



SYSTEMIC LUPUS ERYTHEMATOSUS OVERVIEW

Clinical presentation, pathophysiology, and therapeutic strategies over the course of disease



WELCOME

Before we get started...

ABOUT THIS PROJECT

- The presentation is designed to be easily incorporated into medical school lectures on a variety of topics; they are tailor-made for the classroom setting, and easy to digest
- The PowerPoint presentation is designed for medical students M3 and M4

DRUGS AND DOSES

When prescribing medications, the physician is advised to check the product information sheet accompanying each drug to verify conditions of use and to identify any changes in drug dosage schedule of contra-indications.

USE OF PROFESSIONAL JUDGMENT

This activity, including all educational links, is intended to be used as a tool to assess the base knowledge of the learner. The information presented relates to basic principles of diagnosis and therapy, and is meant in no way to substitute for an individual patient assessment based upon the healthcare provider's examination of the patient and consideration of laboratory data and other factors unique to the patient.

ACR DISCLOSURE STATEMENT

The American College of Rheumatology is an independent, professional organization that does not endorse specific procedures or products of any pharmaceutical/biotech concern.

SUPPORT

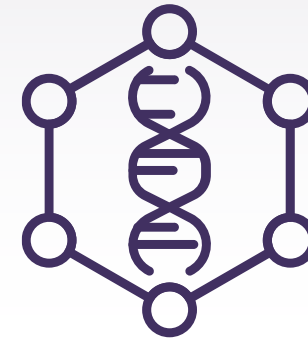
The project described is, in part, supported by the Centers for Disease Control and Prevention under Cooperative Agreement Number NU58 DP006138. Its contents are solely the responsibility of its developers/authors. Points of view or opinions do not, therefore, necessarily represent official views of the Centers for Disease Control and Prevention or the Department of Health and Human Services.

FACULTY REPORTED DISCLOSURES

[To be filled in]

Learning Objectives

- Describe the epidemiology of systemic lupus erythematosus (SLE)
- Identify the signs and symptoms of SLE
- Understand proposed mechanisms for development and progression of SLE, including the role of antinuclear antibodies, genetics, and environmental triggers
- Recognize the options for treatment for people with SLE



Our Patient

History

- A 23-year-old previously healthy woman presented to the emergency department (ED) with an 8-week history of joint pain and swelling in the hands, knees, and ankles; fever; myalgias; pleuritic chest pain; weight loss; and a facial rash that worsened with sun exposure.
- She had been seen initially at a local clinic and treated for “cellulitis” with oral cephalexin.
- Two days prior to this presentation, she was seen in another ED, found to have a temperature of 103°F, proteinuria, and anemia; she was told it was a “viral syndrome” and discharged home.



Our Patient

PMH: None

Allergies: NKDA

Meds: None

FH: Mother with Hashimoto's thyroiditis

SH: She is of Mexican ancestry. Her parents immigrated to the US when she was a baby. No recent travel outside of the US. She recently graduated from college and is interested in pursuing a law degree. She does not smoke or use illicit drugs. She drinks 1-3 beers per week.



Our Patient

Exam: T 37.9°C, BP 130/90, painless ulceration on the palate, erythematous malar rash, diffuse lymphadenopathy, and synovitis of the MCP/PIP joints

Lab	Result	Normal range
WBC	2.5	3.4-10.0 x10 ⁹ /L
Hgb	11	12.0-15.5 g/dL
Plt	96	140-450x10 ⁹ /L
Cr	0.6	0.55-1.02 mg/dL
Albumin	3	3.8-4.9 g/dL
UA	100 mg/dL protein, RBC 20–40, WBC 0–1	NEG prot, <3 RBC/hpf, <5 WBC/hpf
ANA	>1:640 speckled	<1:40
dsDNA ab	51	<27.0 IU/mL

Izmirlly PM, Parton H, Wang L, et al. Prevalence of Systemic Lupus Erythematosus in the United States: Estimates From a Meta-Analysis of the Centers for Disease Control and Prevention National Lupus Registries. Arthritis Rheumatol. 2021 Jun;73(6):991-996



She is diagnosed with SLE and has many questions for you...

1. What is SLE?
2. How did I get it?
3. What is going to happen to me?
4. What can I do to improve my health?

Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum.* 1982;25:1271-1277.

Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. *Arthritis Rheum.* 1997;40:1725.

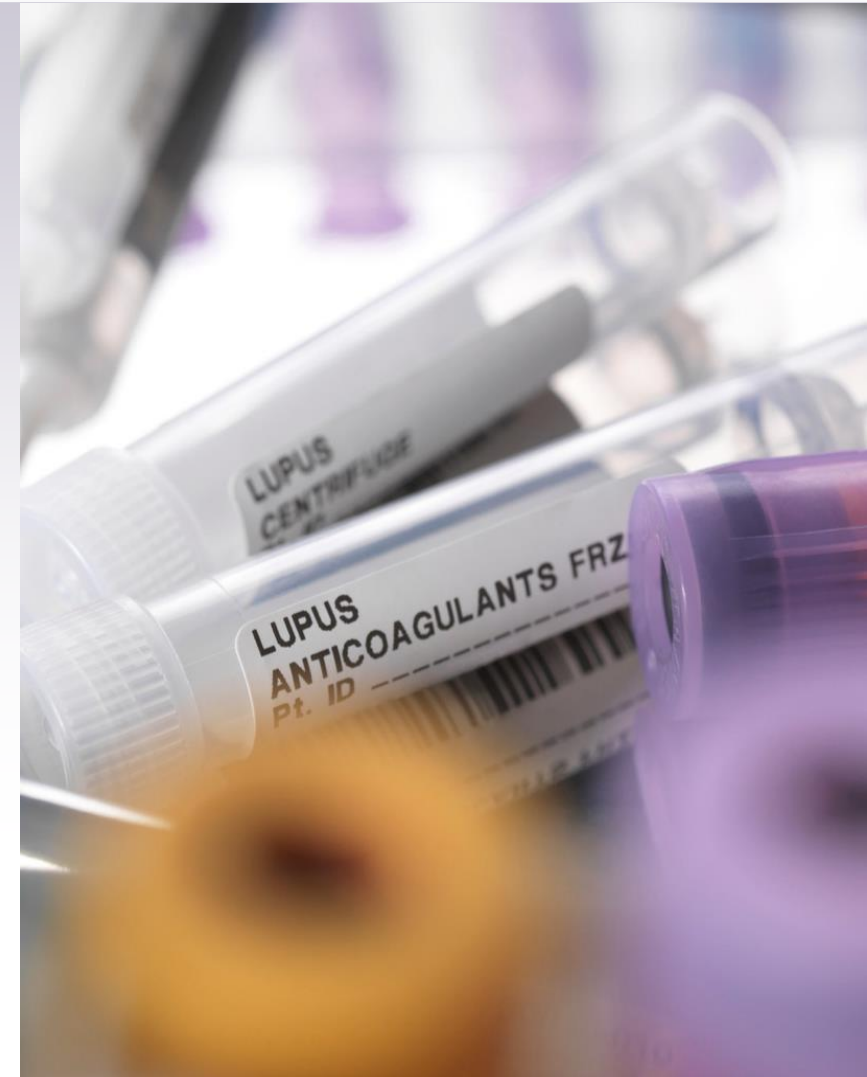
Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. *Arthritis Rheumatol.* 2019;71(9):1400-1412.



What is SLE?

Systemic Lupus Erythematosus

- An inflammatory, multisystem, autoimmune disease of unknown etiology with protean clinical and laboratory manifestations and a variable course and prognosis
- Lupus can be a mild disease, a severe and life-threatening illness, or anything in between



Clinical Manifestations of SLE— Important Concepts

- The diversity of clinical manifestations in SLE is, and all organ systems are vulnerable
- Different ethnic backgrounds are associated with differences in disease prevalence and severity
- Disease prevalence and severity have been reported to vary by ethnic background



Epidemiology

Prevalence: 72.8 per 100,000 person years (2021 meta-analysis of 4 state specific registries in US)

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Incidence: 1–10/100,000 worldwide

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Population at highest risk:

- Women in their reproductive years
- Female: male ratio is approximately 9:1 post puberty and premenopausal

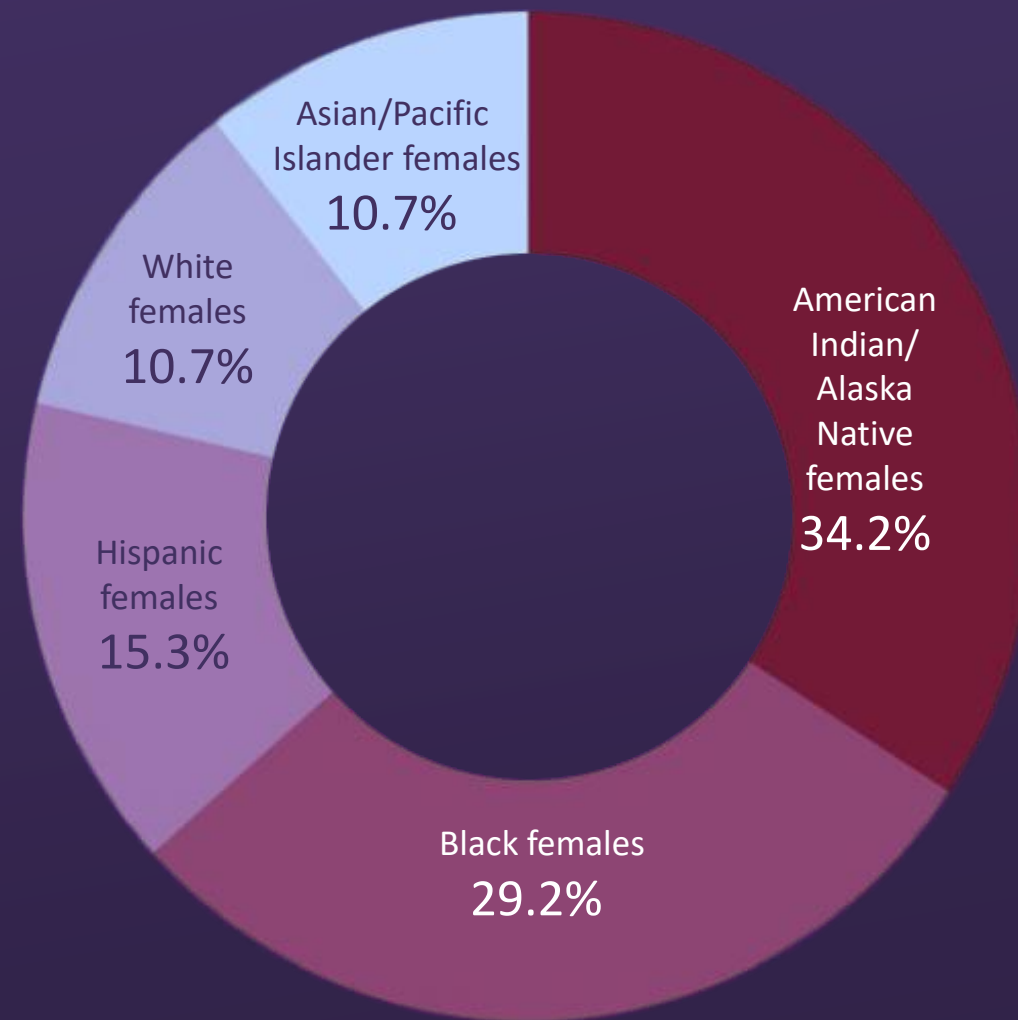


Izmirlly PM, Parton H, Wang L, et al. Arthritis Rheumatol. 2021 Jun;73(6):991-996.

Epidemiology

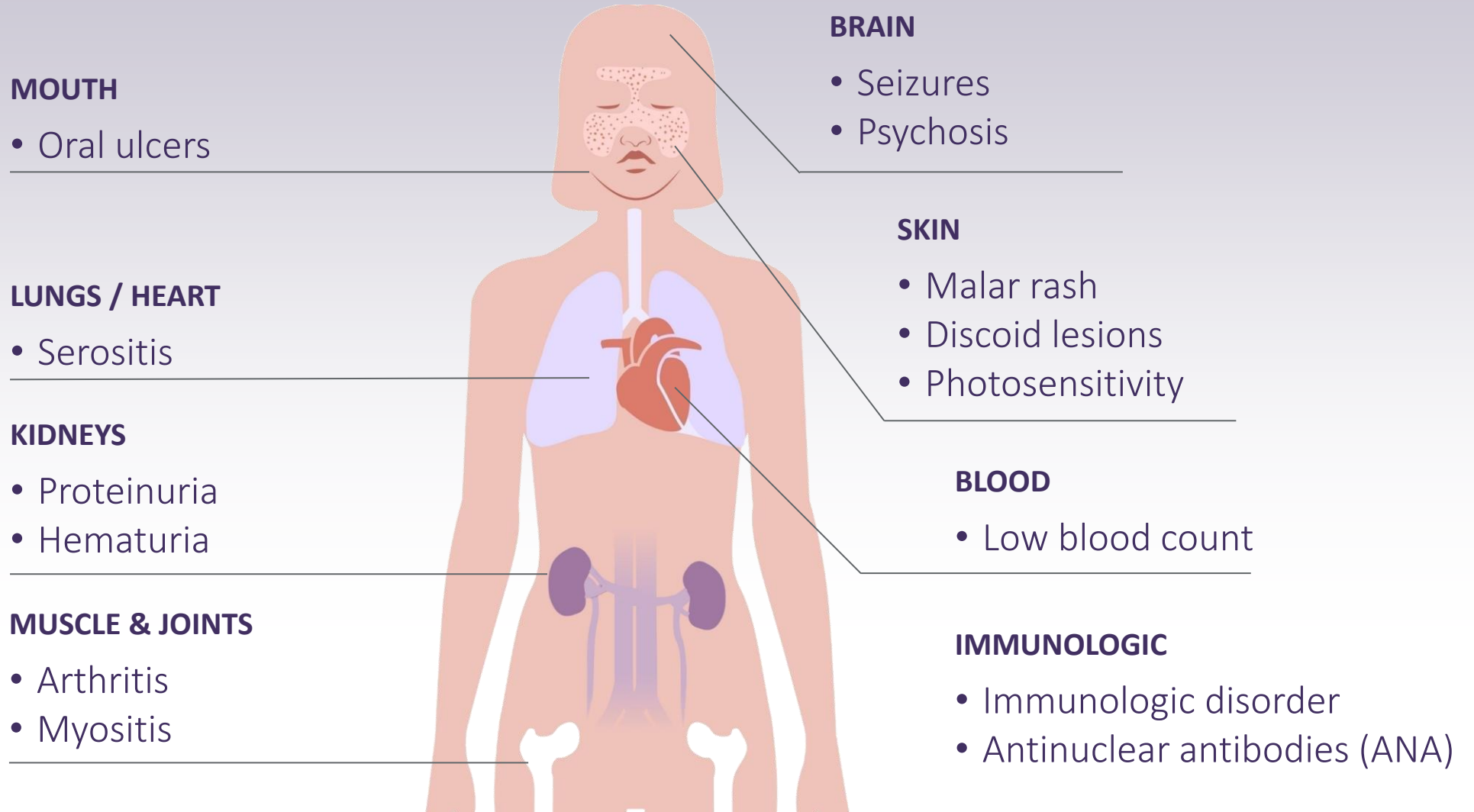
Variable prevalence among ethnic groups:

- American Indian/Alaska Native females 270.6 per 100,000
- Black females 230.9/100,000
- Hispanic females 120.7 per 100,000
- White females 84.7 per 100,000
- Asian/Pacific Islander females 84.4 per 100,000



Izmirly PM, Parton H, Wang L, et al. Arthritis Rheumatol. 2021 Jun;73(6):991-996.

Clinical Features of SLE



Clinical Features Of SLE

Domain	Manifestations
Constitutional	Unexplained fever > 38.3°C
Mucocutaneous	Non-scarring alopecia, oral ulcers, acute cutaneous lupus (malar rash), subacute cutaneous lupus, discoid lupus, photosensitivity
Arthritis	Synovitis, joint pain, morning stiffness
Neurologic	Delirium, psychosis, seizures
Serositis	Pleural/pericardial effusions, pericarditis
Hematologic	Leukopenia, thrombocytopenia, autoimmune hemolysis
Renal	Proteinuria, glomerulonephritis
Immunologic	+ anti-dsDNA antibody, +anti-Sm antibody, low C3 and/or C4, + antiphospholipid antibodies

Tan EM, Cohen AS, Fries JF, et al. *Arthritis Rheum.* 1982;25:1271-1277. Hochberg MC. *Arthritis Rheum.* 1997;40:1725. [Letter]. Aringer M, Costenbader K, Daikh D, et al. *Arthritis Rheumatol.* 2019;71(9):1400-1412.

Lupus on the Outside



Synovitis



Malar rash



Painless oral ulcer



Raynaud's Phenomenon



Discoid rash



Laccoud's
arthropathy



Vasculitis



Alopecia

Lupus on the Inside



Achiness, headache



Fatigue



Cognitive dysfunction/
brain fog



Depression

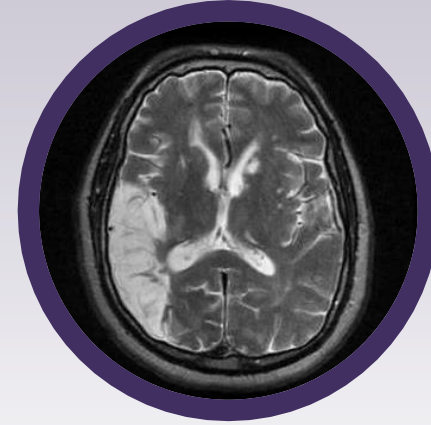
Illustrations of Organs Impacted by Lupus



Serositis



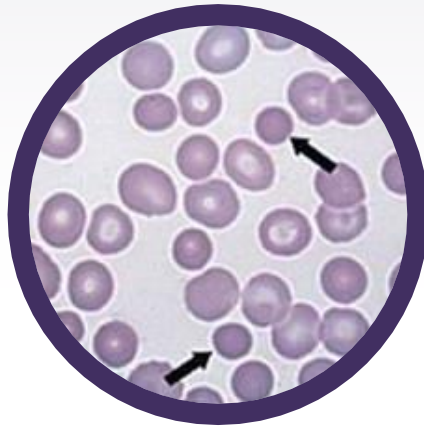
Pericardial effusion



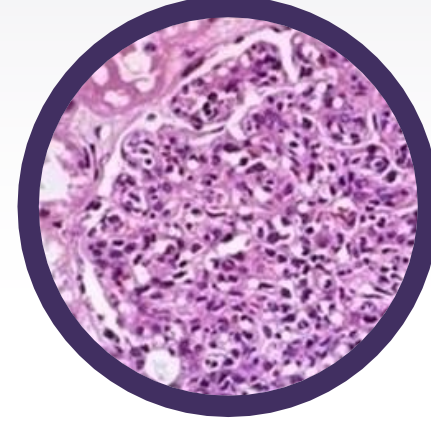
Cerebral infarct



Brain atrophy



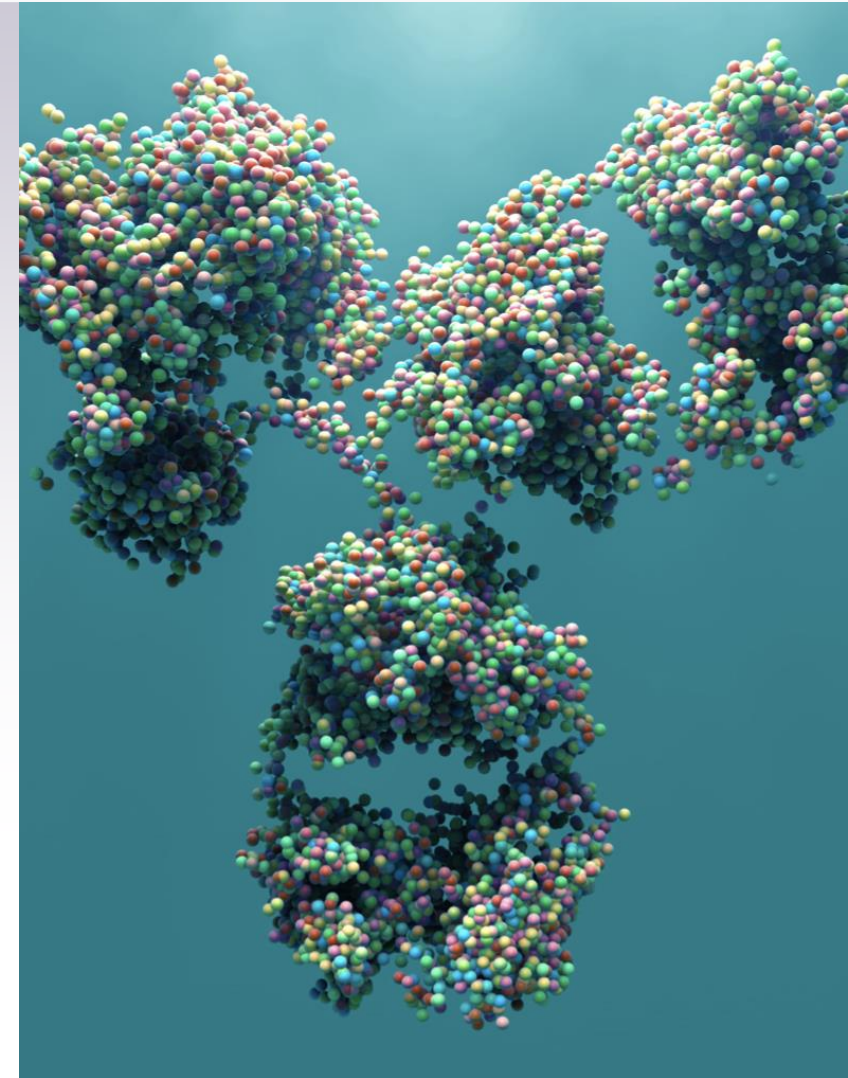
Spherocytes



Glomerulonephritis

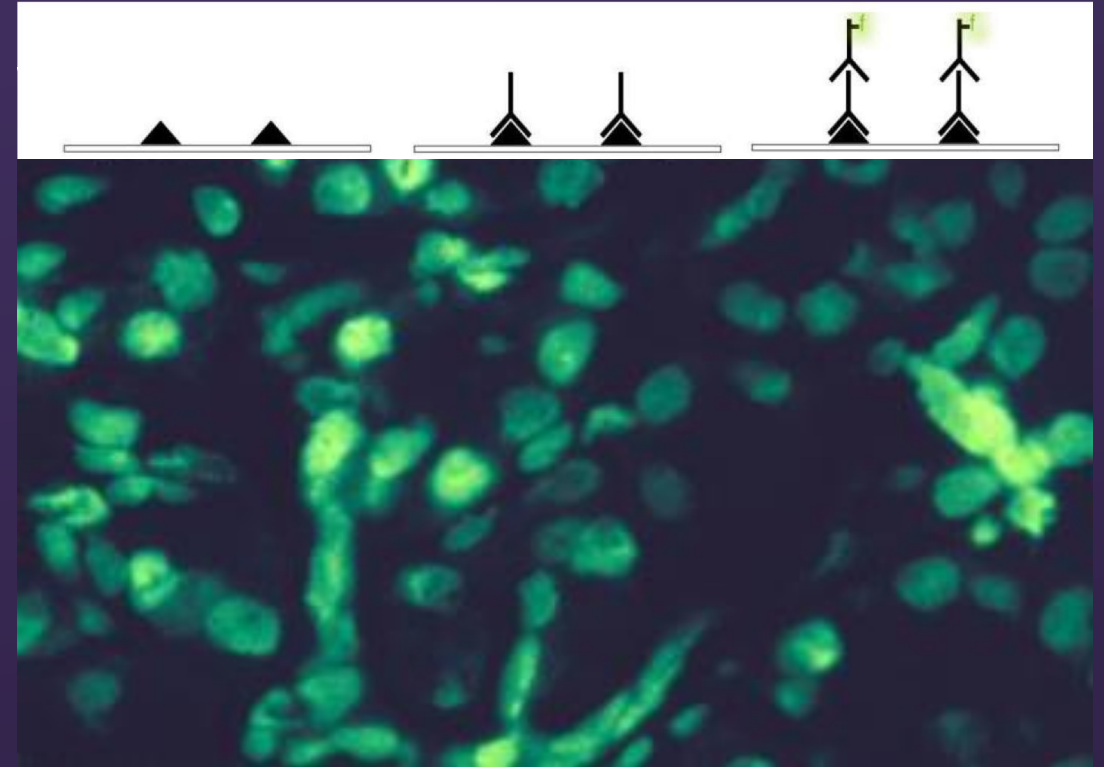
Antinuclear Antibodies (ANA)

- Autoantibodies against various components of the cell nucleus; target antigens include the cell nucleus, surface antibodies, and cytoplasmic contents
- Present in >95% of people with SLE, a highly sensitive test
- Present in people with many other autoimmune disorders as well as some healthy individuals, not a very specific test
- Because of low specificity, ANA usefulness increases if the pretest probability for lupus is high; i.e., the patient has symptoms and signs that can be attributed to SLE
- Because of the high sensitivity of the ANA, a patient with negative ANA is unlikely to have lupus even when her/his clinical presentation is suggestive of lupus



ANA Testing

- Multiple methods for detection but immunofluorescence (IF) is the gold standard
- In an IF ANA assay, a serum sample is applied to a glass slide covered with fixed cells (to allow access to nuclear antigens)
- The antigen-antibody reaction is revealed by fluorochrome conjugated antihuman immunoglobulin antibodies
- The slide is then examined under fluorescence microscope



ANA present in 95%–98% of SLE patients

Incidence of Positive ANA

- Normal subjects 3%–4%
- SLE 95%–99%
- Scleroderma 95%
- Hashimoto's thyroiditis 50%
- Idiopathic pulmonary fibrosis 50%
- Incidence increases with age, chronic infections,
- and other chronic conditions

Arbuckle MR, McClain MT, Rubertone MV, et al. Development of autoantibodies before the clinical onset of systemic lupus erythematosus. N Engl J Med. 2003;349:1526-1533.



Autoantibodies in SLE

Antibodies	Lupus Specificity	Clinical Associations
ANA	Low	Nonspecific
Anti-dsDNA	High	Nephritis
Anti-Sm	High	Nonspecific
Anti-RNP	Low	Arthritis, myositis, lung disease, Raynaud's phenomenon
Anti-SSA	Low	Dry eyes/mouth, subacute cutaneous lupus erythematosus (SCLE), photosensitivity, neonatal lupus, congenital heart block
Anti-SSB	Low	Same as above
Antiphospholipid	Intermediate	Clotting diathesis, pregnancy morbidity

Pathogenic Autoantibodies— Anti-SSA and Anti-SSB

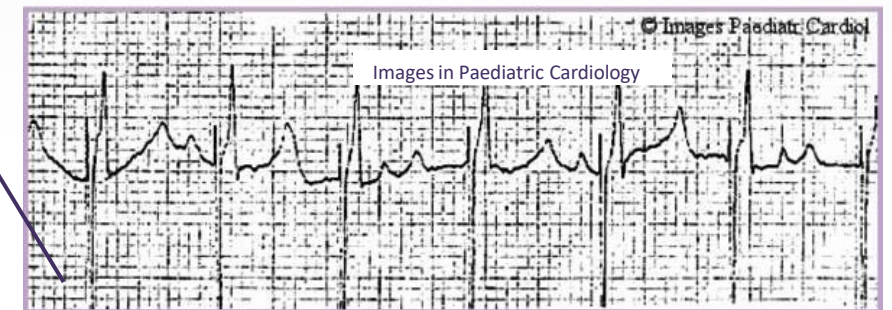
Subacute cutaneous



Neonatal lupus rash



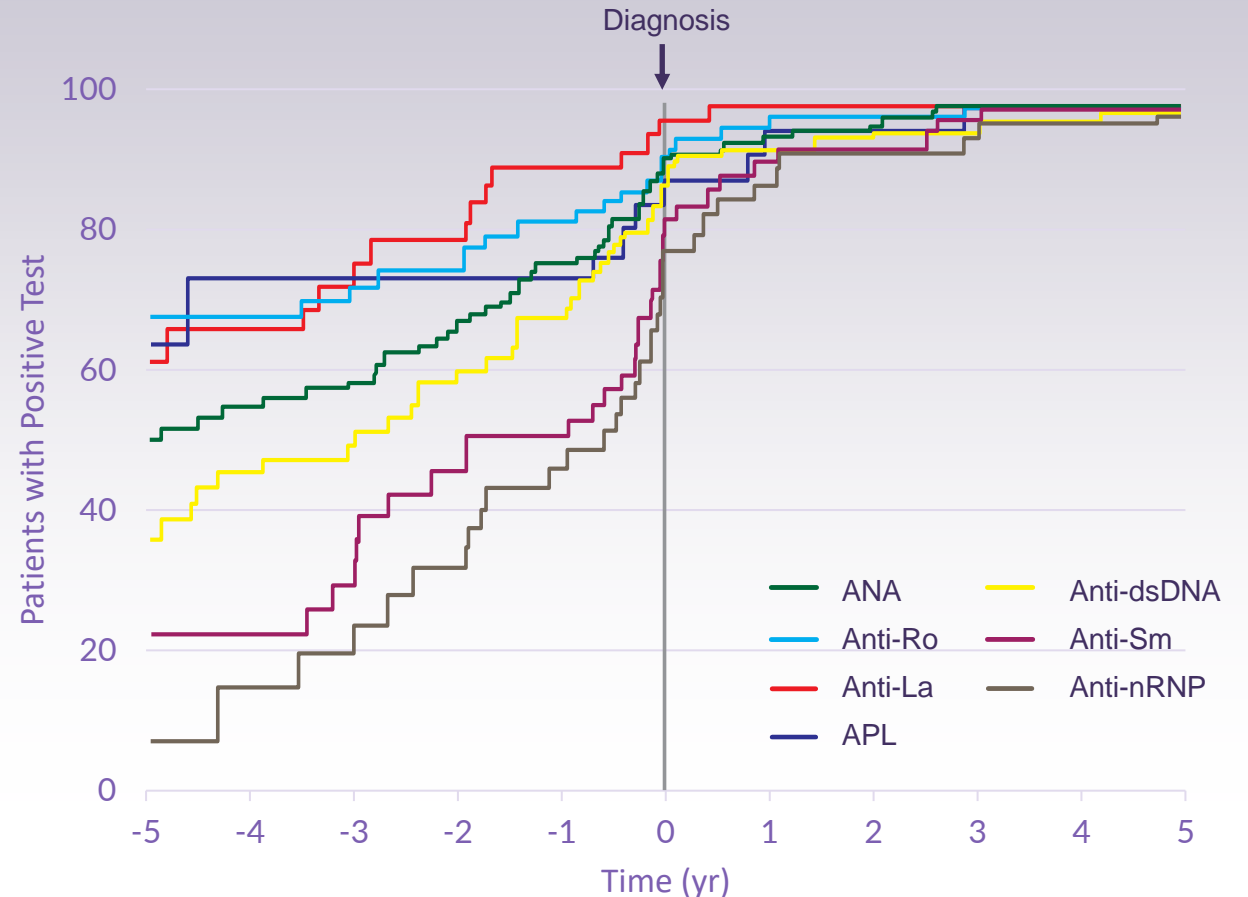
Complete heart block *in utero*



Autoantibodies—Preclinical Detection

- Autoantibodies precede SLE diagnosis by years
- ANA, anti-Ro/La, aPL mean of 3.4 years
- Anti-dsDNA mean of 2.2 years
- Anti-Sm, anti-RNP mean of 1.2 years

*Anti-Ro = Anti-SSA
**Anti-La = Anti-SSB



Arbuckle MR, McClain MT, Rubertone MV, et al. *N Engl J*

Sestak AL, Fürnrohr BG, Harley JB, Merrill JT, Namjou B. The genetics of systemic lupus erythematosus and implications for targeted therapy. *Ann Rheum Dis*. 2011;70(suppl 1):i37-43. doi: 10.1136/ard138057.

How did I get it?

Phases of Disease Pathogenesis

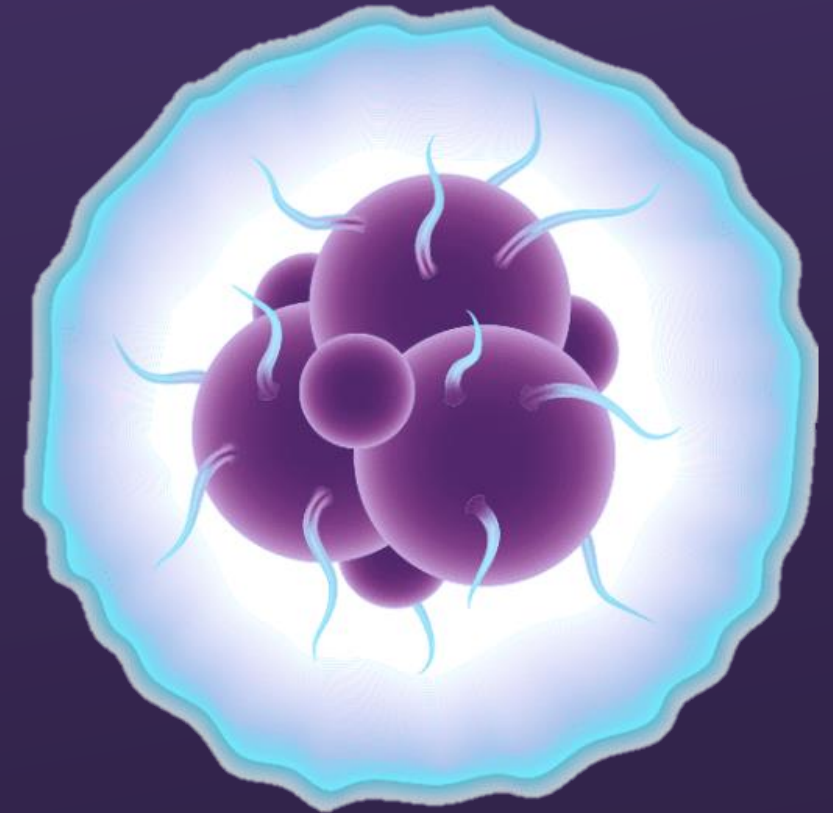
Initiation

- Multiple proposed mechanisms that may vary from patient to patient
- Occurs years prior to onset of clinical symptoms

Type I interferon plays a critical role in the initiation and propagation of SLE

Amplification and perpetuation of dysregulated immune mechanisms and response of target organs to inflammatory insults

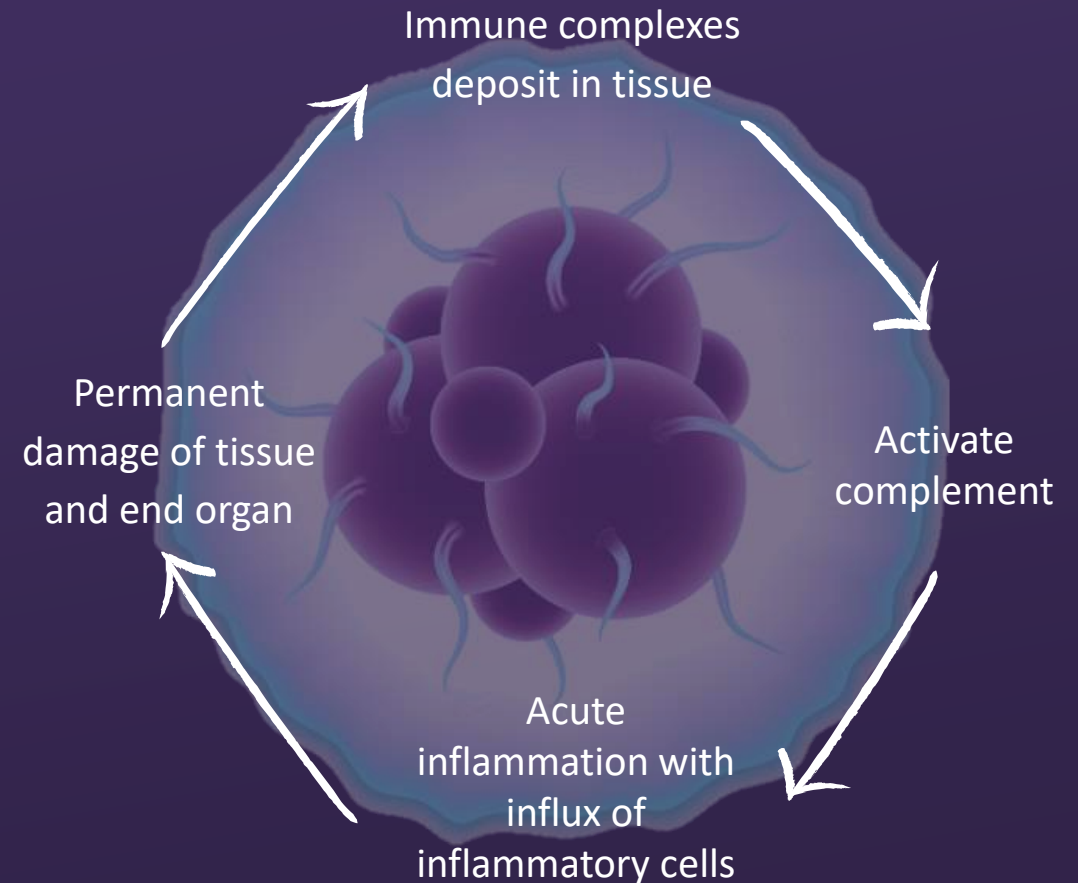
Irreversible damage from disease and secondary effects of treatment



Crampton SP, Morawski PA, Bolland S, Linking susceptibility genes and pathogenesis mechanisms using mouse models of systemic lupus erythematosus, Dis Model Mech, 2014, Fig. 2.

Pathogenesis – Importance of Autoantibodies

- Autoantibodies to self antigens are key to disease onset and tissue damage
- Target antigens:
 - Nuclear antigens (dsDNA, Sm, RNP)
 - Cytoplasmic antigens (ribosomal proteins)
 - Cell surface antigens (red blood cells)
- Immune complexes deposit in tissue → activate complement → acute inflammation with influx of inflammatory cells → permanent damage of tissue and end organ



Crampton SP, Morawski PA, Bolland S, Linking susceptibility genes and pathogenesis mechanisms using mouse models of systemic lupus erythematosus, Dis Model Mech, 2014, Fig. 2.

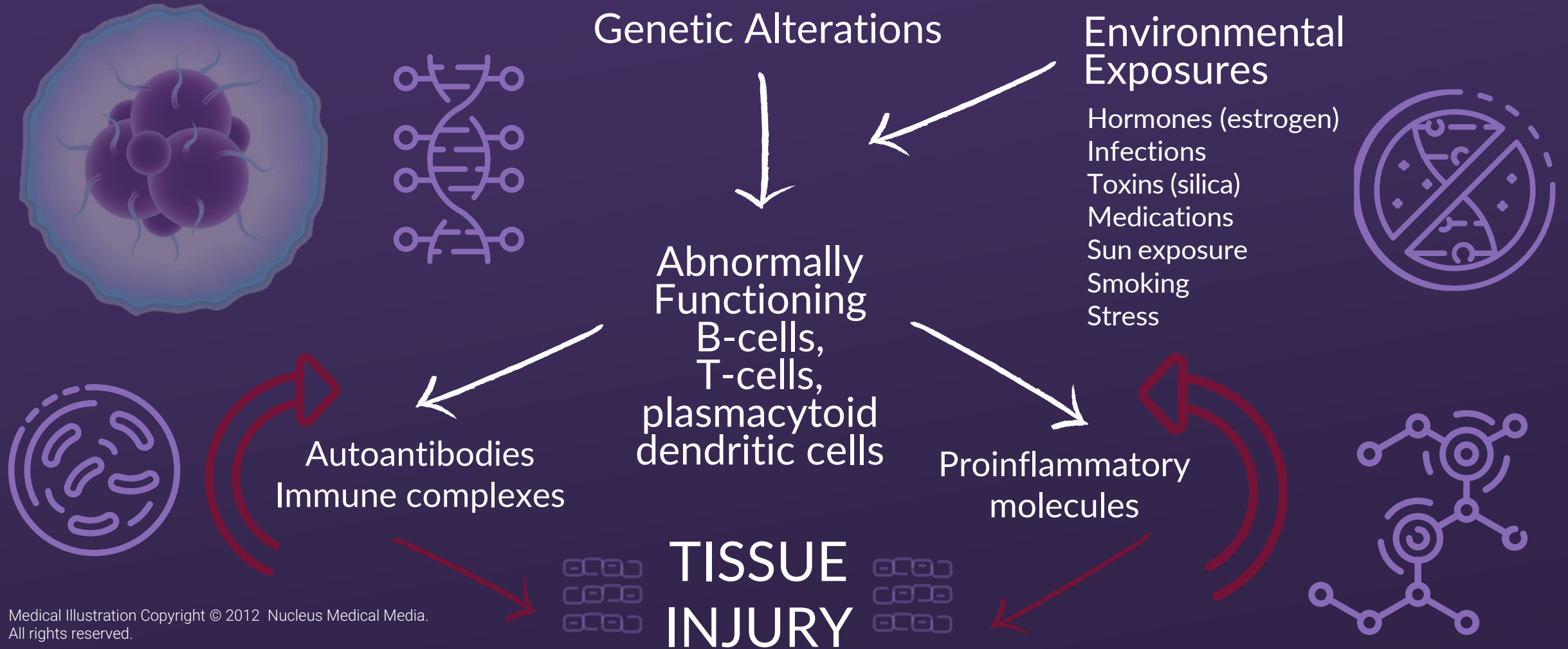
Genetic Susceptibility—Clinical Studies

- Rate of SLE concordance in monozygotic twins is 24%–35%; in dizygotic twins is 2%–5%
- 10%–12% of SLE patients have 1st- or 2nd-degree relatives with SLE compared with
- <1% in healthy individuals
- SLE patients may have family members with other autoimmune diseases



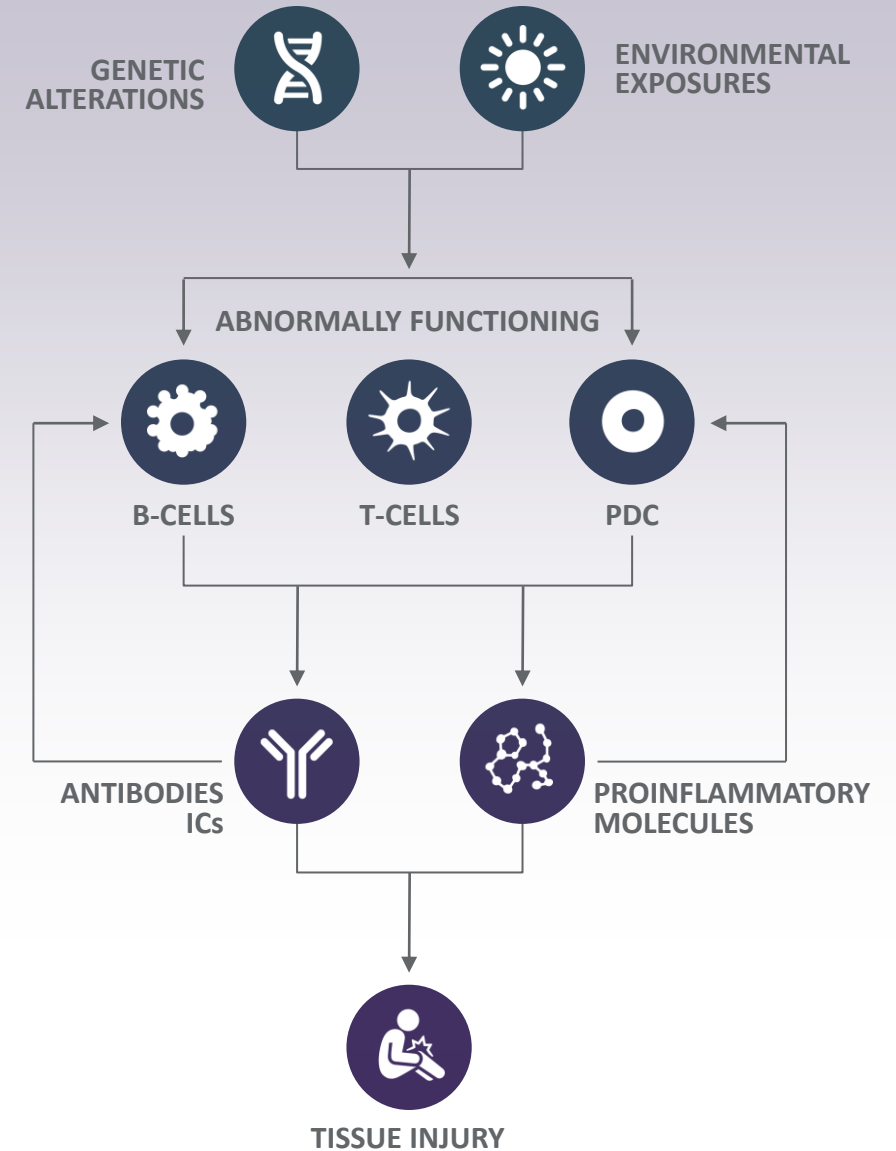
Sestak AL, Fürnrohr BG, Harley JB, et al. Ann Rheum Dis. 2011;70(suppl 1):i37-43. doi: 10.1136/ard.2010.138057.

SLE: Initiation Amplification Perpetuation



Pathogenesis of lupus

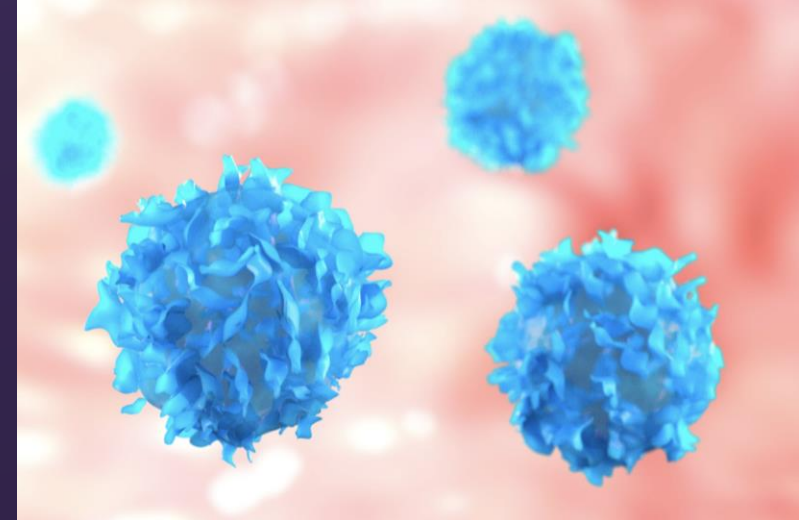
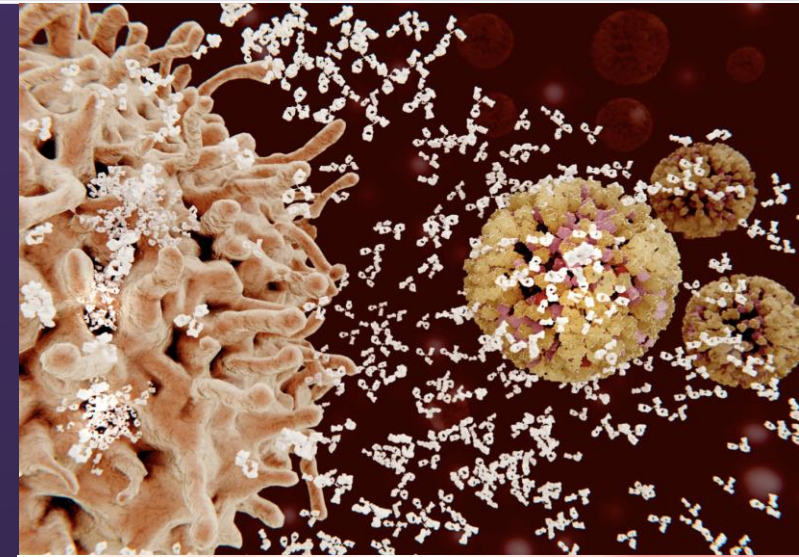
- Autoimmunity is an altered immune homeostasis that leads to auto-reactivity, immunodeficiency and malignancy.
- Immune dysregulation leading to auto-reactivity and autoantibodies in lupus occurs in different phases and likely represents the untoward effects of environmental triggers on the genetically susceptible host.



Examples of Immune Dysregulation in Lupus

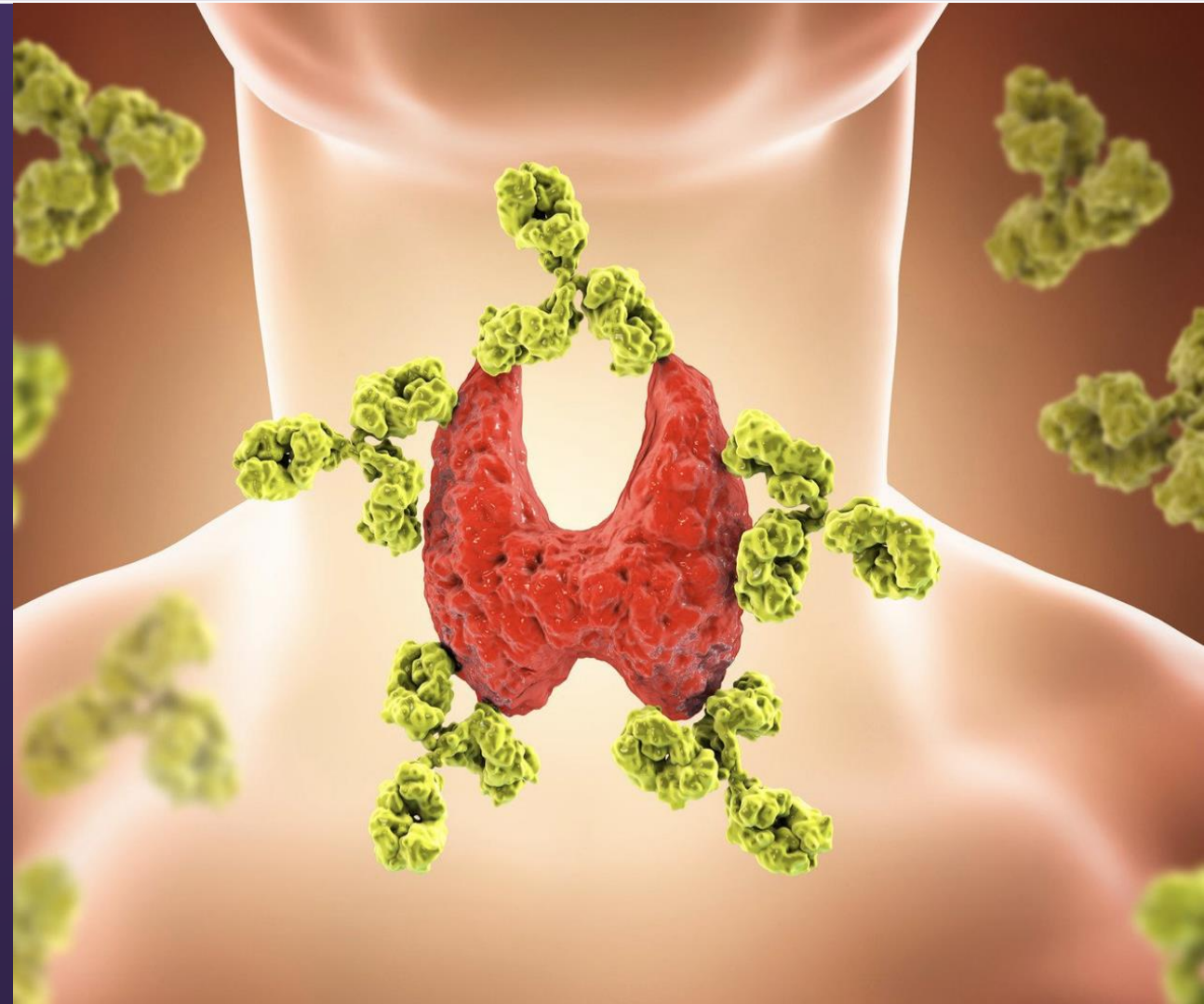
- B-cells
 - Defective selection/signaling
 - Autoantibody production
- T-cells
 - Increased numbers of Th17 and Th2 cells and decreased numbers of Tregs
 - T-cells are less susceptible to activation-induced cell death
- Plasmacytoid dendritic cells
 - Produce large amounts of Type I interferon
 - Plasmacytoid dendritic cells: Stimulate activation and proliferation of autoreactive T- and B-cells
 - PDCs are the main producers of Type 1 interferon
 - Type I interferon has the downstream effects on T and B cells

Bernatsky S, Boivin JF, Joseph L, et al. Mortality in systemic lupus erythematosus. *Arthritis Rheum.* 2006;54:2550-2557.



Pathogenesis of Lupus— Important Concepts

- Autoimmunity is an altered immune homeostasis that leads to autoreactivity, immunodeficiency, and malignancy
- Immune dysregulation leading to autoreactivity and autoantibodies in SLE occurs in different phases and likely represents the untoward effects of environmental triggers on the genetically susceptible host



What is going to
happen to me?

Disease Activity

- SLE is characterized by periods of flare (increased disease activity) and remission or low-level disease activity
- Varying flare rates
- Predictors of flare (in some but not all cases)
 - New evidence of complement consumption (decreasing C3 and/or C4 titers)
 - Rising anti-dsDNA titers



Disease Severity

- Characterized by
 - Abrupt onset of symptoms
 - Increased renal, neurologic, hematologic, and serosal involvement
 - Rapid accrual of damage (irreversible organ injury)
- Associated with
 - Race/ethnicity (Black, Hispanic, Asian, and Native American populations)
 - Younger age of onset
 - Male gender
 - Lower socioeconomic status



Mortality

- 5-year survival rate in 1953 was 50%; currently >90%
- Leading causes of mortality are heart disease, malignancy, and infection
- Factors associated with increased mortality
 - Disease duration
 - High disease severity at diagnosis
 - Younger age at diagnosis
 - Race/ethnicity: (Black, Hispanic, Asian, and Native American) populations are at greater risk
 - Male sex
 - Low socioeconomic status
 - Poor patient adherence
 - Inadequate patient support system
 - Limited patient education



What can I do to
improve my health?

Therapeutic Principles— Important Concepts

- Treatment is tailored to type and severity of organ system involvement
- All patients: sun protection and hydroxychloroquine
- Goals of therapy
 - Stop and reverse ongoing organ inflammation
 - Prevent or limit irreversible end-organ damage
- Potential toxicities of immunosuppressive therapies demand vigilant management



Current Therapy for SLE

- Hydroxychloroquine*
 - Corticosteroids*
 - Cyclophosphamide
 - Rituximab
 - Methotrexate
 - Mycophenolate mofetil
- Azathioprine
 - Belimumab*
 - Voclosporin*
 - Anifrolumab*

*FDA approved for treatment of SLE and/or lupus nephritis



Guiding Therapeutic Strategies

- Therapeutic combinations aimed at **induction of remission, maintenance therapy, supportive therapy, and psychosocial support**
- Titrate dose to treat effectively with focus on involved organs, and to minimize toxicity
- Strategic use of preventive therapies, prophylactic antibiotics, and vaccinations



Guiding Therapeutic Strategies

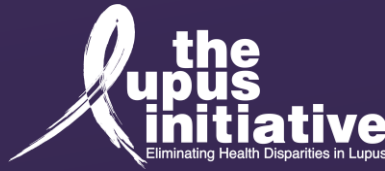
- Ensure patients are up to date on screening for common comorbid conditions and/or complications or disease or treatment, e.g., cardiovascular disease, cancer, and osteoporosis
- Hydroxychloroquine is a cornerstone therapy for SLE
- The use of prednisone in the lowest possible dose for the shortest duration of time



Lupus—In Summary

- Clinical disease is characterized by
 - Diversity of manifestations
 - Periods of flare and remission
- Pathogenesis is related to
 - Genetic susceptibility combined with environmental and/or behavioral triggers
 - Immune dysregulation characterized by autoantibody production
- Treatment is targeted to
 - Clinical manifestations
 - Severity of organ system involvement

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Visit: <https://thelupusinitiative.org/>

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