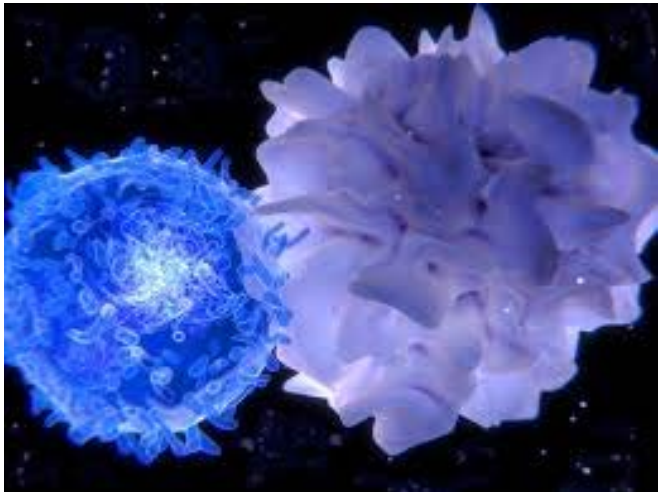
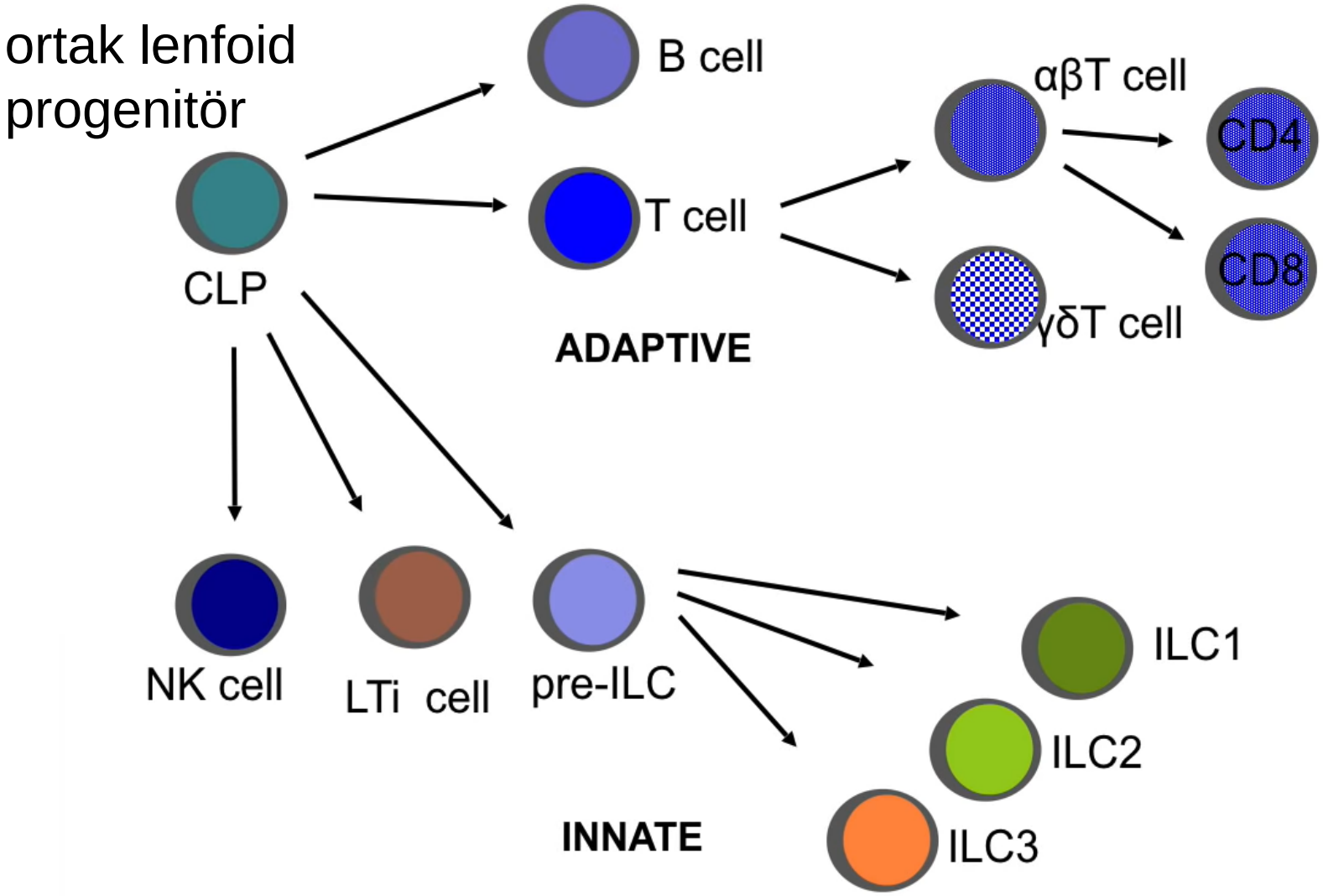


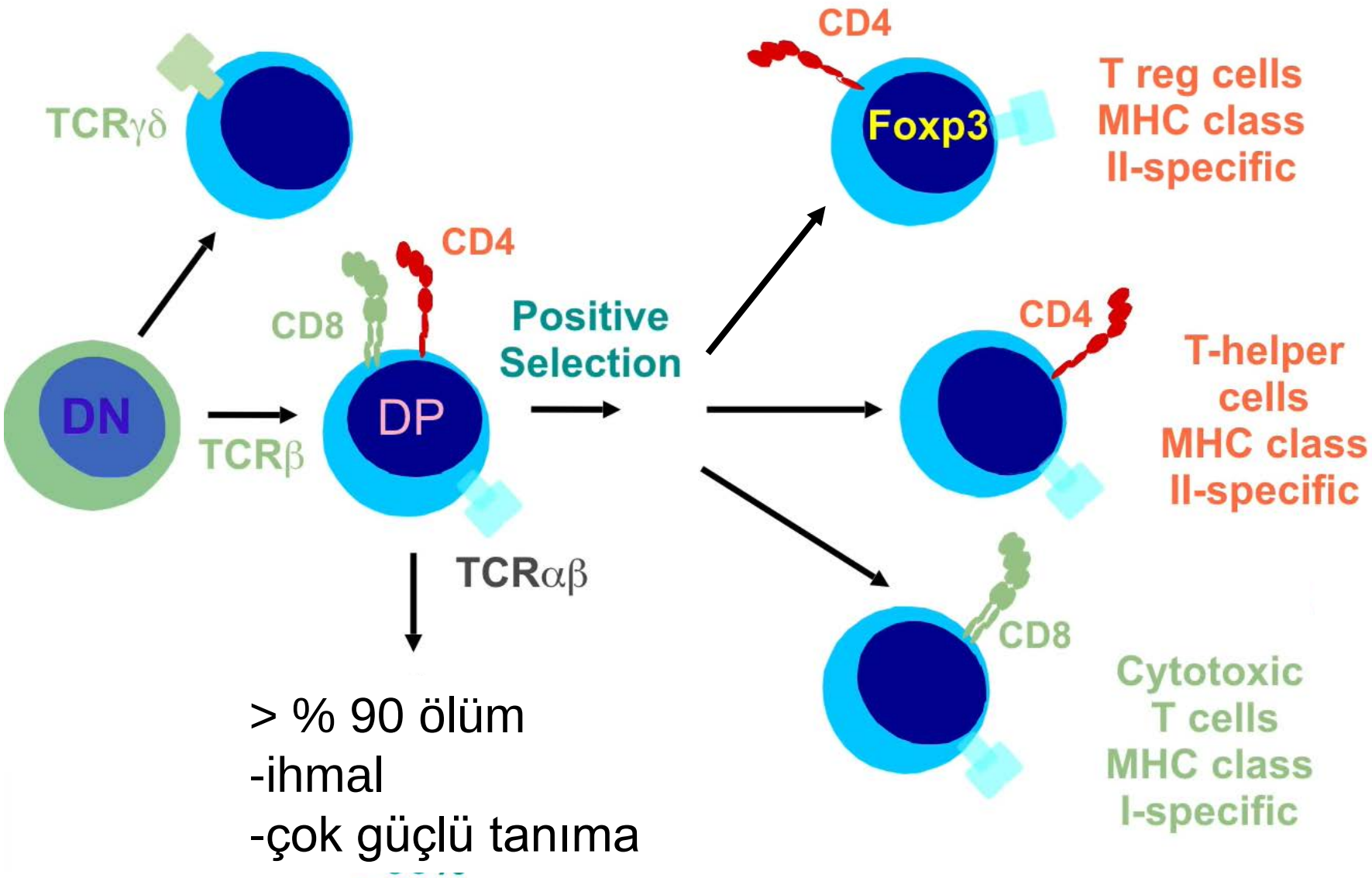
MS’te T hücreler

Mayda Gürsel
Orta Doğu Teknik Üniversitesi
Biyolojik Bilimler Bölümü

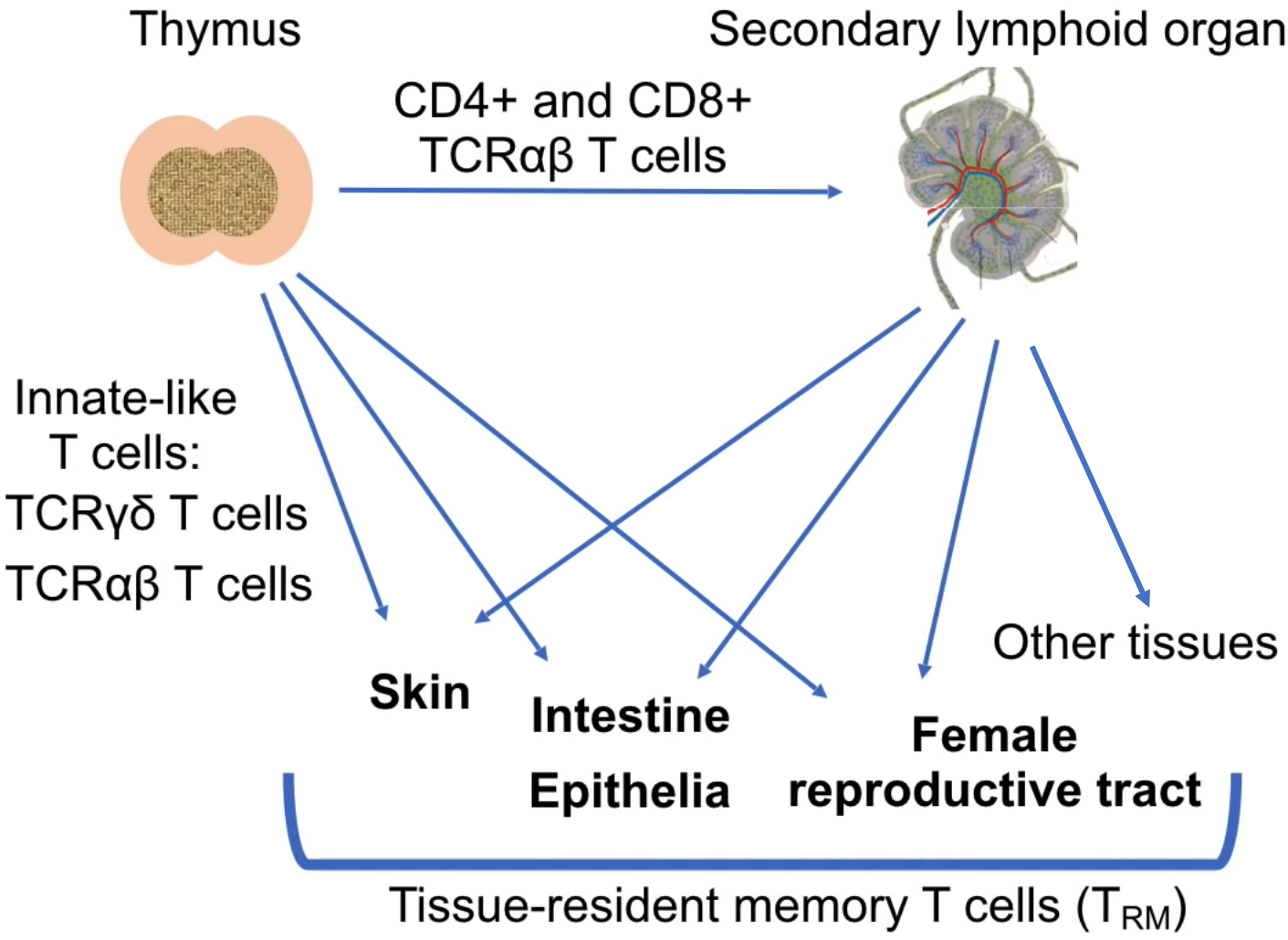
Lenfoid Hücre Gelişimi



Timüste T Hücre gelişimi

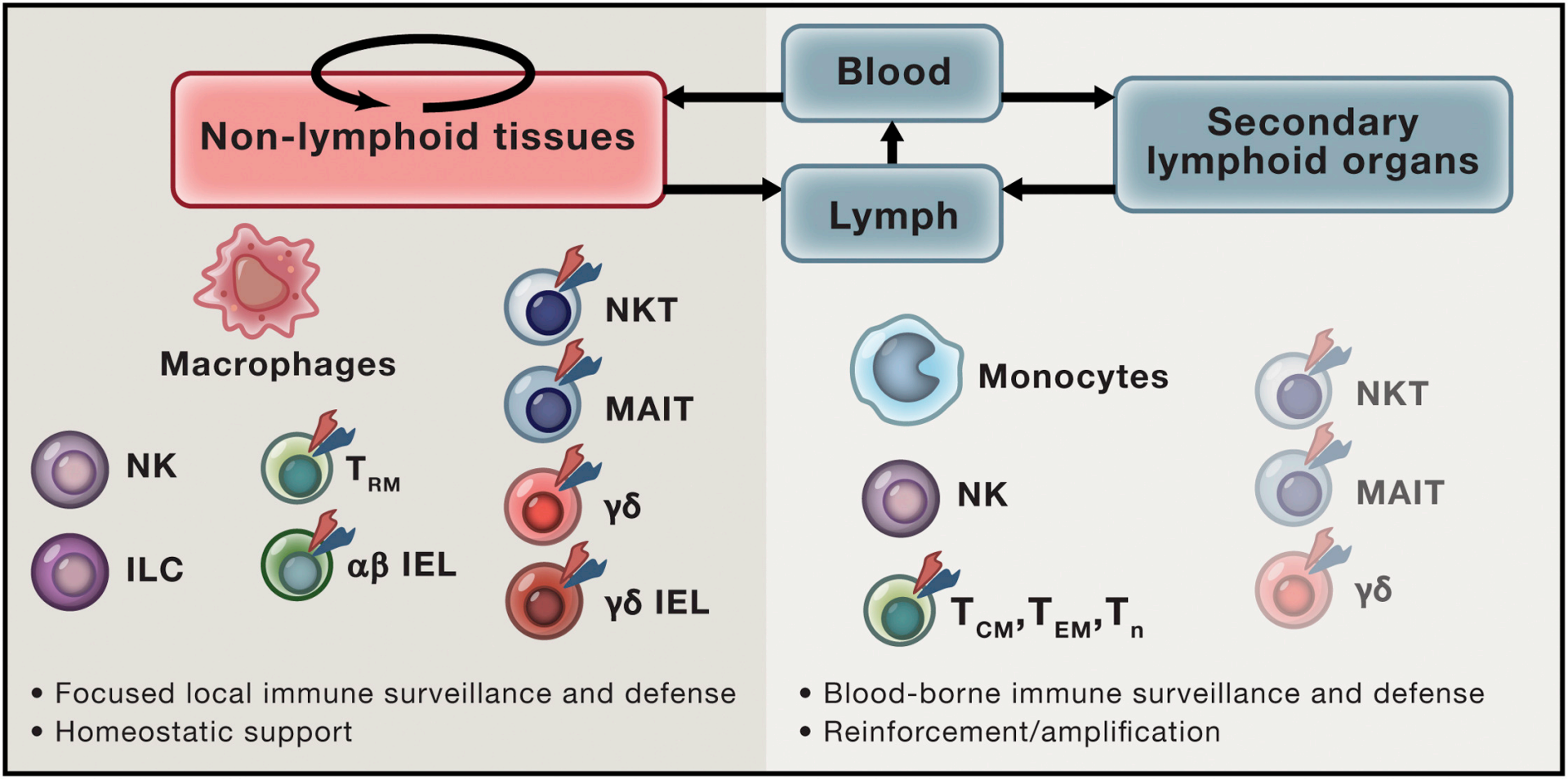


T hücrelerin ikincil lenfoid organlara ve dokulara yayılımı



Dokuya yerleşik

Sürekli dolaşan



Fan & Rudensky, Cell 2016

Naive T hücrelerin effektöre dönüşümü 3 sinyal gerektirir:

1. Peptid/MHC kompleksi
2. Ko-stimülan molekül CD28 etkileşimi
3. Antijen sunum hücresinin salgıladığı sitokinler

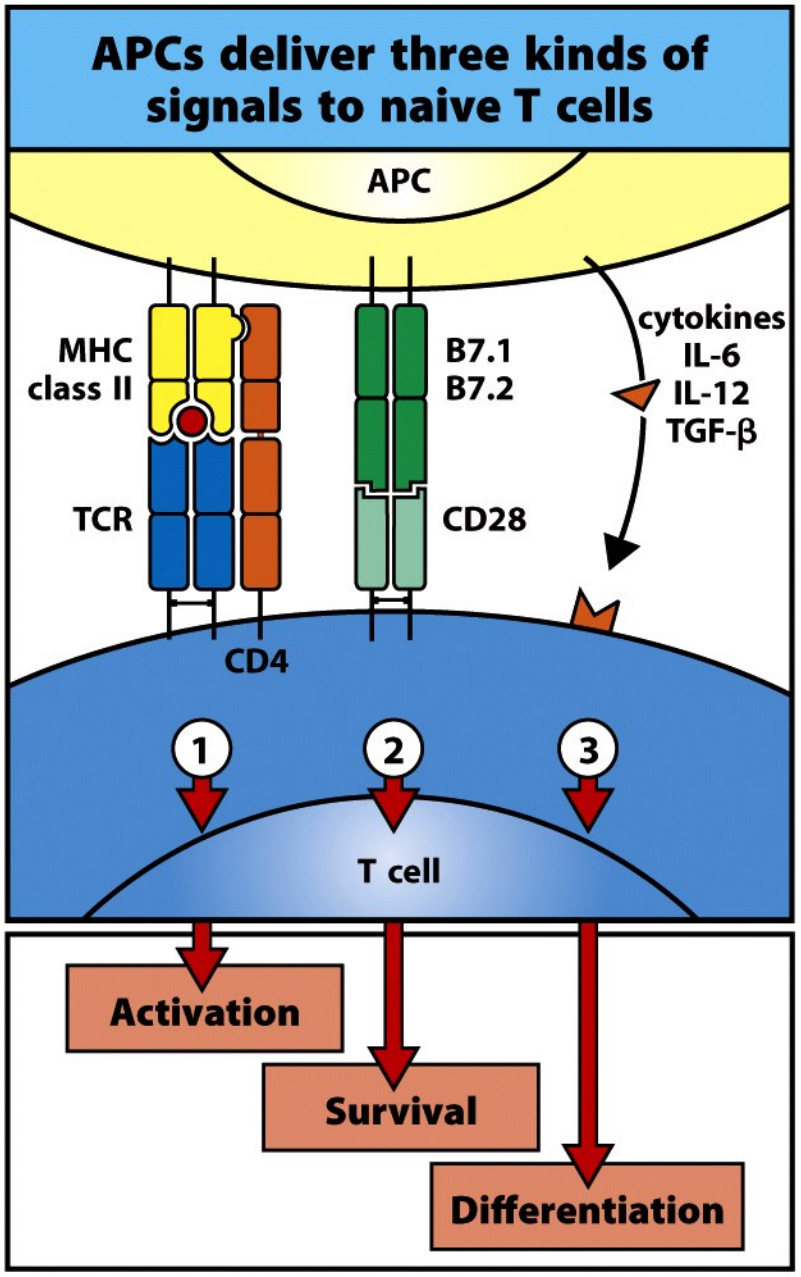
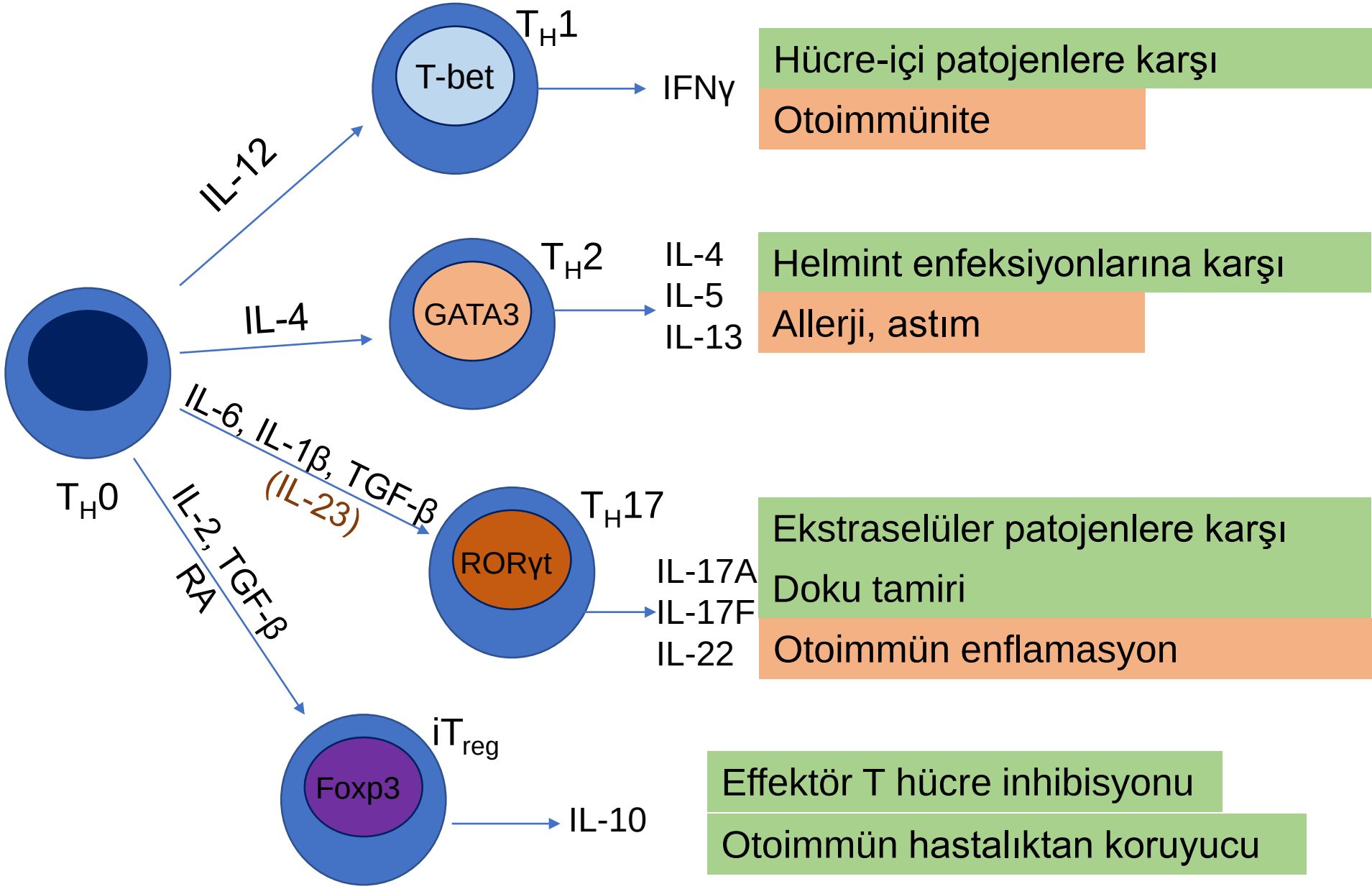


Figure 8-19 Immunobiology, 7ed. (© Garland Science 2008)

Sinyal 3'e göre farklı effektör tipleri



MS MODELİ EAE'DE CD4 T HÜCRELERİN ROLÜ

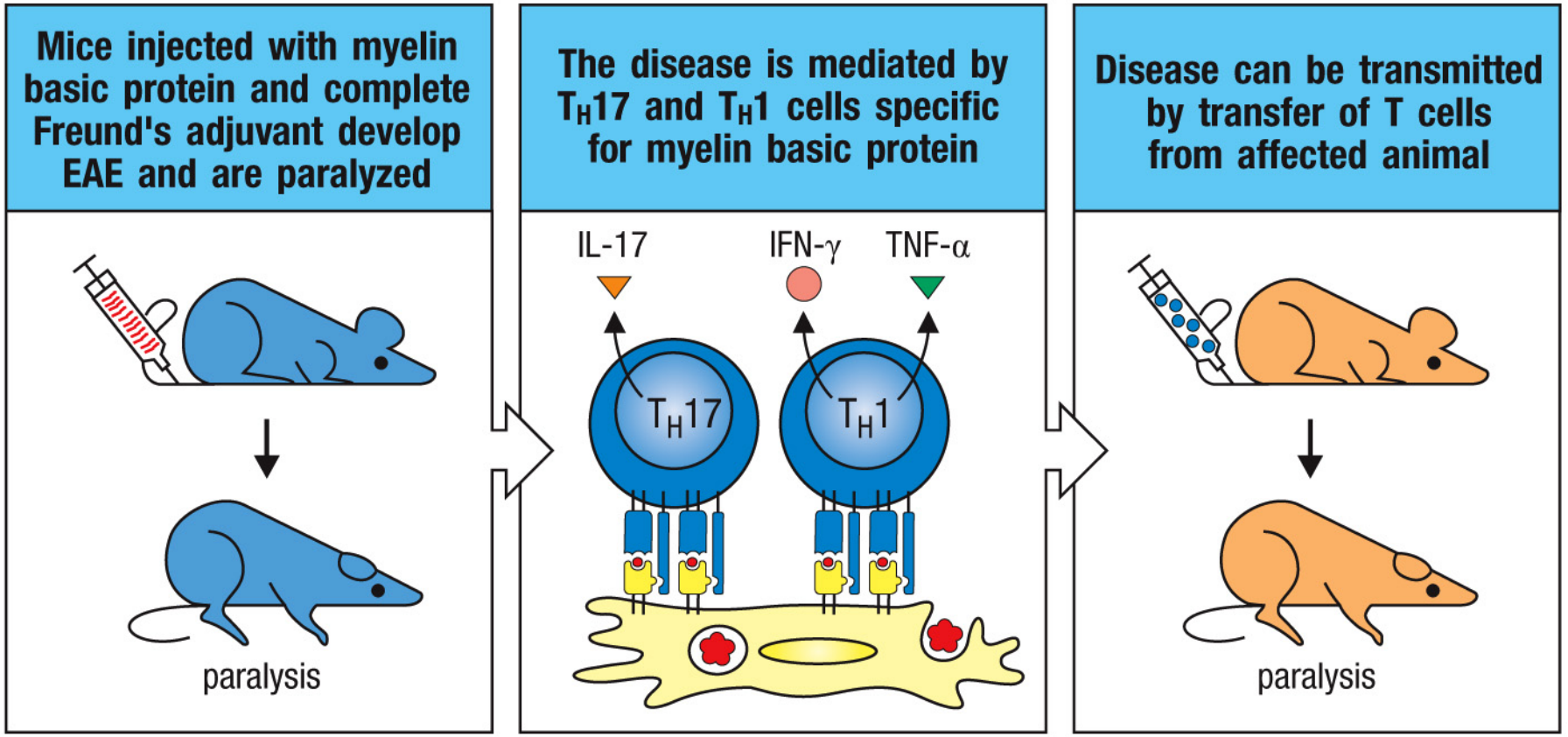


Figure 15.12 (part 2 of 2) Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Ben-Nun A. et al. Eur. J. Immunol. 1981

MS MODELİ EAE'DE MİKROBİYOTA VE TH17 İLİŞKİSİ

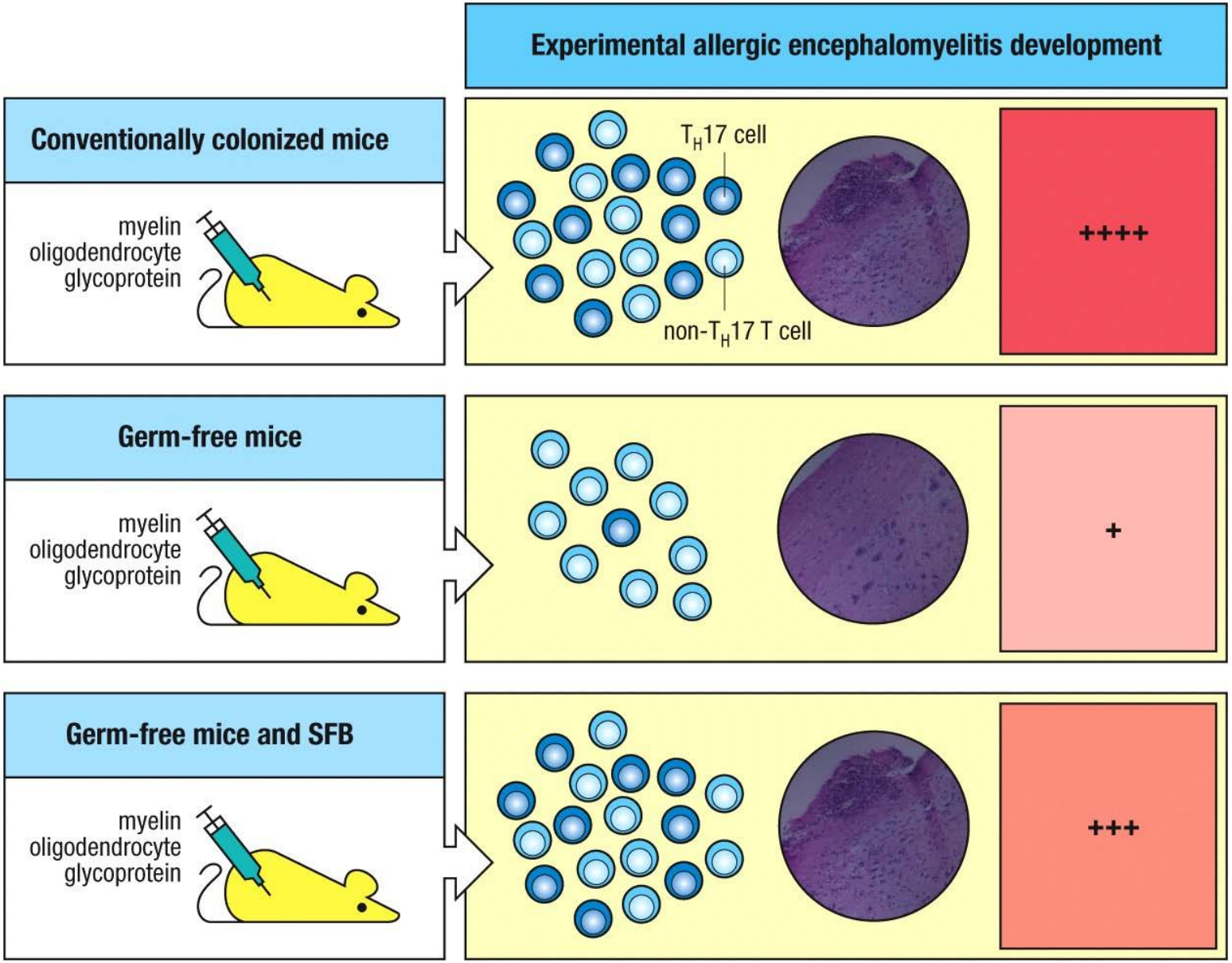
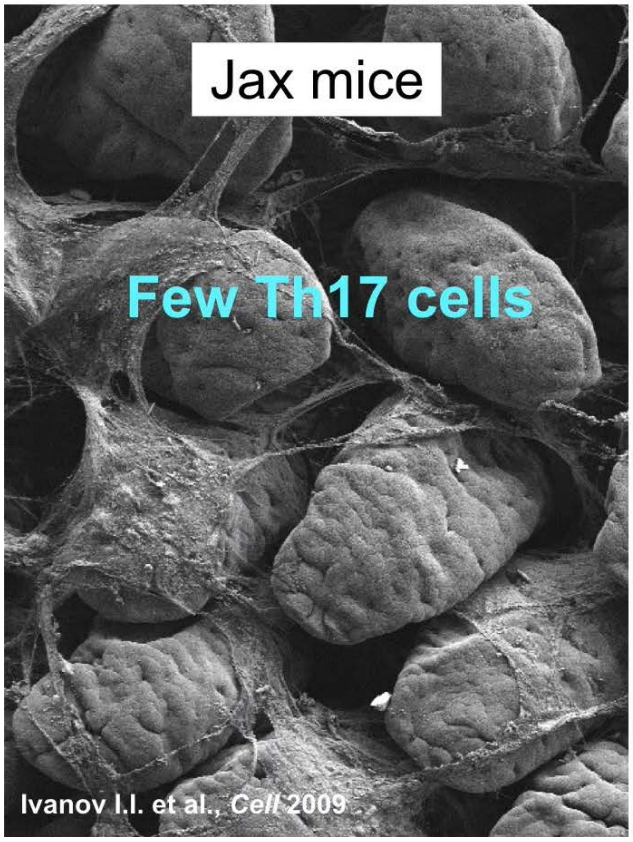
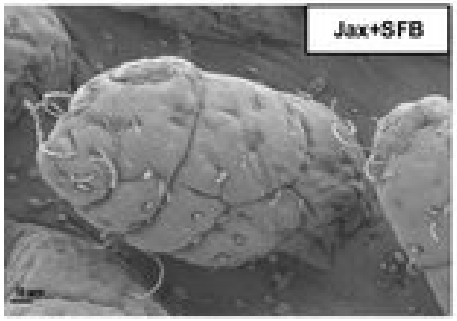


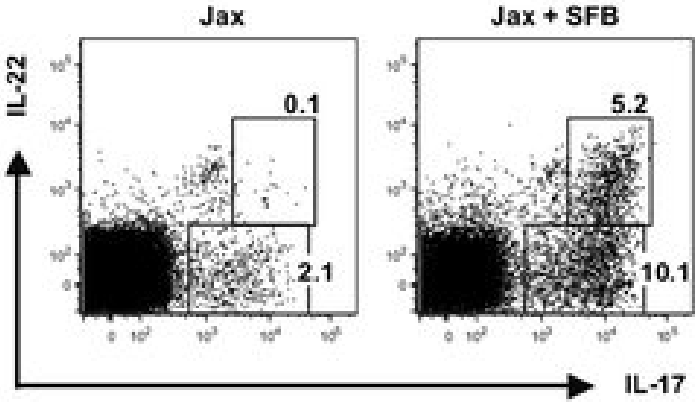
Figure 17.5 Principles of Mucosal Immunology (© Garland Science 2013)

MİKROBİYOTA - TH17 İLİŞKİSİ

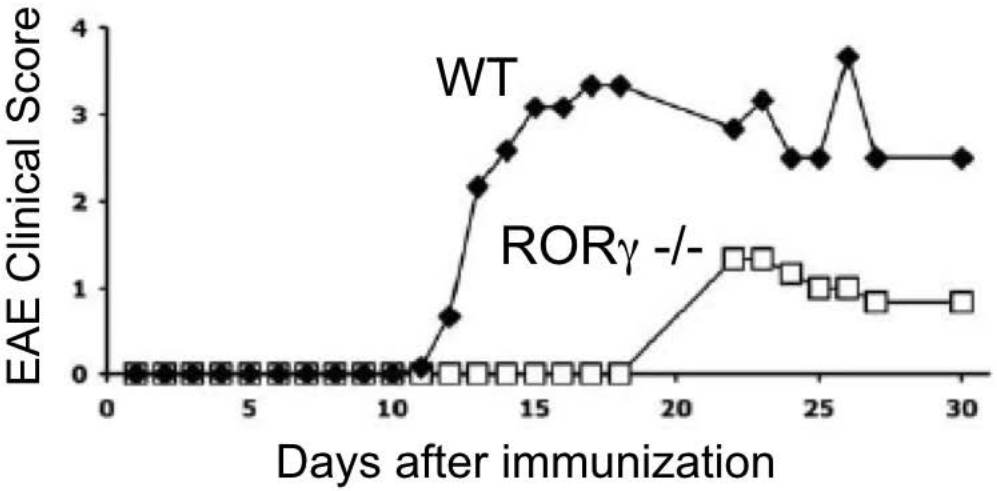
Dan Littman



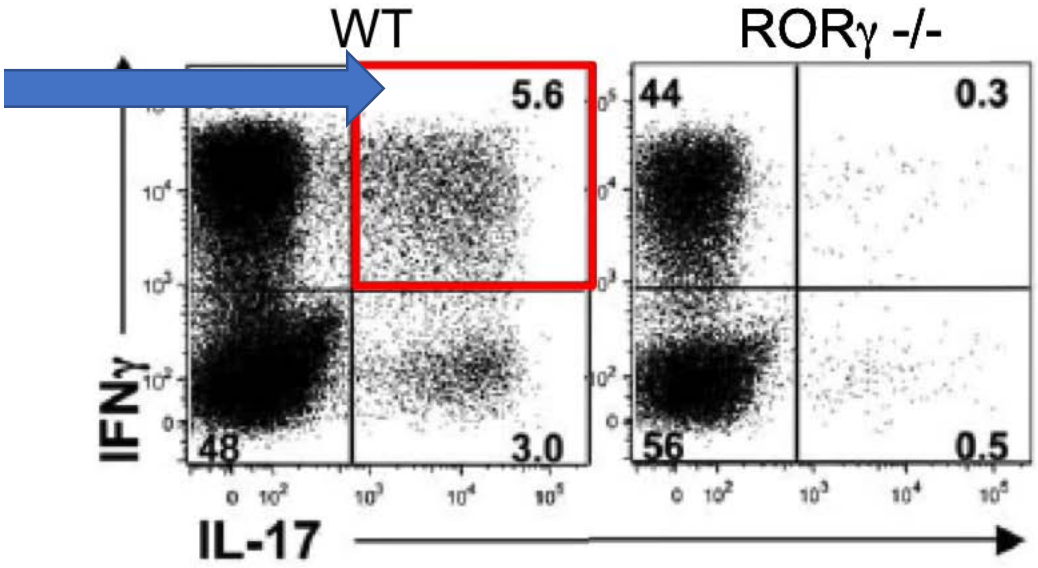




RORγt transkripsiyon faktörü IL-17/IFNγ üreten patojenik Th17 hücre tipi için gereklidir

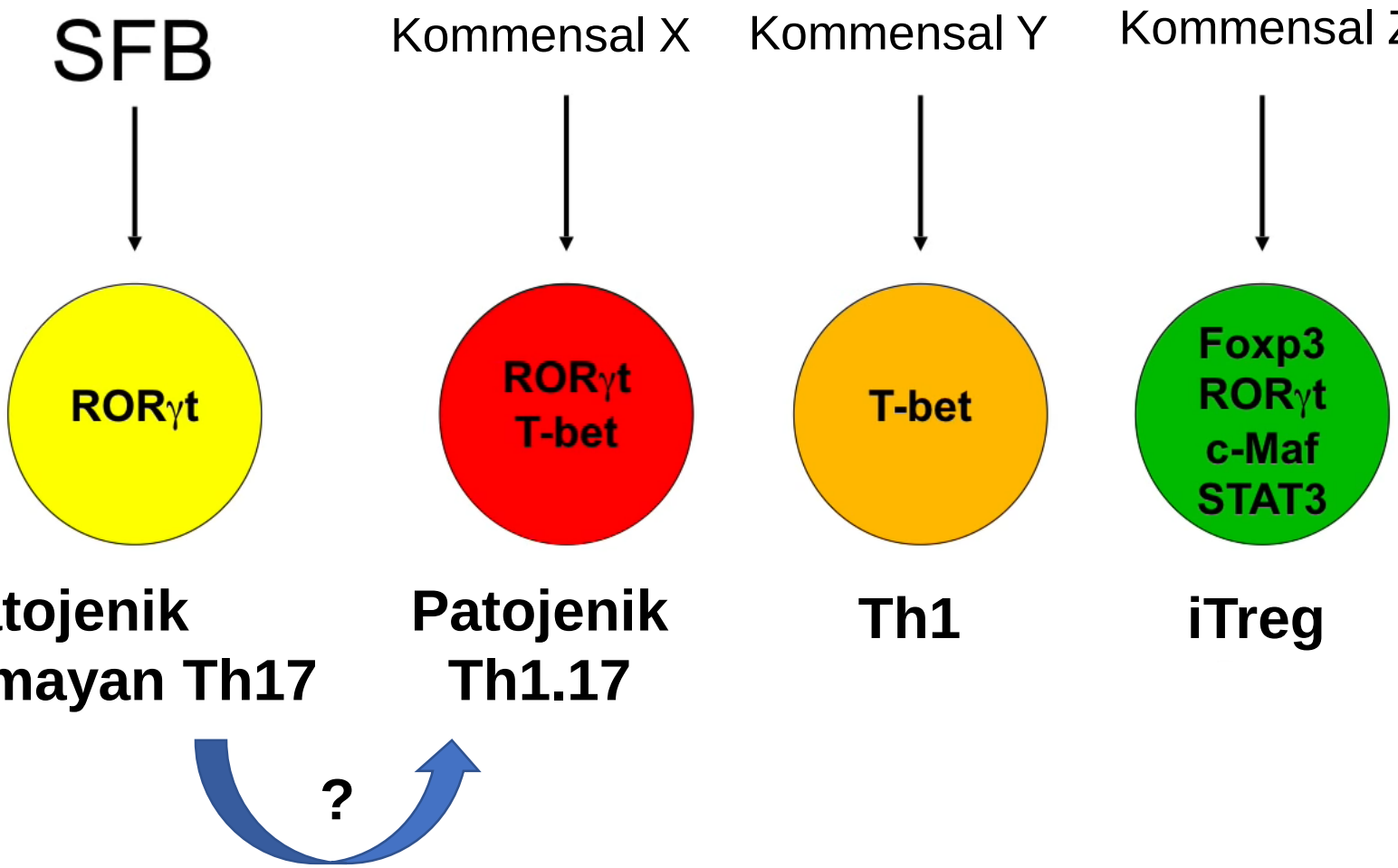


Yeni bir Th17 türü: Th1.17 (patojenik)

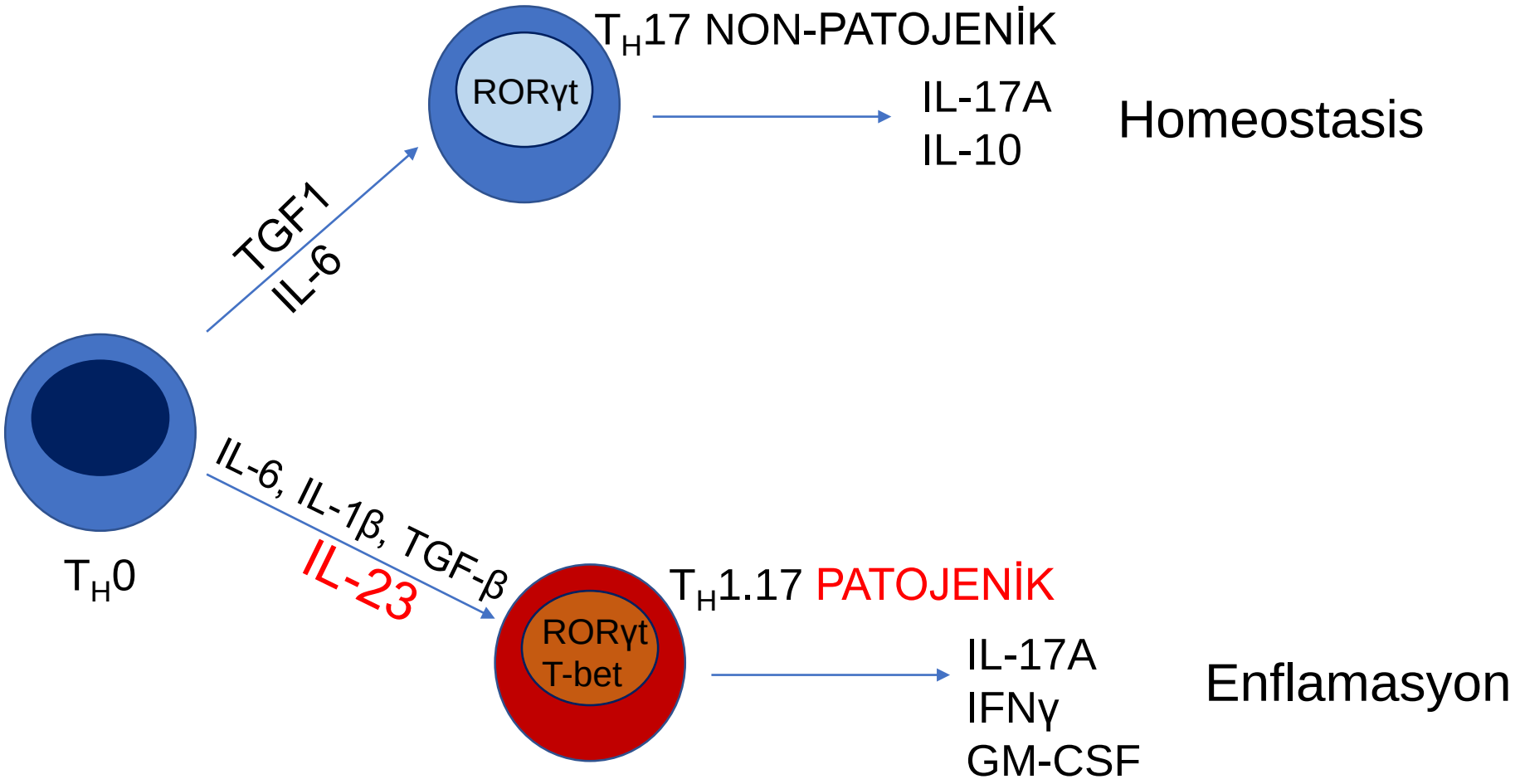


Ivanov, I.I. et al. *Cell* (2006)

MİKROBİYOTA-EFFEKTÖR T HÜCRE DENGESİ

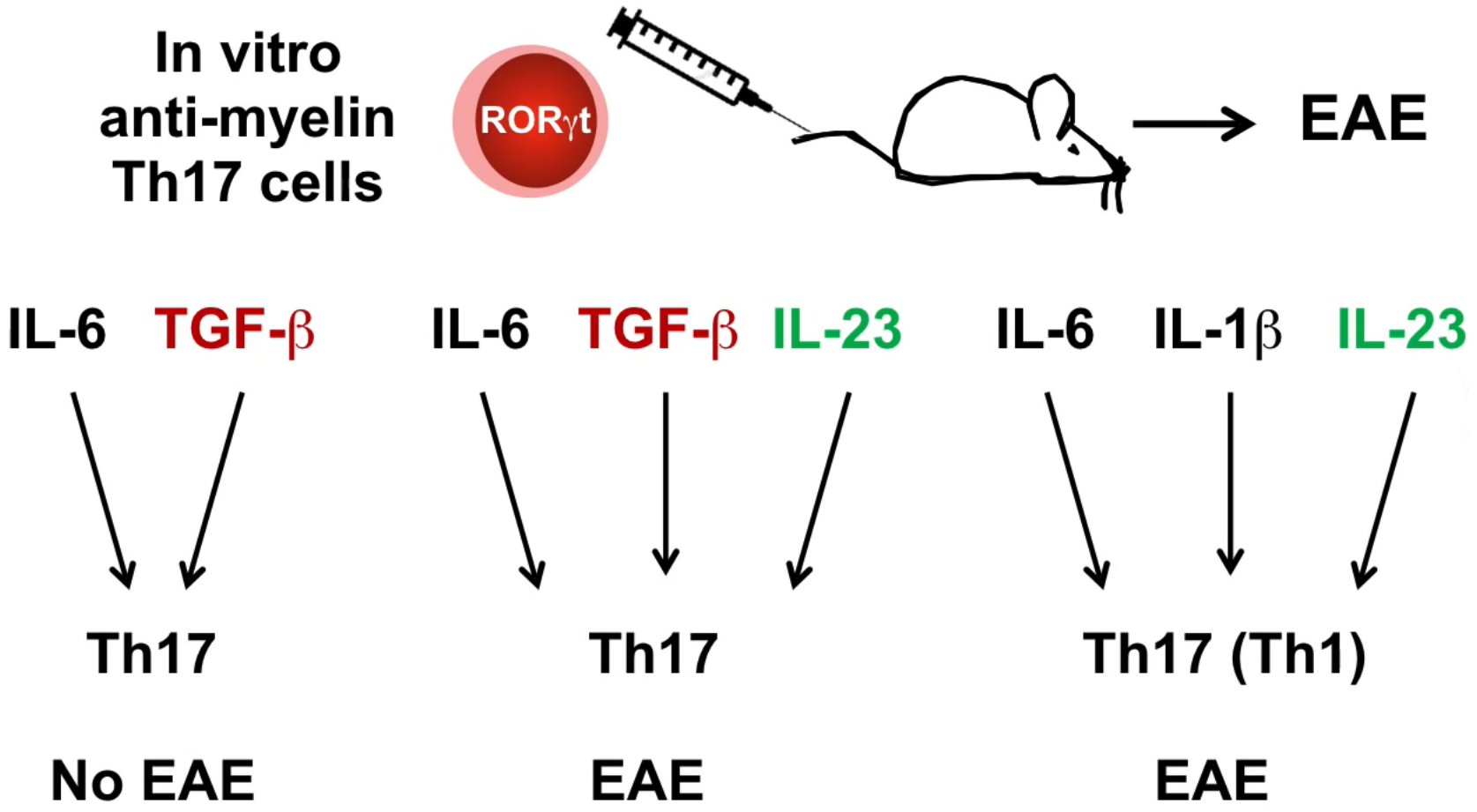


IL-23-PATOJENİK TH17 İLİŞKİSİ



Goreschi et al. Nature 2010
Hirota et al. Nat Immunol 2011
Lee et al. Nat Immunol 2012

EAE MODELİNDE IL-23'ÜN ROLÜ



McGeachy, M.J. et al. *Nat Immunol (*2007); Ghoreschi, K. et al. *Nature* (2010)

Th17 Yolak modülatörlerinin klinik performansı

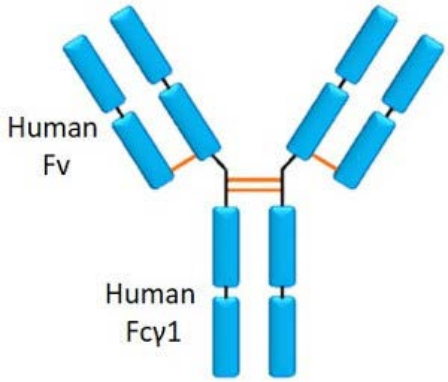
Disease (severity)	IL-12+23	IL-23	IL-17A	IL-17RA
Psoriasis	++	+++	+++	+++
Psoriatic Arthritis	+	n.t.	++	+
Ankylosing Spondylitis	+	n.t.	++	n.t.
Asthma	n.t.	n.t.	n.a.	-/+
Crohn's disease	++	n.a.	–	–
Multiple Sclerosis	–	n.t.	++	n.t.
Rheumatoid Arthritis	+	–	++	–
Uveitis (non-infectious)	n.t.	n.t.	+	n.t.

Patel and Kuchroo, Immunity 2015

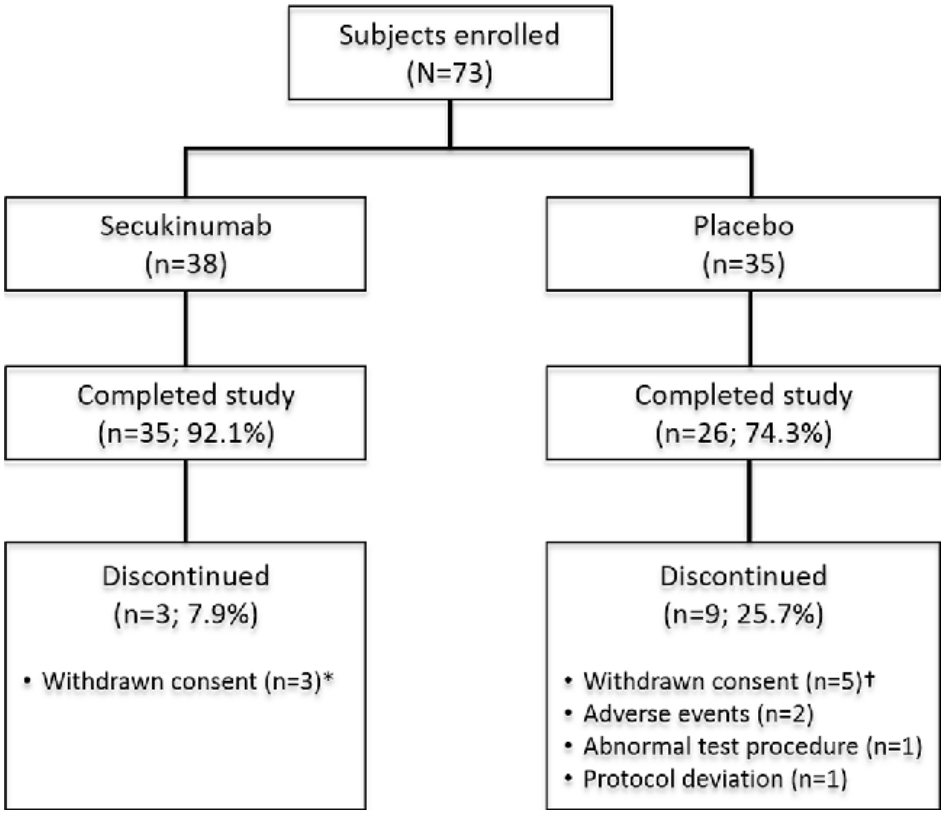
IL-17 bloklamaya yönelik klinik deneyler: Secukinumab (Cosentyx)

T ID	Status	Conditions	Lead Sponsor	Update Time
NCT03516526	Recruiting	Multiple Sclerosis	VU University Medical Center	May 4, 2018
NCT01970410	Active, not recruiting	Multiple Sclerosis	Multiple Sclerosis Center of Northeastern New York	October 28, 2013
NCT02881567	Active, not recruiting	Relapsing-Remitting Multiple Sclerosis (RRMS)	Biogen	August 29, 2016
NCT03157830	Recruiting	Relapsing Remitting Multiple Sclerosis	Providence Health & Services	May 17, 2017
NCT03046251	Recruiting	Multiple Sclerosis	State University of New York at Buffalo	February 8, 2017
NCT03135249	Active, not recruiting	Multiple Sclerosis (MS)	University of Texas Southwestern Medical Center	May 1, 2017
NCT02677077	Active, not recruiting	Relapsing-Remitting Multiple Sclerosis	Biogen	February 9, 2016
NCT02965170	Recruiting	Multiple Sclerosis	Rocky Mountain MS Research Group, LLC	November 16, 2016
NCT02386566	Active, not recruiting	Multiple Sclerosis	Biogen	March 12, 2015
NCT01981161	Recruiting	Multiple Sclerosis	University Hospital, Toulouse	November 11, 2013
NCT02588053	Active, not recruiting	Multiple Sclerosis	University of Colorado, Denver	October 27, 2015
NCT00493298	Recruiting	Relapsing-Remitting Multiple Sclerosis	Biogen	June 28, 2007
NCT03399981	Active, not recruiting	Progressive Multifocal Leukoencephalopathy	Biogen	January 17, 2018
NCT02904876	Recruiting	Multiple Sclerosis	University Hospital, Strasbourg, France	September 19, 2016
NCT01485003	Active, not recruiting	Relapsing-Remitting Multiple Sclerosis	Biogen	December 5, 2011
NCT01065727	Recruiting	Multiple Sclerosis	Rennes University Hospital	February 9, 2010
NCT03193866	Recruiting	Relapsing-remitting Multiple Sclerosis	Karolinska Institutet	June 21, 2017

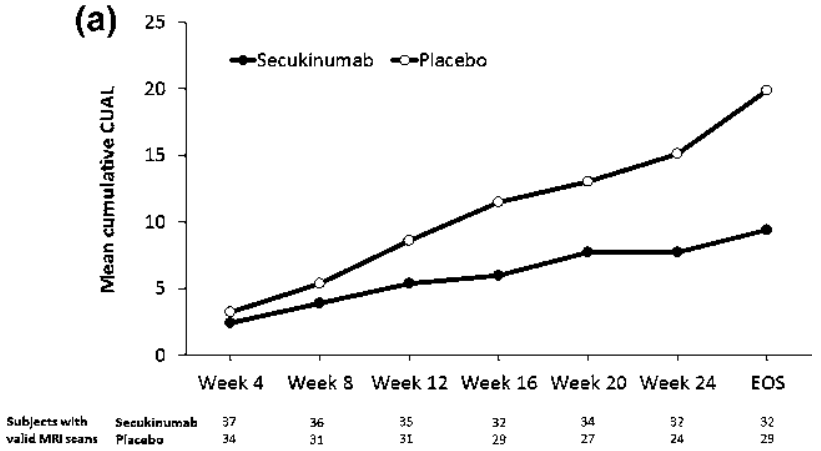
Secukinumab (Cosentyx)

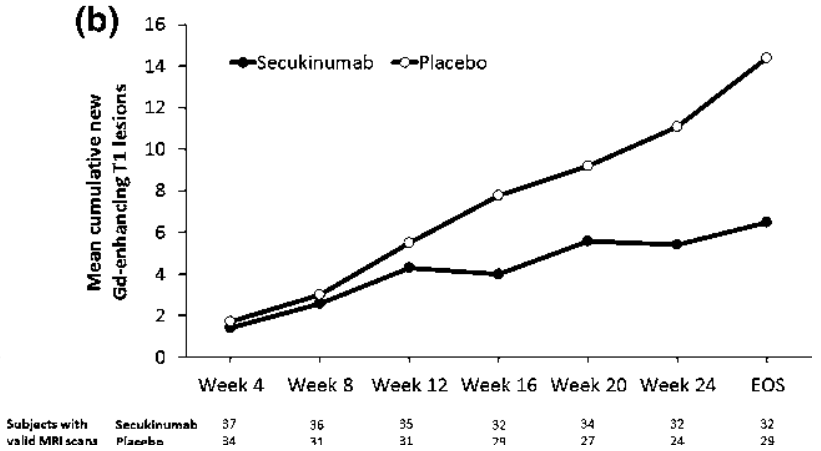


Activity of secukinumab, an anti-IL-17A antibody, on brain lesions in RRMS: results from a randomized, proof-of-concept study
Havrdová et al, Journal of Neurology, 2016



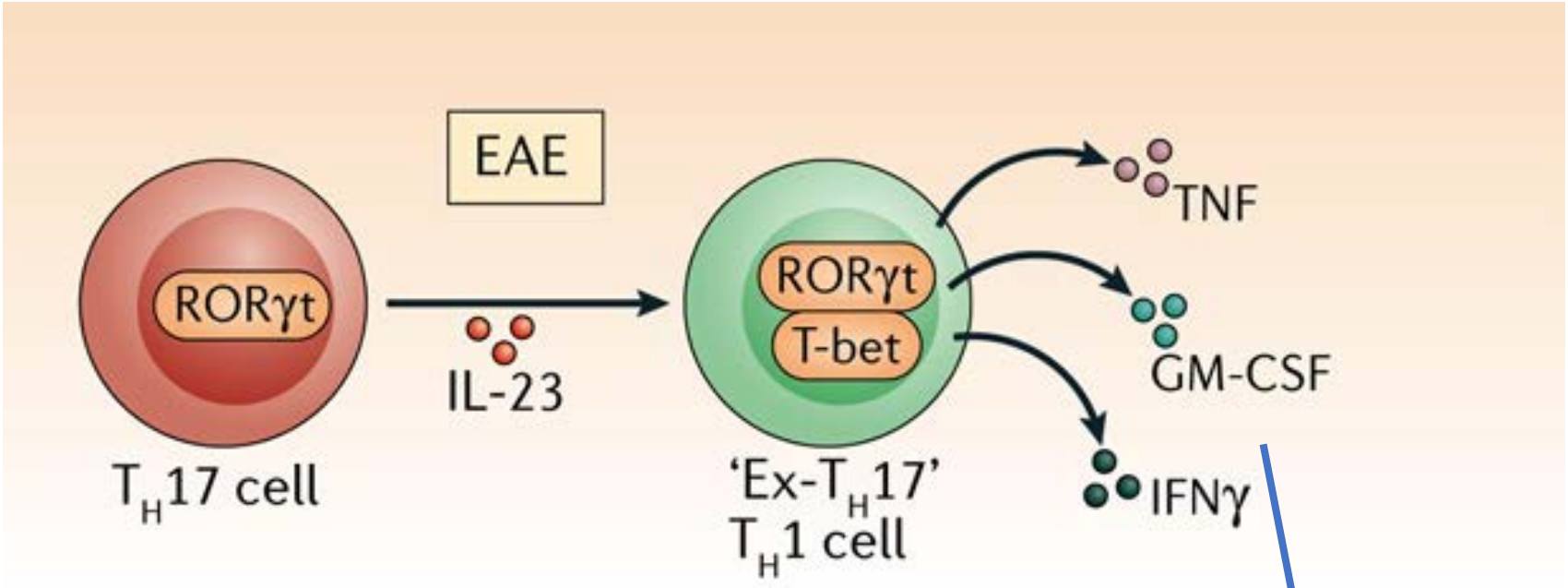
cumulative number of combined unique active lesions (CUAL)





Reduced cumulative new gadolinium-enhancing T1 lesions by 67 % (31–84 %, P = 0.003)

Yeni bulgular: GM-CSF daha mı önemli?



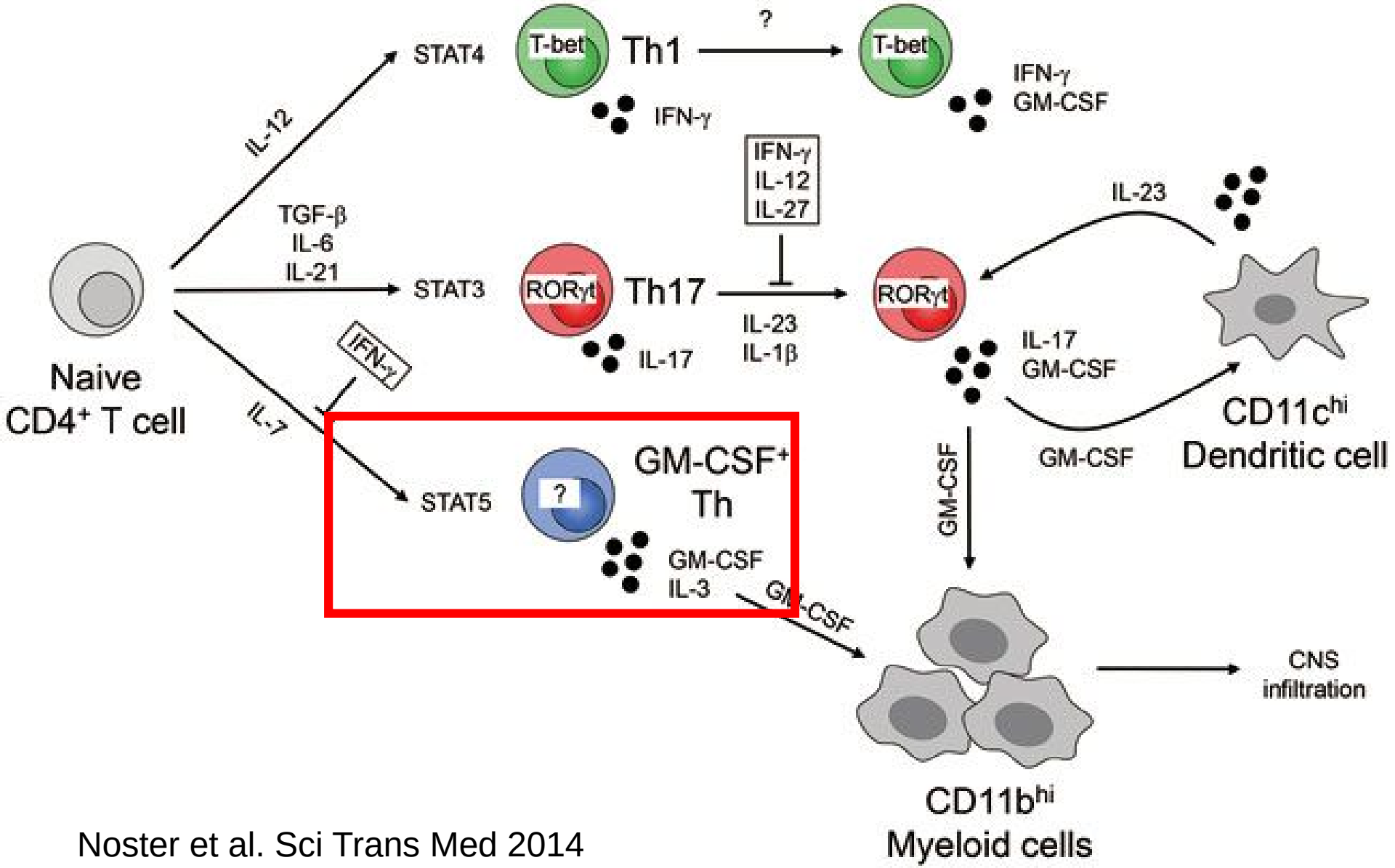
GM-CSF yoksunu farede EAE gelişmiyor

Myeloid hücre aktivasyonu

Beyin enflamasyonu

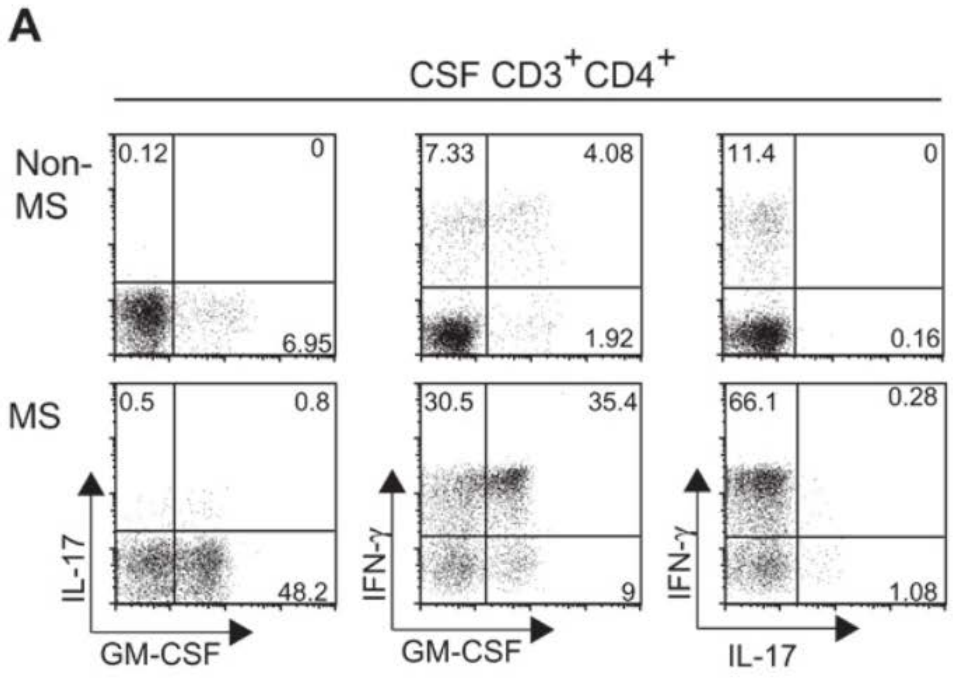
Codarri et al., Nature Immunology 2011
M. El-Behi et al., Nature Immunology 2011

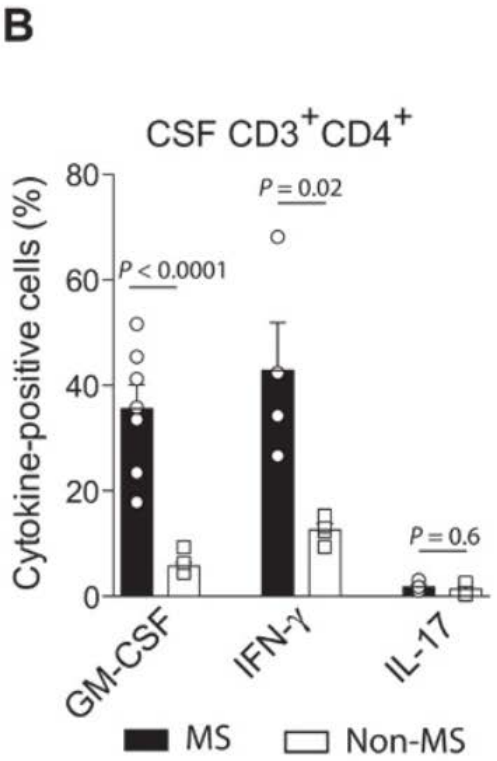
GM-CSF üreten yeni bir effektör hücre tipi?

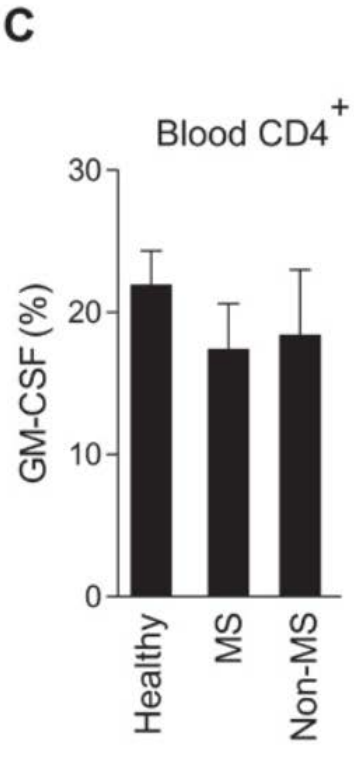


Noster et al. Sci Trans Med 2014

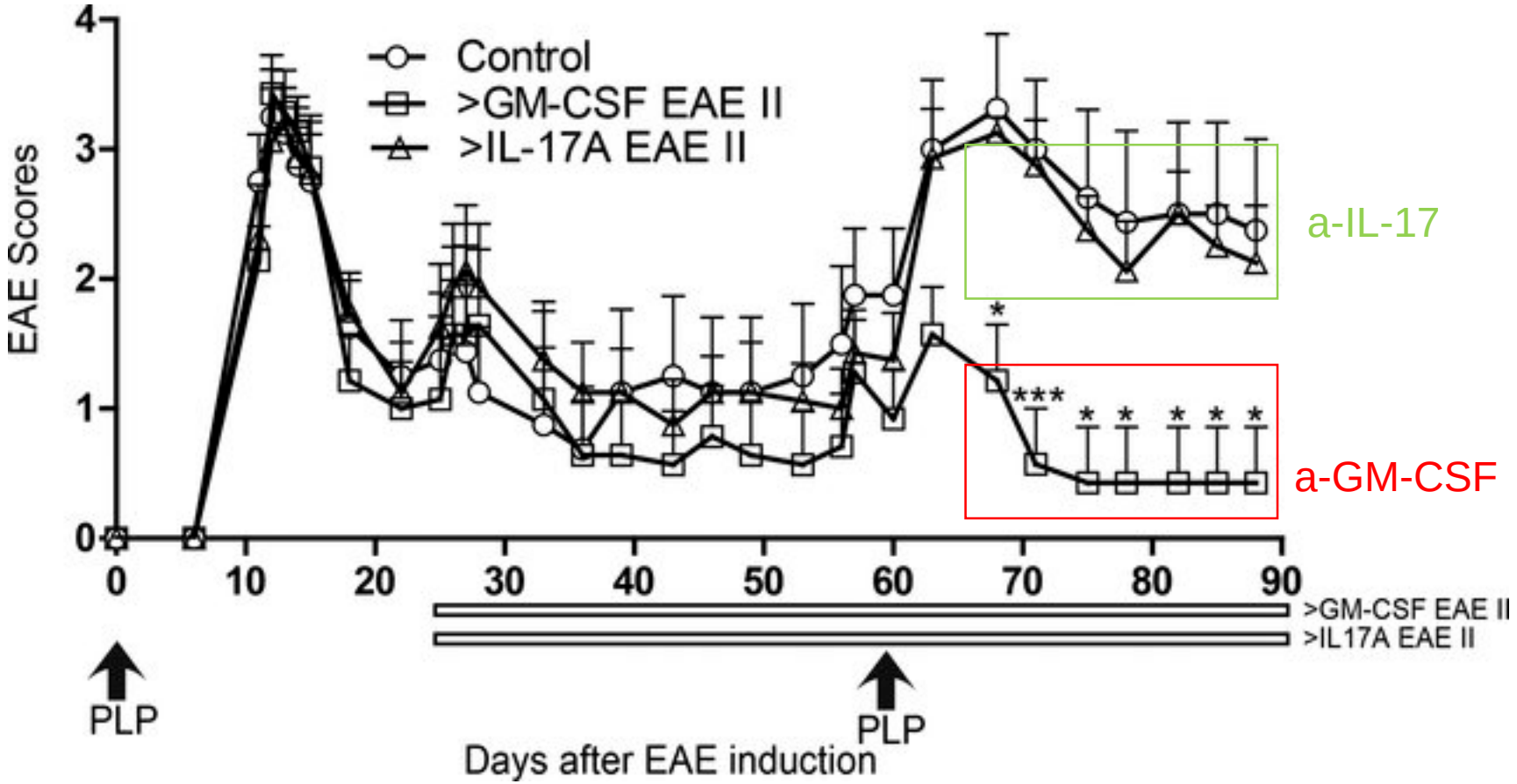
GM-CSF-MS ilişkisi





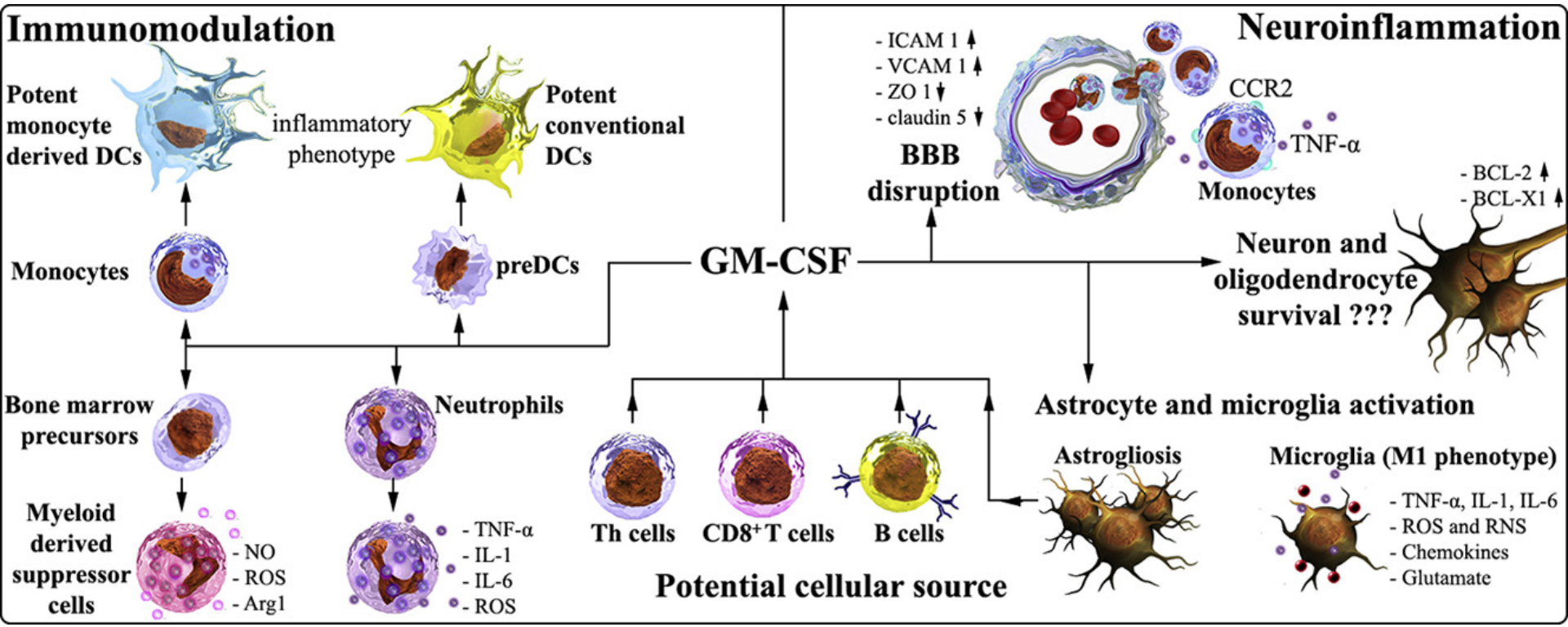


EAE modelinde a-IL-17/a-GM-CSF terapi karşılaştırması



Uyttenhove et al, Eur J. Immunol, 2018

GM-CSF ve MS



Kostic et al, J Neuroimmunol 2018

Teşekkür Ederim