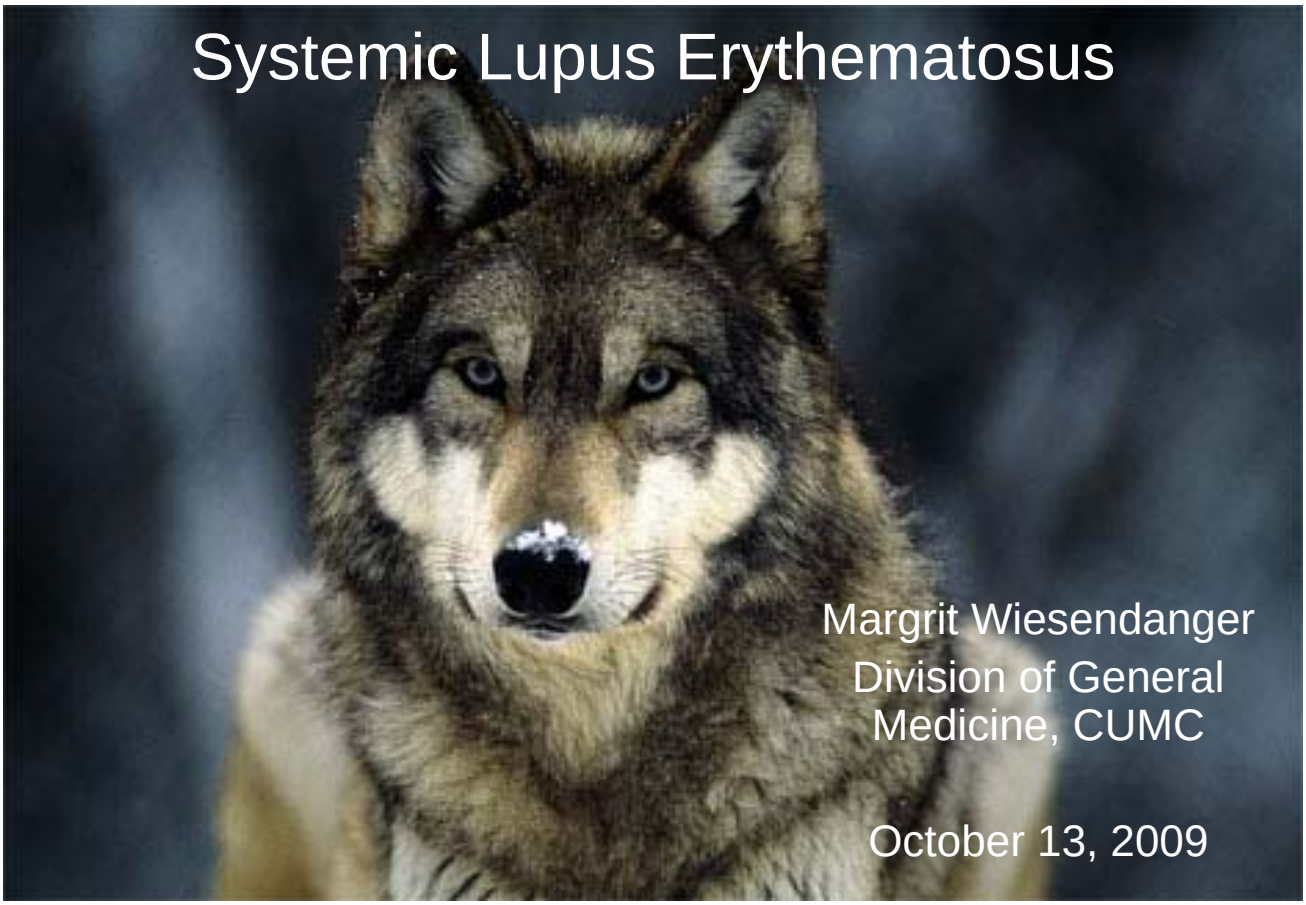
Systemic Lupus Erythematosus



Margrit Wiesendanger
Division of General Medicine, CUMC

October 13, 2009

SLE Epidemiology: who is at risk?

One of the most common autoimmune diseases affecting women of all ages

Predominantly women in child-bearing years (M:F ratio is 1:10)

Incidence in the US: 1.6 - 7.6 cases/100,000

Prevalence in the US: 15 - 50 cases/100,000

Disease prevalence and severity differs among ethnic subsets:
African-American > Hispanic > Asian > Caucasian

Mortality patterns:

Early mortality is due to active disease, thrombosis and infections.

Late mortality is due to late complications of disease, atherosclerotic heart disease, and infections.

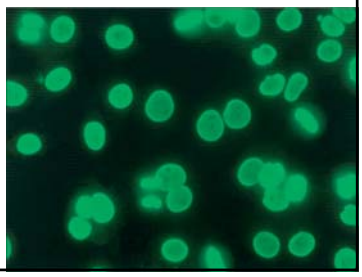
Immune characteristics of SLE

Hallmark: formation of auto-antibodies, whose targets include ubiquitously expressed nuclear and cytoplasmic components

Auto-antibodies can be detected in serum up to 9 years before the first sign or symptom of lupus

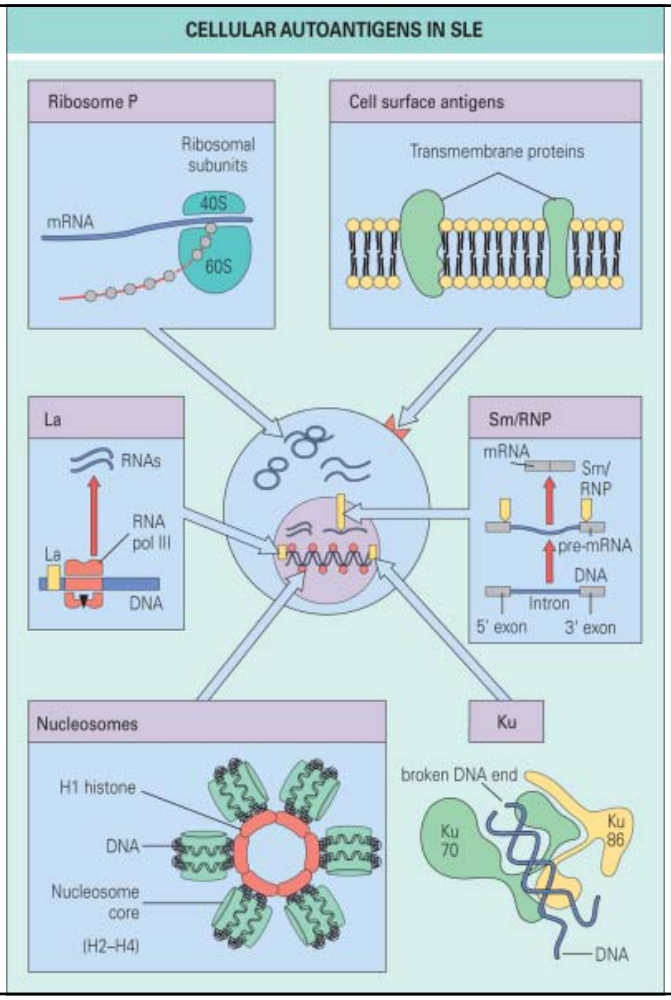
Mechanisms of antibody-mediated pathogenesis include
- the formation of immune complexes,
- triggering the classical pathway of complement activation, and
- Fc receptor-mediated phagocytosis

all of which play protective roles in host defense against microbial pathogens.



Example of an ANA:
Homogeneous pattern

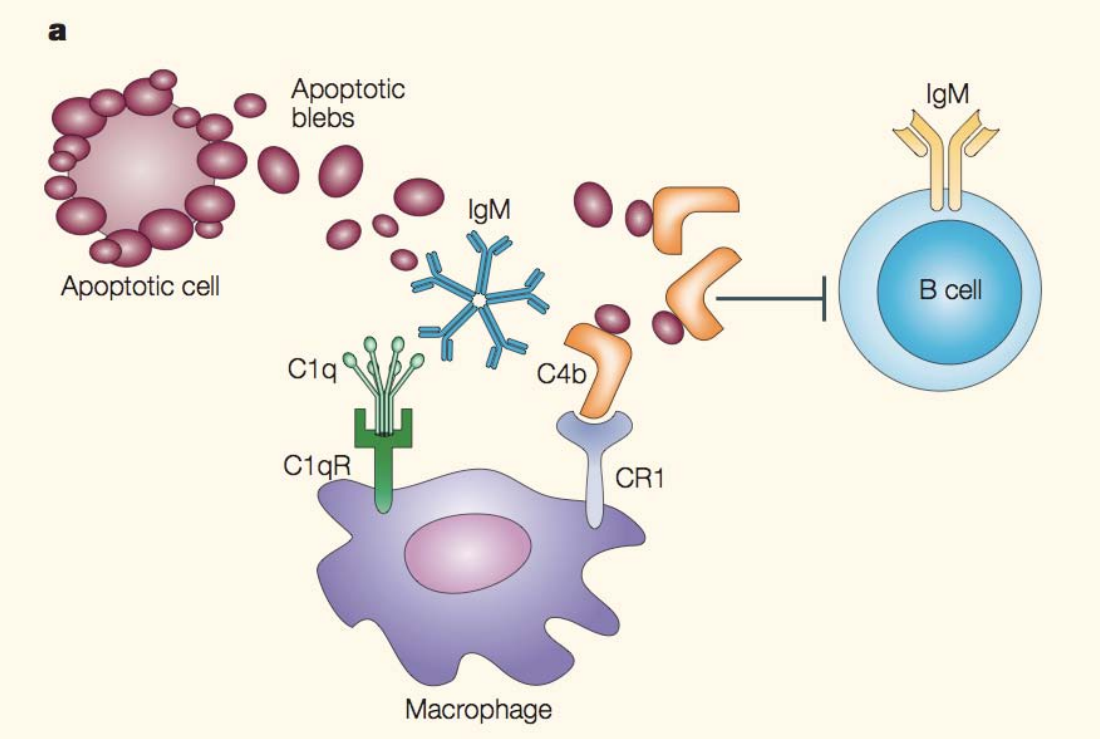
Cellular autoantigens in SLE



Keith Elkon,

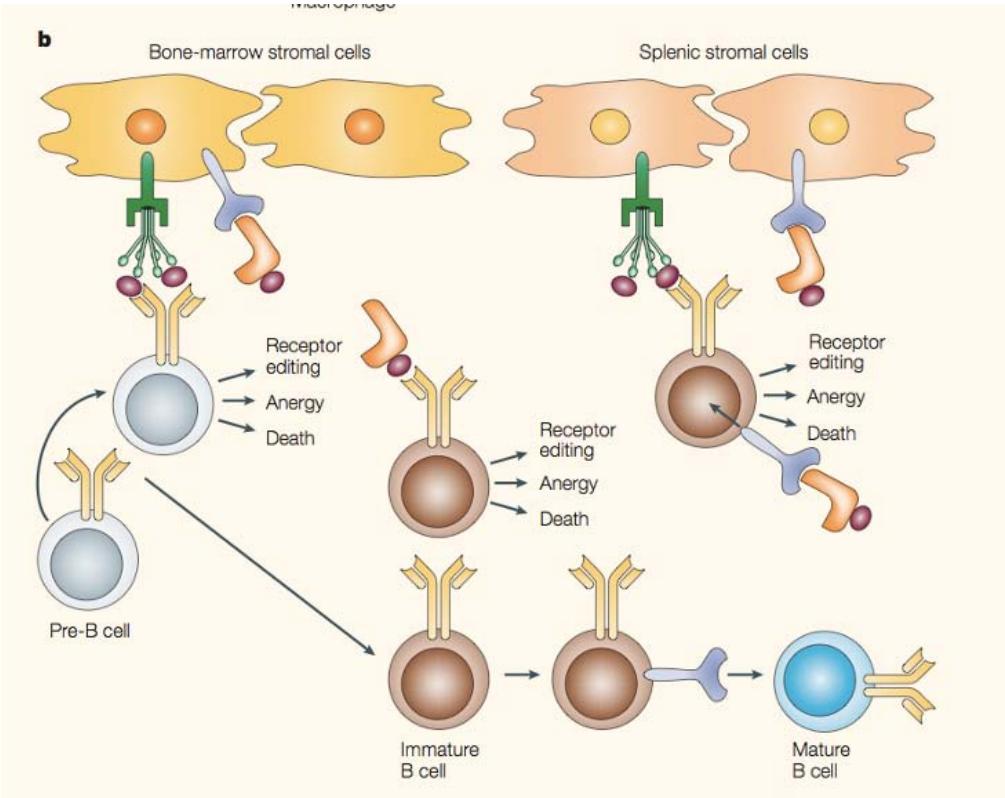
in Hochberg Rheumatology

Cellular apoptosis: a source of self antigens?



Michael C. Carroll
Nature Reviews Immunology 4, 825-831 (2004)

Auto-reactivity: a failure of negative selection?



Michael C. Carroll
Nature Reviews Immunology 4, 825-831 (2004)

Evidence for genetic susceptibility in lupus

- Approximately 10-fold increase in clinical disease in monozygotic vs. dizygotic twins
- 8-fold or greater relative risk for SLE in first-degree relatives, with 10 to 16 percent of patients with SLE having an affected first- or second-degree relative
- Association and linkage studies show a strong association of the disease with particular HLA haplotypes
- Whole genome scans: multiple additional susceptibility loci have been described, each conferring a small risk -- it all adds up

Genetic susceptibility patterns: clues to pathogenesis

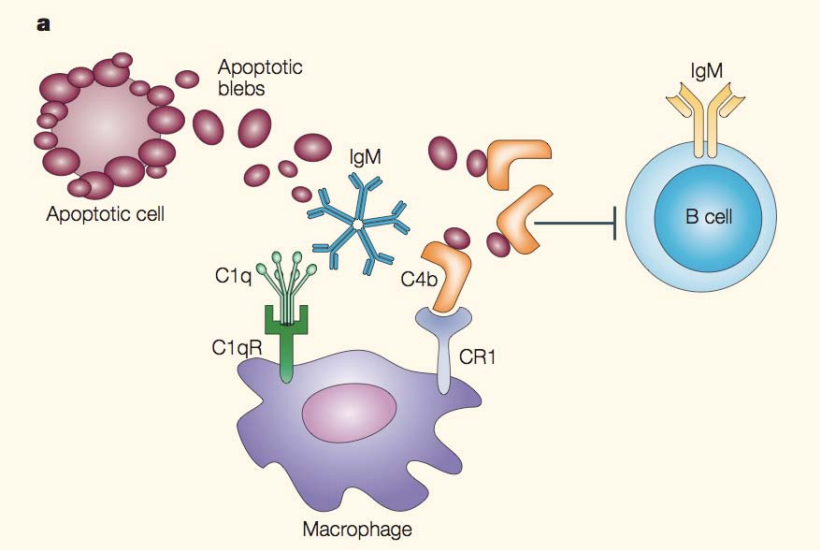
Model:
certain HLA class II alleles may preferentially present selected autoantigens;
the resultant autoantibody profile defines clinical subsets

HLA-DRB1*1501/DQB1*0602	-- nephritis
DR2 with DQw6	-- anti-Smith antibody
HLA DR2/DQw1	-- anti-Ro antibody
HLA DR3/DQw2	-- anti-Ro and La
DR2 or DR3 with DQB1*0201, 0602, 0302	-- anti-dsDNA antibody
DR4 with DQw5	-- anti-U1 RNP antibody
DR4, DR7 with DQw7	-- lupus anticoagulant

Examples are provided for illustrative purposes: do not memorize!

Several important genetic associations in lupus link apoptosis to pathogenesis

Homozygous deficiencies of early complement components (C1q, C2, C4)



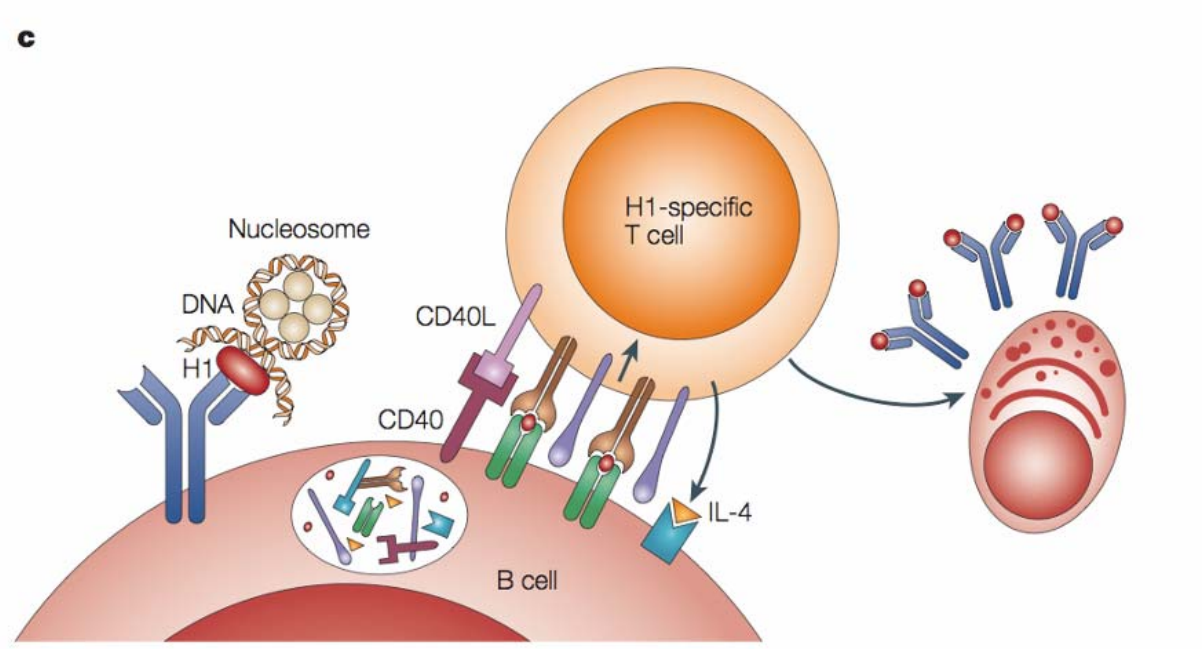
Mannose-binding ligand (MBL) polymorphisms
-> decreased clearance of apoptotic bodies

More recently discovered genetic associations implicate phagocytosis in lupus pathogenesis

FcγRIIB inhibitory receptor -> loss of function mutation

FcγRIIIA stimulatory receptor -> gain of function mutation

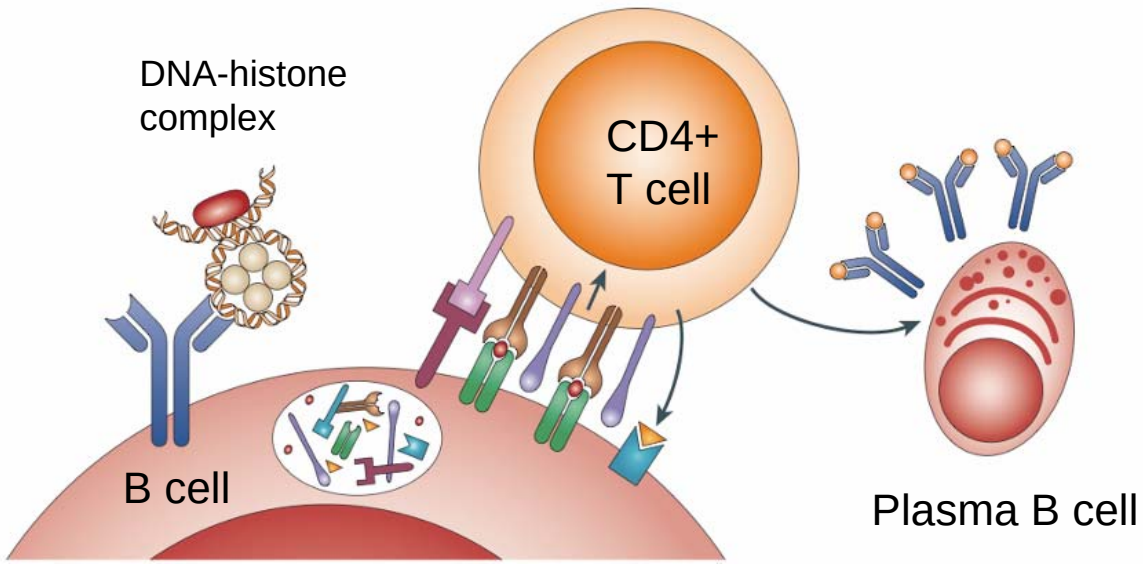
T-B cell cooperation drives the autoimmune response in lupus pathogenesis



Joan T. Merrill, Doruk Erkan & Jill P. Buyon
Nature Reviews Drug Discovery 3, 1036-1046 (2004)

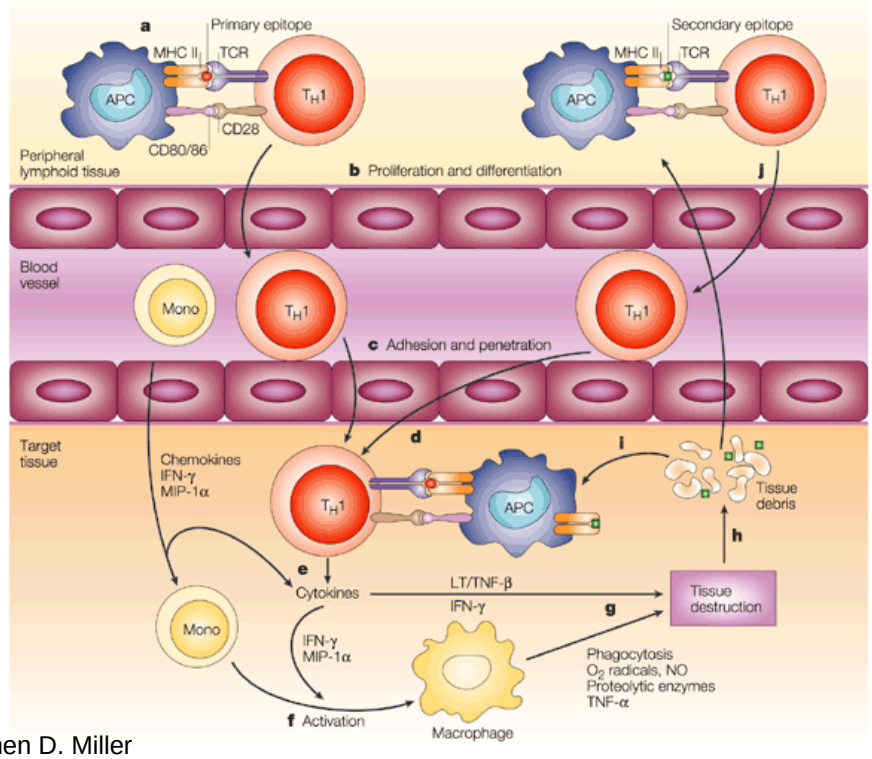
‘Epitope spreading’ in the immune response:

a B cell-targeted autoantigen (DNA) can give rise to
a T-cell response to an associated protein (histone)



Joan T. Merrill, Doruk Erkan & Jill P. Buyon
Nature Reviews Drug Discovery 3, 1036-1046 (2004)

‘Epitope spreading’: tissue damage may allow
the immune response to amplify the scope of its targets



Carol L. Vanderlugt & Stephen D. Miller
Nature Reviews Immunology 2, 85-95 (2002)

Nature Reviews | Immunology

Clinical SLE 1997 Classification Criteria: best at discriminating lupus from other autoimmune diseases

- Positive antinuclear antibody (ANA)
- Malar rash
- Discoid rash
- Photosensitivity
- Oral/nasal ulcers
- Non-erosive arthritis
- Pleuritis/pericarditis
- Glomerulonephritis
- Neuropsychiatric Lupus
- Cytopenias
- Other Lupus serology (Smith Ab, dsDNA Ab, anti-cardiolipin, lupus anticoagulant, false positive RPR)

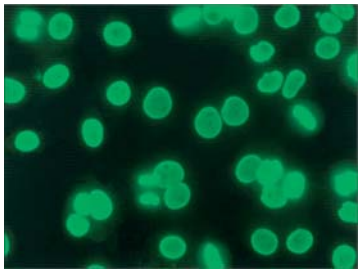
Need 4 criteria to enroll a patient in a clinical study of lupus (very specific)

But:

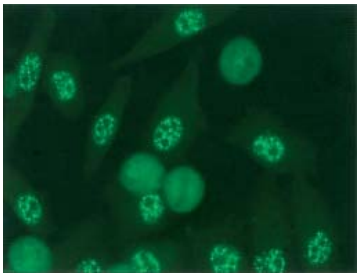
Lack sensitivity for diagnosing an individual patient, and do not include many important manifestations of the disease

Anti-Nuclear Antibodies

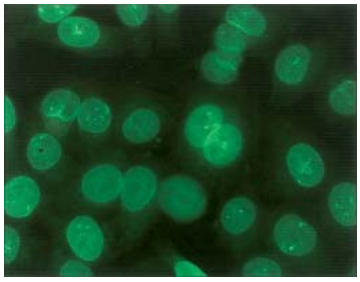
- Positive in >95% SLE patients
- ELISA screen vs. Hep2 cell preparation (immunofluorescence)
- Sensitive but not very specific (superseded the LE cell prep)



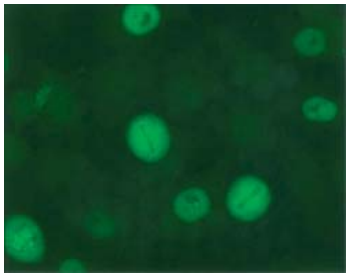
Homogeneous nucleoplasmic



Large speckled nucleoplasmic



Smooth nuclear membrane

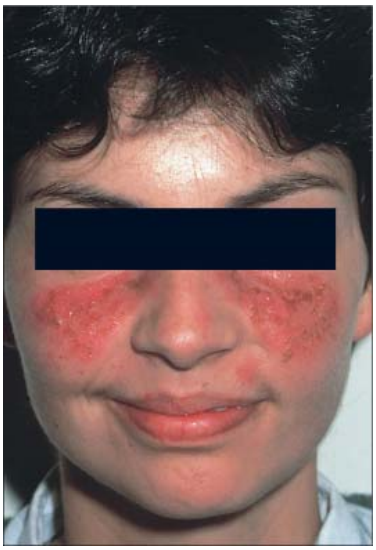


CENP-F staining pattern: seen in a case of malignancy

Lupus rashes are photosensitive

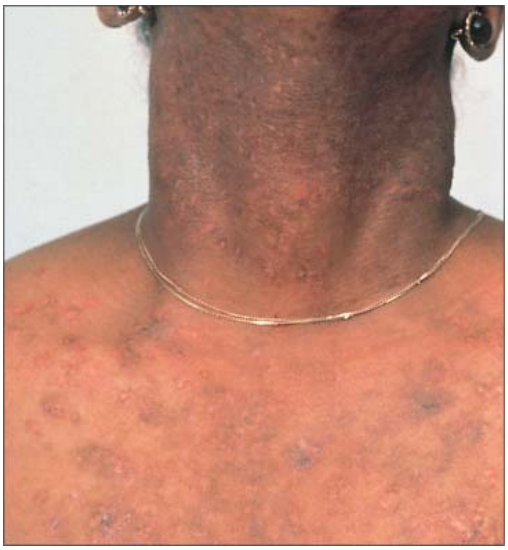
MALAR

- Fixed erythema, flat or raised
- Spares the nasolabial folds
- Heals without scarring
- May correlate with systemic disease



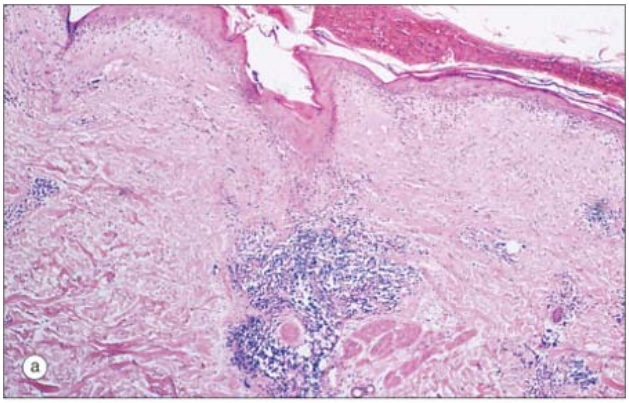
DISCOID

- Erythematous raised patches with keratotic scaling and follicular plugging
- Commonly scars



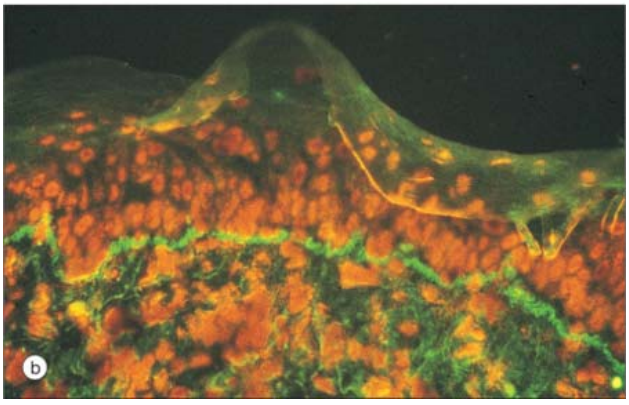
Cutaneous immunopathology

Light microscopy: thickening of the dermal-epidermal junction, inflammatory cells associated with a dermal appendage



The lupus band test:

IgM and C3b at the dermal-epidermal junction in non-sun exposed skin

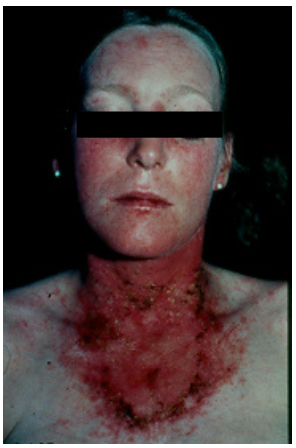


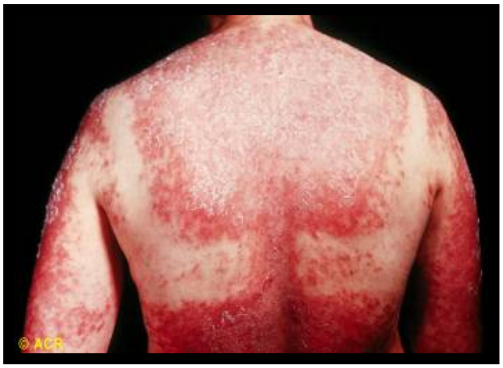
Hochberg Rheumatology

Photosensitivity:
a rash that is induced or exacerbated by sun exposure

Proposed mechanism of systemic complications from sun exposure:

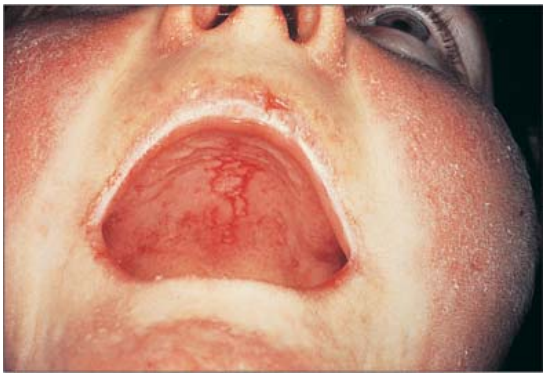
- Ultraviolet A and B exposure induces of apoptosis of keratinocytes
- Activated dendritic cells migrate to draining lymph nodes and initiate a systemic flare of autoimmunity
- Lupus nephritis and other systemic features may result

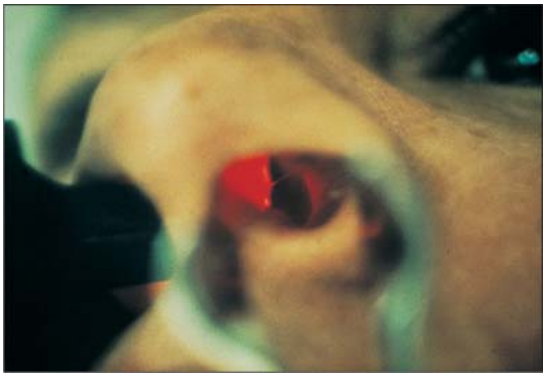




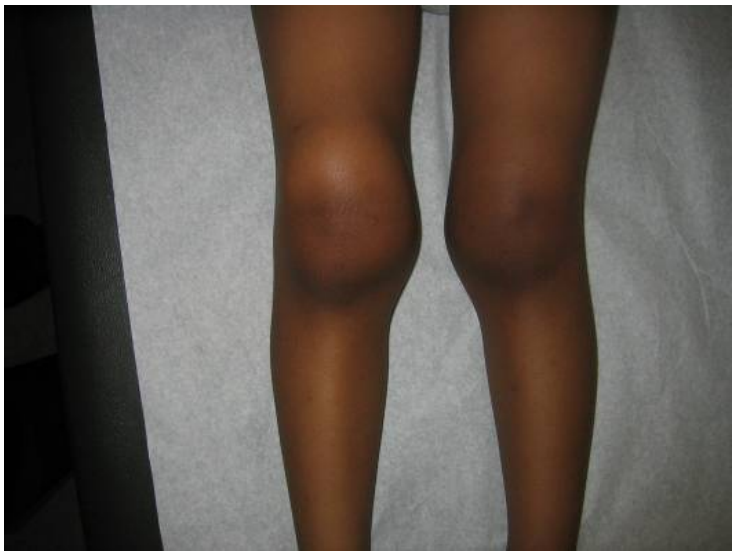
Oral or nasopharyngeal ulcers

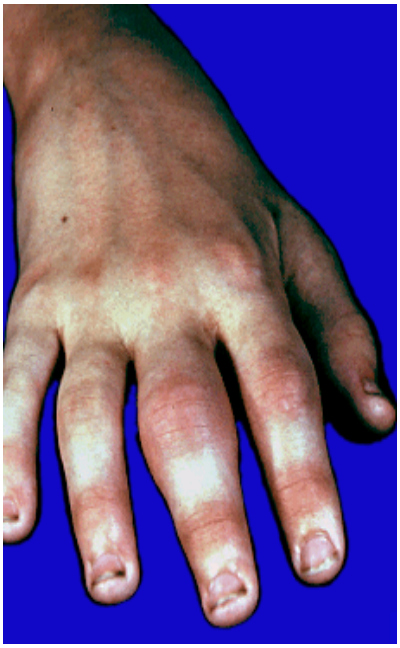
- Typically painless
- Hard palate location
- Sometimes just erythema
- Nasal ulcer may cause erosion/septal perforation
- Can correlate with systemic disease activity





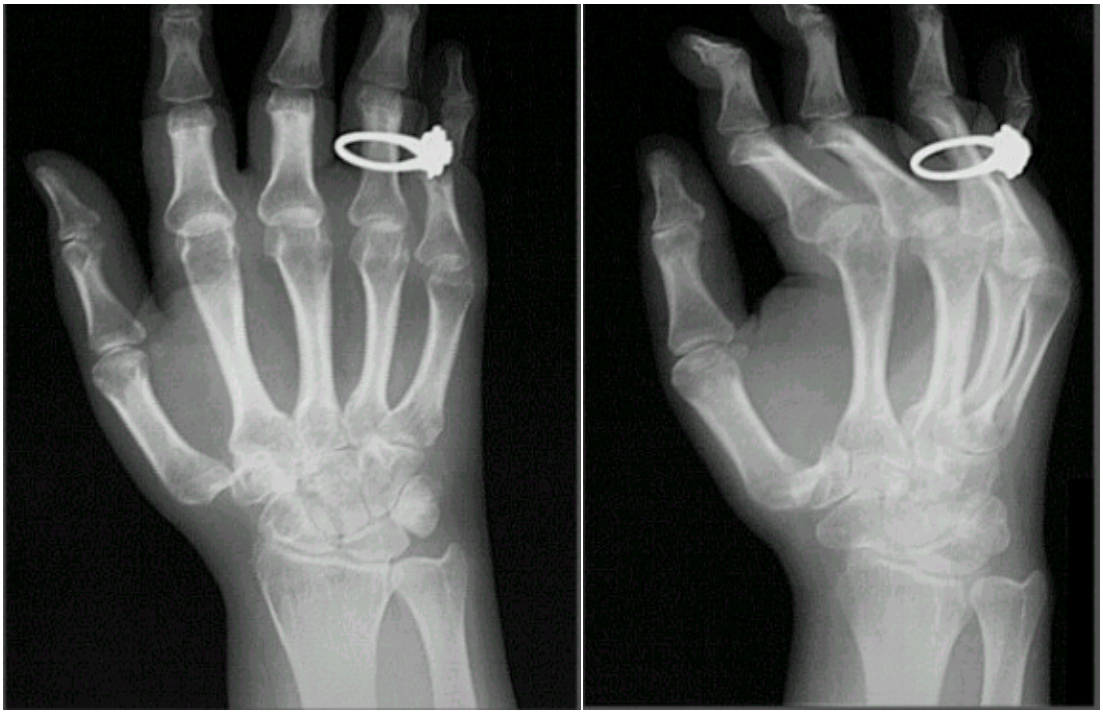
Non-erosive polyarthritis





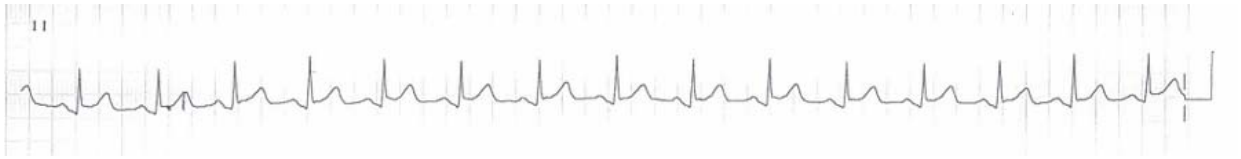
Typically symmetric, involves peripheral (not axial) joints.
In contrast to rheumatoid arthritis,
erosions and overt swelling are uncommon.

Jaccoud’s arthropathy:
ligamentous laxity resulting in deformity



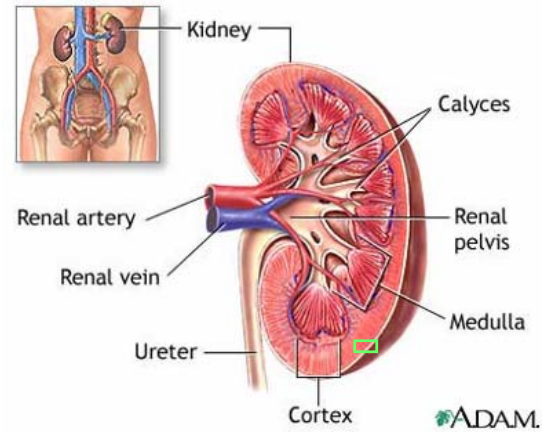
Serositis: inflammation of the pleura or pericardium

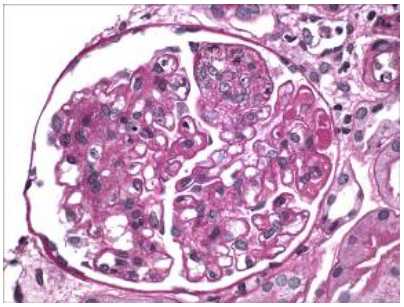
- Pleuritis (40-60%)
  - Inflammation of the pleural lining, leading to pain associated with respiration
- Pericarditis (5-30%)
  - Inflammation of the pericardial lining, leading to chest pain
  - An effusion (accumulation of fluid in the pericardial sac) may occur but rarely interferes with cardiac filling (tamponade)



- Symptoms may vary: chronic cough, chest pain, shortness of breath, exercise intolerance, fatigue

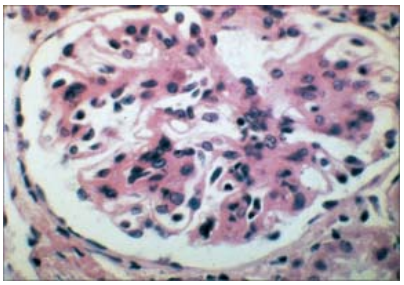
Renal disease in lupus: inflammation of the glomerulus



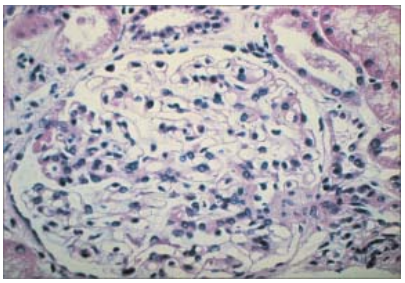


- ACR criterion = glomerulonephritis
- Classes of Lupus Nephritis (LN)
  - WHO Class I-VI
  - Activity index
  - Chronicity index
- Pathology does not always correlate with clinical manifestations

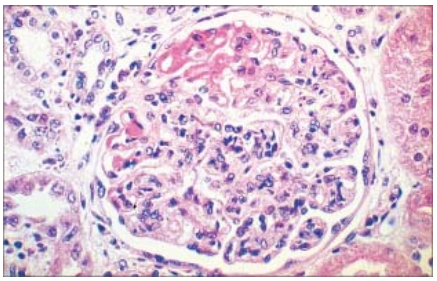
WHO Classification of lupus glomerulonephritis



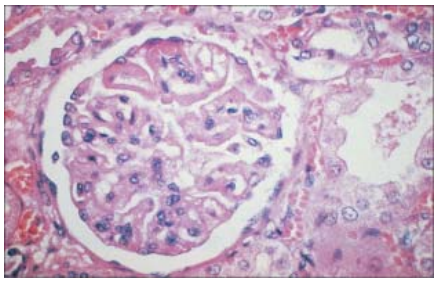
Class II (mesangial)



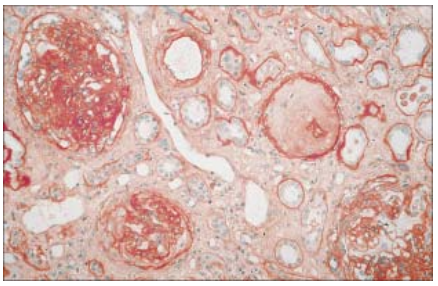
Class III (focal proliferative)



Class IV (diffuse proliferative)



Class V (membranous)



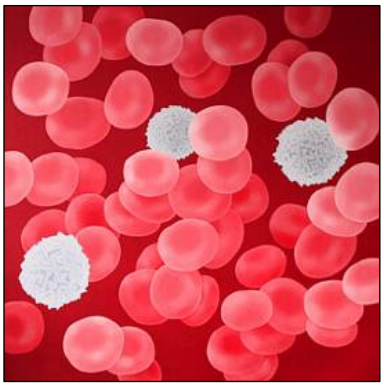
Class VI (advanced sclerosis)

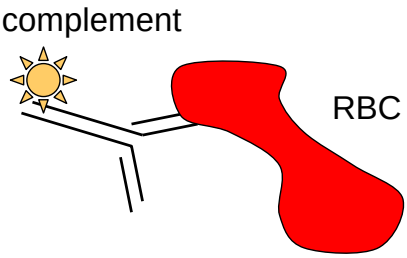
Neuropsychiatric Lupus

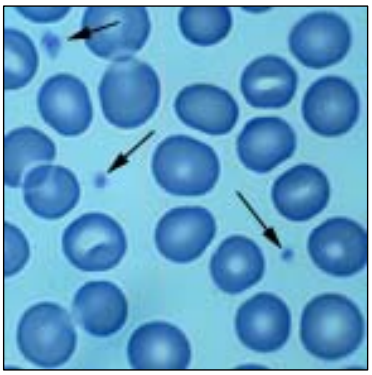
- Seizures or psychosis
  - medications or prior damage must be excluded -- in order to be considered as a classification criterion
- Associated with a higher morbidity and mortality
- Often lack of neuroimaging, biochemical, histologic correlation
- Differential diagnosis: infection, illicit drugs, vasculitis and clot
- Other CNS disease, not included in classification criteria: 17 other syndromes, including transverse myelitis, stroke, depression, headache, cognitive impairment

Cytopenias

- Coomb's positive hemolytic anemia
- Leukopenia (lymphopenia)
- Thrombocytopenia, immune-mediated







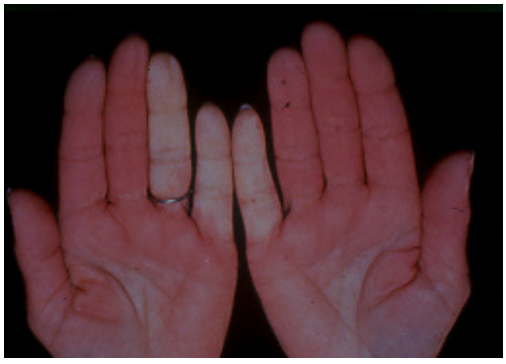
macroplatelets

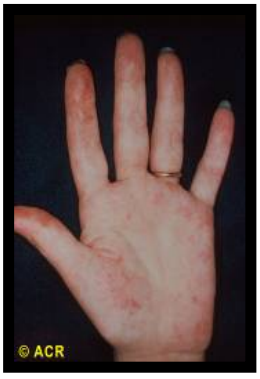
Other Lupus Immunologic Criteria

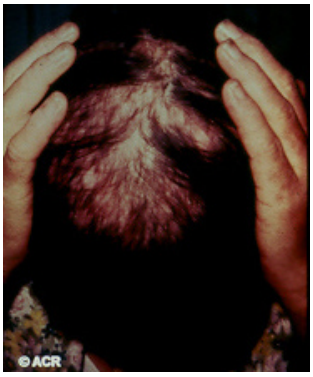
- Anti double stranded-DNA antibody
  - Virtually pathognomonic for SLE
  - May vary with disease activity, along with hypocomplementemia
- Antiphospholipid syndrome immunologic assays
  - False positive RPR (VDRL uses bovine cardiolipin in assay)
  - Anticardiolipin IgM/IgG antibody
  - Lupus anticoagulant
  - Anti β2-glycoprotein I antibody

Popular lupus manifestations that failed to make the cut for “criteria”

- Constitutional features: fever, malaise, fatigue, anorexia/weight loss, lymphadenopathy
- Raynaud’s phenomenon
- Vasculitis
- Alopecia
- Antiphospholipid syndrome





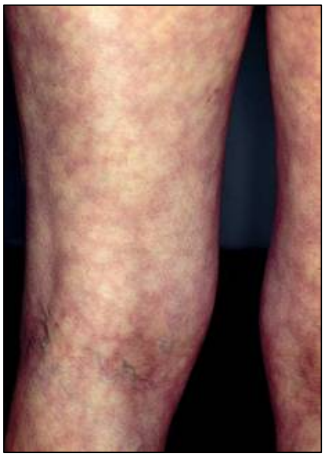


Antiphospholipid Syndrome (APS)

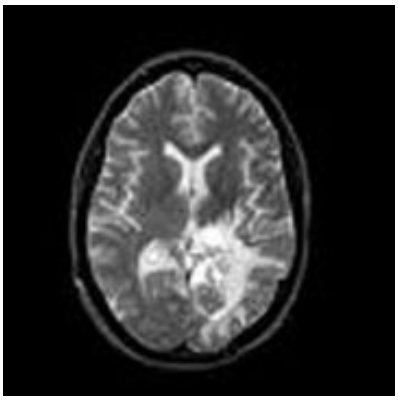
Diagnosis requires: antiphospholipid antibodies (antibodies targeting phospholipid protein complexes), at two time points AND documented clot or pregnancy loss

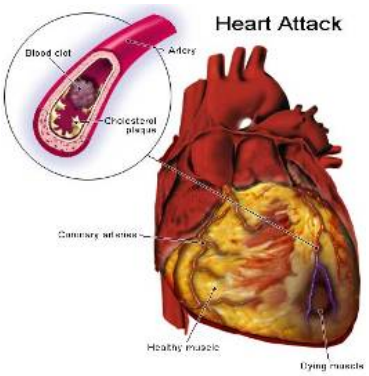
25-40% of lupus patients have antiphospholipid Ab (+/- clot)

Manifests as thrombosis in vessels of any size, resulting in stroke, myocardial infarction, digital gangrene, placental infarction, renal failure, etc.



Livedo reticularis





Management of lupus: goals

- Diagnose early
- Identify (screen for) internal organ involvement
- Target therapy to currently involved organs
- Once remission achieved, prevent relapse/flare
- Prevent damage
  - Treat appropriately and aggressively if warranted
  - Manage/prevent infection
    - Immunizations (Influenza, Pneumococcus, Meningococcus, HPV vaccine)
    - Eternal vigilance: look for and treat infection
    - Prophylaxis for opportunistic infections if potently immunosuppressed
  - Treat or prevent osteoporosis and atherosclerosis

Drugs used in the management of SLE

Agents	Cutaneous	Constitutional	Arthritis/Serositis	Major organ
NSAIDs		√	√	
Corticosteroids				
Topical	√			
Low dose	√	√	√	
High dose				√
Antimalarials	√	√	√	
Dapsone	√			
Thalidomide	√			
Immunosuppressives				
Azathioprine	√	√	√	√
Cyclophosphamide				√
Mycophenolate mofetil				√
Cyclosporin				√
Methotrexate		√	√	
IV Immunoglobulins				√

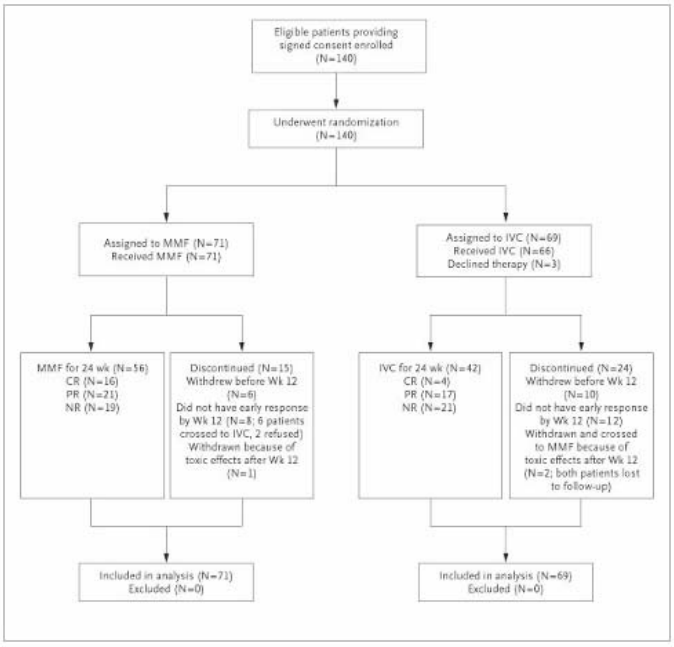
Immunosuppressives: modes of action

- **Corticosteroids**: potent immunosuppressive with multiple modes of action (cytolytic, interferes with cytokine transcription/translation, secretion, etc.)
- **Cyclophosphamide**: alkylating agent that crosslinks DNA, thus causing double-stranded breaks
- **Mycophenolate mofetil**: a reversible inhibitor of inosine monophosphate dehydrogenase, the rate-limiting step in *de novo* purine synthesis --> preferentially affects lymphocytes
- **Azathioprine**: a purine analog, it is a pro-drug for 6-mercaptopurine that antagonizes purine synthesis.
- **Cyclosporin** and **tacrolimus**: calcineurin inhibitors, interfere with signal transduction in T cells (including interleukin-2 expression)

Mycophenolate Mofetil or Intravenous Cyclophosphamide for Lupus Nephritis

Ellen M. Ginzler, M.D., M.P.H., Mary Anne Dooley, M.D., M.P.H., Cynthia Aranow, M.D., Mimi Y. Kim, Sc.D., Jill Buyon, M.D., Joan T. Merrill, M.D., Michelle Petri, M.D., M.P.H., Gary S. Gilkeson, M.D., Daniel J. Wallace, M.D., Michael H. Weisman, M.D., and Gerald B. Appel, M.D.

New Engl J Med 353:2219-2228 (2005)



A 24-week RCT comparing iv monthly cyclophosphamide (titrated from 500 - 1000 mg/m^2) with daily mycophenolate mofetil (titrated from 1 - 3 gm/day) as induction therapy for lupus nephritis

Primary endpoint: complete response at 24 weeks

Table 4. Outcomes during Follow-up after Induction Therapy.*

Event	No. of Events		Relative Risk (95% CI)†	P Value
	Mycophenolate Mofetil	Intravenous Cyclophosphamide		
First renal flare	8	8	0.98 (0.37–2.61)	0.96
Renal failure	4	7	0.53 (0.15–1.81)	0.31
Death	4	8	0.48 (0.15–1.60)	0.24

* Relative risks were determined with the use of the Cox proportional-hazards model.
† Values are for mycophenolate mofetil therapy as compared with intravenous cyclophosphamide therapy.

In general, treatment is tailored to the clinical manifestation, because the most potent interventions are also the most toxic

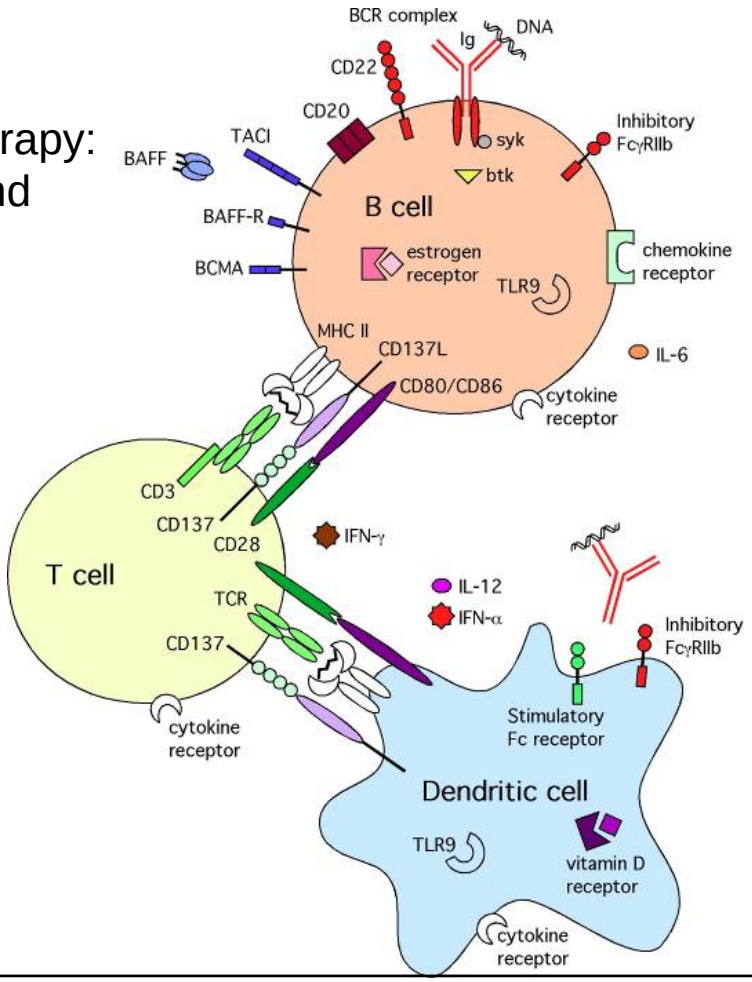
BEFORE:

Severe diffuse discoid rash, alopecia despite antimalarials, moderate dose steroids, dapsone…

AFTER:

Following aggressive treatment with high dose steroids and cyclophosphamide (for CNS vasculitis)

Molecularly targeted therapy: balancing efficacy and safety?

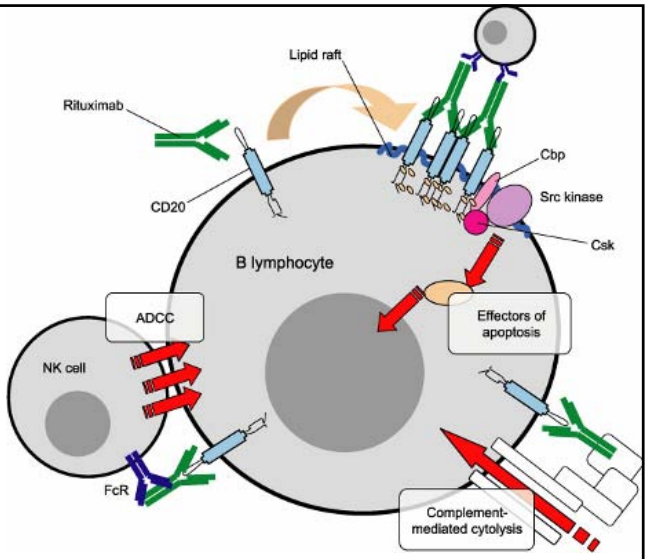


Blockade of antigenic triggering and activation of the B cell compartment: is it too late once symptoms have developed?

- Recombinant human DNAse: no efficacy.
- LJP394: a molecular mimic of DNA structure -- phase III completed.
- Belimumab: blocking antibody against the B-cell survival factor BAFF/Blys -- phase I completed.
- Epratuzumab: blocking antibody against the B cell surface molecule CD22 (tuning of B cell receptor signal): open label study 2006 (Dörner, T), RCT results announced at ACR 2008 (Wallace, DJ) -- improved BILAG response in treatment arms.
- Atacicept (TACI:Fc5): homodimeric fusion protein, soluble decoy receptor for BAFF/Blys -- in phase II/III trials for SLE and nephritis

Depleting B cells: rituximab

- Chimeric monoclonal antibody recognizing CD20
- Depletes most B cells, but not the plasma cell compartment (CD20-variable) nor the lymphoid progenitor
- Postulated to disrupt cytokine networks and interfere with antigen presentation, 'reset' the immune repertoire



Caveat Emptor: 2 RCTs in lupus have failed to meet their primary endpoint:

EXPLORER: A randomized, blinded, placebo-controlled, phase II/III study to evaluate the efficacy and safety of rituximab in subjects with moderate to severe systemic lupus erythematosus (257 patients). Primary endpoint = major or partial clinical response as assessed by the BILAG activity index.

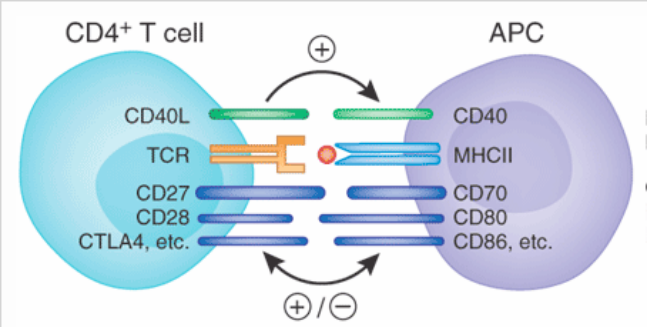
LUNAR: A randomized, blinded, placebo-controlled phase III study to evaluate the efficacy and safety of rituximab in subjects with class III or IV lupus nephritis who were concomitantly treated with mycophenolate mofetil. Primary endpoint = major or partial renal response (proteinuria, CrCl, sediment). No benefit over MMF alone.

Targeting T cells makes sense

- Mycophenolate mofetil / mycophenolic acid, cyclosporin and tacrolimus show efficacy

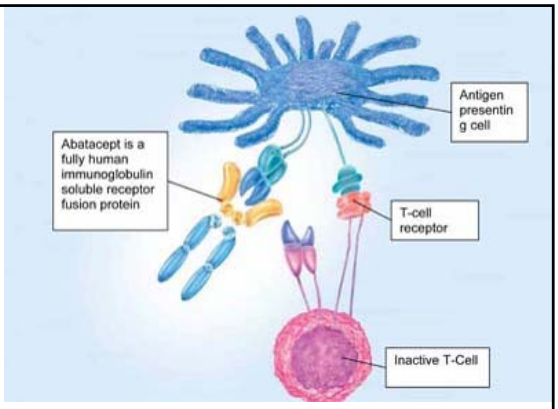
CD40L blocking antibody:

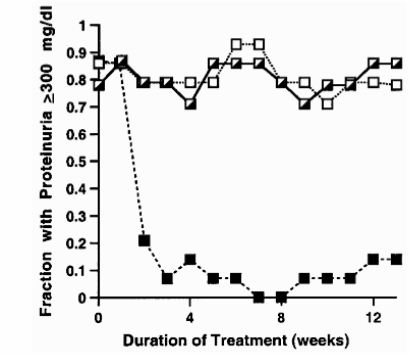
- Interferes with bidirectional signaling between T cells and professional antigen-presenting cells,
- Very effective
- But: unacceptable pro-thrombotic effects in a subset of patients



Targeting T cells: abatacept

- Fusion protein joining the extracellular moiety of CTLA with the Fc portion of IgG
- Binds the costimulatory molecules CD80 and CD86 with high affinity, thus blocking ‘signal 2’ to naïve T cells
- Synergy with cyclophosphamide in a rodent model of lupus nephritis (NZB/W): reversal of established disease (Daikh and Wofsy, UCSF)



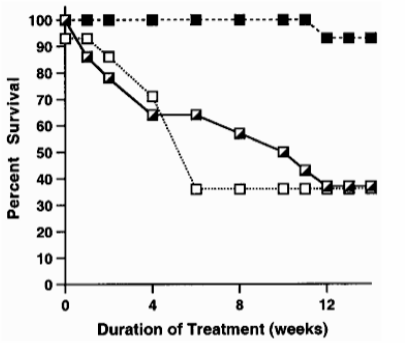


CTX only

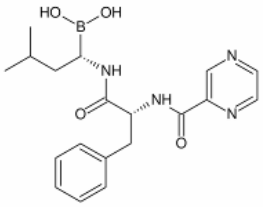
CTLA4-Ig only

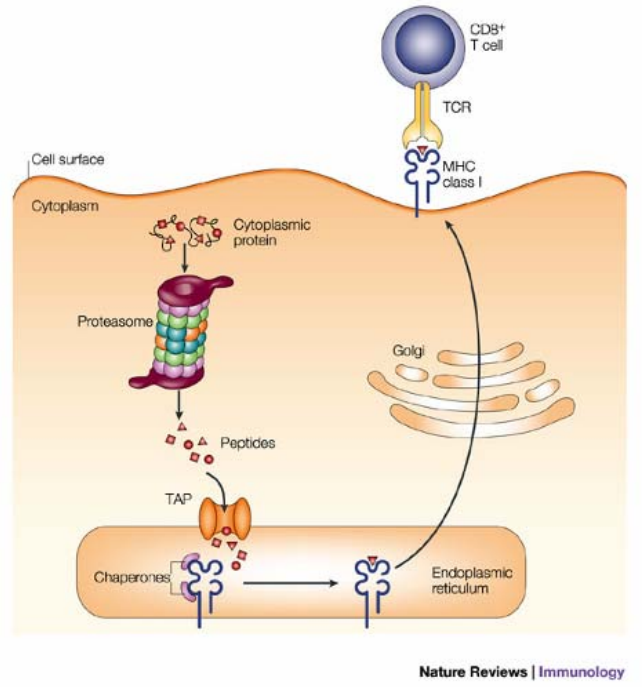
CTX + CTLA4-Ig

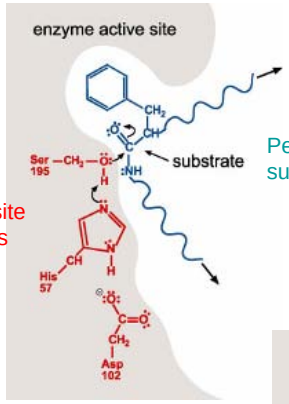
CTX + CTLA4-Ig



Targeting the proteasome: bortezomib



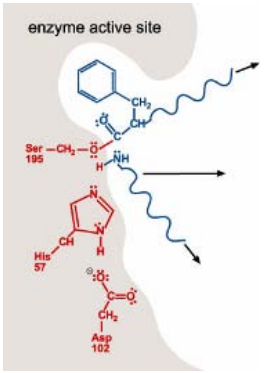




Active site residues

Peptide bond in substrate protein

the chymotryptic site is bound reversibly and with high affinity



From Jonathan W. Yewdell, Eric Reits & Jacques Neefjes
Nature Reviews Immunology 3, 952-961 (December 2003)

Systemic Lupus Erythematosus -- key concepts

A systemic autoimmune syndrome with pleiotropic organ involvement (affects multiple organs in multiple ways)

May present in a variety of ways

The clinical course is unpredictable

Other diseases may mimic lupus

Diagnosis is often delayed

Laboratory testing serves as an adjunct to the clinical history and physical findings