

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

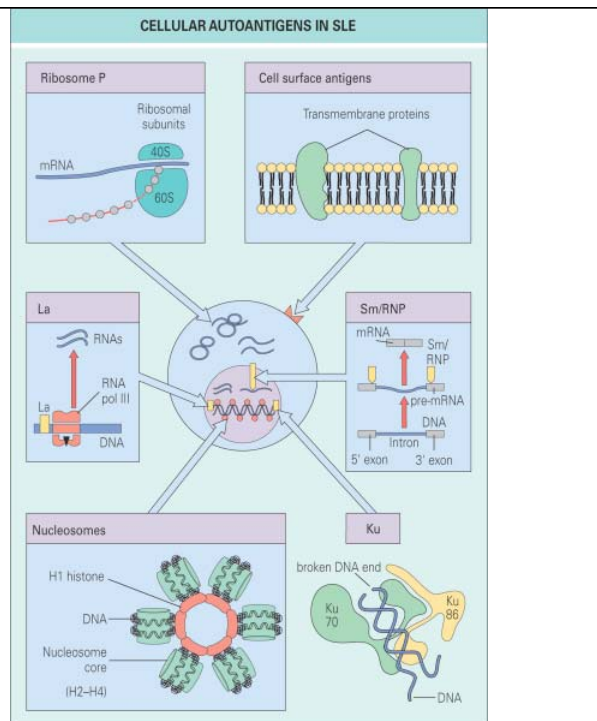
Hallmark: formation of auto-antibodies, whose targets include ubiquitously expressed nuclear and cytoplasmic components

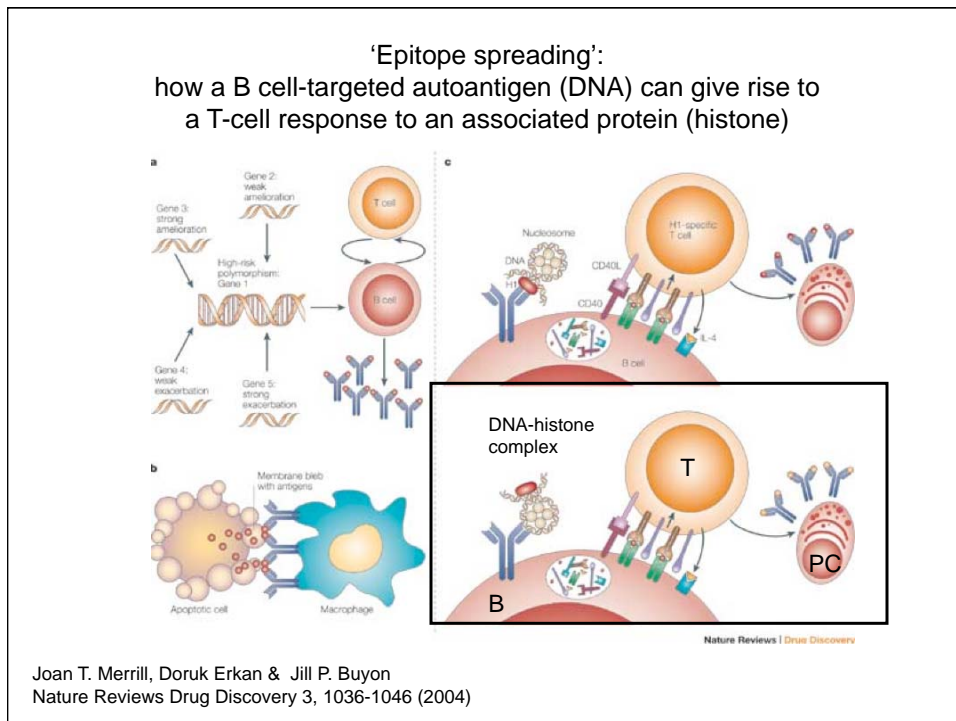
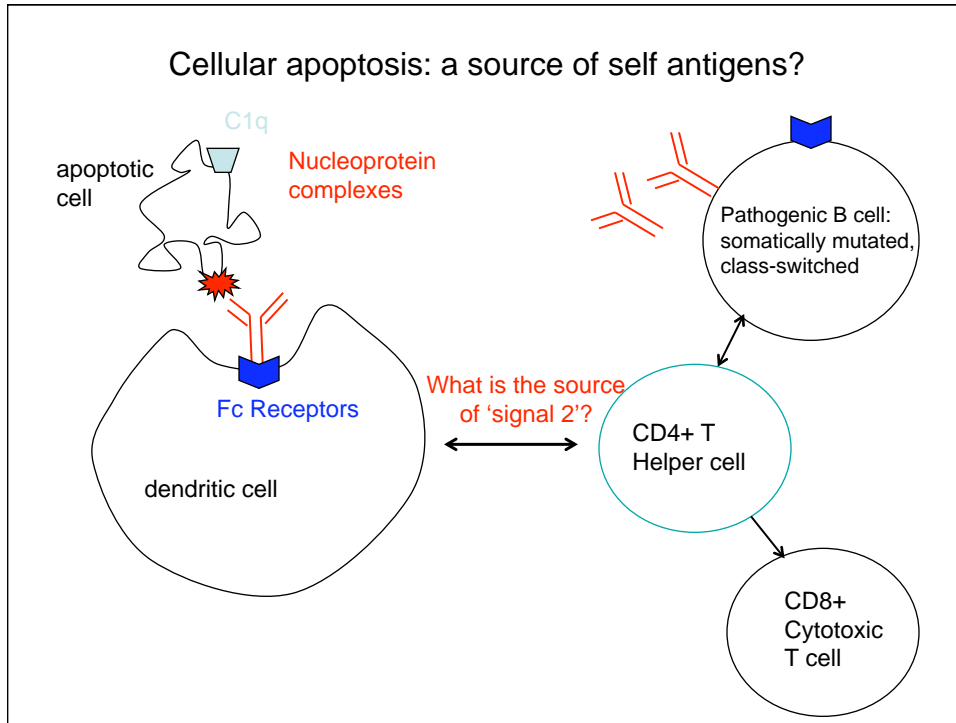
Auto-antibodies can be detected in serum up to 9 years before the first sign or symptom of lupus

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

Cellular autoantigens in SLE

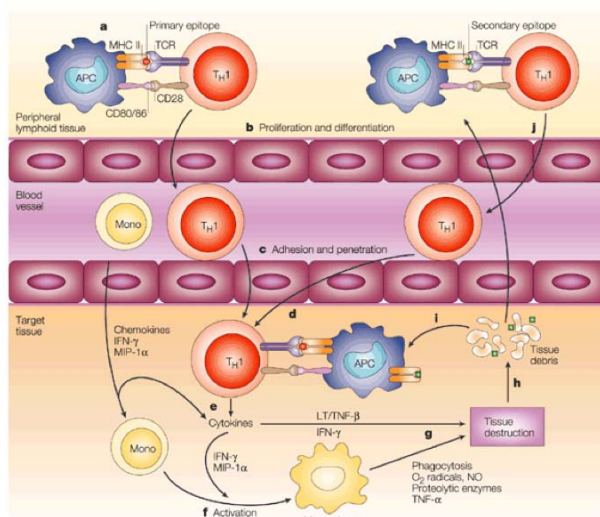
Keith Elkon,
in Hochberg Rheumatology





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

'Epitope spreading': how tissue damage allows 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

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 an 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

Certain HLA class II alleles may preferentially present selected autoantigens; the resultant autoantibody profile defines clinical subsets in SLE

HLA-B8/DRB1*0301/DQB1*0201	-- anti-Ro antibody
HLA-DRB1*1501/DQB1*0602	-- nephritis
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
DR2 with DQw6	-- anti-Smith antibody
DR4, DR7 with DQw7	-- lupus anticoagulant

Examples are provided for illustrative purposes: do not memorize!

Other genetic associations in lupus: apoptosis and phagocytosis

- Homozygous deficiencies of early complement components (C1q, C2, C4) -> loss of apoptotic body clearance
- Mannose-binding ligand (MBL) polymorphisms -> decreased clearance of apoptotic bodies
- Fc γ RIIB receptor allele -> loss of function -> increased inflammation
- Fc γ RIIIA receptor allele -> gain of function -> increased inflammation
- Promoter polymorphisms of interleukin-10 -> loss of regulation

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)

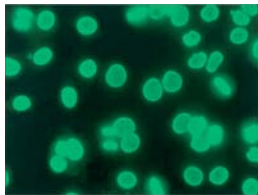
Need 4 criteria to enroll a patient in a clinical study of lupus (very specific)

But:

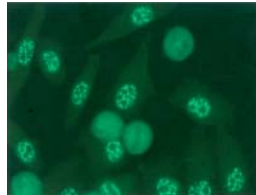
Lack sensitivity for diagnosing an individual patient, and do not include many important manifestations of the disease

Anti-Nuclear Antibodies

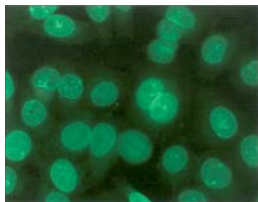
- Positive in >95% SLE patients
- ELISA screen vs. Hep2 cell preparation (immunofluorescence)
- Sensitive but not very specific (superseded the LE cell prep)



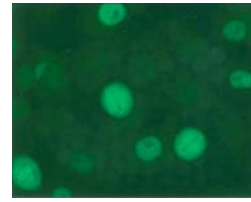
Homogeneous nucleoplasmic



Large speckled nucleoplasmic



Smooth nuclear membrane

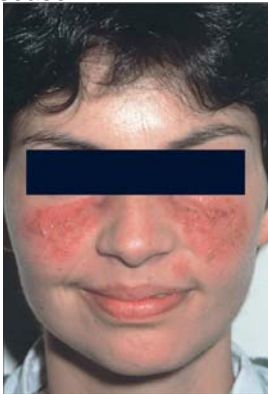


CENP-F staining pattern: seen in a case of malignancy

Lupus rashes are photosensitive

MALAR

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



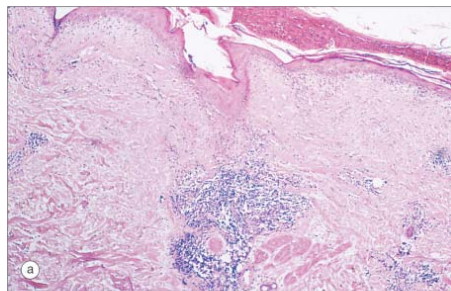
DISCOID

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

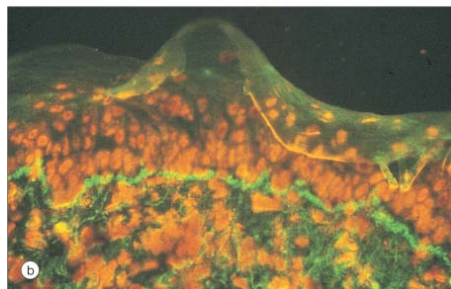


Cutaneous immunopathology

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 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



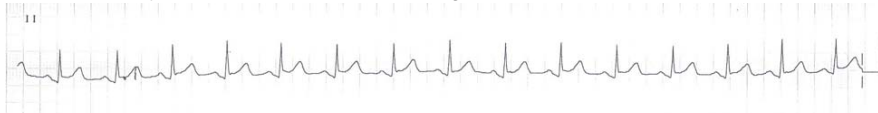
Typically symmetric, involves peripheral (not axial) joints.
In contrast to rheumatoid arthritis,
erosions and overt swelling are uncommon.

Jaccoud's arthropathy: ligamentous laxity resulting in deformity



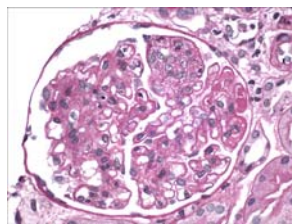
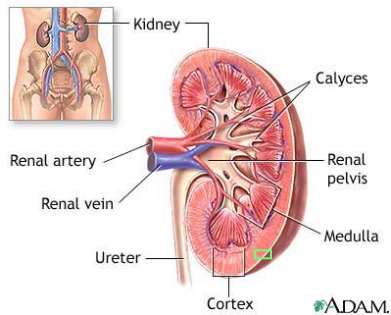
Serositis: inflammation of the pleura or pericardium

- 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)



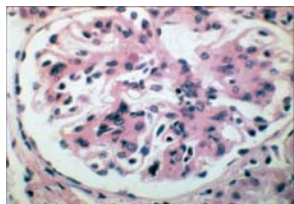
- Symptoms may vary: chronic cough, chest pain, shortness of breath, exercise intolerance, fatigue

Renal disease in lupus: inflammation of the glomerulus

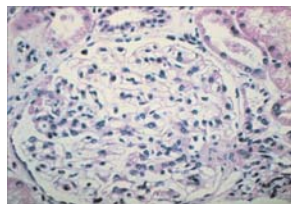


- ACR criterion = glomerulonephritis
- Classes of Lupus Nephritis (LN)
 - WHO Class I-VI
 - Activity index
 - Chronicity index
- Pathology does not always correlate with clinical manifestations

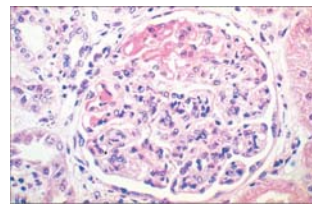
WHO Classification of lupus glomerulonephritis



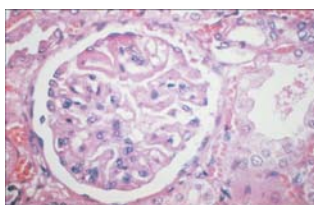
Class II (mesangial)



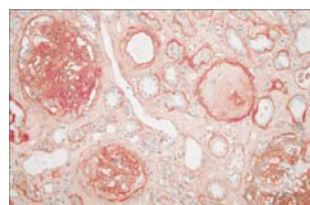
Class III (focal proliferative)



Class IV (diffuse proliferative)



Class V (membranous)



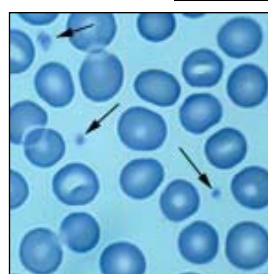
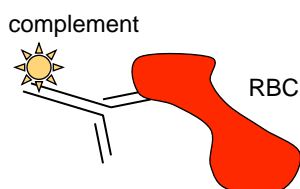
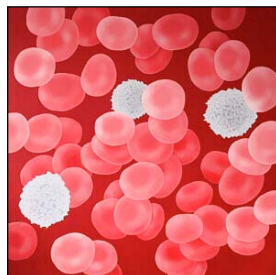
Class VI (advanced sclerosis)

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: 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 β 2-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

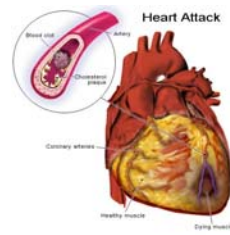
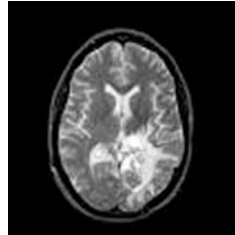


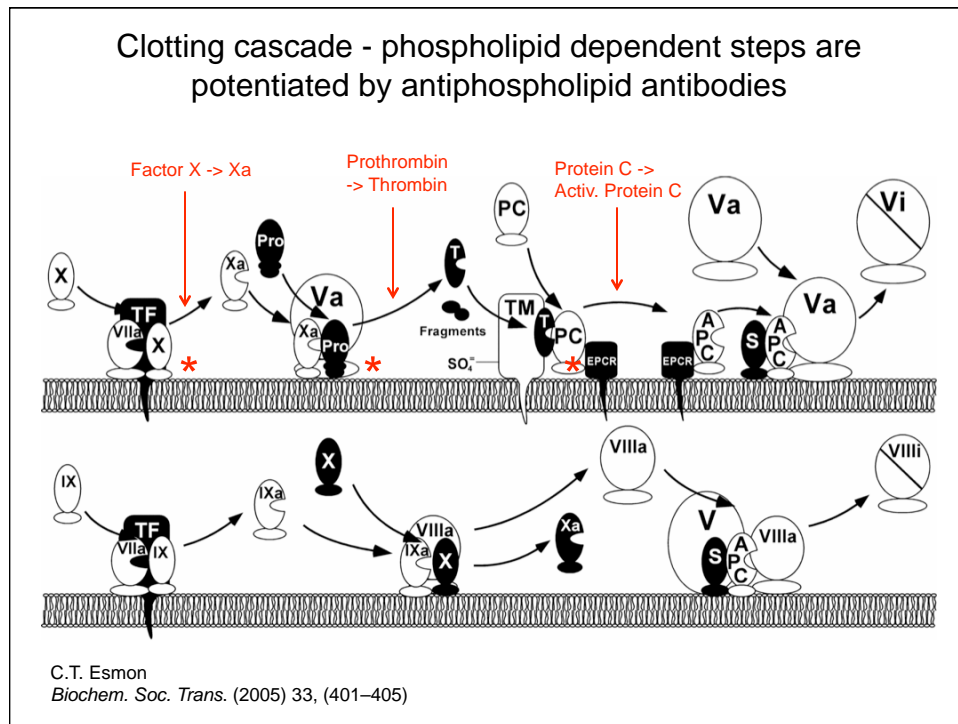
Antiphospholipid Syndrome (APS)

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.





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 potentially immunosuppressed
 - Treat or prevent osteoporosis and atherosclerosis

Drugs used in the management of non-renal SLE					
Agents	Constitutional	Musculoskeletal	Serositis	Cutaneous	Major organ
NSAIDs	√	√	√		
Corticosteroids					
Topical				√	
Low dose	√	√	√	√	
High dose					√
Antimalarials	√	√	√	√	
Dapsone				√	
Thalidomide				√	
Immunosuppressives					
Azathioprine	√	√	√	√	√
Cyclophosphamide					√
Mycophenolate mofetil					√
Cyclosporin					√
Methotrexate		√	√		
IV Immunoglobulins					√

Drugs used in the management of lupus glomerulonephritis

The kidney is the most frequently targeted organ: 60-70% of lupus patients have renal involvement during the course of their disease -- but in the majority of cases, remission can be achieved.

- Corticosteroids: potent immunosuppressive with multiple modes of action (cytolytic, interferes with cytokine transcription/translation, secretion, etc.)
- Cyclophosphamide: alkylating agent that cross-links 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.

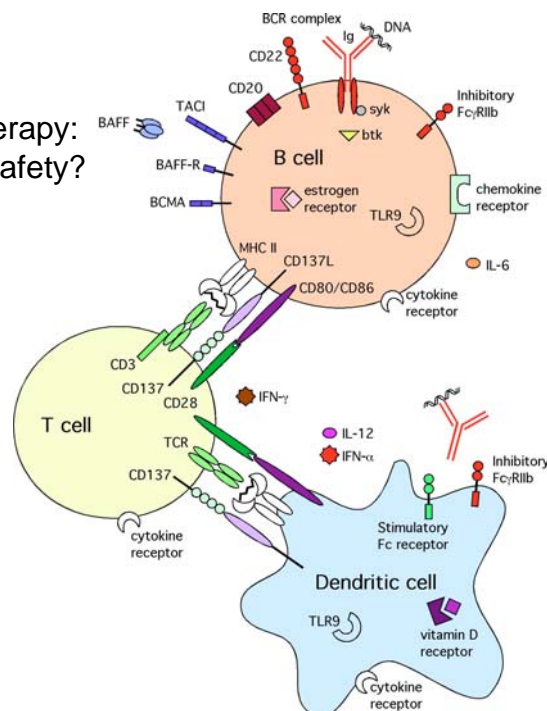
In general, treatment is tailored to the clinical manifestation, because the most potent interventions are also the most toxic



Severe diffuse discoid rash, alopecia despite antimalarials, moderate dose steroids, dapsons...

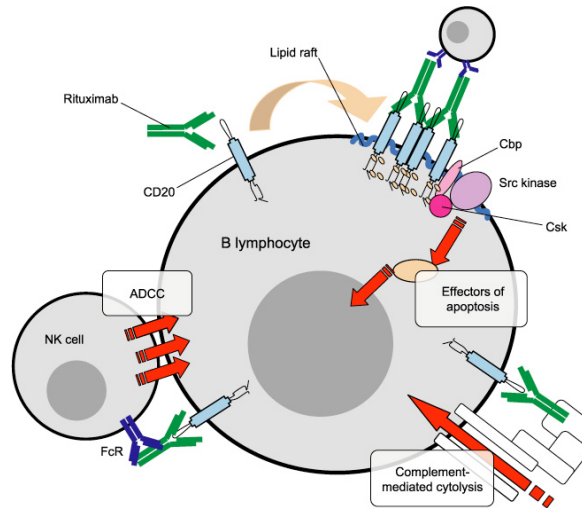
Resolution of rash after aggressive treatment with high dose steroids and cyclophosphamide (for CNS vasculitis)

Molecularly targeted therapy: balancing efficacy and safety?



Targeting B Cells

- **Rituximab:** a chimeric anti-CD20 monoclonal antibody (murine variable region, human framework) first approved for the treatment of B cell lymphoma
- Depletes CD20⁺ B cells, but spares the CD20⁻ plasma B cells
- Postulated to disrupt B cell-driven antigen presentation and cytokine networks



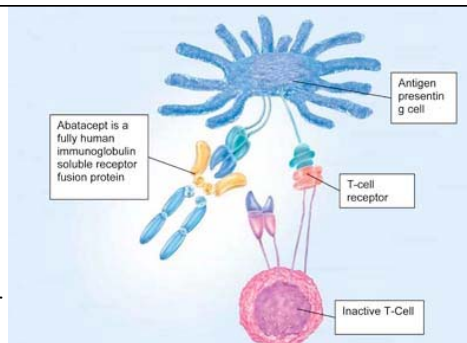
Caveat Emptor:

- The EXPLORER study (large cohort of lupus patients) showed no benefit over placebo
- Unclear if B cell depletion “resets” the immune repertoire -- for good or ill

Targeting T Cells

- **Abatacept (CTLA4-Ig)**

- A fusion protein joining the extracellular moiety of the CTLA4 molecule with the Fc portion of an IgG antibody
- Binds the costimulatory molecules CD80/CD86 with high affinity, preventing the antigen-presenting cell from activating a T cell via CD28 (“signal 2”) -- may also deliver an inhibitory ‘tolerogenic’ signal to the APC itself
- Synergizes with cyclophosphamide in the treatment of lupus nephritis in NZB/W mice -- clinical trials for lupus are ongoing
- Somewhat effective in the treatment-refractory rheumatoid arthritis, and no safety issues to date



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