Thomas Jefferson University

Lupus in 2024:

clinical applications of basic science

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Montefiore Einstein | Center for Continuing Professional Development

ACTIVITY INFORMATION SHEET FOR DEPT OF MEDICINE GRAND ROUNDS (WEST CAMPUS)

Date: March 14, 2024

Presenters: Marianthi Kiriakidou, MD

Activity Title: Medicine Grand Rounds: SLE in 2024

Location: Zoom Conference

This activity is made possible in part by an educational grant: N/A

DISCLOSURES

Course Director/Moderator

Dr. Anand Kumthekar has no relevant financial relationships with an ACCME-defined commercial interest within the past 24 months.

Presenter

Dr. Kiriakidou has no relevant financial relationships with an ACCME-defined commercial interest within the past 24 months.

OBJECTIVES

- Review pathogenic mechanisms in SLE
- Describe molecular pathways effectively targeted in SLE
- Discuss insights on foundations of novel therapies in SLE

Overview

- History
- Pathogenesis
- Rare severe manifestations and effective targeting of pathogenic pathways
- Research-in-progress : The CAR T story
- New guidelines in management of lupus

Learning objectives

- Review pathogenic mechanisms in SLE
- Describe molecular pathways effectively targeted in SLE
- Discuss insights on foundations of novel therapies in SLE

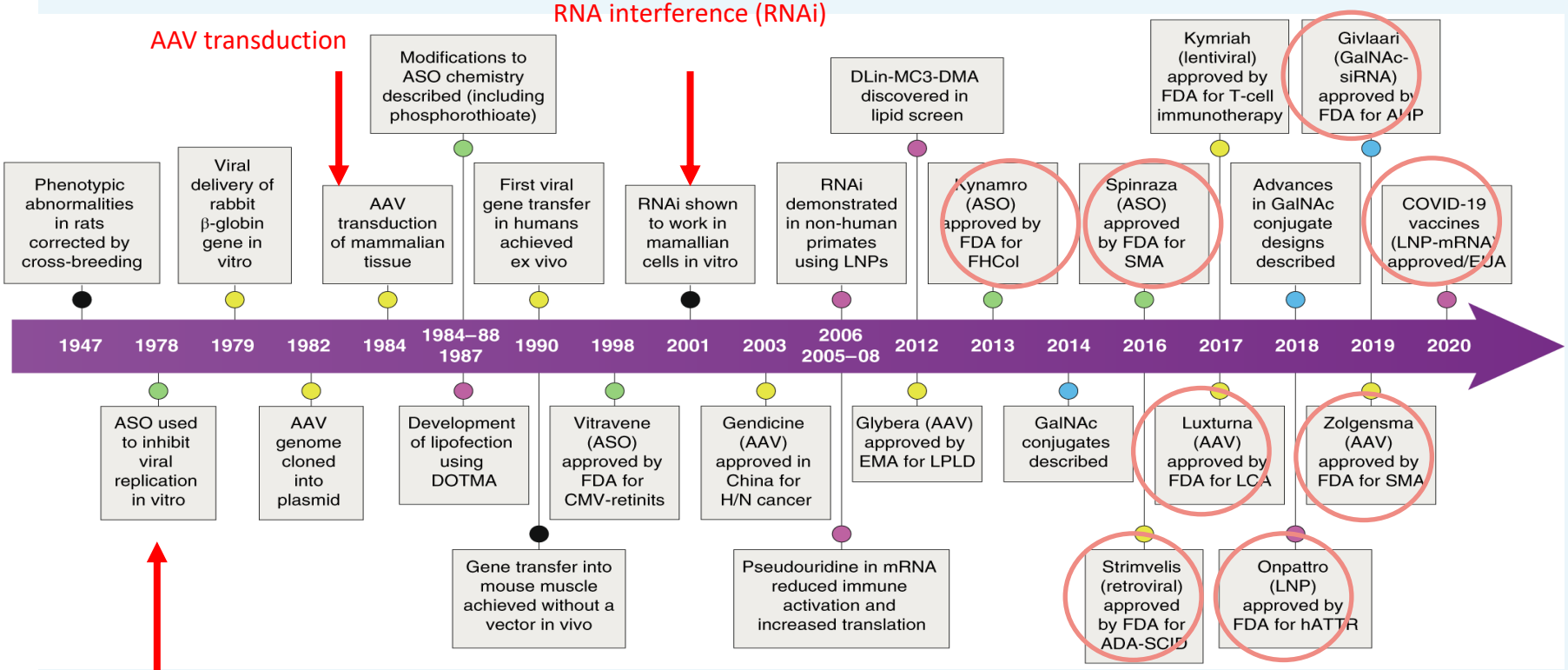
History :Drug classification

‘classic’ small molecules	Large molecules - biologics	Nucleic acid therapies
created in a laboratory via traditional drug discovery techniques	peptides or antibodies	
large libraries of existing compounds can be used as starting points	Able to bind more tightly to their targets, providing a more favorable interaction compared to a weakly bound small molecule	
well-defined chemical structure		
known mechanism of action		
can be designed/modified		

History :Drug classification

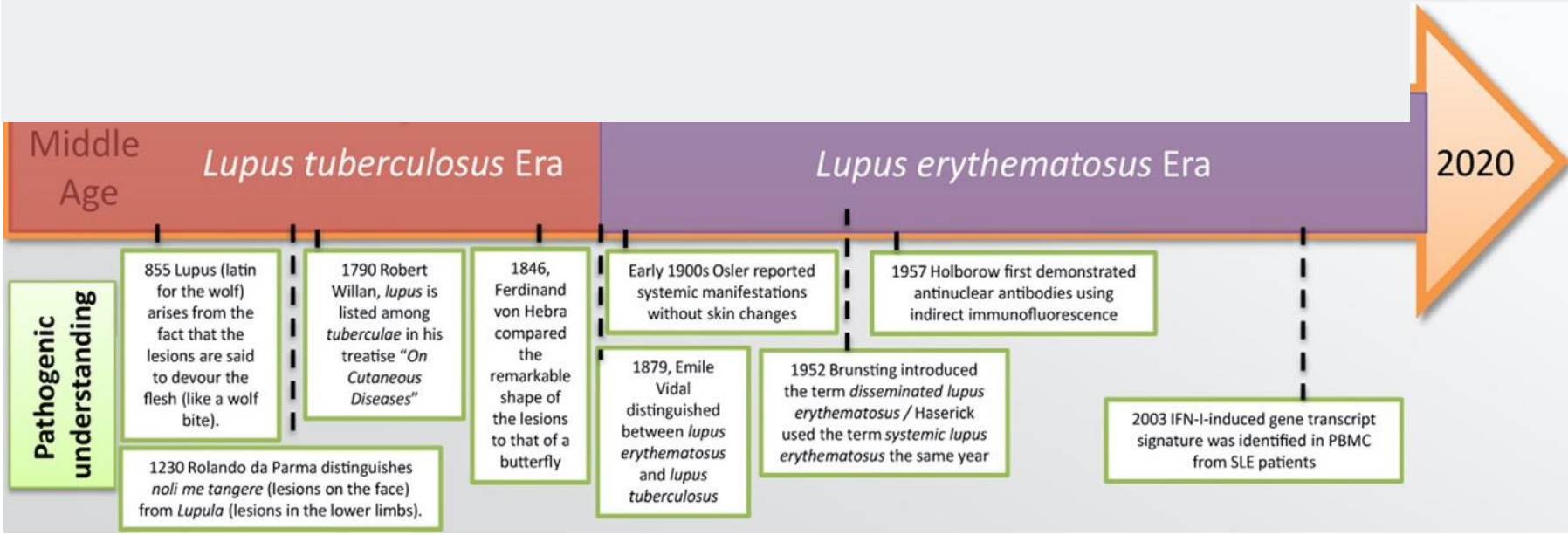
'classic' small molecules	Large molecules / biologics	Nucleic Acid therapies
morphine 1827	muromonab (OKT3, anti CD3) transplant anti-rejection, 1986 (withdrawn in 2000)	
Aspirin 1899	Abciximab (Reopro, glycoprotein IIb/IIIa receptor antagonist) 1994	
	Infliximab (Remicade) 19	

The journey of nucleic acid therapeutics



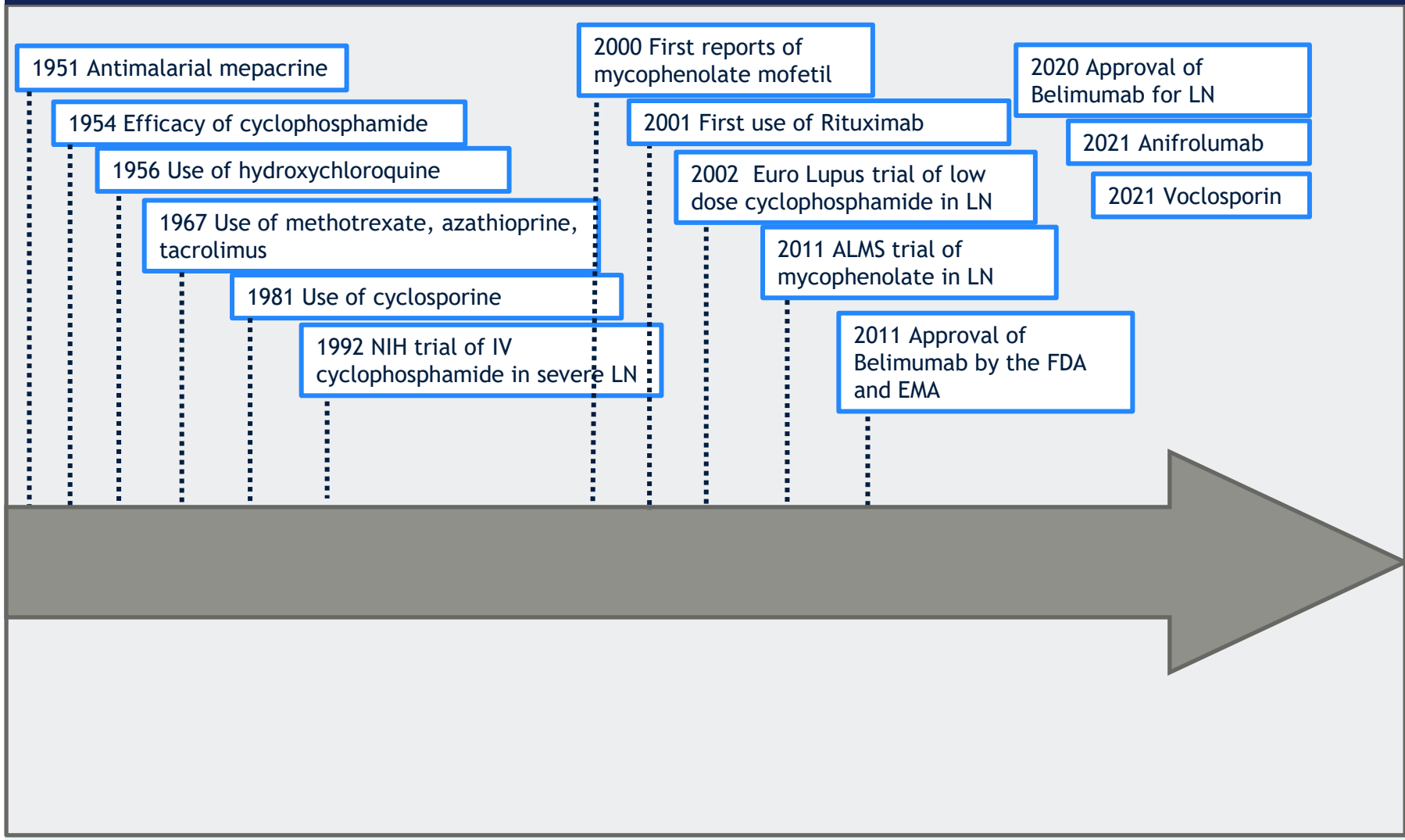
Kulkarni et al NATuRe NANoTeChNoLogy | VOL 16 | JUNE 2021

Lupus over the ages



Felten et al 2020 by the American Academy of Dermatology, Inc. https://doi.org/10.1016/j.jaad.2020.04.150

Lupus therapeutics



Adapted from Felten et al 2020 by the American Academy of Dermatology, Inc. https://doi.org/10.1016/j.jaad.2020.04.150

1894 Quinine

1950s Cortisone / antimalarials

1960s Azathioprine/methotrexate/tacrolimus

1970 Cyclophosphamide
(Lancet) and then 1992 and 2002

2000 Mycophenolate Mofetil (NEJM)

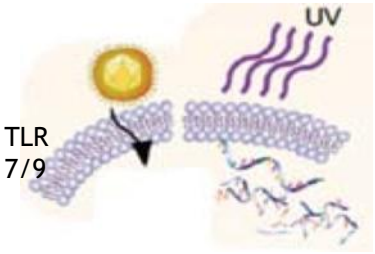
2011 Belimumab

2021 Anifrolumab. voclosporin

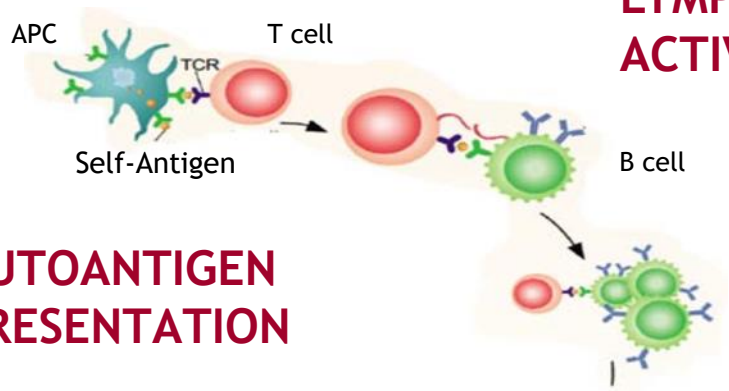
What is wrong with lupus?

Pathogenesis of SLE

Environmental triggers



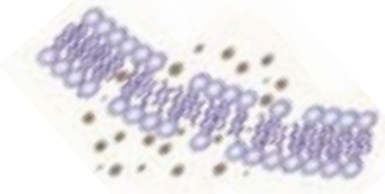
INNATE IMMUNE RESPONSE



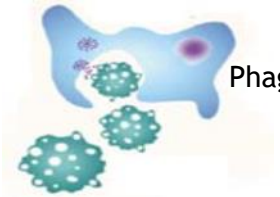
LYMPHOCYTE ACTIVATION

AUTOANTIGEN PRESENTATION

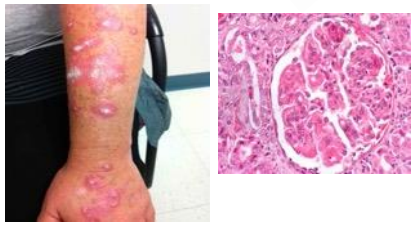
Cytokines/IFN



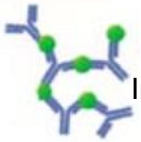
INEFFICIENT APOPTOTIC CLEARANCE



AUTOREACTIVE GERMINAL CENTER



TISSUE DESTRUCTION



Crampton et al *Disease Models & Mechanisms, 2014*

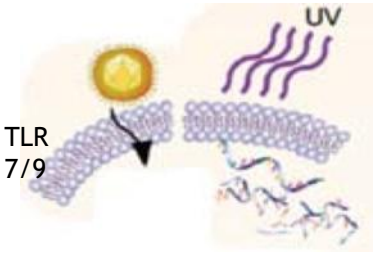
Pathogenesis of SLE

Environmental triggers

Virus

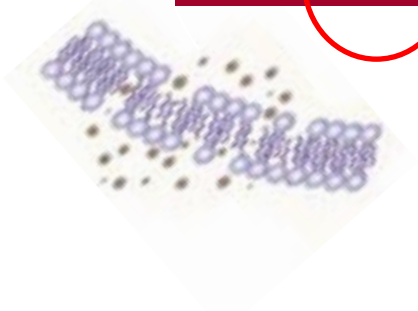
TLR 7/9

UV

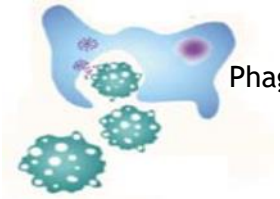


INNATE IMMUNE RESPONSE

Cytokines/IFN



INEFFICIENT APOPTOTIC CLEARANCE



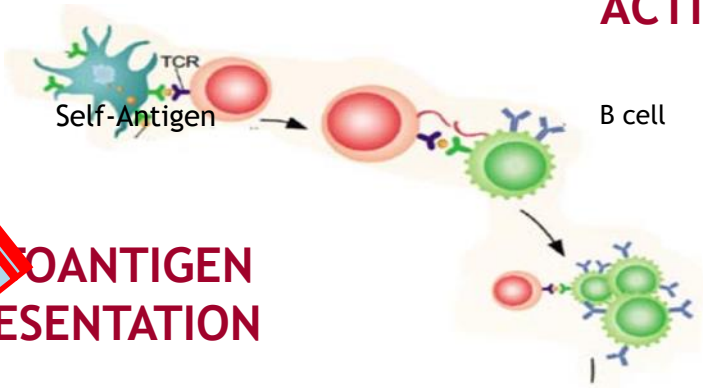
Apoptotic cells

TOANTIGEN RESENTATION

LYMPHOCYTE ACTIVATION

APC

T cell



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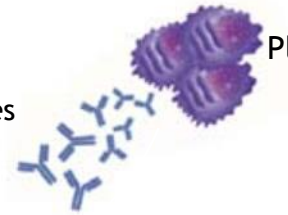
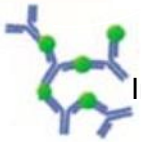
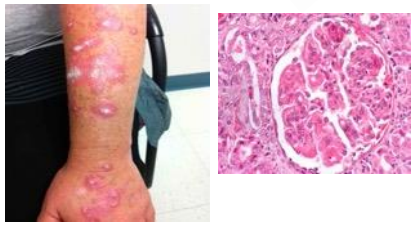


Autoantibodies



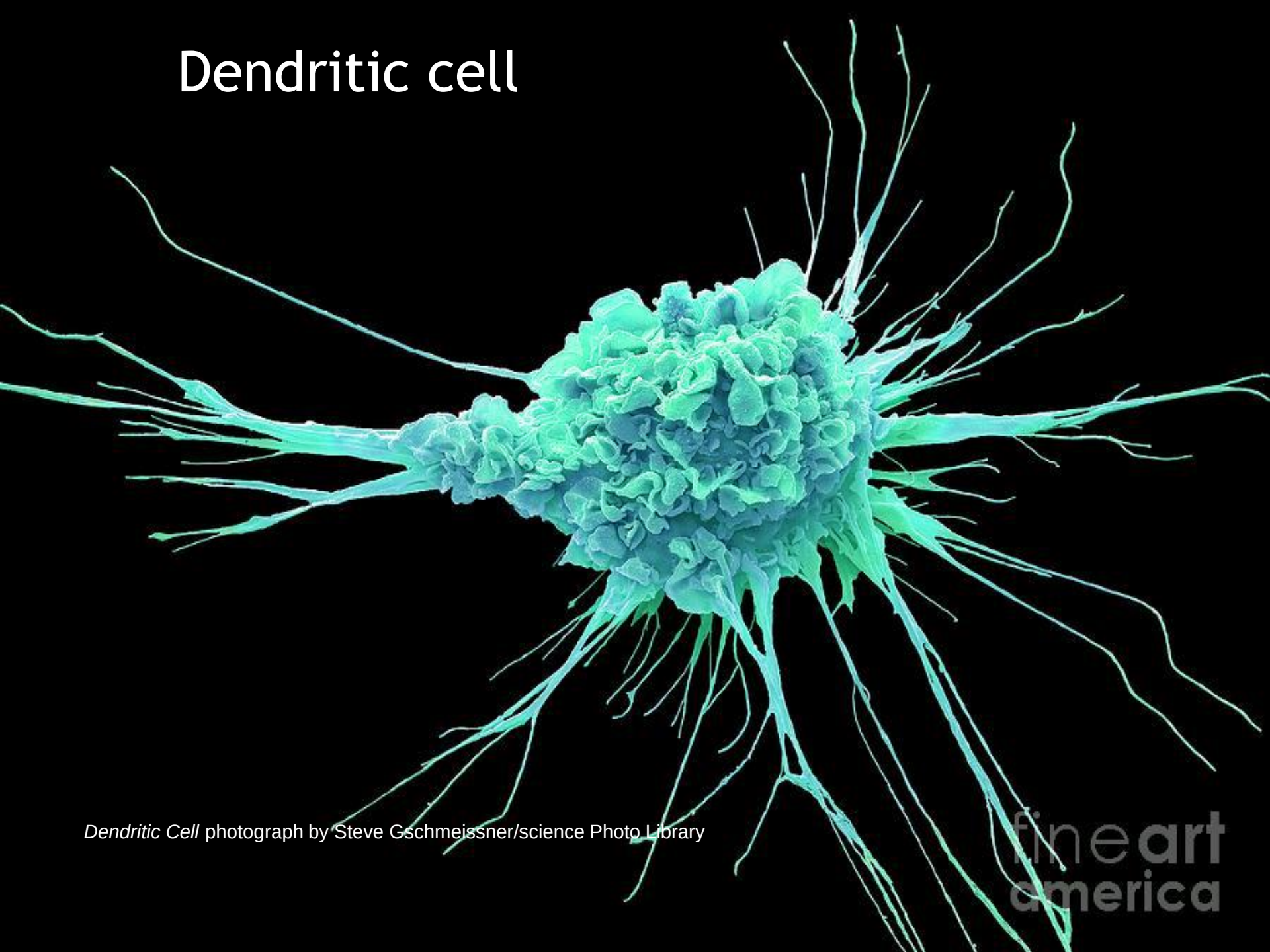


TISSUE DESTRUCTION

Complement fixation

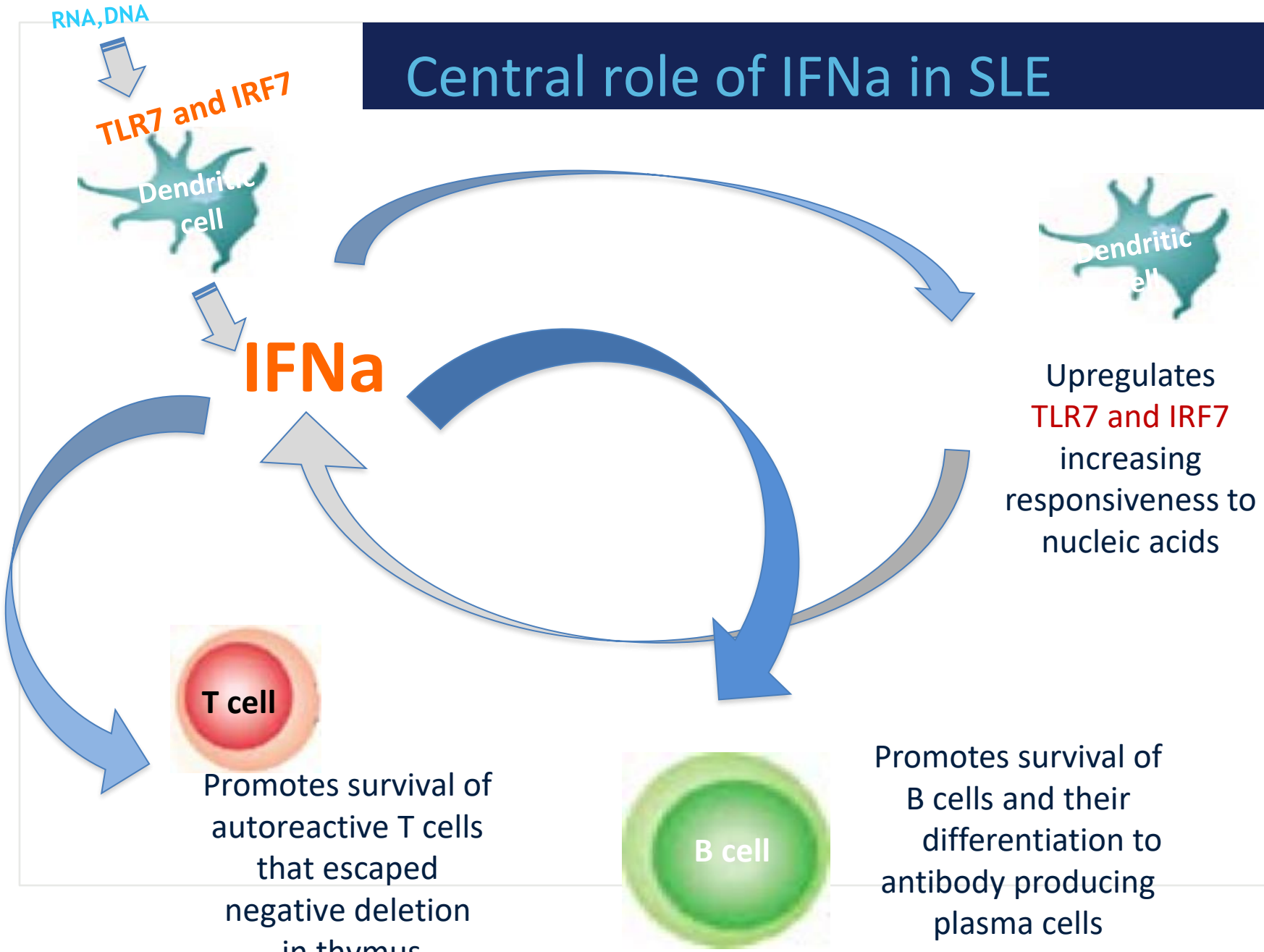
Crampton et al *Disease Models & Mechanisms, 2014*

Dendritic cell



Dendritic Cell photograph by Steve Gschmeissner/science Photo Library

Central role of IFNa in SLE



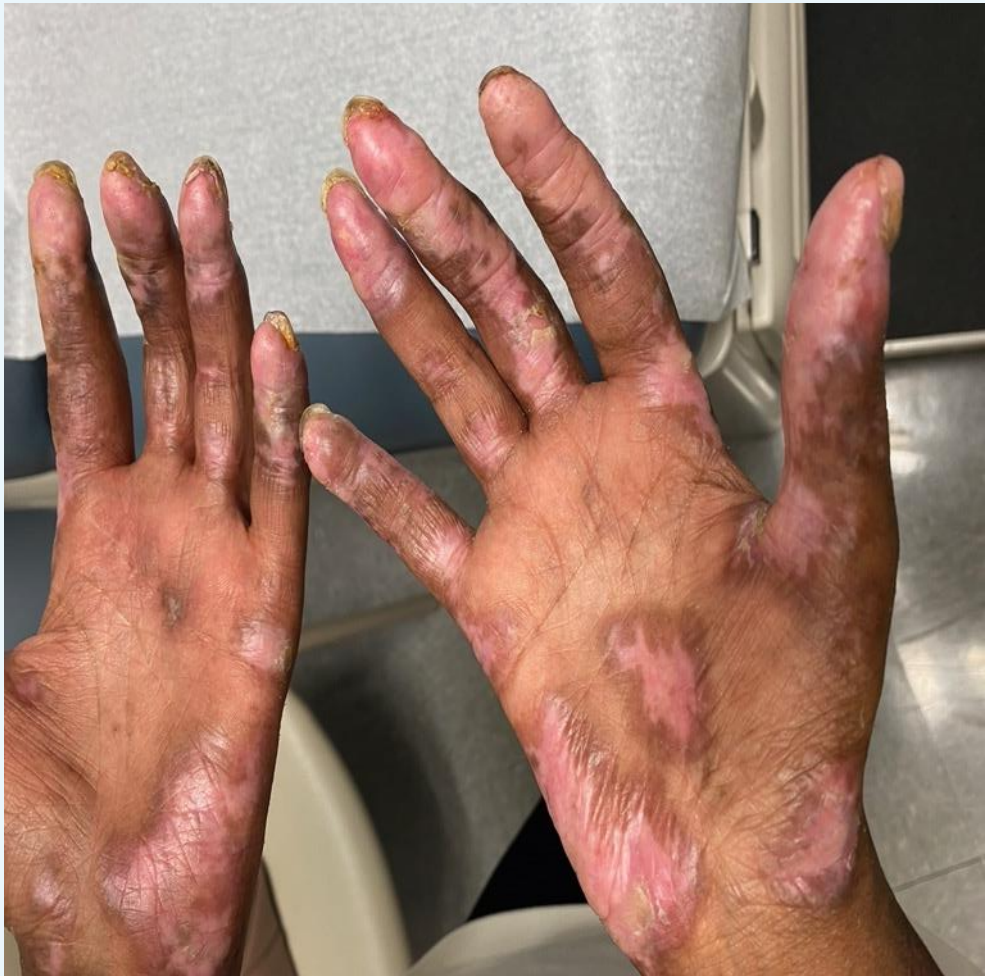
Chilblains

from Jefferson Lupus Clinic

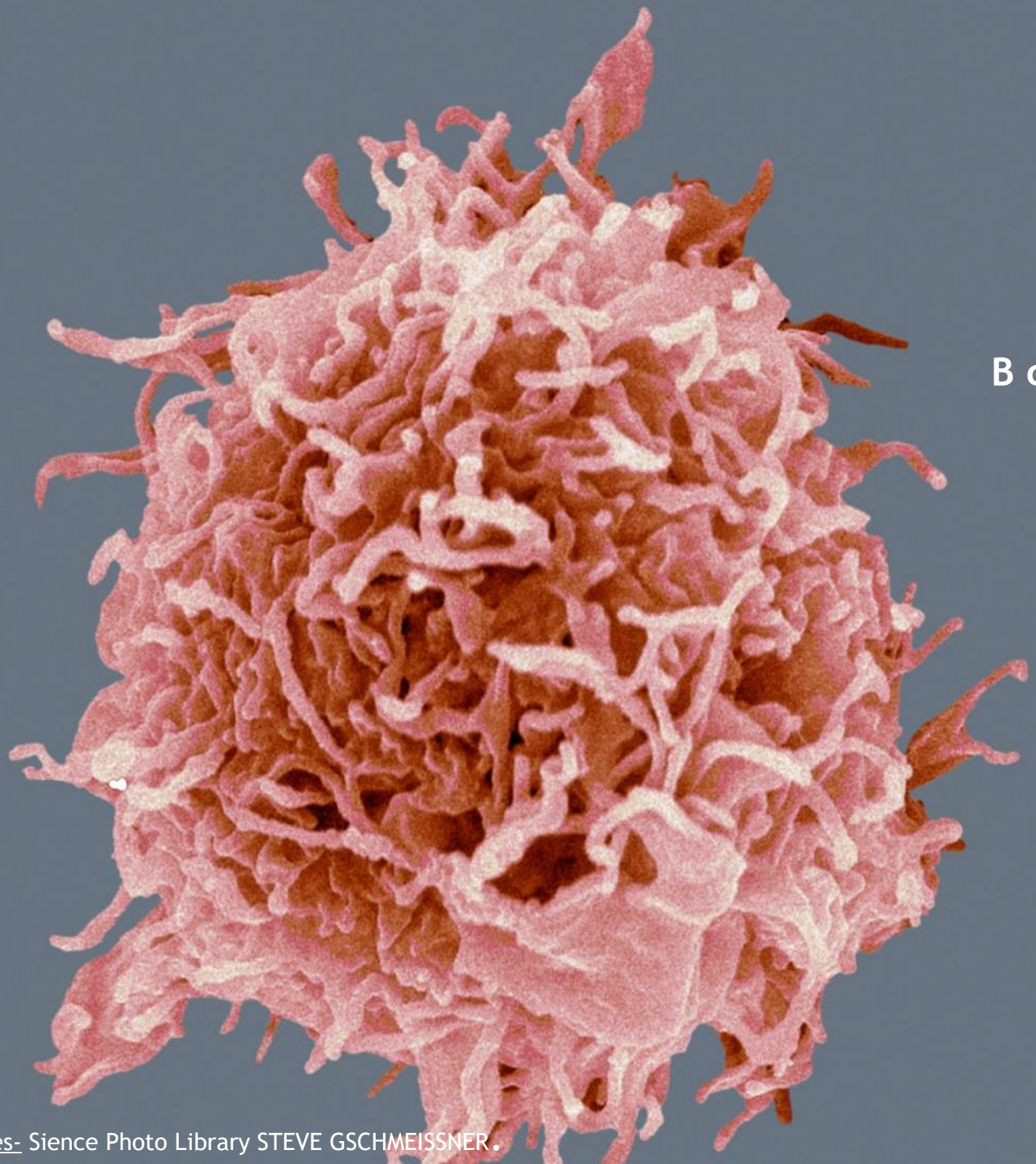
Anifrolumab

- Anifrolumab is a type I interferon receptor antagonist
- In a phase III RCT (TULIP 2 study) use of anifrolumab resulted in reduction in moderate-to-severe baseline disease activity
- Anifrolumab was authorized in 2021, as an add-on to standard therapy for the treatment of adult patients with moderate to severe, active autoantibody-positive SLE.

Morand EF, et al Ann Rheum Dis (2018)
Furie R, et al Arthritis Rheumatol (2017)
Morand EF et al N Engl J Med (2020)



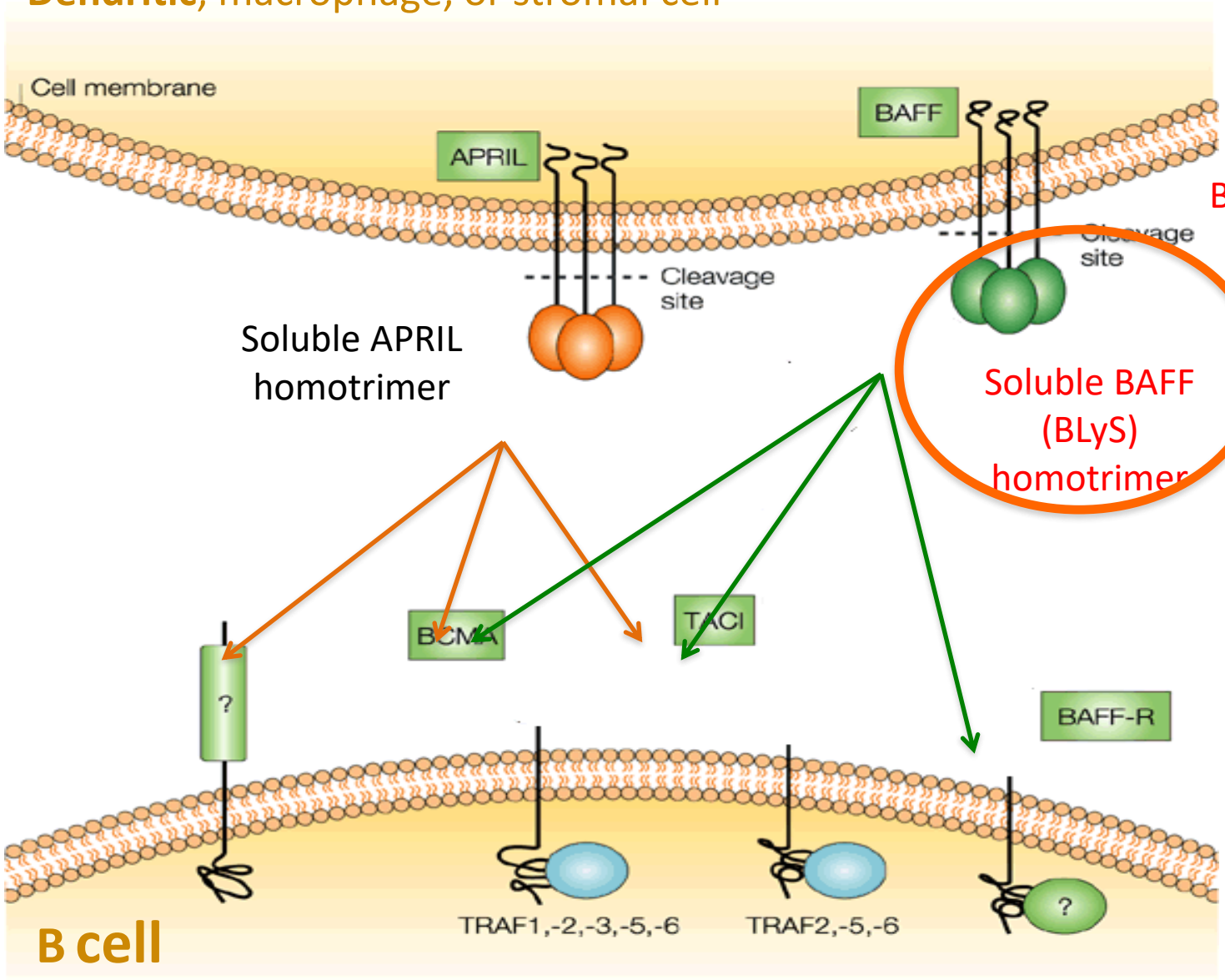
from Jefferson Lupus Clinic



B cell

https://www.gettyimages- Sience Photo Library STEVE GSCHMEISSNER.

Dendritic, macrophage, or stromal cell



Belimumab blocks BLyS

Apoptosis of transitional B cells

Belimumab

2011

musculoskeletal and mucocutaneous manifestations

immunological parameters

Hematological parameters

2020

belimumab (10 mg/kg dose) approved for lupus nephritis in combination with standard therapy either

mycophenolate mofetil for remission induction and maintenance,

or cyclophosphamide for remission induction followed by azathioprine for maintenance

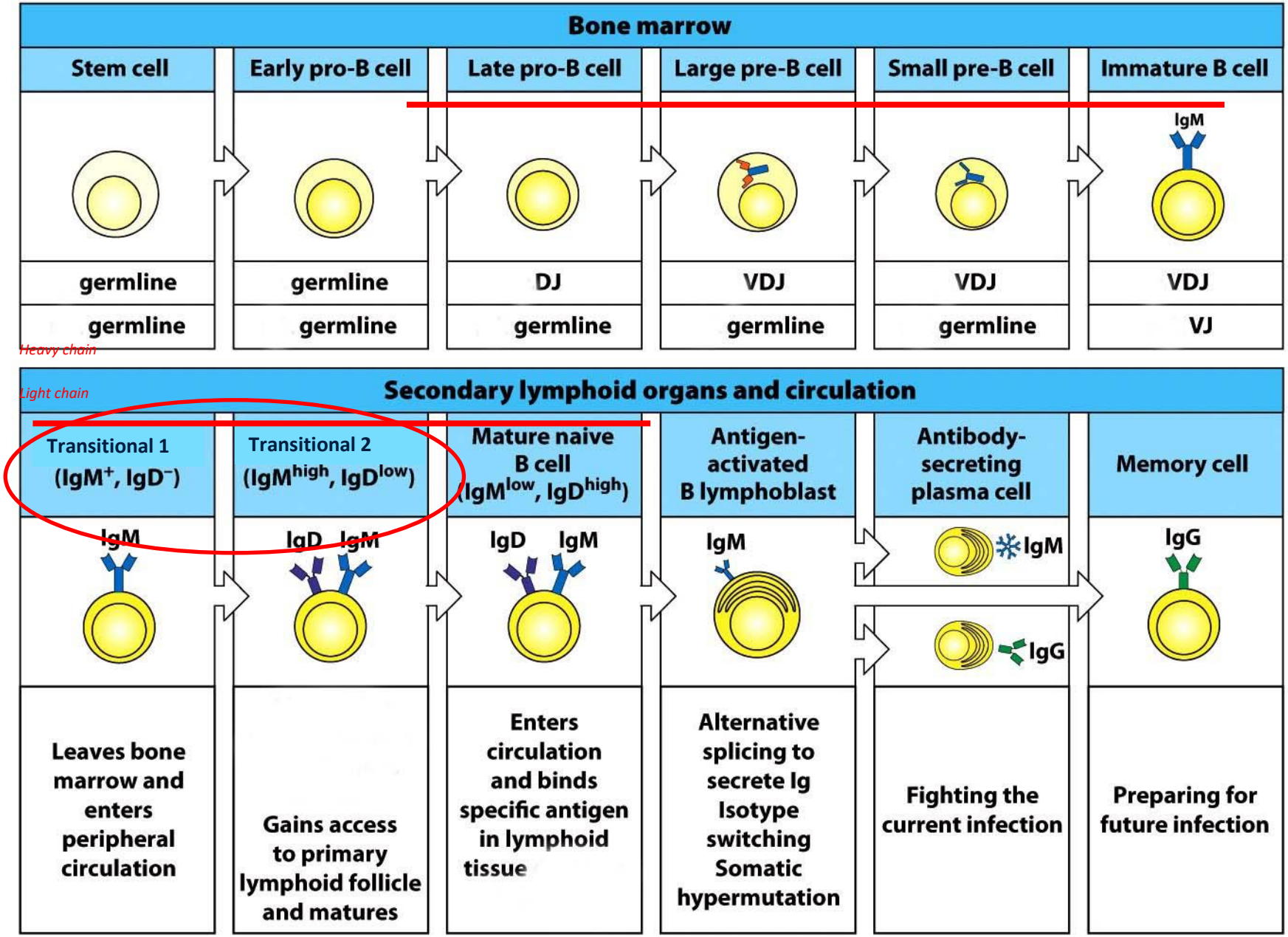
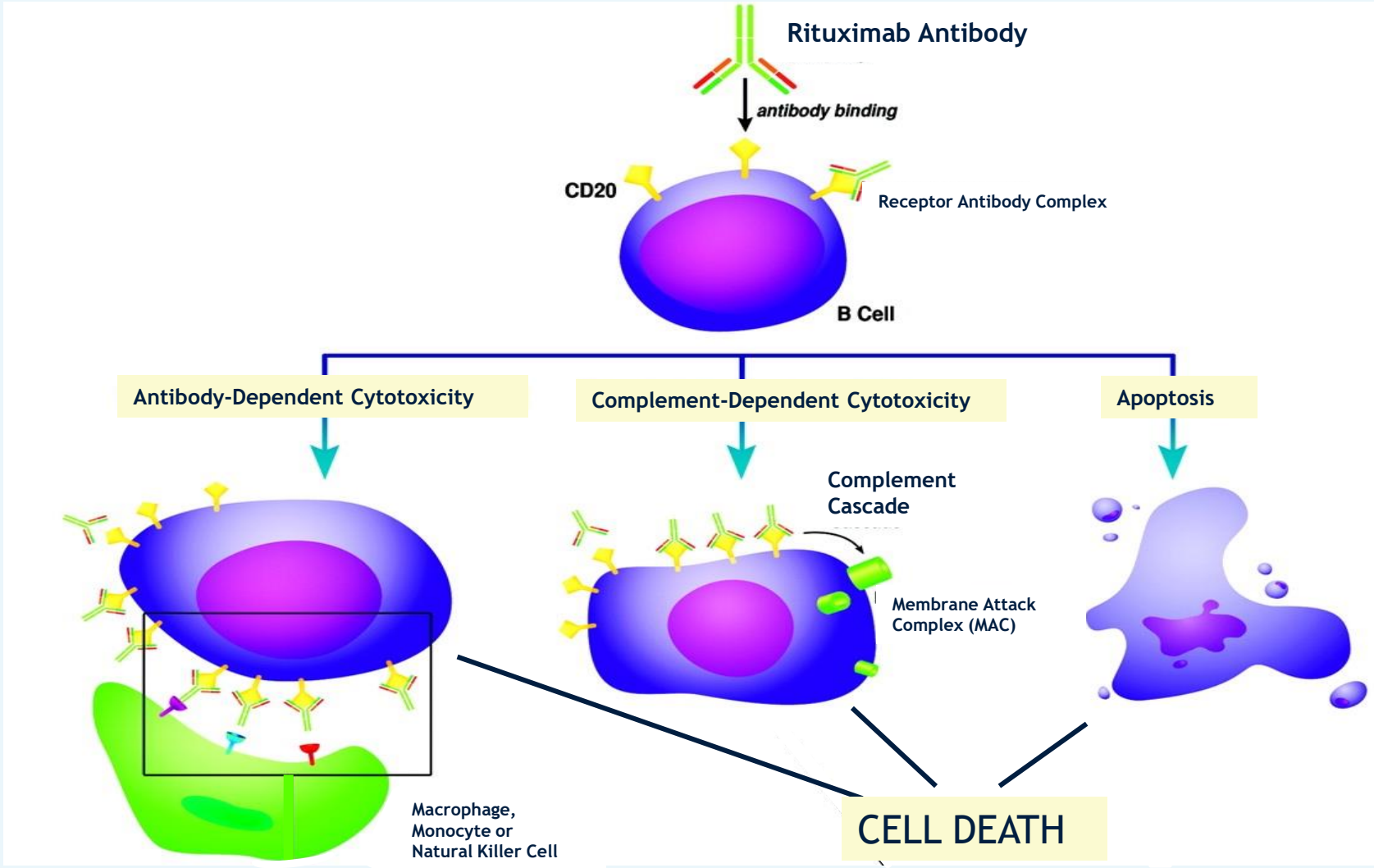


Figure 6.25 The Immune System, 3ed. (© Garland Science 2009)

Rituximab



D.T. Selewski et al. AJNR Am J Neuroradiol 2010;31:1178-1180

Rituximab in SLE

RCTs have not shown efficacy of rituximab in treatment of SLE and Lupus Nephritis

Observational studies including registries and

Large retrospective studies

Safe and effective treatment for refractory SLE or Lupus Nephritis class IV or V; with low incidence of adverse events

Discrepancies could be due to

- heterogeneity of SLE
- methodological problems of RCTs

Marinho A, et al Front. Immuno. 2023

Rituximab in SLE

Rituximab has been used successfully:

in SLE-associated refractory cytopenias including

- thrombocytopenia
- autoimmune hemolytic anemia
- microangiopathic hemolytic anemia

in refractory cases with neuropsychiatric involvement including delirium or psychosis, severe cognitive dysfunction or other NPSLE manifestations

in ocular SLE manifestations

Marinho et al Frontiers in Immunology, 2023

Other anti CD-20 targeting antibodies in Lupus

Rituximab: chimeric monoclonal Ab

Ocrelizumab : humanized monoclonal Ab

Small observational studies patients achieved and maintained clinical response; high incidence of serious infections)

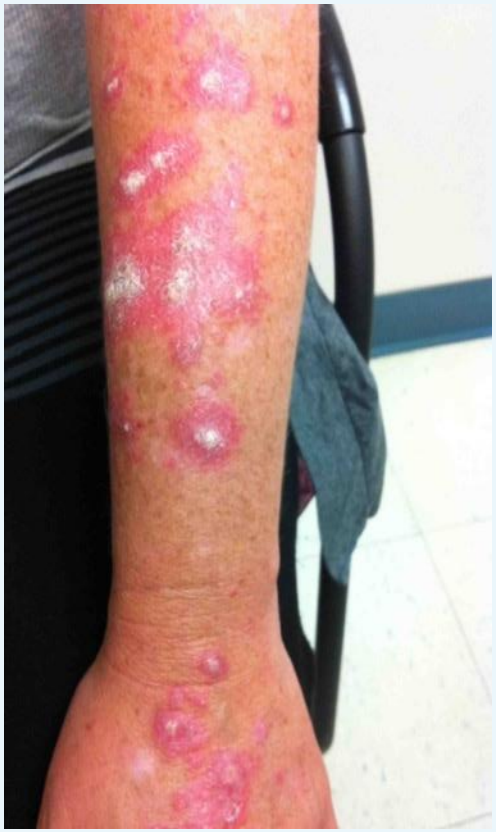
Obinutuzumab : humanized monoclonal Ab

Ongoing clinical trials including phase II placebo controlled in combination with mycophenolate and steroids in active lupus nephritis class III/IV.

Ofatumumab : human monoclonal Ab

In case series, patients achieved lasting disease remission

Chronic Cutaneous Lupus Erythematosus *(hypertrophic discoid lupus)*

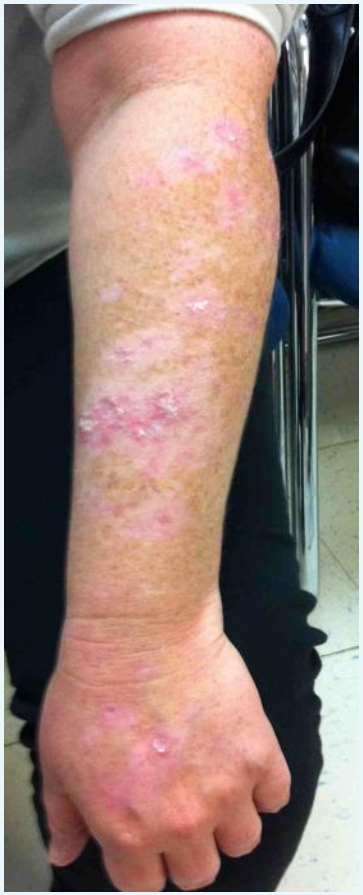


July 2014

Rituximab

Mycophenolate Mofetil

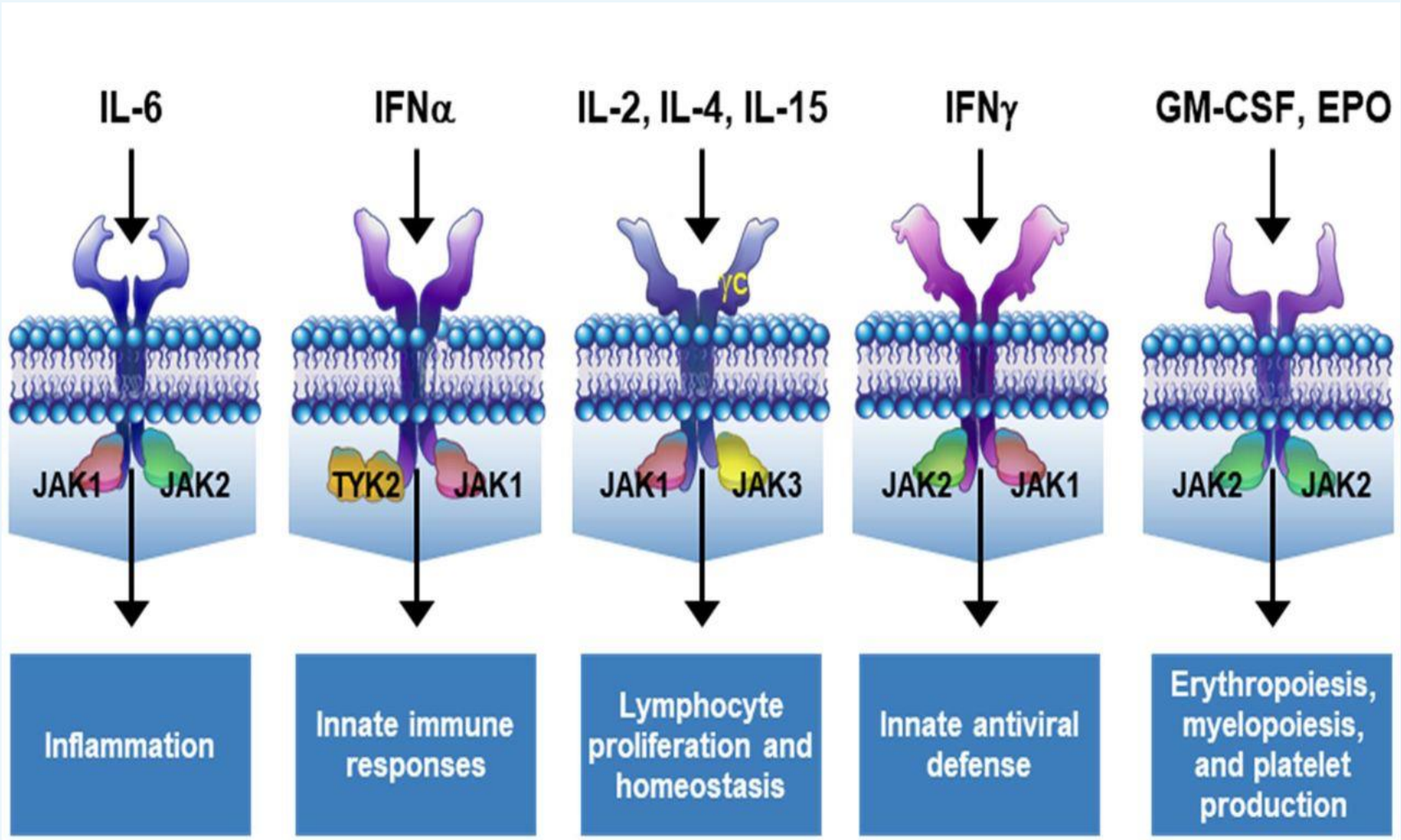
Dapsone



October 2015

from Jefferson Lupus Clinic

JAK inhibitors



Traves PG, *et al*. *Ann Rheum Dis* 2021

JAK signaling inhibition in Lupus : baricitinib

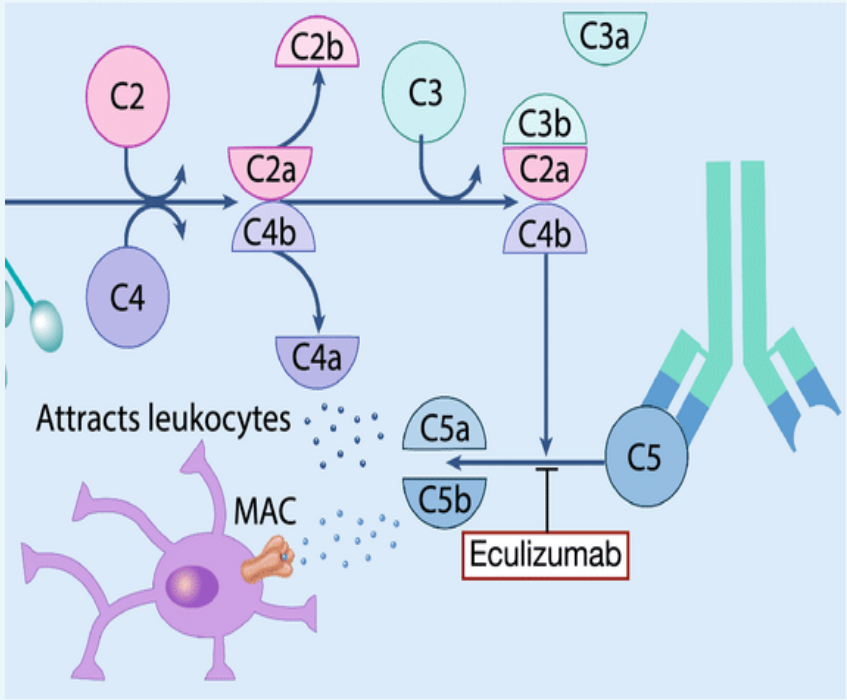
Selective JAK1 and JAK2 inhibitor

A double-blind phase II RCT, with 314 SLE participants showed efficacy in management of arthritis or rash, however there was high rate of serious infections (although similar to what was observed with belimumab)

A phase III study was deferred

Alunno A, Padjen I, Fanouriakis A, Boumpas DT. Cells (2019)
Wallace DJ, Furie RA, Tanaka Y, Kalunian KC, Mosca M, Petri MA, et al. Lancet (2018)

C5 inhibition in SLE: eculizumab



Humanized monoclonal antibody that binds to and prevents C5 activation

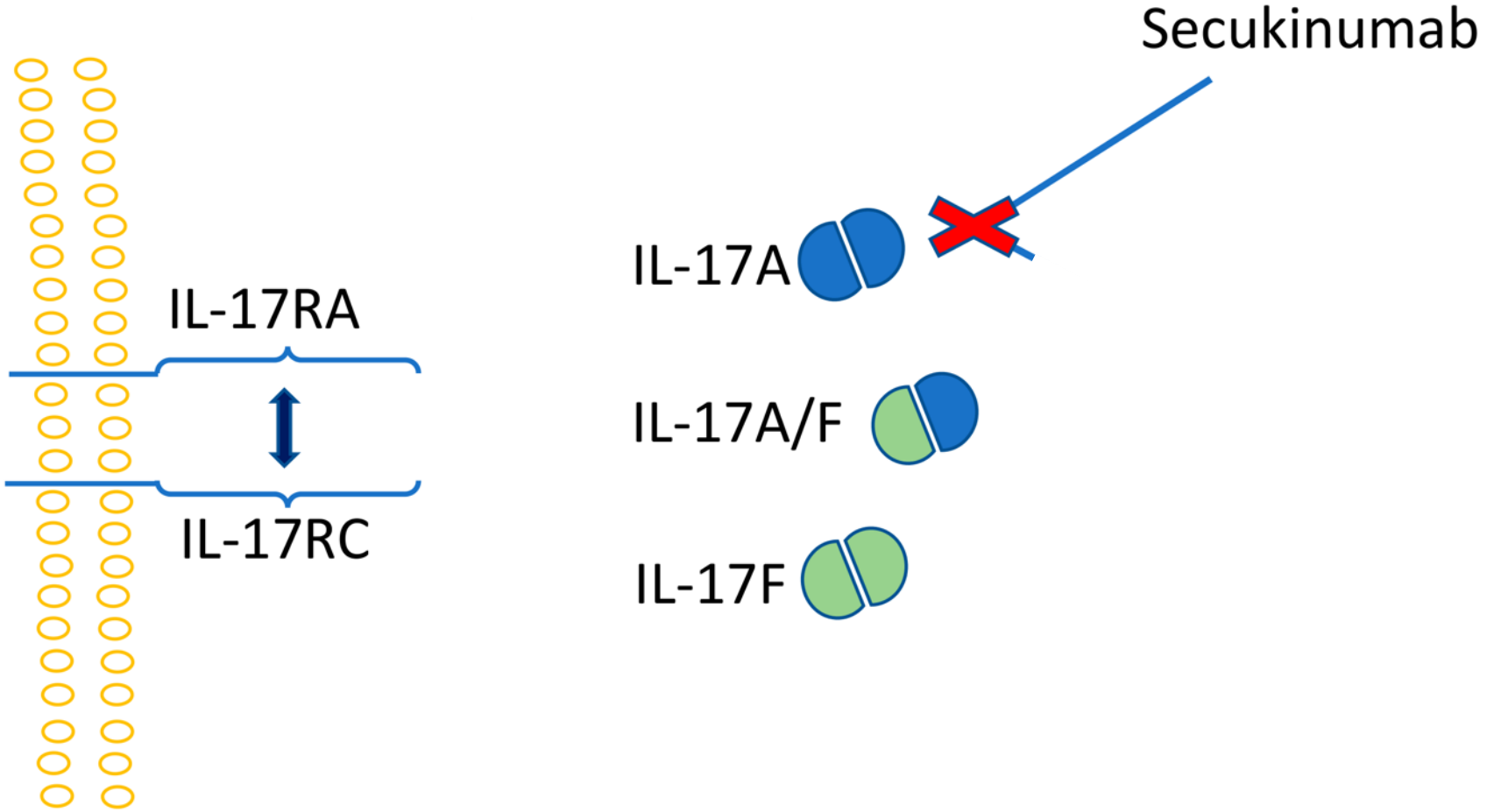
In case reports and case series treatment with eculizumab resulted in sustained improvement in renal function and normalization of complement parameters (median follow-up of 9 months)

Successful response was also observed in patients with refractory thrombotic microangiopathy in SLE

A randomized placebo-controlled, double-blind phase I RCT failed to demonstrate efficacy in SLE (assessed by laboratory and clinical parameters and SLEDAI scores).

Furie R, et al Arthritis Rheum (2004); PickeringMC,et al IsmajliM,CondonMB,McKennaN,HallAE,LightstoneL,etal Rheumatology (2015)
Ono M, et al Intern Med (2018)

IL-17 inhibition in SLE



Kübra Bunte and Thomas Beikler *Int. J. Mol. Sci.* 2019, *20*, 3394;

IL-17 inhibition in SLE: Secukinumab

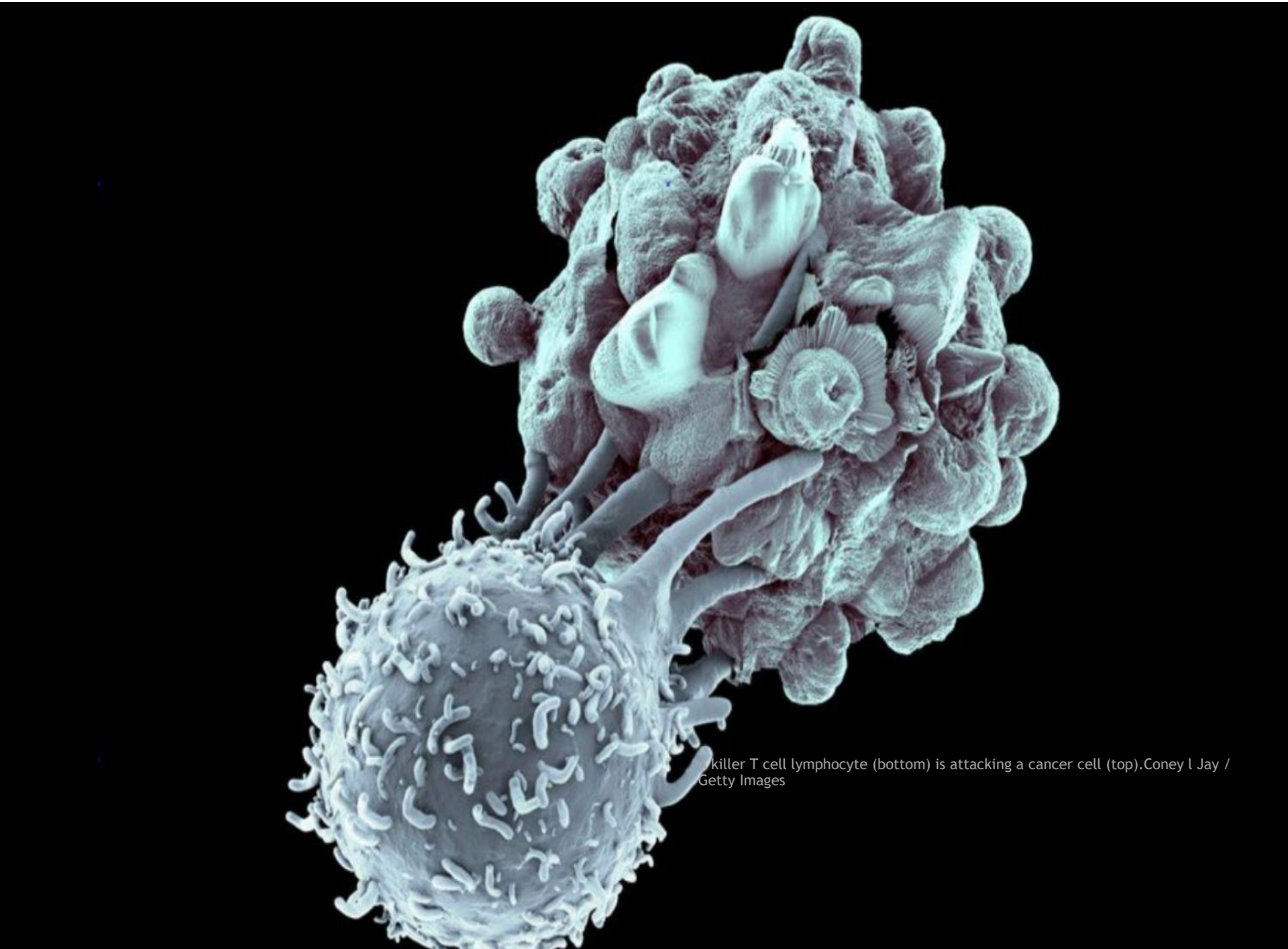
- Human mAB against interleukin 17 A
- Several studies have demonstrated the role of T-helper 17 cells in SLE pathogenesis
- In case report of a patient with psoriasis vulgaris and refractory lupus nephritis (showing proliferation of activated T h 17 cells in peripheral blood, and T h 17 renal infiltration) secukinumab was effective in treating both psoriasis and lupus nephritis
- A phase 3 RCT to evaluate subcutaneous secukinumab vs. placebo, in combination with standard of care, in patients with active LN was terminated by sponsor due to futility analysis
- A study to assess the safety and efficacy of secukinumab in discoid lupus erythematosus was also terminated due to difficulty in recruiting participants

RM, Mohamed SF, Bassyouni IH, Raouf AA. Cytokine (2015)
SatohY,NakanoK,YoshinariH,NakayamadaS,IwataS,KuboS,et al.. Lupus (2018)

IL 6 inhibition in SLE :Tocilizumab

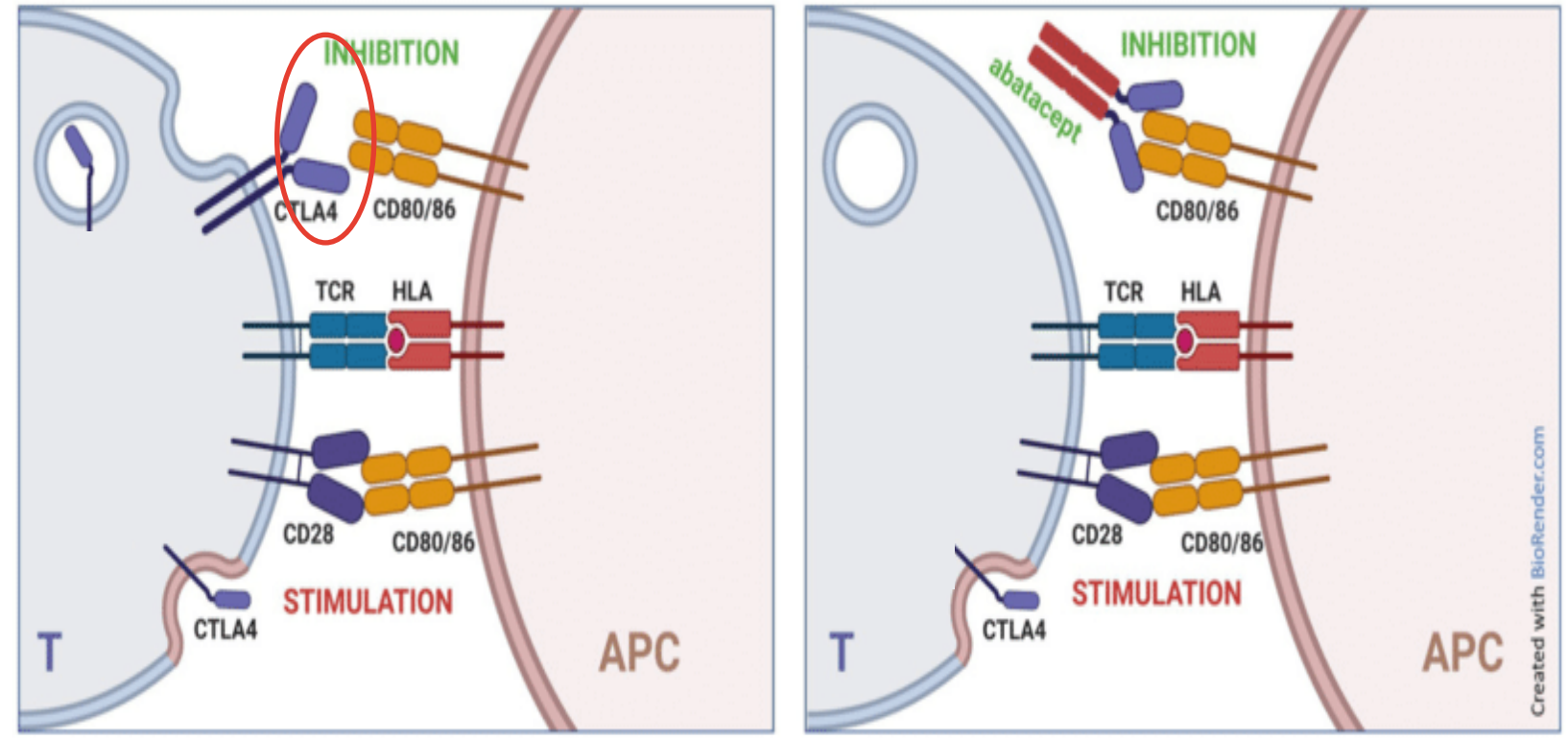
- An open-label, phase I study 16 participants with mildly to moderately active SLE showed clinical and serological response
- Tocilizumab as add-on therapy in SLE has been described in case reports, with successful outcomes in management of arthritis or refractory serositis
- It has also been used successfully in SLE AIHA refractory to rituximab
- **High risk for neutropenia and infections**

Illei GG et al .Arthritis Rheum (2010) ; Juptner M et al Lupus (2014) ; Maeshima K, et al Lupus (2012) ; Ocampo V, et al BMJ Case Rep (2016) ; Kamata Y et al BMJ Case Rep (2012) Garcia-Hernandez FJ et al Rheumatology (2012



killer T cell lymphocyte (bottom) is attacking a cancer cell (top).Coney l Jay / Getty Images

CD80/86 inhibition in SLE

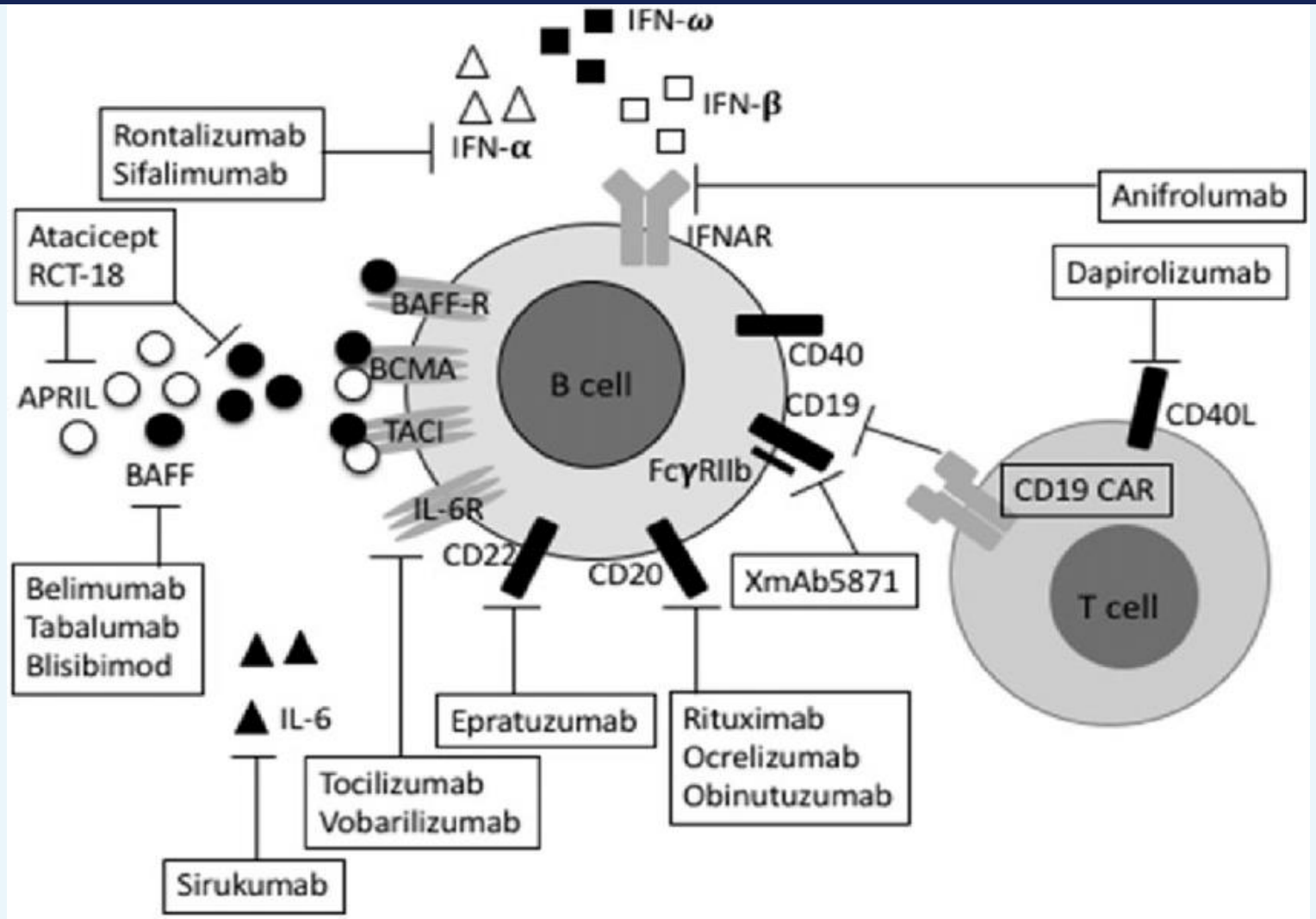


Boz et al;Frontiers in Immunology 12;2021

T cell signal II inhibition in SLE: abatacept

- RCTs failed to demonstrate efficacy of CTLA 4 inhibition in the treatment of active lupus and lupus nephritis, although some exploratory endpoints related to arthritis response, showed response

Summary



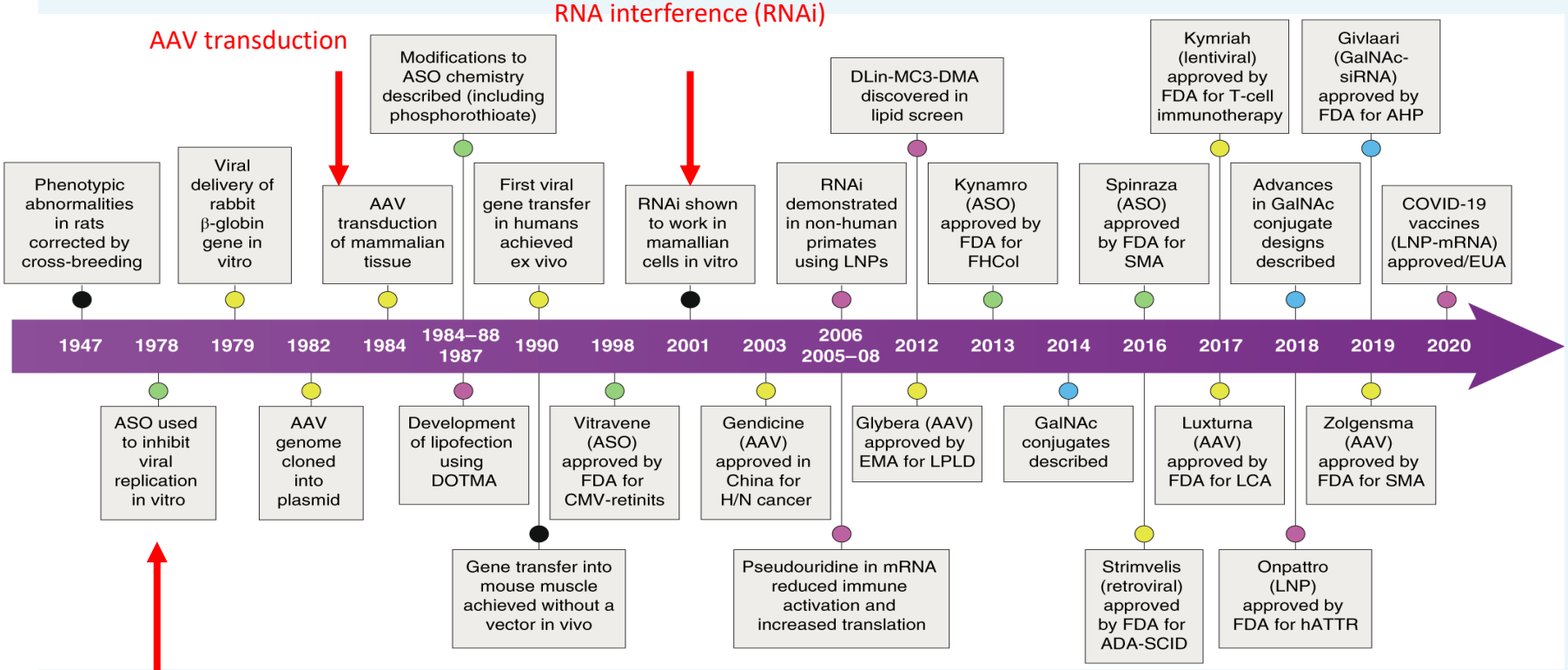
Wen Shi Lee & Olga Amengual

TNFa

- The use of anti-tumor necrosis factor (TNFa) in SLE is controversial, due to the risk of disease exacerbation
- Short- term use of infliximab was successful in an open-label study with moderately active SLE patients.
- However, patients with lupus arthritis maintained clinical response for less than 2 months after the last infusion.
- Long-term therapy was associated with serious adverse events (SAEs)

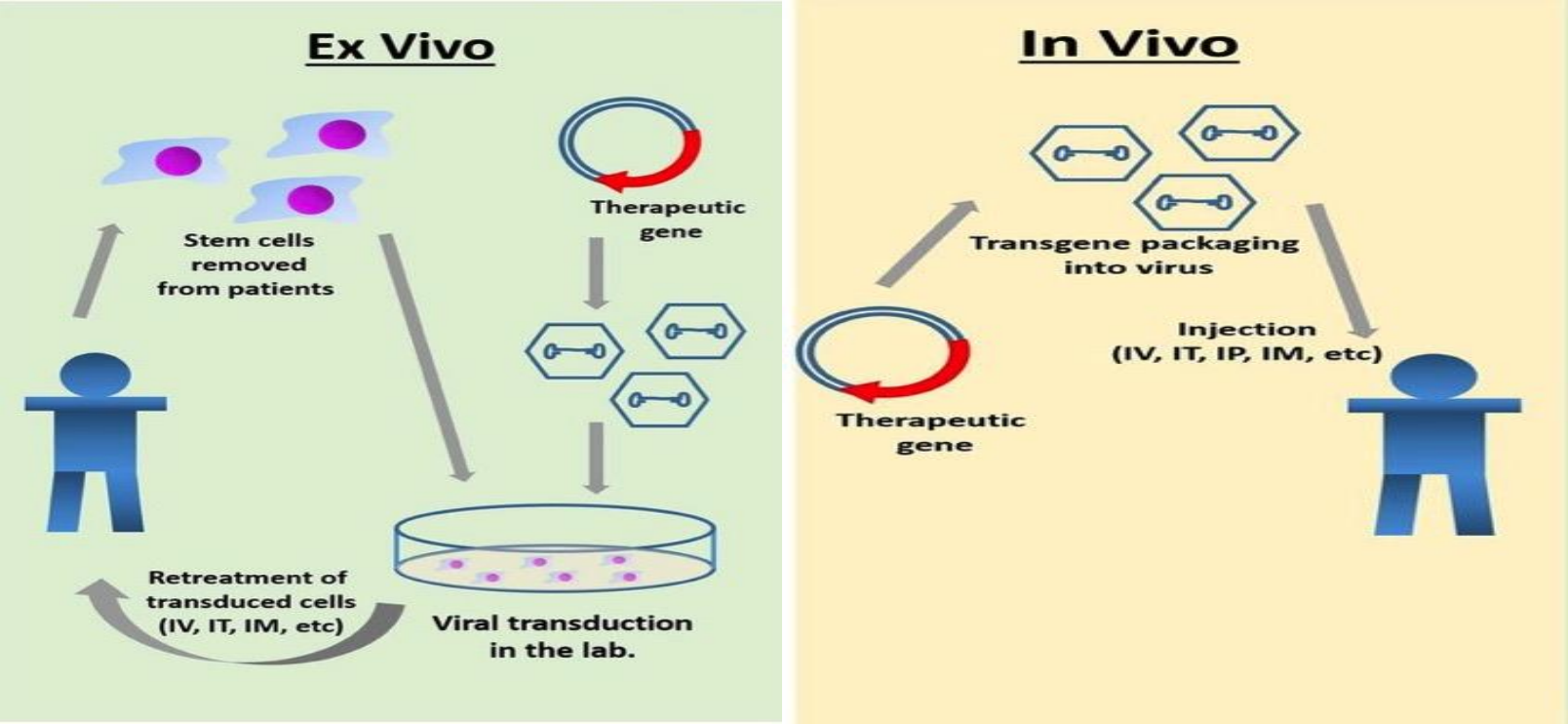
Marinho A, et al Front. Immuno. 2023

The journey of nucleic acid therapeutics



Kulkarni et al NATuRe NANoTeChNoLogy | VOL 16 | JUNE 2021

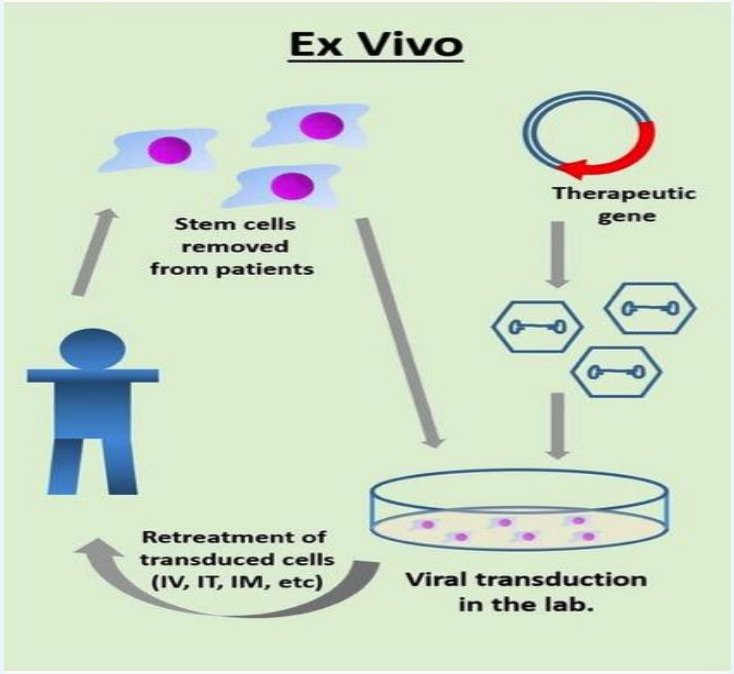
Adenovirus mediated therapies



Tomatsu, Shunji & Sawamoto, Kazuki & Chen, Hui-Hsuan & Mason, Robert. (2018). Molecular Genetics and Metabolism.

Ex-vivo nucleic acid therapies - example 1:

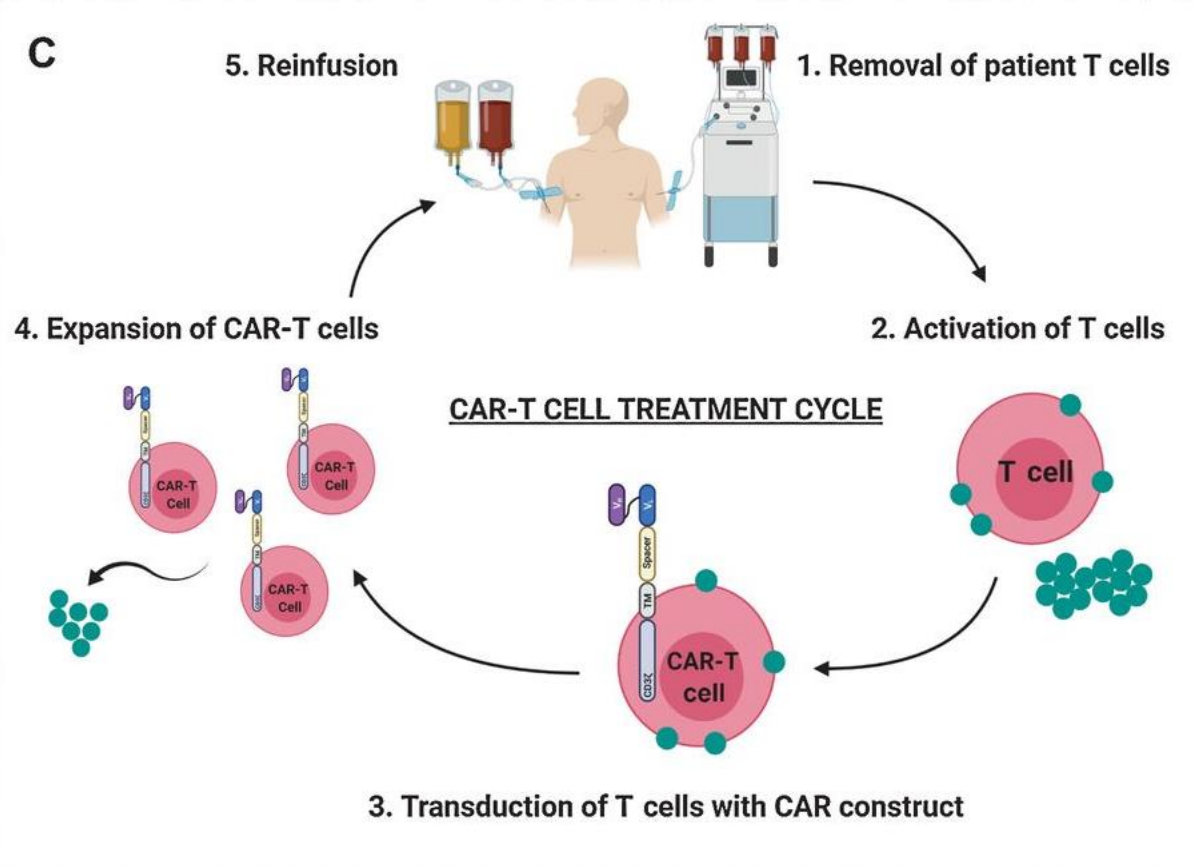
Severe combined immunodeficiency due to ADA deficiency (ADA-SCID)



Strimvelis: patient-derived CD34+ cells transduced with a γ-retroviral vector to express DNA encoding the human adenosine deaminase (ADA) enzyme

Ex-vivo nucleic acid therapies - example 2:

Chimeric Antigen Receptor – T cell therapy in cancer

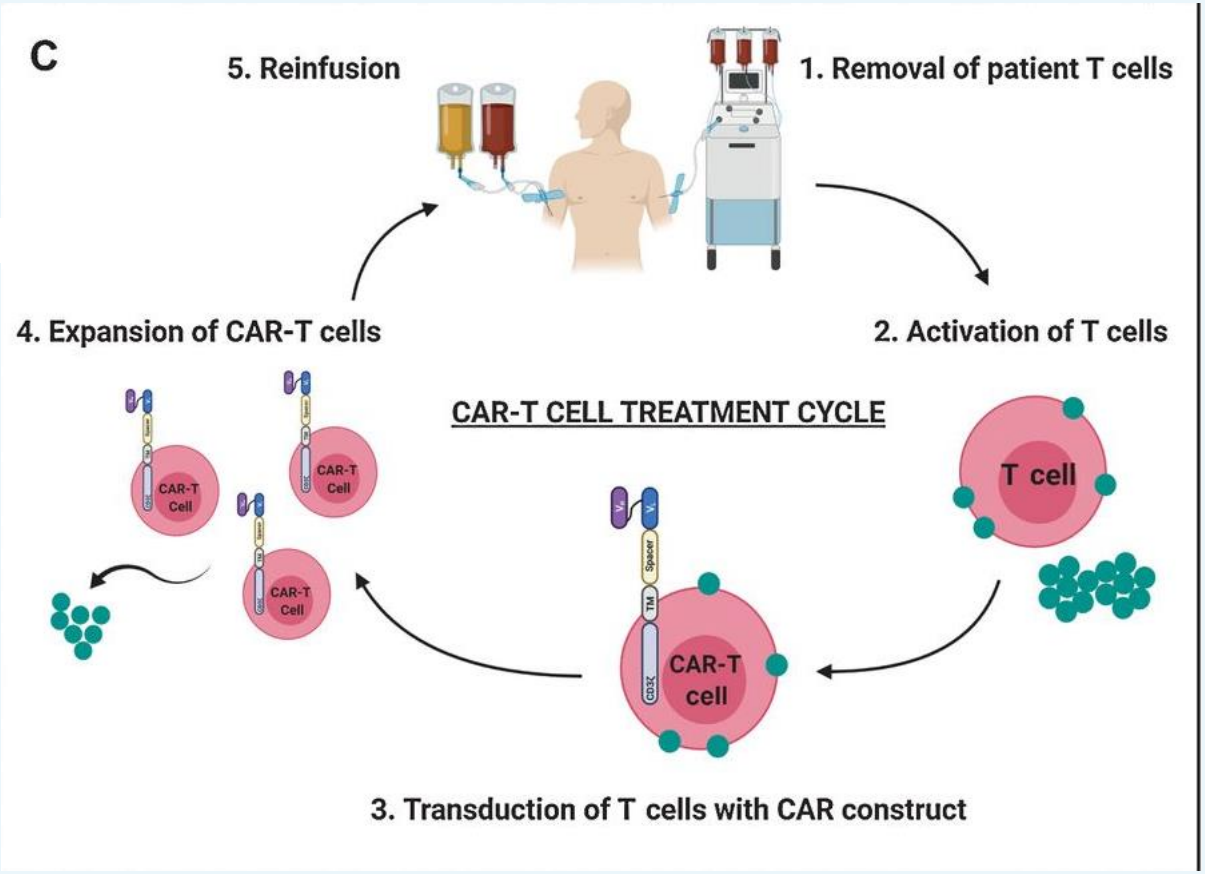


Autologous CAR-T cell production

1. removal of patient T cells
2. activation ex vivo
3. introduction of CAR constructs via viral vectors (lentivirus, retrovirus, adenovirus), non-viral vectors (synthetic DNA, mRNA transposons, CRISPR-Cas9) or plasmids
4. expansion of CAR-modified T cells
5. administration of chemotherapy
6. infusion of CAR-T cells into the patient

Sundee Dees, Rajkumar Ganesan, Sanjaya Singh and Iqbal S. Grewal; Molecular Cancer therapeutics, 2020

FDA approved CAR-T cell therapy in cancer



Leukemia or Lymphoma

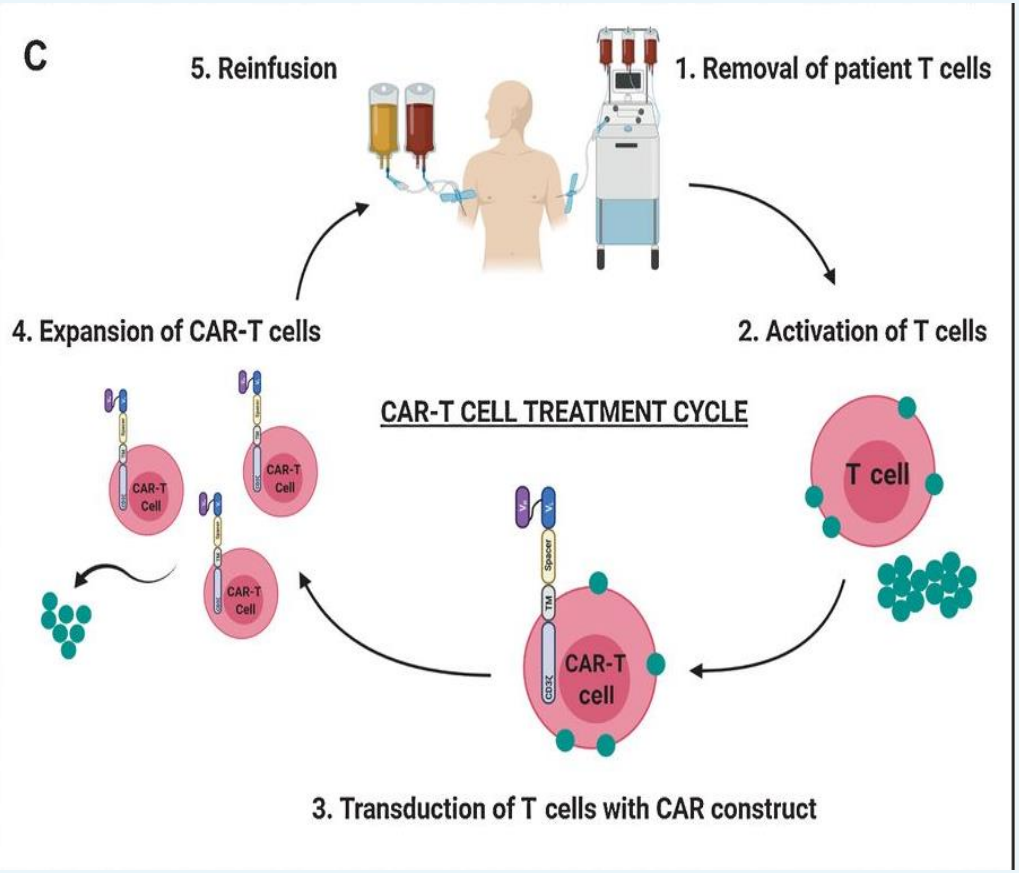
- Yescarta (axicabtagene ciloleucel)
- Tecartus (brexucabtagene autoleucel)
- Kymriah (tisagenlecleucel)

Engineering autologous T cells using lentiviral or γ-retroviral vectors to express chimeric antigen receptors specific for the CD19 protein (B cells)

Sundee Dees, Rajkumar Ganesan, Sanjaya Singh and Iqbal S. Grewal; Molecular Cancer therapeutics, 2020

Ex-vivo nucleic acid therapies - example 3:

Chimeric Antigen Receptor – T cell therapy in Lupus



Autologous CAR-T cell production

1. removal of patient T cells
2. activation ex vivo
3. introduction of CAR constructs via viral vectors (self inactivating lentivirus expansion of CAR-modified T cells for 12 days
4. administration of lymphodepleting therapy
5. infusion of CAR-T cells into the patient

CAR-T cell therapy in Lupus

- Leukapheresis of T cells and activation
- CAR constructs
  self inactivating lentivirus vector encoding a single-chain variable fragment derived from the murine anti-human CD19 antibody binding to exon 4 of human CD19
- Expansion of CAR-modified T cells for 12 days
- Lymphodepletion with fludarabine 25 mg/m2/d intravenously (i.v.) on days -5, -4, - 3 and cyclophosphamide 1000 mg/m2 i.v. on day -3 before
- Infusion of CAR-T cells

Fabian Müller, et al; N Engl J Med Feb 2024;390:687-700.

Disease activity after CAR-T cell infusion

Disease activity assessed by several different criteria (LLDAS criteria. aDORIS SLEDAI-2K BILAG) at baseline and follow-up

Resolution of all major SLE manifestations

Long-term follow-up of up to 29 months showed that SLE disease activity remained quiescent in all patients

anti-dsDNA antibodies disappeared and remained negative

C3 levels normalized

proteinuria disappeared during the entire observation period *

- one patient had rebound of proteinuria 4 months after CAR T-cell therapy.
- Renal biopsy showed podocytopathy
- Had very mild proteinuria at 24 months after treatment

Fabian Müller, et al; N Engl J Med Feb 2024;390:687-700.

B cell subtypes after CAR-T cell infusion

- Analysis of B-cell subsets was performed at baseline, 4 months, and 12 months after CAR T-cell infusion
- Reconstituted B cells at 4 and 12 months showed a naive B-cell phenotype
- Immature CD38+ B cells, indicating reconstitution of B cells from the bone marrow, increased at 4 months and decreased thereafter
- CD19+CD27+ memory B cells were drastically reduced
- Limited increase in CD19+CD27+ memory B cells between 4 and 12 months, which was predominantly seen in **preswitched** IgD+ CD27+ B cells.
- CD27+CD38+ plasmablasts and SLE-associated activated CD11c+ memory B cells were not detected after B-cell reconstitution
-

Fabian Müller, et al; N Engl J Med Feb 2024;390:687-700.

Adverse effects

Patients were screened daily during the first 10 days for symptoms of cytokine-release syndrome (CRS) and immune-effector cell associated neurotoxicity syndrome (ICANS)

Cytokine release syndrome (after 1 day lasting for a median of 5 days) :

Mostly grade 1 (fever)

No moderate- or high-grade

ICANS: none

Pneumonia (one patient) 7 weeks after CAR T infusion. Responded to antibiotics

Other complications/ adverse reactions were mild and mostly upper respiratory tract infections.

Fabian Müller, et al; N Engl J Med Feb 2024;390:687-700.

Summary

Stable remission stateafter treatment as assessed by:

- Absence of clinical disease manifestations
- Sustained diminution of autoantibodies
- Appearance of naive non–class-switched B-cells
- Disappearance of circulating plasmablasts

- CD19 CAR T-cell therapy may have induced a reset of pathologic autoimmunity in these patients

- Although CAR T-cell therapy is directed to both pathogenic and nonpathogenic B cells, rebooting of the B-cells after the disappearance of CAR T cells occurs in the absence of autoreactive B cells.

- Given that patients had full B-cell reconstitution for up to 2 years without having relapses, a single infusion of CD19 CAR T-cell therapy may lead to a long-lasting remission.

Updates on management of SLE

EULAR recommendations for the management of systemic lupus erythematosus: 2023 update

- HCQ is recommended for all patients with lupus at a target dose 5 mg/kg real body weight/day,
- GC are used as 'bridging therapy' during periods of disease activity; for maintenance treatment, they should be minimized to equal or less than 5 mg/day (prednisone equivalent) and, when possible, withdrawn.
- Prompt initiation of immune suppressive therapy (methotrexate, azathioprine, mycophenolate) and/or biological agents (anifrolumab, belimumab) should be considered to control the disease and facilitate GC tapering/discontinuation.
- Cyclophosphamide (CYC) and rituximab should be considered in **organ-threatening and refractory disease, respectively.**
- For active lupus nephritis, GC, mycophenolate or low-dose intravenous CYC are recommended as anchor drugs, and add-on therapy with belimumab or calcineurin inhibitors (voclosporin or tacrolimus) should be considered.

Updated specific recommendations are also provided for

- cutaneous,
- neuropsychiatric and
- hematological disease,
- SLE-associated antiphospholipid syndrome,
- kidney protection
- preventative measures for infections, osteoporosis, cardiovascular disease.

Fanouriakis A, *et al*. *Ann Rheum Dis* 2024

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