

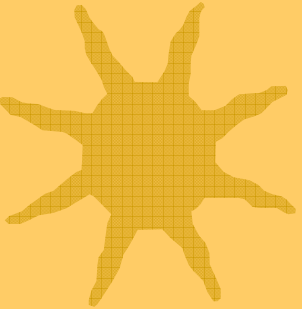
# ***Autoimmunity***

Department of Immunology  
2nd Medical Faculty  
Charles University,  
University Hospital Motol

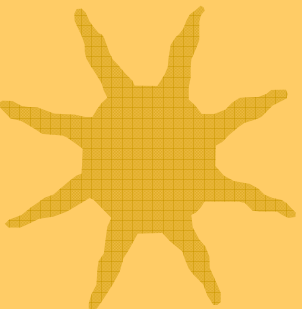


## *Autoimmunity - definition*

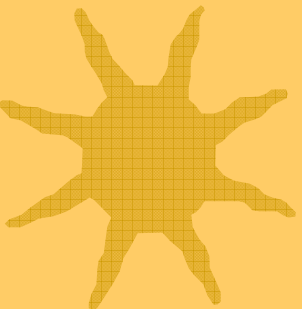
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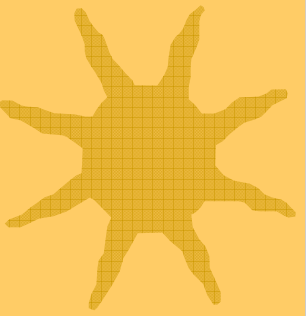
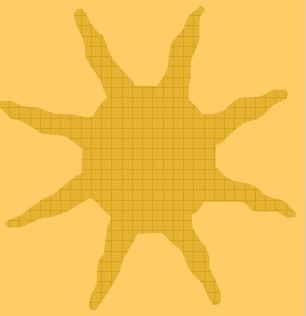
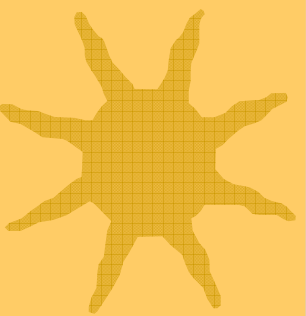
The reaction of immune system with self-antigen



*discrimination between useful/damaging*



- ➔ Autoimmunity physiology
- ➔ Autoimmunity pathology - autoimmune diseases



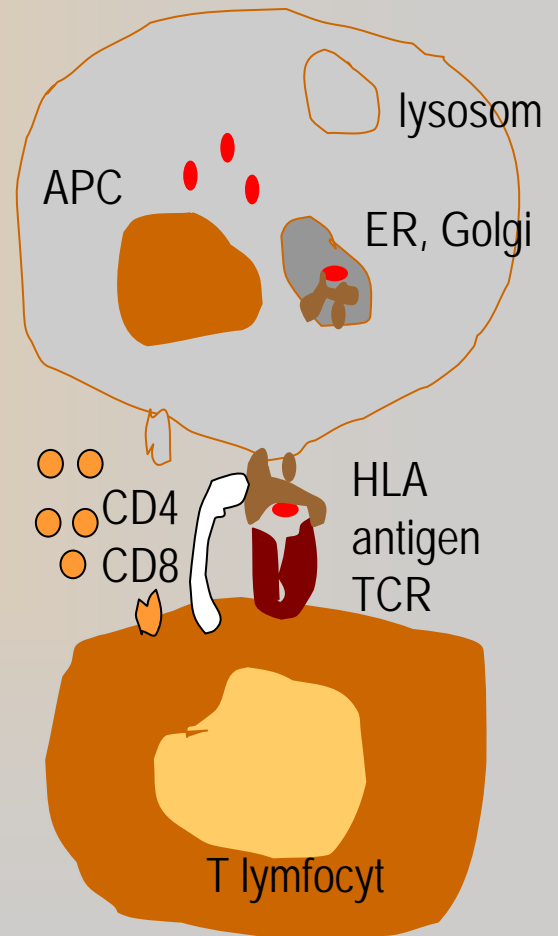
# *Central tolerance*

## ★ positive selection

- preservation of T lymphocytes binding HLA/peptid (autoantigen) with medium affinity, elimination of T lymphocytes with weak affinity to HLA/peptid

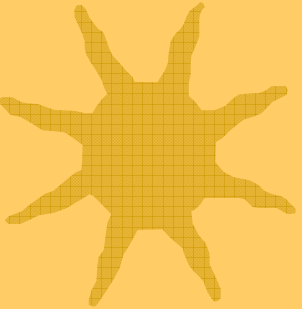
## ★ negative selection

- elimination of T lymphocytes binding HLA/peptid with strong affinity

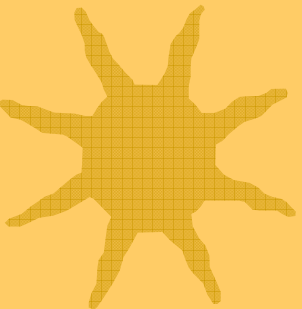




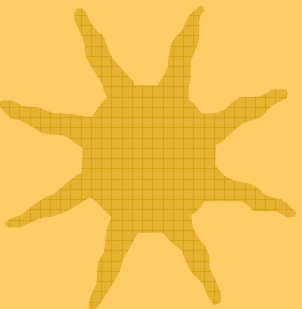
# *APS 1 – failure of negative selection in the thymus*



autoimmune polyglandular syndrome type 1 (APS1)



APECED - autoimmune polyendocrinopathy – candidiasis -  
ectodermal dystrophy



autosomal recessive

autoimmune regulator – AIRE gene

chromosom 21  
q22.3



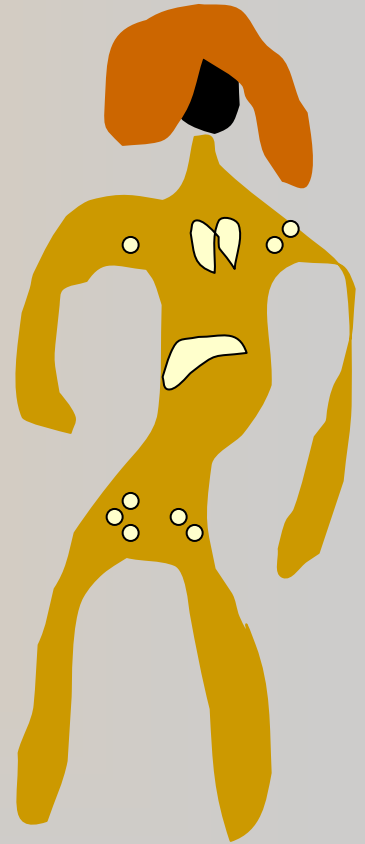


# *AIRE*

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**AIRE** protein -transcription factor

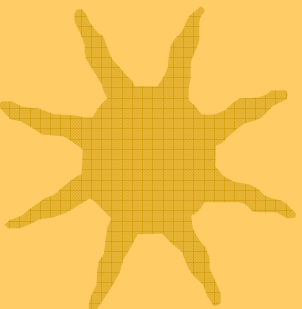
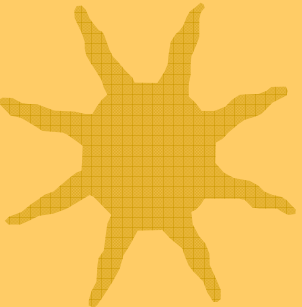
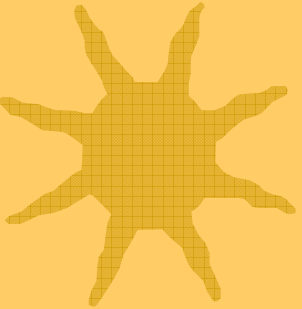
- ★ role in the immune tolerance
- ★ expressed in lymphoid organs
- ★ controls expression of important self-antigens on thymic medullary epithelial cells





## *Peripheral tolerance*

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- ★ **clonal deletion** - elimination of autoreactive clones
- ★ **clonal anergy** - functional depression (insufficient costimulation)
- ★ **clonal ignorance** - inability of recognition of autoantigen
- ★ **suppression** – suppression of autoreactive T lymphocytes by other immunocompetent cells

# *Autoimmunity and allergy X linked IPEX – deficiency of Tregs*

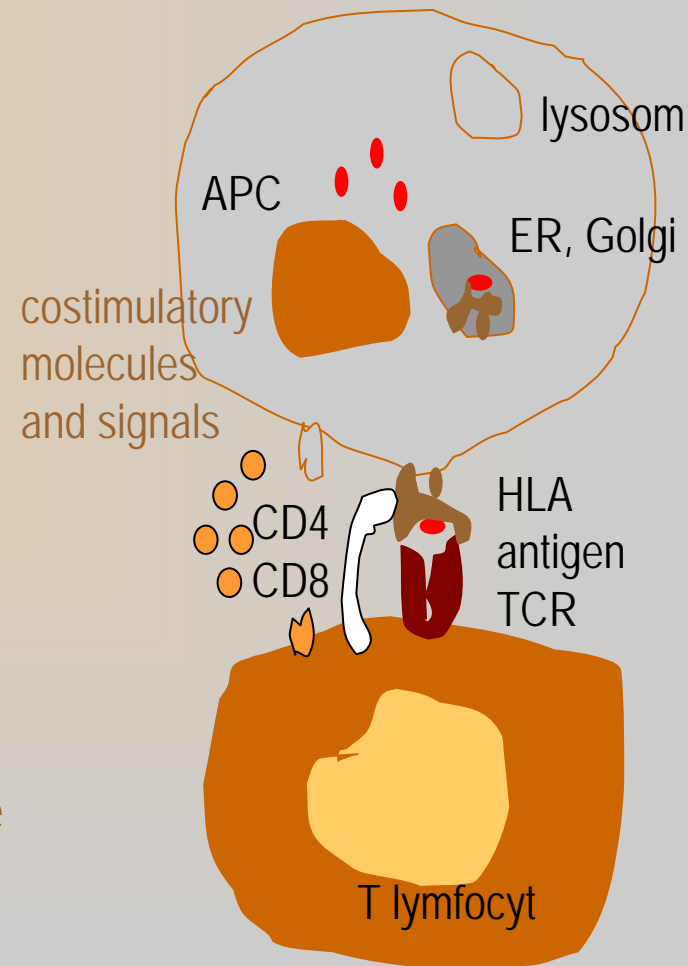
break down of tolerance

ID, polyendocrinopathy

(diabetes, thyreopathy), diarrhea,  
eczema, allergy

Scurfy gene - protein scurfin -  
transcription factor

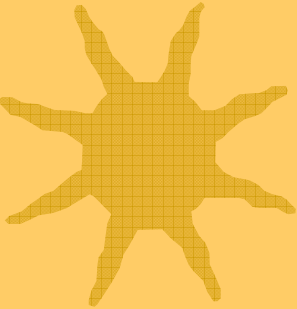
★ Due to deficiency of FoxP3 gene





# *Autoimmunune lymphoproliferative syndrome* *- ALPS, Canale-Smith syndrome*

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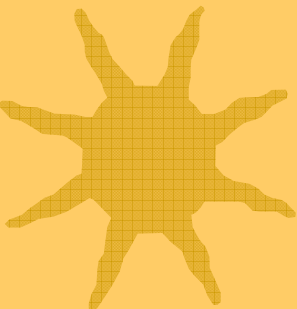


lymphoproliferation

splenomegaly

double negative TCR  $\alpha/\beta$ , CD4 CD8 lymphocytes

associated clinical picture

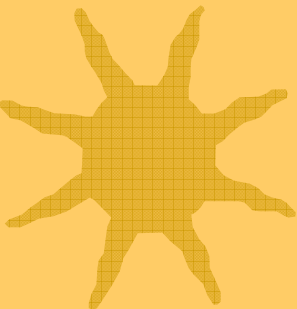


★ deficient apoptosis

deficit Fas (CD95/Apo1)

deficit Fas L

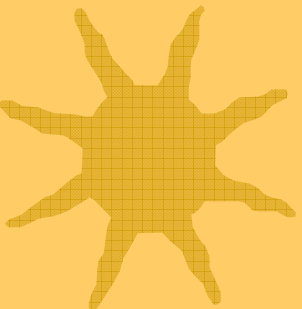
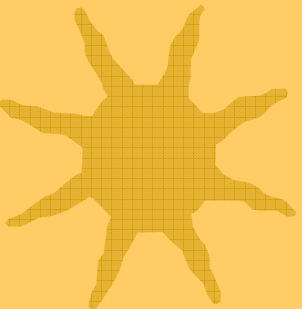
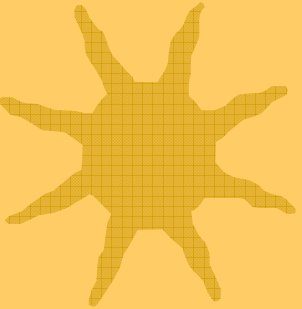
deficit in other apoptotic pathways





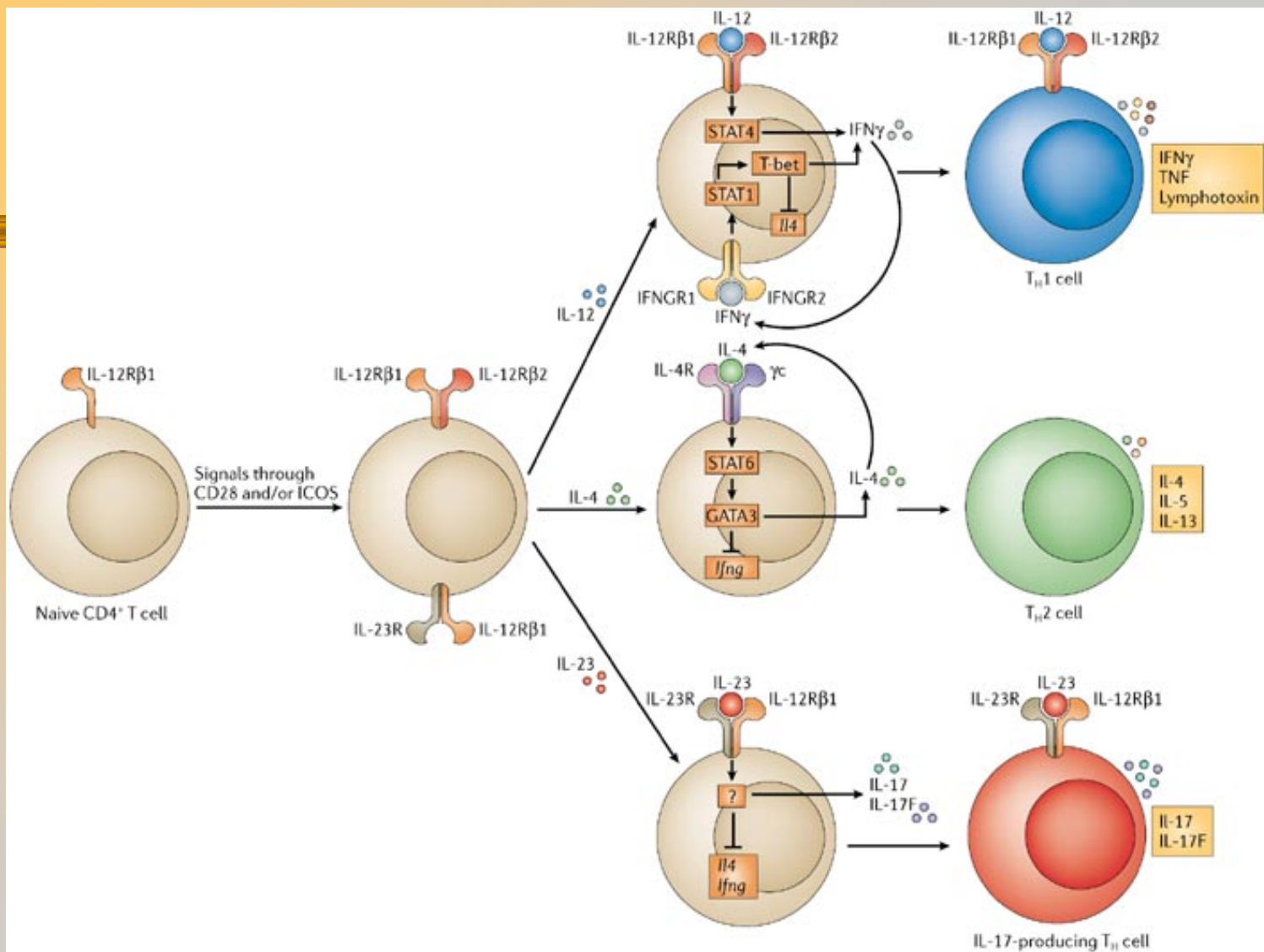
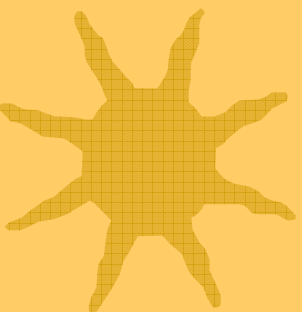
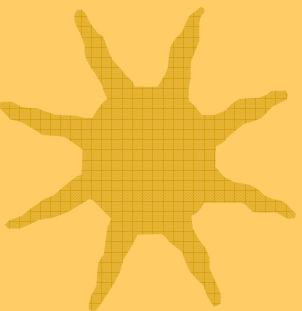
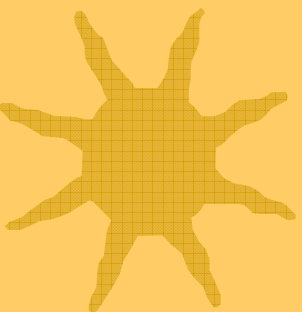


# ***Pathogenesis***



## CD4<sup>+</sup> T cells

- ★ A number of animal models of autoimmune disease are inhibited by treatment with anti-CD4 mAbs (collagen induced arthritis [CIA], EAE, Type I diabetes in NOD mice, nephritis in MRL lupus prone mice)
- ★ CD4<sup>+</sup> T cells isolated from autoimmune donors can adoptively transfer disease to normal recipients
- ★ Activation of Th1 cells,  $\gamma$ -TNF- $\alpha$ , IFN- $\gamma$ , IL-12, activation of macrophages (CIA, EAE, IBD in SCID mice, diabetes in NOD mice)





# ***Animal models***

## **Insulin dependent diabetes mellitus**

Spontaneous: NOD mouse, BB rat

Induced: Rat insulin promoter transgenics, thymectomy and sublethal irradiation in rats

## **Arthritis**

Induced: Collagen induced arthritis in rats and mice, adjuvant arthritis in mice

## **Systemic lupus erythematosus (glomerular nephritis)**

Spontaneous: NZBxNAW F1, NZBxSWR F1, MRL1pr

Induced: Mercuric chloride in BN rats

## **Autoimmune thyroiditis**

Spontaneous: Obese strain chickens

Induced: Experimental autoimmune thyroiditis in mice

## **Alkylosing spondylitis**

Induced: HLA-B27 transgenic rats

## **Inflammatory bowel disease**

Spontaneous: IL-2, IL-10, TCR- $\alpha$  chain knock-out mice, SCID mice restored with CD4<sup>+</sup> Tcell subsets

Induced: Haptenated colonic proteins in mice, proteoglycans in Lewis rats

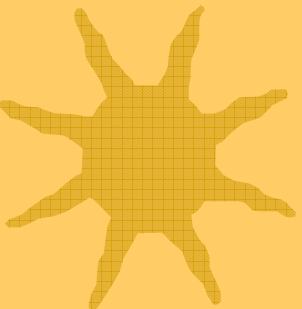
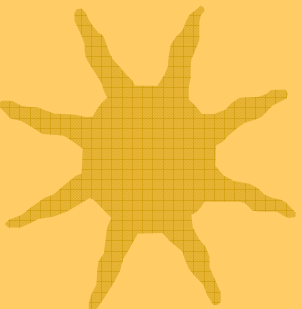
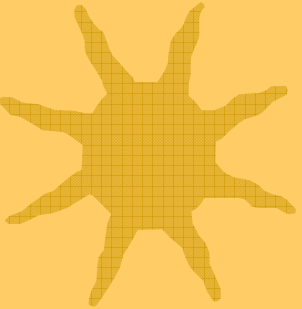
## **Multiple sclerosis**

Induced: experimental allergic encephalomyelitis in a variety of laboratory animals



## ***Pathogenesis 2***

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- type II. by Coombs and Gel: cytotoxic immune reaction
  1. damage of tissue
  2. functional impact (stimulation, inhibition, neutralization)
- type III. by Coombs and Gel: immune complex
- type IV. by Coombs and Gel

## Autoimmune diseases classified by mechanism of tissue damage

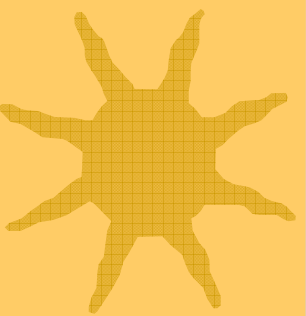
Some common autoimmune diseases classified by immunopathogenic mechanism		
Syndrome	Autoantigen	Consequence
<b>Type II antibody against cell-surface or matrix antigens</b>		
Autoimmune hemolytic anemia	Rh blood group antigens, I antigen	Destruction of red blood cells by complement and FcR <sup>+</sup> phagocytes, anemia
Autoimmune thrombocytopenic purpura	Platelet integrin GpIb:IIIa	Abnormal bleeding
Goodpasture's syndrome	Noncollagenous domain of basement membrane collagen type IV	Glomerulonephritis, pulmonary hemorrhage
Pemphigus vulgaris	Epidermal cadherin	Blistering of skin
Acute rheumatic fever	Streptococcal cell-wall antigens. Antibodies cross-react with cardiac muscle	Arthritis, myocarditis, late scarring of heart valves
<b>Type III immune-complex disease</b>		
Mixed essential cryoglobulinemia	Rheumatoid factor IgG complexes (with or without hepatitis C antigens)	Systemic vasculitis
Systemic lupus erythematosus	DNA, histones, ribosomes, snRNP, scRNP	Glomerulonephritis, vasculitis, rash
Rheumatoid arthritis	Rheumatoid factor IgG complexes	Arthritis
<b>Type IV T cell-mediated disease</b>		
Insulin-dependent diabetes mellitus	Pancreatic $\beta$ -cell antigen	$\beta$ -cell destruction
Rheumatoid arthritis	Unknown synovial joint antigen	Joint inflammation and destruction
Experimental autoimmune encephalomyelitis (EAE), multiple sclerosis	Myelin basic protein, proteolipid protein, myelin oligodendrocyte glycoprotein	Brain invasion by CD4 T cells, weakness

Figure 13-27 Immunobiology, 6/e. (© Garland Science 2005)

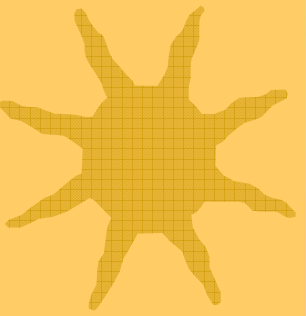


# *Incidence of autoimmune diseases*

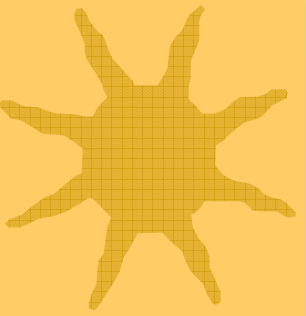
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- ★ RA 1-3%
- ★ Sjögren's sy 1/20 000
- ★ Vasculitis 1/100 000



- ★ Prevalence of autoimmune diseases



**5-7% of population**



# *Factors influencing autoimmune disease*

---

## Internal triggering factors

- ★ genotype / HLA
- ★ cytokines
- ★ apoptosis genes
- ★ ID (IgA, CID, CVID, WA, C1,2,4),
- ★ hormones

## External triggering factors

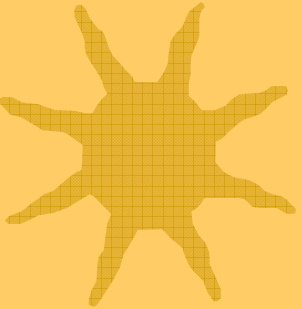
- ★ infections
- ★ UV
- ★ drugs
- ★ chemicals (including food)
- ★ stress



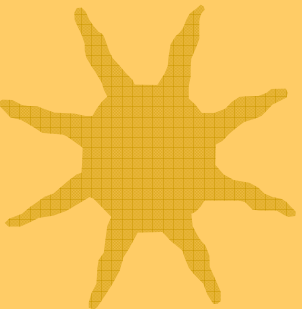


## *Genes associated with autoimmunity*

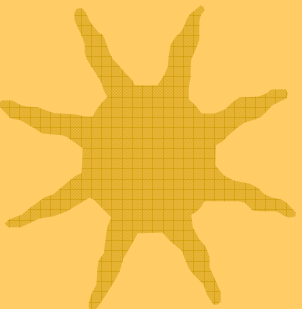
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★ HLA



★ non-HLA genes



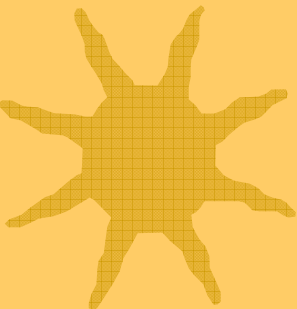
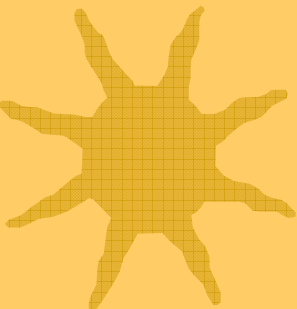
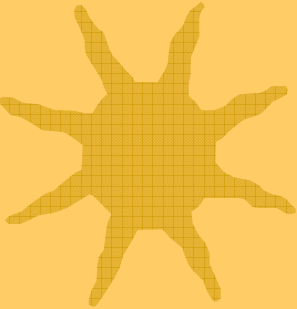
★ cytokines genes polymorphism (CTLA 4)

★ APECED





## *Many autoimmune diseases are associated with certain HLA types and with gender*

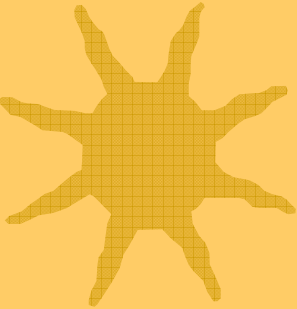


Associations of HLA serotype with susceptibility to autoimmune disease			
Disease	HLA allele	Relative risk	Sex ratio (♀:♂)
Ankylosing spondylitis	B27	87.4	0.3
Acute anterior uveitis	B27	10	<0.5
Goodpasture's syndrome	DR2	15.9	~1
Multiple sclerosis	DR2	4.8	10
Graves' disease	DR3	3.7	4-5
Myasthenia gravis	DR3	2.5	~1
Systemic lupus erythematosus	DR3	5.8	10-20
Type I insulin-dependent diabetes mellitus	DR3/DR4 heterozygote	~25	~1
Rheumatoid arthritis	DR4	4.2	3
Pemphigus vulgaris	DR4	14.4	~1
Hashimoto's thyroiditis	DR5	3.2	4-5

Figure 13-20 Immunobiology, 6/e. (© Garland Science 2005)

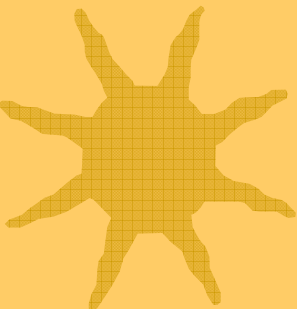


# *Autoimmune disease - genetic factors*



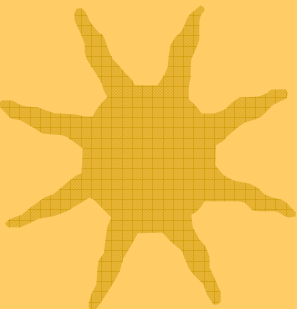
## **Increased sibling risk in:**

		MHC, susceptibility allele
Rheumatoid arthritis	8	DR1 DR4
Type 1 diabetes	15	DR3 DR4
Ankylosing spondylitis	54	B-27
Multiple sclerosis	20	
Ulcerative colitis	12	
SLE	20	
Crohn's disease	20	



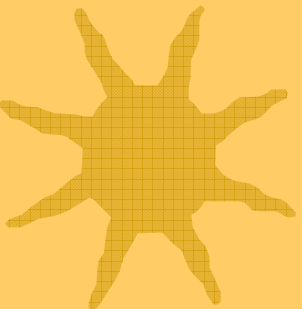
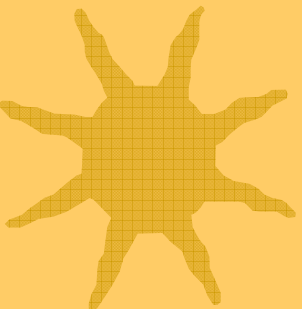
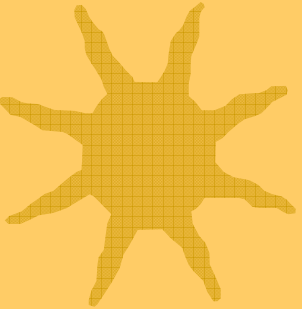
## **Major genetic loci in a number of autoimmune diseases are the MHC genes**

Class I and Class II	Antigen presentation (RA, diabetes)
Complement	SLE
TNF	IBD





# *Genetic factors*

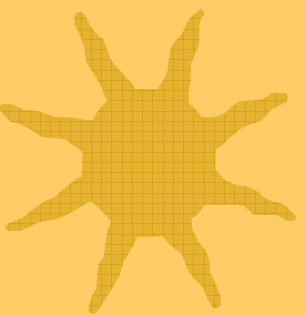


- ★ Non MHC loci
  - 13 mapped genes-NOD mouse
  - 18 mapped genes in human Type 1 diabetes (genome wide scan)
- ★ IDDM-2 Allelic variation of a minisatellite tandem repeat in the regulatory region of the insulin gene <expression of insulin in the thymus of susceptible individuals
- ★ Idd-3 Maps to IL-2, allelic variation in coding region of IL-2
- ★ MRL 1pr/pr: Mutation in the Fas gene leading to impaired apoptosis
- ★ The same loci have been mapped in a number of different autoimmune diseases probably reflecting key immune regulatory genes



# ***Autoimmune disease*** ***- escape from immunological tolerance***

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## **1. Infection**

Evidence that infection may be involved in development of autoimmunity:

Disease occurrence in clusters

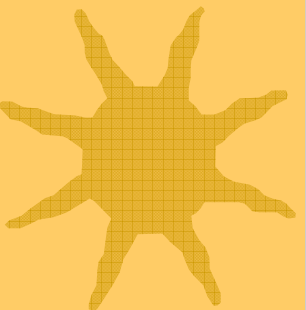
Discordance in identical twins

Immune pathology associated with many infectious diseases looks like autoimmune disease

Lyme disease

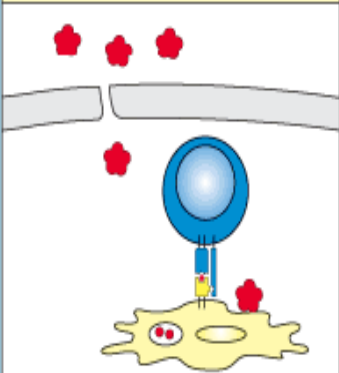
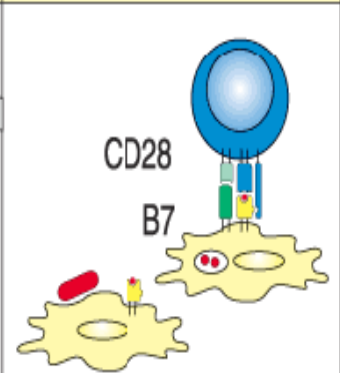
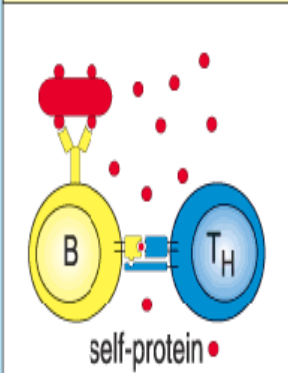
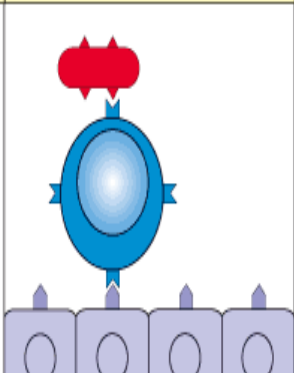
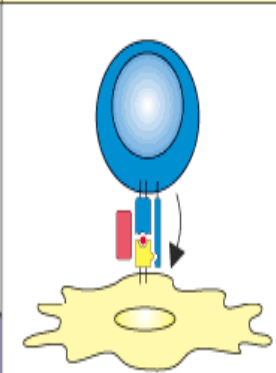
*Borrelia burgdorferi*

Late phase is accompanied by skin lesions like scleroderma and inflammation in the joints like arthritis



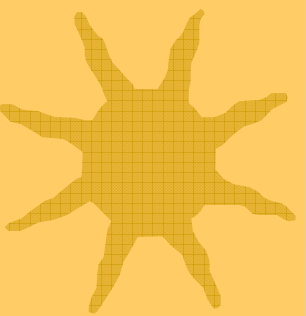


## How could infection work?

<b>Mechanism</b>	Disruption of cell or tissue barrier	Infection of antigen-presenting cell	<b>Mechanism</b>	Binding of pathogen to self protein	Molecular mimicry	Superantigen
<b>Effect</b>	Release of sequestered self antigen; activation of nontolerized cells	Induction of co-stimulatory activity on antigen-presenting cells	<b>Effect</b>	Pathogen acts as carrier to allow anti-self response	Production of cross-reactive antibodies or T cells	Polyclonal activation of autoreactive T cells
<b>Example</b>	Sympathetic ophthalmia	Effect of adjuvants in induction of EAE	<b>Example</b>	? Interstitial nephritis	Rheumatic fever ? Diabetes ? Multiple sclerosis	? Rheumatoid arthritis
						



How could infection work?



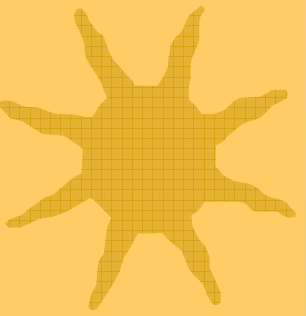
### A. Disruption of tolerance

- Smoking can trigger Goodpasture's syndrome

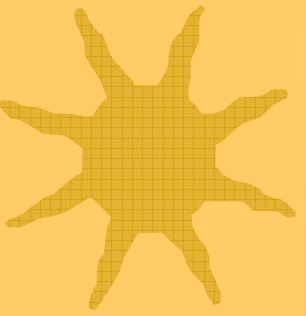
Alveolar basement membrane normally not exposed to immune system

Smoking damages alveoli, exposes collagen

Anti-collagen Ag damages lung and kidney



- Anti-sperm Ab produced in some men after vasectomy
- Injection of myelin basic protein (MBP) produces MS-like EAE in mice

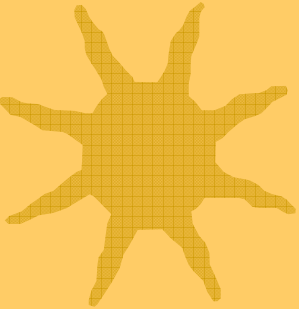


- May be triggered by injury or infection



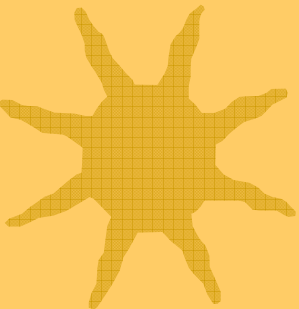
## B. Immune stimulation

- ❖ Inappropriate MHC II expression
- ❖ High level of APCs with "second signal" breaks anergy
- ❖ Activation of T and B responses to self Ag



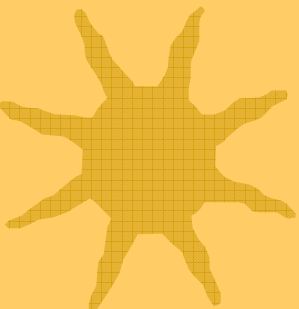
## C. Superantigen

- ★ Several infectious agents (ie. Mouse mammary tumour virus) contain antigens with the ability to polyclonally activate a subset of CD4<sup>+</sup> T cells bearing particular V $\beta$  TCR families
  - Hypothesis is that this may activate autoreactive cells
  - If this were true, we would expect to see > of certain V $\beta$  in autoimmune lesions
  - Isolated reports in rheumatoid arthritis and diabetes
  - No strong evidence



## D. Cross reaction

- ★ Cross reaction of peptide present in micro-organism with self peptide present in the host
  - Coxsackie virus peptide contains homology to a T cell epitope in GAD which is recognised by a subset of patients with type I diabetes

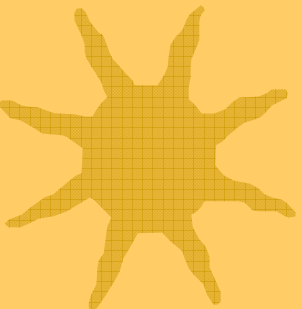
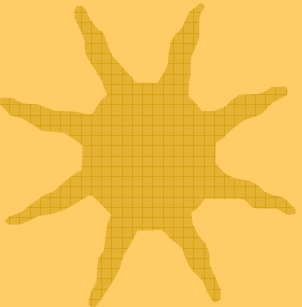
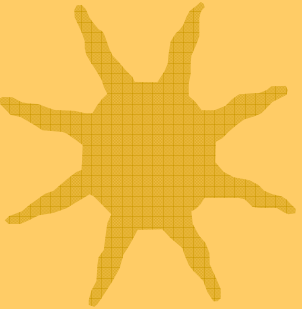




# *UV radiation*

- ★ (Modification of autoantigens)
- ★ failure of control of suppression of autoreactive T lymphocytes

*TLI (high doses 42,5 Gy a frakcionované 17x2,5) - induction of organ-specific autoimmune diseases in mice – prevention by adoptive transfer of CD4+ lymphocytes*







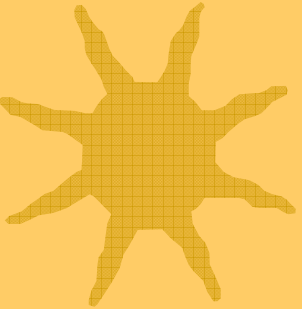
# *Drugs and foods*

- ★ **gluten – celiac disease**
- ★ cow milk - diabetes type I.?
- ★ L-tryptofan, oil - eosinofil fasciitis
- ★ L-canavanin - SLE
- ★ aromatic amines (hydrazines) - SLE
- ★ saturated fats – diferent AI diseases (radicals of oxygen)
- ★ **beta-blocators, hydantoins**
- ★ **Prokainamid** (inhibition of DNA metyl-transferase)
- ★ **D- penicilamin, hydralazin, oral contraceptives, isonizaid** (acetylation)  
induction of autoantibodies (ds- DNA, histony, cardiolipin)
- ★ N-nitroso-compound (diabetes type I.)
- ★ SiO<sub>2</sub> (silicosis, vasculitis, SLE, sclerodermia, RA, D-PM, glomerulonefritis)
- ★ silicone´s polymers (sclerodermia, SLE, RA)



# *Diagnosis*

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clinical picture

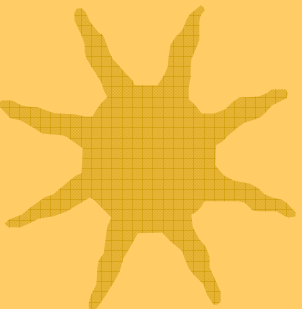
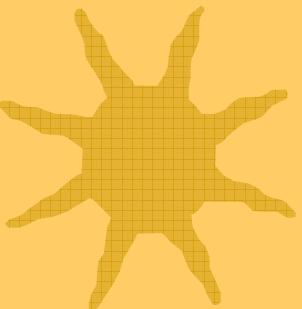
laboratory

autoantibodies

autoreactive lymphocytes

autoantigens

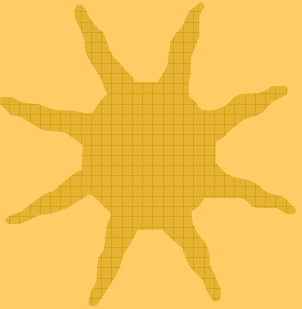
related genes



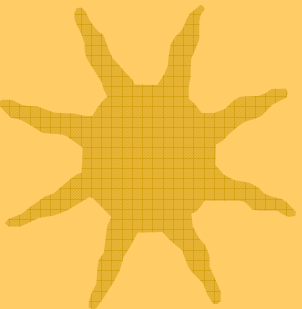


## *Mozaic of autoimmunity*

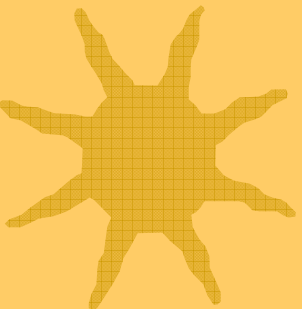
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★ break down of autotolerance



★ „normal“ immune reaction against autoantigens



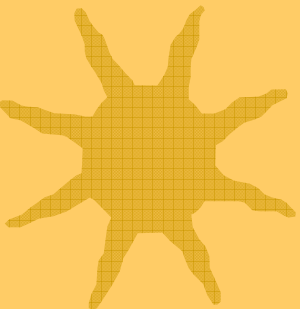
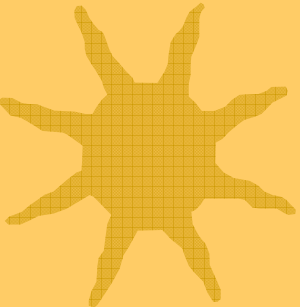
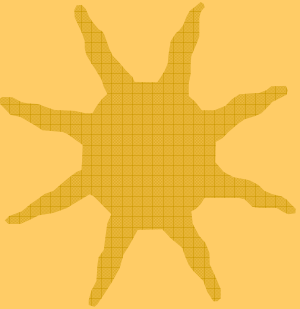
★ redundancy of mechanisms involved in tolerance

★ combination of influencing factors



# *Systemic autoimmune diseases*

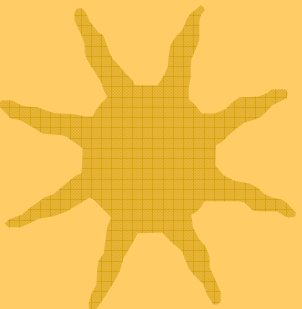
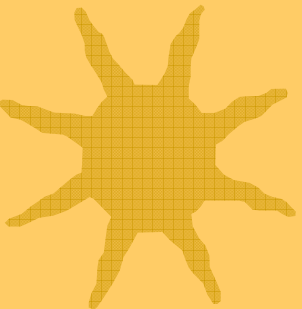
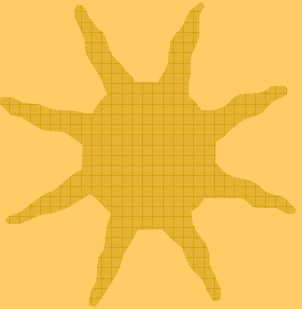
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- SLE
- Dermatomyositis
- Skleroderma
- Sjögren's syndrome
- Vasculitis
- Rheumatoid arthritis
- MCTD – mixed connective tissue disease
- Antiphospholipide syndrom
- Sarcoidosis



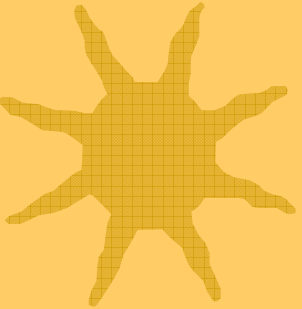
# *SLE*



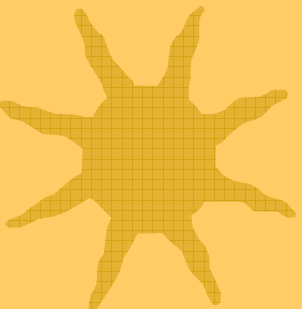
- 
- ★ “ A multisystem disease characterised by autoantibodies directed against nuclear components”
  - ★ Incidence 1:4000
  - ★ Complex multifactorial etiology
  - ★ Relapsing and remitting
  - ★ Clinical and serological diversity



# *SLE*



American College of Rheumatology criteria (4/11)



Arthralgia

Neurological abn

Oral ulcers

Haematological abn

Serositis

Renal disease

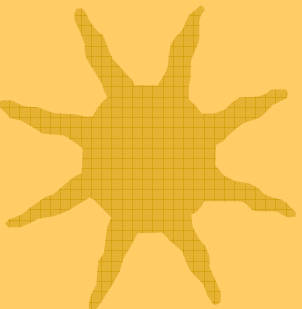
Malar rash

Anti-nuclear factor

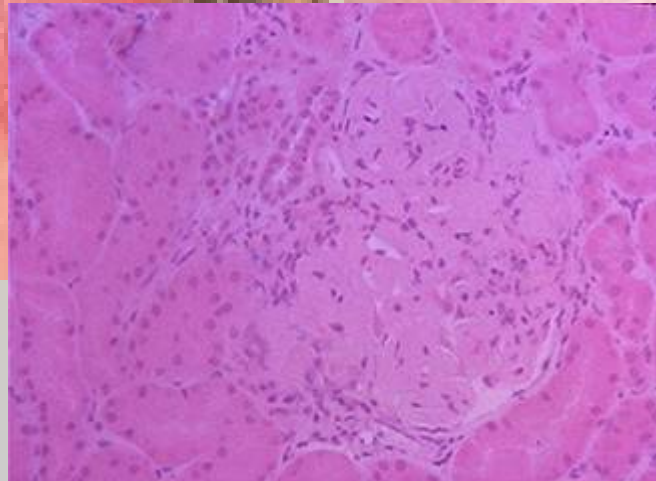
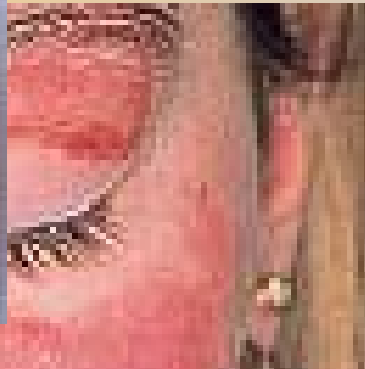
Discoid rash

Immunological abn

Photosensitivity

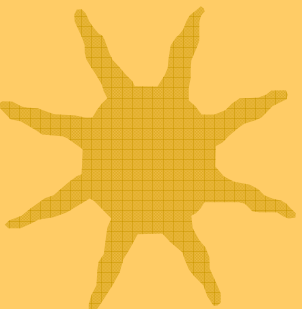
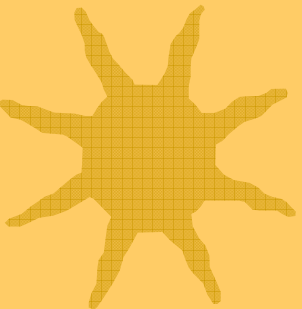
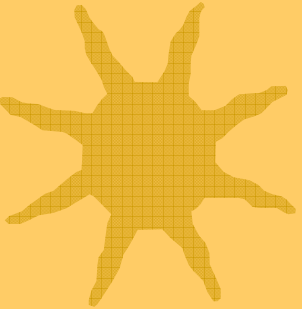


# *Clinical features of SLE*

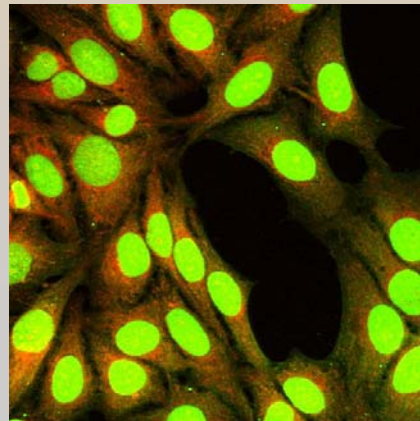




## *Autoantibodies in SLE*



- ★ ANA (prevalence ~ 100%)
- ★ anti – dsDNA (prevalence 40-90%, levels fluctuate with disease activity)
- ★ ENA (anti – Sm)
- ★ antoantibodies against blood cells

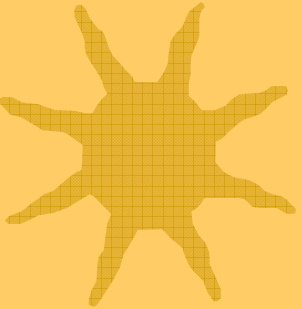




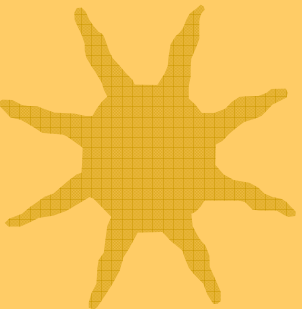


# *Sjögren's syndrom*

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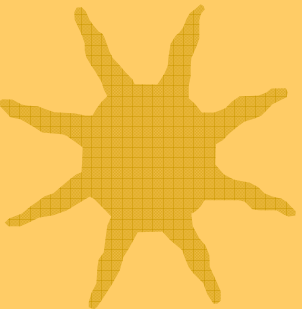


★ Sicca syndrom – dryness of eyes, nose, mouth, airways, vagina, skin



★ polyarthralgia

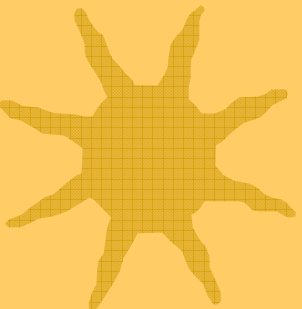
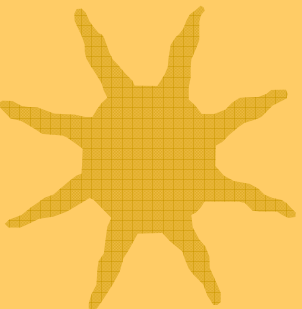
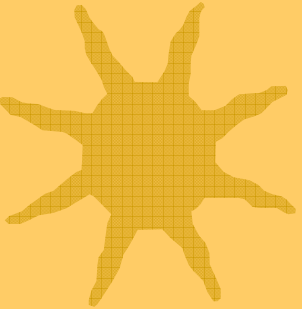
- autoantibodies: ENA - SS-A  
- SS-B



risk of AV block in newborns



# *Dermatomyositis*

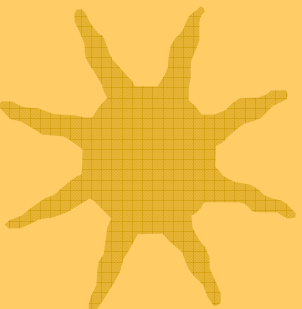
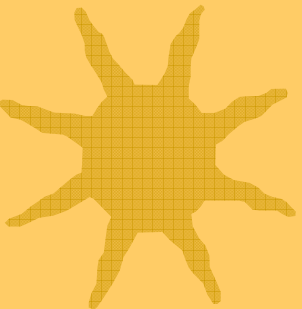
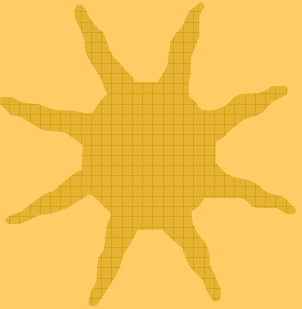


- proximal muscle weakness
- arthralgia, arthritis, dyspnea, dysphagia, arrhythmia, and dysphonia
- paraneoplastic manifestation: breast ca, ca GIT, lung ca
- autoantibodies: ENA – Jo1, PM/Scl





# *Systemic sclerosis*



- ★ Systemic connective tissue disease
- ★ Essential vasomotor disturbances; fibrosis; subsequent atrophy of the skin, subcutaneous tissue, muscles, and internal organs
- ★ Raynaud's phenomenon
- ★ Major features include centrally located skin sclerosis that affects the arms, face, and/or neck.
- ★ Minor features include sclerodactyly, erosions, atrophie of the fingertips, and bilateral lung fibrosis.
- ★ SSc is diagnosed when a patient has 1 major and 2 minor criteria.



# *Systemic sclerosis*

- autoantibodies: ANA  
ENA (anti-topoisomerase I - Scl-70)  
anti-centromerane (ACA)



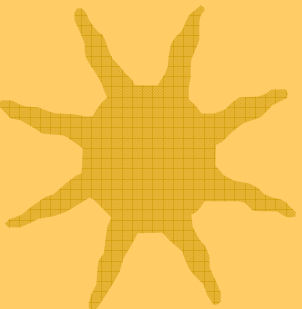
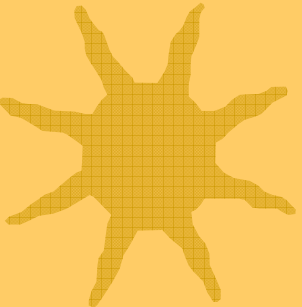
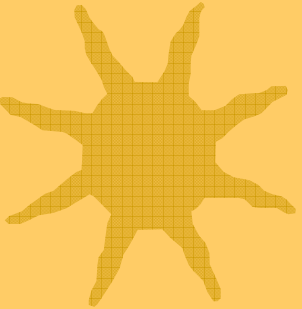


# *Antiphospholipid syndrome*

- ★ excessive clotting of blood and/or certain complications of pregnancy

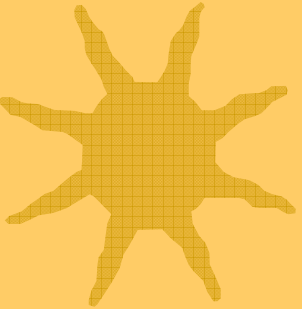
→  
trombosis  
abortus

- ★ presence of antiphospholipid antibodies (cardiolipin - ACLA or lupus anticoagulant antibodies)
- ★ prolonged APTT
- ★ in over half of patients with SLE



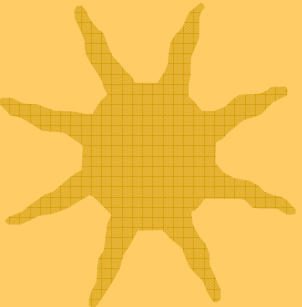


# *Vasculitis*



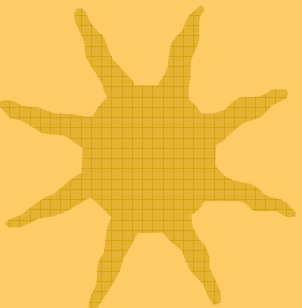
## ★ **Large vessel**

- Takayasu
- Giant cell (temporal) arteriitis



## ★ **Medium and small vessel**

- Polyarteritis nodosa
- Churg-Strauss arteritis



## ★ **Small vessel**

- Kawasaki disease
- Henoch-Schönlein purpura
- Wegener's granulomatosis

★ IK deposits

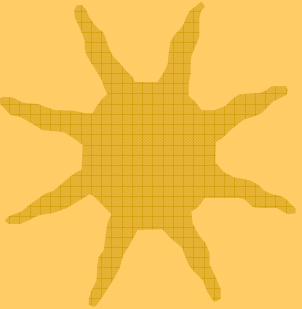
★ autoantibodies: ANCA



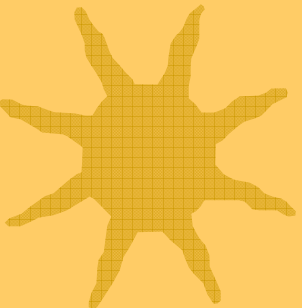
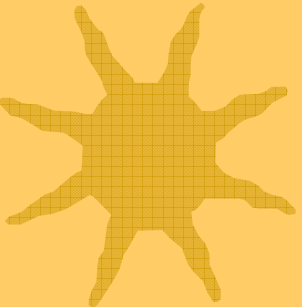
# *Autoimmune systemic diseases*

## *- characteristic autoantibodies*

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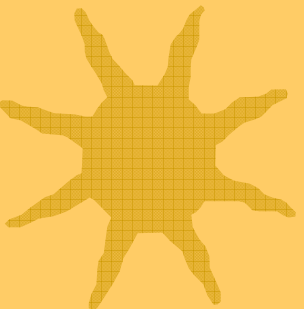
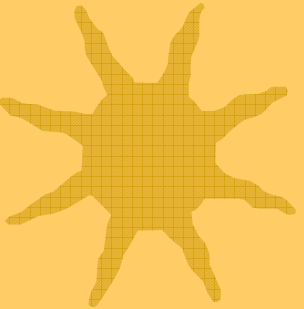
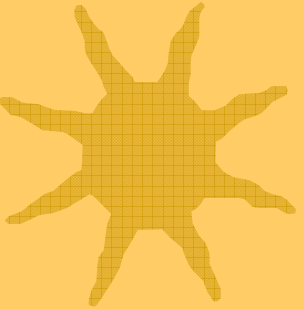


★ SLE	ANA, dsDNA
★ Rheumatoid arthritis	RF
★ Dermato/polymyositis	ENA Jo-1
★ Sjögren´s syndrome	ENA SS-A, SS-B
★ Sklerodermia	ENA Scl 70
★ MCTD	ENA RNP
★ Antiphospholip. syndrome	anti-phospholipides
★ Vasculitides	ANCA





# *Organ-specific autoimmune diseases*



## **Endocrine system**

- Autoimmune (Hashimoto's) thyroiditis
- Hyperthyroidism (Graves' disease; thyrotoxicosis)
- Type I diabetes mellitus (insulin-dependent or juvenile diabetes)
- Insulin-resistant diabetes
- Autoimmune adrenal insufficiency (Addison's disease)
- Autoimmune oophoritis

## **Hematopoietic system**

- Autoimmune haemolytic anemia
- Paroxysmal cold hemoglobinuria
- Autoimmune thrombocytopenia
- Autoimmune neutropenia
- Pernicious anemia
- Pure red cell anemia

## **Neuromuscular system**

- Myasthenia gravis
- Autoimmune polyneuritis
- Multiple sclerosis
- Experimental allergic encephalomyelitis

## **Skin**

- Pemphigus and other bullous diseases

## **Cardiopulmonary System**

- Rheumatic carditis
- Goodpasture's syndrome
- Postcardiotomy syndrome (Dressler's syndrome)

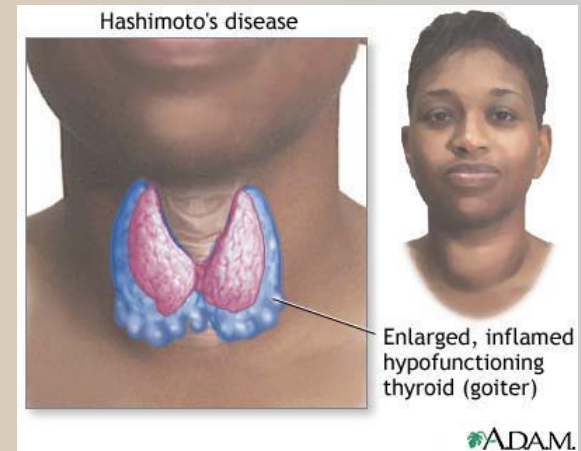




# *Autoimmune diseases of thyreoid*

## 1. Hashimoto's thyreoiditis

- hypofunction of thyreoid
- autoantibodies against thyreoglobulin and microsomes of thyreocytes



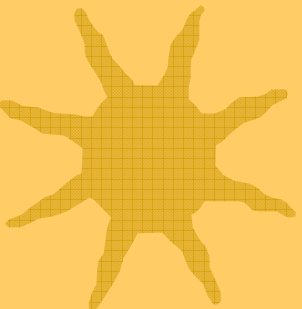
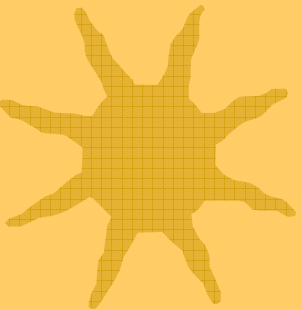
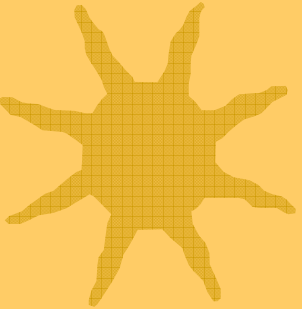
## 2. Graves-Basedow's disease

- hyperfunction of thyreoid, thyreotoxicosis
- autoantibodies against TSH receptor

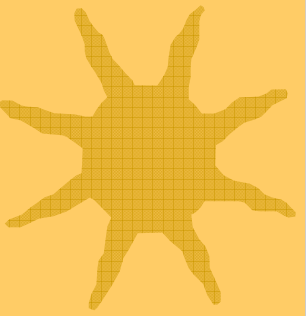
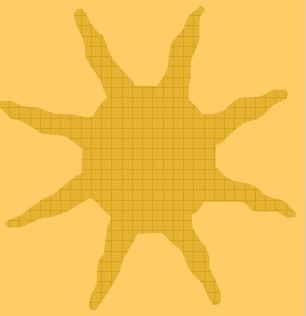
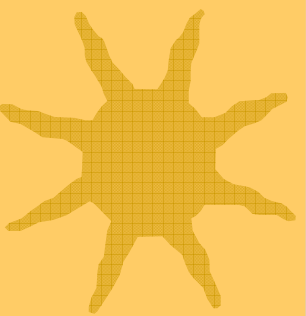




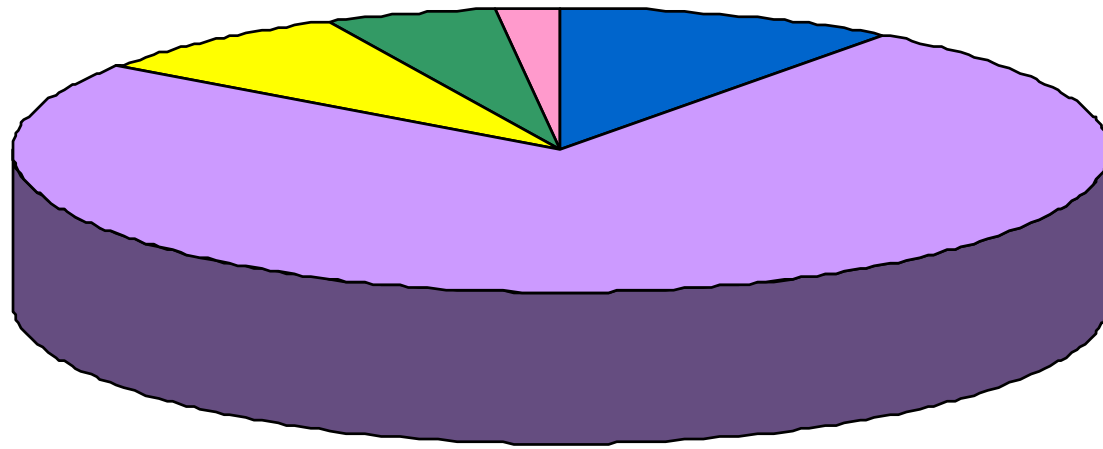
# *Diabetes*



- ❖ Hyperglycaemia
- ❖ Different mechanisms cause different forms
- ❖ Genetic and environmental component to all forms
- ❖ Diabetes gives rise to complications;
  - microvascular- nephropathy, neuropathy, retinopathy
  - macrovascular - cardiovascular disease
- ❖ Two major forms of diabetes:
  - Type 1 diabetes (autoimmune)
  - Type 2 diabetes (metabolic)



## *Diabetes subgroups*



■ Type 1 ■ Type 2 ■ LADA ■ MODY ■ MIDD

LADA = Latent Autoimmune Diabetes in Addults

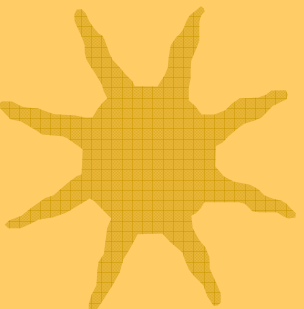
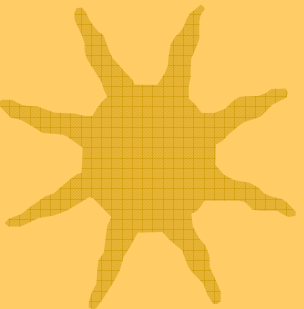
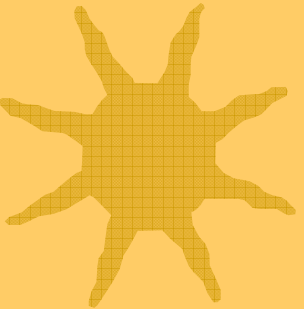
MODY = Maturity Onset Diabetes in the Young

MIDD = Mitochondrial Diabetes and Deafness

❖ Autoimmune diabetes = Type 1 diabetes + LADA



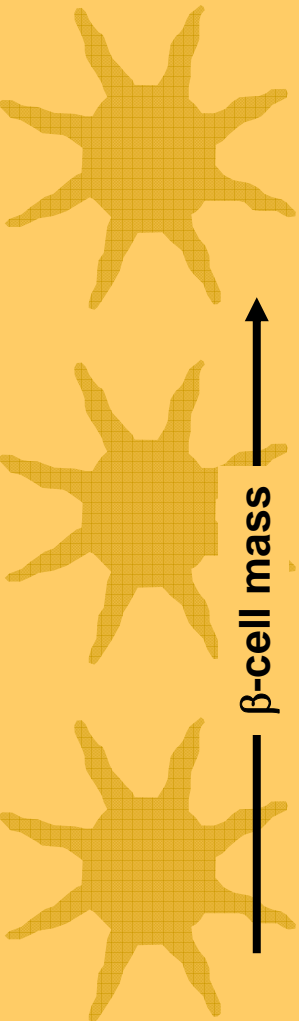
# *Type 1 diabetes (T1D)*



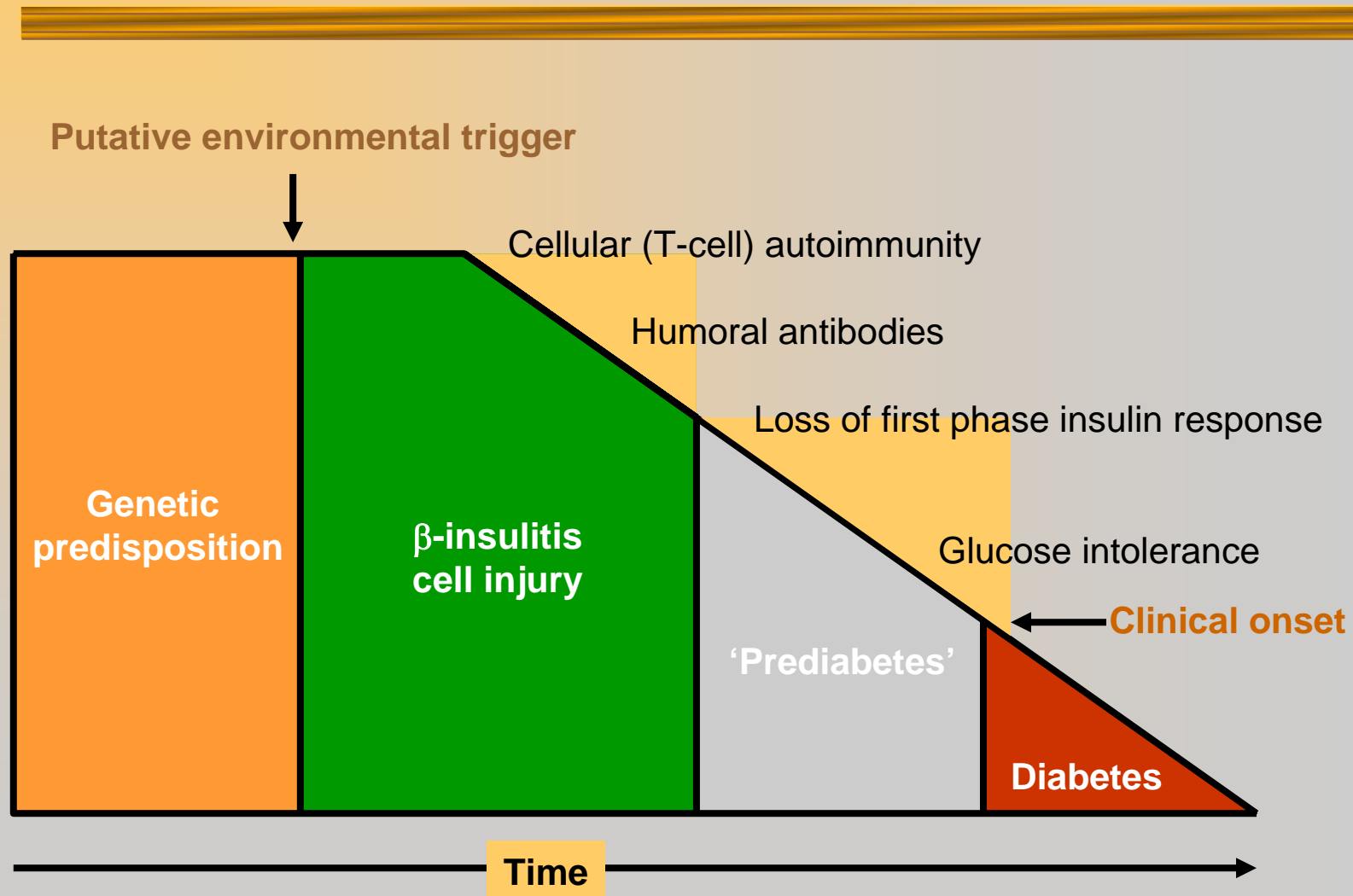
- ❖ Also known as  
insulin-dependent diabetes mellitus (IDDM) or  
juvenile-onset diabetes
- ❖ Organ-specific autoimmune disorder (pancreatic islets)
- ❖ Hyperglycaemia results from:
  - specific auto-destruction of insulin-secreting  $\beta$ -cells in the islets of Langerhans in the pancreas
  - autoantibodies against GAD65
- ❖ Etiology and pathogenesis of autoimmune diabetes largely unknown



# *Summary: natural history of T1D*



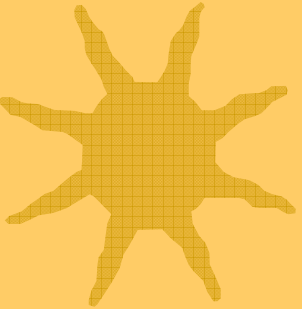
β-cell mass



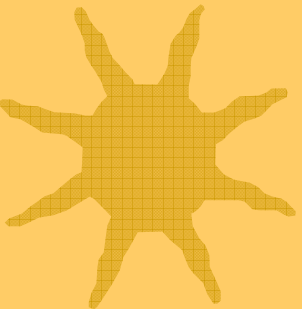
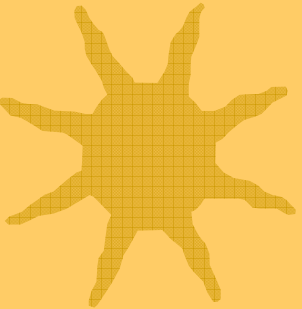


## *Localized autoimmune diseases with systemic autoantibodies*

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- ★ IBD: Crohn disease  
ulcerative colitis
- ★ celiac disease
- ★ autoimmune hepatitis
- ★ primary biliary cirrhosis

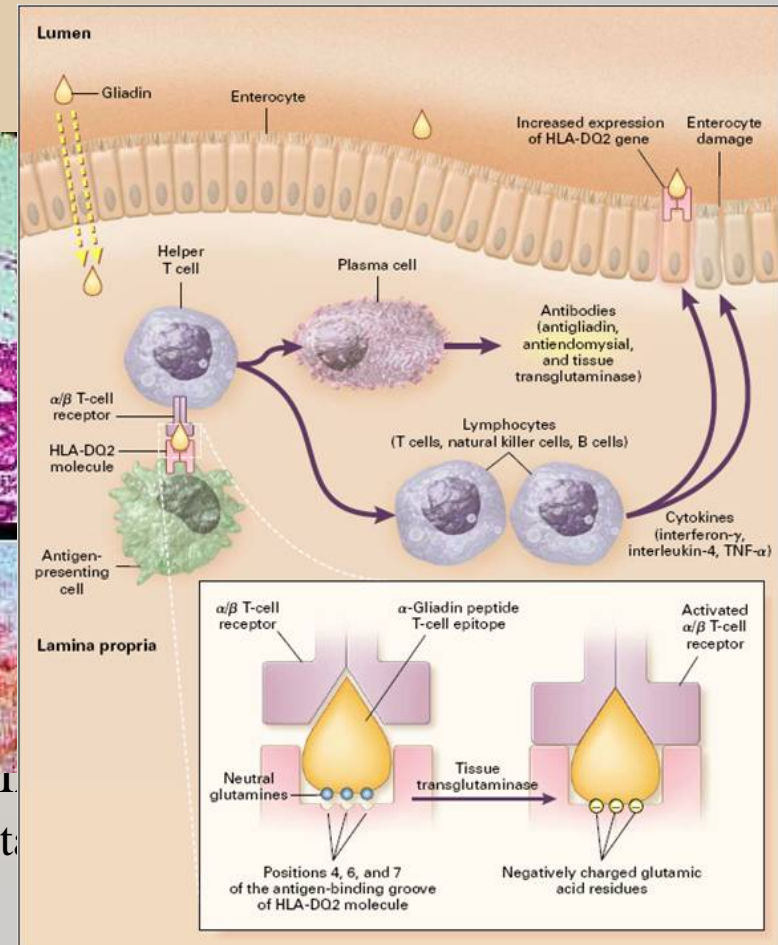
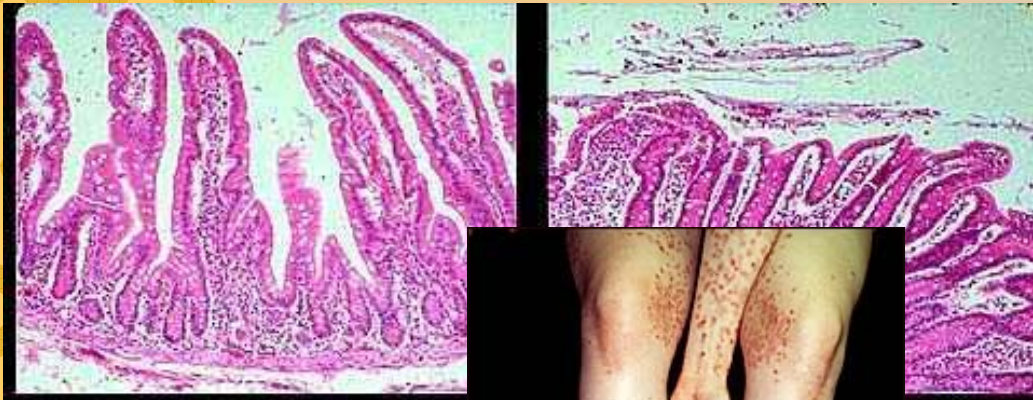






# *Localized autoimmune diseases with systemic autoantibodies*

## ★ Celiac disease



★ autoant

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ansglut

ADAM

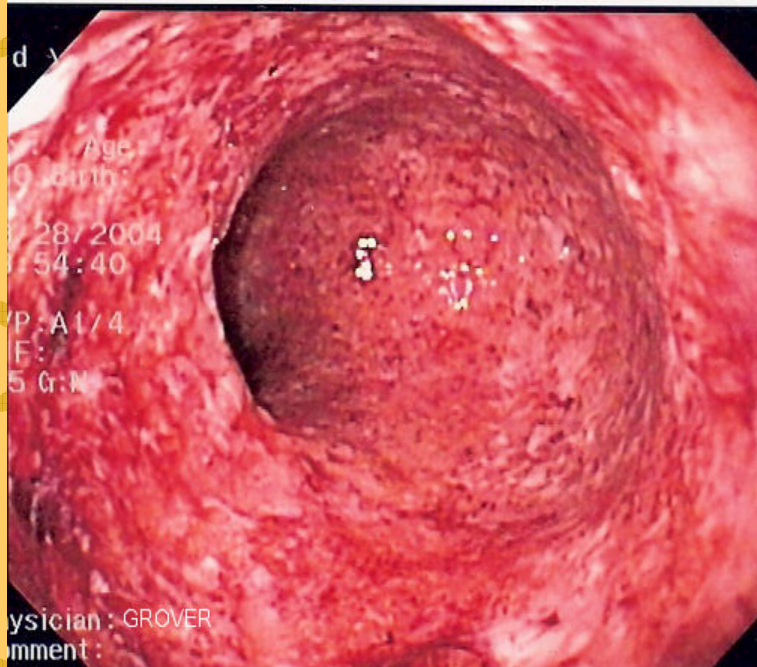




# *IBD – inflammatory bowel diseases*

CROHN'S DISEASE

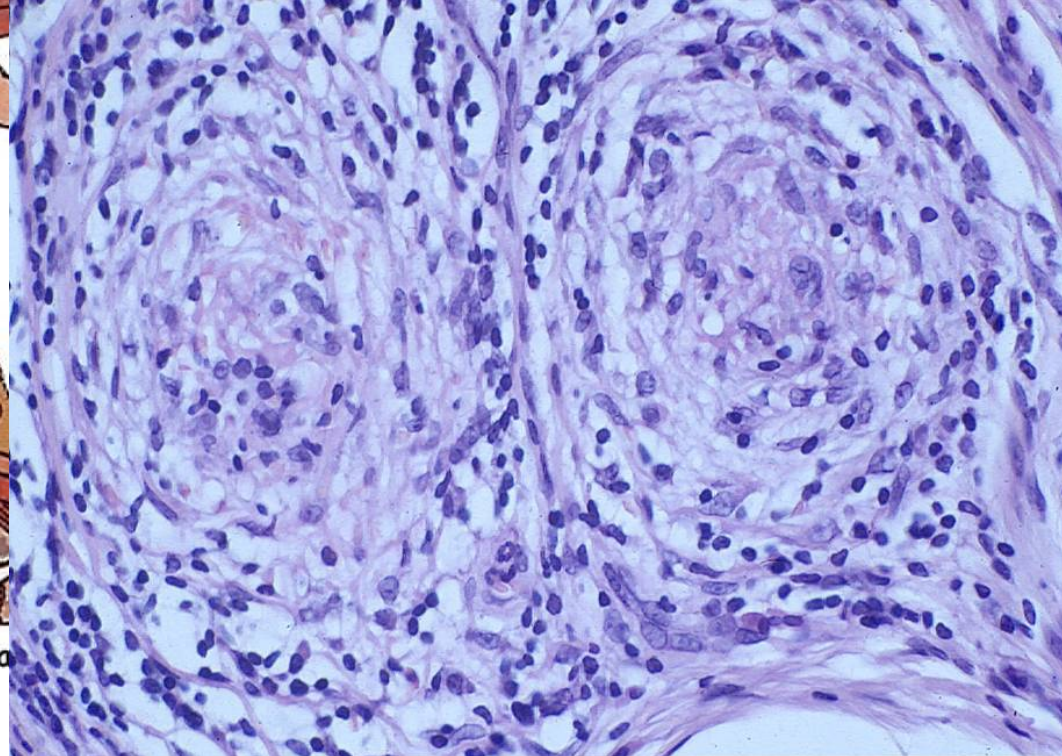
ULCERATIVE COLITIS



Small intestine



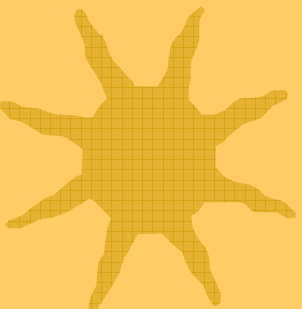
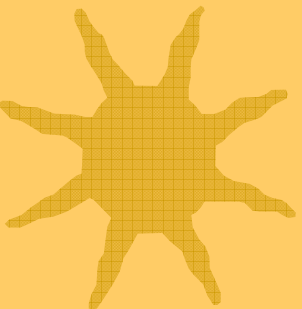
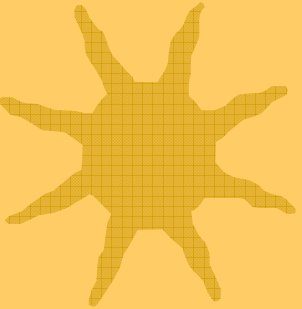
Transmural infla







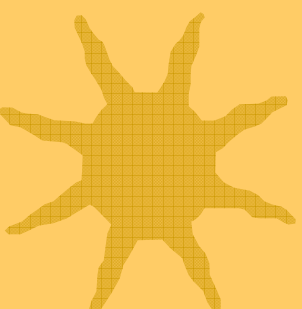
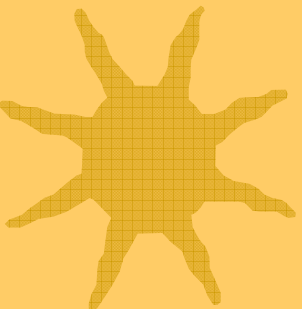
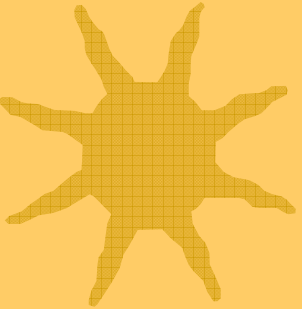
# *Therapy of autoimmune diseases*



corticosteroids	complex.action, cytokin inhibition	Prednison metylprednisolon
antiproliferative	inhib .DNA synthesis	cyclofosfamid azathioprin methotrexate mykofenolate
inhibitors of immunophilins	inhib. of cytokines	CyA, tacrolimus, rapamycin
iv.lg	immunoglobulins complex, antiidiotypes	IVIG
Ab against T ly.	inhib. depletion	ATG, anti CD3



# *Therapy*

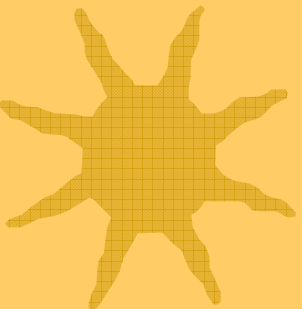
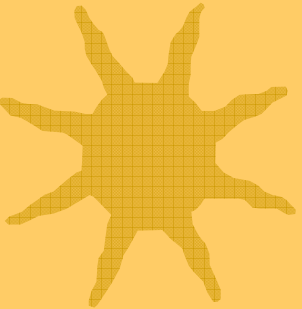
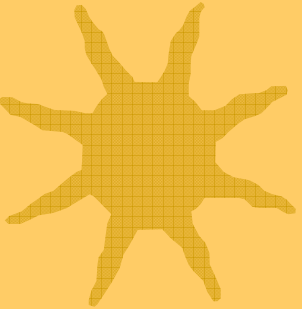


## Antigen-specific

- systemic application of Ag
  - Copaxone
- Ag po.
  - $\gamma/\delta$  T lymphocytes
  - insuline
- experimental approaches
  - modified Ag
  - gene therapy



# *Antigen non specific treatment*



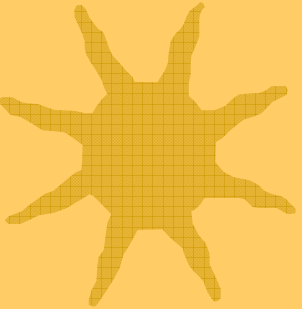
## Cytokine mediated treatment

- TNFalpha
  - infliximab, etanercept
- antiinflammatory cytokines
  - IL-10
  - IL-1
  - IFN beta
- others
  - blockade of adhesion molecules
  - blockade of costimulatory signals

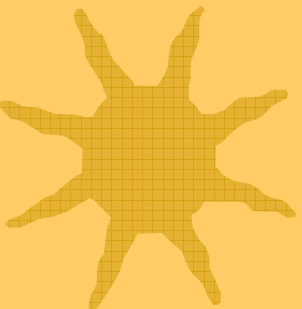


# *Bone marrow transplantation*

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Stem cell transplantation



ALPS

rheumatoid arthritis, systemic scleroderma,  
multiple sclerosis

allogenic (mortality risk) or autologous (risk of relaps)

