AUTOIMMUNE DISEASES

AUTOIMMUNE DISEASES

- **chronic** and usually **irreversible**
- prevalence: 5% - 7% of population
- higher frequencies in women
- incidence increases with age

Autoimmune diseases - etiology

- **Self tolerance** - all individuals are tolerant of their own (self) antigens, **the fundamental characteristic of the immune system**

- Autoimmune diseasses result from a **failure of self-tolerance**, immune response is activated against self antigens - causes damage of own tissues.

AUTOIMMUNE PATOLOGICAL RESPONSE - ETIOLOGY

Factors contributing to autoimmunity:

- internal (polymorphism of cytokine genes, defect in genes regulating apoptosis, HLA association, association with immunodeficiency, hormonal factors)

Internal triggering factors

- genotype / HLA (HLA B 27- ankylosing spondylitis, HLA DR 4 – rheumatoid arthritis)
- cytokines
- apoptosis genes
- ID (IgA, CVID, C 2, C4),
- hormones

AUTOIMMUNE PATOLOGICAL RESPONSE - ETIOLOGY

Factors contributing to autoimmunity:

- external (infection, stress by activation of neuroendocrinal axis and hormonal dysbalance, drug and ionization through modification of autoantigens)

External triggering factors

- infections
- stress
- UV
- drugs
- chemicals

How can infection work?

Mechanism	Disruption of cell or tissue barrier	Infection of antigen-presenting cell
Effect	Release of sequestered self antigen; activation of nontolerized cells	Induction of co-stimulatory activity on antigen-presenting cells
Example	Sympathetic ophthalmia	Effect of adjuvants in induction of EAE

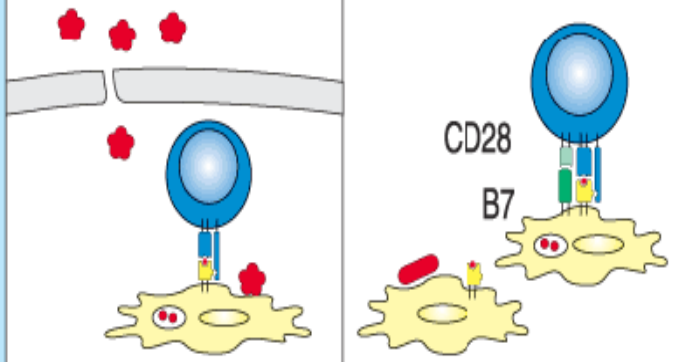


Fig 13.42 part 1 of 2 © 2001 Garland Science

Mechanism	Binding of pathogen to self protein	Molecular mimicry	Superantigen
Effect	Pathogen acts as carrier to allow anti-self response	Production of cross-reactive antibodies or T cells	Polyclonal activation of autoreactive T cells
Example	? Interstitial nephritis	Rheumatic fever ? Diabetes ? Multiple sclerosis	? Rheumatoid arthritis

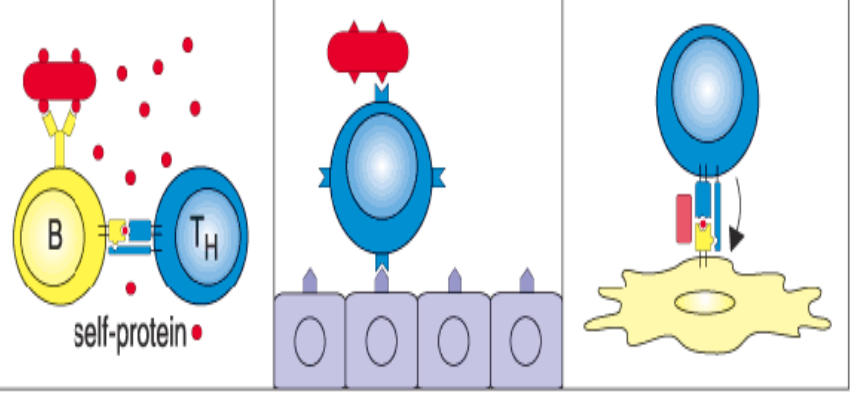
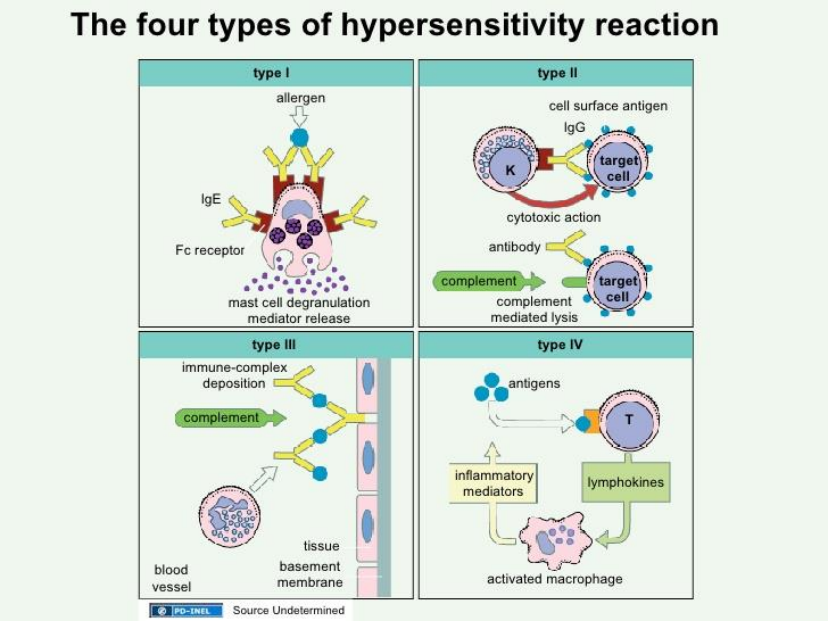


Fig 13.42 part 2 of 2 © 2001 Garland Science

AUTOIMMUNE PATOLOGICAL RESPONSE - PATHOGENESIS

Mechanism of tissue damage:

- type II. by Coombs and Gel
- type III. by Coombs and Gel
- type IV. by Coombs and Gel



Type II immunopatological reaction

- IgM and IgG Ab **promote the phagocytosis** of cells which they bind (cytotoxic reaction) or may **interfere with the functions** of cells (inhibit, stimulate) by binding to essential molecules and receptors.

- **Autoimmune hemolytic anemia** cytotoxic antibodies
- **Myasthenia gravis** blocking of acetylcholin receptor→ blocking of neuromuscular transmission
- **Graves‘ disease** stimulating antibodies against the receptor for TSH

Type III immunopatological reaction

- IgG Ab may bind to circulating antigens to form immune complexes, which deposit in vessels and cause tissue injury

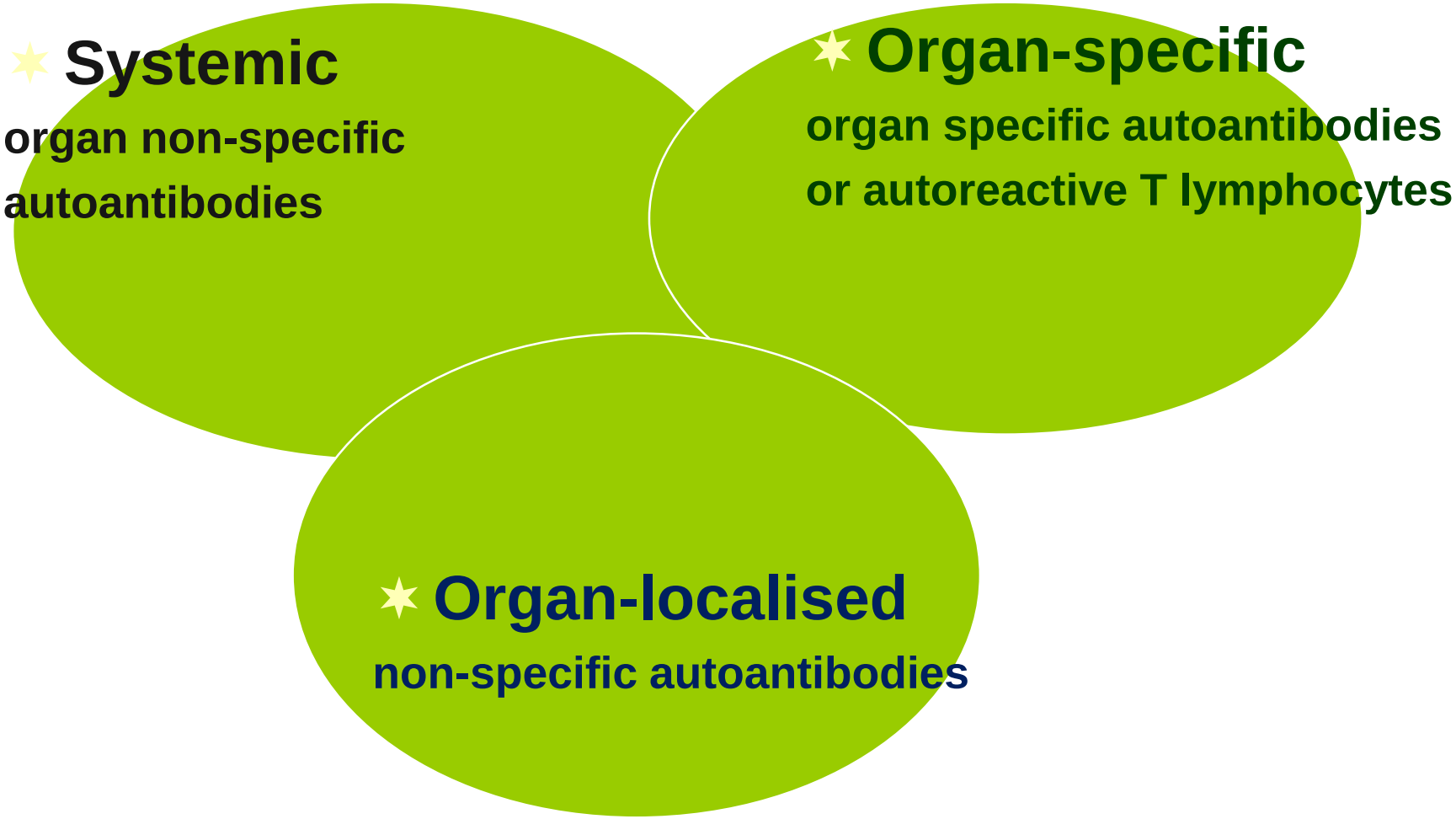
- **Systemic lupus erythematosus**

Type IV immunopatological reaction

- delayed-type hypersensitivity reaction
- T cell- mediated diseases, caused by Th1 and Tc

- **Diabetes mellitus (insulin-dependent)**
- **Multiple sclerosis**
- **Inflammatory bowel disease**

Autoimmune diseases



CLINICAL CATEGORIES

- **systemic**
  - affect many organs and tissues
  - organ non-specific autoantibodies

- **organ specific**
  - affect one organ
  - organ specific autoantibodies or autoreactive T lymphocytes

- **organ localised**
  - affect predominantly one organ, usually accompanied by systemic symptoms
  - organ non-specific autoantibodies

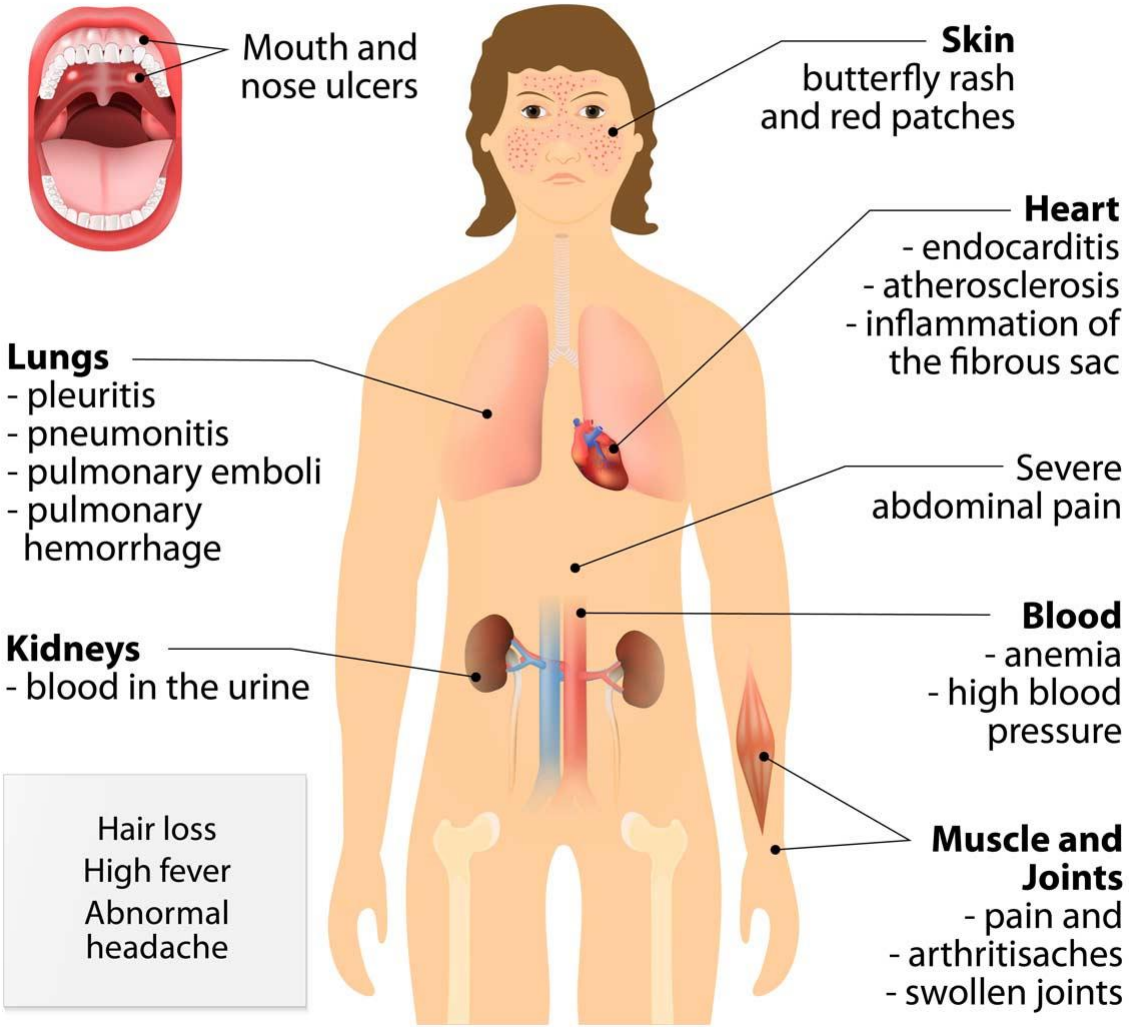
SYSTEMIC AUTOIMMUNE DISEASES

- Systemic lupus erythematosus
- Rheumathoid arthritis
- Sjögren‘s syndrome
- Dermatopolymyositis
- Systemic sclerosis
- Mixed connective tissue disease
- Vasculitis

SYSTEMIC LUPUS ERYTHEMATOSUS

- chronic, inflammatory, multiorgan disorder
- autoantibodies react with nuclear material, form immune complexes with dsDNA - deposit in the tissue
- multiple tissues are involved including the skin, mucosa, kidney, joints, brain and cardiovascular system

Systemic lupus erythematosus



general symptoms: fatigue, fever, weight loss

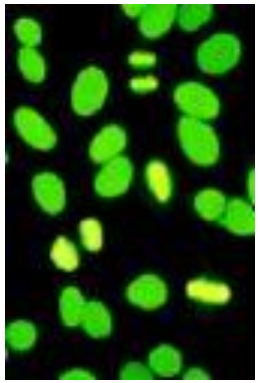
AUTOANTIBODIES

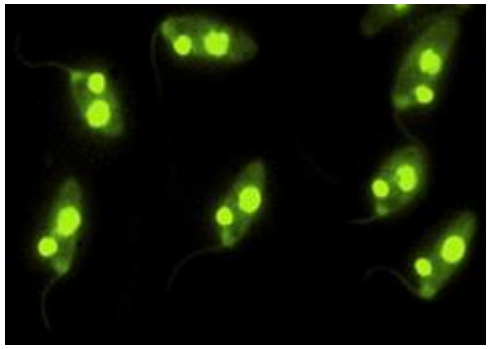
- **Autoantibodies: ANA**

  dsDNA (double-stranded)

  ENA (Sm)

  against **histones, phospholipids**





DIAGNOSTIC TESTS

- an elevated **ESR** (erythrocyte sedimentation rate)
- **low CRP**
- trombocytopenia, leucopenia, hemolytic anemia
- decreased levels of complement compounds (C4, C3)
- elevated serum Ig levels
- immune complexes in serum

2012 SLICC Classification Criteria for SLE

CLINICAL

- Acute cutaneous lupus
- Chronic cutaneous lupus
- Oral ulcers
- Non-scarring alopecia
- Synovitis ≥2 joints
- Serositis
- Renal
- Neurologic
- Hemolytic anemia
- Leucopenia / Lymphopenia
- Thrombocypotenia

IMMUNOLOGIC

- ANA
- Anti-dsDNA
- Anti-Sm
- aPL antibodies
- Low complement
- Direct Coomb's test

Petri M, Orbai AM, Alarcon GS, et al. Derivation and validation of the SLICC Classification Criteria for SLE. Arth & Rheum 2012; 64 (8): 2677--86

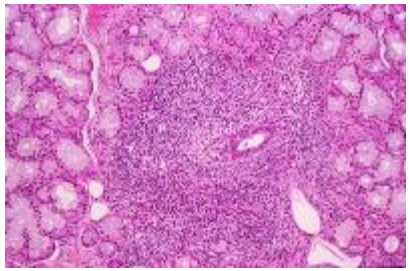
- https://www.youtube.com/watch?v=KaWBUgkd_oo

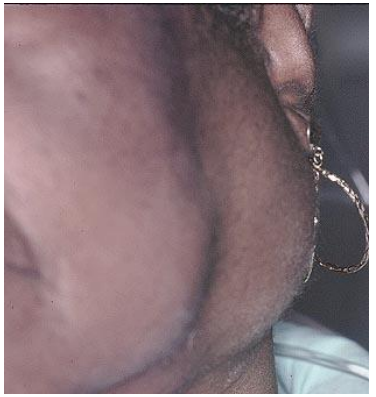
RHEUMATOID ARTHRITIS

- chronic, inflammatory disease
- characterized by an inflammatory joint lesion in the synovial membrane, destruction of the cartilage and bone, results in the joint deformation
- *clinical features:* arthritis, fever, fatigue, weakness, weight loss
- *systemic features*: pericarditis, uveitis, nodules under skin, intersticial pulmonary fibrosis

- **<u>diagnostic tests:</u>**
  - **autoantibodies** against Fc part IgG = rheumatoid factor (**RF**)
  - **a-CCP** (cyclic citrulline peptid)
  - elevated CRP and ESR, elevated serum Ig levels
  - **X-rays** of hands and legs - show a periarticular porosis, marginal erosion

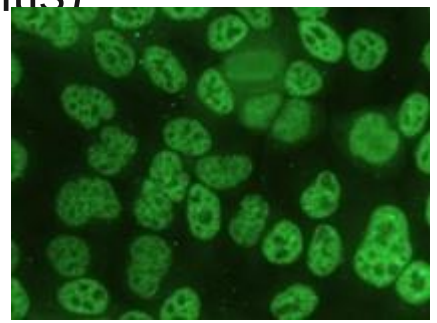
SJÖGREN‘S SYNDROME





- chronic inflammatory disease affecting exocrine glands
- the primary targets are the lacrimal and salivary gland duct epithelium
- **typical clinical features**: dry eyes and dry mouth, swollen salivary glands, dryness of the nose, larynx, bronchi and vaginal mucosa
- **general features**: fatigue, weakness, fever

- **primary** syndrome
- **secondary** syndrome – is associated with other AI diseases (SLE, RA, sclerosis, polymyositis, primary biliary cirhosis, AI thyroiditis)



<u>Diagnostic tests:</u>

autoantibodies ANA, ENA (SS-A, SS-B)

The Schirmer test - measures the production of tears

Dermatopolymyositis

- connective-tissue disease characterized by inflammation of the muscles and the skin.

Gottron's sign is an erythematous, scaly eruption occurring in symmetric fashion over the MCP and interphalangeal joints

Heliotrope rash is a violaceous eruption on the upper eyelids, often with swelling

Dermatopolymyositis

Diagnostic tests:

- autoantibodies **– ANA, ENA (Jo-1)**
- elevated creatine phosphokinase (CK), myoglobin
- muscle biopsy (a mixed B- and T-cell perivascular inflammatory infiltrate, perifascicular muscle fiber atrophy)
- EMG (electromyogram)

Systemic sclerosis

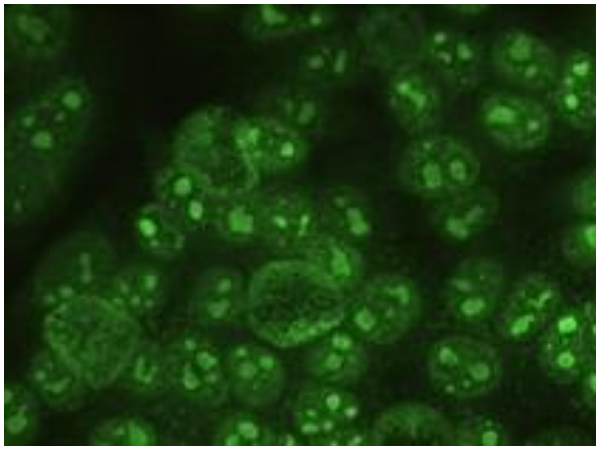
- sclerosis of the skin or other organs
- **Diffuse scleroderma** (progressive systemic sclerosis) is the most severe form, involves skin, generally cause internal organ damage (specifically the lungs and gastrointestinal tract)

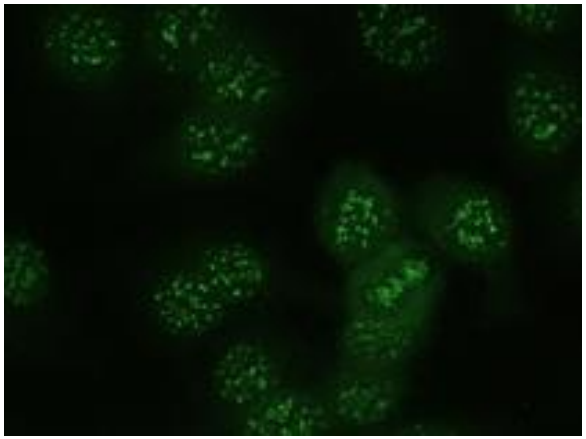
- The **limited form** is much milder

- The limited form is often referred to as **CREST syndrome** (CREST is an acronym for the five main features: **C**alcinosis, **R**aynaud's syndrome, **E**sophageal dysmotility, **S**clerodactyly, **T**elangiectasia)

Immunological findings

- ANA, ENA - anti-Scl-70 *(fluorescence of nucleolus)* or anti-centromers



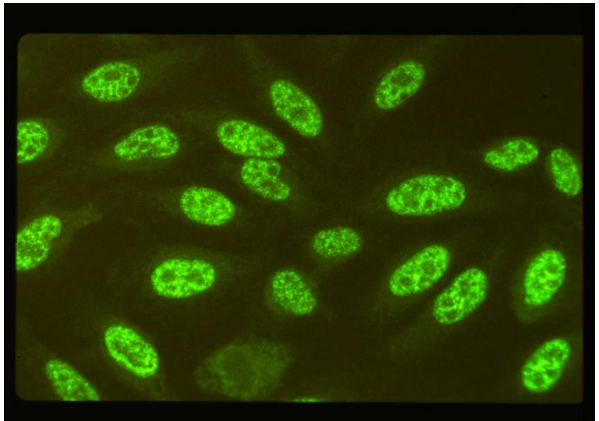


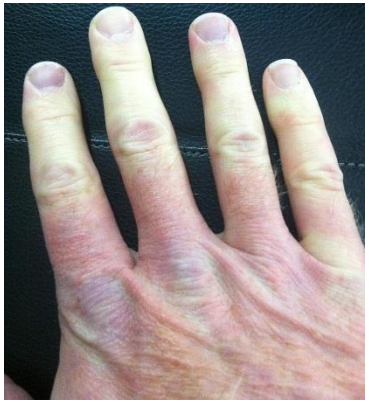
Mixed connective tissue disease

- combines features of systemic lupus erythematosus, systemic sclerosis and dermatomyositis (overlap syndrome)

- Clinical features : joint pain/swelling, fatique, Raynaud's phenomenon, muscle inflammation and sclerodactyly (thickening of the skin of the pads of the fingers)

- Diagnostic tests: ANA (speckled anti-nuclear antibody)
  ENA (U1-RNP)

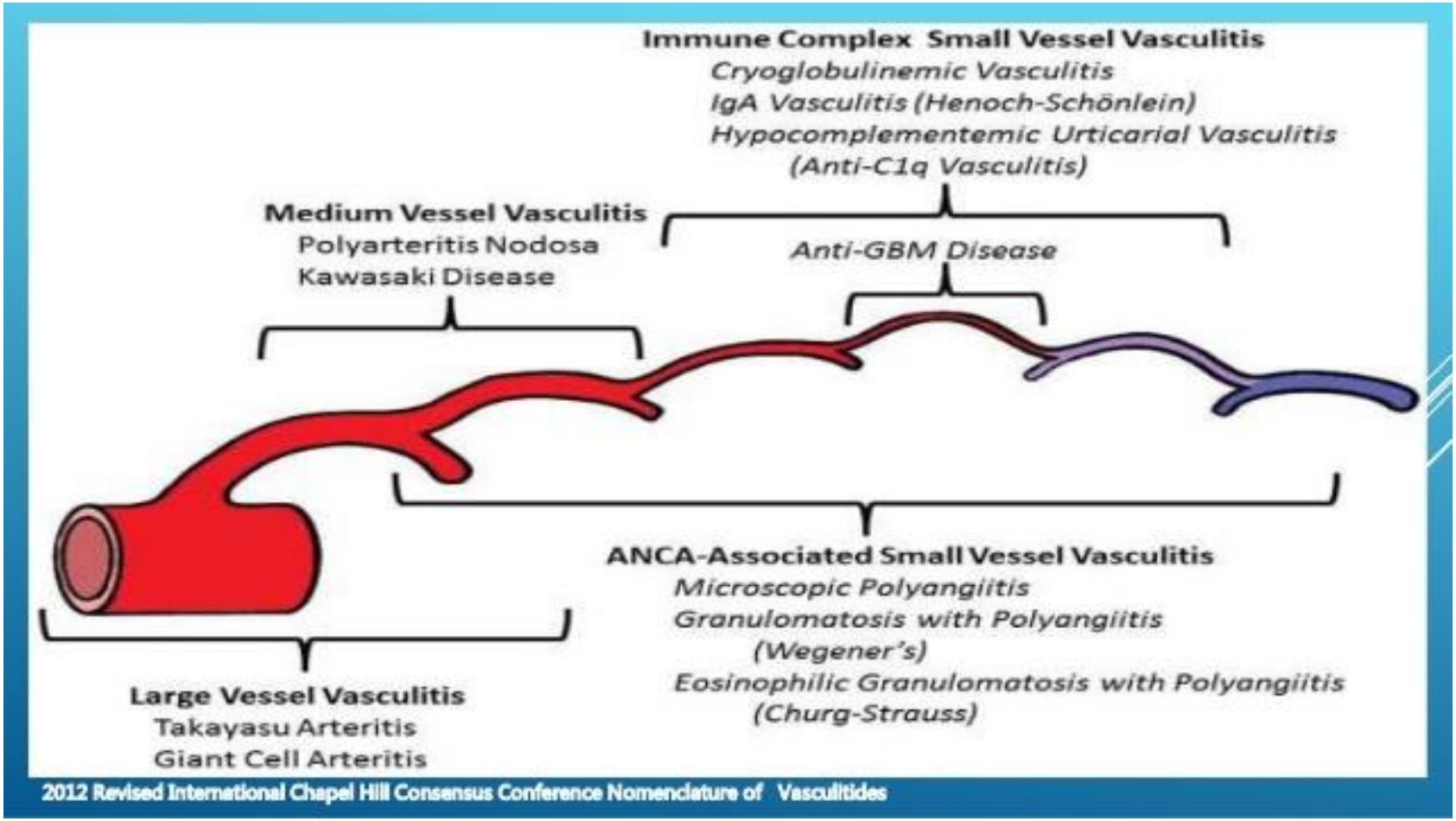




Vasculitis

- characterized by inflammatory destruction of vessels leading to thrombosis and aneurysms formation
- affect mostly lung, kidney, skin
- **Symptoms:** fatigue, weakness, fever, joint pain, abdominal pain, hypertension, renal insufficiency, neurologic dysfunction…

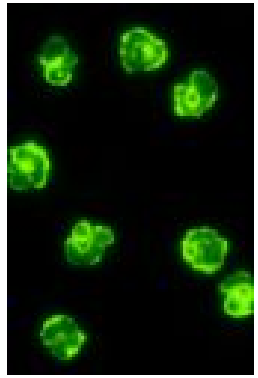
Clasification of vasculitis



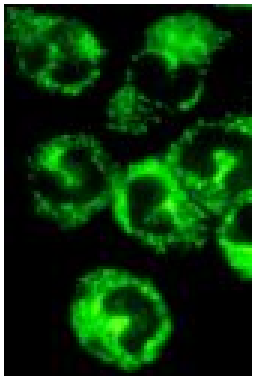
Vasculitis

diagnostic tests: elevated ESR, CRP, leucocytosis, biopsy of affected organ (necrosis, granulomas), angiography, ANCA (antineutrophil cytoplasmic antibodies)

- **p- ANCA** (myeloperoxidase) positivity (Eosinophilic Granulomatosis with polyangiitis „**Churg- Strauss“, Polyarteritis nodosa)**



- **c- ANCA** (serin proteinase) positivity (Granulomatosis with polyangiitis „**Wegener granulomatosis“**)



- https://www.youtube.com/watch?v=A4b_-uUNv7w

Autoimmune systemic diseases - characteristic autoantibodies

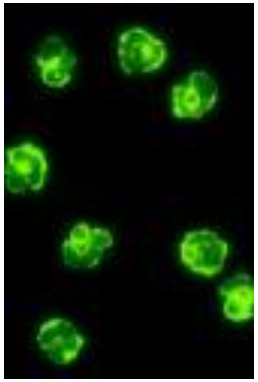
SLE	ANA, dsDNA, ENA-Sm
Rheumatoid arthritis	RF
Dermato/polymyositis	ANA, ENA Jo-1
Sjögren´s syndrome	ANA, ENA SS-A, SS-B
Sklerodermia	ANA, ENA Scl 70
MCTD	ANA, ENA RNP
Vasculitis	ANCA

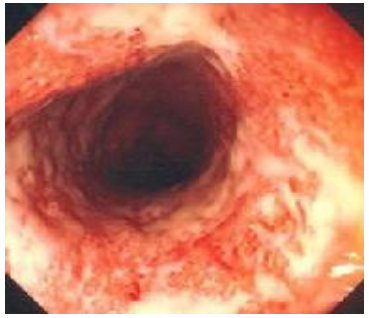
ORGAN LOCALIZED AUTOIMMUNE DISEASES

- Ulcerative colitis
- Crohn‘s disease
- Autoimmune hepatitis
- Primary biliary cirhosis

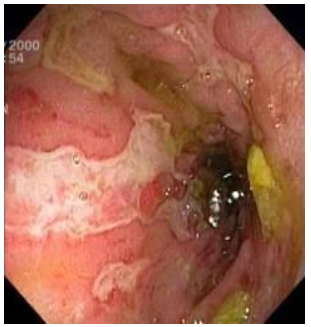
Ulcerative colitis

- chronic inflammation of the large intestine mucosa and submucosa
- features: diarrhea, bloody and mucus stools
- extraintestinal features (arthritis, uveitis)
- **autoantibodies** against atypical **ANCA (lactoferin, cathepsin…)**, a- large intestine





Crohn‘s disease



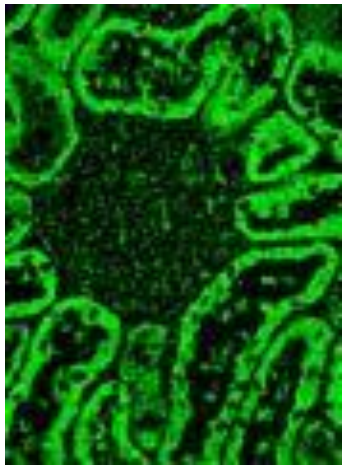
- the granulomatous inflammation of whole intestinal wall with ulceration and scarring that can result in abscess and fistula formation

- the inflammation in Crohn's disease the most commonly affects the terminal ileum, presents with diarrhea and is accompanied by extraintestinal features - iridocyclitis, uveitis, artritis, spondylitis

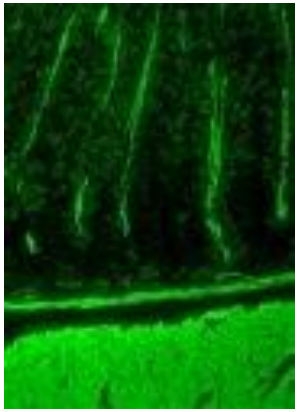
- **antibodies against** *Saccharomyces cerevisiae* (**ASCA**), a- pancreas

Primary biliary cirhosis

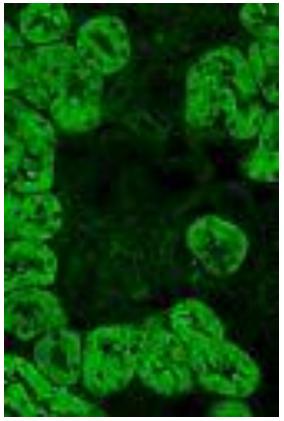
- autoimmune disease of the liver marked by the slow progressive destruction of the small bile ducts; can lead to cirhosis
- **AMA**= antimitochondrial autoantibodies



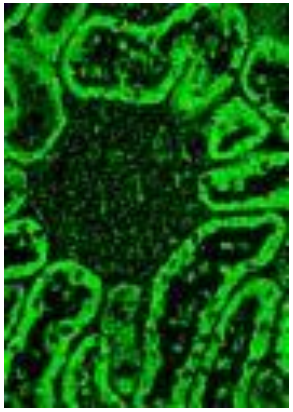
AUTOIMMUNE HEPATITIS



- **type I** – association with autoantibodies against smooth muscles **SMA**



- **type II –** autoantibodies against microsomes **LKM-1** = liver-kidney microsomes



- **type III** – autoantibodies against **SLA** (solubile liver antigen)

ORGAN SPECIFIC AUTOIMMUNE DISEASES

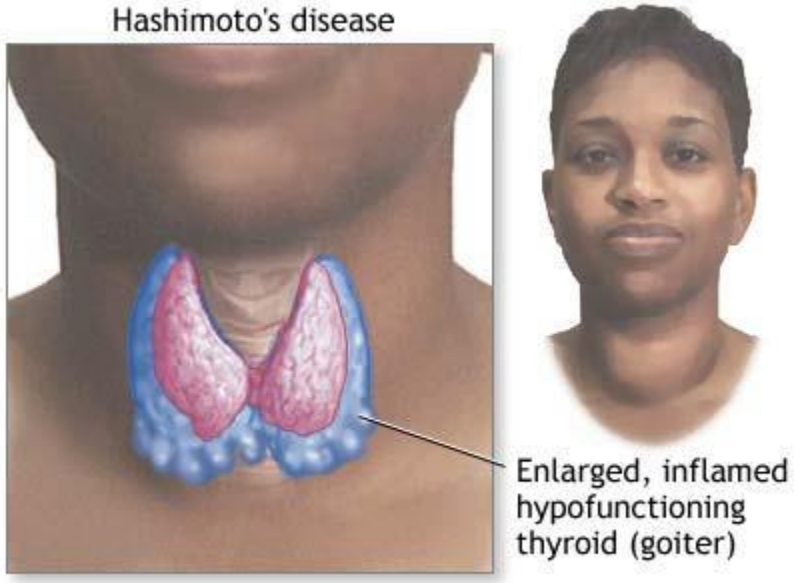
- Autoimmune endocrinopathy
- Autoimmune neurological diseases
- Autoimmune cytopenia

AUTOIMMUNE ENDOCRINOPATHY

- Hashimoto‘s thyroiditis
- Graves-Basedow disease
- Diabetes mellitus I. type
- Addison‘s disease
- Autoimmune polyglandular syndrome
- Pernicious anemia

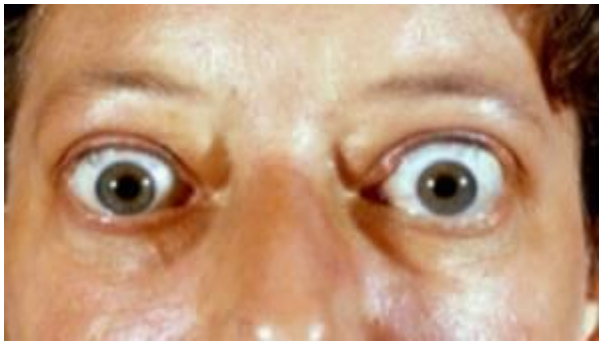
Hashimoto‘s thyroiditis

- thyroid disease result in hypothyroidism
- autoantibodies against thyroidal peroxidase (**a-TPO**) and/or against thyroglobulin (**a-TG**)



Grave‘s disease

- thyrotoxicosis from overproduction of thyroid hormone (increased sweating, palpitations, weight loss, exophtalmus)



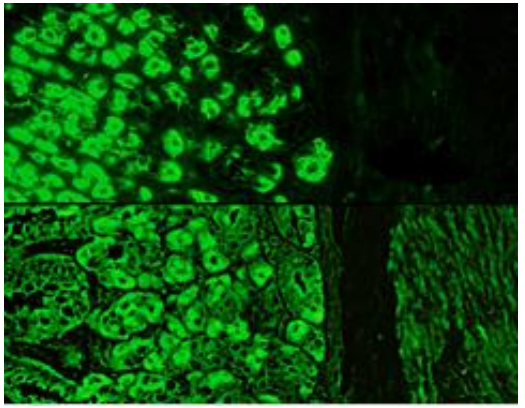
- autoantibodies against **thyrotropin receptor,** autoantibodies cause thyroid cells proliferation

Diabetes mellitus (insulin - dependent)

- characterized by inability to process sugar in the diet, due to a decrease in or total absence of insulin production
- results from immunologic destruction of the insuline-producing β-cells of the islets of Langerhans in the pancreas
- autoantibodies against **GAD** - glutamic acid decarboxylase = primary antigen), autoantibodies anti - islet cell, anti - insulin

Pernicious anemia

- autoantibodies against gastric parietal **cells** producing intrinsic factor (transportation of B12 vitamin)
- the deficiency of the intrinsic factor results in vitamin B12 malabsorption with the development of macrocytic anemia



AUTOIMMUNE NEUROLOGICAL DISEASES

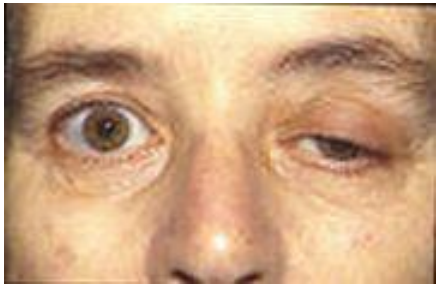
- Guillain-Barré syndrome (acute idiopathic polyneuritis)
- Myasthenia gravis
- Multiple sclerosis

Guillain-Barré syndrome

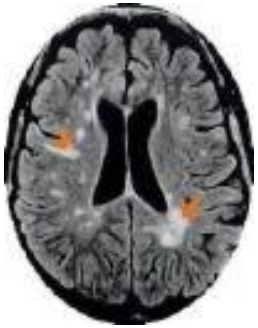
- autoantibodies against **ganglioside membrane**
- occurs often 1-3 weeks after infection (Campylobacter jej.)
- inflammation demyelinates peripheral nerves
- features**:** progressive weakness of the lower and later upper extremities and respiratory muscles, weakness can leads to paralysis and respiratory failure

Myasthenia gravis

- chronic disease with impaired neuromuscular transmission and muscle weakness
- caused by autoantibodies against **Ach receptors**
- neuromuscular dysfunction results from blockage and depletion of acetylcholine receptors at the myoneural junction
- **ptosis of the eye**



Multiple sclerosis



- chronic demyelinating disease with abnormal reaction of **T cells to** myeline on the base of mimicry between a virus and myeline protein
- features: weakness, ataxia, impaired vision, urinary bladder dysfunction, paresthesias, mental abberations

- **magnetic resonance** imaging of the brain and spine shows areas of demyelination

- The cerebrospinal fluid is tested for **oligoclonal bands**, can provide evidence of chronic inflammation of the central nervous system

AUTOIMMUNE CYTOPENIA

- **AI hemolytic anemia** - autoantibodies against membrane erythrocyte antigens
- **AI trombocytopenia** - autoantibodies against trombocyte antigens (GPIIb/IIIa)
- **AI neutropenia** - autoantibodies against membrane neutrofil antigens

Laboratory measurement of autoantibodies

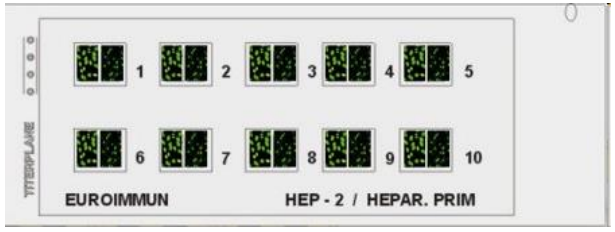
Methods:

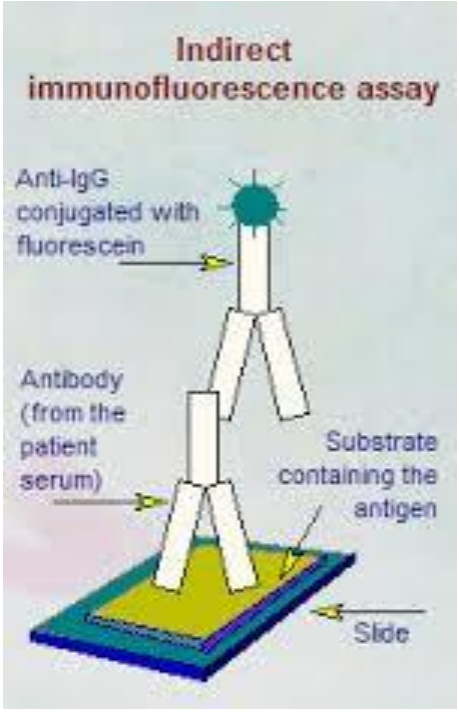
- the gold standard is **indirect immunofluorescence**
  allows the detection of organ nonspecific autoantibodies
- other method – **ELISA**
  determine the specificity of autoantibody

Indirect immunofluorescence

- tissue sections are used as antigen substrates

- if sample is positive, autoantibodies in the diluted serum sample attach to the substrate antigens
- in a second step, the attached antibodies are stained with fluorescein-labeled anti-human antibodies and vizualized with the fluorescence microscope.

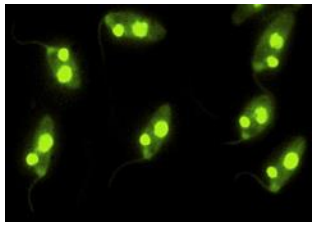




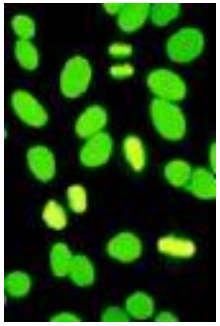
Indirect immunofluorescence

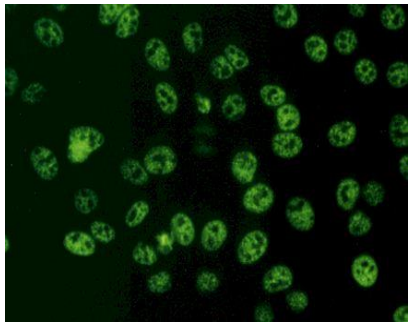
Autoantibodies are detected on specific substrates:

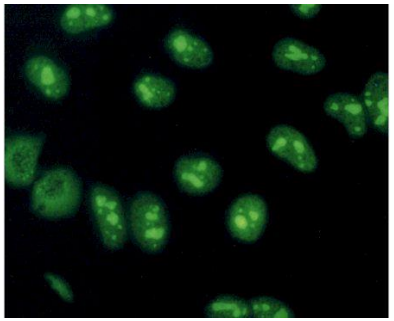
- ds-DNA on protozoan Crithidia Lucilae substrate



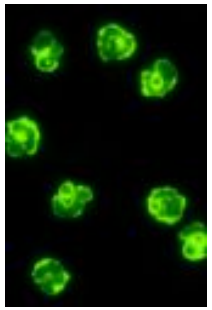
- ANA - on Hep-2 substrate

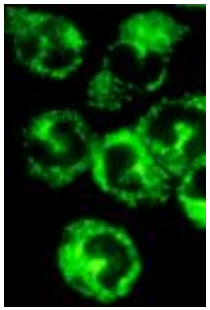




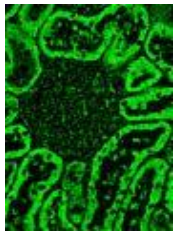


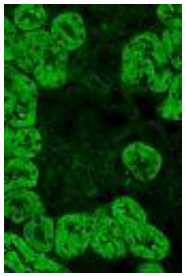
- ANCA on neutrophil substrate



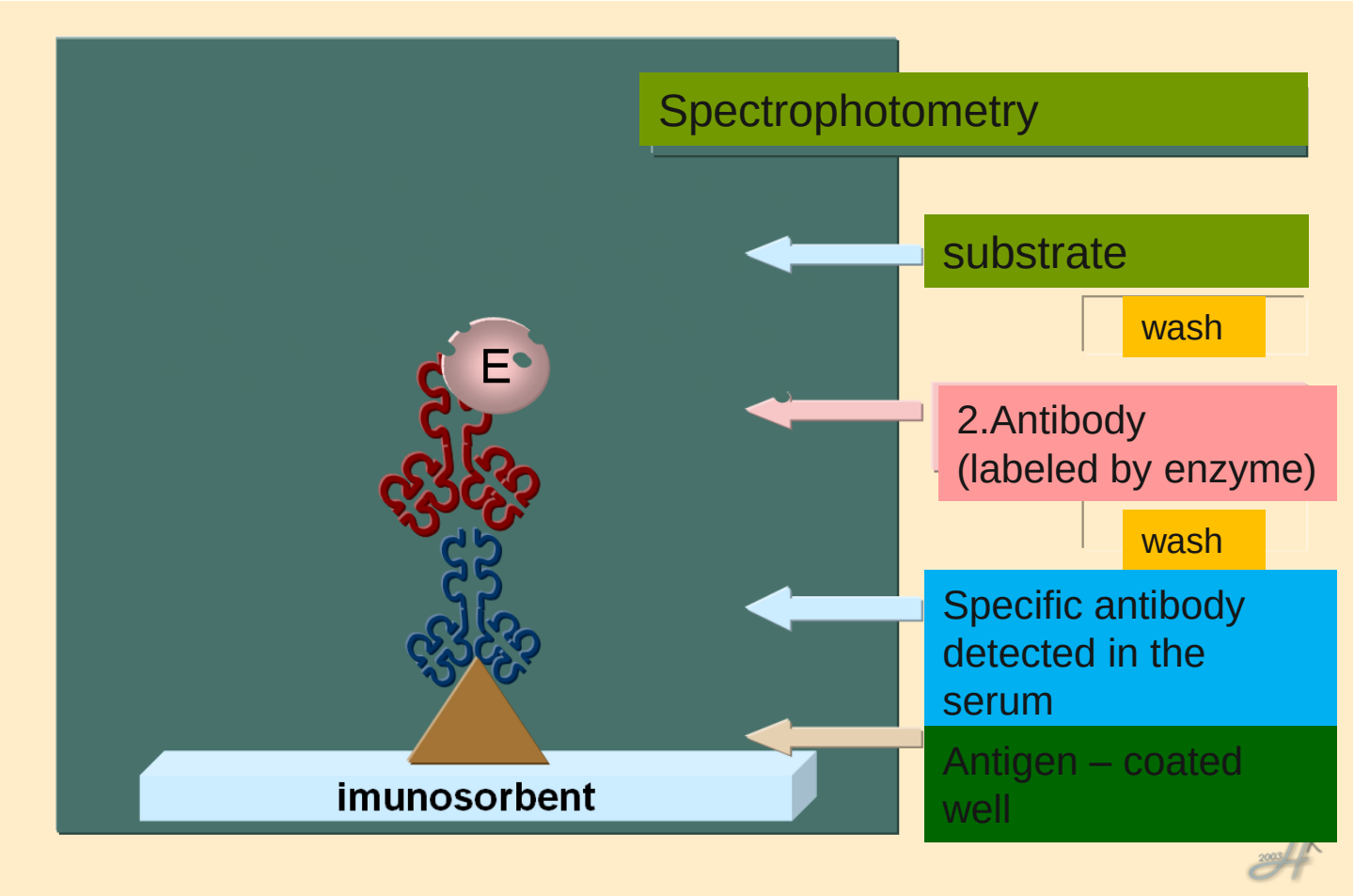


- AMA- on mouse stomach
- Anti LKM- on mouse liver, stomach, kidney





ELISA
assessment of specific antibodies



The substrate will trigger a reaction with enzyme attached to a second antibody to produce coloured substance.

Immunosuppressants

- Drugs that inhibit or prevent activity of the immune system
- They are used to:
- ***Prevent the rejection*** of transplanted organs and tissues (bone marrow, kidney, liver)
- *Treat* ***autoimmune diseases*** (rheumatoid arthritis, multiple sclerosis, myasthenia gravis, systemic lupus erythematosus, Crohn's disease, ulcerative colitis).
- *Treat some other* ***non-autoimmune inflammatory*** **diseases** (allergic asthma, atopic eczema).

Immunosuppressants

- Glucocorticoids
- Drugs affecting the proliferation of both T cells and B cells (affecting the metabolism of DNA)
- Drugs selectively inhibiting T cells
- Monoclonal antibodies

Glucocorticoids

- anti-inflammatory, immunosuppressive effects
- suppress the expression of some genes

  (IL-2, IL-1, phospholipase A, MHC gp II, adhesion molecules)
- inhibition of histamine release from basophils
- higher concentrations induce apoptosis of lymfocytes

Drugs affecting the proliferation of both T cells and B cells

- **Cyclophosphamide** (alkylating agent)
  very efficient in the therapy of SLE, autoimmune hemolytic anemias
  high doses cause pancytopenia and hemorrhagic cystitis

- **Methotrexate** (folic acid antagonist)
  used in the treatment of autoimmune diseases (**RA, Crohn's disease**) and in transplantations

- **Azathioprine** (purine synthesis inhibitor)
  SLE, RA, sclerosis multiplex, transplantation

Drugs selectively inhibiting T cells

- suppressing the expression of IL-2 and IL-2R in activated T lymphocytes

- **Tacrolimus**

  Used to prevent rejection reactions, atopic eczema

- **Cyclosporin A**

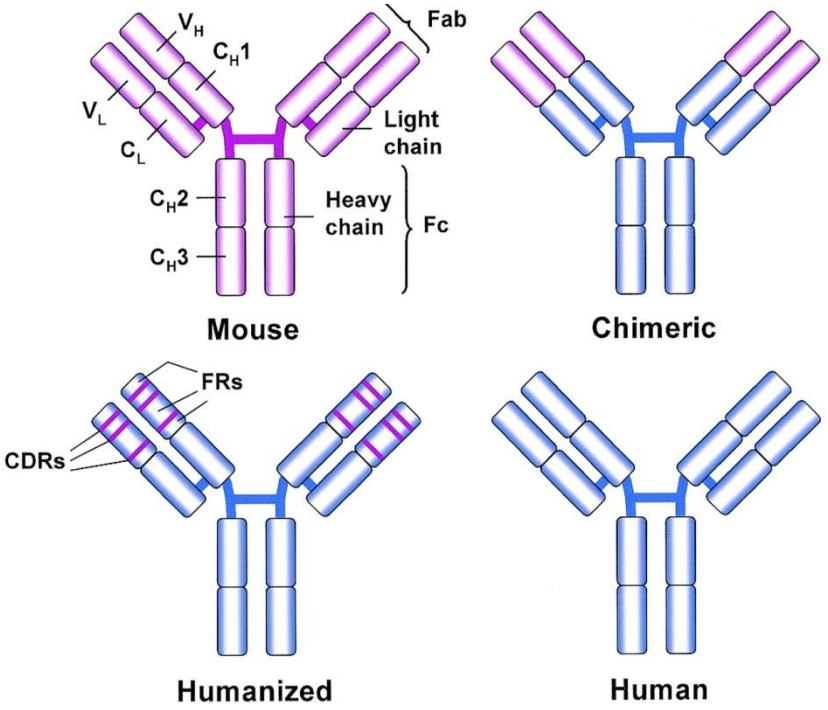
  Used to prevent rejection reactions

- **Side effects**: nephrotoxicity, neurotoxicity, hypertension, dyslipidemia, hyperglycemia

Monoclonal antibodies

- Monoclonal antibodies are directed towards exactly defined antigens (solubile molecules or membrane proteins) - block function or cause cell apoptosis

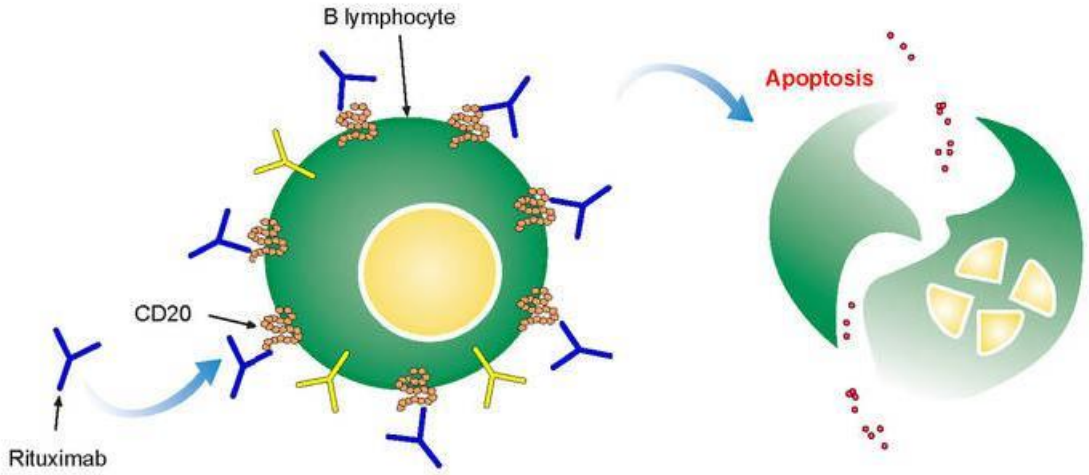
- Treatment of
  - autoimmune diseases
  - cancer
  - transplantation



MONOCLONAL ANTIBODIES...FEW EXAMPLES AND INDICATIONS

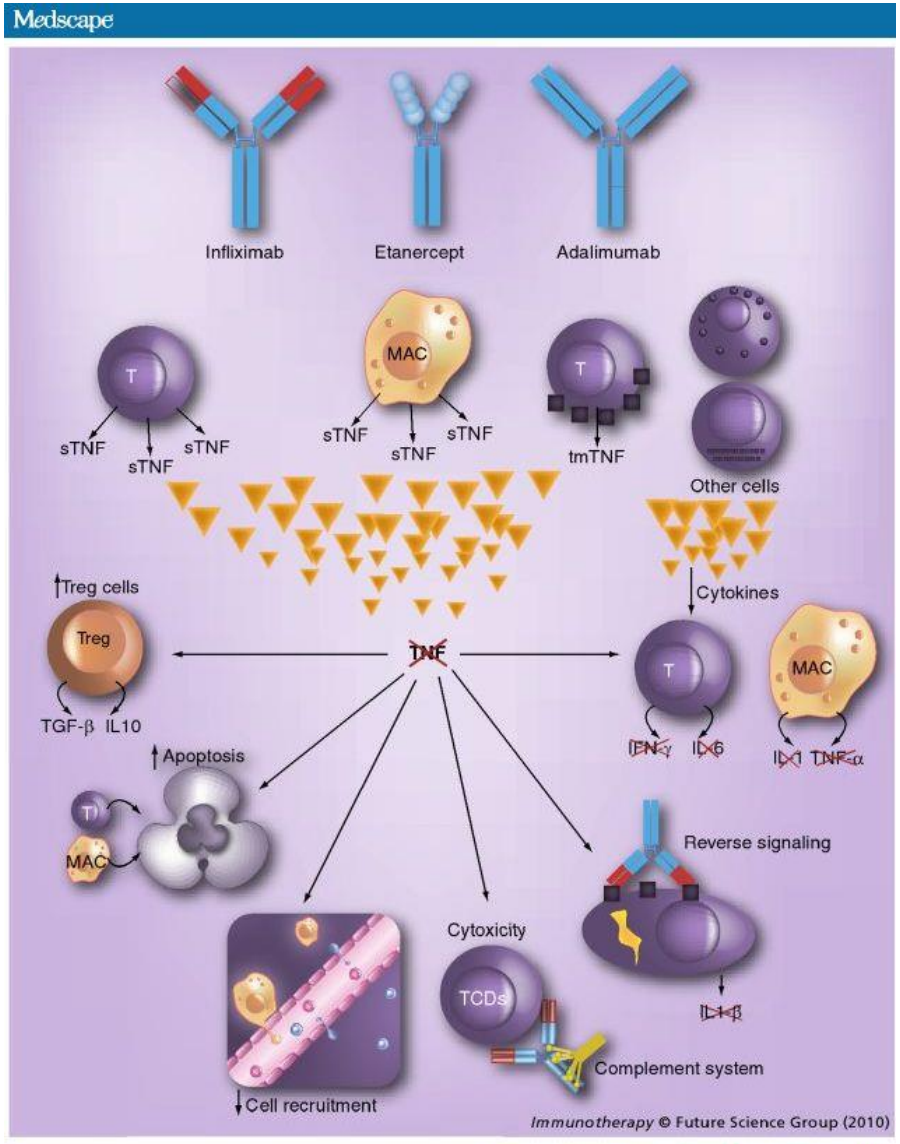
MONOCLONAL ANTIBODY	TARGET	INDICATION
Rituximab,Ibritumonab	CD 20	B cell NHL
Gemtuzumab,Ozogamicin	CD 33	CD 33 positive AML
Ocrelizumab,oftamumab	CD 20	SLE
Alemtuzumab	CD 52	B cell CLL
Adalimumab,Infliximab	TNF-alpha	Rheumatoid arthritis
Trastuzumab	Her2-neu	Breast cancer
Donesumab	RANK ligand	Osteoporosis
Bevazicumab	VEGF	Colorectal cancer
Ranibizumab	VEGF	Neovascular macular degeneration
Cetuximab	EGFR	Head neck CA.colorectal CA
Panitimumab	EGFR	Colorectal carcinoma

Rituximab



TNF Inhibitors

- Etanercept (Enbrel) – soluble receptor – Ig dimer
- Infliximab (Remicade) – mouse-human anti-TNF
- Adalimumab (Humira) – human anti-TNF



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