Lupus in the year 2023

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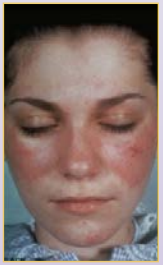
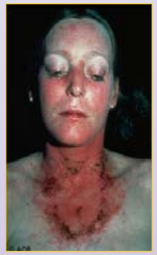
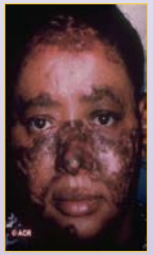
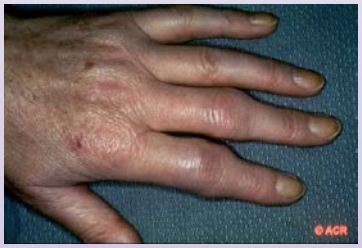
Systemic Lupus Erythematosus SLE

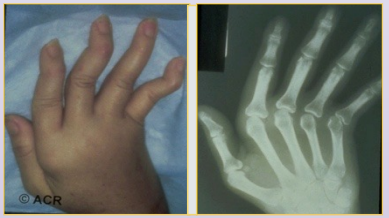
- Lupus is a multi-organ inflammatory disease with its basis in autoimmunity
- Manifestations can change frequently, and unexpectedly with involvement of any organ system
- Lupus symptoms can range from mild to severe
- Characterized by periods of flare and remission
- It is also associated with characteristic autoantibodies*

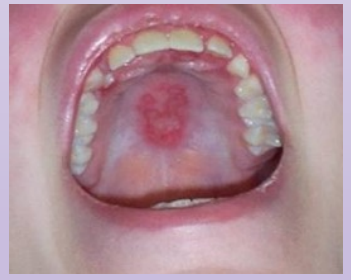
Image Credit: ustas7777777/Shutterstock.com

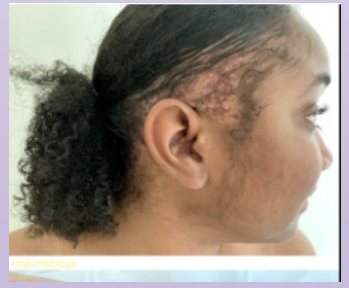
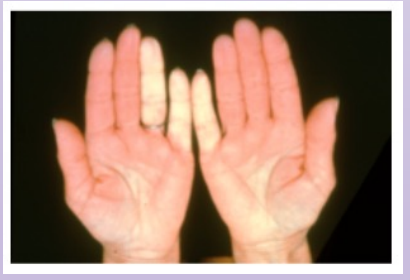
- *Autoantibodies are immune proteins that mistakenly target and react with a person's own tissues/organs

External manifestations of lupus

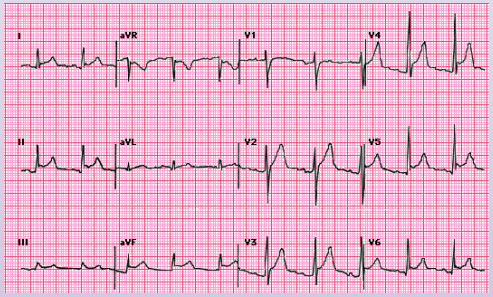





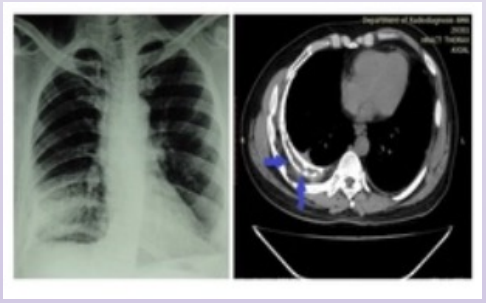


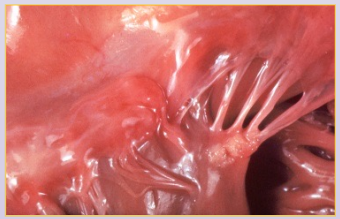


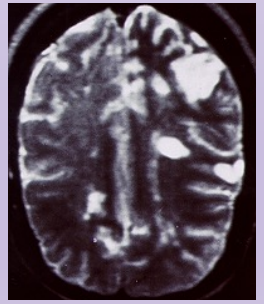



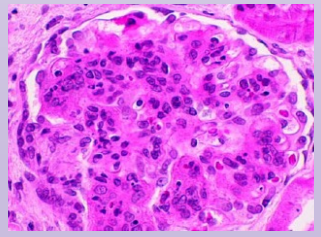
Internal manifestations of lupus

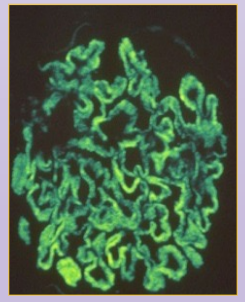




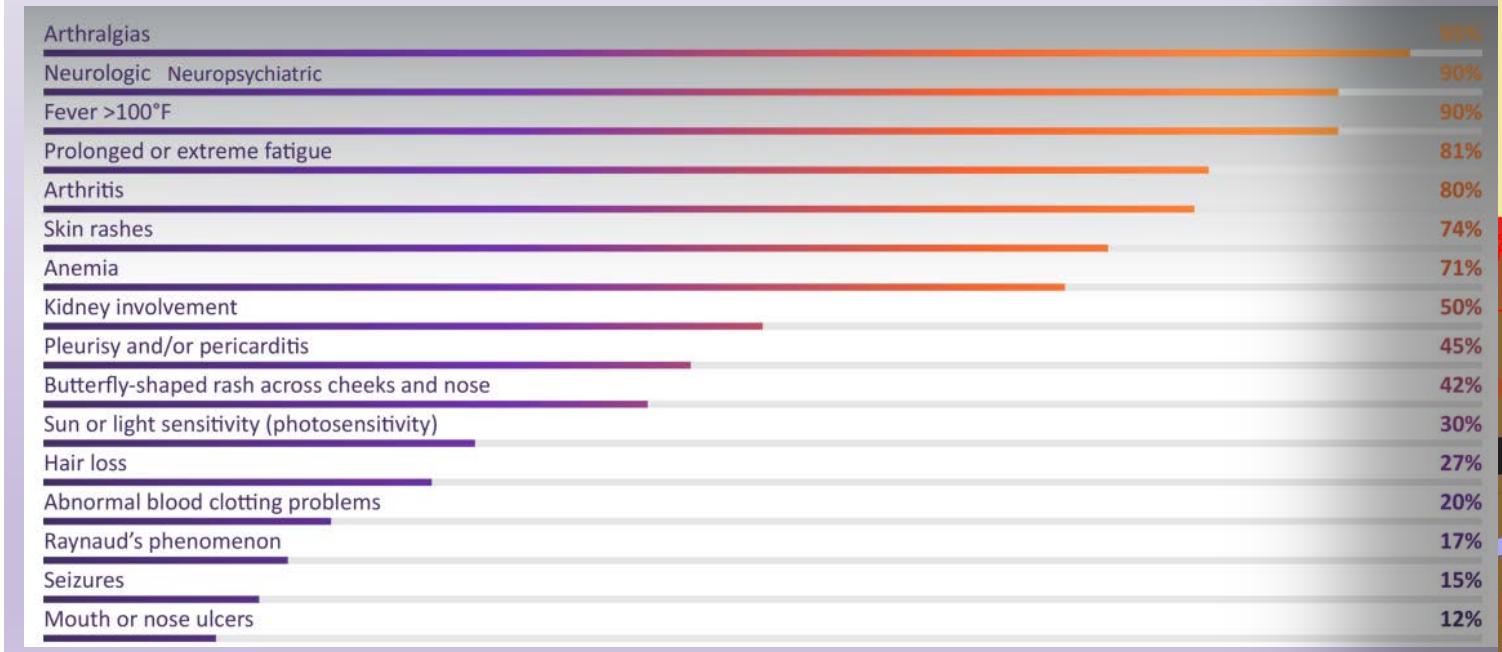


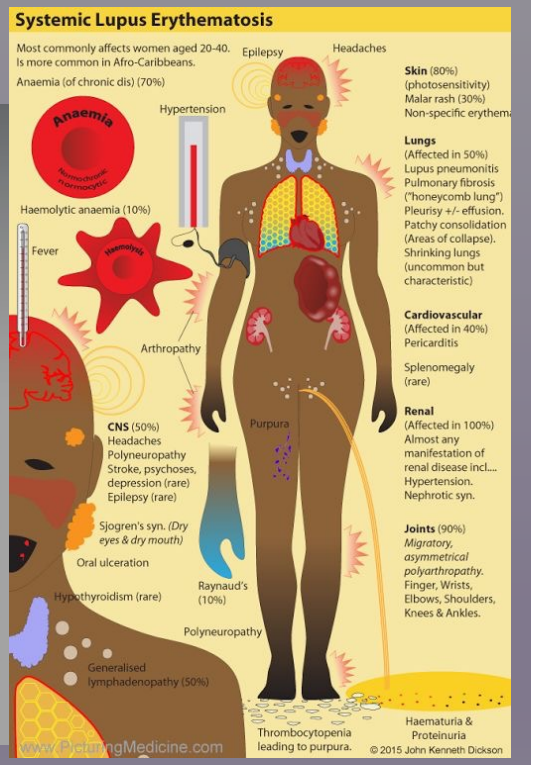






Frequency of signs and symptoms of lupus





More non-specific symptoms

- Muscle aches
- Depression
- Fatigue
- Memory issues/brain fog

Why does lupus happen?

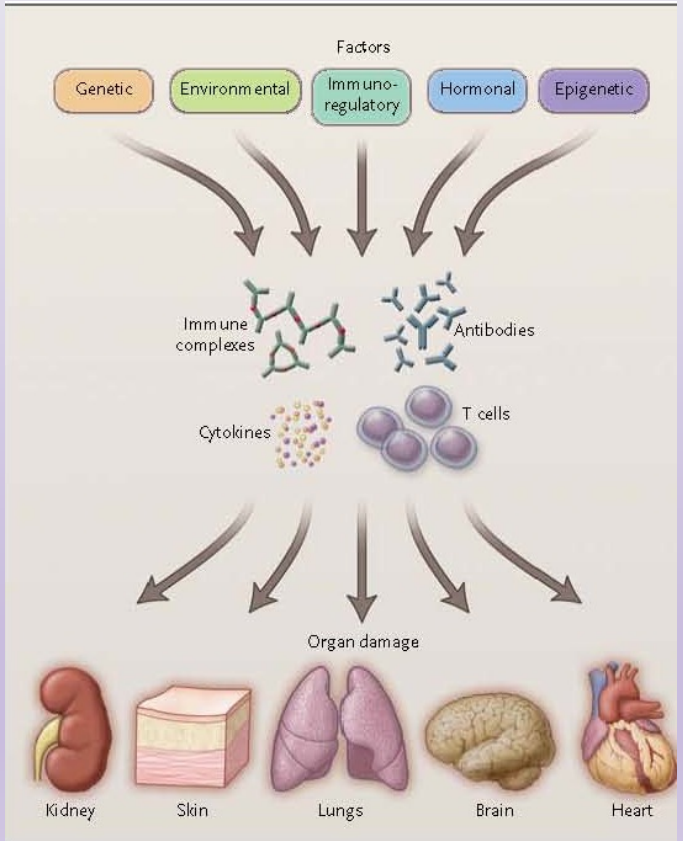


Figure 1. Overview of the Pathogenesis of Systemic Lupus Erythematosus.

- Lupus is based in **autoimmunity**
  - Our own immune systems see the body's healthy cells as foreign and attacks them
  - Lupus involves characteristic autoantibodies
- Overall etiology is unknown but we know that there are several contributing factors
  - Genetic, environmental, immunologic, and environmental factors
- Immune dysregulation leads to formation of autoantibodies and abnormally functioning cells of the immune system
  - This causes inflammation and organ damage

TSOKOS, SYSTEMIC LUPUS ERYTHEMATOSUS N ENGL J MED 2011; 365:2110-2121

Genetic component of SLE

- There is a genetic component to SLE
  - High concordance among identical twins (15-60%)
  - Increased risk in families (5-12% of relatives of patients with SLE will develop SLE)
- Genome wide association studies (GWAS) have identified >100 gene loci with alterations that predispose an individual to developing SLE
- TLR7 gene- found on X chromosome- causes TLR7 protein to bind a molecule making it more active
  - This leads to healthy tissues being incorrectly recognized as foreign and they are subsequently attacked

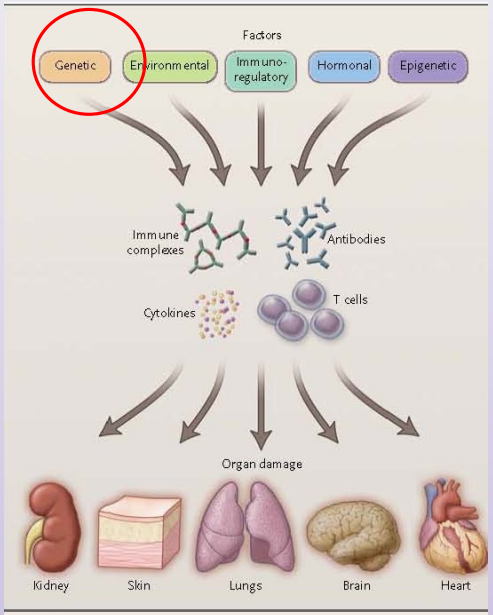
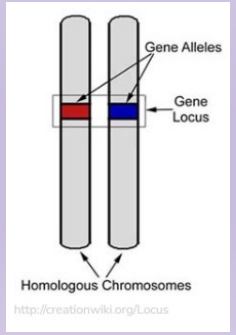


Figure 1. Overview of the Pathogenesis of Systemic Lupus Erythematosus.



IDENTIFICATION OF 38 NOVEL LOCI FOR SYSTEMIC LUPUS ERYTHEMATOSUS AND GENETIC HETEROGENEITY BETWEEN ANCESTRAL GROUPS. *NAT COMMUN* 2021

Other contributing factors

- Environmental
  - UV light
  - Medications
  - Smoking
  - Silica dust
  - Viruses
- Hormones
- Epigenetics- how our genes are affected by our environment
  - Microbiome

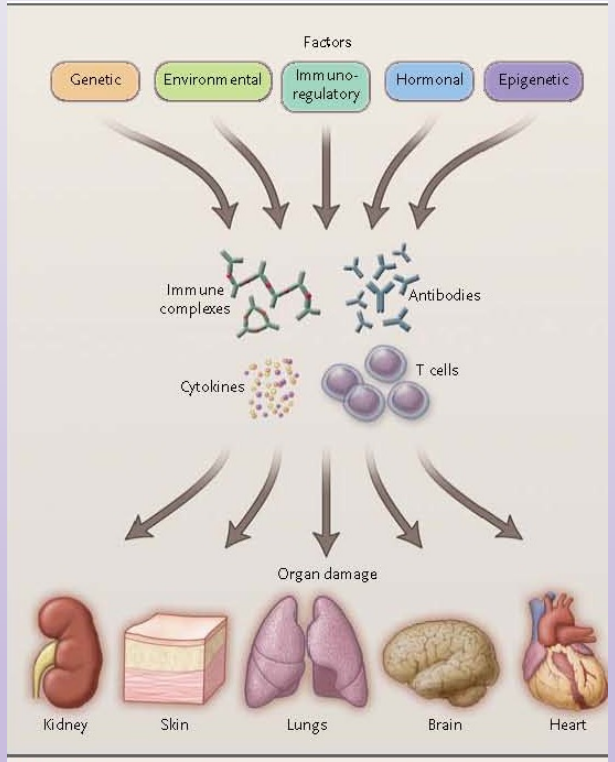
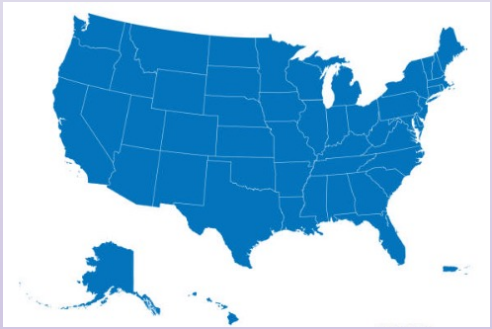


Figure 1. Overview of the Pathogenesis of Systemic Lupus Erythematosus.

AZZOUZ. ANNALS OF RHEUM DIS 2019

Who gets lupus?

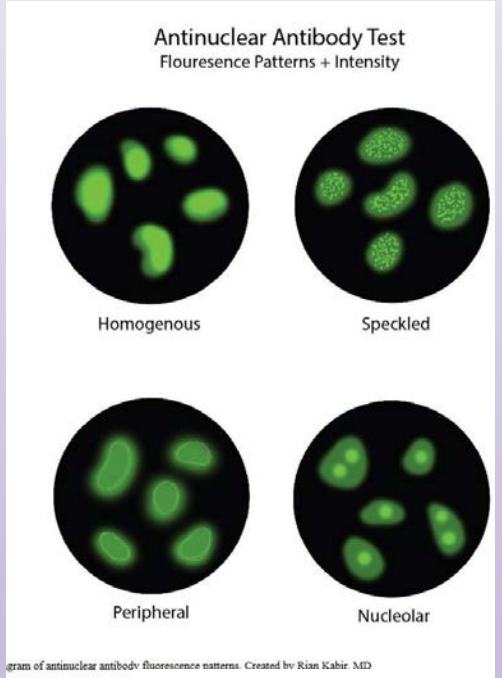


- In the United States, there are about 200,000-300,000 adults that are affected by SLE
  - Lupus foundation estimates that there may be 1.5 million people with some form of the disease
- Women account for more than 90% of lupus cases
  - Men can get lupus as well, and oftentimes it is quite severe
- Affects women mainly in their reproductive years (15-45 yo)
- It is more common, more frequent and more severe among non-white populations (greater disease activity at younger age and faster accrual of organ damage)
  - Black, Latino, Asian and American Indian/Alaska Native women have highest prevalence of the disease
  - Low income individuals are less likely to receive recommended care
  - Poverty associated with poor outcomes

How do we diagnose lupus?

- Medical History including family history
- Physical examination
- Laboratory testing
  - Most common screen is the antinuclear antibody (or the ANA)
- Tissue biopsy (ie skin, kidney)

- **There is no gold standard diagnostic test for lupus*



gram of antinuclear antibody fluorescence patterns. Created by Rian Kabir, MD
From: Biochemistry, Antinuclear Antibodies (ANA)

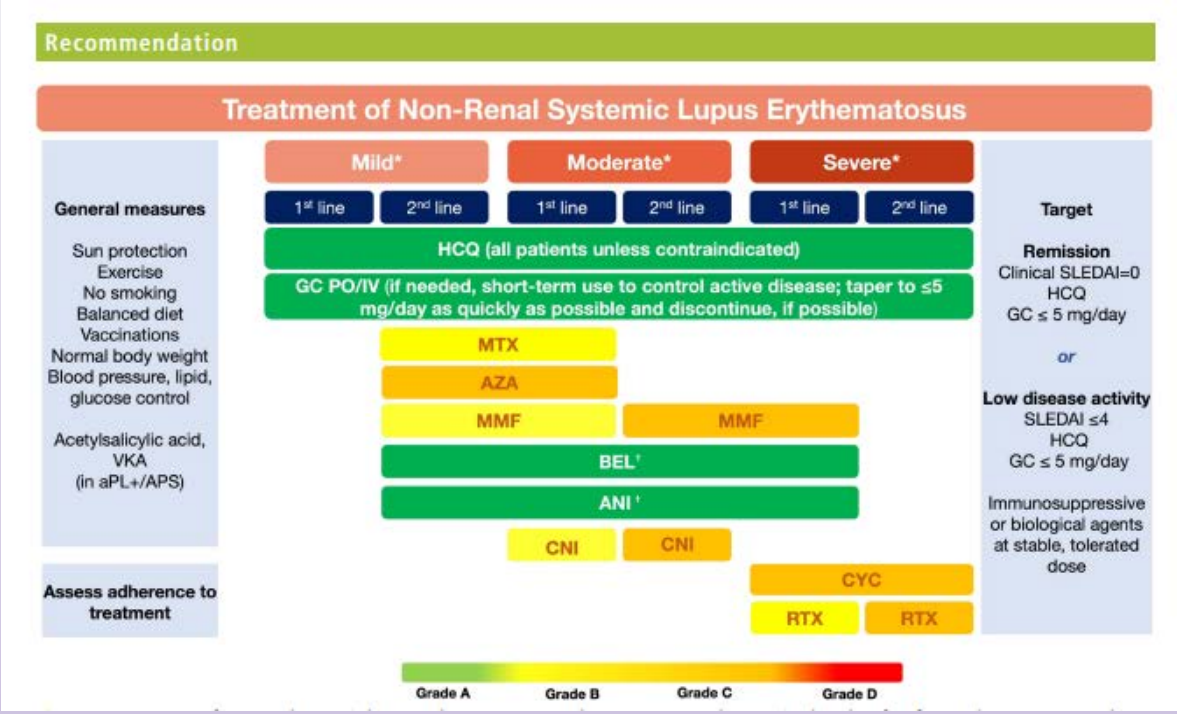
How do we treat lupus?

Goals of treatment

- To treat **active disease and prevent lupus flares** by targeting therapy to organ systems involved to **prevent organ damage**
- Improve quality of life
- We also need to **avoid toxicity** from treatment

Current treatments

- FDA Approved
  - Aspirin (1950s)
  - Corticosteroids (1950s)
  - Hydroxychloroquine (Plaquenil) (1956)
  - Belimumab (Benlysta) (2011)
    - Belimumab for lupus with kidney involvement: 2020
  - Voclosporin for lupus with kidney involvement (January 2021)
  - Anifrolumab (Saphenlo) (August 2021)
- Off label medications- used as standard of care for lupus patients
  - Cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, tacrolimus, rituximab, cyclosporine



EULAR 2023 Lupus treatment guidelines

New therapies

- Why do we need new therapies?
  - Current treatments do not always work
  - Sometimes, they are not tolerated because of side effects/toxicity
- There are other unmet needs that are important for quality of life
  - Fatigue, brain fog, depression, chronic pain
- In this vein, we are always looking to develop safer and more effective therapies with fewer side effects
  - We eventually would like to replace immune-suppressives/chemotherapy with more targeted treatment

Challenges in finding new treatments

- Lupus is a heterogeneous disease
- There is difficulty in identifying best outcomes to study- how do we capture improvements in disease activity best?
- We need large numbers of patients- involving multi sites
- We need better representation of minority patients so that medications can be generalized to a representative lupus population

New(er) therapies

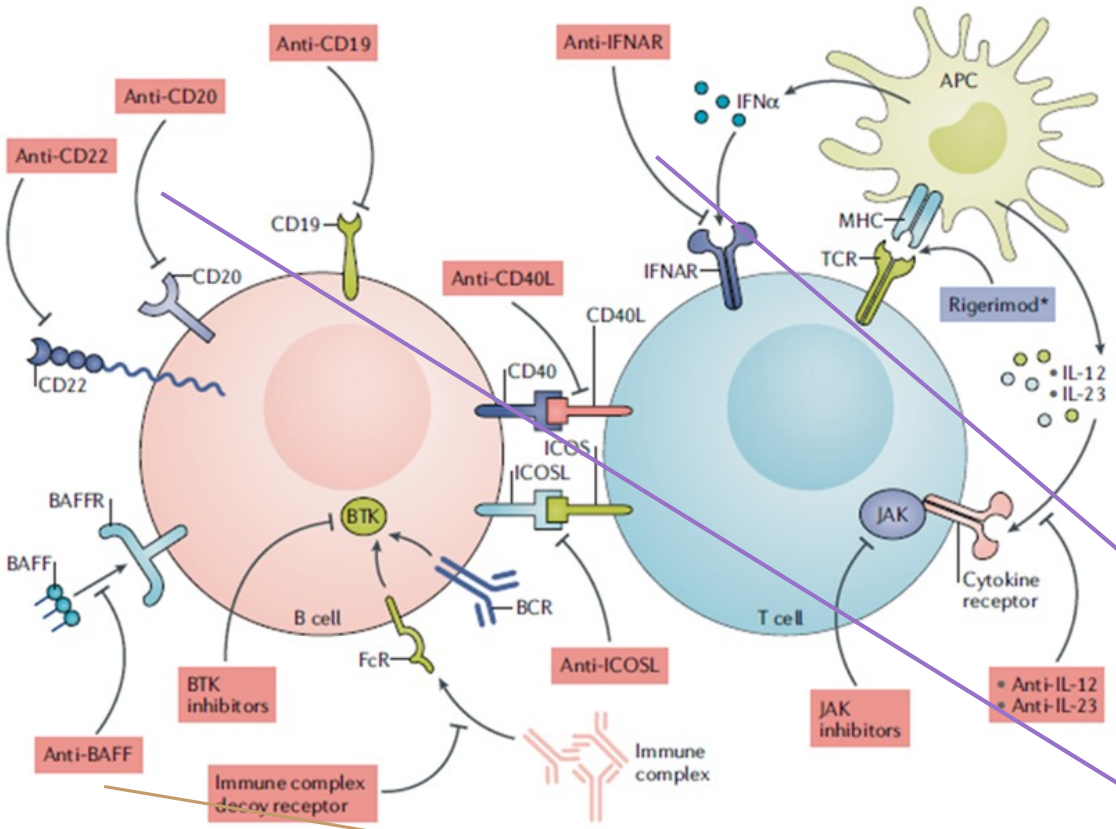


Fig. 1 | **Therapeutic targets in systemic lupus erythematosus.** Various immune cells and molecules interact during the pathogenesis of systemic lupus erythematosus and are the target of monoclonal antibodies and other treatments that have the potential to offer therapeutic advantage. *The mechanism of action of rigerimod is not fully elucidated. APC, antigen-presenting cell; BAFF, B cell-activating factor; BAFFR, BAFF receptor; BCR, B cell receptor; BTK, tyrosine-protein kinase BTK; CD40L, CD40 ligand; FcR, Fc receptor; ICOS, inducible T cell co-stimulator; ICOSL, ICOS ligand; IFNAR, type I interferon receptor; JAK, Janus kinase; TCR, T cell receptor.

Nature Reviews Rheum 2019

Rituximab

Anifrolumab

Belimumab

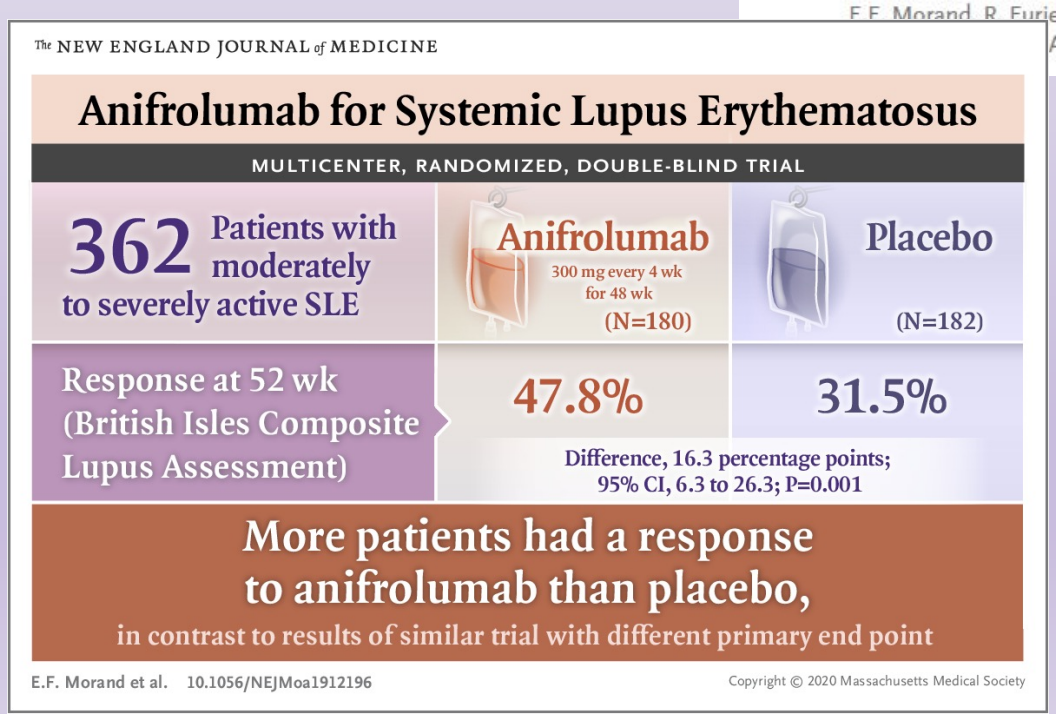
Targets Interferon pathway—a key player in causing lupus inflammation

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 16, 2020 VOL. 382 NO. 3

Trial of Anifrolumab in Active Systemic Lupus Erythematosus

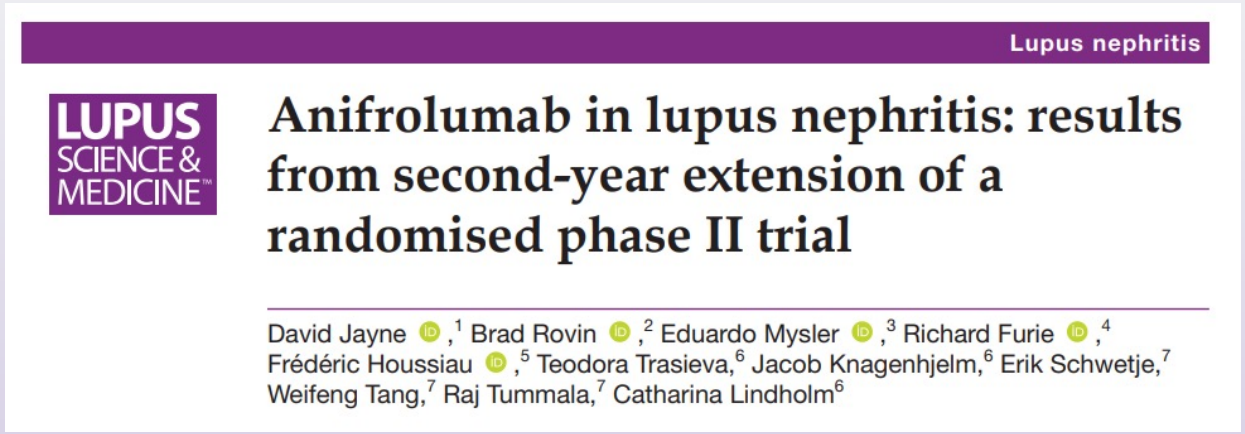
E.F. Morand, R. Furie, Y. Tanaka, I.N. Bruce, A.D. Askanase, C. Richez, S.-C. Bae, P.Z. Brohawn, L. Pineda, A. Berglind, and R. Tummala, for the TULIP-2 Trial Investigators*



Primary outcomes: Evaluated a lupus disease activity measure called the BICLA

Greater improvements in treatment group of 48 % vs 32 % in placebo

Other outcomes:
-52% vs 30% Patients were able to lower steroid use to less than 7.5 mg daily



- More patients on the IR attained complete renal response at Week 104 compared with those on BR or placebo (27.3% vs 18.6% and 17.8%) and simultaneously achieved sustained glucocorticoid tapering (IR: 25.0%; BR: 18.6% and placebo: 17.8%)

WHAT THIS STUDY ADDS

⇒ This 2-year analysis of the placebo-controlled TULIP-LN study shows acceptable long-term safety and tolerability of anifrolumab.

⇒ Treatment with anifrolumab using an IR dosing regimen added to standard of care with mycophenolate mofetil and glucocorticoids, improved renal and non-renal disease outcomes in patients with active class III or IV LN.

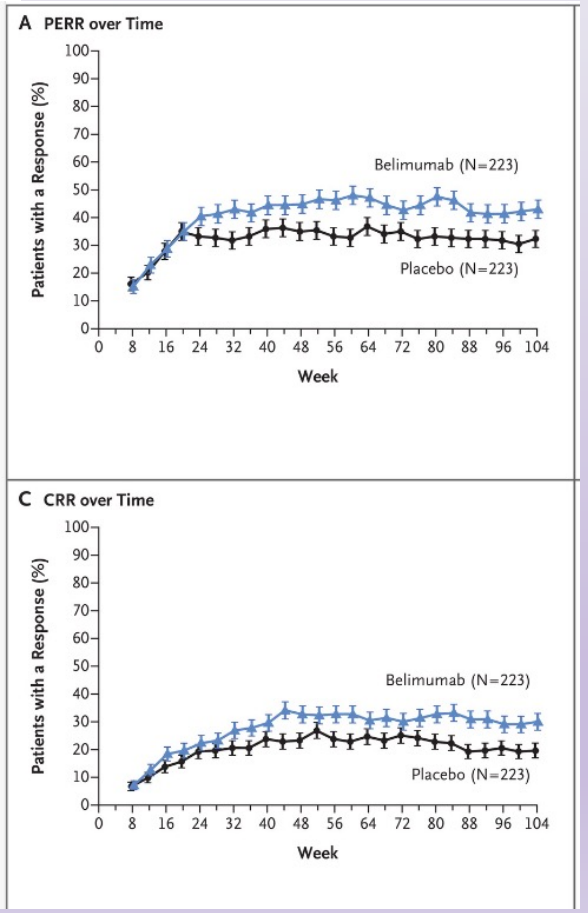
- We are awaiting completion of the phase III IRIS study

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Two-Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis

Richard Furie, M.D., Brad H. Rovin, M.D., Frédéric Houssiau, M.D., Ph.D., Ana Malvar, M.D., Y.K. Onno Teng, M.D., Ph.D., Gabriel Contreras, M.D., M.P.H., Zahir Amoura, M.D., Xueqing Yu, M.D., Chi-Chiu Mok, M.D., Mittermayer B. Santiago, M.D., Amit Saxena, M.D., Yulia Green, M.D., Beulah Ji, M.D., Christi Kleoudis, M.P.H., Susan W. Burriss, M.S., Carly Barnett, M.P.H., and David A. Roth, M.D.



- Benlysta initially approved for non kidney lupus in 2011

Monthly infusion

Phase 3, two year trial looking at addition of benlysta to standard care treatment for lupus nephritis

Statistically significant benefits in reducing protein in the urine (marker of kidney function) and/or kidney function itself

Safety profile was similar with that of prior trials involving benlysta

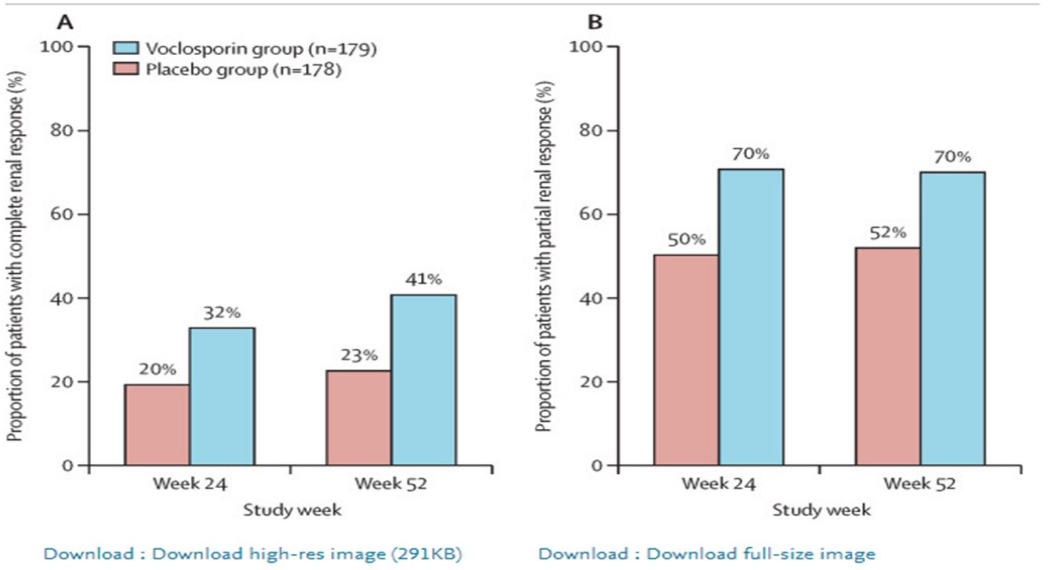
Can help with other lupus symptoms such as arthritis and rashes

THE LANCET

Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial

Prof Brad H Rovin, MD • Y K Onno Teng, MD • Ellen M Ginzler, MD • Cristina Arriens, MD • Dawn J Caster, MD • Juanita Romero-Diaz, MD • et al. Show all authors

- Approved for add on to standard of care treatment in Lupus Nephritis
- A type of calcineurin inhibitor (similar to cyclosporine and tacrolimus)
- Oral tablet (3 tablets twice a day)
- Effective for reducing protein in the urine rapidly (thought to be associated with better kidney function outcomes)
- Limits: May not be a good option for someone who has a lot of other lupus symptoms besides kidney disease and not for patients with reduced GFR (or elevated creatinine)



Download : Download high-res image (291KB)

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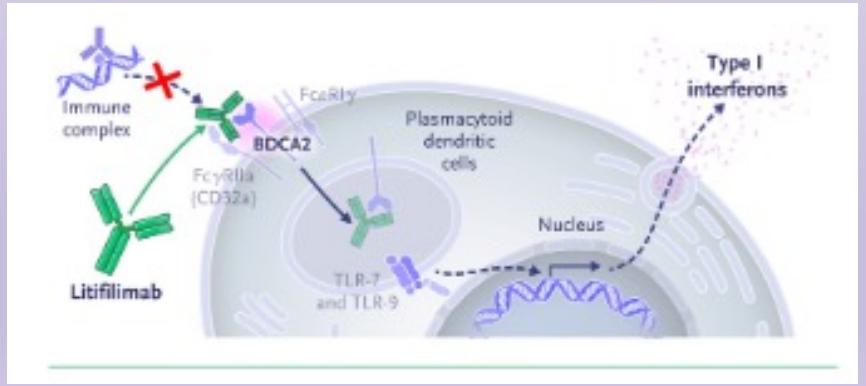
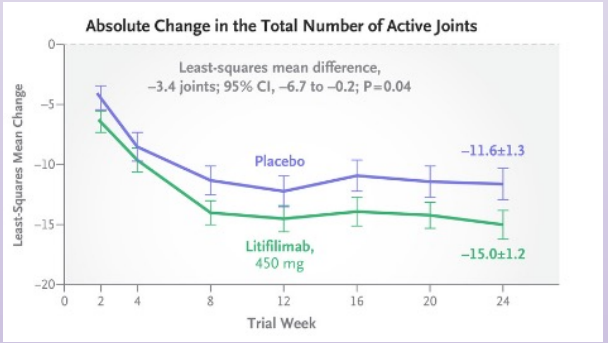
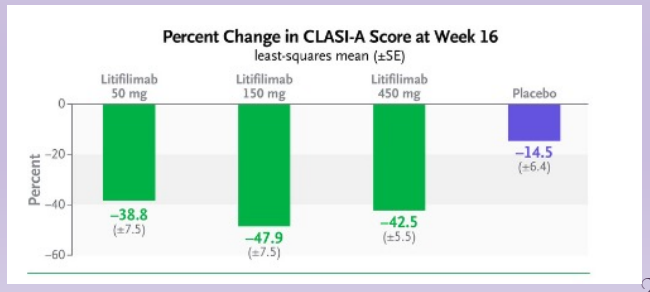
Figure 2. Complete and partial renal response endpoints (intention-to-treat population)

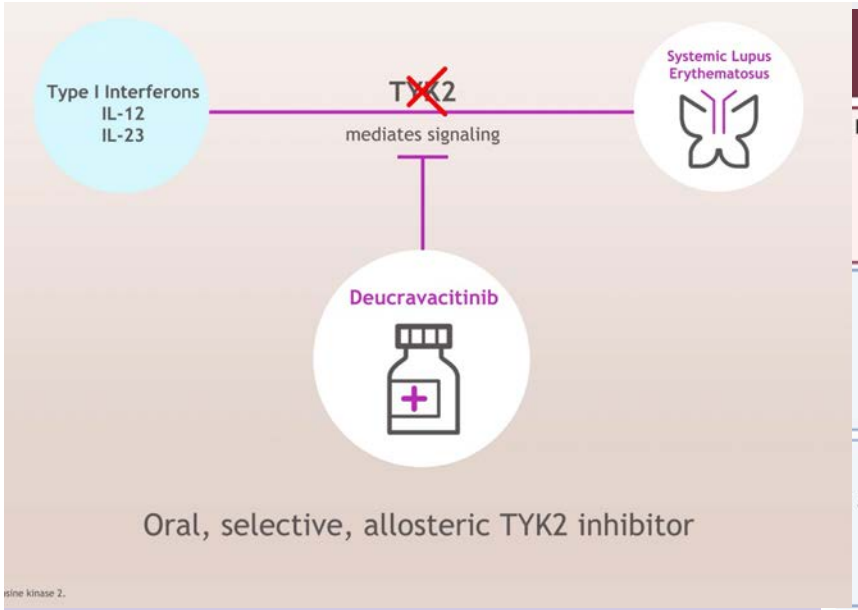
Potential new therapies

- Litifilimab (injection)
  - targets a receptor, BDCA2 on dendritic cells—leading to the reduction of release of type I interferon
  - Injection every 4 weeks
  - URMC is currently recruiting and enrolling patients for Phase III trial









Deucravacitinib in Systemic Lupus Erythematosus

Deucravacitinib
- Oral, selective, allosteric tyrosine kinase 2 (TYK2) inhibitor
- Unique mechanism of action distinct from Janus kinase (JAK) 1/2/3 inhibitors

PAISLEY Trial
- Phase 2, randomized, double-blind, multicenter, placebo-controlled
- Evaluated efficacy and safety of deucravacitinib in adult patients with active SLE on standard therapy
- Primary endpoint: SRI(4) at week 32

363 patients with active SLE	Placebo N=90	Deucravacitinib 3 mg Twice Daily N=91	Deucravacitinib 6 mg Twice Daily N=93	Deucravacitinib 12 mg Once Daily N=89
Primary endpoint SLE Responder Index 4 [SRI(4)] at week 32	34.4%	58.2%	49.5%	44.9%

Difference (placebo and 3 mg twice daily): 23.8%; 95% CI, 8.5 to 37.7; *P*<0.001

Difference (placebo and 6 mg twice daily): 15.0%; 95% CI, -0.0 to 29.2; *P*=0.02

Patients who received deucravacitinib were more likely to achieve an SRI(4) response at week 32 than those who received placebo

All secondary endpoints were achieved or meaningfully improved at week 48, including SRI(4), BICLA, LLDAS, CLASI-50, and change in joint counts

- **Well tolerated**
- **Safety consistent with trials in psoriasis**

Eric Morand, Marilyn Pike, Joan T. Merrill, Ronald van Vollenhoven, Victoria P. Werth, Coburn Hobar, Nikolay Delev, Vaishali Shah, Brian Sharkey, Thomas Wegman, Ian Catlett, Subhashis Banerjee, Shalabh Singhal - Deucravacitinib, a Tyrosine Kinase 2 Inhibitor, in Systemic Lupus Erythematosus: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Trial, *Arthritis Rheumatol*, 2022

Arthritis & Rheumatology ACR

Arthritis & Rheumatology
Vol. 75, No. 2, February 2023, pp 242–252
DOI 10.1002/art.42391

American College of Rheumatology
Empowering Rheumatology Professionals

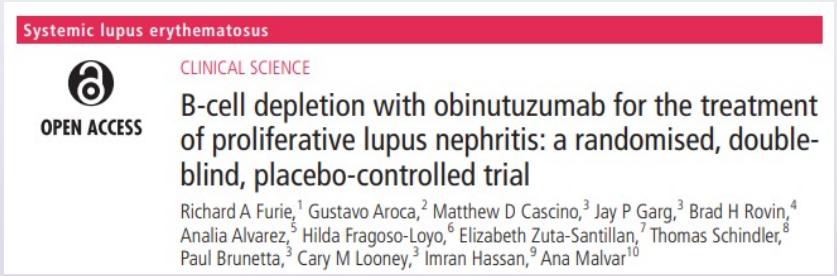
Deucravacitinib, a Tyrosine Kinase 2 Inhibitor, in Systemic Lupus Erythematosus: A Phase II, Randomized, Double-Blind, Placebo-Controlled Trial

Eric Morand,[1] Marilyn Pike,[2] Joan T. Merrill,[3] Ronald van Vollenhoven,[4] Victoria P. Werth,[5] Coburn Hobar,[6] Nikolay Delev,[6] Vaishali Shah,[6] Brian Sharkey,[6] Thomas Wegman,[6] Ian Catlett,[6] Subhashis Banerjee,[6] and Shalabh Singhal[6]

**URMC is currently recruiting for Phase III trial

Potential new therapies

- Obinutuzumab: humanized type II anti-CD20 monoclonal antibody that induces potent B-cell depletion (similar to rituximab-but better at evoking direct b cell death)
  - A phase II stuN Engl J Med 2011; 365:2110-2121dy published in 2022 showed improvement in kidney response in patients treated with this medication and standard therapies

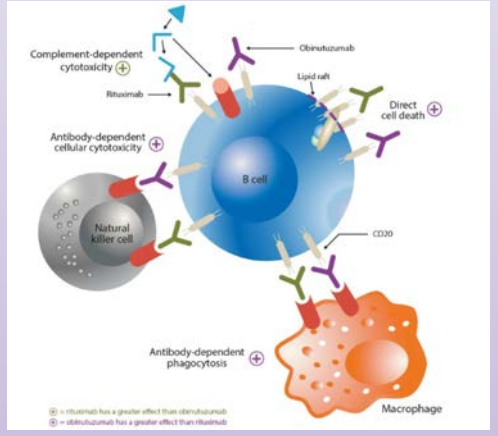

Systemic lupus erythematosus

OPEN ACCESS

CLINICAL SCIENCE

B-cell depletion with obinutuzumab for the treatment of proliferative lupus nephritis: a randomised, double-blind, placebo-controlled trial

Richard A Furie,[1] Gustavo Aroca,[2] Matthew D Cascino,[3] Jay P Garg,[3] Brad H Rovin,[4] Analia Alvarez,[5] Hilda Fragoso-Loyo,[6] Elizabeth Zuta-Santillan,[7] Thomas Schindler,[8] Paul Brunetta,[3] Cary M Looney,[3] Imran Hassan,[9] Ana Malvar[10]



- Cenerimod :
  - Inhibits trafficking of autoreactive T and B cells the circulation

- Daratumumab: targets plasma cells (these come from B cells and make autoantibodies) via a CD38 molecule
  - Recent case series showed improvement in renal function in patients with refractory kidney involvement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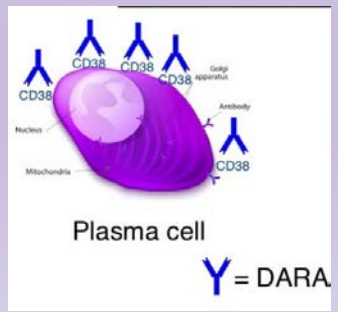
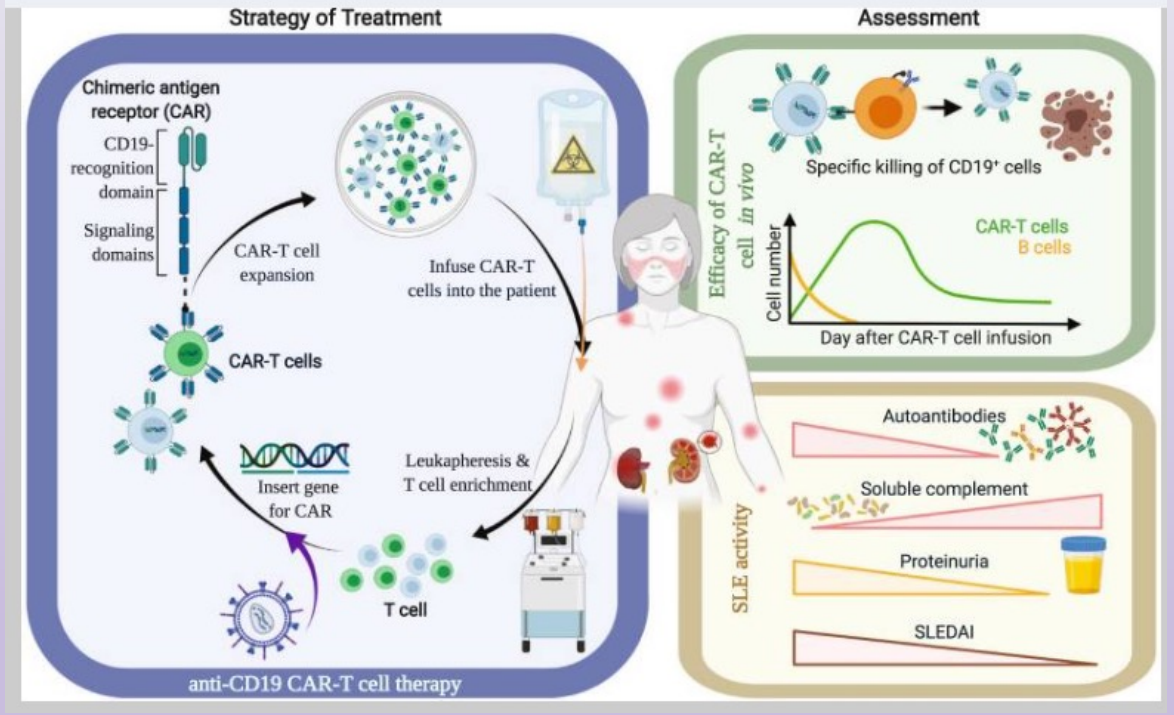
Daratumumab monotherapy for refractory lupus nephritis

Dario Roccatello, Roberta Fenoglio, Ilaria Caniggia, Joelle Kamgaing, Carla Naretto, Irene Cecchi, Elena Rubini, Daniela Rossi, Emanuele De Simone, Giulio Del Vecchio, Martina Cozzi & Savino Sciascia

Nature Medicine 29, 2041–2047 (2023) | Cite this article



Chimeric antigen receptor T-cell (CAR-T) therapy

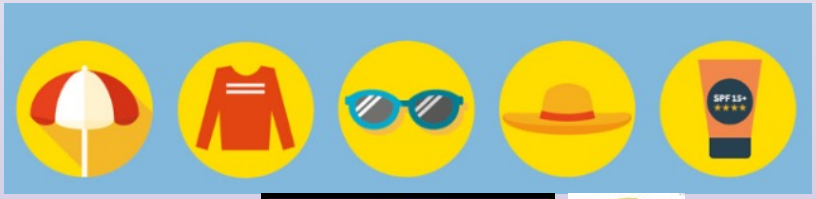


CAR-T cell therapy: new hope for systemic lupus erythematosus patients

Xuexiao Jin[1], Yongmei Han[1], James Q. Wang[2] and Linrong Lu[1,2]✉

Non pharmacologic guidelines

- EULAR 2023 guidelines include:
  - Smoking habits assessed and cessation strategies should be implemented
  - Avoidance of cold exposure
  - Physical exercise
  - Photoprotection
  - Patient education and self management support should be considered
  - Psychosocial interventions to improve health related quality of life, anxiety and depression
- Other non-pharm issues
  - Birth control counseling
  - Standard immunizations, including covid
  - Cardiovascular monitoring (cholesterol levels, blood pressure)
  - Bone density
  - Treating widespread pain
  - Treating depression and anxiety







Currently enrolling clinical trials at URMC

- **TOPAZ study** Phase 3 study examining drug BIIBO59 (lifitilimab-monthly infusion) compared to placebo
- **POETYK study** Phase 3 study examining deucravacitinb (daily oral medication) compared to placebo
- **MiSLE study** Phase 2 study evaluating the efficacy and safety of mesenchymal stem cells (one infusion) vs placebo

In the pipeline

- CAR-T cell therapy

Also at URMC:
Accelerating Medicines Partnership (AMP) Initiative

- Goal:
  - Identifying molecular + cellular features that define distinct subsets of nephritis in order to develop specific therapeutics targeting subsets of nephritis (working towards “precision medicine”)
- Learn more: Accelerating Medicines Partnership® Program – Rheumatoid Arthritis, Systemic Lupus Erythematosus | FNIH

Thank you!

Systemic Lupus Erythematosus

SLE

- What is it