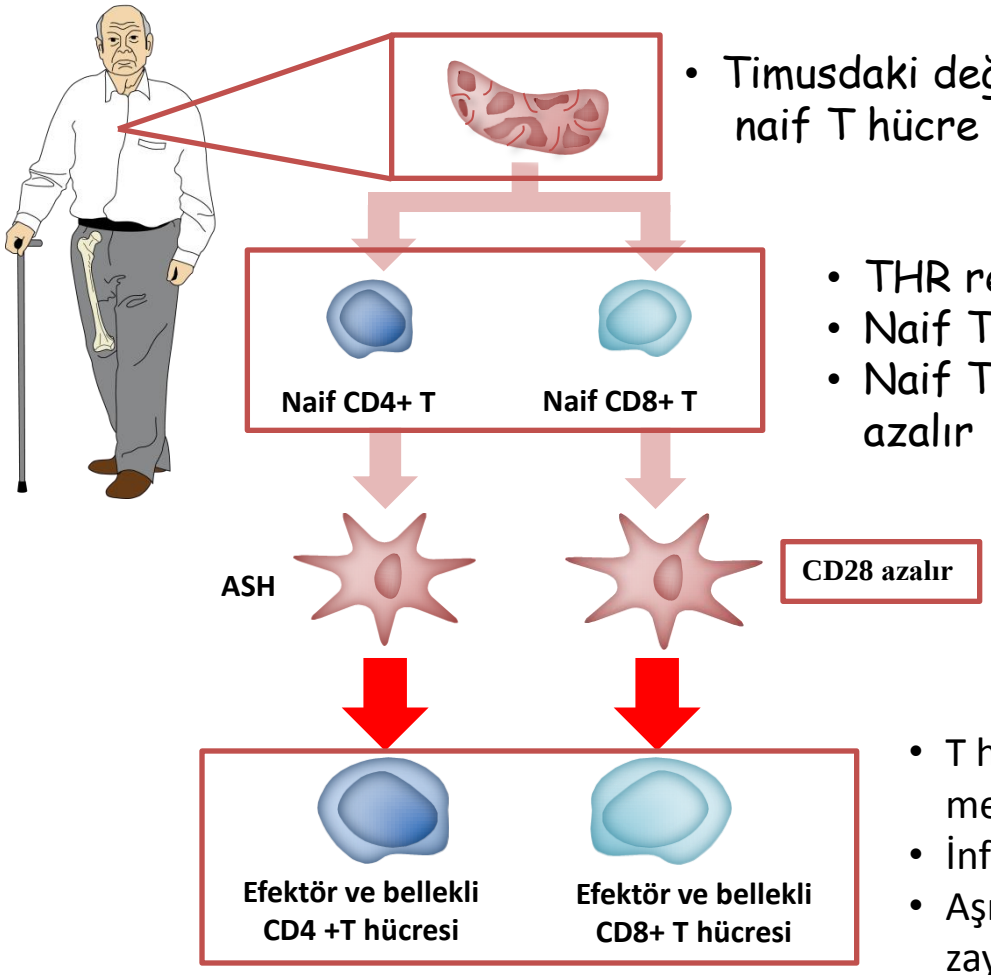
NK' larda değişim
. NK işlevinde azalma
. NK sayısında artış
. Sitotoksik kapasitede azalma

B hücrelerinde değişim
. Sayısal azalma
. BHR repertuarında zayıflama
. Yeni B hücre sentezinde azalma
. Proliferasyon kapasitesinde azalma
. Otoantikor üretiminde artış
. IgG ve IgA düzeylerinde artış

T hücrelerinde değişim
. THR çeşitliliğinde azalma
. Naif T hücre lerin işlevselliğinde azalma
. Naif T hücre üretiminde azalma
. İşlevsiz bellekli T hücre yığımı
. Yüzey özelliklerinde NK' lara kayış

Curr Opinion Immunol 2014;29: 62

Yaşlanma ile sayısı ve işlevi azalan T hücreleri nedeniyle edinsel yanıt zayıflar



- Timusdaki değişime bağlı olarak naif T hücre sayısı azalır.

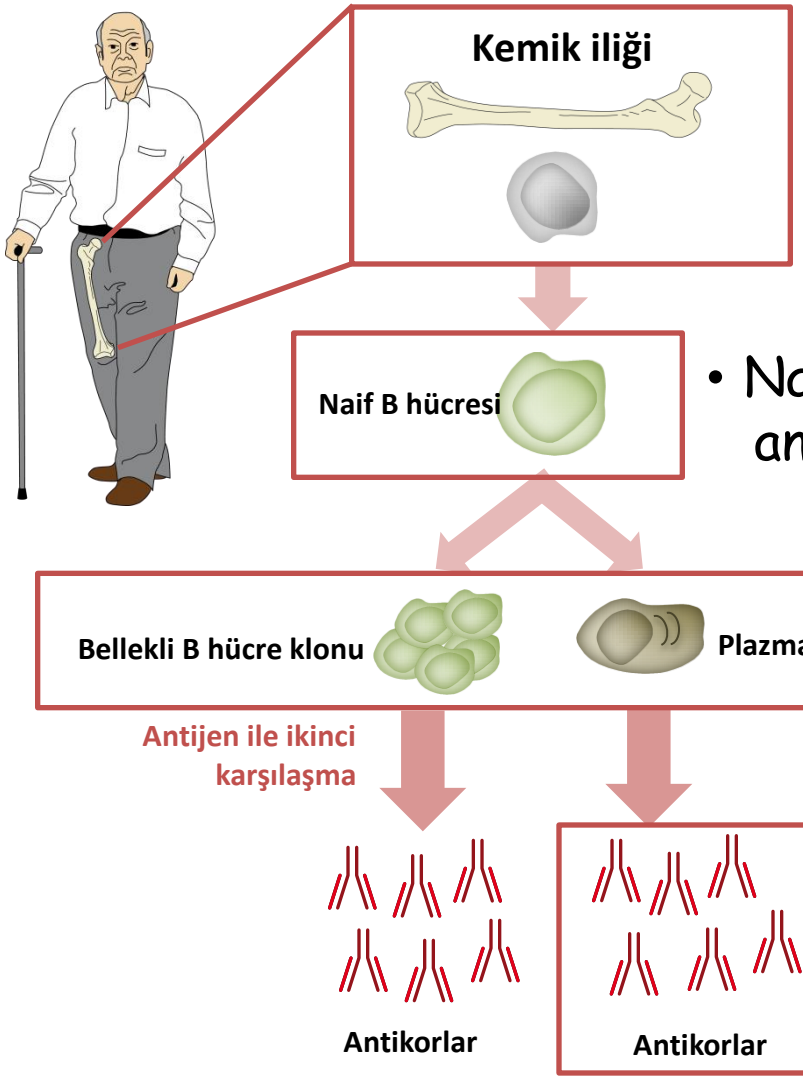
- THR repertuarı azalır
- Naif T hücrelerinin göç kapasitesi zayıflar
- Naif T hücrelerinin proliferasyon kapasitesi azalır

- CD28 azalmasına bağlı olarak CD8 T hücrelerinin replikasyonu azalır

- T hücrelerince üretilen proinflamatuar mediatörler artar
- İnflamasyon artar
- Aşı ve enfeksiyon etkenlerine karşı edinsel yanıt zayıflar

.Immunity & Ageing. 2007;4:1-9. doi:10.1186/1742-4933-4-9
CID 2008;46:1078-1084.

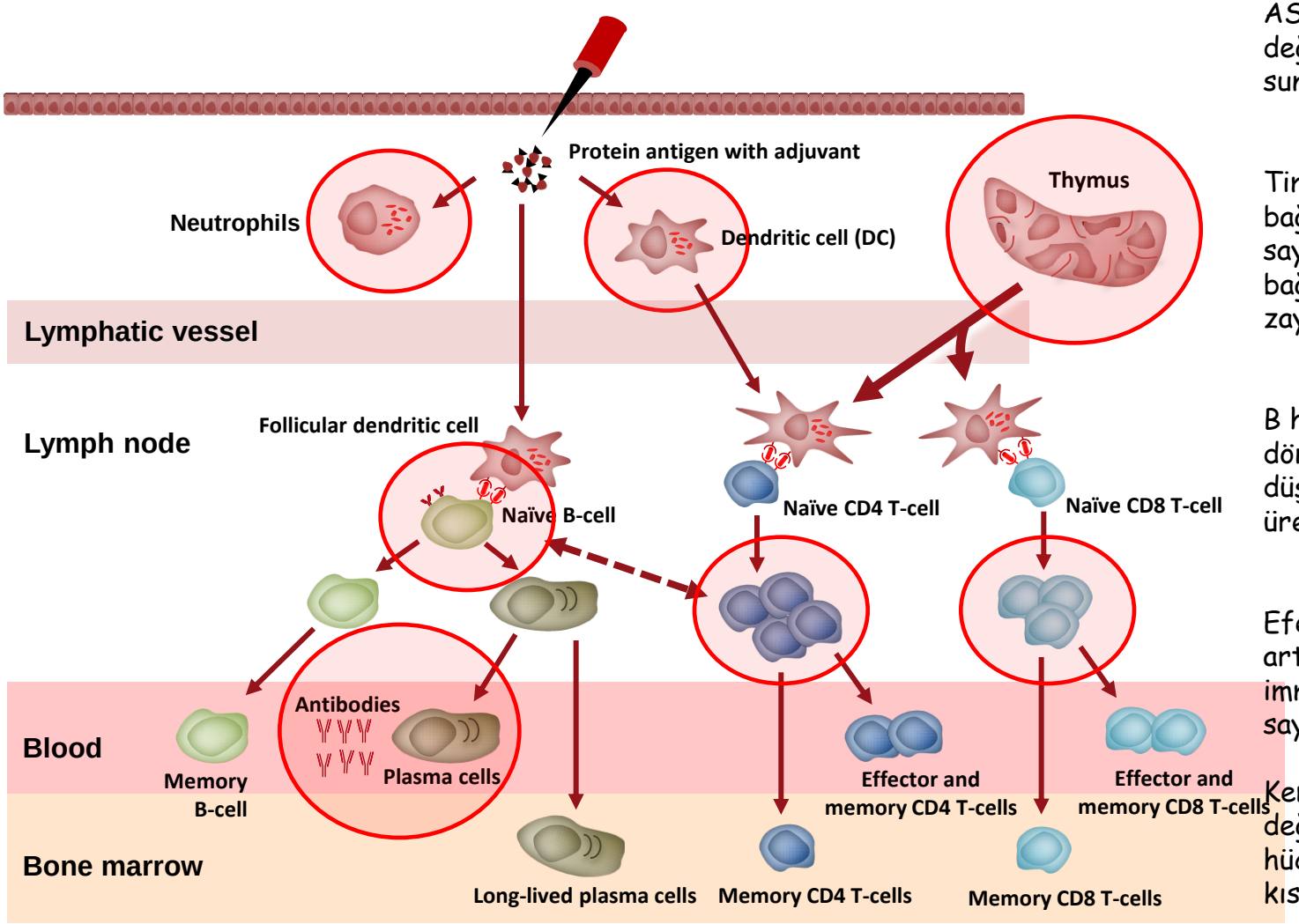
Yaşlanma ile naif B hücre havuzu azalır ve Antijene Yanıt Zayıflar



- Öncü B hücre sayısı azalır
- Naif B hücre üretimi zayıflar ve antijen uyarısına yanıt azalır
- Kısıtlı özgüllüğe sahip bellekli ve naif B hücresi artar
- Üretimi farklılaşan plazma hücrelerinden monoklonal IgG üretimi olur

Nature Reviews Immunology 2009;9:185

Aşıya karşı Yanıtın Yaşlanma İle Zayıflaması



ASH' lerdeki işlevsel değişiklikler sonucu antijen sunumu aksar

Timusun «yaşlanmasına» bağlı olarak naif T hücre sayısı azalır: primer bağışıklamaya yanıt zayıflar

B hücre üretimi ve izotip dönüşümü zayıflar; zayıf ve düşük afiniteli antikor üretimi olur

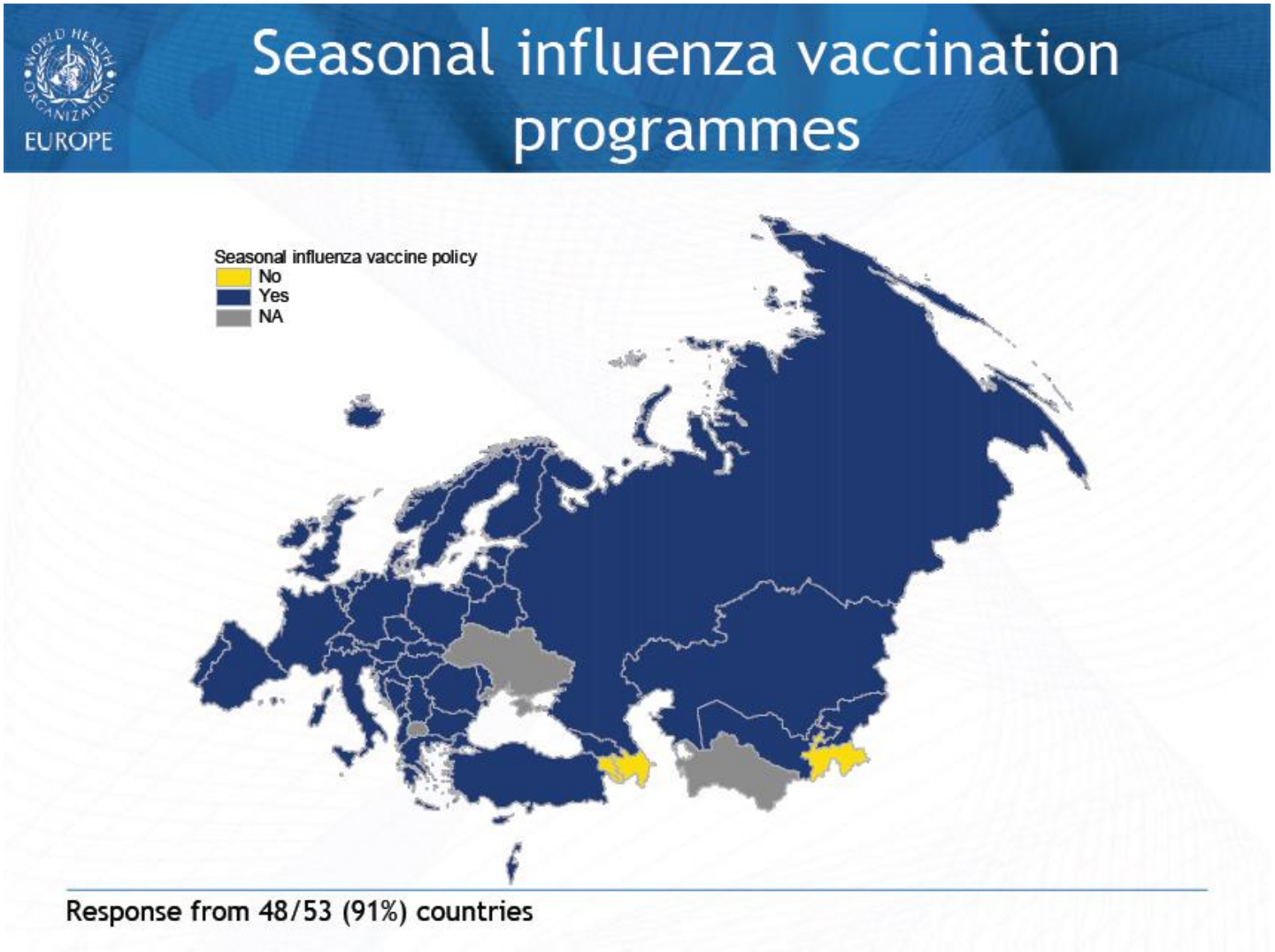
Efektör T hücre sayısında artışa bağlı olarak immünokompetan hücre sayısı azalır

Kemik iliği stromasında değişim sonucu plazma hücrelerinin yaşam süresi kısalır

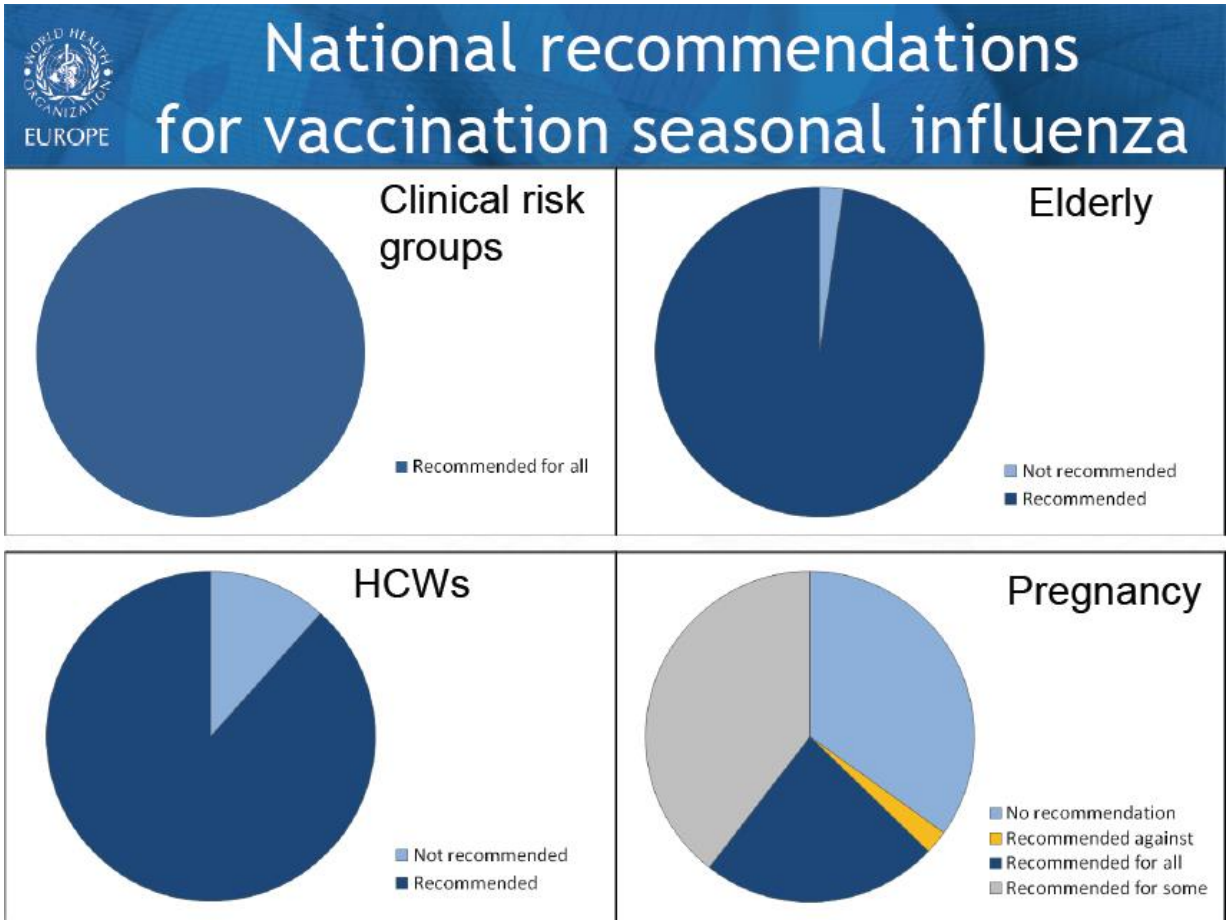
Vaccine. 2011. doi: 10.1016/j.vaccine.2010.12.121.
CID. 2008:46:1078-84.

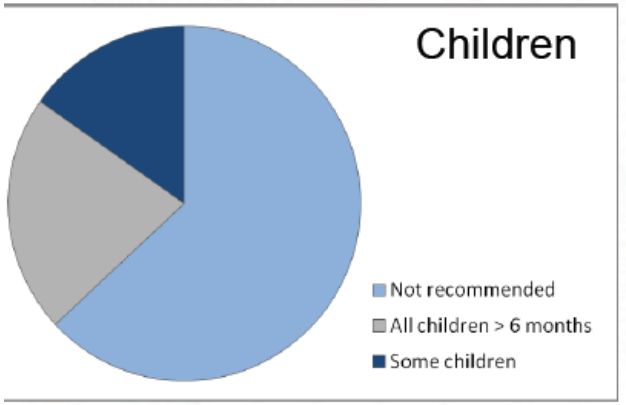
Serkan Altuniğne © www.komikaze.net

Toplam 48 Ülkede Aşılama Programı Var (DSÖ-Avrupa Bölgesi)



Ulusal Aşılama Önerileri





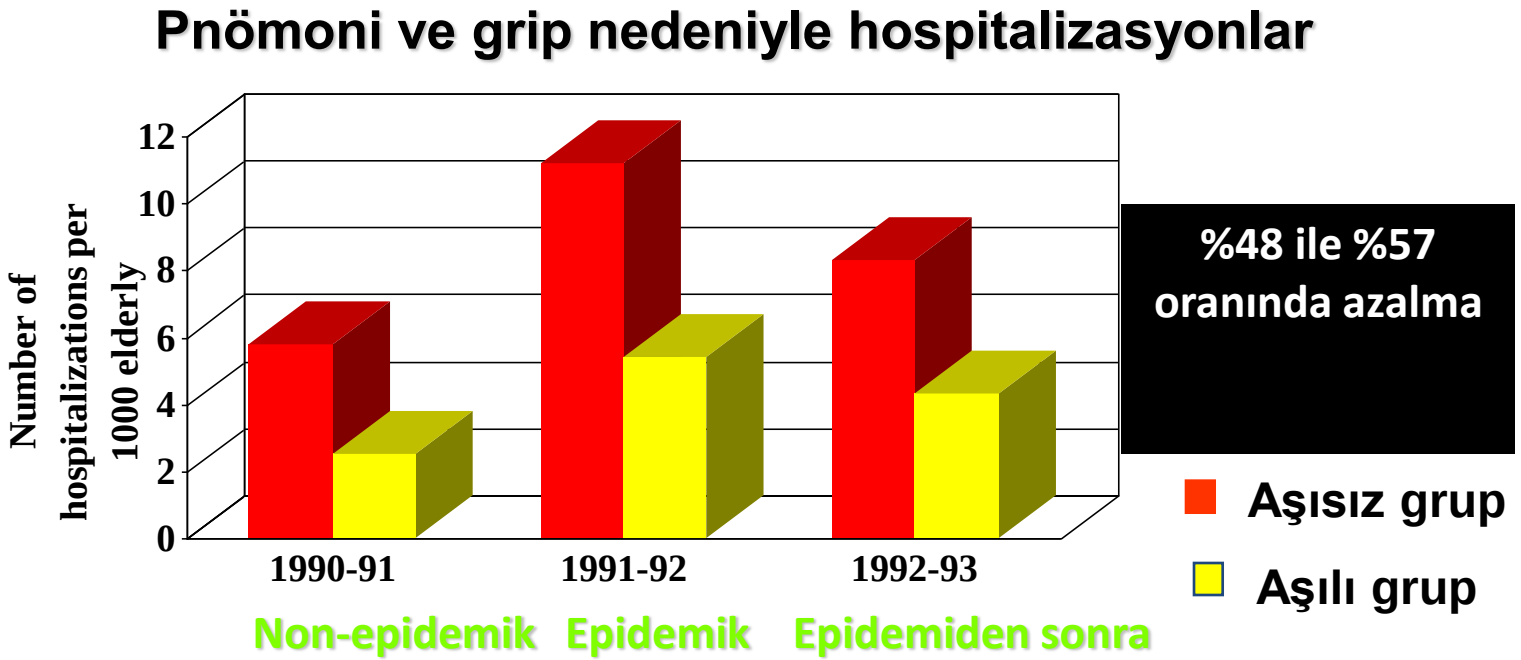
Risk Gruplarına Göre Aşıdan Sağlanan Yararın Değerlendirilmesi

Risk Grubu	Uygulama Kolaylığı	Hastalık Şiddeti	Aşı Etkinliği	Dolaylı Yarar
Gebeler	++	+++	+++	++
Sağlık Çalışanları	++	+	+++	+
Çocuklar, 2-5 yaş	+	++	++	-
Çocuklar, <2 yaş	++	+++	+	-
Yaşlılar	+	+++	+	-
Kronik Hastalığı Olanlar	+	+++	+	-

Caroline Brown, WHO, ESWI Flu Summit 23 May, 2012, Brussels, WHO reginoal meeting, Warsaw 2012

Aşının Etkililik ve Etkinlik Sonuçları

Yaşlılarda grip aşısının getirileri-1



Her grupta 25.000'den fazla bireyin bulunduğu pnömoni ve influenza çalışmasında 1000 yaşlı kayıtlı hasta için ortalama hospitalizasyon sayısı (ABD)

Nichol KL, Margolis KL, Wuorenma J., Von Sternberg T. The efficacy and cost effectiveness of vaccination against influenza among elderly persons living in the community. NEJM 1994;778-84

Yaşlılarda grip aşısının getirileri-2

- Meta-analiz 20 kohort çalışması,

	% (95% CI)
Solunum yolu hastalığına yakalanma	56 (39–68)
Pnömoni	53 (35–66)
ASYE nedeniyle hastaneye yatış	50 (28–65)
Ölüm	68 (56–76)

Ann Intern Med 1995; 123: 518

AŞININ ETKİNLİĞİ

- Yıldan yıla
- Virüs tipi/alttipine göre
- Aşı tipine göre
- Daha önce aşılanmış olup-olmamaya göre (immüniteye)
- Olgu tanımına göre
- Aşılanın yaşına göre
- Atak hızına göre

DEĞİŞİR

Vaccines for Seasonal and Pandemic Influenza

Kristin L. Nichol[1] and John J. Treanor[2]

Vaccine Efficacy and Effectiveness

Vaccine efficacy and effectiveness studies tend to evaluate different outcomes, making comparisons between studies difficult. Cause-specific outcomes—that is, where there is laboratory confirmation of the influenza virus causing illness or infection—provide the highest and most precise estimate of vaccine impact, because there are fewer false-positive results. "All-cause" outcomes—for example, clinical illness without laboratory confirmation, all respiratory illnesses, or all otitis media episodes—are less specific, because they would not all be caused by influenza, and, hence, vaccination will give a lower percentage reduction. However, although all-cause outcomes have a lower relative risk reduction ratio (RRR), they have an increased absolute risk reduction (ARR), because including all-cause outcomes enhances sensitivity. The evidence of vaccine efficacy and effectiveness in children, adults, and the elderly is provided by several systematic reviews and meta-analyses.

J Infect Dis 2006;194 (Suppl 2): S111


BANA DA AYNISINDAN..!..
OLMAZ, SEN KONTROL GRUBUSUN..!

Aşı Etkinliği Yaşa Göre Değişiyor

Trivalent inactivated influenza vaccine (TIV) immunogenicity in children 6 through 23 months of age: Do children of all ages respond equally?

Emmanuel B. Walter[a,*], Shilpa Rajagopal[a], Yuwei Zhu[b], Kathleen M. Neuzil[c], Mary P. Fairchok[d,e], Janet A. Englund[d]

We assessed the effect of age on immunogenicity to trivalent inactivated influenza vaccine (TIV) by comparing the immune responses to influenza vaccine antigens among three age cohorts of vaccine-naïve children aged 6–11 months, 12–17 months, and 18–23 months. In children 6–23 months of age, antibody responses to TIV appear to increase with increasing age. Despite this finding, TIV was immunogenic even

Table 2
Proportion of children seroprotected (HAI titer ≥ 1:32) by age group, year, antigen, and dosing group after two doses of TIV.

	Age[a] (months)			
	6–11	12–17	18–23	*p*-Valu
H3N2 antigen				
2003				
Early	79.0 (54.4, 94.0)	90.2 (78.6, 96.7)	90.9 (70.8, 98.9)	0.256
Standard/nonrandomized	77.8 (52.4, 93.6)	90.5 (80.4, 96.4)	92.3 (79.1, 98.4)	0.149
2004				
Early	47.0 (35.9, 58.3)	81.7 (73.0, 88.6)	96.3 (81.0, 99.9)	<.001
Standard/nonrandomized	83.7 (74.2, 90.8)	84.4 (77.3, 90.0)	79.5 (63.5, 90.7)	0.658
H1N1 antigen				
2003[b]				
Early	57.9 (33.5, 79.8)	78.4 (64.7, 88.7)	86.4 (65.1, 97.1)	0.036
Standard/nonrandomized	50.0 (26.0, 74.0)	76.2 (63.8, 86.0)	92.3 (79.1, 98.4)	<.001
2004[b]				
Early	77.1 (66.6, 85.6)	90.4 (83.0, 95.3)	100.0 (87.2, 100.0)	0.001
Standard/nonrandomized	86.0 (76.9, 92.6)	92.9 (87.3, 96.6)	97.4 (86.5, 99.9)	0.022
B antigen				
2003				
Early	42.1 (20.3, 66.5)	58.8 (44.2, 72.4)	77.3 (54.6, 92.2)	0.022
Standard/nonrandomized	22.2 (6.4, 47.6)	54.0 (40.9, 66.6)	61.5 (44.6, 76.6)	0.012
2004				
Early	30.1 (20.5, 41.2)	38.5 (29.1, 48.5)	66.7 (46.0, 83.5)	0.002
Standard/nonrandomized	83.7 (74.2, 90.8)	88.7 (82.2, 93.4)	92.3 (79.1, 98.4)	0.147

Vaccine 2010;28: 4376

Aşının Tipine (TIV vs LAIV) Göre Farklı Sonuçlar

Table 1
Results of meta-analyses assessing influenza vaccine efficacy and effectiveness illness in children

Study and Type of vaccine	Efficacy against laboratory/culture confirmed influenza illness	Effectiveness against clinical illness
Jefferson et al.[a]		
Live attenuated	82% (71–89%)	33% (28–38%)
Inactivated	59% (41–71%)	36% (24–46%)
Negri et al.[b]		
Live attenuated	80% (53–91%)	34% (31–38%)
Inactivated	65% (45–77%)	33% (22–42%)
Overall	79% (66–87%)	33% (28–36%)
Manzoli et al.[c]		
Live attenuated	72% (38–87%)	35% (30–40%)
Inactivated	62% (45–75%)	45% (33–55%)
Overall	67% (51–78%)	36% (31–40%)

Shown are the percent reductions (95% confidence interval).

Vaccine 2008;26S: D17

Aşı İçeriği ve Dolaşımdaki Suşların Uyum Derecesi

Table 6
Impact of inactivated vaccine mismatch on estimates of vaccine efficacy and effectiveness

	Good match	Poor match
Younger adults – VE against culture confirmed influenza illness		
Jefferson et al.[a]	80% (56–91%)	50% (27–65%)
Edwards et al.[b]	74–79%	71–79%
Ohmit et al.[c]	–	77% (37–92%)
Older adults in the community – VE against influenza complications[d]		
Hospitalization for pneumonia or influenza	29% (24–34%)	25% (15–34%)
Death	52% (49–54%)	37% (31–43%)
Older adults in nursing homes – VE Against influenza complications[e]		
Respiratory illness	49% (27–66%)	66% (42–80%)
Pneumonia	59% (35–74%)	68% (17–88%)
Hospitalization	66% (32–72%)	70% (−7–92%)
Death	69% (54–79%)	79% (57–90%)

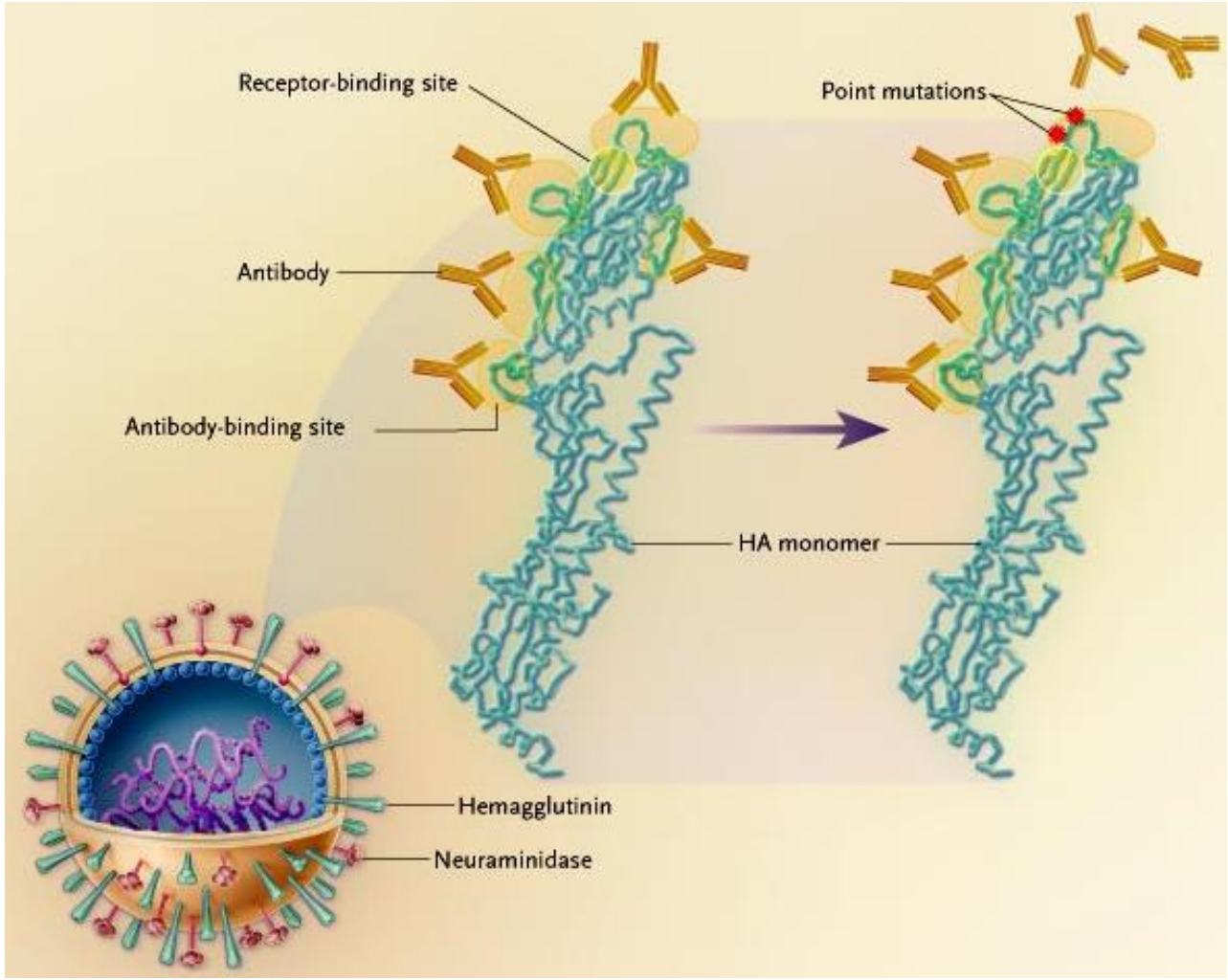
Shown are the percent reductions (95% confidence interval). VE denotes vaccine effectiveness.

Vaccine 2008;26S: D17

SEZON	DOLAŞIMDAKİ SUŞ	AŞI İÇERİĞİ
2003-2004	A/H3N2: A/Fujian/411/02	A/H3N2: A/Moscow/10/99 A/H1N1: A/New Caledonia/20/99 B: B/Hong Kong/330/01 (Victoria)
2004-2005	A/H1N1: A/New Caledonia/20/99 A/H3N2:A/Netherlands/128/2004 ve A/Shantou/1219/2004	A/H1N1: A/New Caledonia/20/99 A/H3N2: A/Fujian/10/99 B: B/Shanghai/361/2002 (Yamagata)
2005-2006	A/H3N2: A/Hong Kong/443/05 B:B/Jiangsu/10/03 (Yamagata) ve B/Malaysia/2506/04 (Victoria)	A/H1N1: A/New Caledonia/20/99 A/H3N2: A/California/7/2004 B: B/Shanghai/361/2002 veya B /Jiangsu/10/2003 (Yamagata)
2006-2007	A/H3N2:A/Wisconsin/67/2005 ve A/California/7/2004 B: B/Victoria/2/87 ve B/Yamagata/10/88	A/H1N1: A/New Caledonia/20/99 A/H3N2: A/Wisconsin/67/2005 veya A/Hiroshima/52/2005 B: B/Malaysia/2506/2004 veya B/Ohio/1/2005 (Victoria)

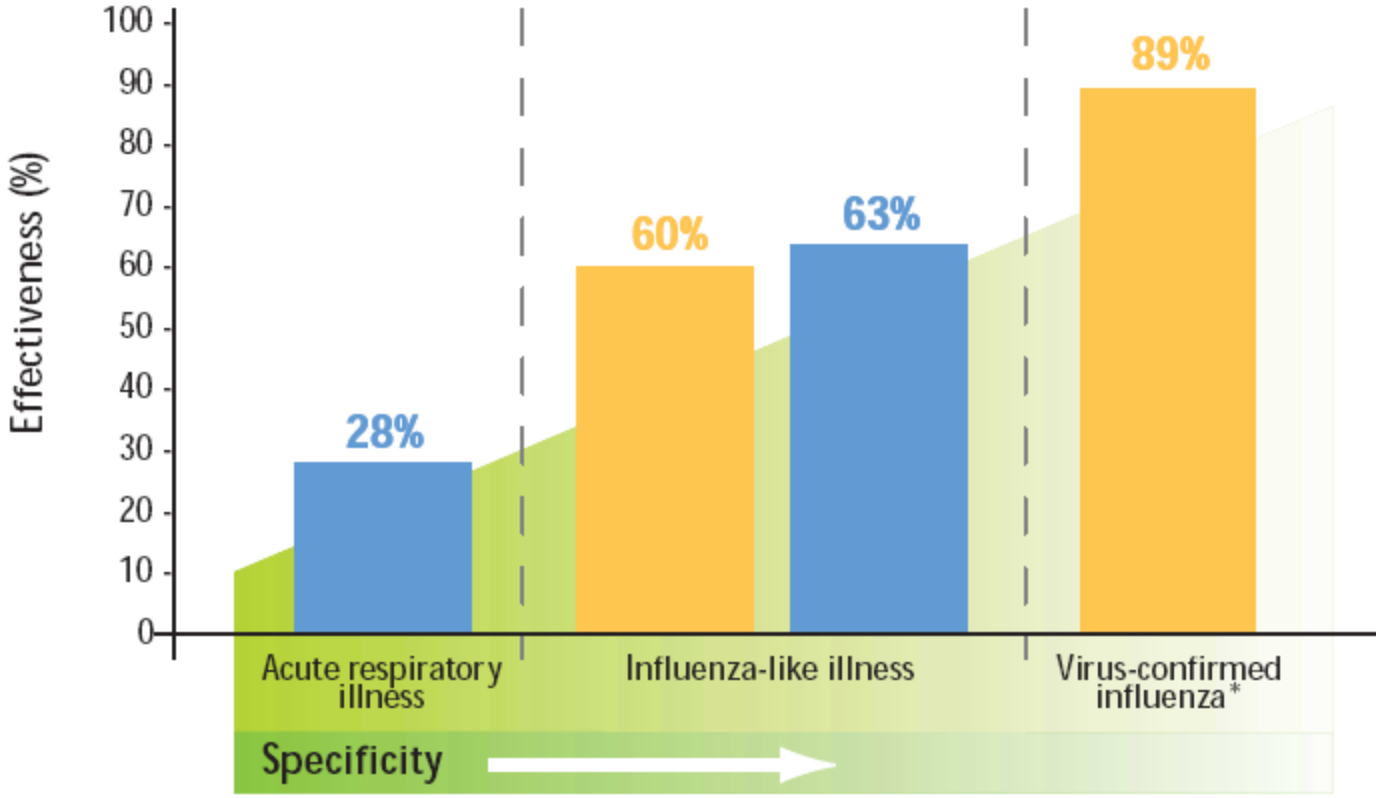
H3N2 virüsünde antijenik değişim

A/Panama/200/99 **A/Fujian/411/2002**



N Engl J Med 2004;350:218

Olgu Tanımına Göre Aşı Etkinlik Oranları



Wood et al,
N=90 000
working adults

Merlin et al,
N=53 000
military personnel

Wood SC, et al *Vaccine* 17 (Suppl. 3); S81–S87
Merlin et al BEH 41;1975–6.

Tanı İçin Kullanılan Yöntemler (Farklı kriterler=Farklı sonuçlar)

Table 1
Results of meta-analyses assessing influenza vaccine efficacy and effectiveness illness in children

Study and Type of vaccine	Efficacy against laboratory/culture confirmed influenza illness	Effectiveness against clinical illness
Jefferson et al.[a]		
Live attenuated	82% (71–89%)	33% (28–38%)
Inactivated	59% (41–71%)	36% (24–46%)
Negri et al.[b]		
Live attenuated	80% (53–91%)	34% (31–38%)
Inactivated	65% (45–77%)	33% (22–42%)
Overall	79% (66–87%)	33% (28–36%)
Manzoli et al.[c]		
Live attenuated	72% (38–87%)	35% (30–40%)
Inactivated	62% (45–75%)	45% (33–55%)
Overall	67% (51–78%)	36% (31–40%)

Shown are the percent reductions (95% confidence interval).

Vaccine 2008;26S: D17

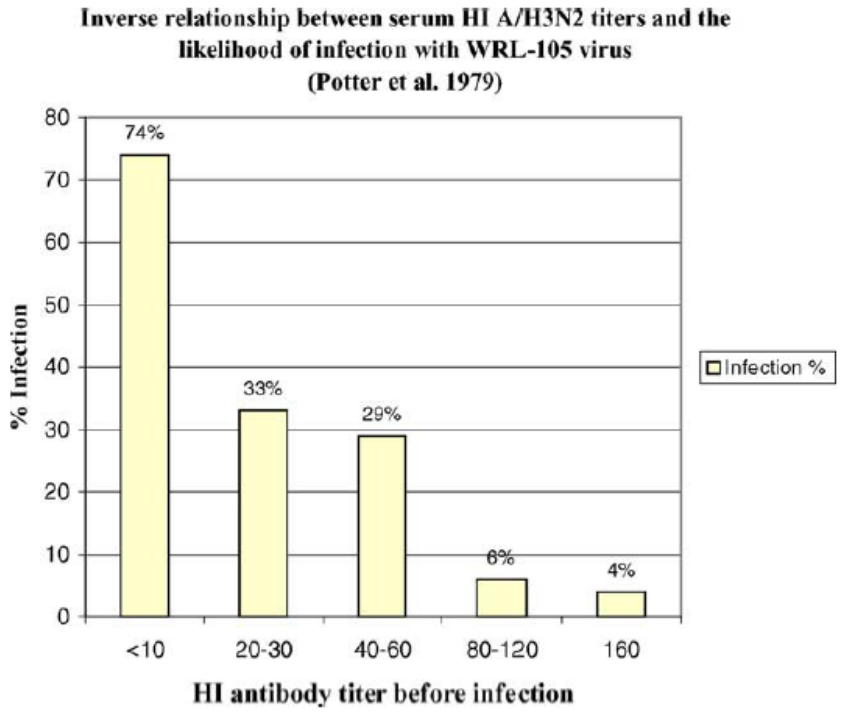
Eskiden Var Olan bağışıklık...

Immunogenicity and protective efficacy of influenza vaccination

Claude Hannoun [a,*], Francoise Megas [b,1], James Piercy [c,d,2]

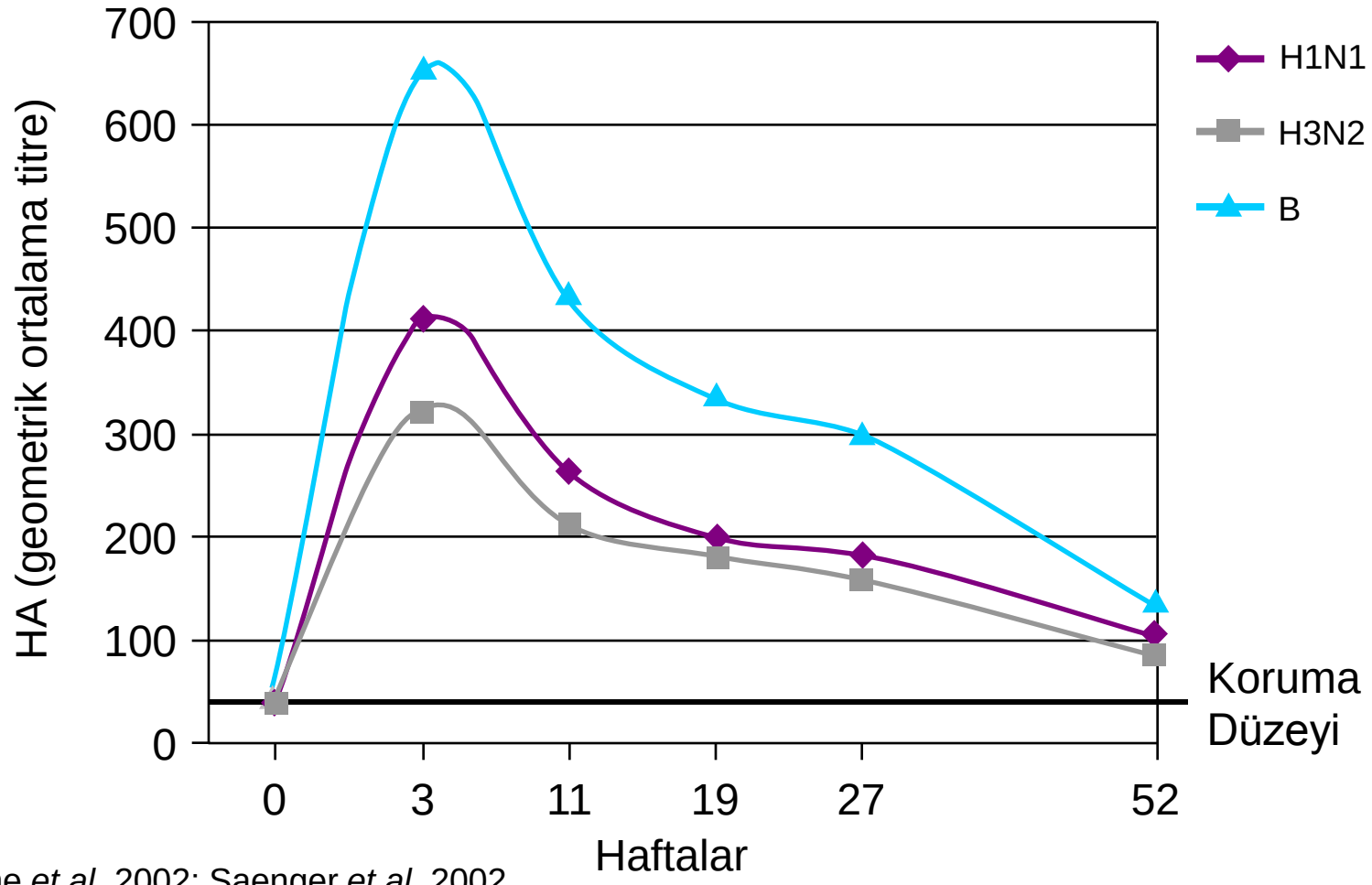
5. Discussion

Currently available inactivated influenza vaccines offer substantial protection against influenza, particularly in terms of limiting disease severity and reducing the potential for serious complications (Couch, 2000; Podda, 2001). However, the efficacy of these influenza vaccines may be influenced by a range of different of factors, including age, health status and use of concurrent medications, prior vaccination and prevaccination HI antibody titres. Clinical effectiveness in adults aged less than 65 years may be as high as 70–90%, but is generally lower in older adults aged ≥65 years, typically ranging from 30 to 40% (Palache, 1997; Strassburg et al., 1986). One possible explanation for this finding may be the lower antibody response to currently available influenza vaccines seen in older subjects (Phair et al., 1978; Keren et al., 1988). Indeed, the need for influenza vaccines with improved



Virus Res 2004;103: 133

Grip Sezonu Boyunca Koruma!!!



Hehme *et al*. 2002; Saenger *et al*. 2002


ÖMÜR BOYU (7 YIL)
GARANTİLİ

Influenza A/Philippines/2/82 outbreak in a nursing home: Limitations of influenza vaccination in the aged

Julio C. Arroyo, M.D., F.A.C.P.
B. Postic, M.D., F.A.C.P.
Arnold Brown, M.D.
Kathy Harrison, R.N.
Robert Birgenheier, R.N.
Harold Dowda, Ph.D.

cine.[13, 16] Here the individual immunologic response to the vaccine is an important factor because it is generally not as successful in elderly persons as it is in younger ones.[23] A poor antibody response to influenza vaccine in aged volunteers correlated with preexisting levels of homologous antibody and with decreased B-lymphocytes bearing immunoglobulin D.[24] Howells et al.[25] compared the geometric mean antibody titer in older people with that of younger age groups before and after influenza vaccination and found that the antibody response was much less in the older group. Furthermore, a second dose of influenza vaccine did not produce a booster effect in elderly subjects who had not had a response to the first injection.[26] A serologic survey of elderly people showed that individuals born between 1876 and 1925 had levels of antibody that should be protective against influenza A (H3N2)[27]; however, in natural outbreaks these people were not spared. Moreover, the protective level of

Am J Infect Control 1984;12: 329

Rapid Decline of Influenza Vaccine–Induced Antibody in the Elderly: Is It Real, or Is It Relevant?

Danuta M. Skowronski,[1] S. Aleina Tweed,[1,a] and Gaston De Serres[2]

J Infect Dis 2008;197: 490

decline. Both studies reporting seroprotection rates that failed CPMP criteria ≥4 months after influenza immunization for each of the H1N1 and B components had also reported failed seroprotection at 1 month after immunization. If initially achieved after immunization, seroprotection rates of 70%–100% were maintained not just at 4 months (2 studies) but also at 5 months (2 studies) and even at >6 months (4 studies), for the H3N2 and H1N1 vaccine components. Seroprotection rates appeared less consistent for the B vaccine component, throughout the postimmunization period. Seroconversion appears to vary substantially and inversely with preimmunization titers but not with age. In 2 of 6 studies reporting seroconversion alone, CPMP criteria were still met at 4 months. In the other 4 studies, the main reason for failure at 4 months was primary failure at 1 month. A total of 6 studies compared antibody persistence by age, and no consistent differences were found on that basis. The historic concern that the influenza vaccine–induced antibody response in the elderly declines more rapidly and below seroprotective levels within 4 months of immunization should be reconsidered.

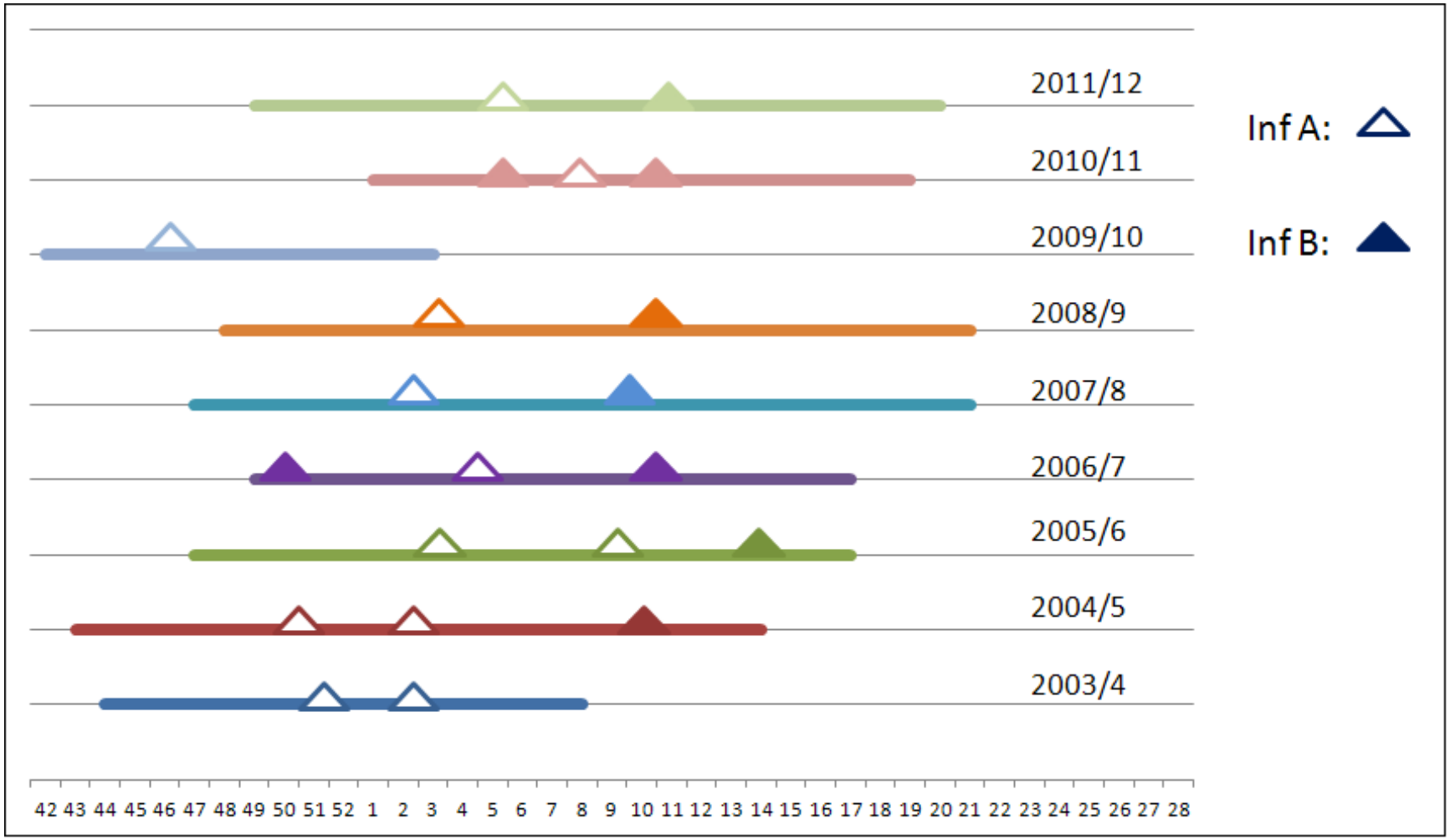
Biology of Immune Responses to Vaccines in Elderly Persons

Birgit Weinberger, Dietmar Herndler-Brandstetter, Angelika Schwanninger, Daniela Weiskopf, and Beatrix Grubeck-Loebenstein

decrease the effect of booster vaccination. As a result, antibody responses of elderly vaccinees are weaker and decline faster, and long-term protective effects of vaccination cannot be taken for granted in elderly persons. Improved vaccination strategies, new adjuvants, and new vaccines that specifically target the aged immune system will help to overcome the limitations of immunosenescence and ensure a better protection of the vulnerable elderly population.

Clin Infect Dis 2008;46: 1078

Türkiye'de Influenza Sezonundaki Değişim



Who's Afraid of Peer Review?

On 4 July, good news arrived in the inbox of Ocorrafoo Cobange, a biologist at the Wassee Institute of Medicine in Asmara. It was the official letter of acceptance for a paper he had submitted 2 months earlier to the *Journal of Natural Pharmaceuticals*, describing the anticancer properties of a chemical that Cobange had extracted from a lichen.

In fact, it should have been promptly rejected. Any reviewer with more than a high-school knowledge of chemistry and the ability to understand a basic data plot should have spotted the paper's shortcomings immediately. Its experiments are so hopelessly flawed that the results are meaningless.

Science 2013;342: 60

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I know because I wrote the paper. Ocorrafoo Cobange does not exist, nor does the Wassee Institute of Medicine. Over the past 10 months, I have submitted 304 versions of the wonder drug paper to open-access journals. More than half of the journals accepted the paper, failing to notice its fatal flaws. Beyond that headline result, the data from this sting operation reveal the contours of an emerging Wild West in academic publishing.

Science 2013;342: 60

Yaşlılarda Bağışıklama

- Grip, pnömoni vb aşılar önerilmekte
- ANCAK SORUN: aşılar bu yaş diliminde daha az etkili!
- Bu nedenle başka stratejiler önem kazanıyor…

Grip Aşısı Konusunda Yeni Gelişmeler

- Farklı uygulama biçimleri, yeni adjuvanlar

Antibody responses to intradermal or intramuscular MF59-adjuvanted influenza vaccines as evaluated in elderly institutionalized volunteers during a season of partial mismatching between vaccine and circulating A(H3N2) strains

Barbara Camilloni[1], Michela Basileo[1], Angela Di Martino[2], Isabella Donatelli[2] and Anna Maria Iorio[1*]

Immunity Ageing 2014;11:10

- Kuadrivalan aşı (2 farklı InfB soyu içeren)
- Farklı epitopların kullanımı
- Üniversal aşı

The need for quadrivalent vaccine against seasonal influenza

Robert B. Belshe*

2B or not 2B!

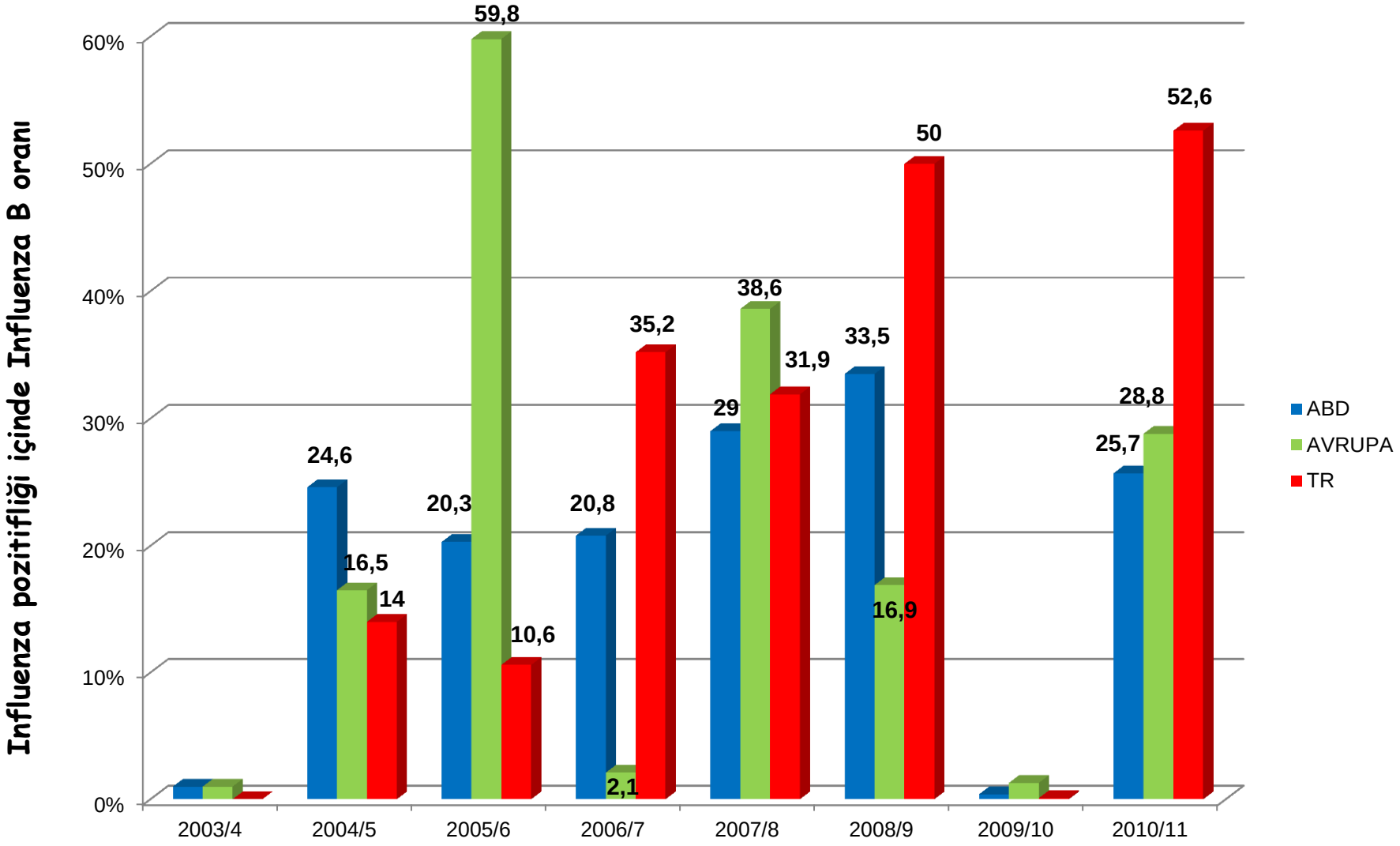
1- Çünkü Inf B sıklığı artıyor…

2- Çünkü 2 farklı Inf B soyunun çapraz koruması yok

3- Çünkü farklı bölgelerde farklı Inf B soyları dolaşımda

Vaccine 2010;28S: D45

Yıllara göre, ABD, Avrupa ve TR' de Influenza B saptama oranları

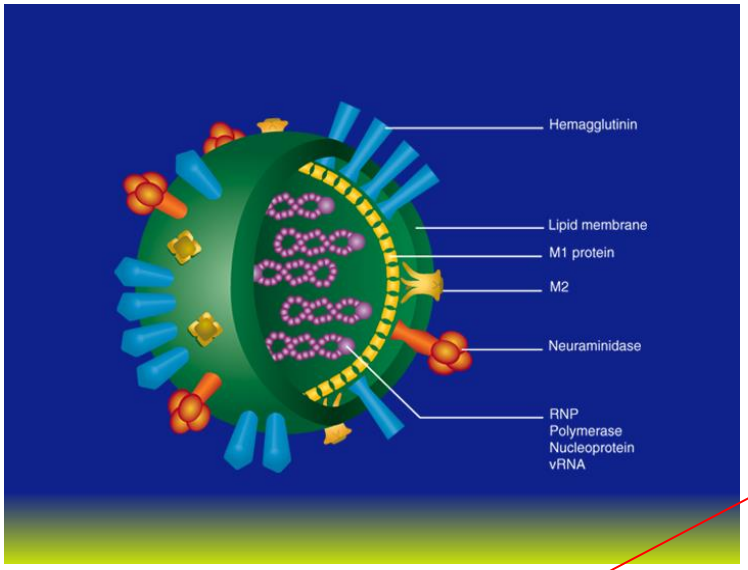


Dünyadan Farklılık
Aşı İçeriğindeki ve Ülkemizdeki InfB

Antijenik Karakter

Sezon	TR	Aşı İçeriği
2008-9	B/Malaysia/2560/2004 (Victoria soyu)	B/Florida/4/2006 (Yamagata soyu)
2010-11	B/Bangladesh/133/07 (Yamagata soyu)	B/Brisbane/60/2008 (Victoria soyu)

Farklı Antijen Arayışı



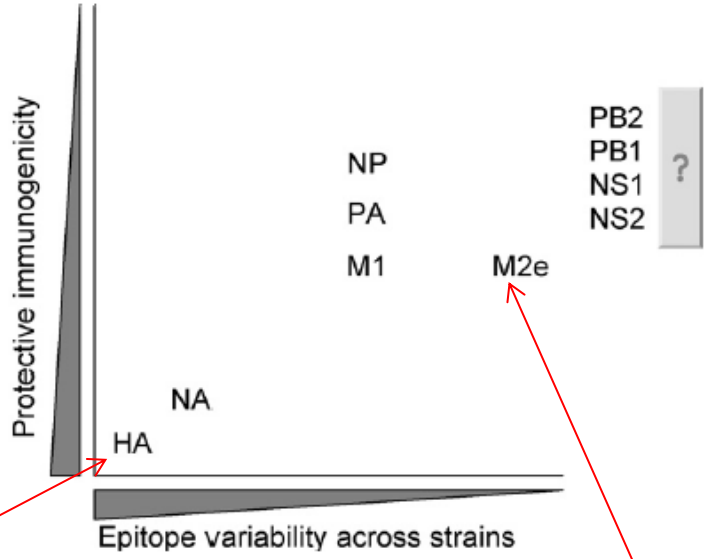


Fig. 1. The dilemma of influenza vaccination. Generally speaking, the most protective antigens, HA and NA, are also the most variable viral proteins. The key is finding the balance between immunogenicity and protein variability or enhancing methods of delivering HA antigen.

Vaccine 2009;27: D65

Contribution of antibody production against neuraminidase to the protection afforded by influenza vaccines

Glendie Marcelin[1†], Matthew R. Sandbulte[2†] and Richard J. Webby[1*]

Rev Med Virol 2012;22: 267

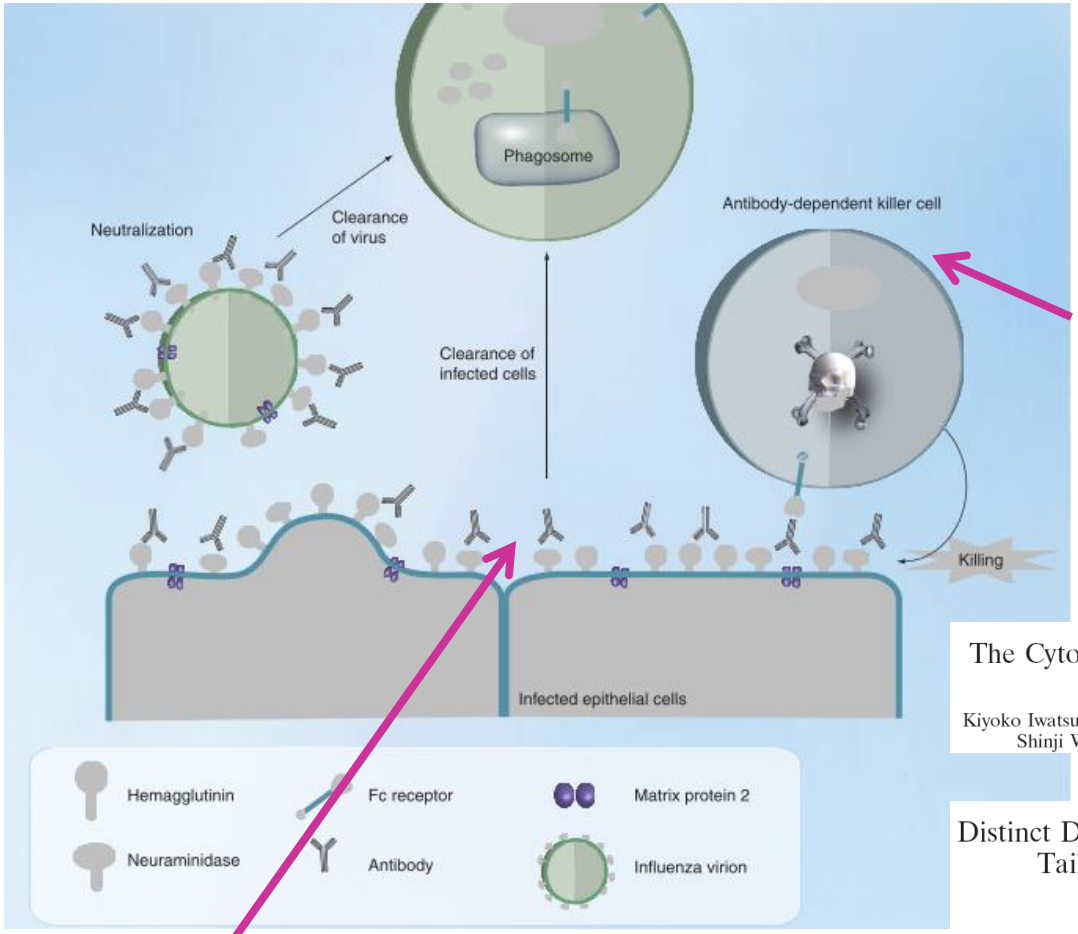
Universal Vaccine Based on Ectodomain of Matrix Protein 2 of Influenza A: Fc Receptors and Alveolar Macrophages Mediate Protection

Karim El Bakkouri,[*,†] Francis Descamps,[*,†,1] Marina De Filette,[*,†] Anouk Smet,[*,†] Els Festjens,[*,†] Ashley Birkett,[‡,2] Nico Van Rooijen,[§] Sjef Verbeek,[¶] Walter Fiers,[*,†] and Xavier Saelens[*,†]

J Immunol 2011;186: 1022

M2 Aşılarında Hedef: M2e

(M2 proteininin eksternal domeni)



*M2=CTL epitopları taşır
*M2e antikorları enfekte hücrelerdeki M2'ye bağlanır
*Oluşan IC'leri Fc taşıyan efektör hücreler (NK) tanır
*ADCC uyarınca yıkım gerçekleşir

*Anti-M2e'lerle opsonize olmuş enfekte hücreler fagositlerce yakalanıp yıkıma uğratılır

The Cytoplasmic Tail of the Influenza A Virus M2 Protein Plays a Role in Viral Assembly

Kiyoko Iwatsuki-Horimoto,[1,2] Taisuke Horimoto,[1,2] Takeshi Noda,[2,3] Maki Kiso,[1,2] Junko Maeda,[4] Shinji Watanabe,[5] Yukiko Muramoto,[1,2,6] Ken Fujii,[1,2] and Yoshihiro Kawaoka[1,2,3,5]*

Distinct Domains of the Influenza A Virus M2 Protein Cytoplasmic Tail Mediate Binding to the M1 Protein and Facilitate Infectious Virus Production

Matthew F. McCown[1]† and Andrew Pekosz[1,2]*

The Influenza A Virus M_2 Cytoplasmic Tail Is Required for Infectious Virus Production and Efficient Genome Packaging

Matthew F. McCown[1] and Andrew Pekosz[1,2]*

Expert Rev Vaccines 2009;8: 499

Üniversal AŞI

- Tüm Influenza virüslerine karşı koruyucu aşı
- Tüm toplumun Influenza'ya karşı bağışıklanması

* «Heterosubtypic» koruma:
- Değişmeyen antijenlere spesifik T hücreleri üzerinden
- İki internal antijene (NP ve M1) karşı var olan CD4 hücreleri sayesinde
- Bu hücrelerin sitotoksik özellikleri gösterilmiş
- Ancak koruma süresi: 2-3 yıl

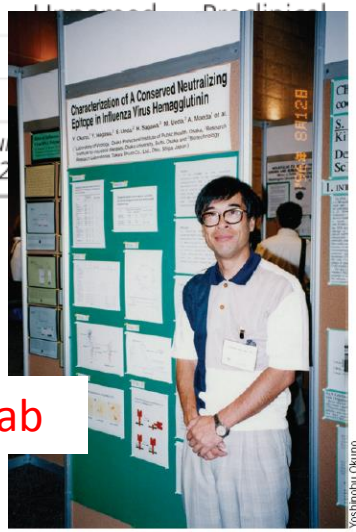
Towards universal influenza vaccines?

Table 1. Universal influenza vaccines under development.

Company	Product	Phase	Mechanism of action	Technology	ClinicalTrial.gov identifier	Manufacturing
BiondVax	M-001	Phase II	T and B cell	Epitope	NCT00877448, NCT01010737, NCT01146119	Recombinant
Dynavax	N8295	Phase I	B cell	NP and M2e	NA	Recombinant
Inovio	VGX-3400	Preclinical	T and B cell	DNA vaccine	NCT01142362	
Sanofi Pasteur	ACAM-FLU-A™	Back to preclinical	B cell and minor T cell	M2e	NCT00819013	Recombinant
Gamma Vaccines	GammaFlu®	Preclinical	T cell	Whole-cell inactivated	–	Cell culture
Immune Targeting Systems	FP-01	Phase I	T cell	Fluoro-conjugated peptides	–	Synthetic
Juvaris			T cell			Recombinant
SEEK			T cell			binant
VaxInnate			B cell		921947	binant

A gene immu… (i.e., a DNA plasm… immune molecule… vaccine).
M2e: Matrix 2… n the ClinicalTrials.

C179 Mab



At post: Okuno presented C179 data in 1996.

F16v3

Sweet 16: Lanzavecchia's antibody binds broadly.

CR8020

Crystal clear: Wilson studied CR6261's shape.

Future Virol 2011:6: 237

SONUÇ

Kullanımdaki trivalan grip aşıları >65 yaş grubunda:

- Hastaneye yatışları %27-45
- Ölümleri %43-50 oranında azaltıyor
- Bu durumda bile kullanımı uygun

ANCAK: Yeni yaklaşımlara gereksinim var

"Orada iyi niyet suistimal oldu. **Masum direnişçilerin saflığı kullanıldı.** Sonuçta ülkenin en önemli gelir kaynağı olan turizm büyük darbe aldı…”

“Gezi' nin başlangıcı haklı bir direnişti ama saptırıldığını hepimiz gördük. İşin içine **vandalizm** girdiğinde bu meşru ve güzel tepki çirkinleşir, kutuplaştırma başlar"...

ANCAK

- şehrin merkezindeki bir yeşil alana kışla ya da AVM yapmak için diretmekten,
- şehrin en büyük kültür merkezini fiilen karakola çevirmekten,
- **gencecik çocukları kuytularda döve döve öldürmekten,**
- **gözü çıkan onlarca kişiden,**
- **biber gazından zehirlenen yüz binlerce insandan,**
- **cenaze evinde göz yaşı döken anayı meydanlara yuhalatmanın tarif edilemez hoyratlığından söz etmeden**

vandalizm cümlesini kurmak, vandalizmin ta kendisidir.....