Autoimmunity

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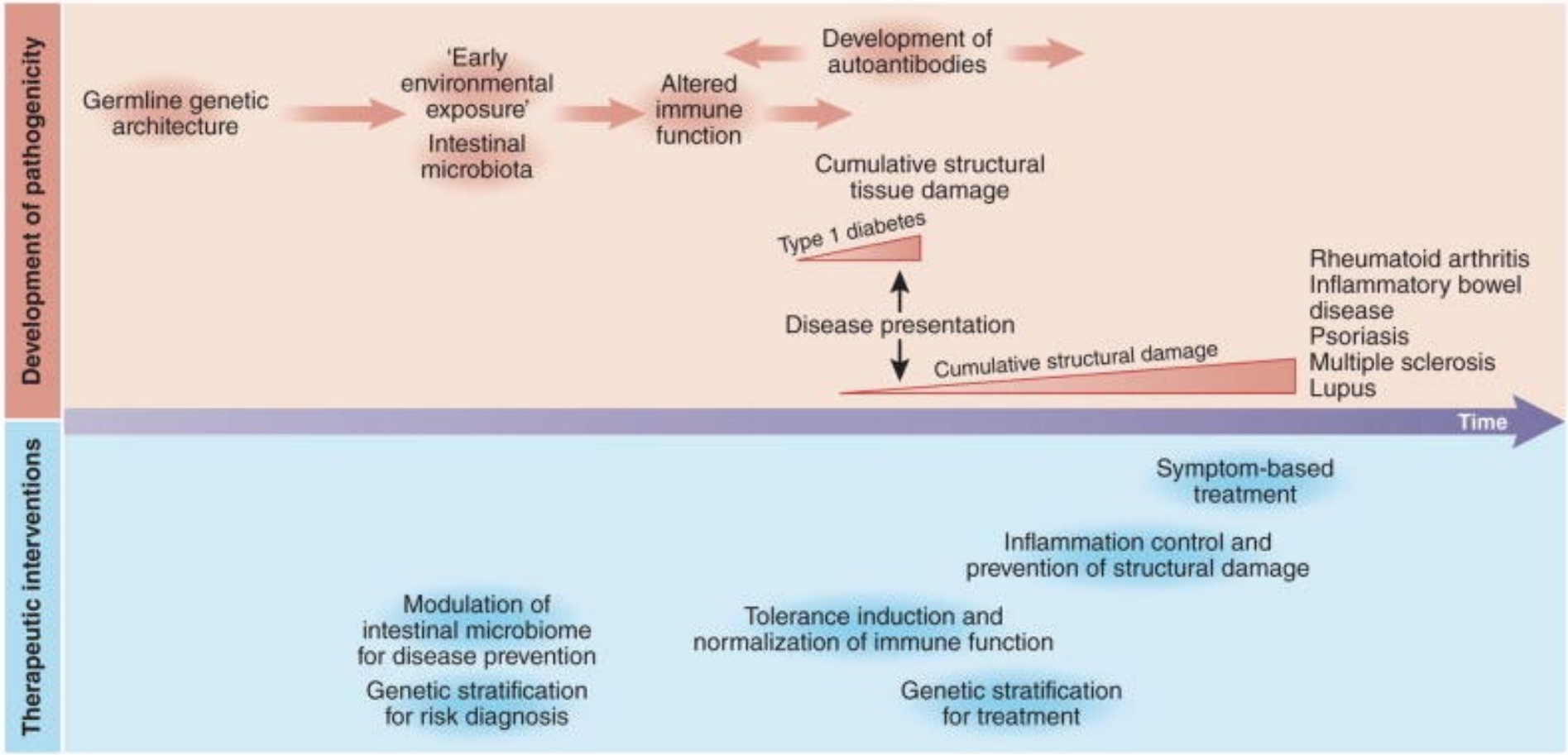
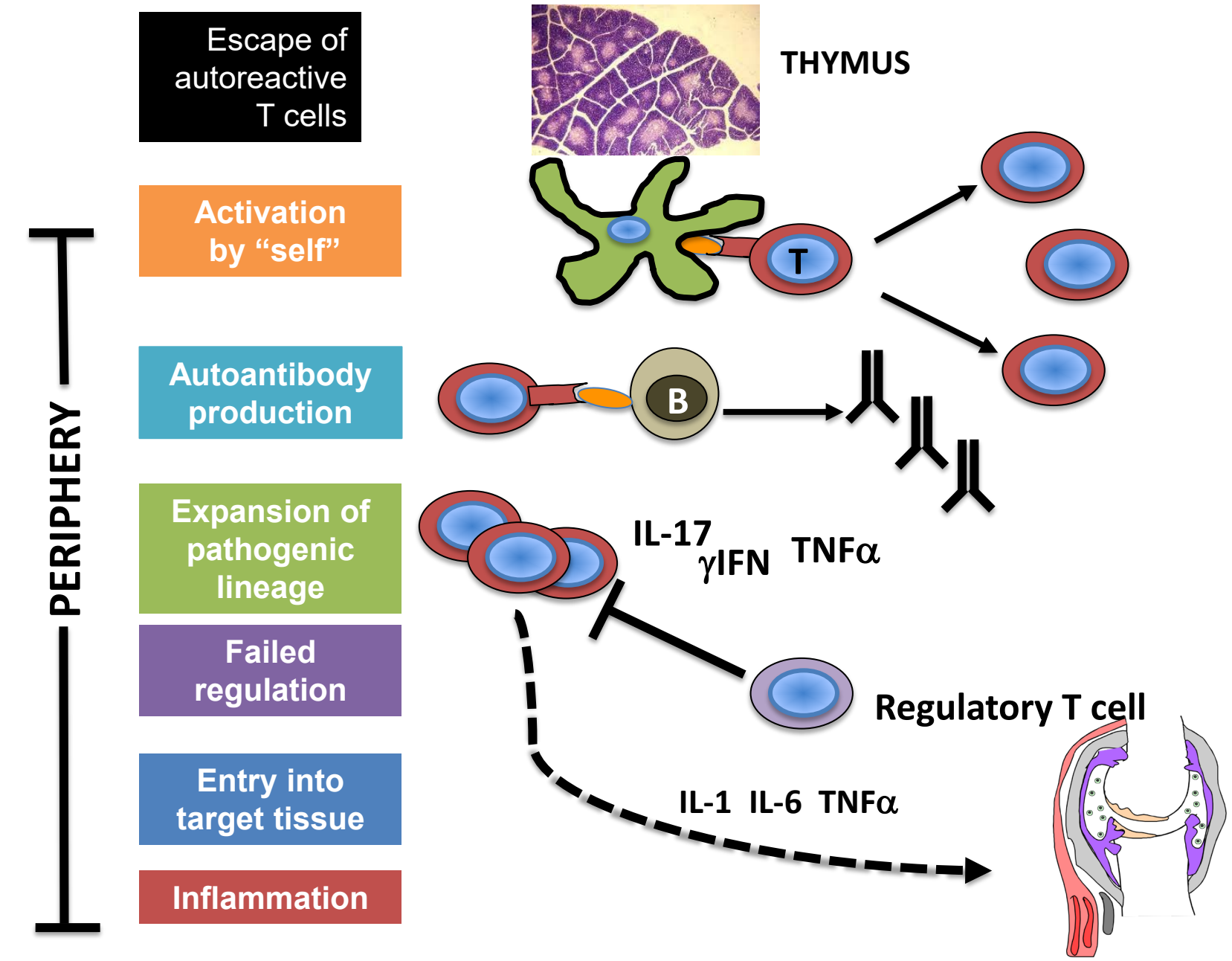
- Definition:
  - Immune response directed against self (auto) antigens that results in inflammation and destruction of healthy tissues
- General principles:
  - Significant health and economic burden (5% of the population)
  - Reflects failure of self tolerance
  - Multiple factors contribute to autoimmunity, including genetic predisposition, gender, and environmental effects
- Therapeutic and diagnostic problems:
  - Disease presents years after inappropriate immune response is initiated
  - Very heterogeneous disease manifestations
  - Target antigens remain largely unknown

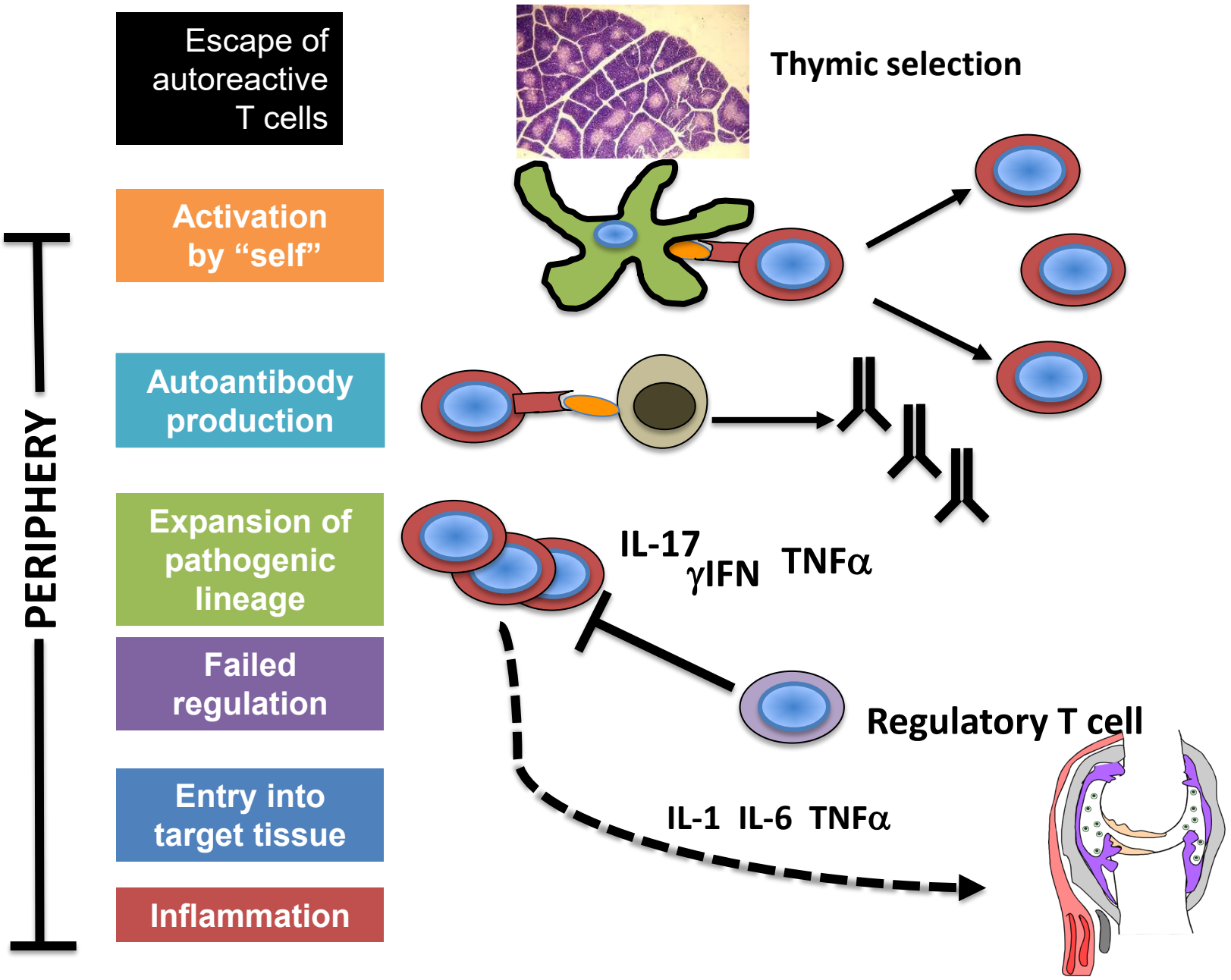
Timeline of pathogenicity and therapeutic interventions in autoimmunity



Cho and Feldmann, Nat Med. 2015 Jul; 21(7): 730–738


Escape of autoreactive T cells
Activation by "self"
Autoantibody production
Expansion of pathogenic lineage
Failed regulation
Entry into target tissue
Inflammation
PERIPHERY
THYMUS
T
B
IL-17
γIFN
TNFα
Regulatory T cell
IL-1 IL-6 TNFα

How is tolerance lost?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Genetic predisposition to autoimmunity

- Increased incidence in twins
- Multiple genes are associated with autoimmunity – Only very rare diseases are monogenic.
- Polygenic susceptibility to disease

  MHC genes--Major genetic association with autoimmune disease (relative risk)

  --Disease-associated alleles may be found in normal individuals

  – Non-MHC genes

Single gene mutations in humans associated with systemic autoimmunity

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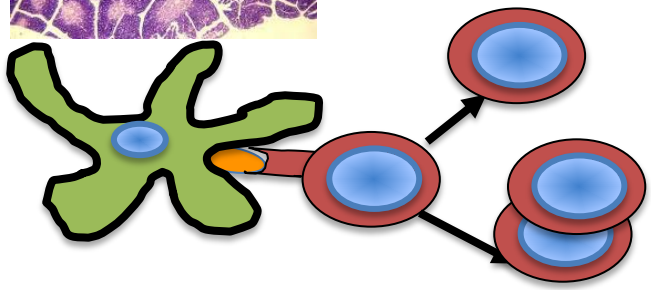
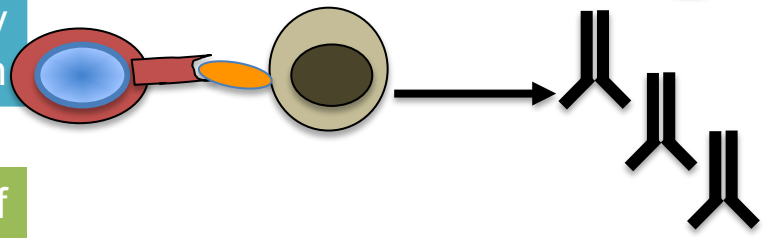
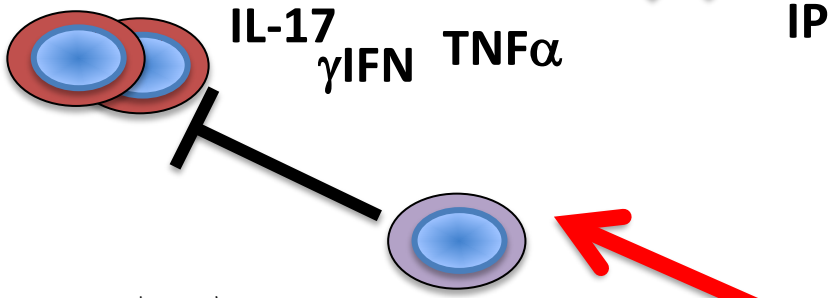
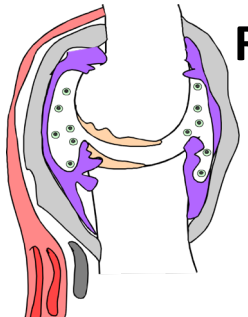






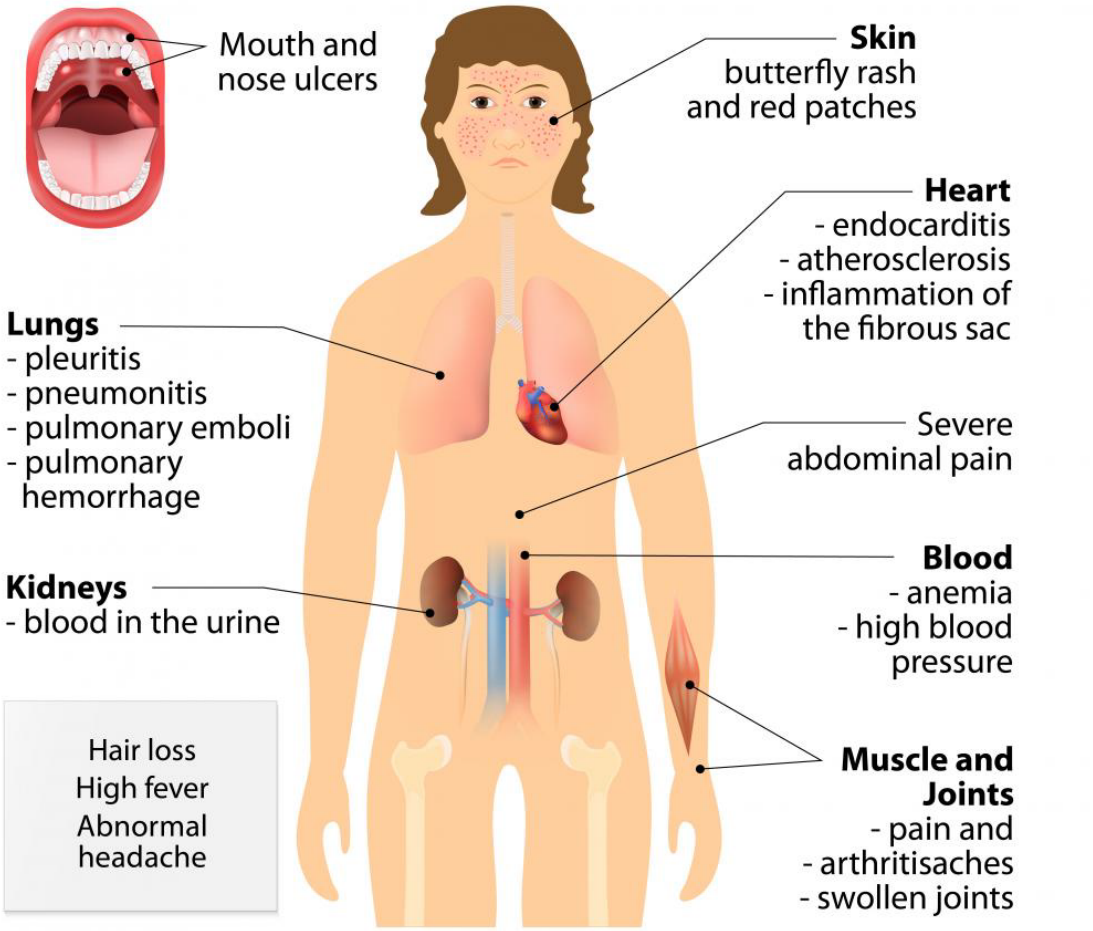
Regulatory T cell



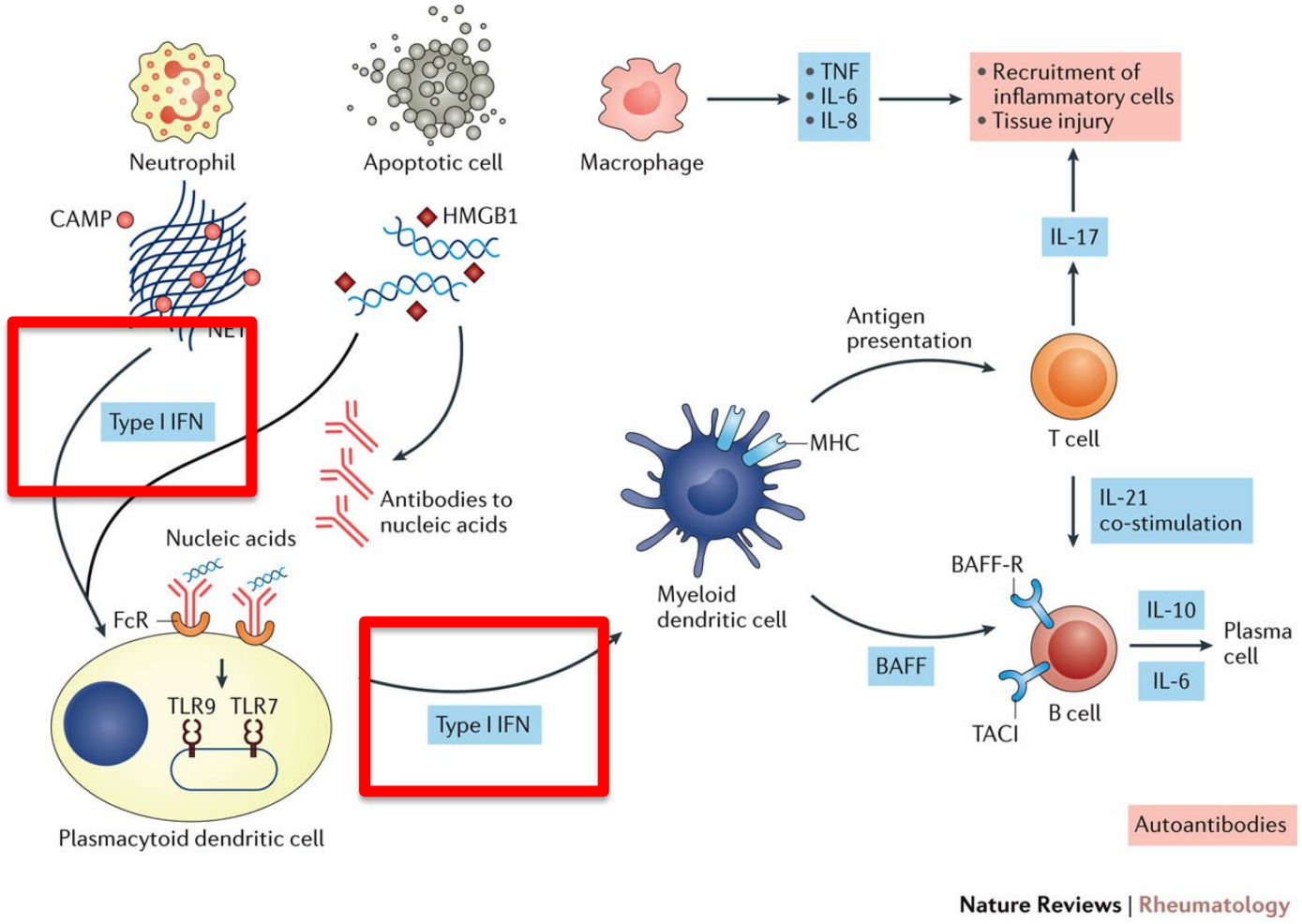
APS-1 (APECED)-a mutation in the AIRE gene: lack of negative selection leads to autoreacitve T cells - *Autoimmune Polyendocrinopathy Syndrome*

IPEX- a mutation in FOXP3 results in a lack of functional Tregs and the development of autoimmunity. - *Immunodysregulation polyendocrinopathy enteropathy X-linked syndrome*

Lupus is a complex multisystem autoimmune disease



Production of Type I interferons is a key first event in the pathophysiology of lupus

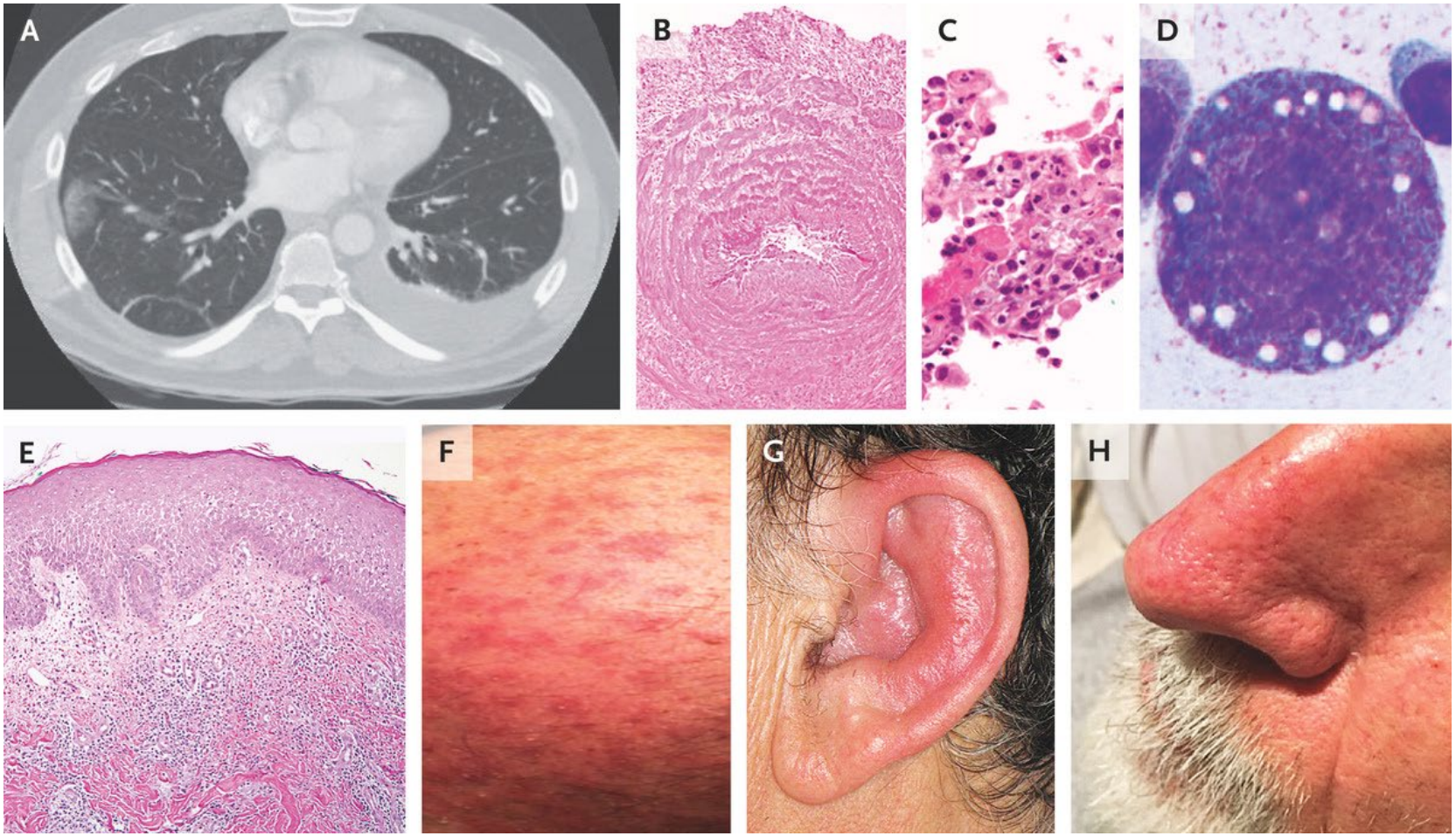


Tsokos, G. C. *et al.* (2016) New insights into the immunopathogenesis of systemic lupus erythematosus
Nat. Rev. Rheumatol. doi:10.1038/nrrheum.2016.186

Multiple gain-of-function mutations are associated familial lupus syndromes

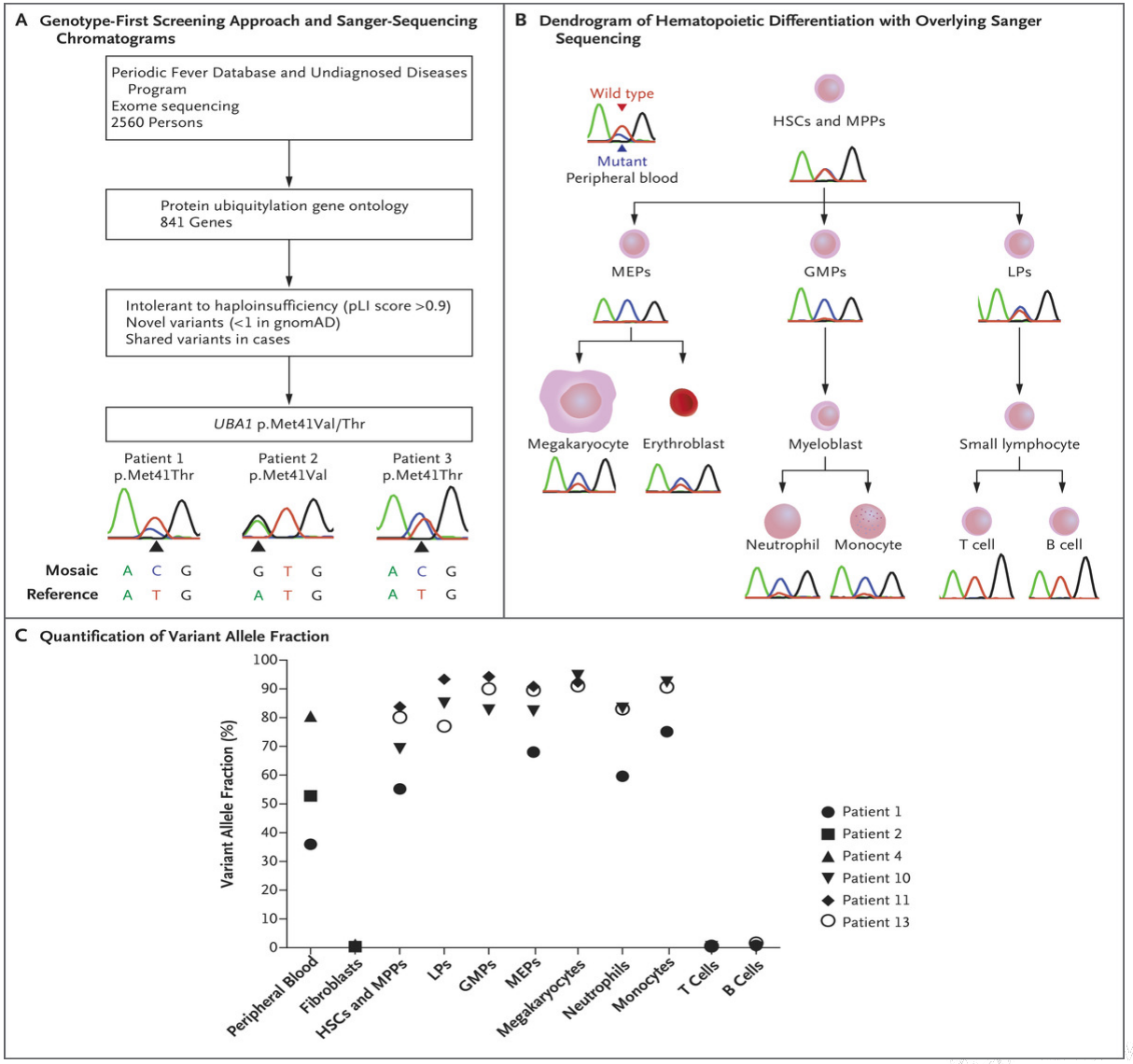
Phenotype	Genes
Interferonopathies (increased nucleic acid sensing with cGAS-STING activation)	TREX1, DNases, Rnases TLR7 gain-of-function
Complement deficiencies (clearance of apoptotic bodies)	C1q, C4, C2

Clinical Manifestations of the VEXAS Syndrome.



N Engl J Med
. 2020 Dec 31;383(27):2628-2638.
doi: 10.1056/NEJMoa2026834. Epub 2020 Oct 27.

Identification of Lineage-Restricted *UBA1* Somatic Variants in the VEXAS Syndrome



HLA is the strongest genetic association with autoimmunity

HLA-associated risk factors for autoimmune disease

Disease	HLA allotype	Frequency (%)		Relative risk
		Patients	Control	
Ankylosing spondylitis	B27	> 95	9	> 150
Narcolepsy	DQ6	> 95	33	> 40
Celiac disease	DQ2 and DQ8	95	28	30
IDDM	DQ8 and DQ2	81	23	14
Subacute thyroiditis	B35	70	14	14
Multiple sclerosis	DQ6	86	33	12
Rheumatoid arthritis	DR4	81	33	9
Juvenile rheumatoid arthritis	DR8	38	7	8
Psoriasis vulgaris	Cw6	87	33	7
Addison's disease	DR3	69	27	5
Graves' disease	DR3	65	27	4
Myasthenia gravis	DR3	50	27	2
IDDM	DQ6	< 0.1	33	0.02

Figure 11-23 The Immune System, 2/e (© Garland Science 2005)

Multiple autoimmune diseases share genetic susceptibility alleles

Table 1

Major genetic association signals across autoimmune diseases

	MHC class	*IL23R*	*PTPN22*	*CTLA4*[a]
Type 1 diabetes	Class II		Arg620___	

diseases.

Cho and Feldmann, Nat Med. 2015 Jul; 21(7): 730–738

Activation by "self" and inflammation may have environmental components.

Escape of autoreactive T cells

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Inflammation

Thymic selection

IL-17

γIFN

TNFα IL-6 IL-1

Regulatory T cell

Known environmental exposures

- **Vitamin D deficiency - linked to development of T1D and MS**
- **Oral Contraceptives-protective in RA**
- **Toxins - Cleaning compounds associated with scleroderma**
- **Infections - coxsackie virus/ T1D?**

  - EBV in multiple sclerosis?

Type I diabetes

- T cell mediated attack against the β cells of the pancreatic islets

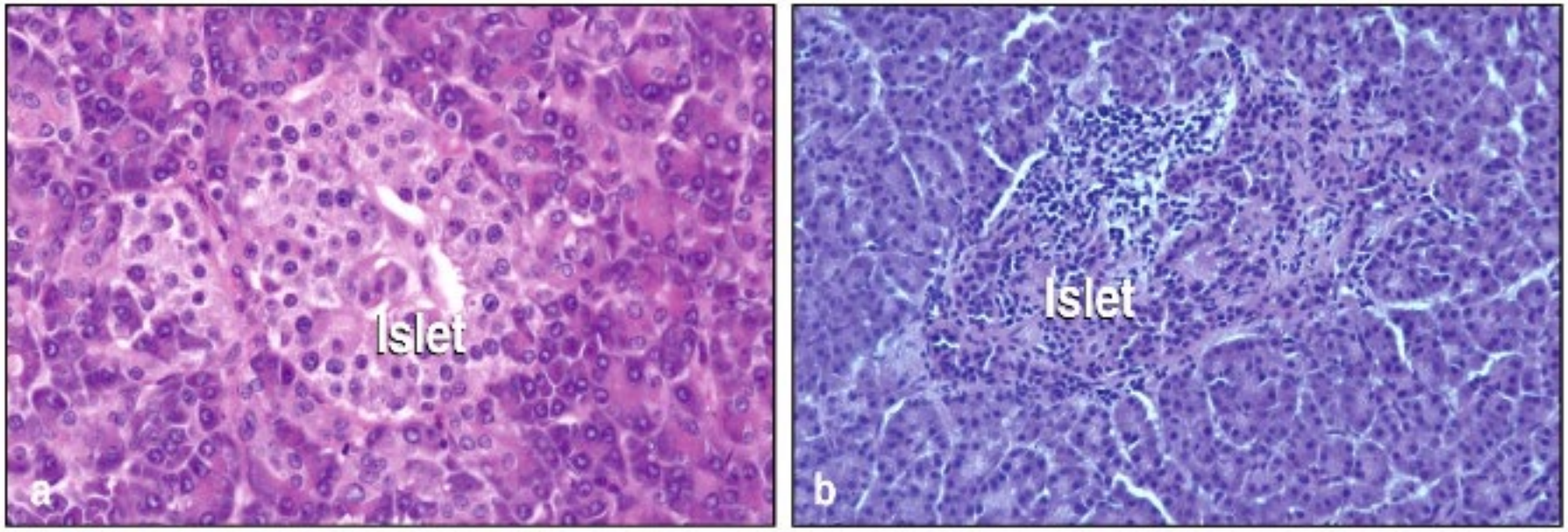
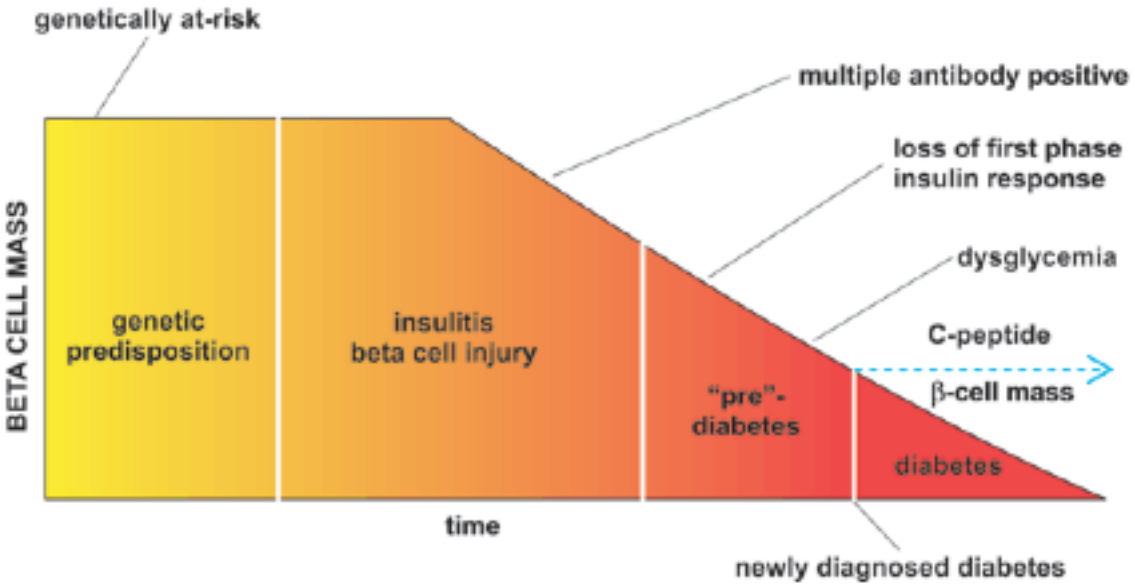


Figure 11-8 The Immune System, 2/e (© Garland Science 2005)

Natural history of Type I diabetes

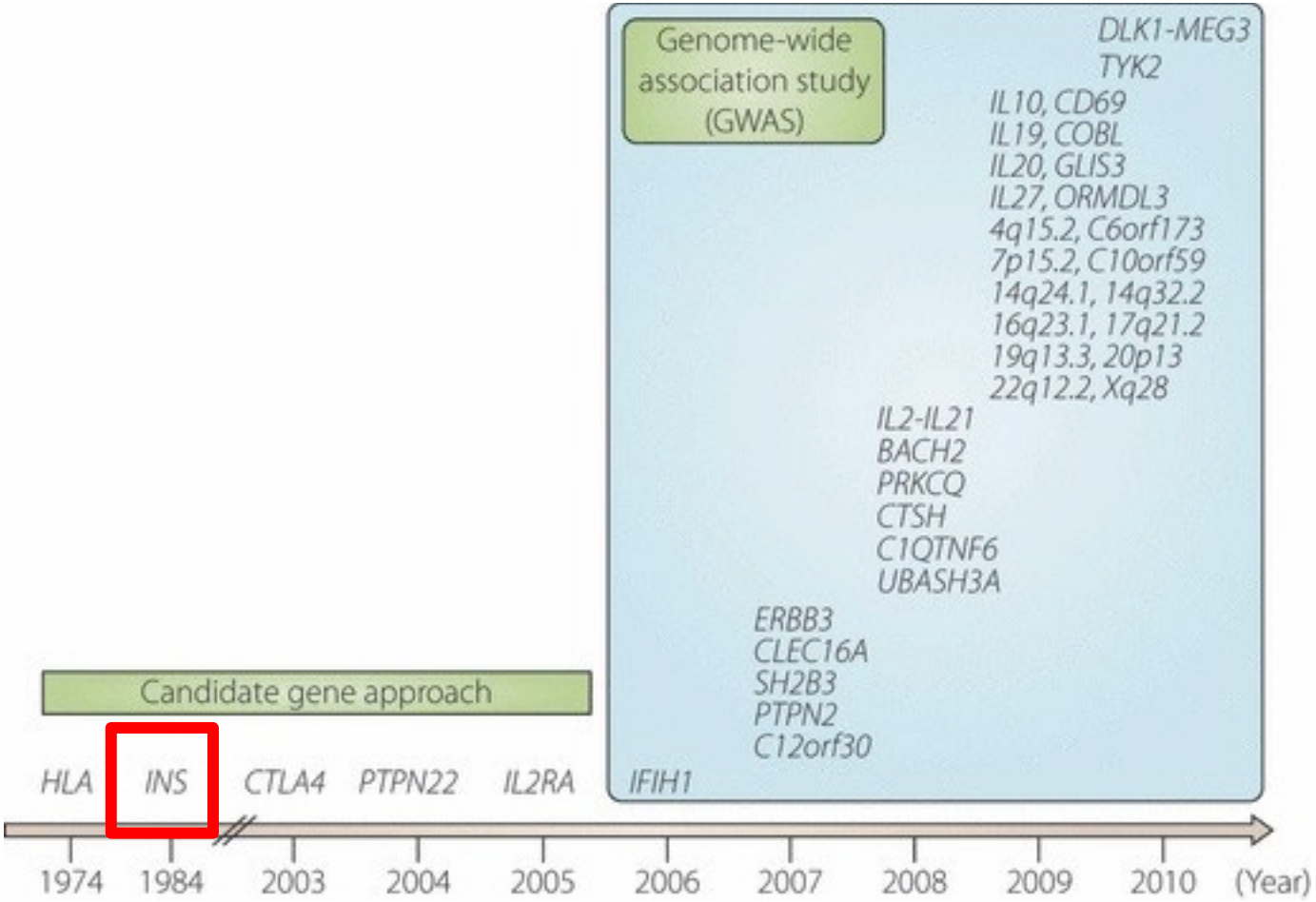
- **HLA class II alleles and relatives with T1D lead to increased genetic risk for disease**
- **Patients develop Ab directed at islet antigens prior to disease onset.**
- **T cells respond to antigens expressed in the β-cells of the islets**
- **– Proinsulin/Insulin, GAD, I-A2**
- **– T cell response is Th1 “like”, makes γ-IFN and helps recruit a tissue/cell destruction response**
- **• >90% islet destruction needed for the disease to be expressed**



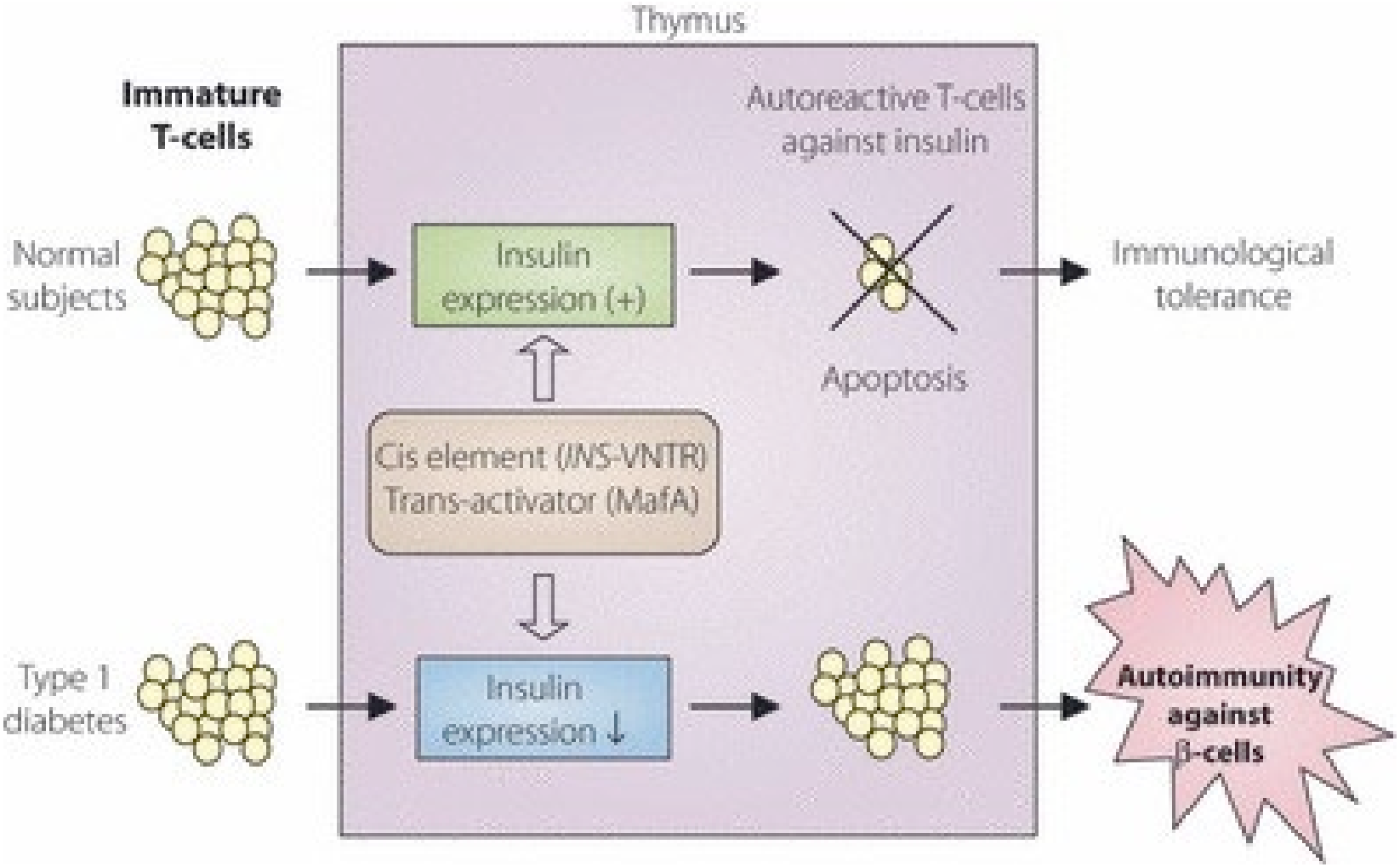
Diabetes genetics

- **Diabetes occurs in 0.2% of children**
- **Diabetes occurs in 5% of the population with the highest risk HLA type by age 15**
- **Diabetes occurs in 30% of first degree relatives with the highest risk HLA type**
- **If the Insulin SNP is present onset of disease is much earlier (20% in 5 years)**

Diabetes susceptibility genes



Decreased insulin expression in the thymus confers diabetes susceptibility



Are regulatory T cells defective in human autoimmunity?

Escape of autoreactive T cells

PERIPHERY

Activation by "self"

Autoantibody production

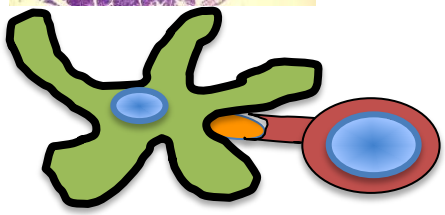
Expansion of pathogenic lineage

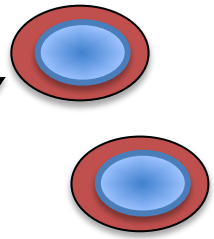
Failed regulation

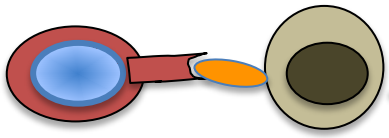
Entry into target tissue

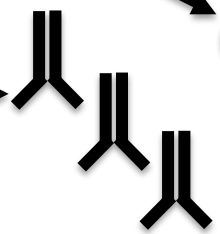
Inflammation

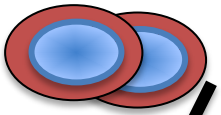
Thymic selection



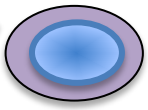




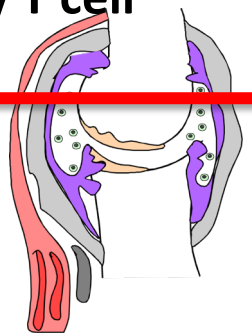




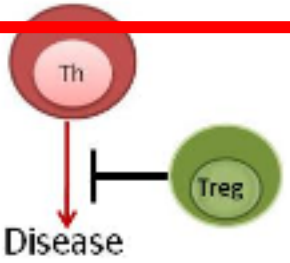
IL-17
γIFN
TNFα



Regulatory T cell



Are the numbers of Tregs decreased in human autoimmune diseases?



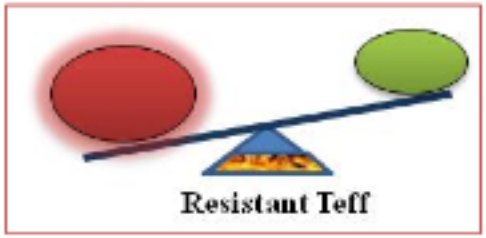
Treg can be counted in the peripheral blood in subjects with autoimmunity?

Does Treg number in the blood reflect the number in tissues?

Tregs from patients can be tested for their ability to suppress T cells of healthy subjects?

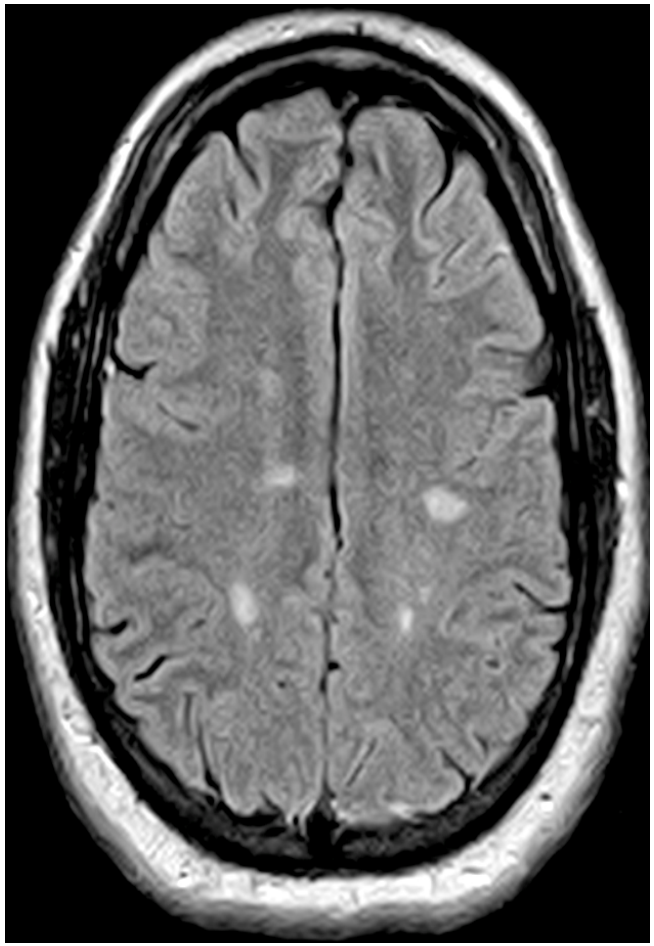
Does function in a test tube reflect function in vivo?

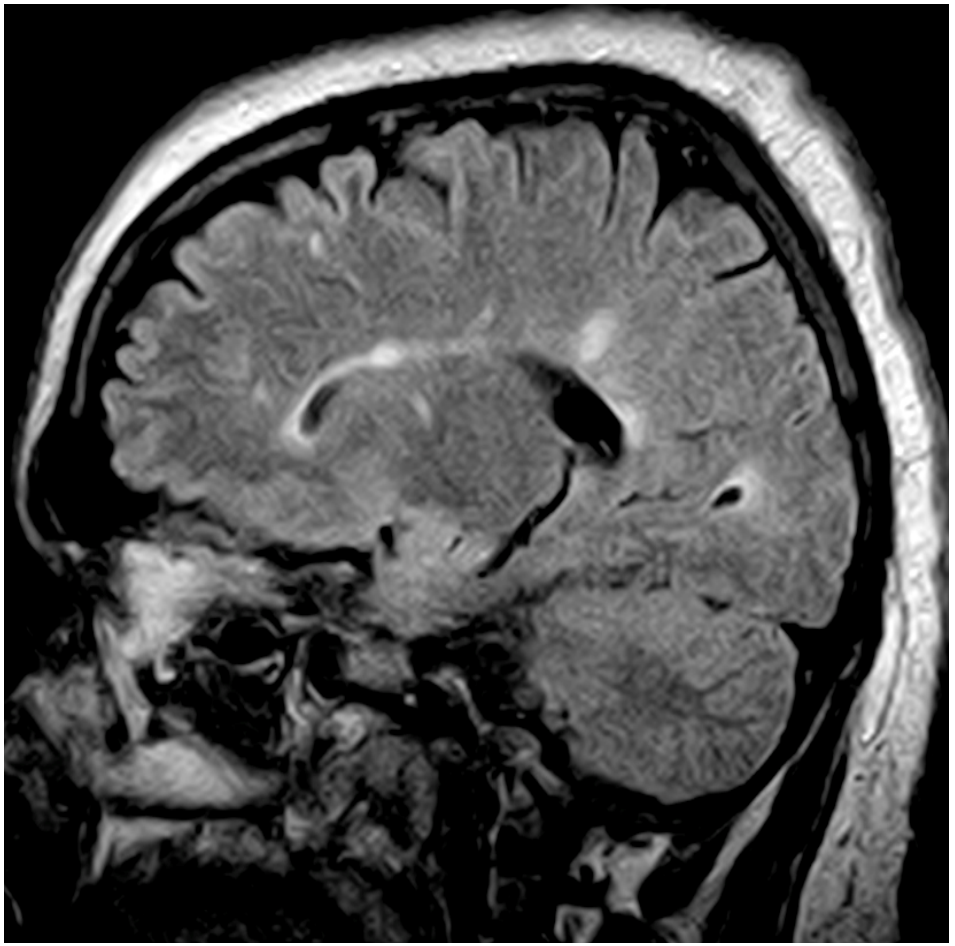
The suppression of T cells of patients by Treg of healthy subjects can be measured in vitro.



Are the autoreactive T cells uniquely resistant to regulation?

Multiple sclerosis

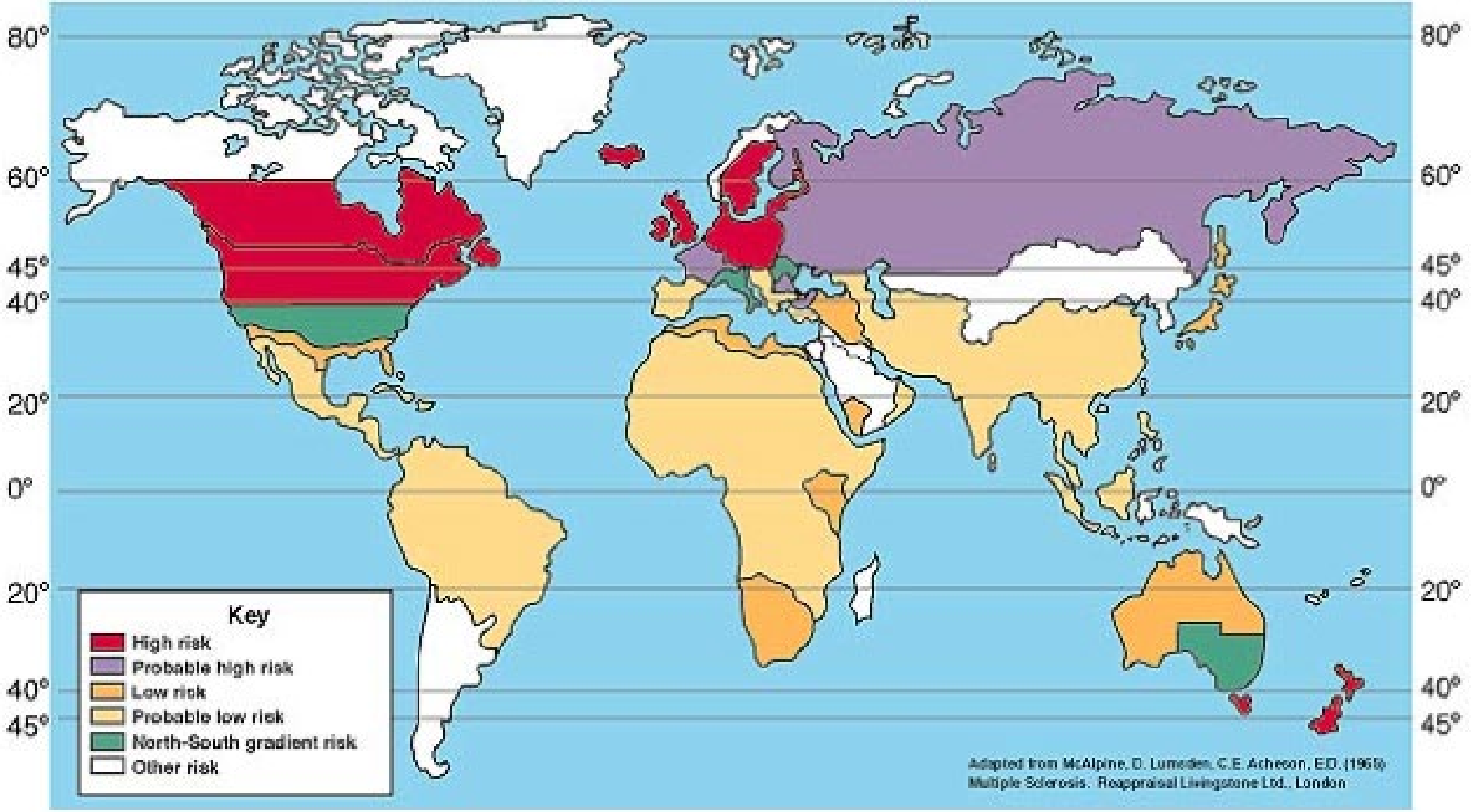




Multiple sclerosis

- **Inflammation and damage of the CNS present as sclerotic plaques on MRI**
- **Symptoms: Symptoms of neurologic deficits: motor weakness, impaired vision, lack of coordination, spasticity, bladder dysfunction, fatigue and many more.**
- **Incidence: (nearly 1 in 1000)**
  - **Onset early to mid-adult (age 20s-40s)**
- **Disease mechanisms:**
  - **CD4 T cells and CD8 T cells specific for myelin antigens**
  - **B cells participate but mechanism yet unknown.**
- **Treatment: High dose immunosuppressive drugs, IFN-β, copaxone, rituximab/ocrelizumab (deplete CD20+ B cells [!], natalizumab (inhibits T cell entry into tissues), fingolimod (sequesters T cells in lymph nodes).**

Epidemiology of MS—genetics and environment



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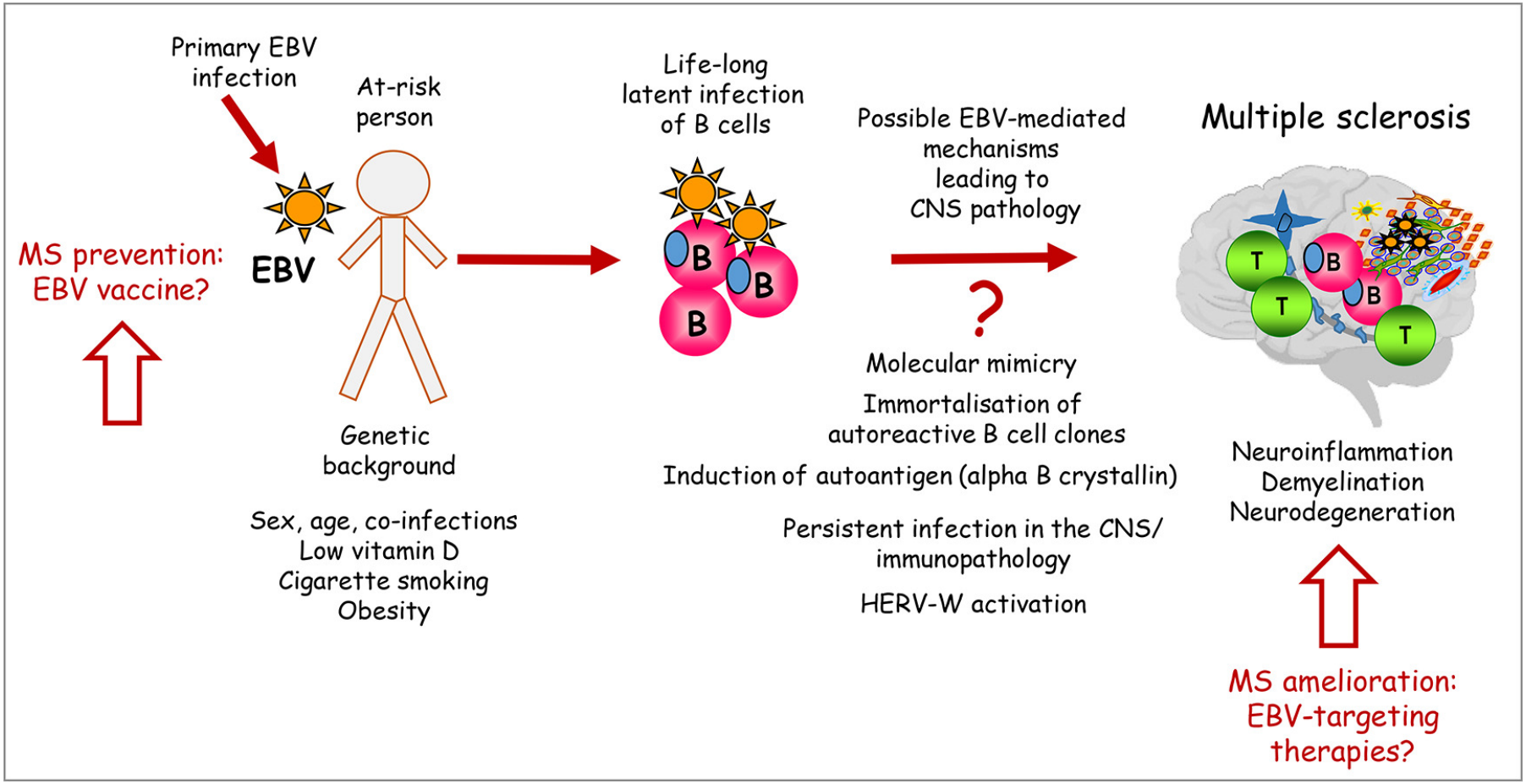
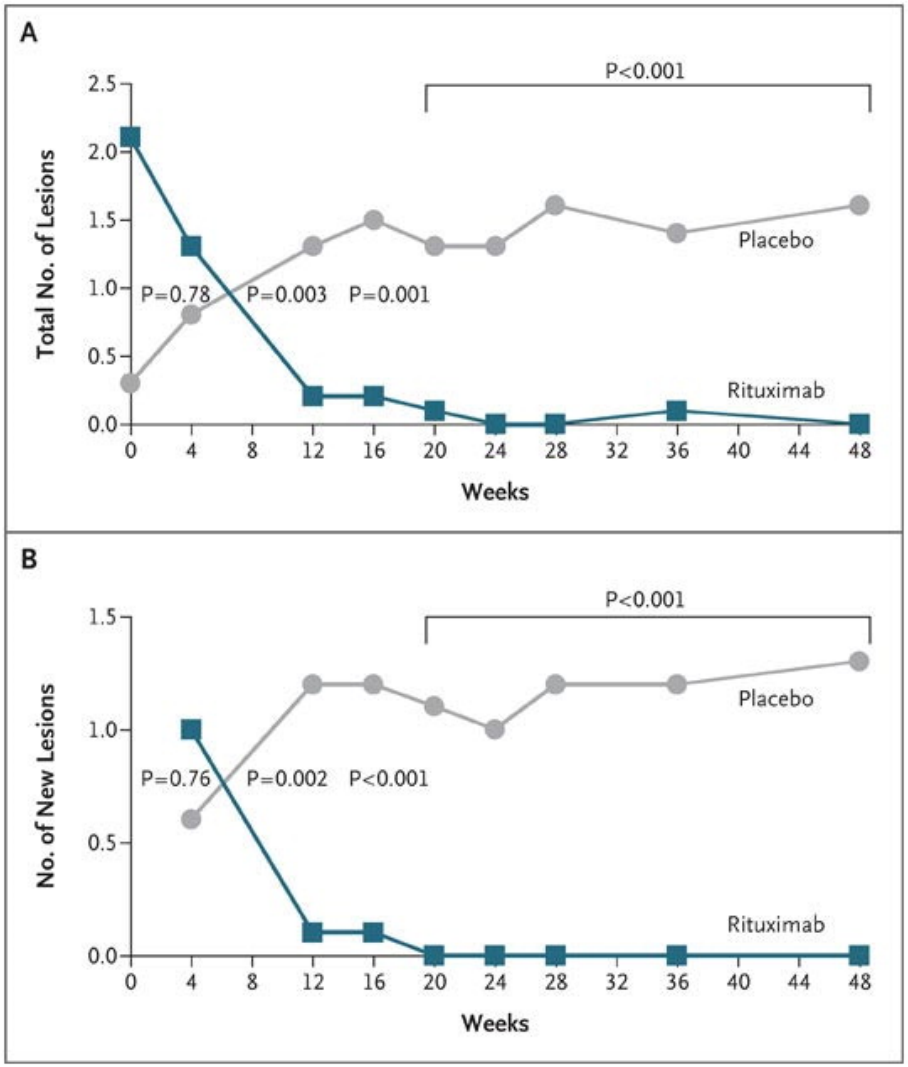


Aloisi et al., https://doi.org/10.1016/j.jneuroim.2022.577935

Treatment success suggests disease mechanisms

B cell depletion (anti-CD20) is an effective therapy for multiple sclerosis

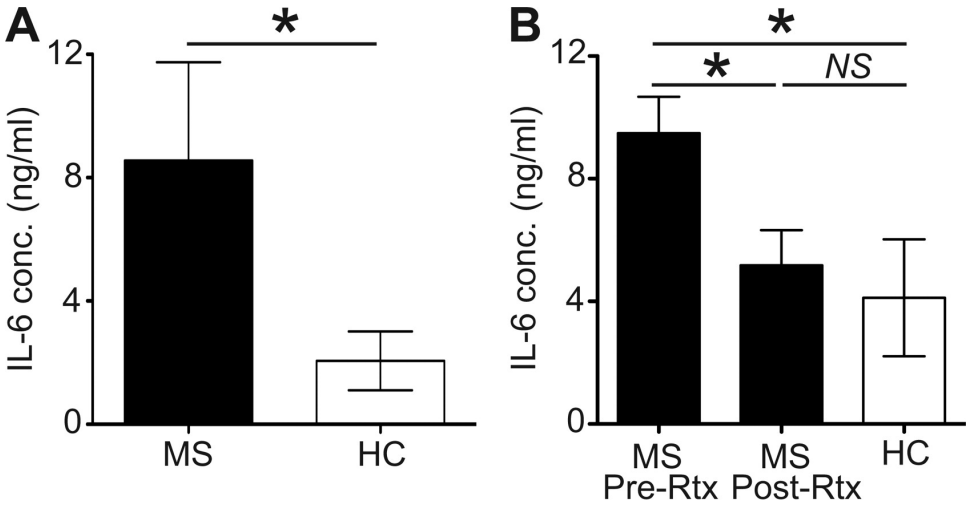


Why does B cell depletion work?

- Removal of autoantibodies?
- Removal of a large population of antigen presenting cells?
- Removal of a cytokine secreting population?

NEJM (2008) 358: 676

Rituximab (B cell depleting antibody) efficacy correlates with depletion of IL-6-producing B cells



JEM (2012) 209: 1001

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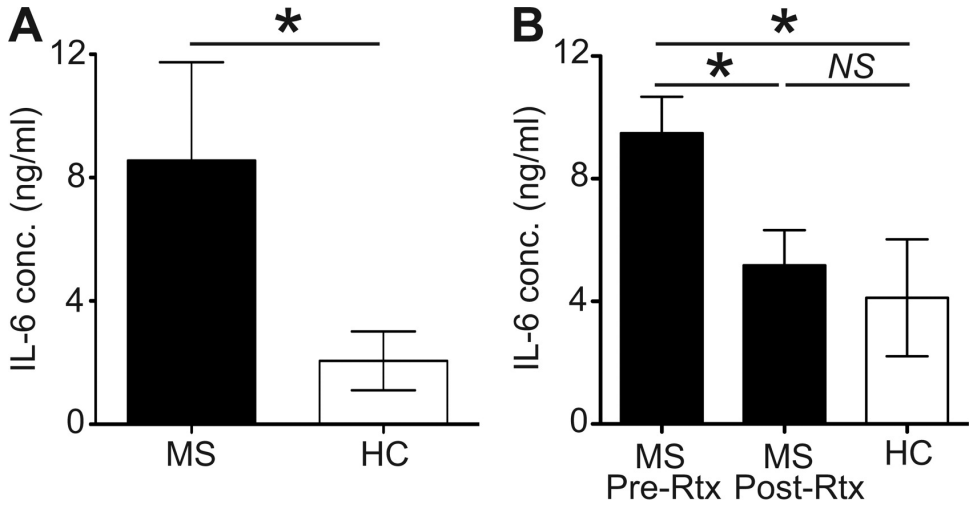

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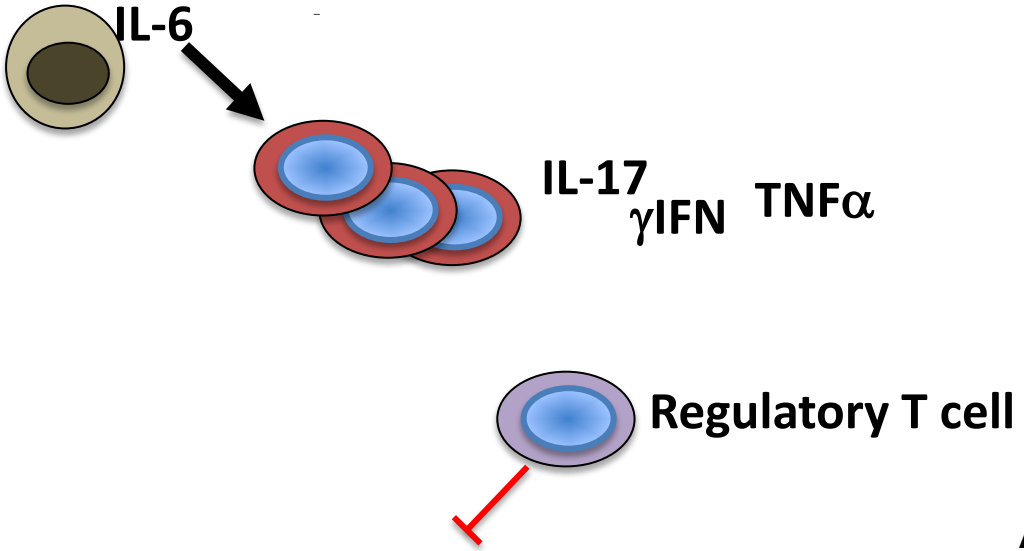


A. Schneider et al., Sci Transl Med 2013;5:170ra15

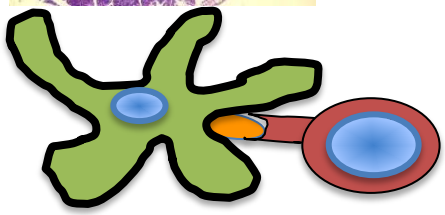
Treatment successes suggest disease mechanisms.

Escape of autoreactive T cells

Thymic selection

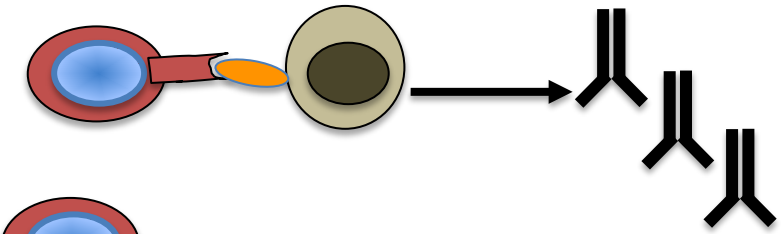
PERIPHERY

Activation by "self"

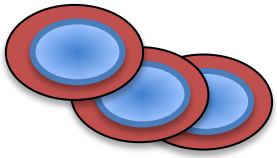


Block activation of autoreactive T cells

Autoantibody production

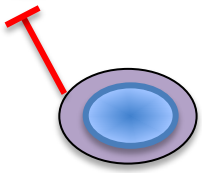


Expansion of pathogenic lineage



IL-17 γIFN TNFα

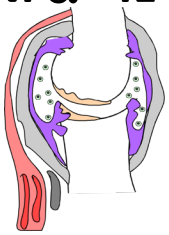
Failed regulation



Regulatory T cell

Entry into target tissue

TNFα IL-6 IL-1



Inflammation

Escape of autoreactive T cells

Thymic selection

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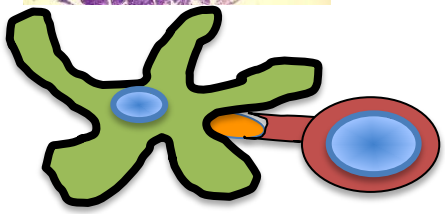
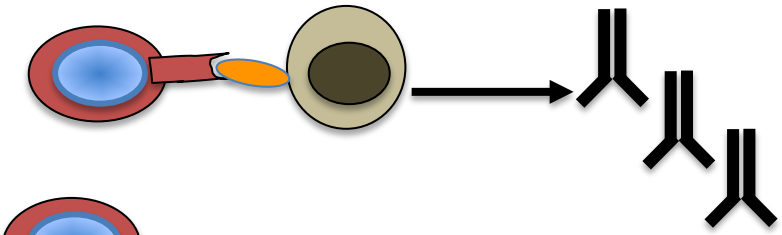
Activation by "self"



Abatacept—interferes with CD28-CD80/86 interactions

Autoantibody production



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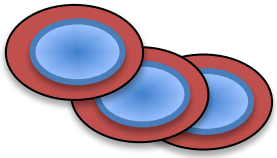

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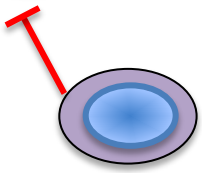
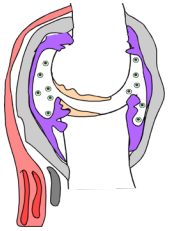


Regulatory T cell

Entry into target tissue

TNFα IL-6 IL-1



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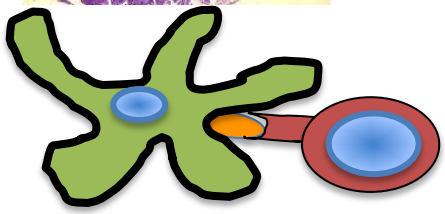
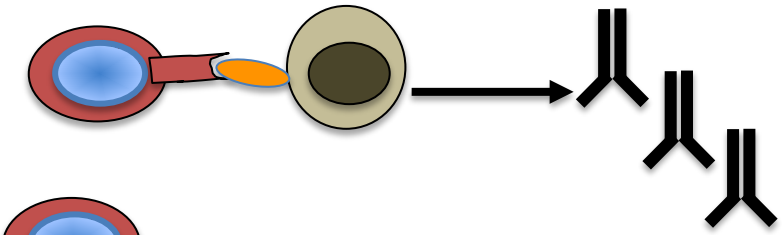
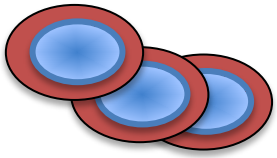


Autoantibody production



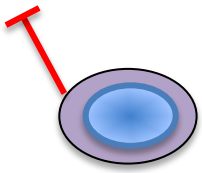
Block autoantibody production and activity

Expansion of pathogenic lineage



IL-17 γIFN TNFα

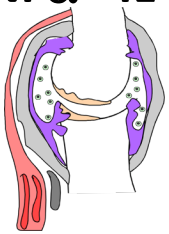
Failed regulation



Regulatory T cell

Entry into target tissue

TNFα IL-6 IL-1



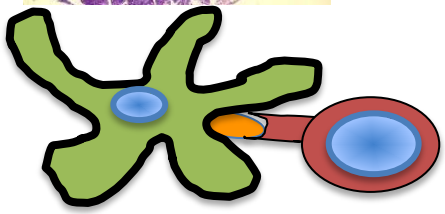
Inflammation

PERIPHERY

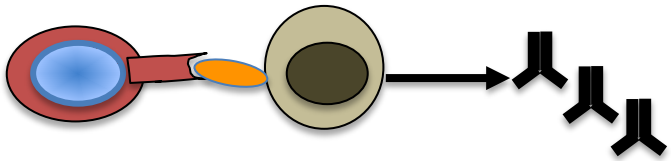
Escape of autoreactive T cells

Thymic selection

Activation by "self"

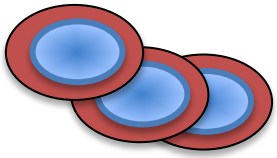


Autoantibody production



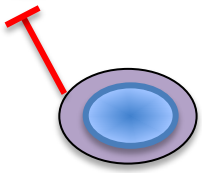
Rituximab—depletes CD20+ B cells
IVIG—inhibits Ab signaling via Fc receptors

Expansion of pathogenic lineage



IL-17
γIFN
TNFα

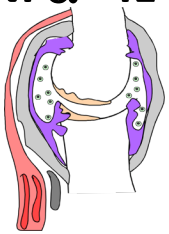
Failed regulation



Regulatory T cell

Entry into target tissue

TNFα IL-6 IL-1



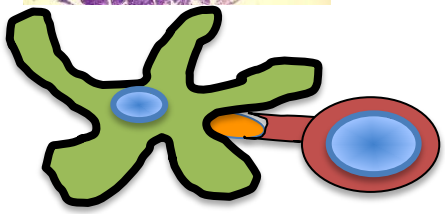
Inflammation

PERIPHERY

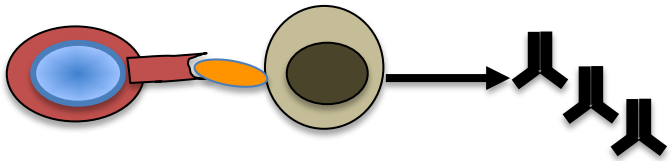
Escape of autoreactive T cells

Thymic selection

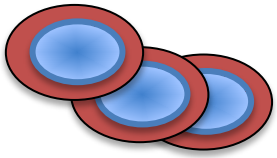
Activation by "self"



Autoantibody production

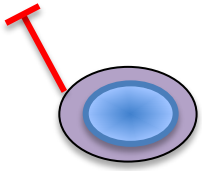


Expansion of pathogenic lineage



IL-17 γIFN TNFα

Failed regulation



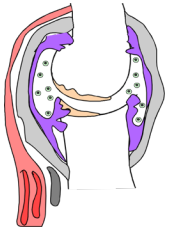
Regulatory T cell

- Prevent differentiation of pathologic effector populations.
- Block effects of pathologic cytokines.

Entry into target tissue

TNFα IL-6 IL-1

Inflammation

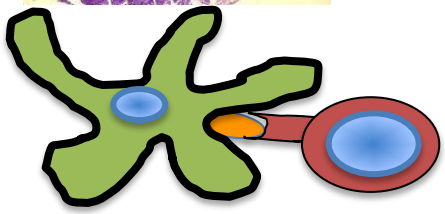


PERIPHERY

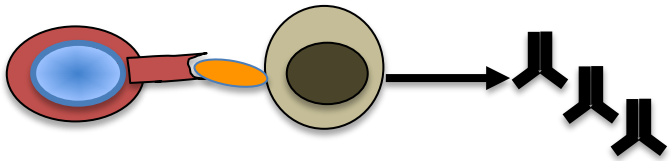
Escape of autoreactive T cells

Thymic selection

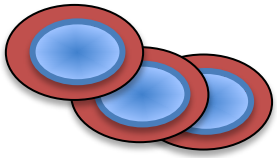
Activation by "self"



Autoantibody production

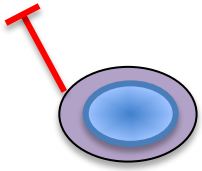


Expansion of pathogenic lineage



IL-17 γIFN TNFα

Failed regulation



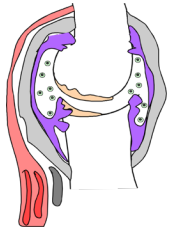
Regulatory T cell

- Ustekinumab—Blocks IL-12/IL-23 p40 to prevent differentiation of Th1 and Th17s.
- Secukinumab—anti-IL-17.

Entry into target tissue

TNFα IL-6 IL-1

Inflammation

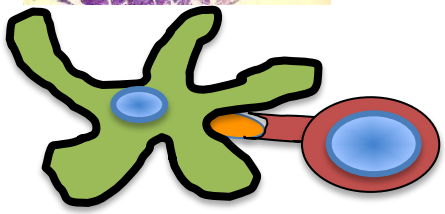


PERIPHERY

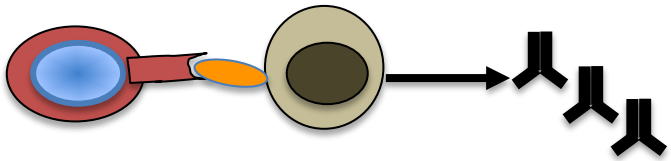
Escape of autoreactive T cells

Thymic selection

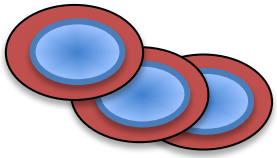
Activation by "self"



Autoantibody production



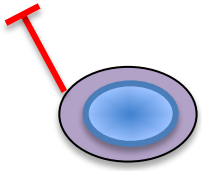
Expansion of pathogenic lineage



IL-17 γIFN TNFα

- Jak inhibitors

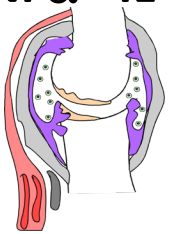
Failed regulation



Regulatory T cell

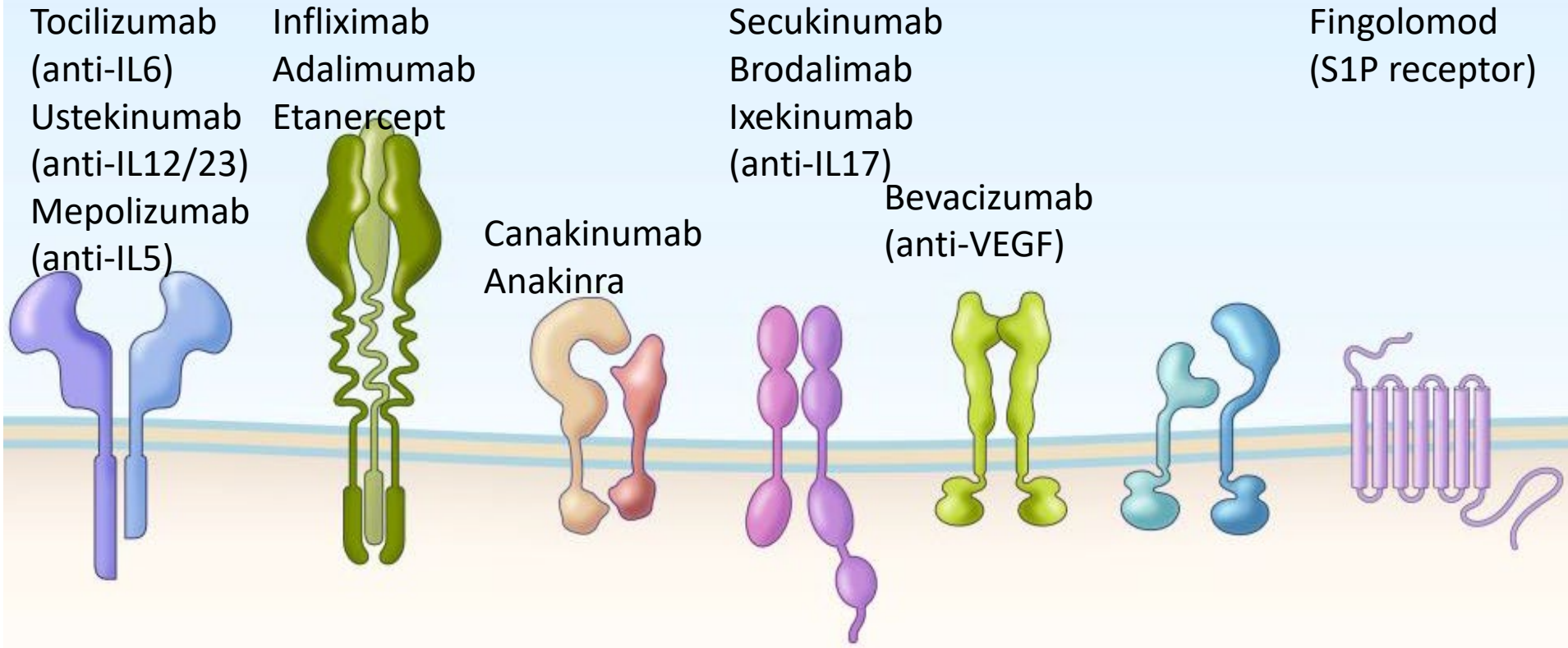
Entry into target tissue

TNFα IL-6 IL-1



Inflammation

Cytokines and Cytokine receptors can be directly inhibited

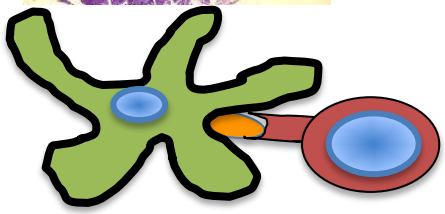


PERIPHERY

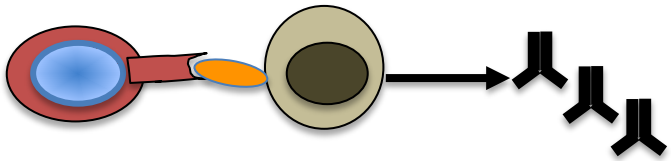
Escape of autoreactive T cells

Thymic selection

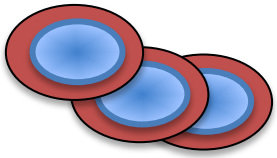
Activation by "self"



Autoantibody production

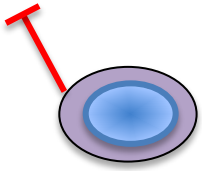


Expansion of pathogenic lineage



IL-17
γIFN
TNFα

Failed regulation

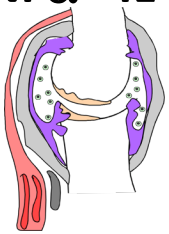


Regulatory T cell

Enhance Treg number or function

Entry into target tissue

TNFα IL-6 IL-1



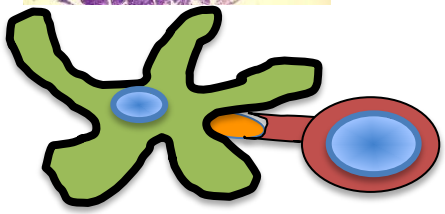
Inflammation

PERIPHERY

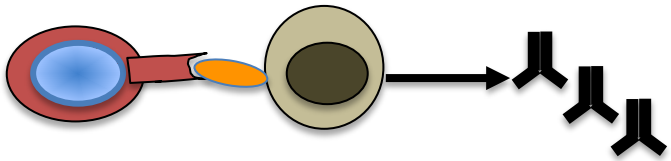
Escape of autoreactive T cells

Thymic selection

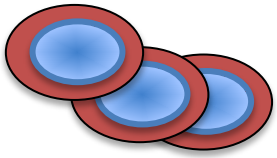
Activation by "self"



Autoantibody production

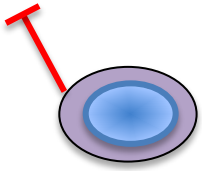


Expansion of pathogenic lineage



IL-17
γIFN
TNFα

Failed regulation

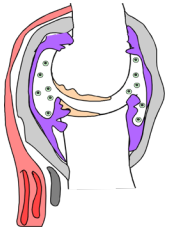


Regulatory T cell

Treg infusion
Low dose IL-2
Rapamycin

Entry into target tissue

TNFα IL-6 IL-1



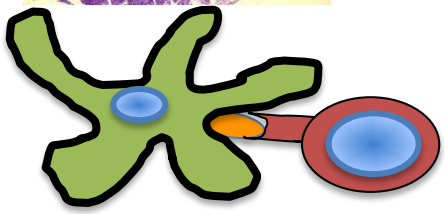
Inflammation

PERIPHERY

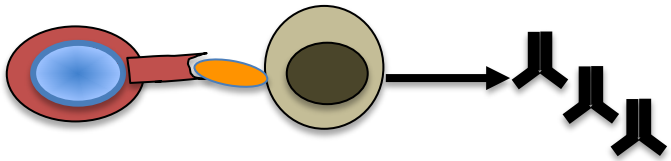
Escape of autoreactive T cells

Thymic selection

Activation by "self"



Autoantibody production



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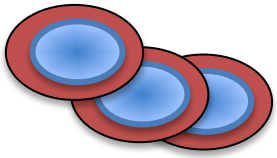
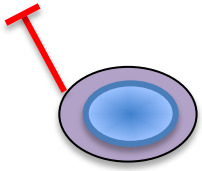


IL-17
γIFN
TNFα

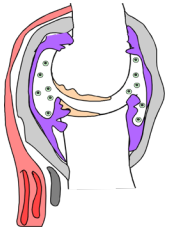
Failed regulation



Regulatory T cell

Entry into target tissue

TNFα IL-6 IL-1



Inflammation

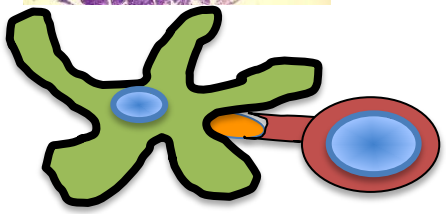
Block entry of inflammatory cells into target tissues

PERIPHERY

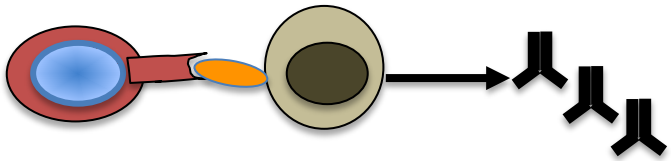
Escape of autoreactive T cells

Thymic selection

Activation by "self"



Autoantibody production



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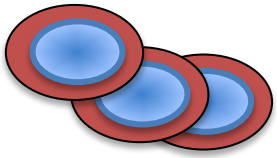
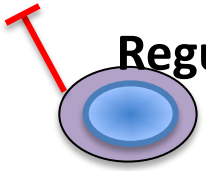


IL-17 γIFN TNFα

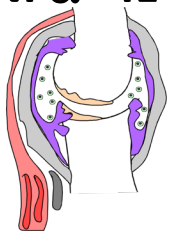
Failed regulation



Regulatory T cell

Entry into target tissue

TNFα IL-6 IL-1



Inflammation

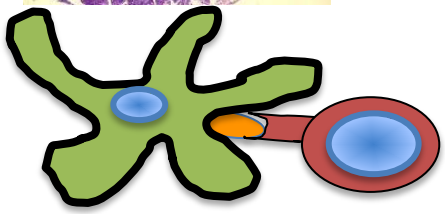
Fingolomod—Blocks egress of activated T cells from the LN
Natalizumab—anti-a4 integrin—block entry of cells into gut and brain
Vedolizumab-anti-a4b7 integrin—block entry of cells into gut

PERIPHERY

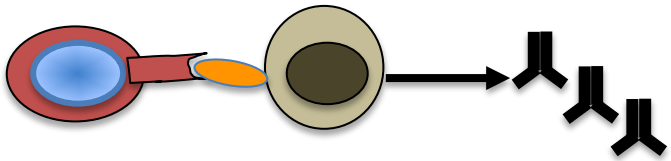
Escape of autoreactive T cells

Thymic selection

Activation by "self"



Autoantibody production



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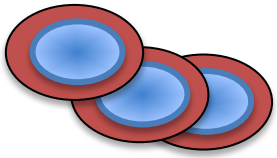
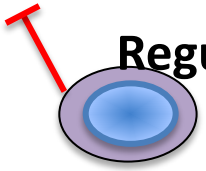


IL-17
γIFN
TNFα

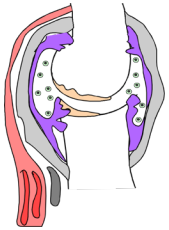
Failed regulation



Regulatory T cell

Entry into target tissue

TNFα IL-6 IL-1



Inflammation

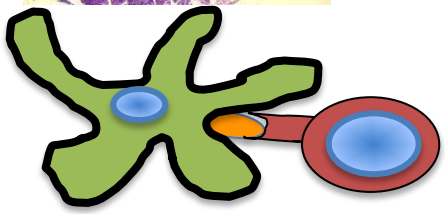
Block inflammatory cytokines

PERIPHERY

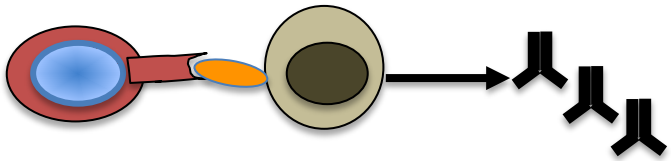
Escape of autoreactive T cells

Thymic selection

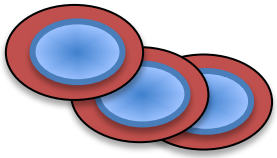
Activation by "self"



Autoantibody production

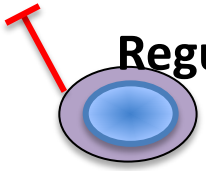


Expansion of pathogenic lineage



IL-17
γIFN
TNFα

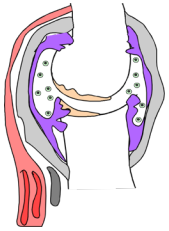
Failed regulation



Regulatory T cell

Entry into target tissue

TNFα IL-6 IL-1



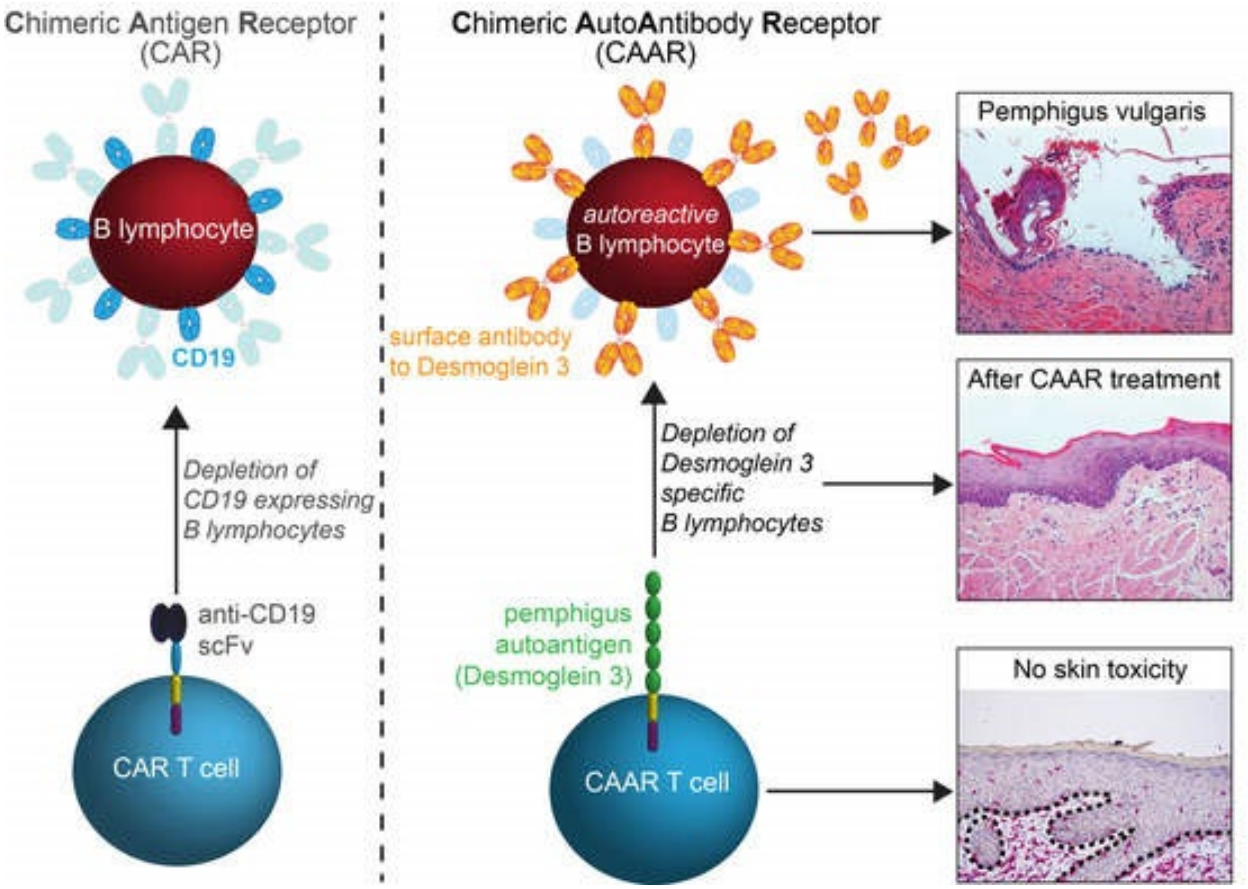
Inflammation

Tocilizumab-anti-IL6R
(Anakinra, Canakinumab)-IL1 blockade
TNF blockade

Advent of cell therapy to treat autoimmunity

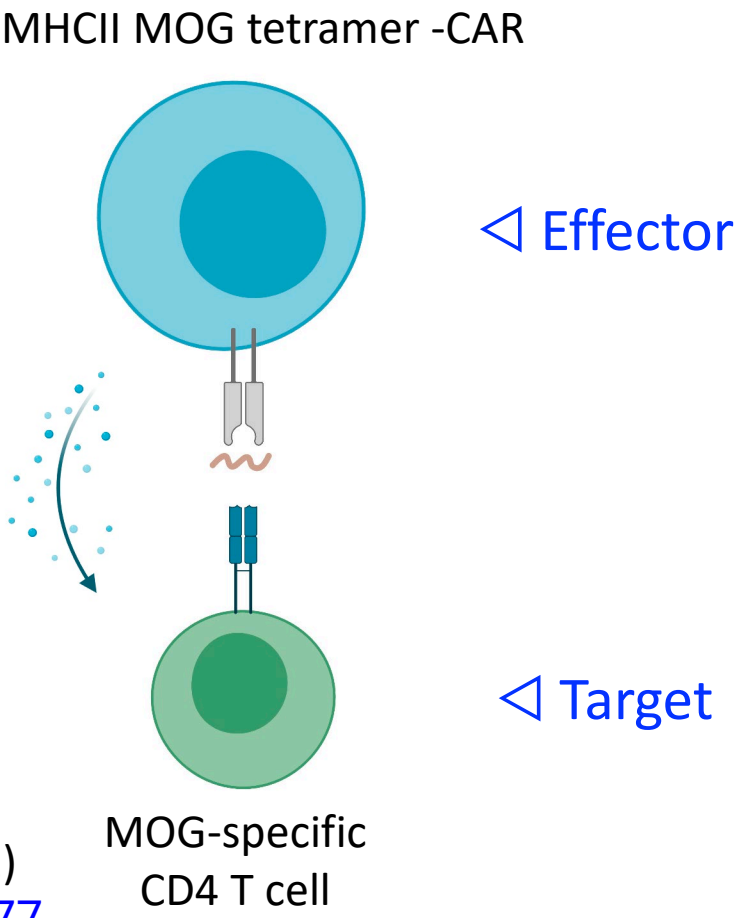
- There is significant interest in developing regulatory T cell adoptive cell therapy
- anti-CD19 CAR T's may have worked in a small number of patients with refractory lupus.
- Can CAR's be used to deplete pathologic lymphocytes?

CARs expressing autoantigen can deplete autoreactive B cells



https://www.aimeepaynelab.org/research.html

CARs expressing MHCII-peptide complexes can deplete autoreactive T cells that cause EAE



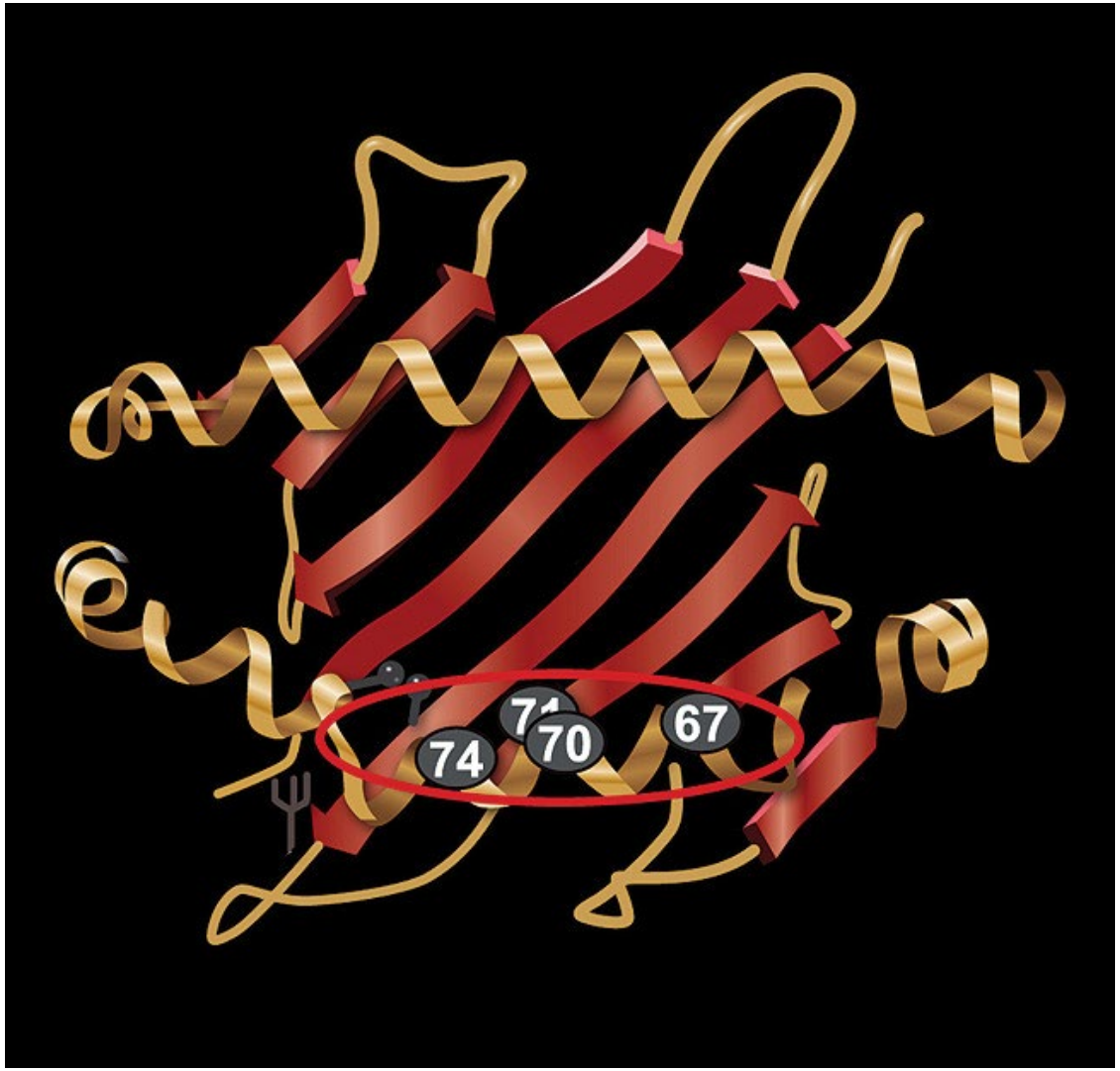
Yi et al, Science Immunology (2022)
DOI: 10.1126/sciimmunol.abo077

Rheumatoid arthritis

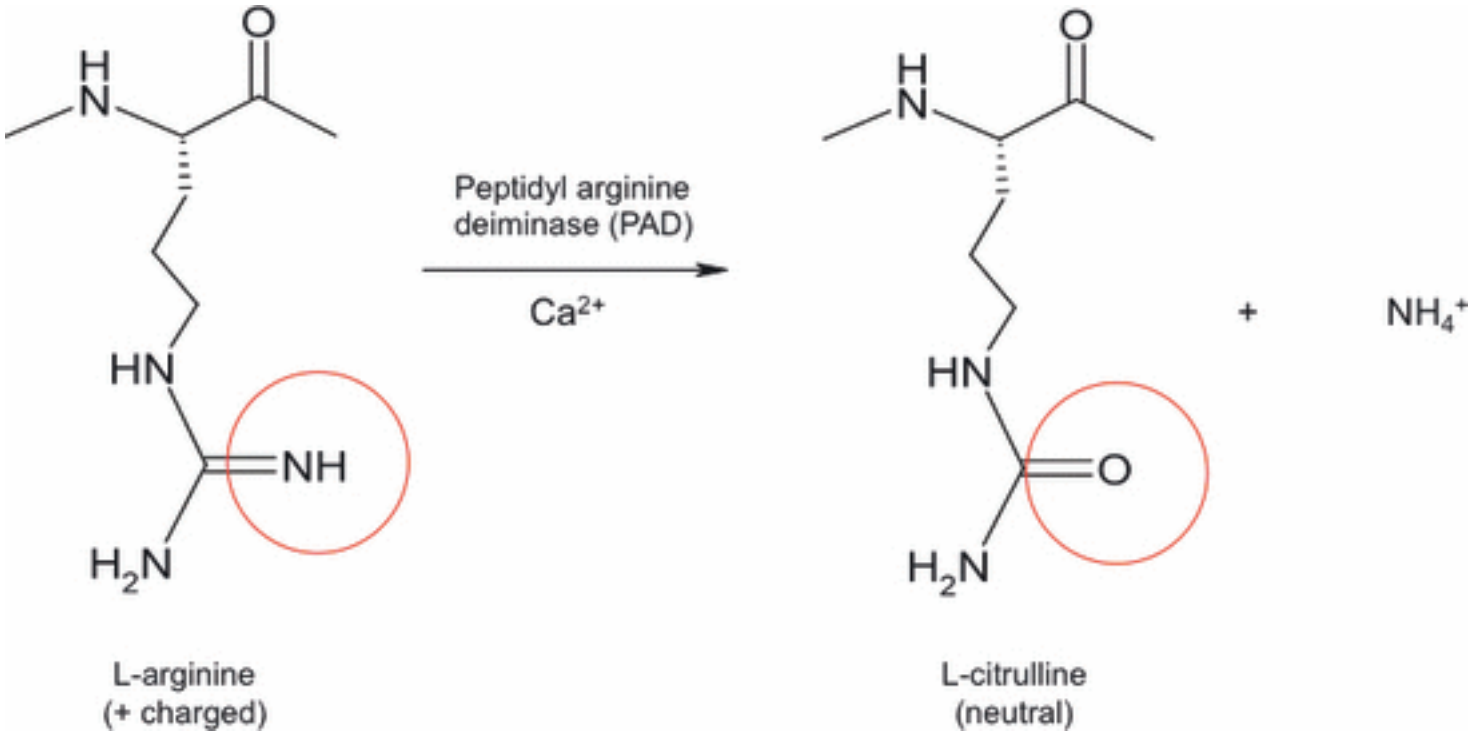
Rheumatoid arthritis

- **Epidemiology: Rheumatoid arthritis (RA) affects 1-3% of the population; highest rate in 20-40 year old women**
  - **Autoantibodies predate disease by years**
  - **Rheumatoid Factor (RF)= autoantibodies against Fc portions of self IgG**
  - **Anti CCP Ab-directed against citrulline residues (posttranslational modification of arginine)**
- **Inflammation in synovium includes: immune complexes, cellular infiltration of CD4 and CD8 T cells, macrophages, neutrophils.**
- **Strong association with HLA Class II HLA DR0401/ 0404 and 0101.**

HLA susceptibility alleles for RA have a shared epitope



Anti-citrulline antibodies



Immunological Reviews
Volume 233, Issue 1, pages 9-33, 23 DEC 2009 DOI: 10.1111/j.0105-2896.2009.00853.x
http://onlinelibrary.wiley.com/doi/10.1111/j.0105-2896.2009.00853.x/full#f2

T-B interactions are necessary for and contribute to autoimmunity

Escape of autoreactive T cells

Activation by "self"

Autoantibody production

Expansion of pathogenic lineage

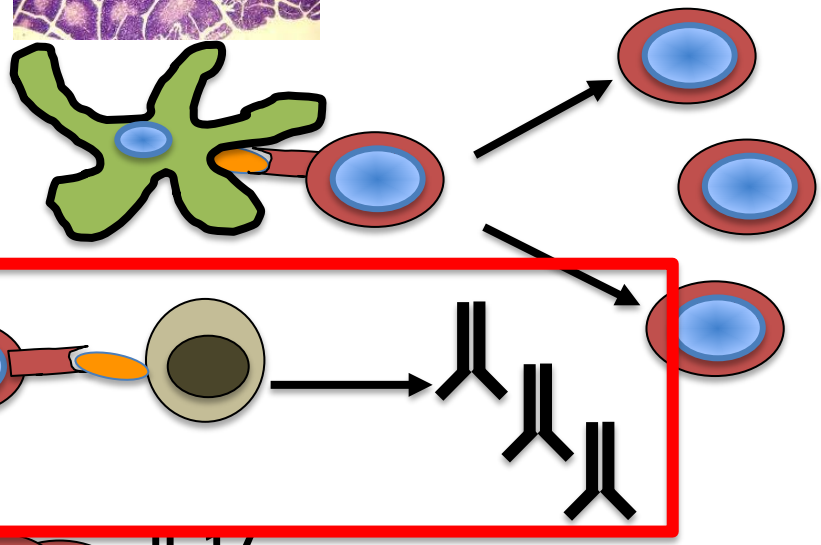
Failed regulation

Entry into target tissue

Inflammation

PERIPHERY

Thymic selection

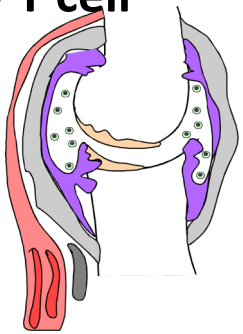


IL-17

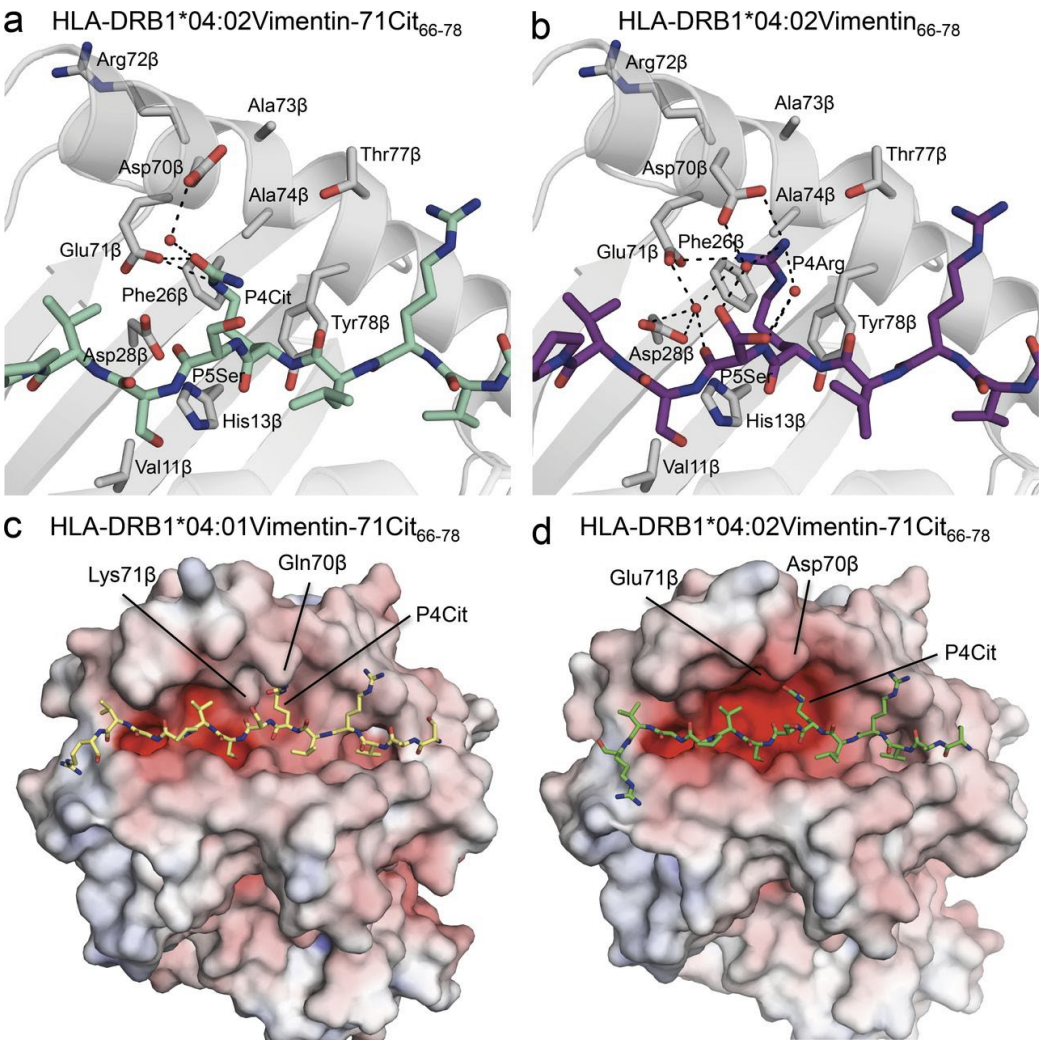
γIFN

TNFα

Regulatory T cell



Susceptibility allele accommodates citrulline with binding to SE aa 71 but not arginine.



Stephen W. Scally et al. J Exp Med 2013;210:2569-2582
JEM

Do anti-citrullinated protein Abs contribute to tissue specificity in RA?

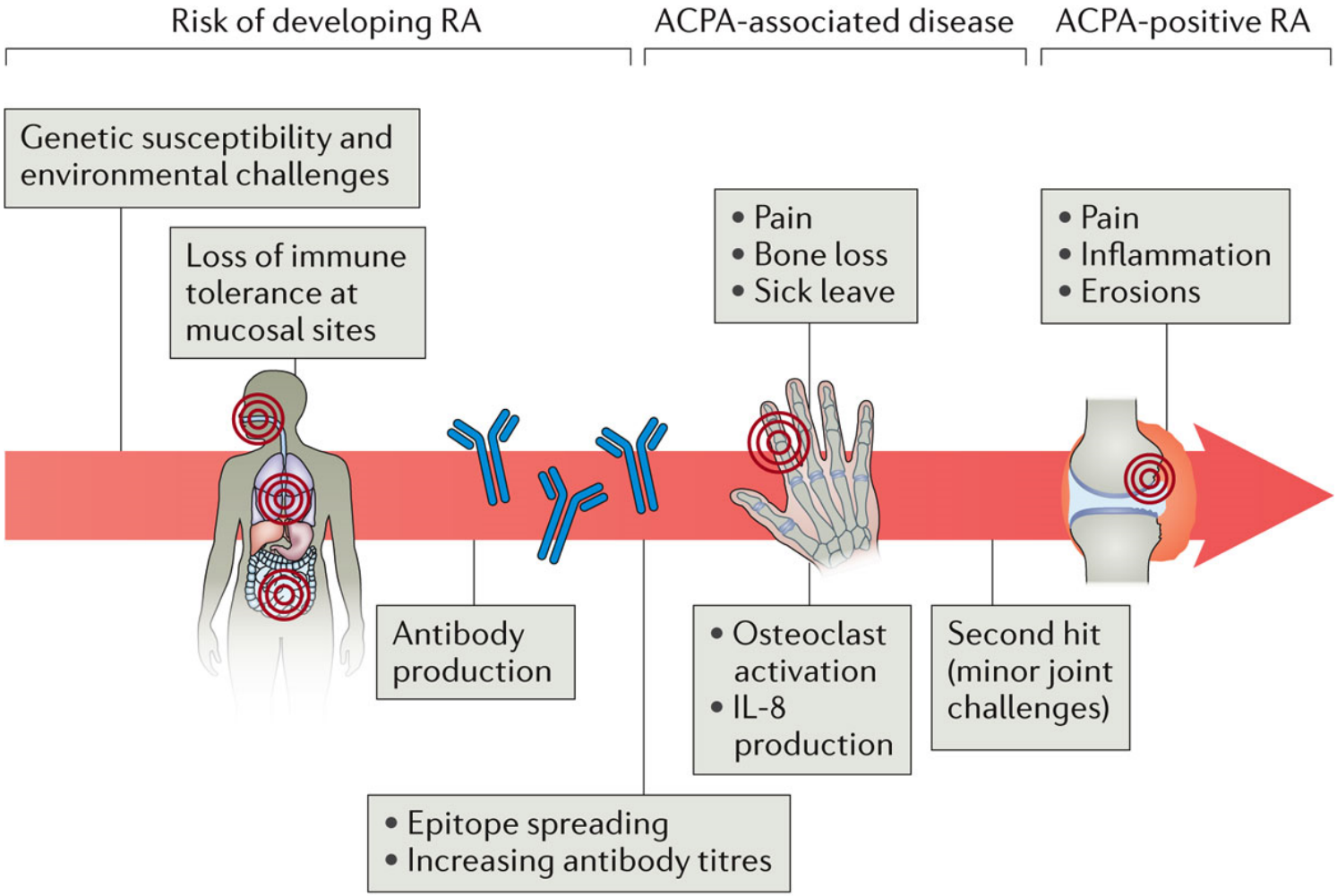
- Production of anti-citrullinated protein Abs precedes disease development by many years.
- Disease may originate outside the joint: sites of citrullination may include the lung and the gums.
- Anti-citrullinated protein Abs are much more common in smokers and smoking is the greatest environmental risk factor for RA.

Periodontal gum disease and other mucosal surfaces might precede and lead to rheumatoid arthritis

- RA related antibody prevalence correlates with prevalence of serum antibodies to *Porphyrmonas gingivalis*.
- There are bacteria in the periodontium that induce neutrophil cirullination (*Aggregatibacter actinomycetemcomitans*).
- RA-related anti-citrullinated antibodies can be found in lung fluid (bronchioalveolar lavage) prior to the development of joint disease.
- Citrullinated antigens in periodontitis are very similar to those in the RA joint.

Reviewed in Catrina et al., Rheumatology (2014) 55:391

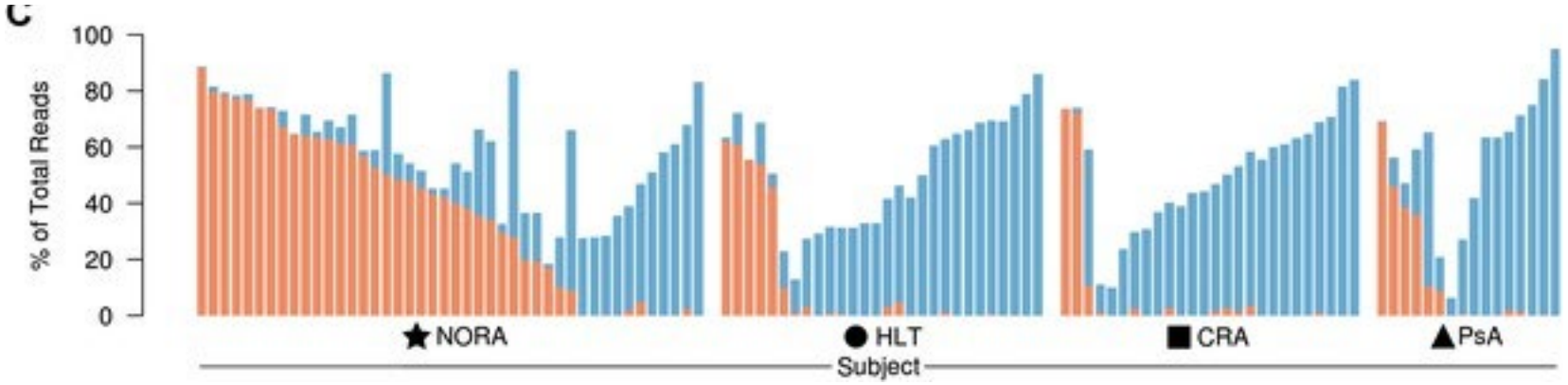
Stages in the development of seropositive rheumatoid arthritis



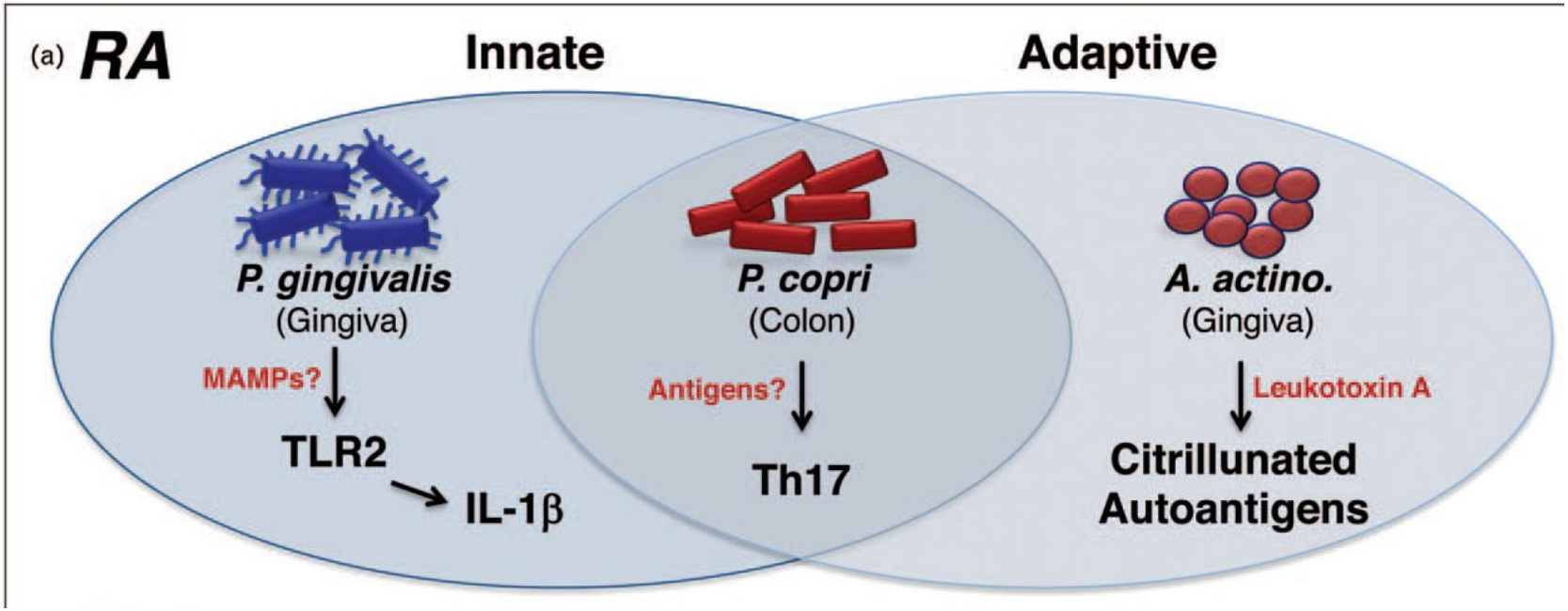
Nature Reviews | Rheumatology

Patients with new onset rheumatoid arthritis have altered gut microbiota

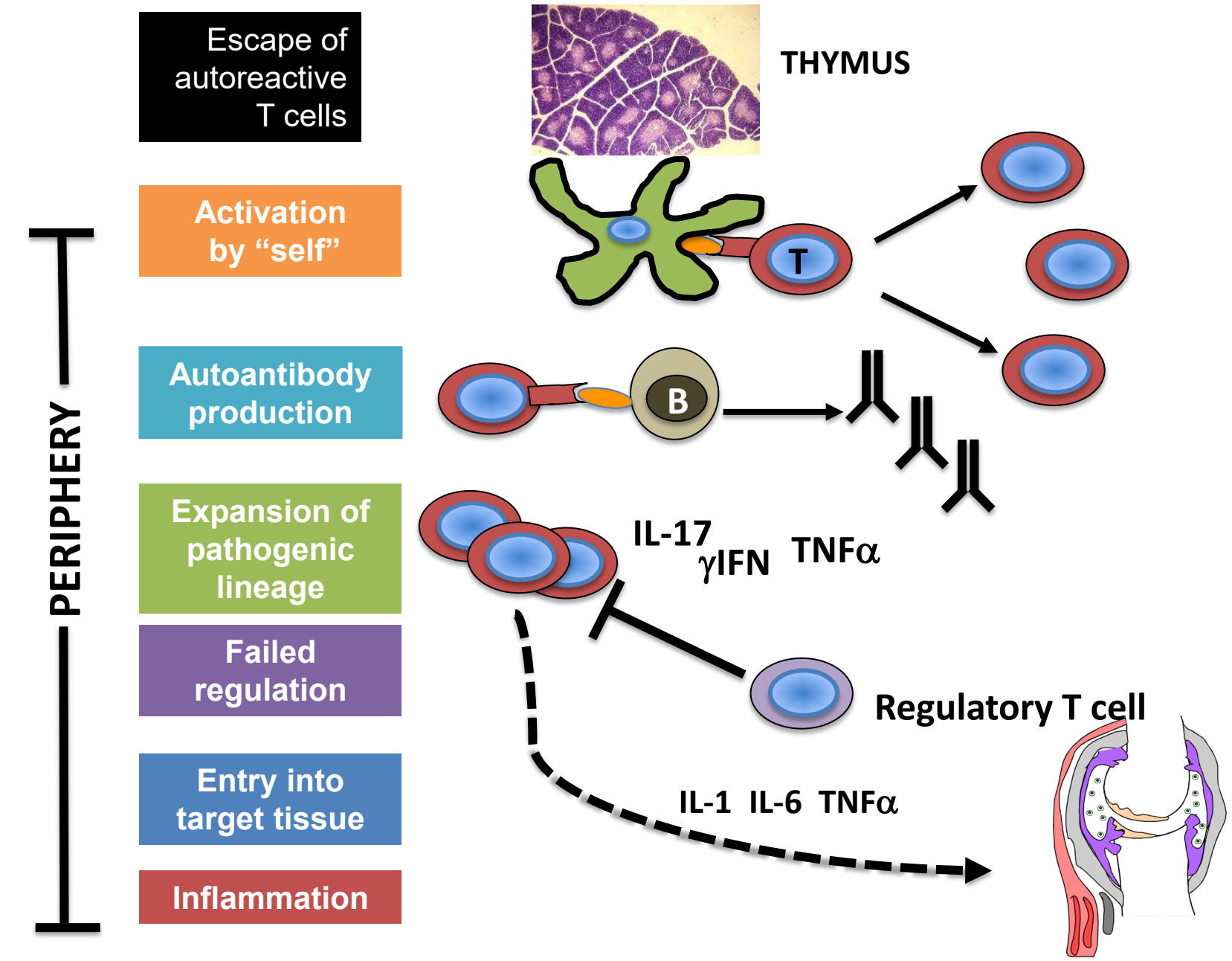
Patients with new onset rheumatoid arthritis are significantly more likely to have *Prevotella copri* in their gut microbiome.



Scher et al., eLife, 2013;2:e01202


(a) RA
Innate
Adaptive
P. gingivalis
(Gingiva)
MAMPs?
TLR2
IL-1β
P. copri
(Colon)
Antigens?
Th17
A. actino.
(Gingiva)
Leukotoxin A
Citrillunated
Autoantigens

- Autoimmunity requires failure of multiple aspects of immune tolerance: central tolerance, activation of autoreactive T cells, activation of autoreactive B cells, activation of effector pathways.
- Genetic susceptibility to autoimmunity includes HLA alleles and susceptibility loci common to multiple diseases
- Environmental effects include intercurrent infections, altered commensal microbial repertoire, nutritional effects.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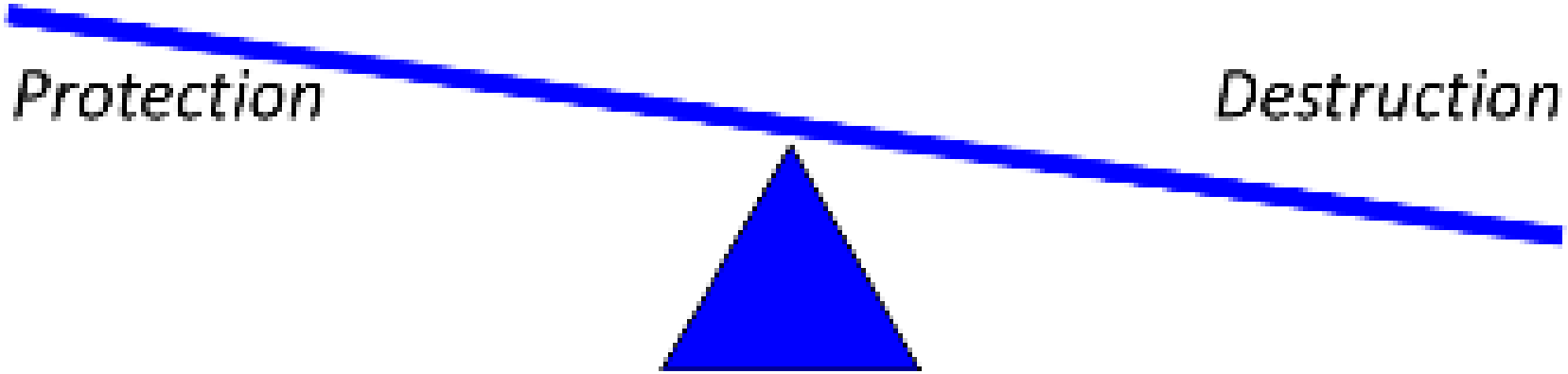
Protection
Destruction