VANCOUVER 2026

CAR T-cells and Beyond

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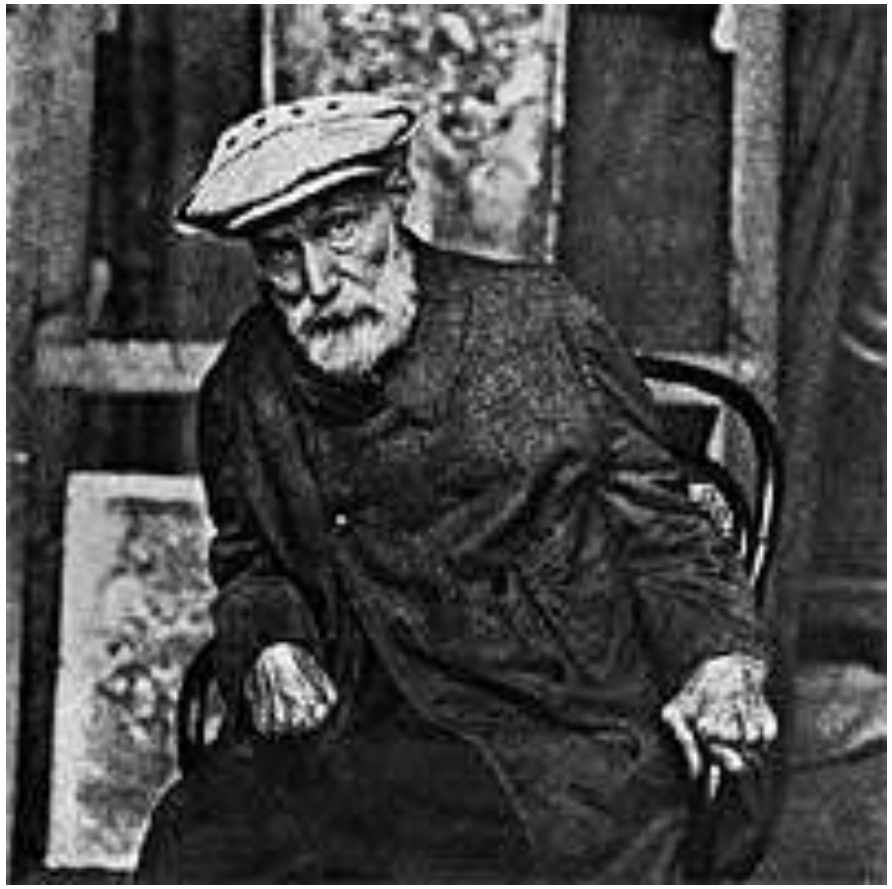
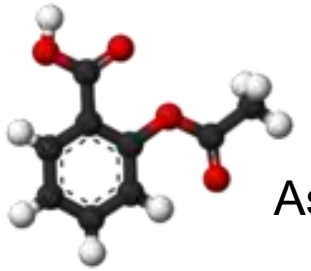
Past, present and future aims in treating autoimmune diseases



Renoir (1841-1919)

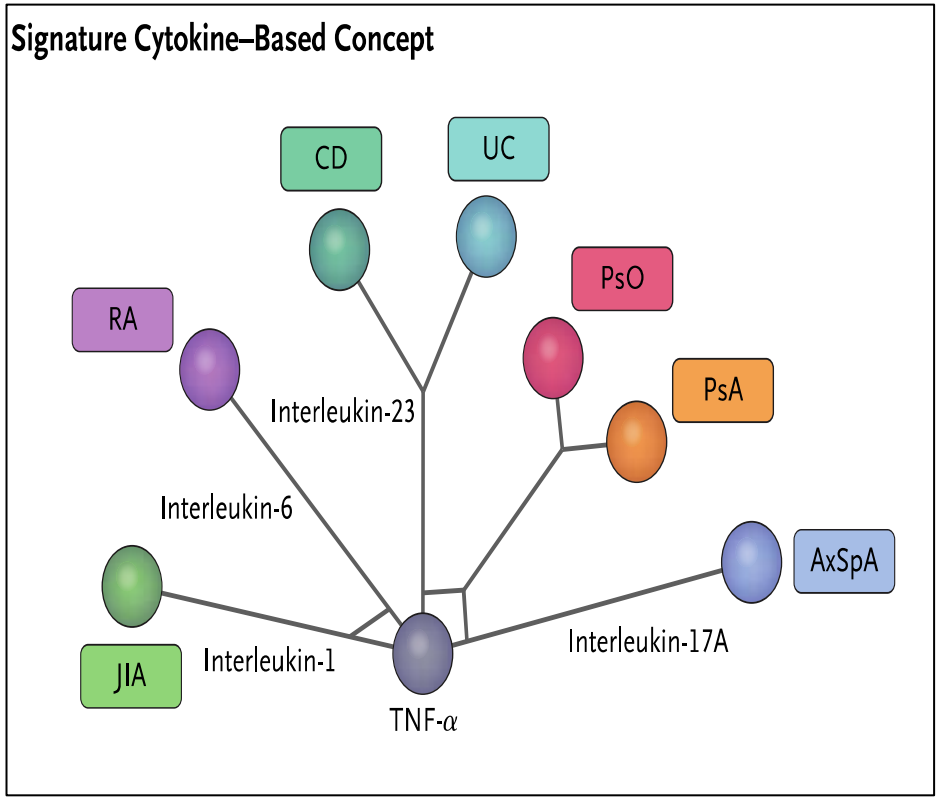


Aspirin/Bayer 1897

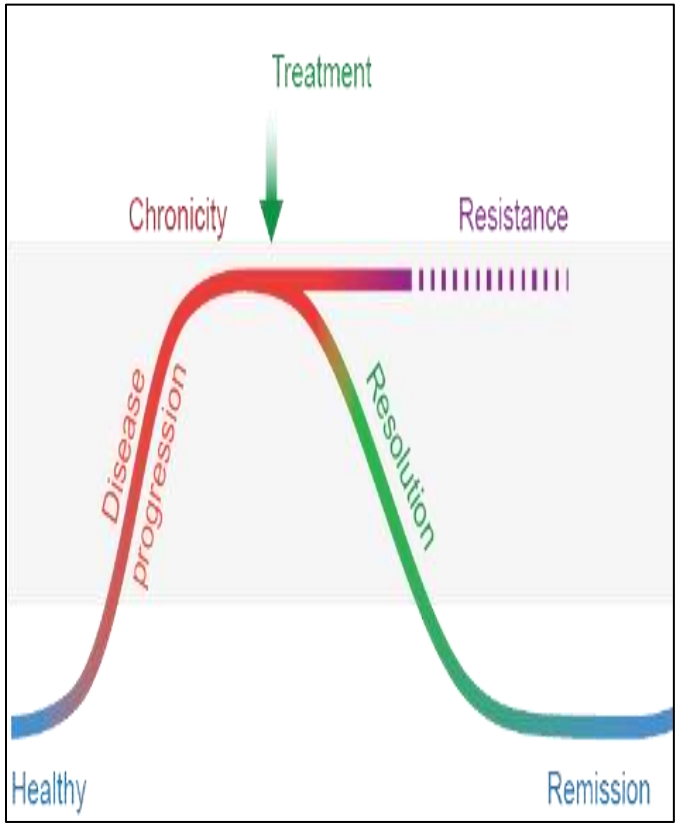
A drug has to ...

Improve symptoms	(++)	now required
Provide safety	(+/-)	now required
Interfere with disease process	(-)	now required
Cure the disease	(-)	now wished

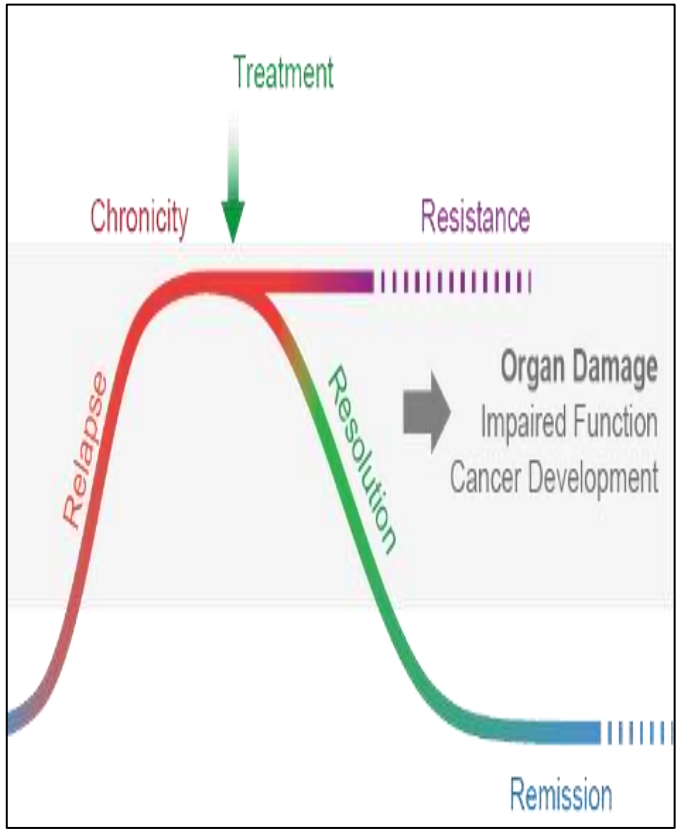
Cytokine inhibition: Better control but no cure of autoimmune disease



Schett G, McInnes IB and Neurath M.
N Engl J Med 2021;385:628-39.



Resistance-Remission

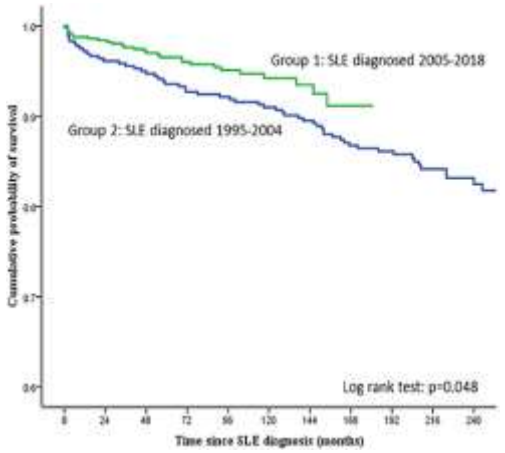


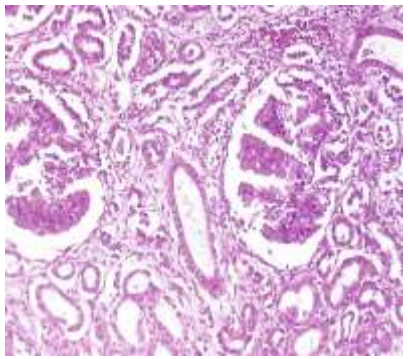
Relapse- Resistance

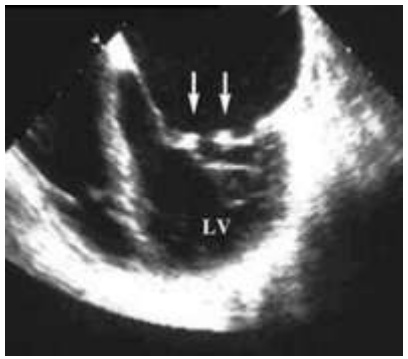
Systemic Autoimmune Disease can be life-threatening and are associated with increased mortality

Systemic Lupus Erythematosus

doi.org/10.3389/fmed.2020.00552

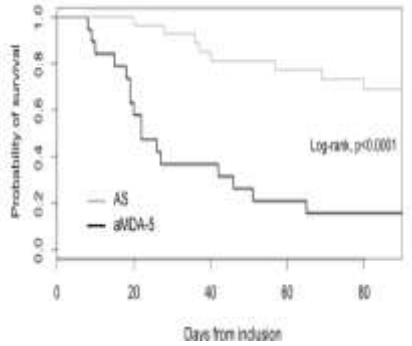






Dermatomyositis/Polymyositis

DOI:10.1186/s13613-018-0433-3



January 2nd

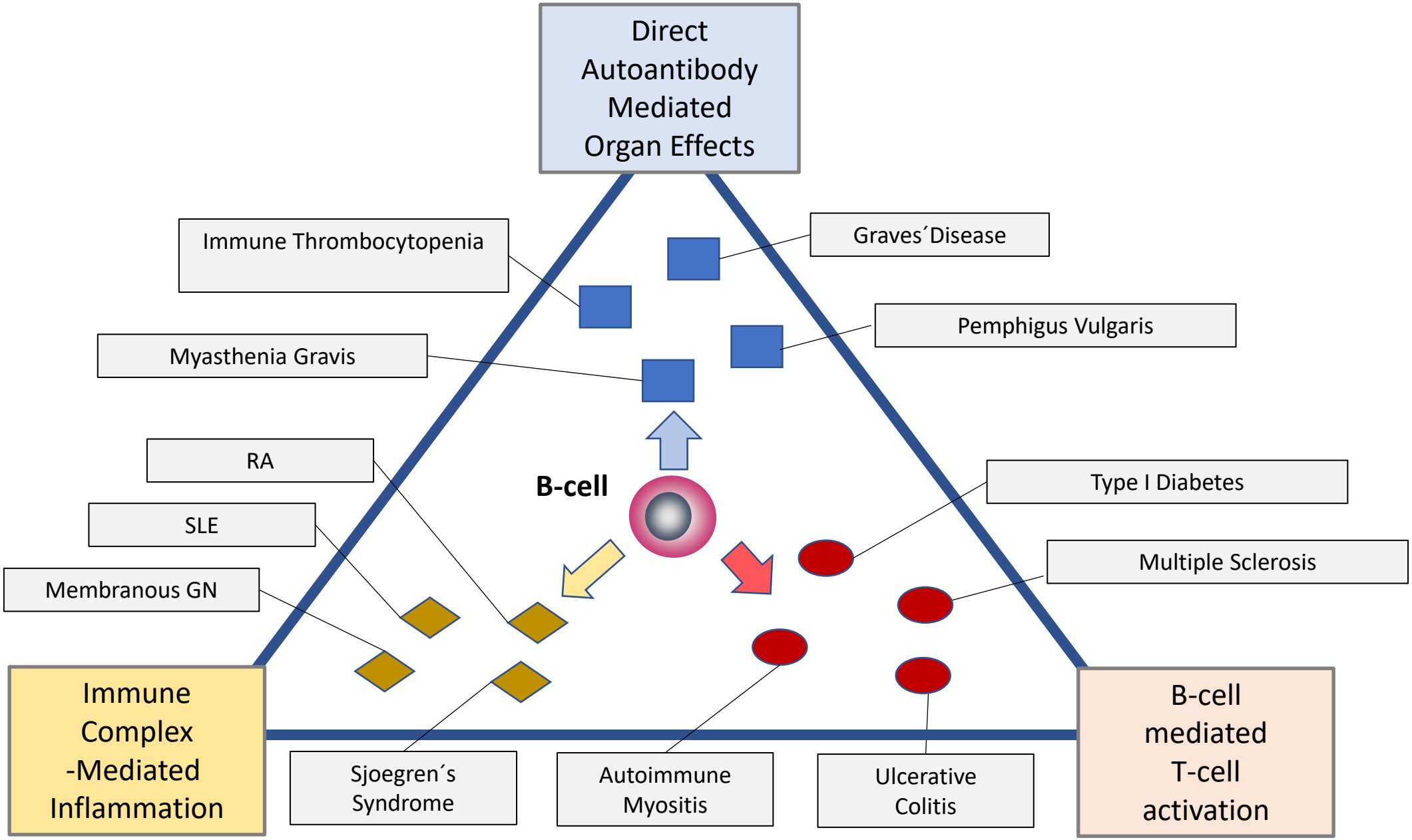
January 29th

Organ Damage and Failure

Infections due to chronic immune suppression

Glucocorticoid toxicities

Challenges for reproduction


Direct Autoantibody Mediated Organ Effects
Immune Thrombocytopenia
Graves´Disease
Pemphigus Vulgaris
Myasthenia Gravis
RA
B-cell
Type I Diabetes
SLE
Multiple Sclerosis
Membranous GN
Immune Complex -Mediated Inflammation
Sjoegren´s Syndrome
Autoimmune Myositis
Ulcerative Colitis
B-cell mediated T-cell activation

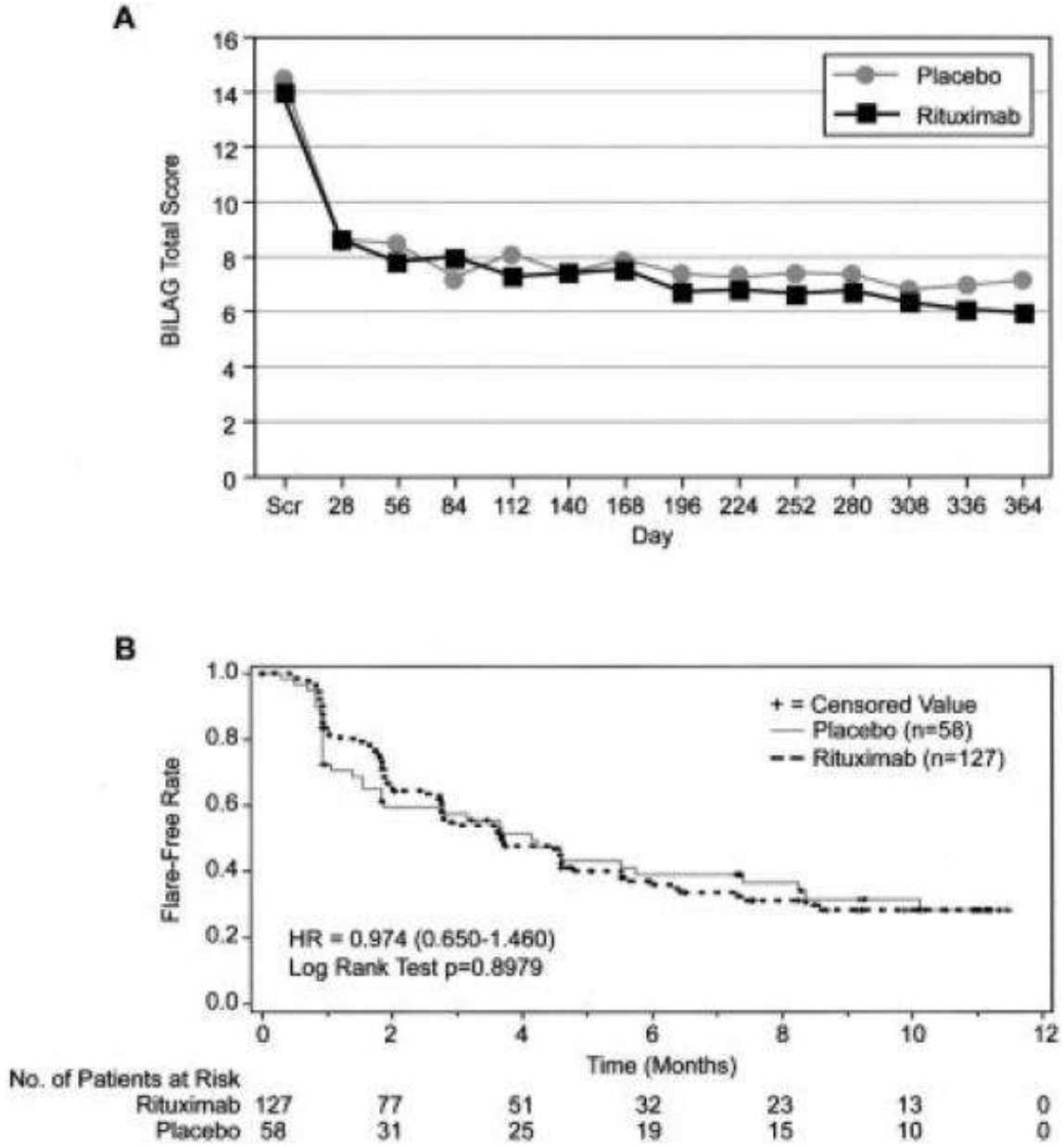
Randomized –controlled studies with B cell depleting MAb

Target	MAB	Population/ Mode	Comparator	Name	Phase	Outcome	PE
CD20	RTX	RA (MTX-IR)	PBO	-	II	ACR50	+
CD20	RTX	RA (MTX-IR)	PBO	DANCER	II	ACR20	+
CD20	RTX	RA (TNF-IR)	PBO	REFLEX	III	ACR20	+
CD20	RTX	RA (Re-dosing)	PBO	SUNRISE	III	ACR20	+
CD20	RTX	RA (Re-dosing)	PBO	SERENE	III	ACR20	+
CD20	RTX (dose)*	RA (MTX-IR)	RTX (dose)	MIRROR	III	ACR20	-
CD20	RTX+TNFi	RA (TNF-IR)	PBO+TNFi	-	II	Infections	-
CD20	RTX	RA (MTX naïve)	PBO	III	III	GmS score	+
CD20	RTX	AAV	CP	RACE	III	BVAS	+
CD20	RTX	AAV	AZA	MAINRITSAN	III	BVAS	+
CD20	RTX	AAV	AZA	MAINRITSAN2	III	BVAS	+
CD20	RTX	Pemphigus	MMF	PEMPHIX	III	PDAI	+
CD20	RTX	Myastenia gravis	PBO	RINOMAX	III	QMG	+
CD20	RTX	Relapsing MS	PBO	HERMES	II	Relapse	+
CD20	RTX	Progressive MS	PBO	OLYMPUS	II/III	Progress	-
CD20	RTX	SLE (renal)	PBO	LUNAR	III	Renal Response	-
CD20	RTX	SLE (nonrenal)	PBO	EXPLORER	II/III	BILAG	-
CD20	RTX+BEL	SLE (renal)	RTX	CALIBRATE	II	Safety	-
CD20	RTX (early)	IIM	RTX (delayed)	RIM	II	DOI	+
CD20	RTX	PSS	PBO	TRACTISS	II	Fatigue/Dryness	-
CD20	RTX	SSc	PBO	DESIRES	II	mRSS	+
CD20	Ocrelizumab	RA (MTX-naive)	PBO	FILM	III	TSS	+**
CD20	Ocrelizumab	RA (MTX-IR)	PBO	STAGE	III	ACR20	+
CD20	Ocrelizumab	RA (TNF-IR)	PBO	SCRIPT	III	ACR20	+
CD20	Ocrelizumab	SLE (renal)	PBO	BELONG	III	RR	-**
CD20	Ocrelizumab	Relapsing MS	IFNb	OPERA	III	Relapse	+
CD20	Ocrelizumab	Progressive MS	PBO	ORATORIO	III	Progress	+
CD20	Obinutuzumab	SLE (renal)	PBO	NOBILITY	II	Renal Response	+
CD20	Ofatumumab	Relapsing MS	TFM	ASCLEPIOS	III	Relapse	+
CD20	Ublituximab	Relapsing MS	TFM	ULTIMATE	III	Relapse	+
CD19	Inebilizumab	NMOSD	PBO	N-MOmentum	II/III	Relapse	+
CD19/ FCgRII	Obexelimab	SLE (non-renal)	PBO	-	II	Relapse	-
CD22	Epratuzumab	SLE (non-renal)	PBO	EMBODY	III	BILAG	-
BAFFR	Ianalumab	PSS	PBO	VAY736A2201	II	ESSDAI	+
TACI	Telitacicept	SLE	PBO	-	II	SRI-4	+

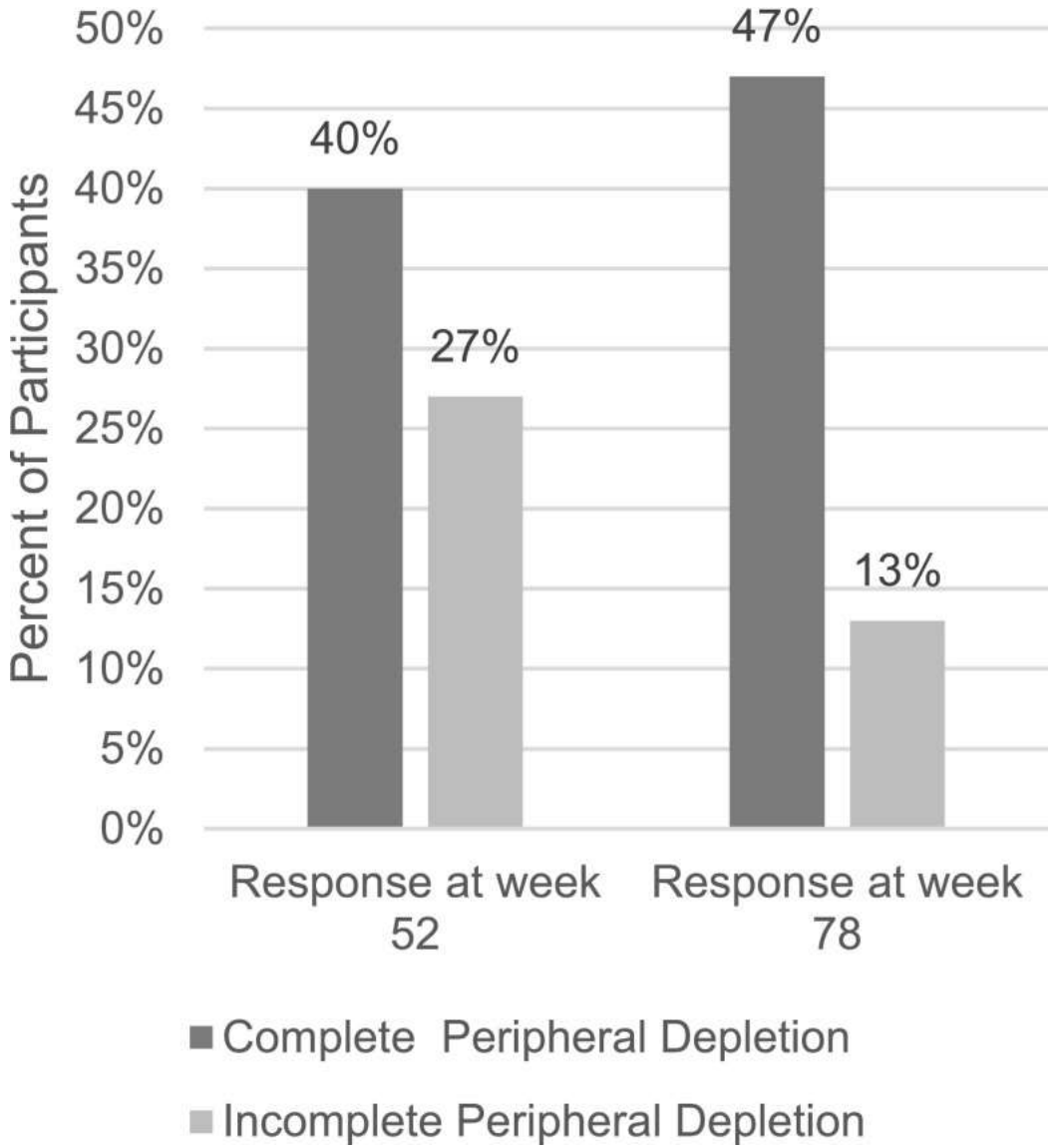
Schett et al. Ann Rheum Dis 2024

Negative RCT with rituximab in SLE

Rituximab did not improve SLE disease activity (BILAG score) and flare –free survival in patients with SLE as compared to placebo in a randomized controlled study



Merrill JT, et al. Arthritis Rheum 2010;62:222-233.



B cell depletion and SLE response

Rituximab works better in SLE with complete depletion of peripheral B cells

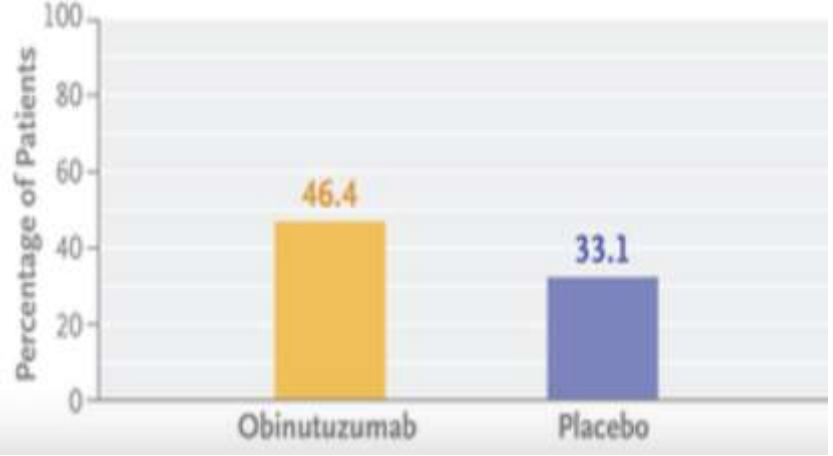
Post hoc analysis of the LUNAR trial

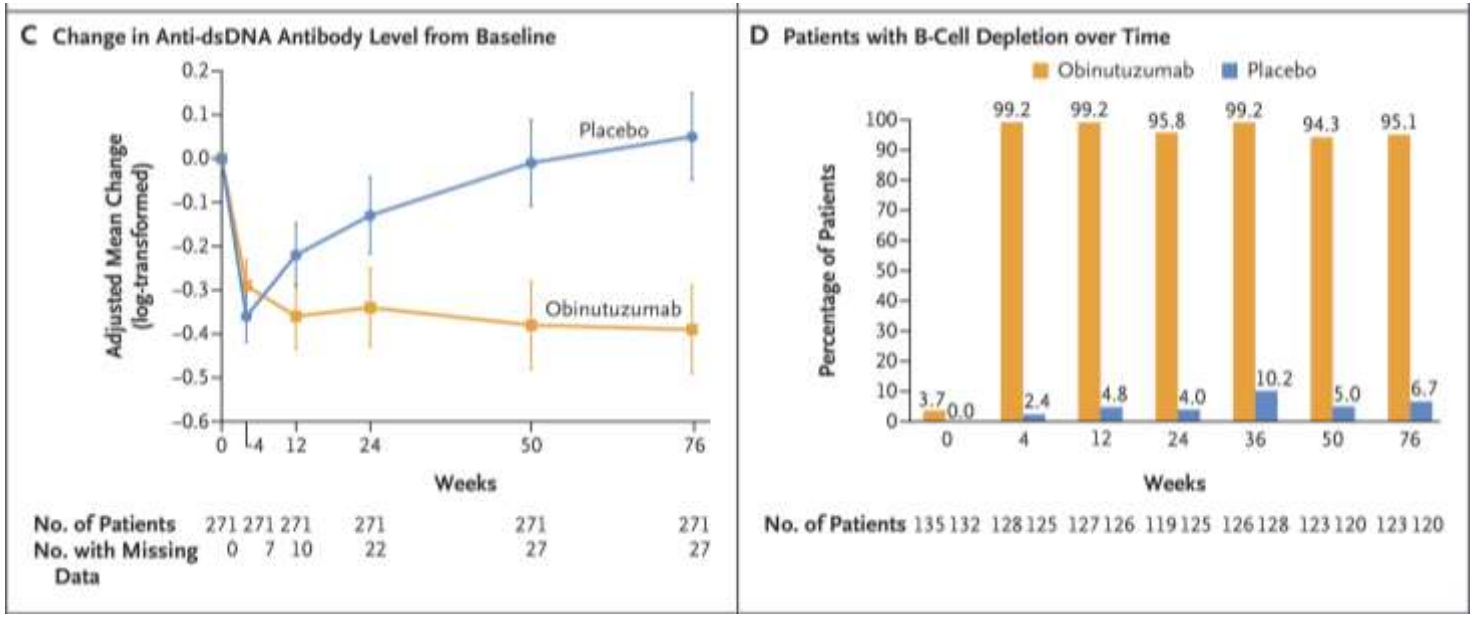
Gomez Mendez LM et al. Clin J Am Soc Nephrol 2018;13:1502–9

Glycoengineered anti-CD20 Mab obinutuzumab shows efficacy in LN

Complete Renal Response

Adjusted difference 13.4 percentage points
(95% CI 2.0 to 24.8); p= 0.02

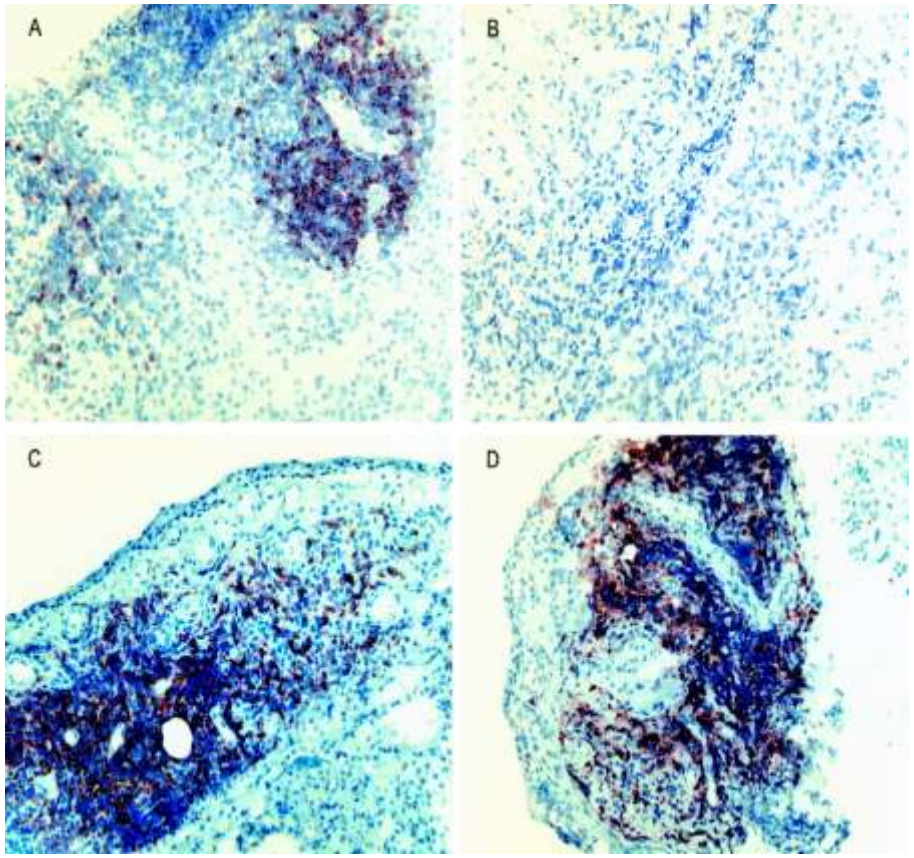


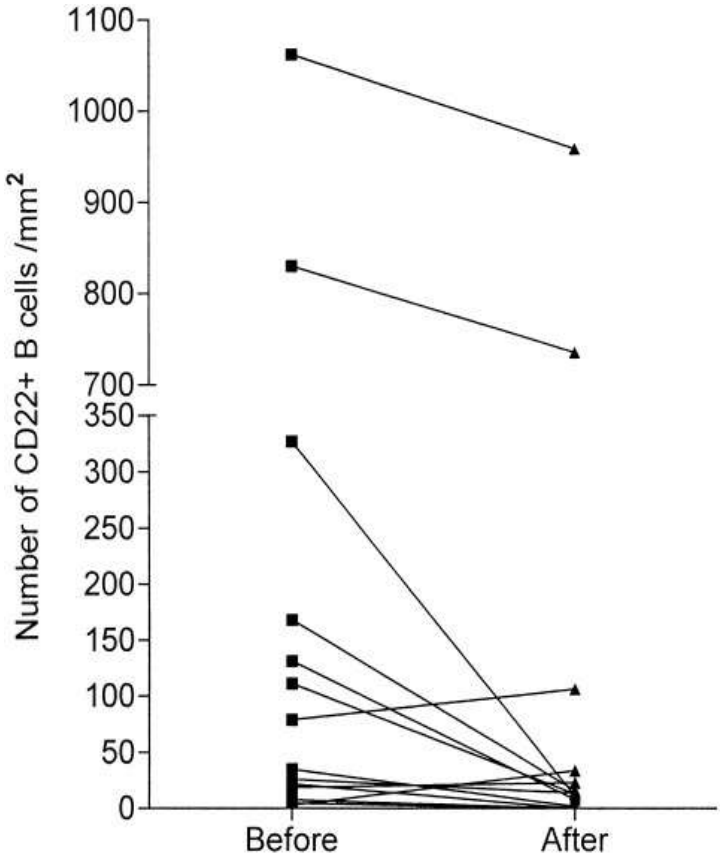


Data from the phase 3 REGENCY study

Furie RA, et al. N Engl J Med. 2025 Apr 17;392(15):1471-1483.

Limitation of B cell depletion via anti- CD20 Mab

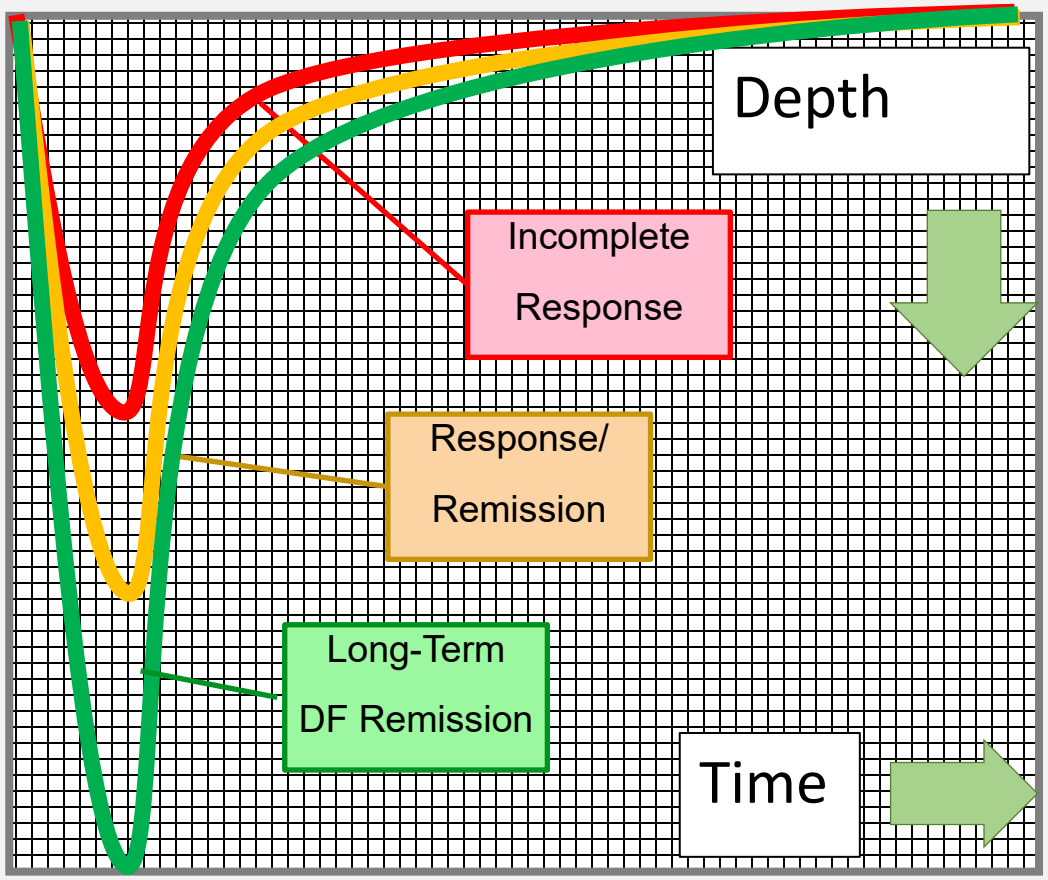




Analysis of synovial biopsies from RTX-treated patients with RA

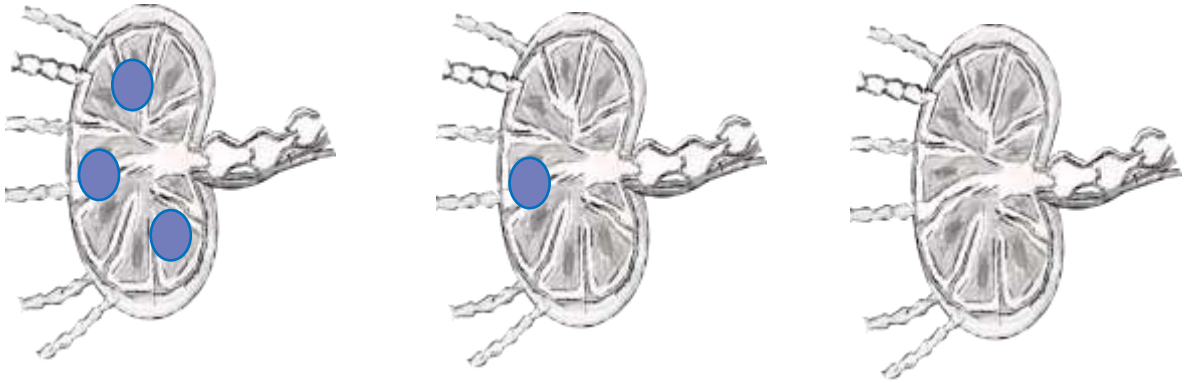
Vos K et al., Arthritis & Rheumatism, 2007; 56: 772-778

Depth of B cell depletion in the tissue

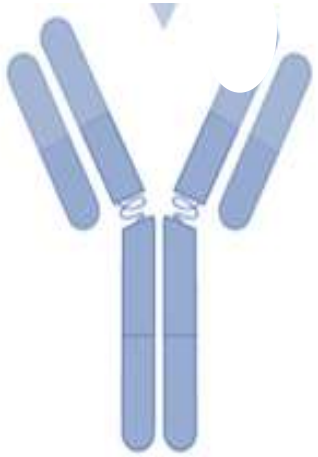


HYPOTHESIS

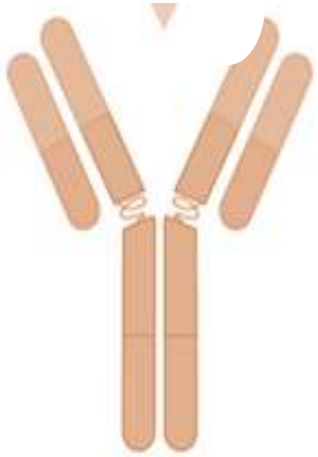
Long-term Drug-Free Remission of autoimmunedisease may require deep B-cell depletion in the lymph nodes, which is not achieved by conventional B-cell depleting agents



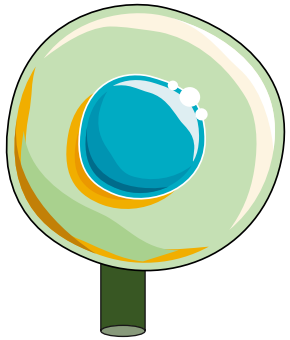
Taking biological principles of host defence as drugs



IgG antibody aginst measles



IgG antibody aginst CD20



Cytotoxic T cell

CAR T-cell

High specificity, no chemical toxicity

How do CAR T-cells work?

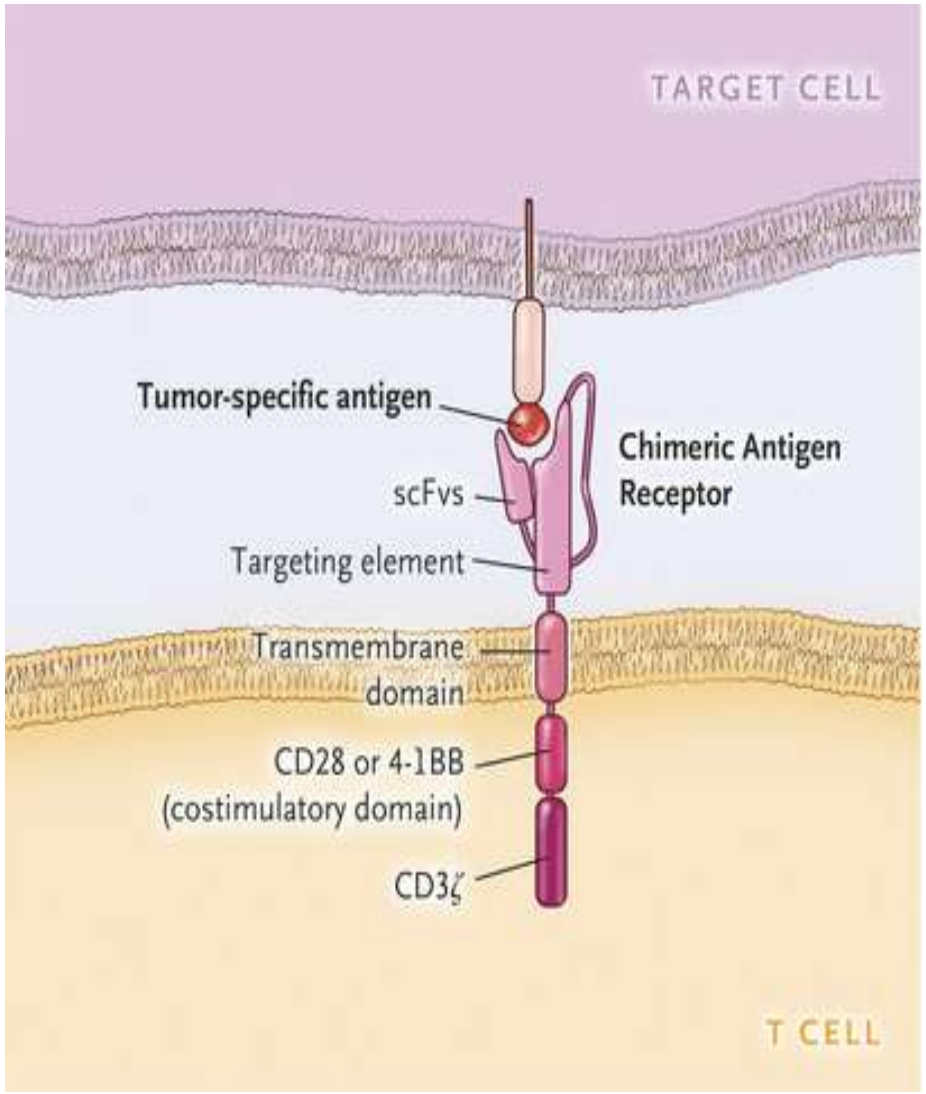
Recognition Process

"Good" Target
Approach

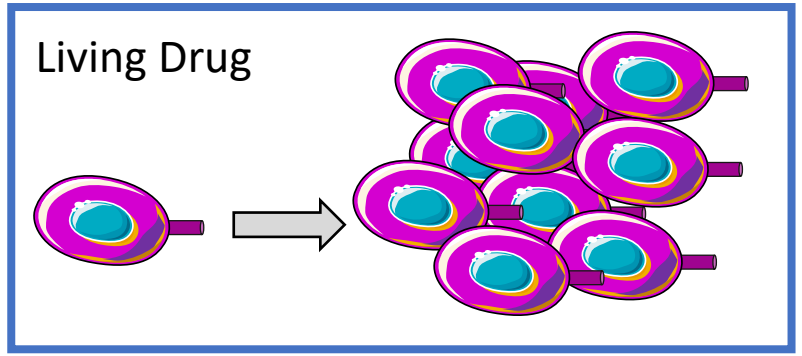
"Bad" Target
Avoid

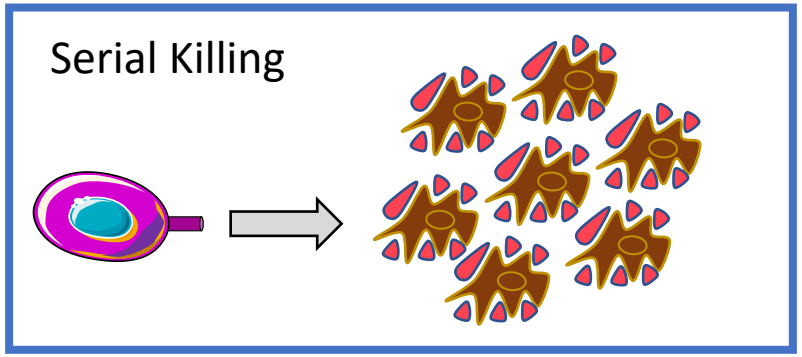
Activation Process

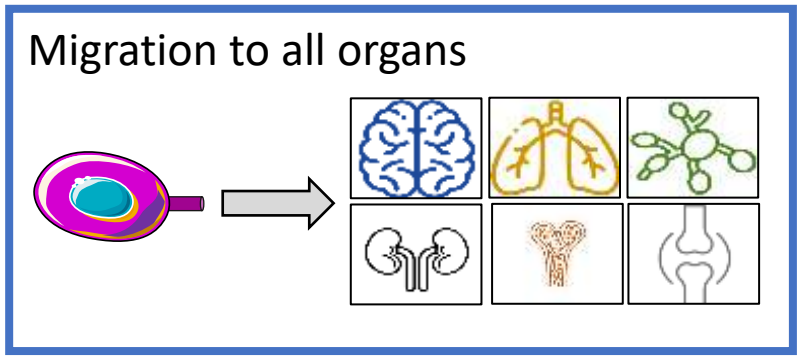
Kill the Target



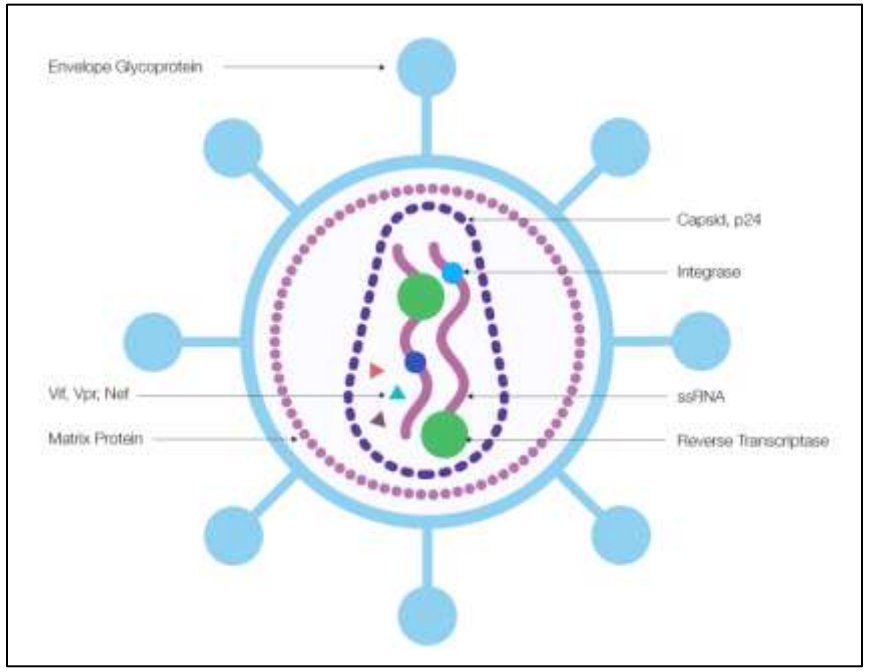
CAR T-cells effectively kill target cells







A lentiviral vector brings the CAR to the T-cells

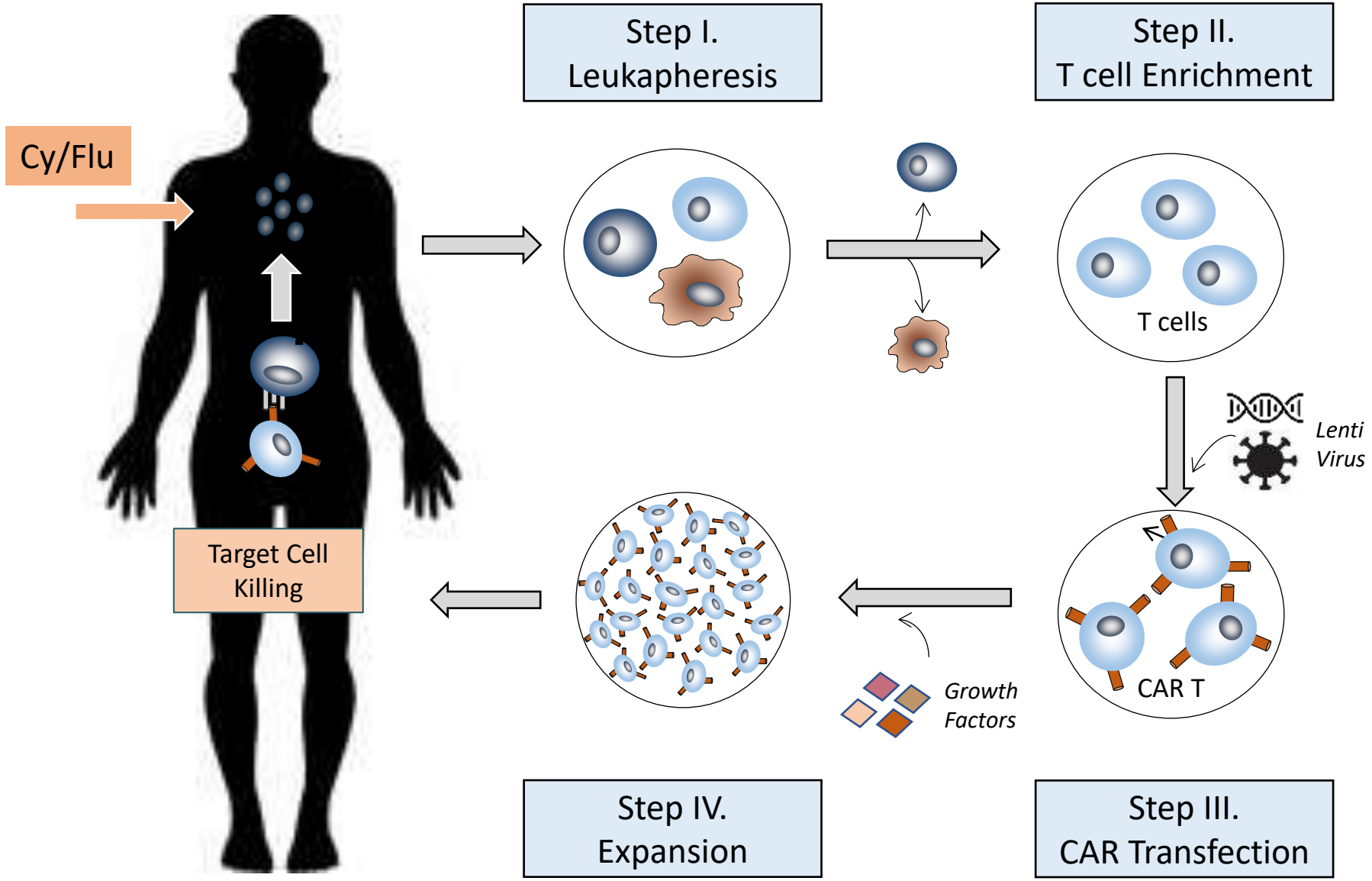


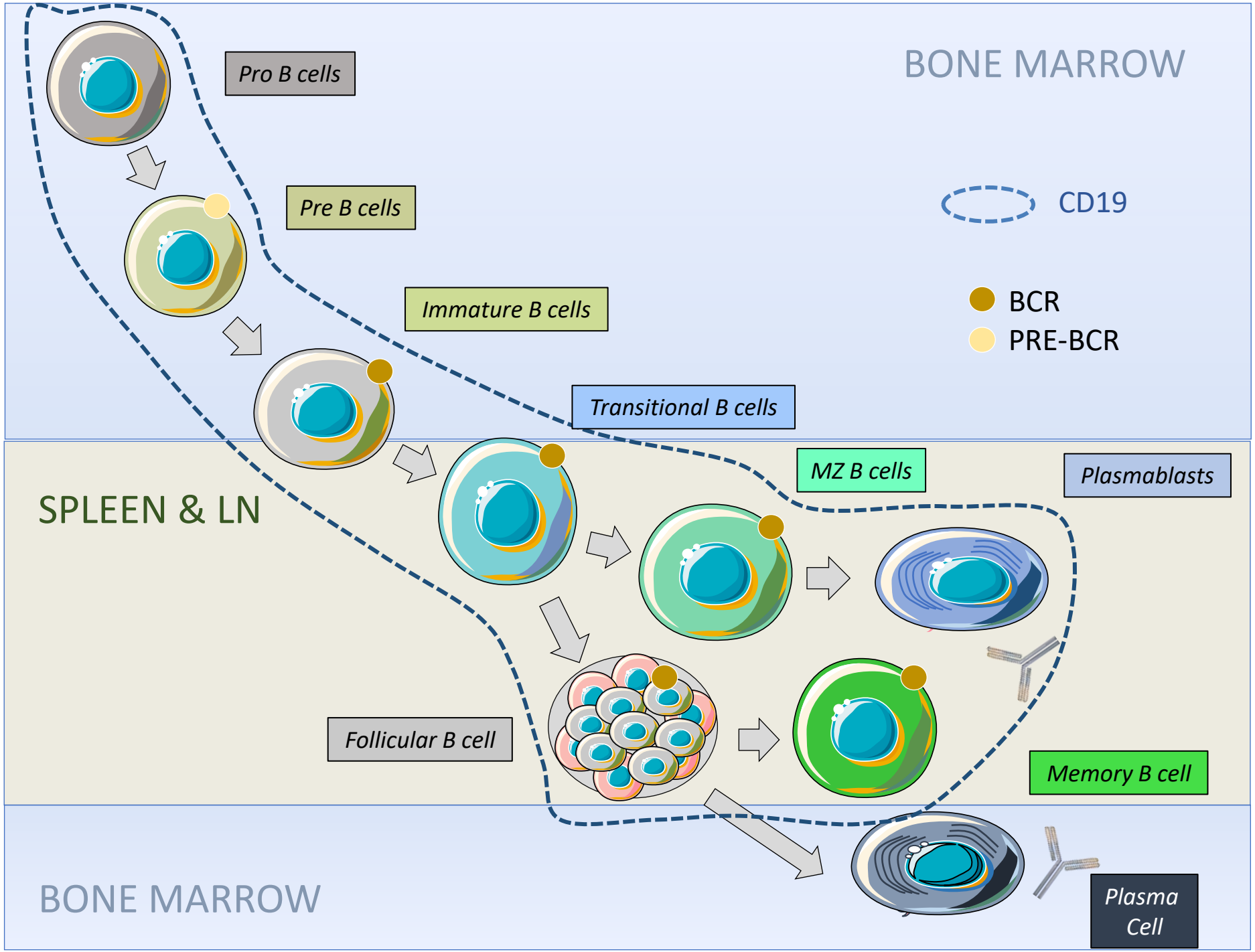
DNA Integration
The CAR is given from thr mother to the daugther cell

Broad Transfection:
Transfection of dividing and resting cells

High Cargo Capacity:
8- bis 10.000 Bases

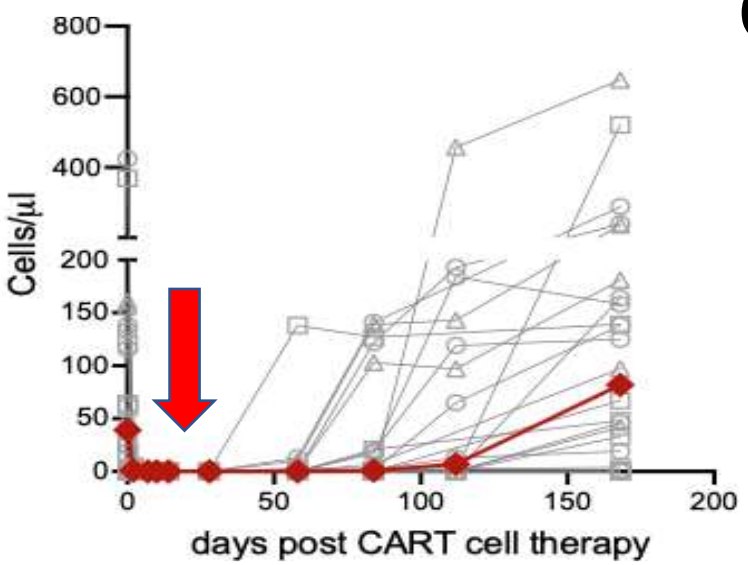
Procedure of autologous CAR T cell therapy

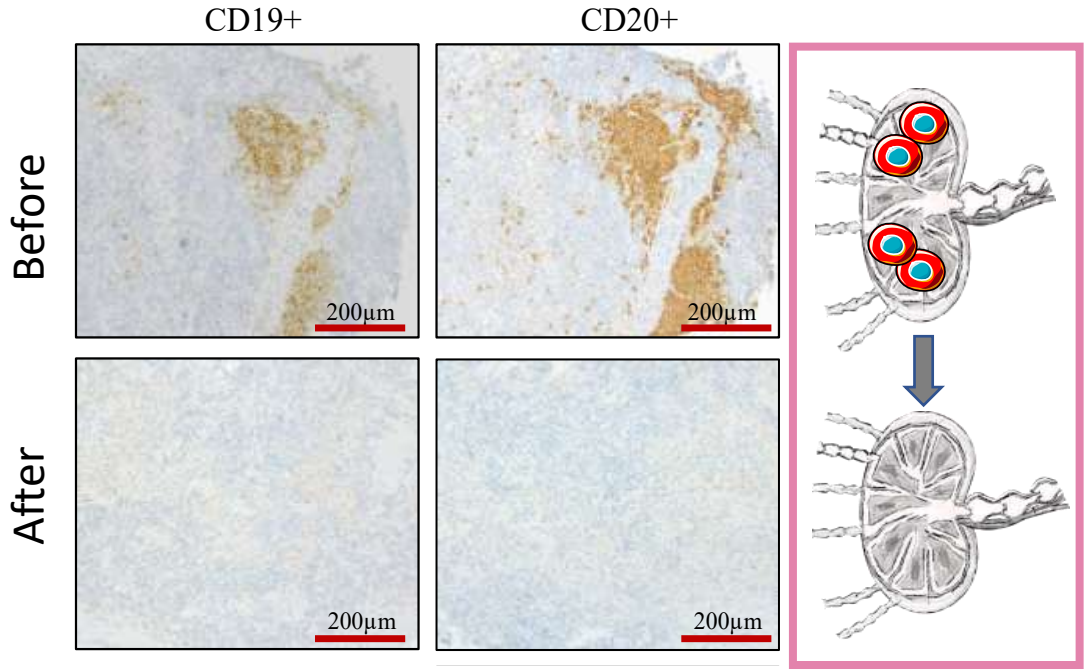


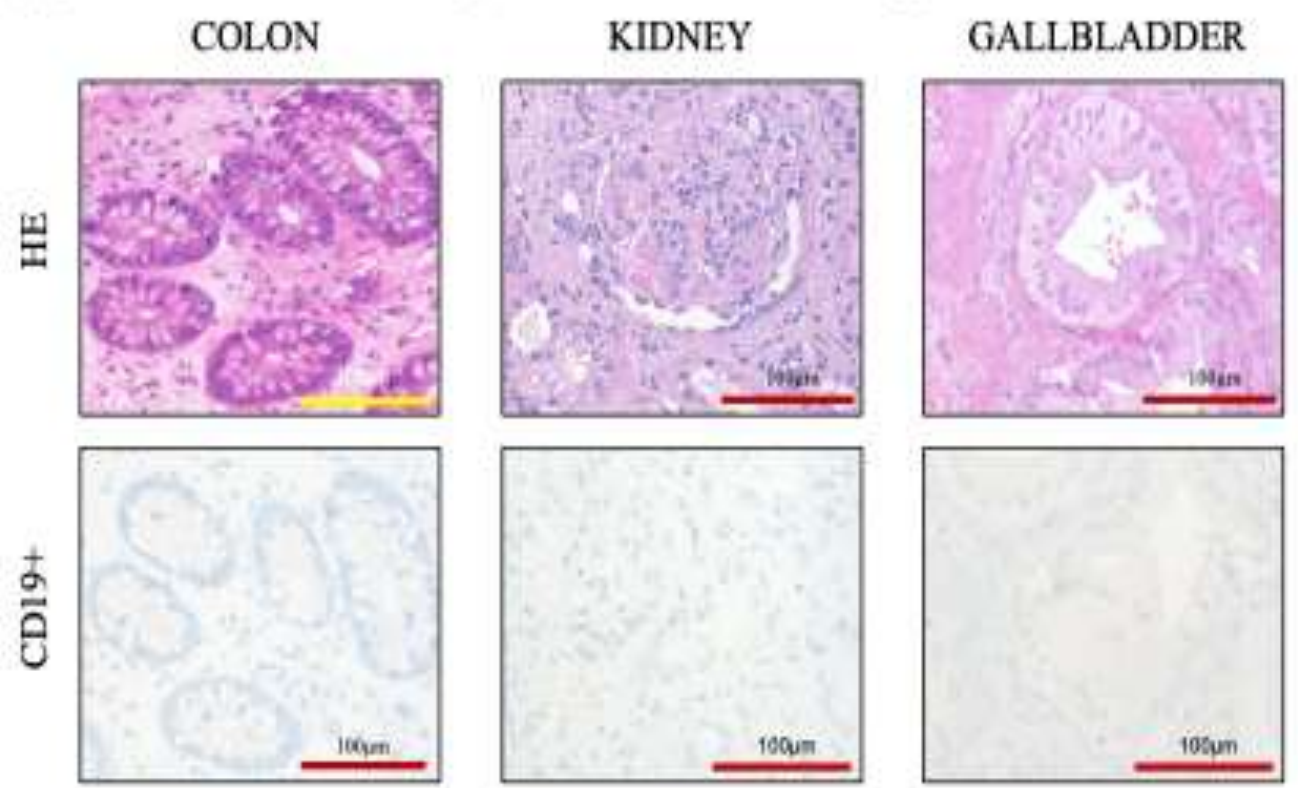

BONE MARROW
Pro B cells
Pre B cells
Immature B cells
Transitional B cells
CD19
BCR
PRE-BCR
SPLEEN & LN
MZ B cells
Plasmablasts
Follicular B cell
Memory B cell
BONE MARROW
Plasma Cell

Complete B-cell depletion the blood and organs

Short but complete B-cell depletion in the peripheral blood; Eradication of B-cells in the lymph nodes as a difficult-to-deplete compartment as well as full depletion in inner organs, even in the gut bearing large amounts of B-cells

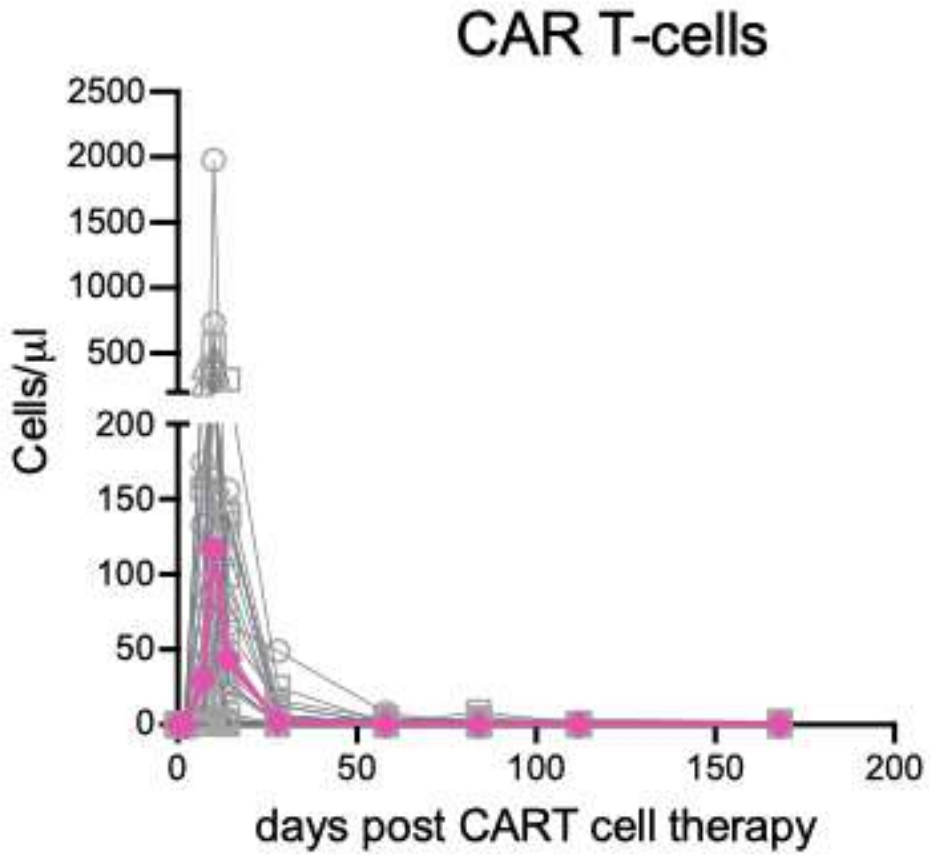


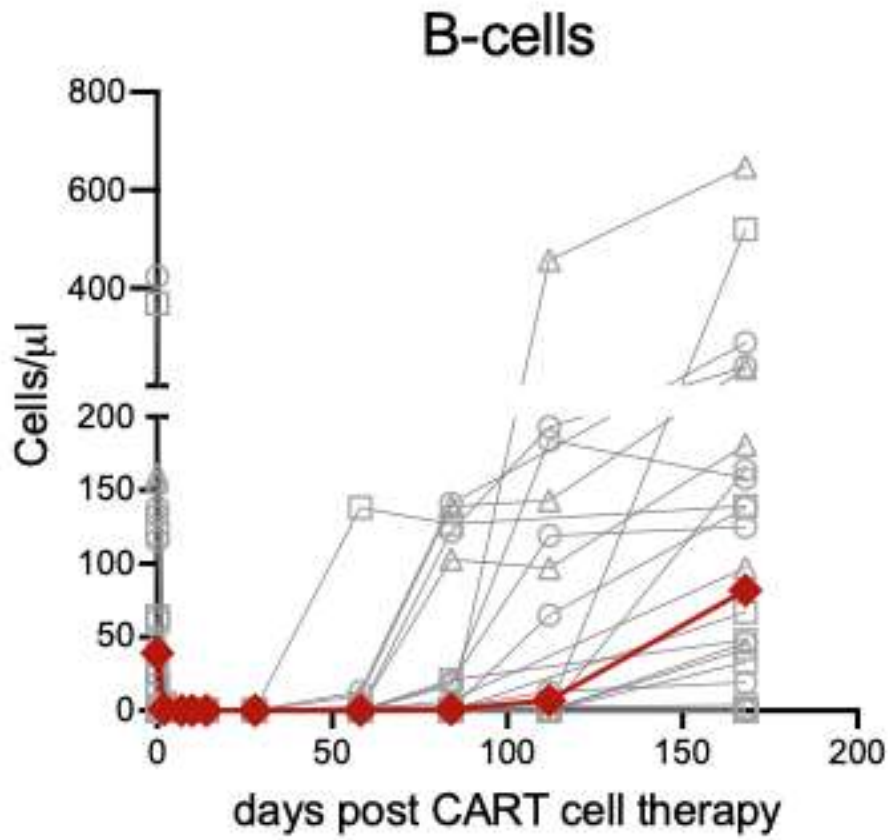




Mueller F, Hagen M, Wirsching A, et al. Nature Medicine 2026- Jan 7; Tur C. et al. Ann Rheum Dis 2025

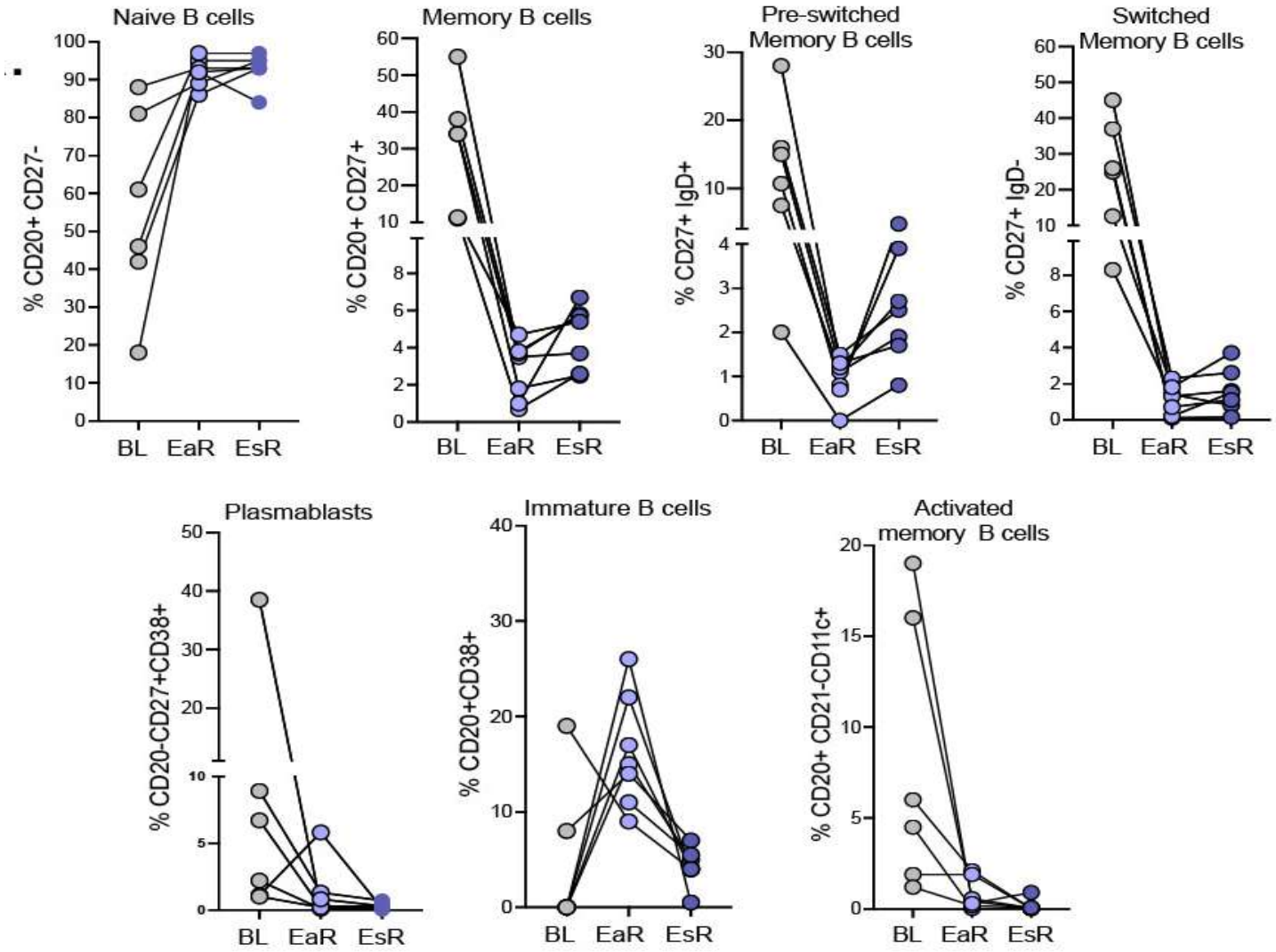
Insights from CASTLE study: Homogeneous dynamics of CAR T-cell expansion and B cell depletion





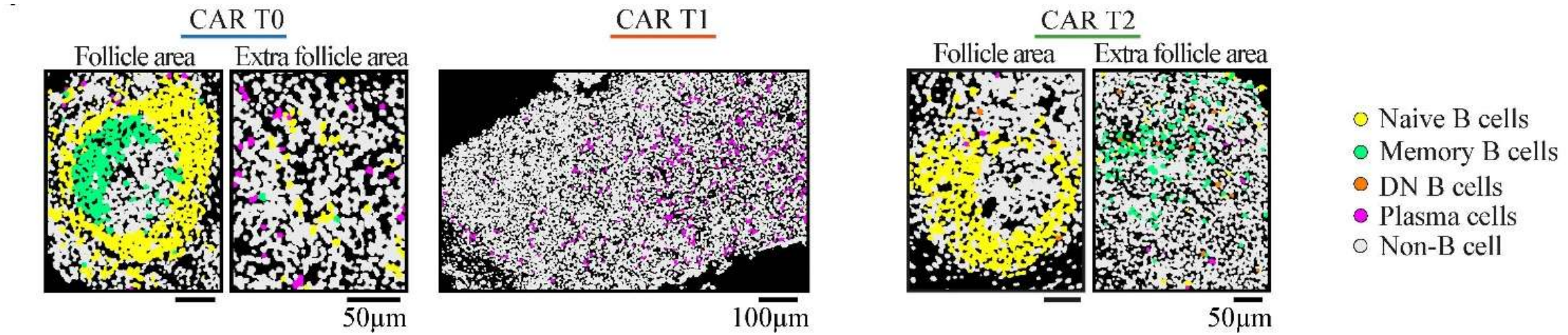
24 patients with autoimmune disease (10 SLE, 9 SSc and 5 IIM) receiving autologous CAR T-

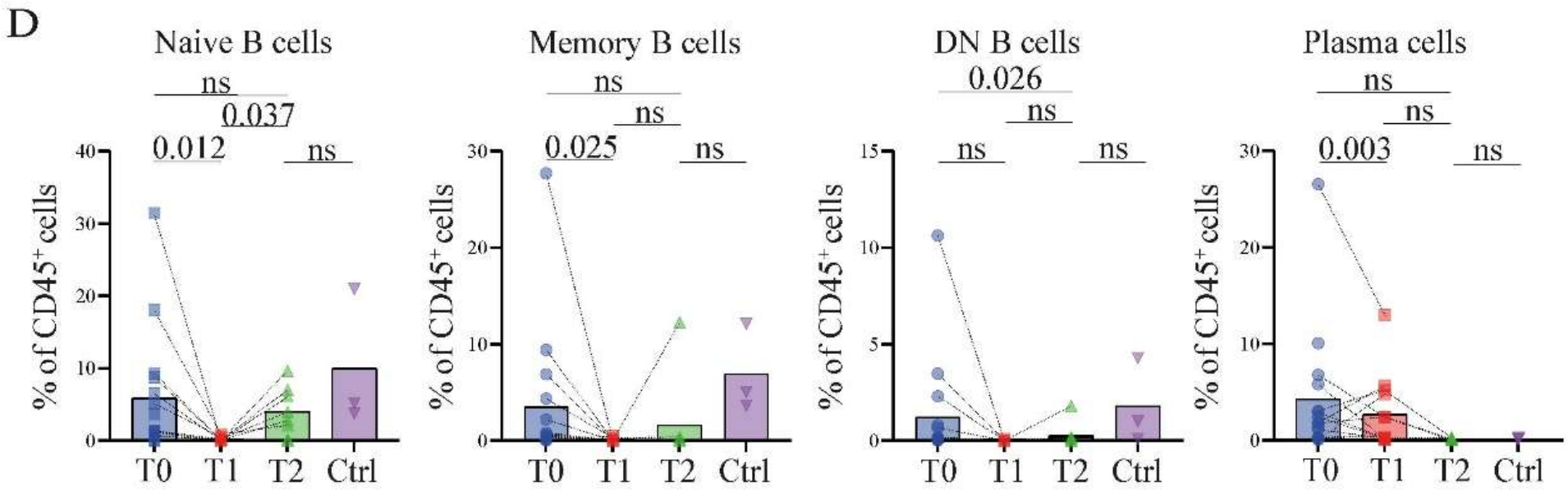
Analysis of memory B cells and plasmablasts in early and established reconstitution of B cells



Muller F, Taubmann J et al. N Engl J Med 2024 Feb 22;390(8):687-700.

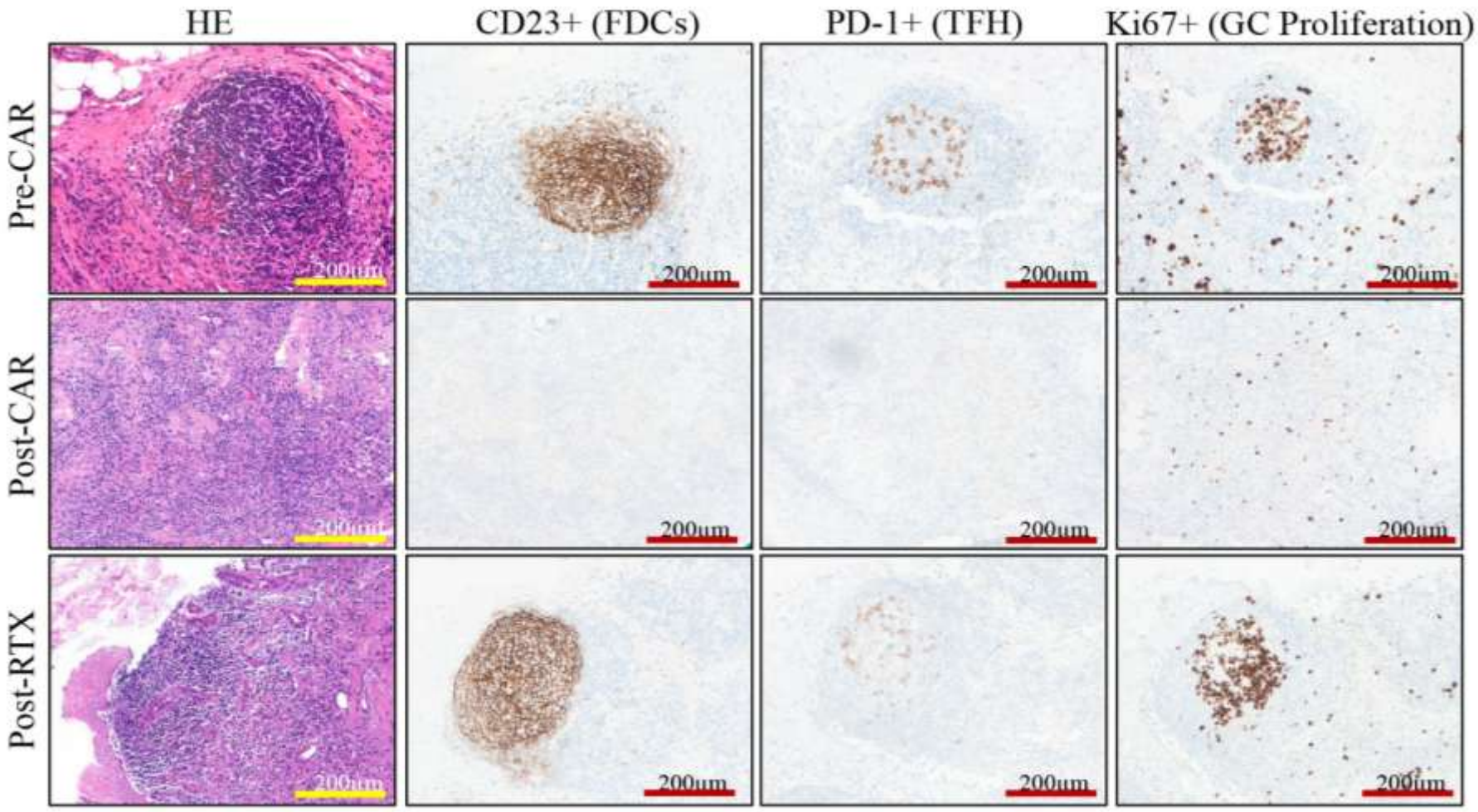
Re-establishment of a naïve B-cell compartent in LN after CAR T-cells

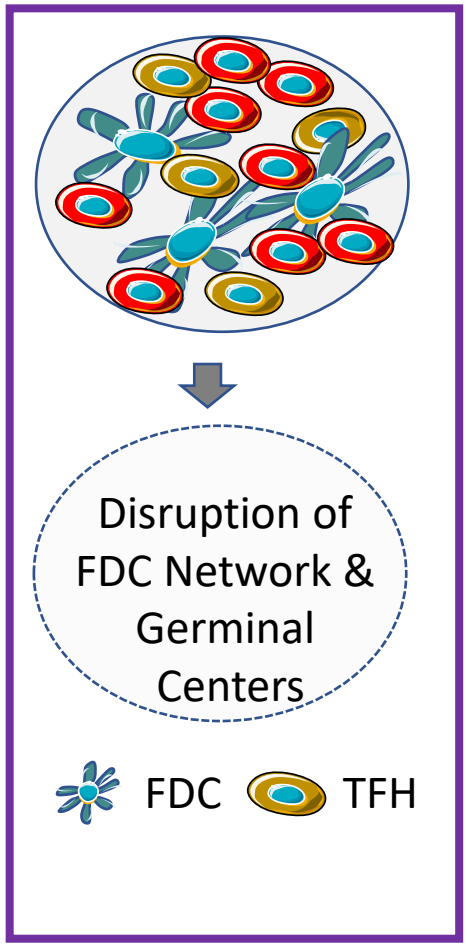




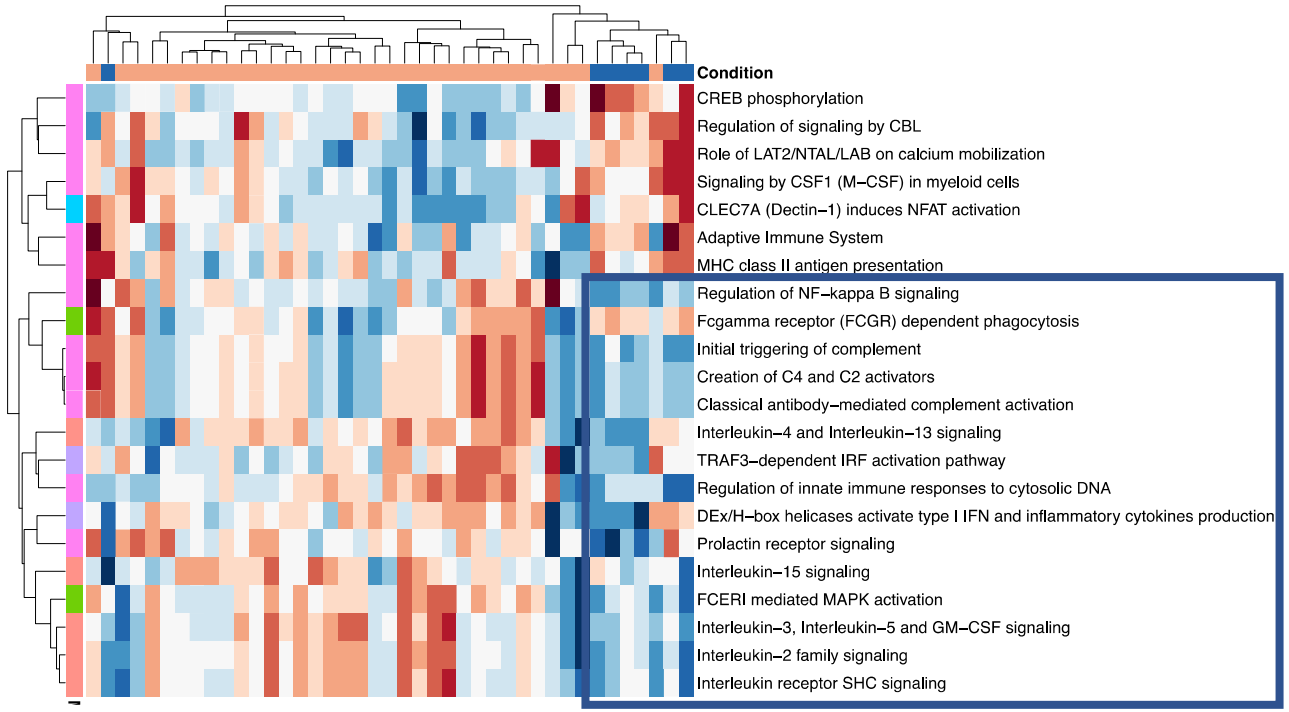
Mass cytometry based analysis and lymph nodes of SLE patients before and after CD19-CAR T-celltherapy

Disruption of germinal center in the lymph nodes



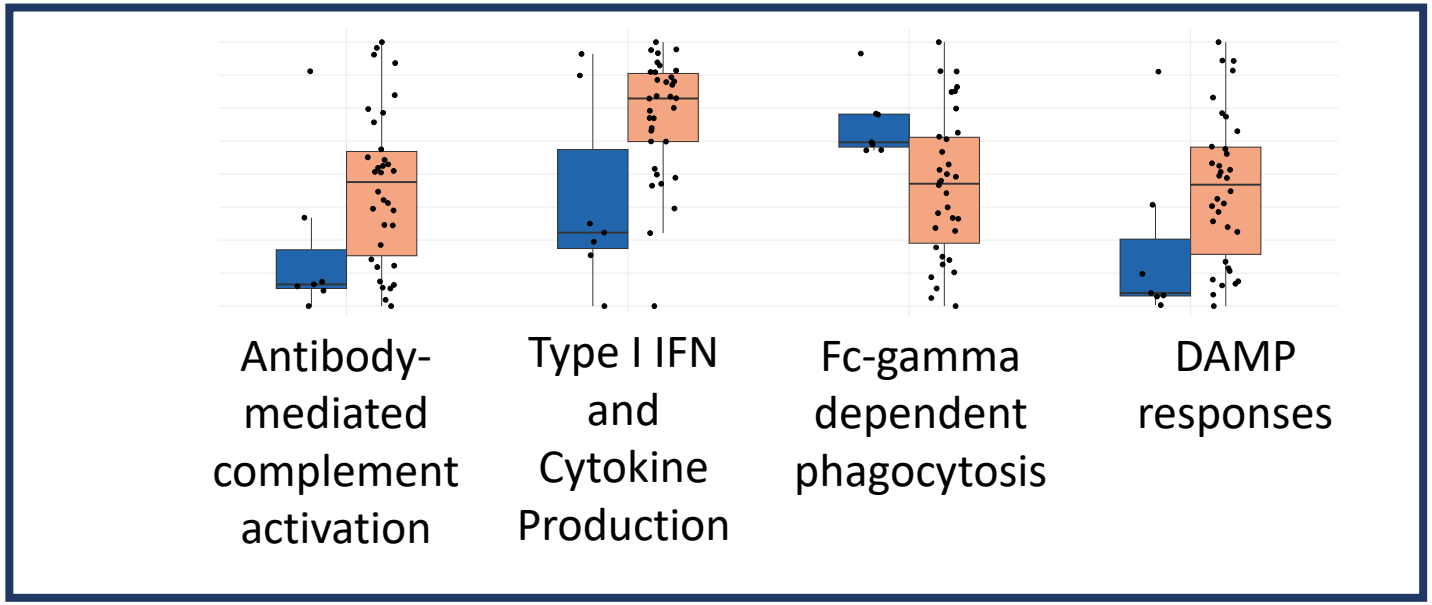


Tur C. et al. Ann Rheum Dis 2025



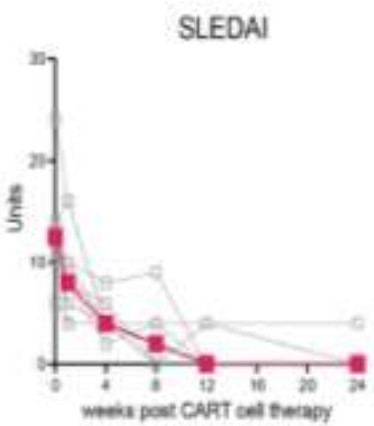
Deep and widespread downregulation of immune pathways after CAR T-cell therapy compared to standard immuno-suppression in SLE

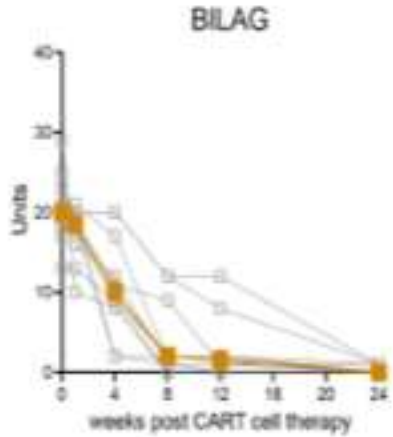
Garantziotis P et al. Ann Rheum Dis 2025

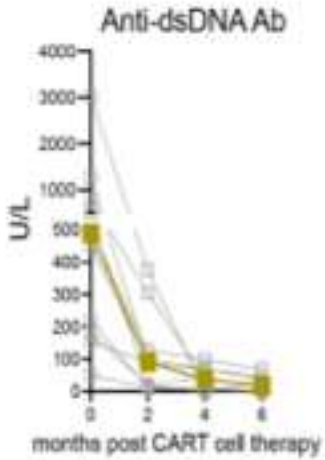


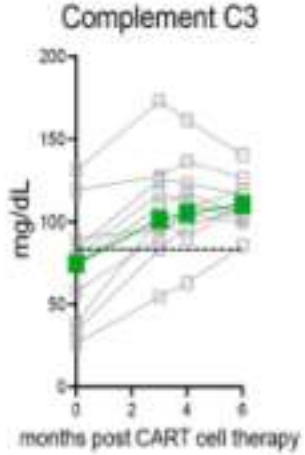
High-level responses in Systemic Lupus Erythematosus

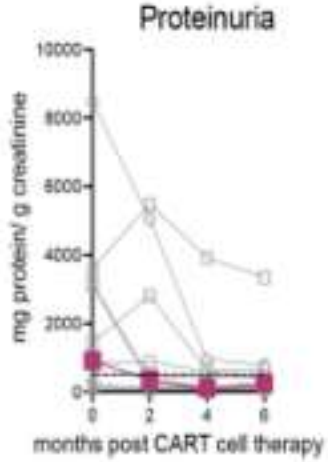
Consistent effects in all disease domains; induction of Remission











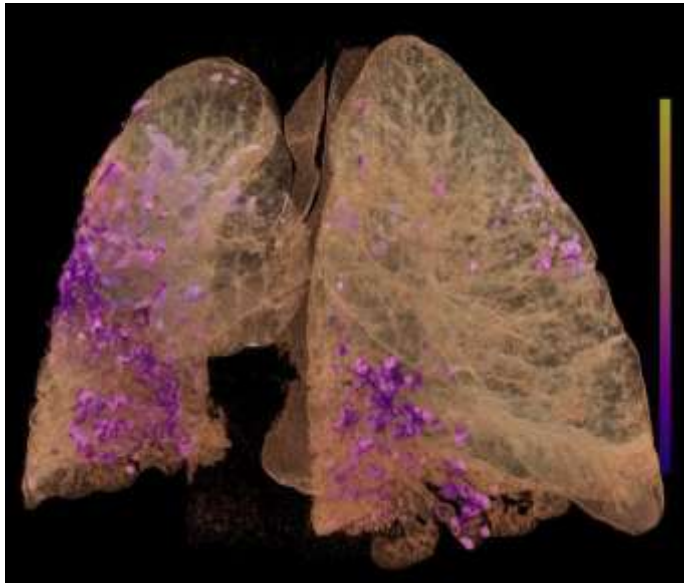
Baseline 6 months

Baseline 6 months

Mueller F, Hagen M, Wirsching A, et al. Nature Medicine 2026- Jan 7

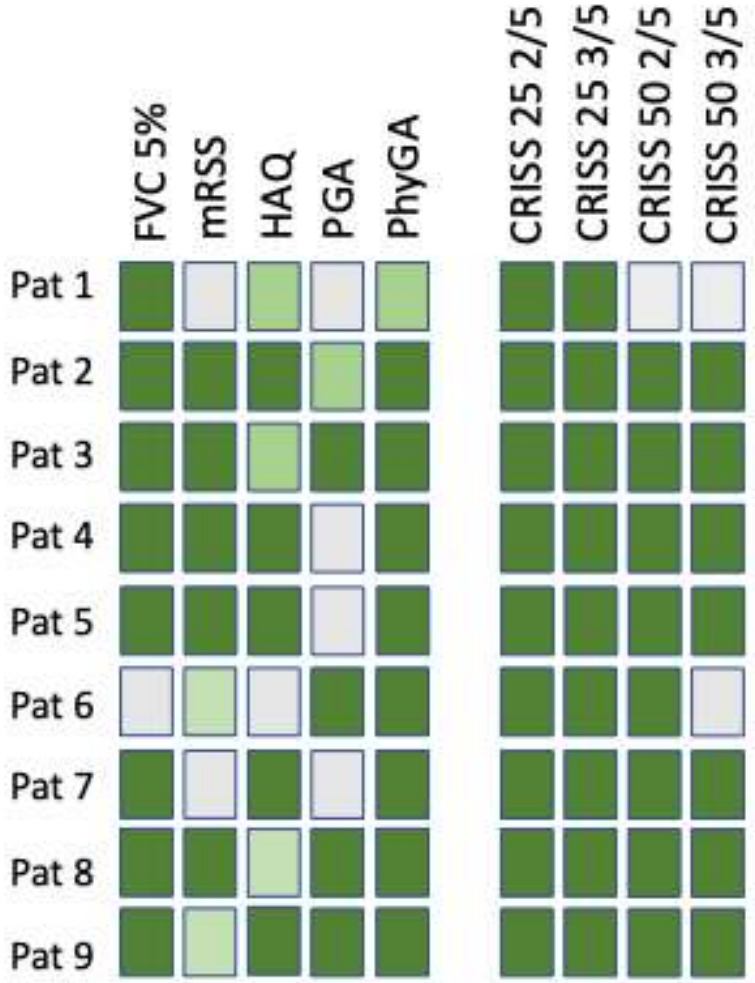
Regression of fibroblast activation and clinical improvement in patients with systemic sclerosis

Baseline



6-months

FVC improvement from 2.8 L to 3.2 L (+14,1%) =400 mL
DLCO improvement from 4.2 to 5.4 mmol/(ml*kPa) (+29.5%)

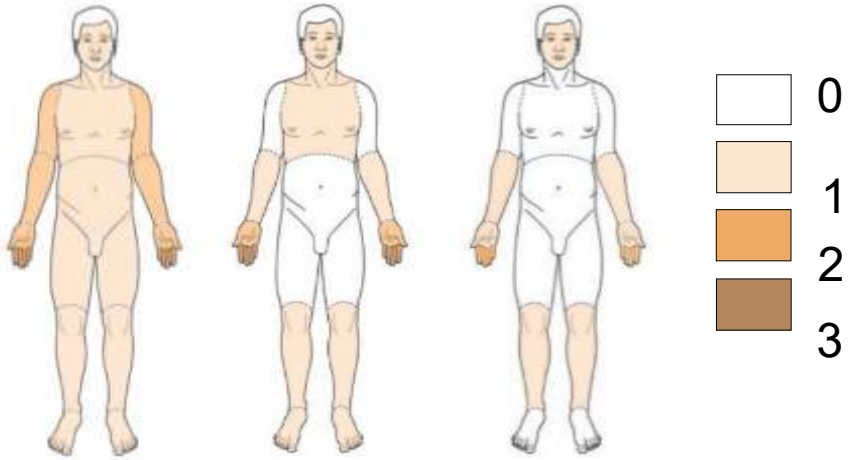


Mueller F, Hagen M, Wirsching A, et al. Nature Medicine 2026- Jan 7; Rigau A, et al. Nat Communications 2026 in press

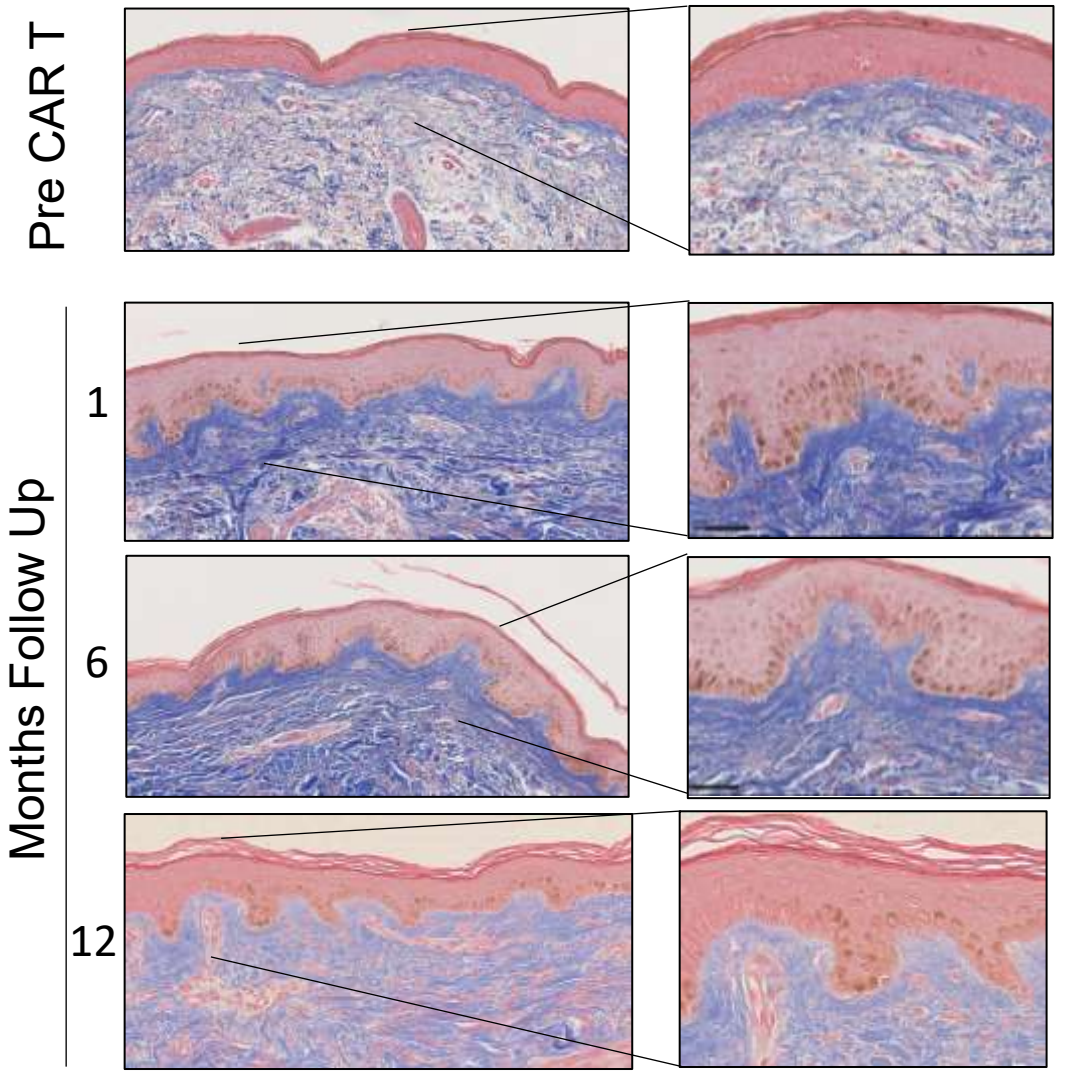
Responses in systemic sclerosis with CAR-T cells

Improvement in mRSS and partial restoration of the skin papillae

mRSSS

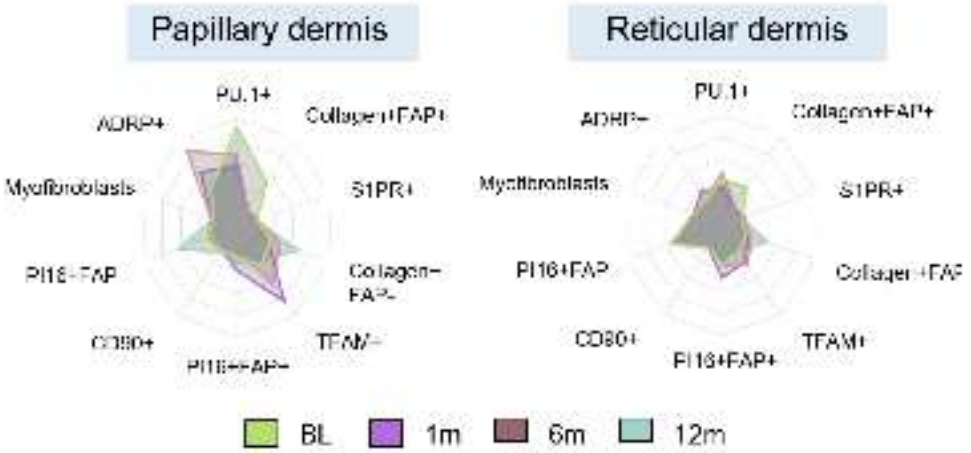


Digital ulcerations

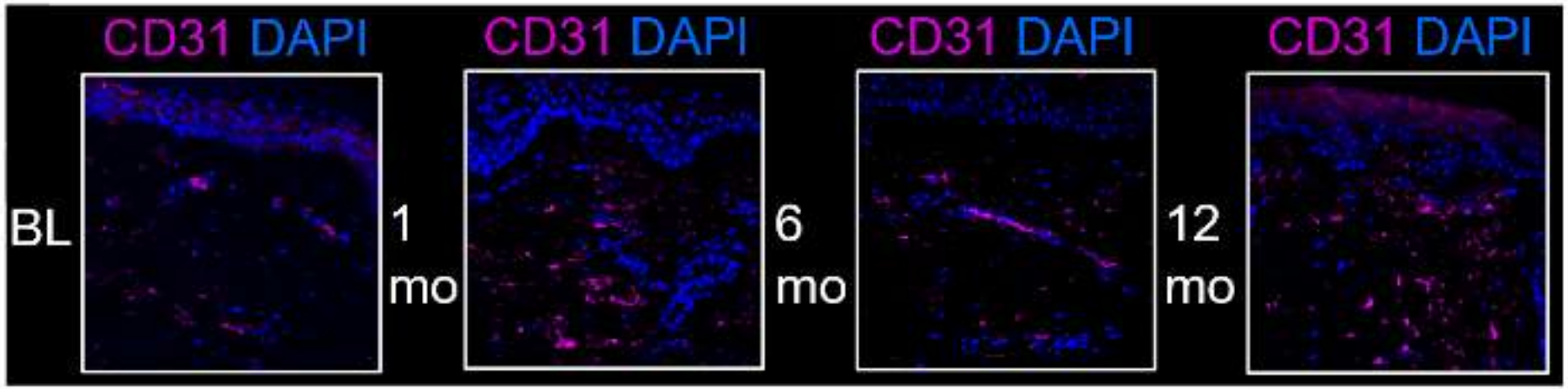


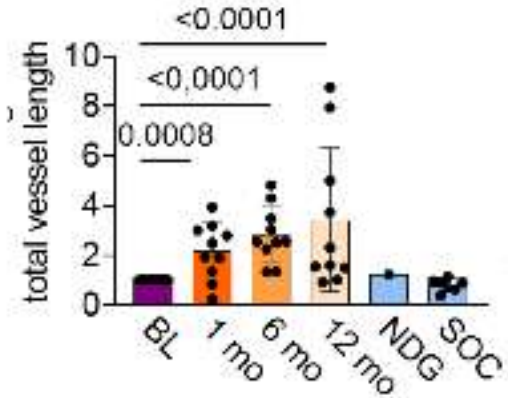
Bergmann C et al. Ann Rheum Dis. 2023 Aug;82(8):1117-1120. Auth J et al. Lancet Rheumatology 2024

Molecular remodeling of the skin after CAR-T cells



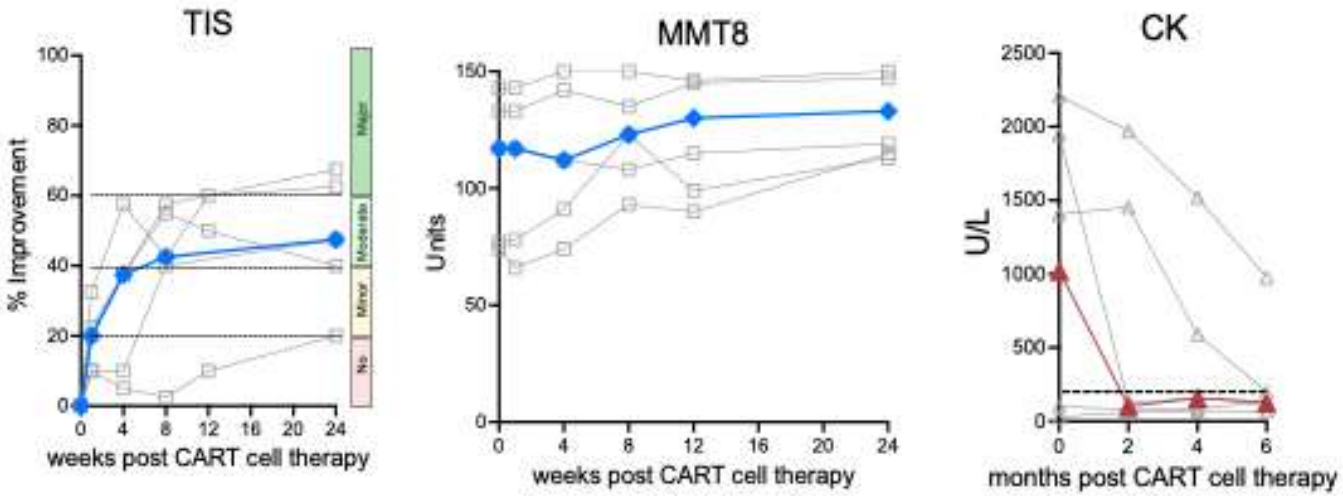
Change of the fibroblast landscape towards a regulatory non-matrix producing phenotype especially in the papillary dermis; Increase of blood vessels in the dermis with reconstruction of papillary structure





Rigau A, et al. Nat Communications 2026 in press

Responses in Idiopathic Inflammatory Myositis



Effects of on main outcomes in IIM

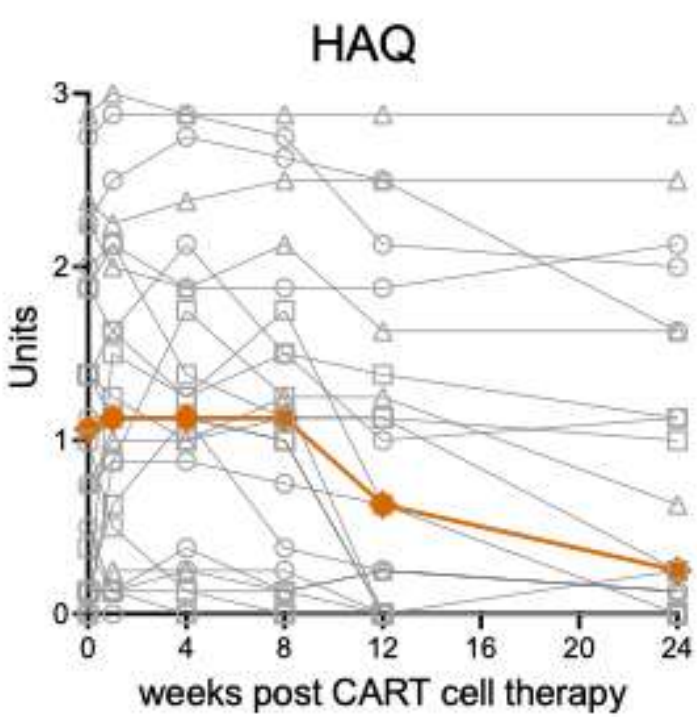
1 Jo-1+, 1 MI-2 + 2 HMG-CoAR +, 1 MDA5+

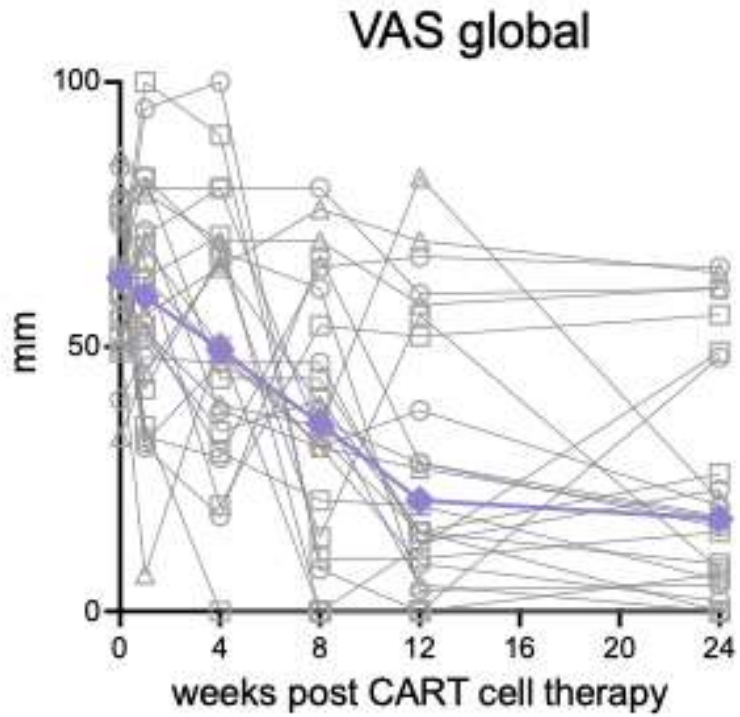
Before After

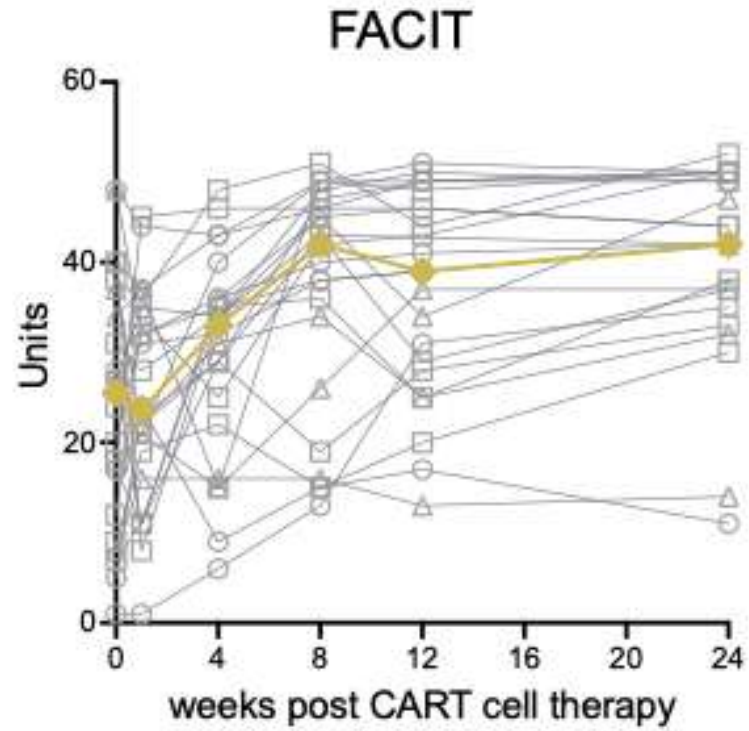
FAPI-PET based “staging” of IIM and effects of CAR T cells

Mueller F, Hagen M, Wirsching A, et al. Nature Medicine 2026- Jan 7

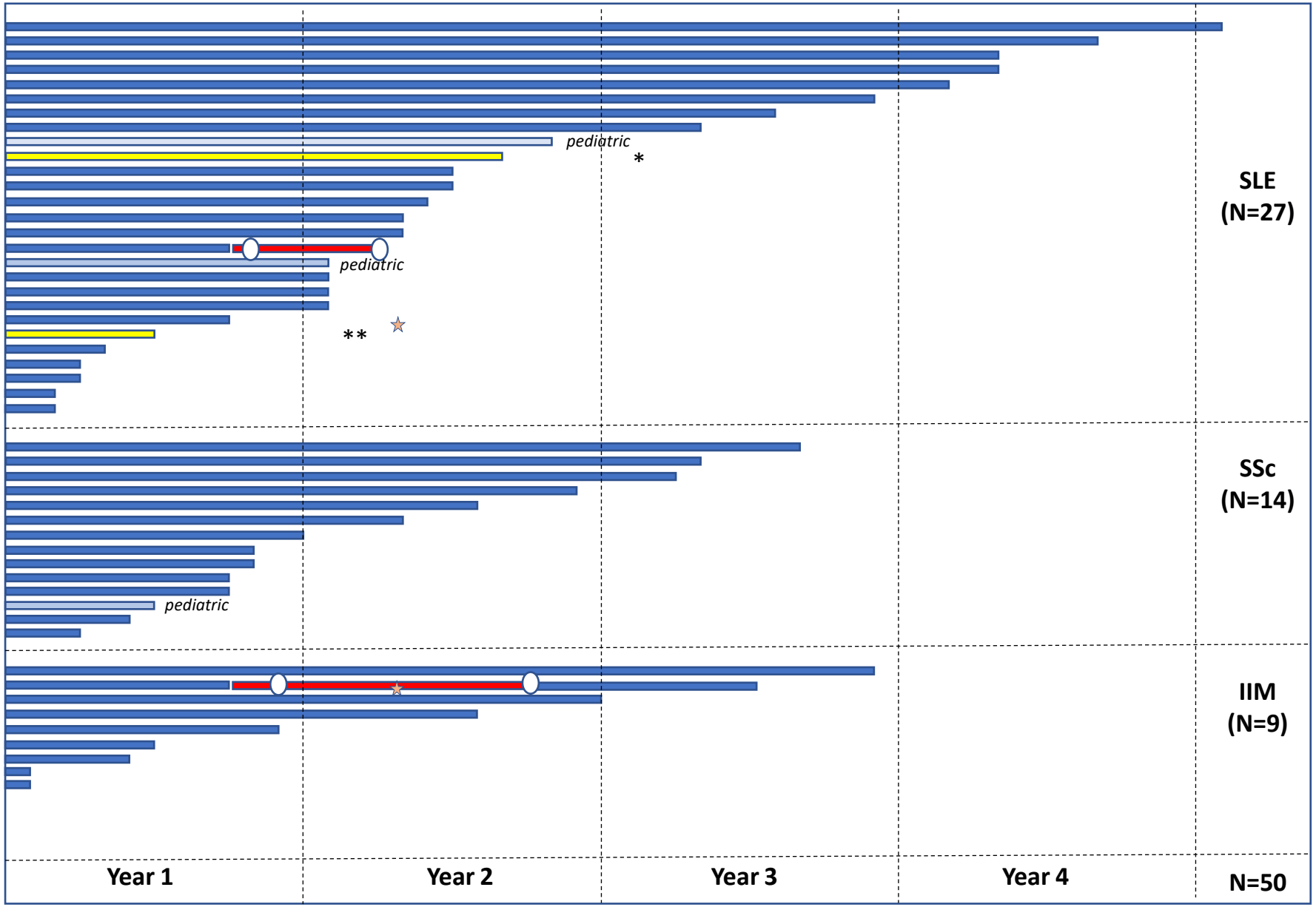
Improvement of function, life quality and fatigue







24 patients with autoimmune disease (10 SLE, 9 SSc and 5 IIM) receiving autologous CAR T-cell therapy with a second-generation 4-1BB lentiviral vector and standard lymphodepletion



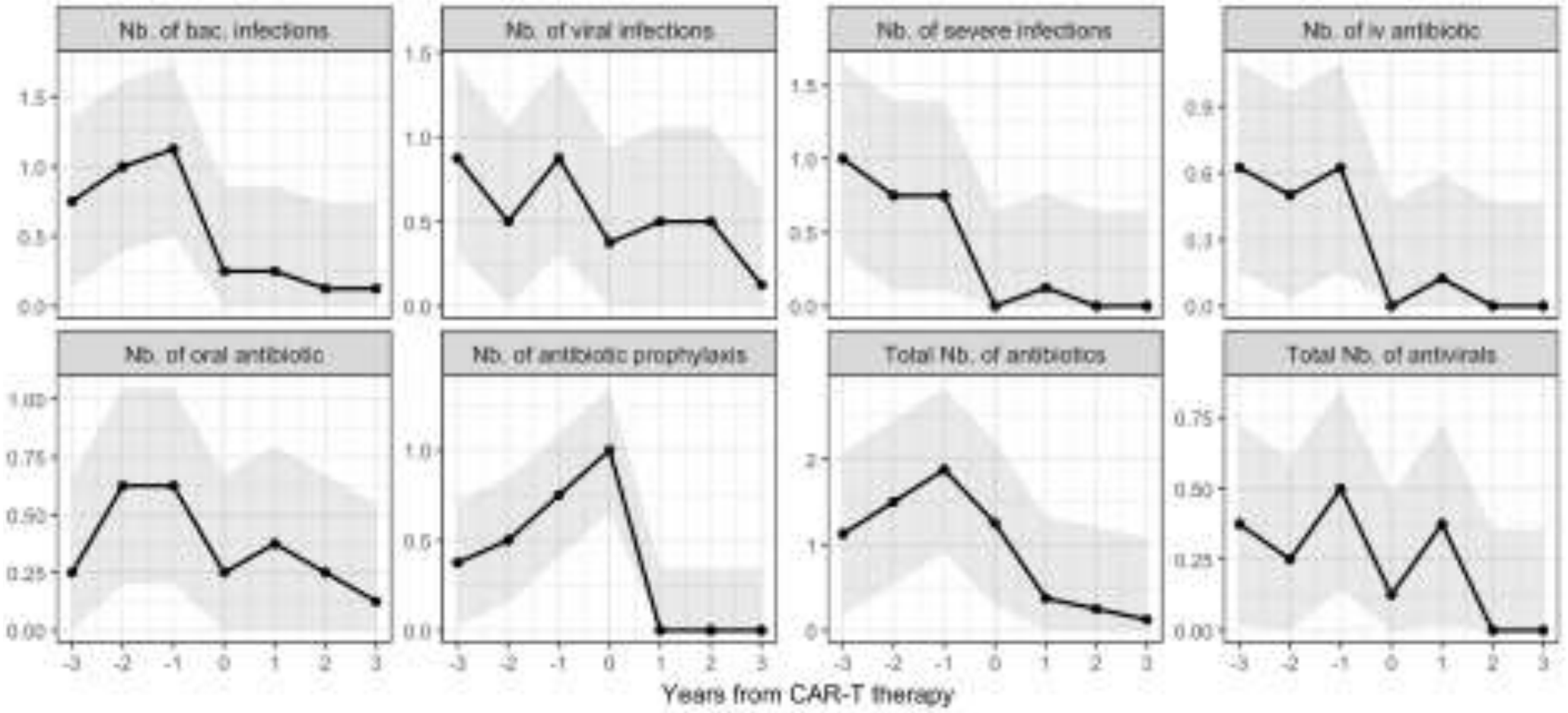
Long-Term Effects in a nutshell

50 patients
72,5 patient years

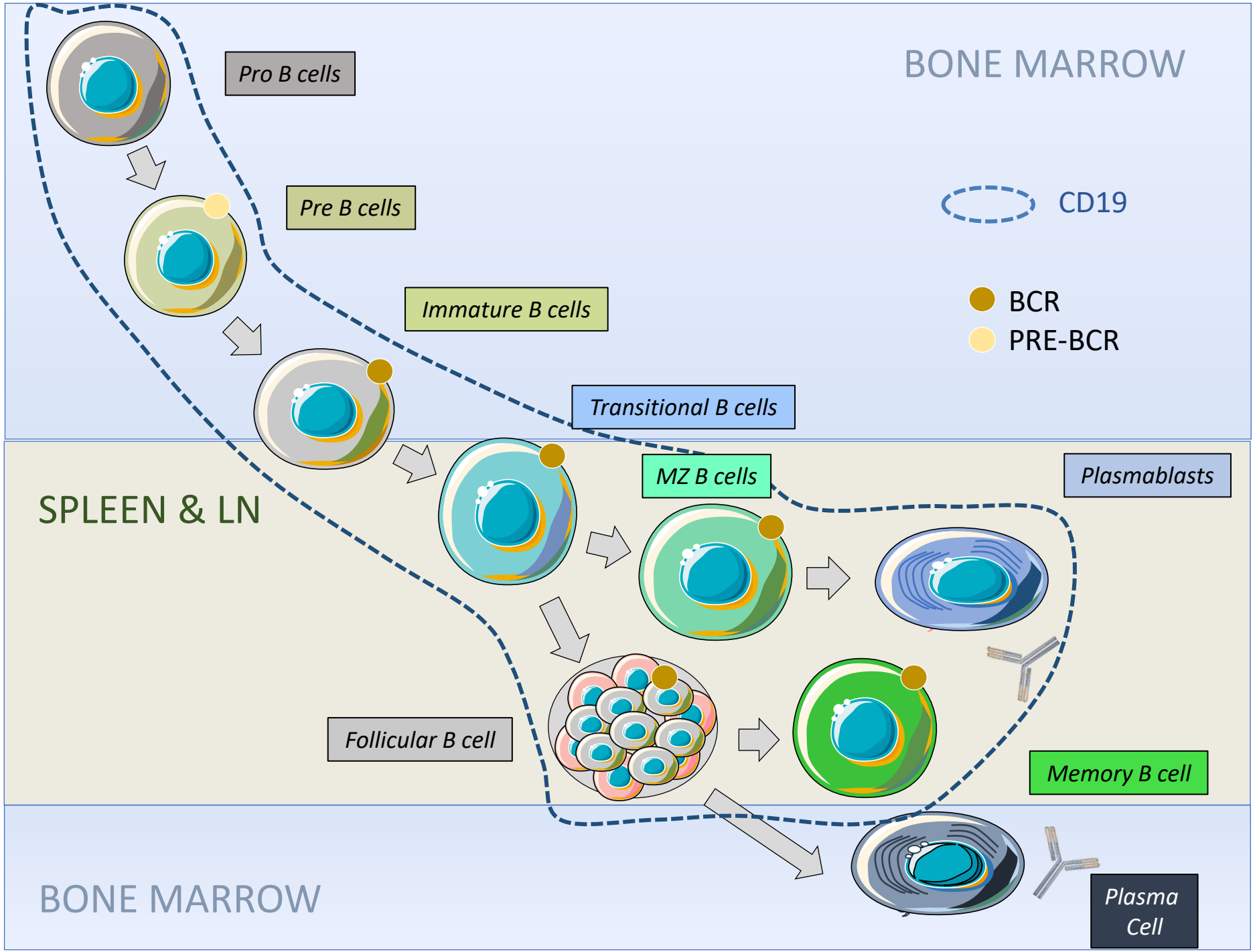
- 0 deaths
- 2 relapses
- 96% off drugs
- 92% in remission (SLE, IIM) or no progress (SSc)

*SLE:renal damage due to thombotic microangiotahy
**SLE: transverse myelitis (so far not improved)

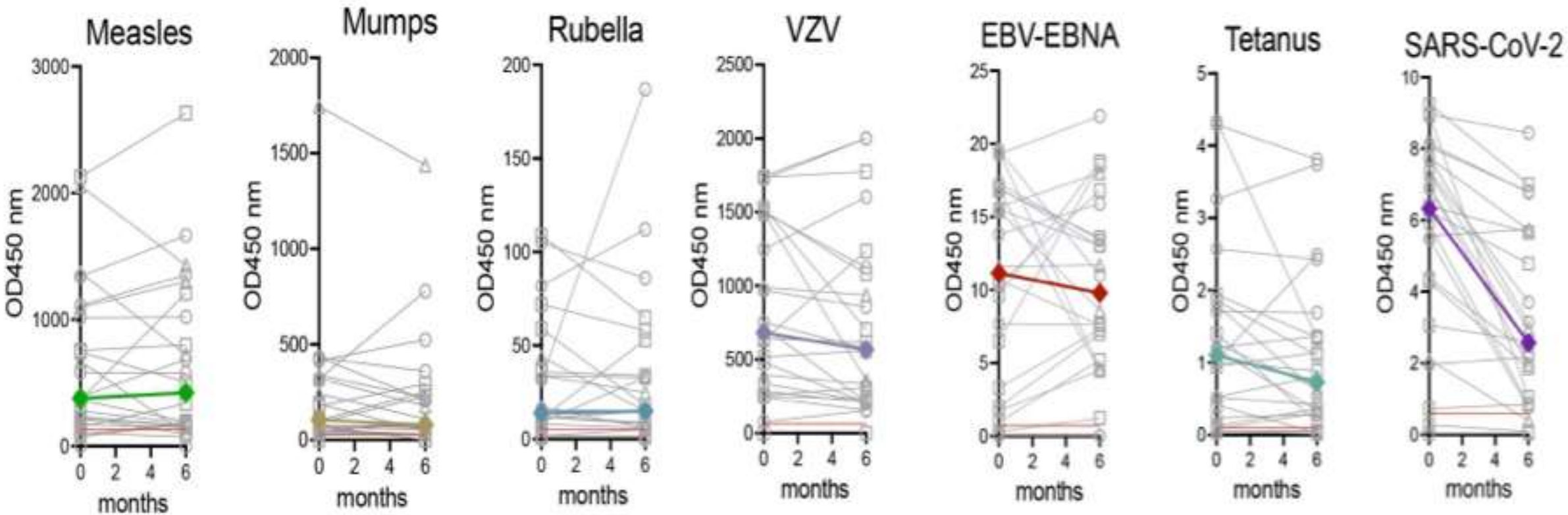
Sustained decrease in infection rates after CAR T-cell therapy



Data from 8 SLE patients with >3 years drug-free remission


BONE MARROW
Pro B cells
Pre B cells
Immature B cells
Transitional B cells
CD19
BCR
PRE-BCR
SPLEEN & LN
MZ B cells
Plasmablasts
Follicular B cell
Memory B cell
BONE MARROW
Plasma Cell

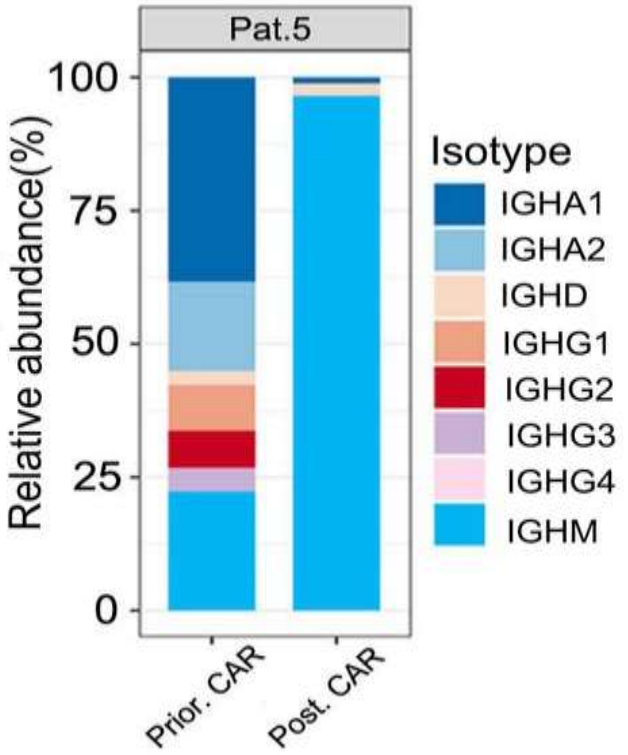
Vaccination-related antibodies

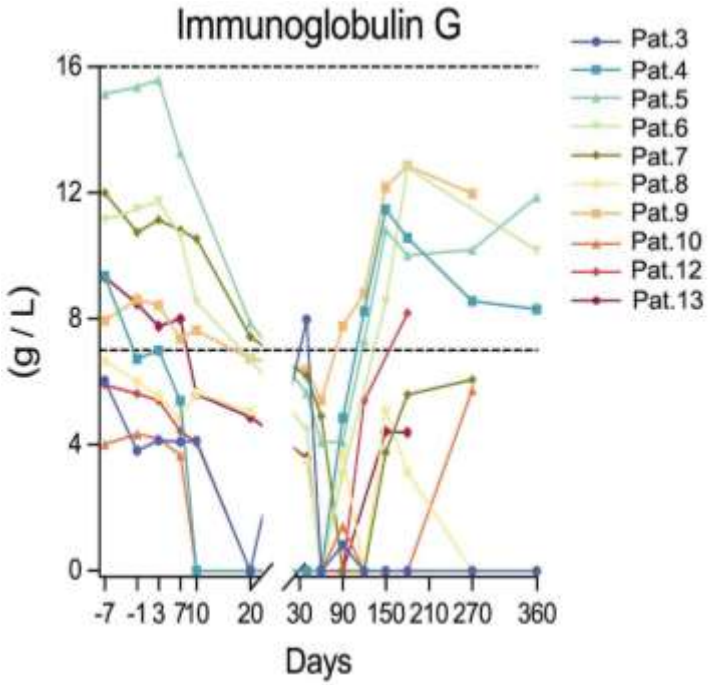


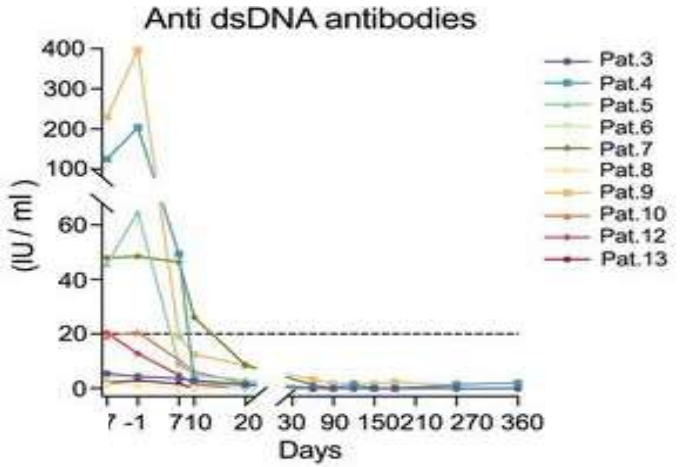
Müller F. et al. Nat Med 2026; Jan-7.

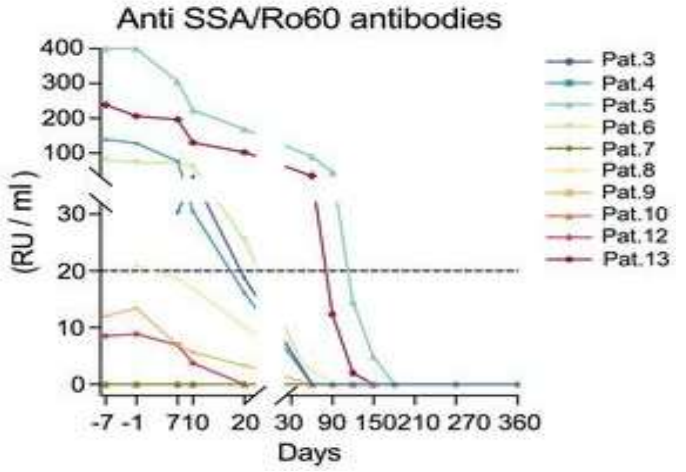
CD19/BCMA CAR T- cells in SLE

3 x10^6 CAR T-cells /kg body weight in 13 SLE patients
Clinical efficacy: 9 achieved DORIS remission and 12 LLDAS
SLEDAI decreased from 10.6 to 2.7



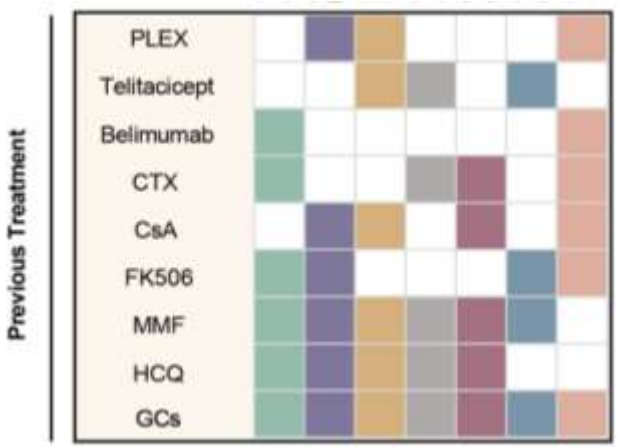


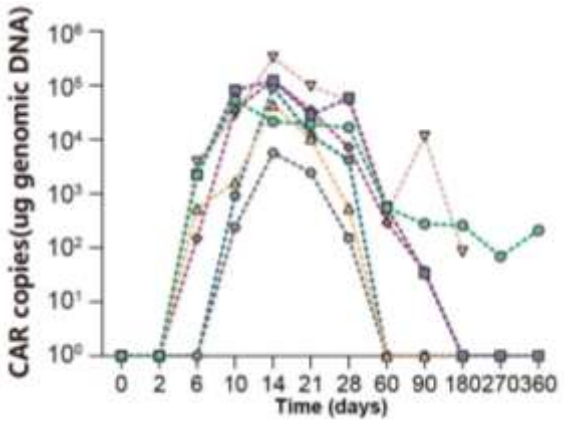


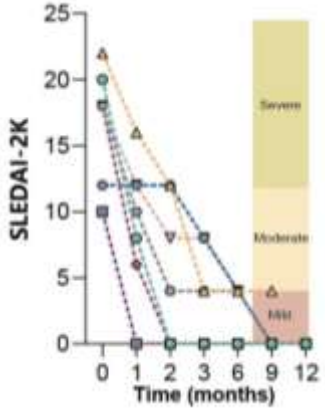


Wang W et al., Ann Rheum Dis 2024, May 30.

BCMA CAR T- cells in SLE

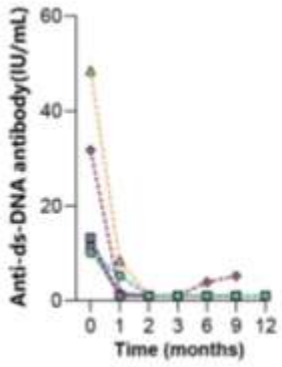


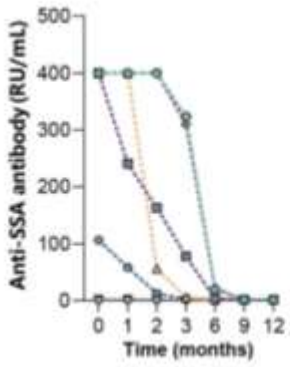


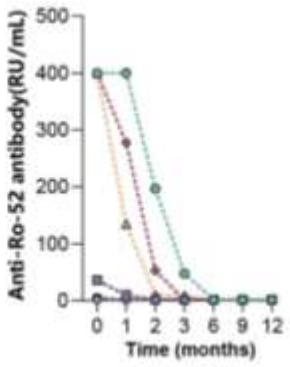


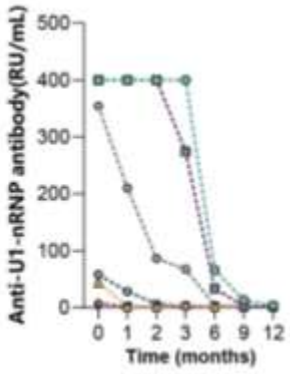
Seven biopsy-confirmed LN patients (4x WHO IV, 1x WHO IV/V, 1x WHO III, 1x WHO III/V)

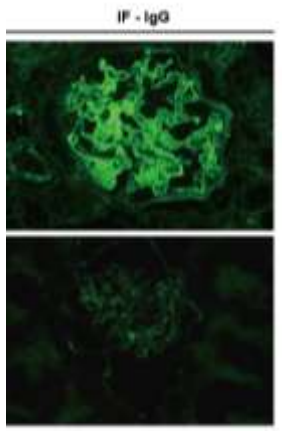
Autologous 4-1BB based second generation CAR





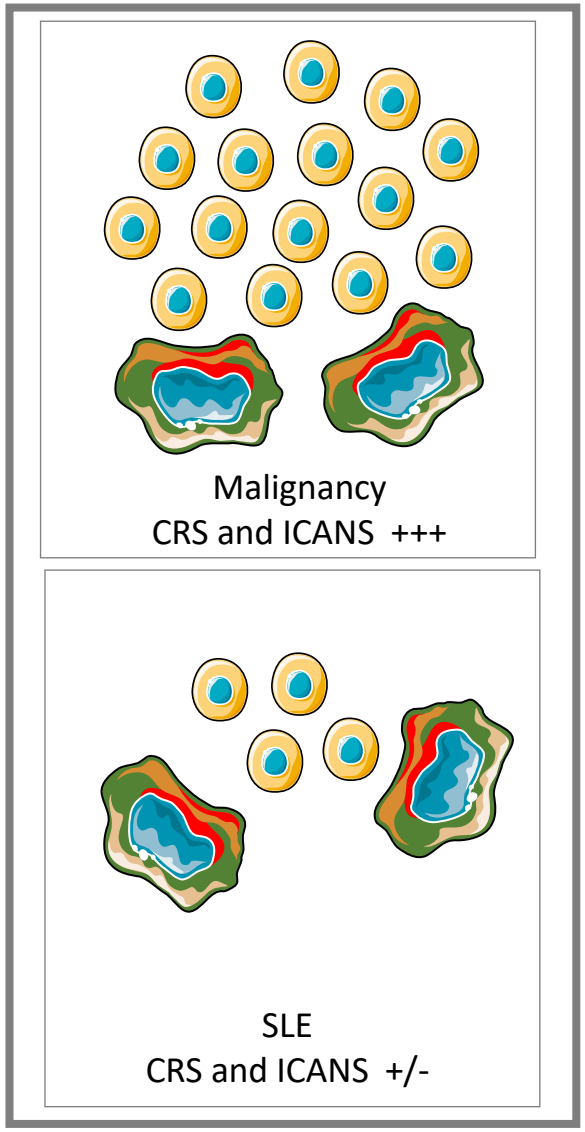






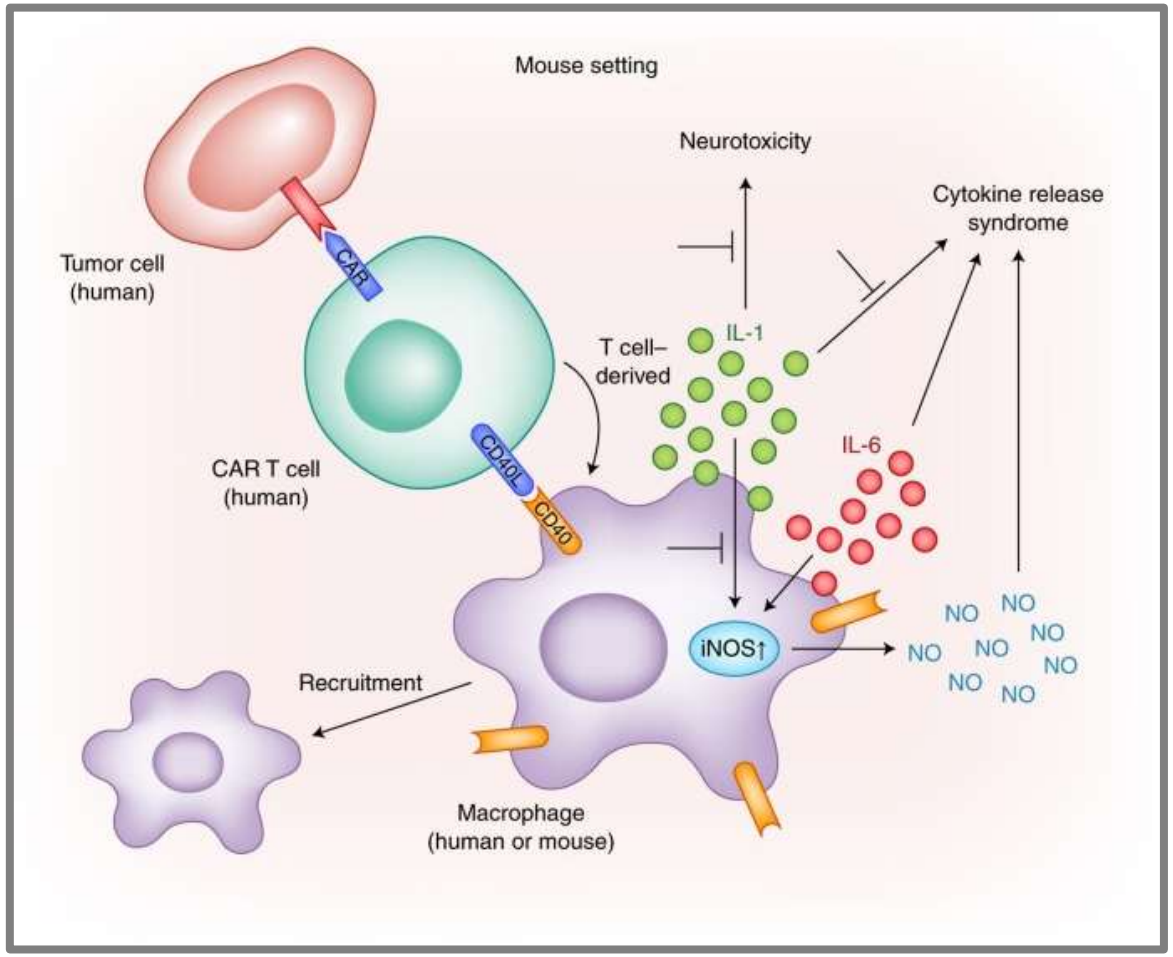
Hu, Z et al. BCMA-targeted CAR T cell therapy can effectively induce disease remission in refractory lupus nephritis Ann Rheum Dis 2025; 84: 1675-1683

Tolerability (Cytokine Release Syndrome)



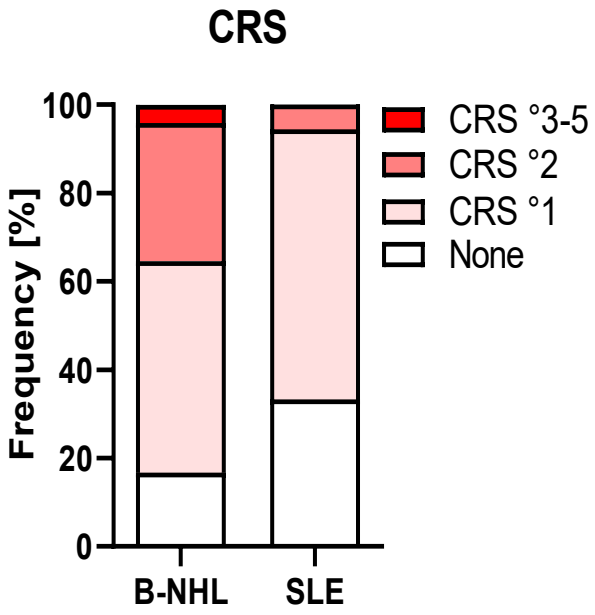
Malignancy
CRS and ICANS +++

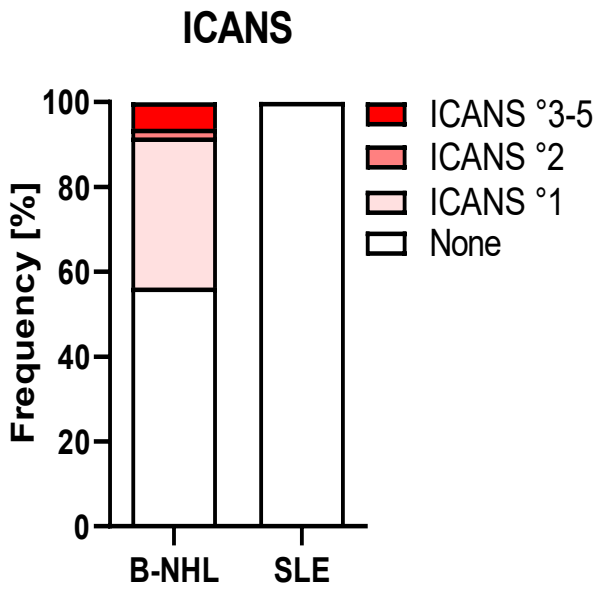
SLE
CRS and ICANS +/-

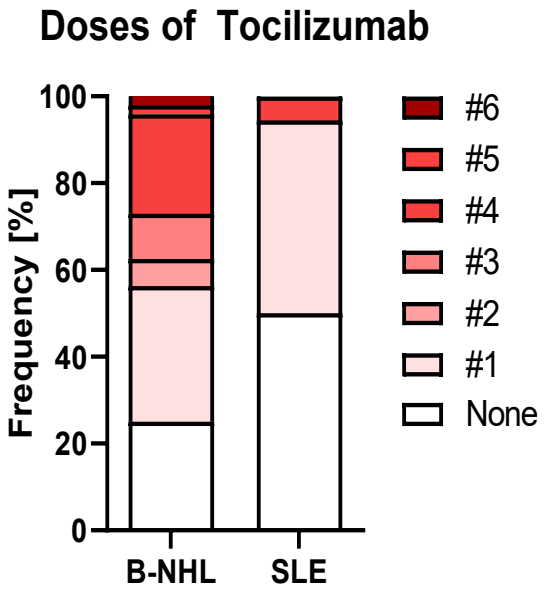


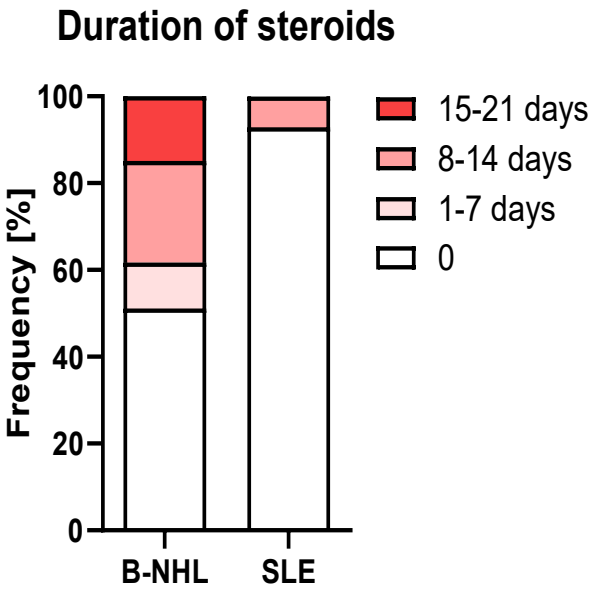
Autoreactive B cell B cells Naïve B cells Plasmablasts Plasma Cells CAR T Cells

Safety of CAR T-cell therapy in AID is different from NHL



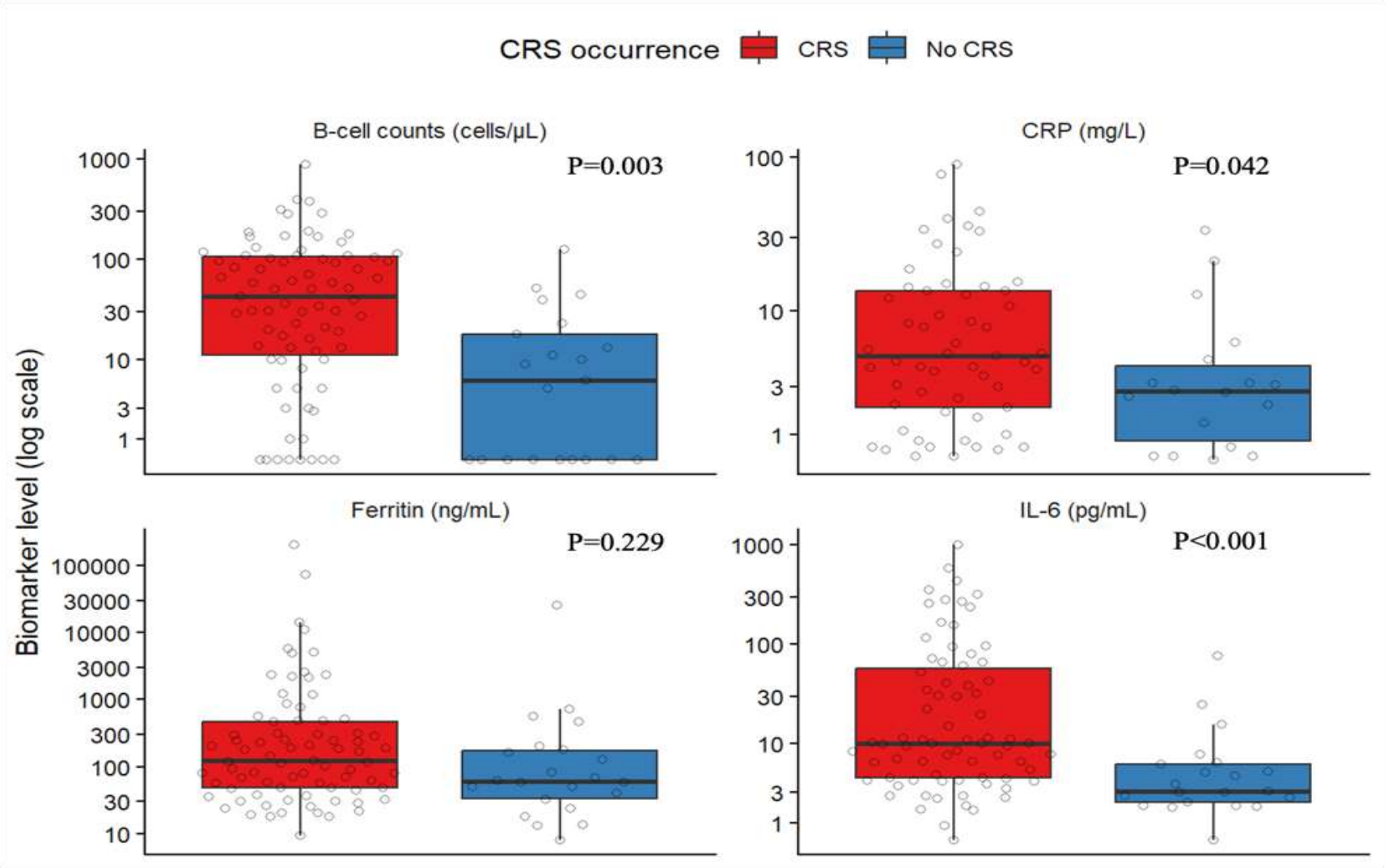






Müller F, et al. Blood. 2025 Aug 28;146(9):1088-1095.

B-cell counts and inflammation are associated with CRS

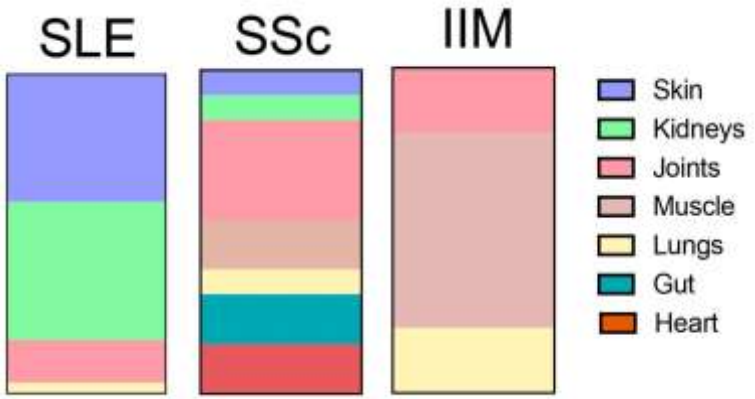


Analyses from 108 patients with AID treated with CAR T-cells

Local Immune effector Cell-Associated Toxicity Syndrome (LICATS)

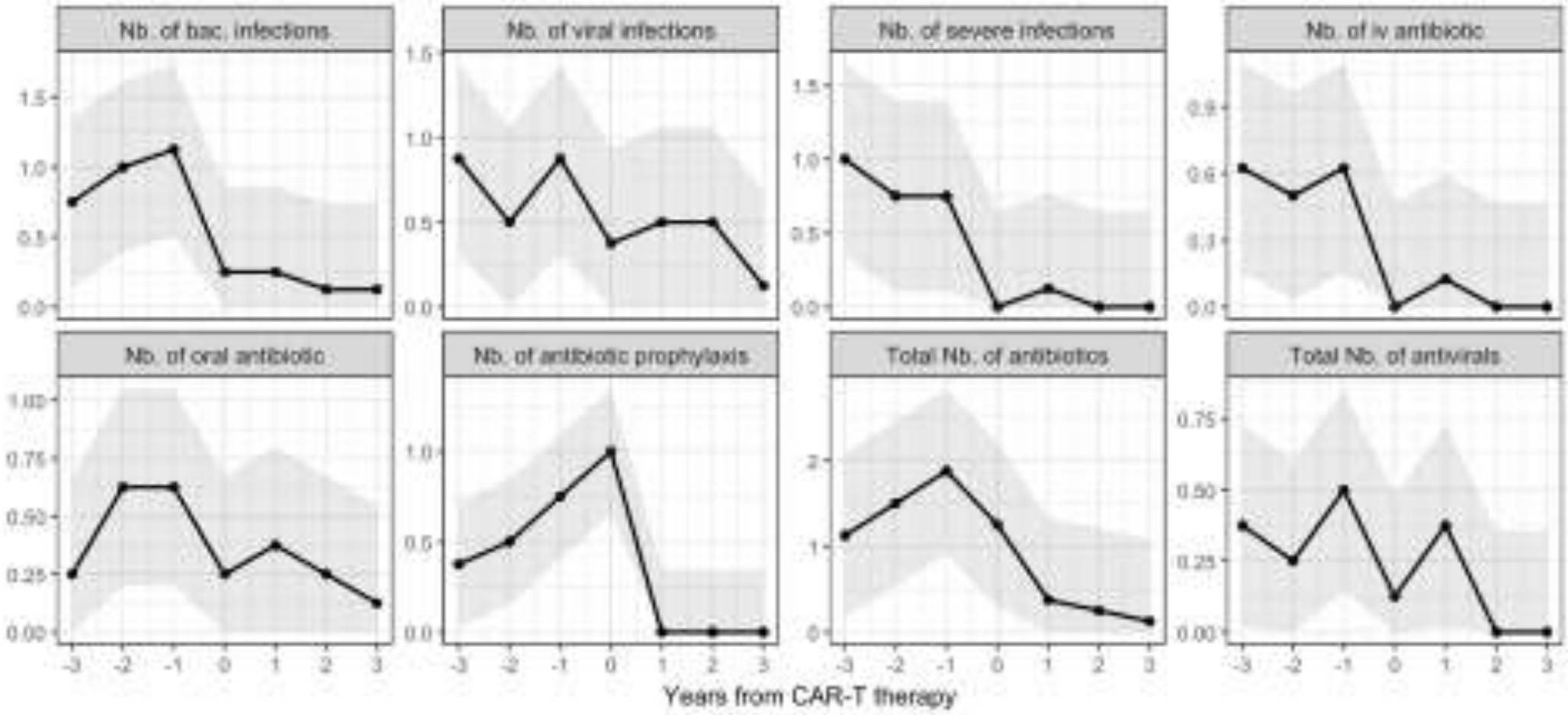
LICATS is
- mild
- self-limited
- organ-specific

LICATS occurs at a median time of 10 days after the CAR T-cell infusion



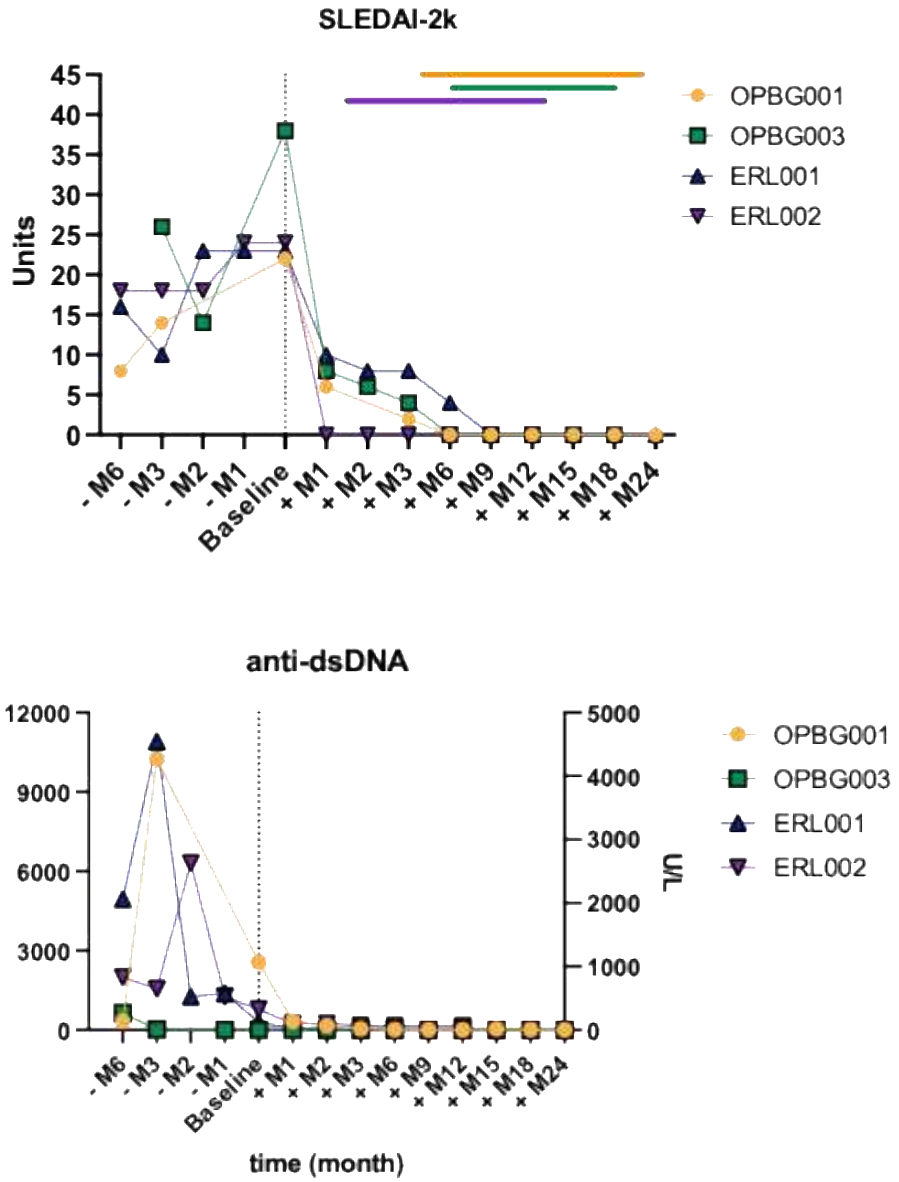
Hagen M etal. Lancet Rheumatol 2025

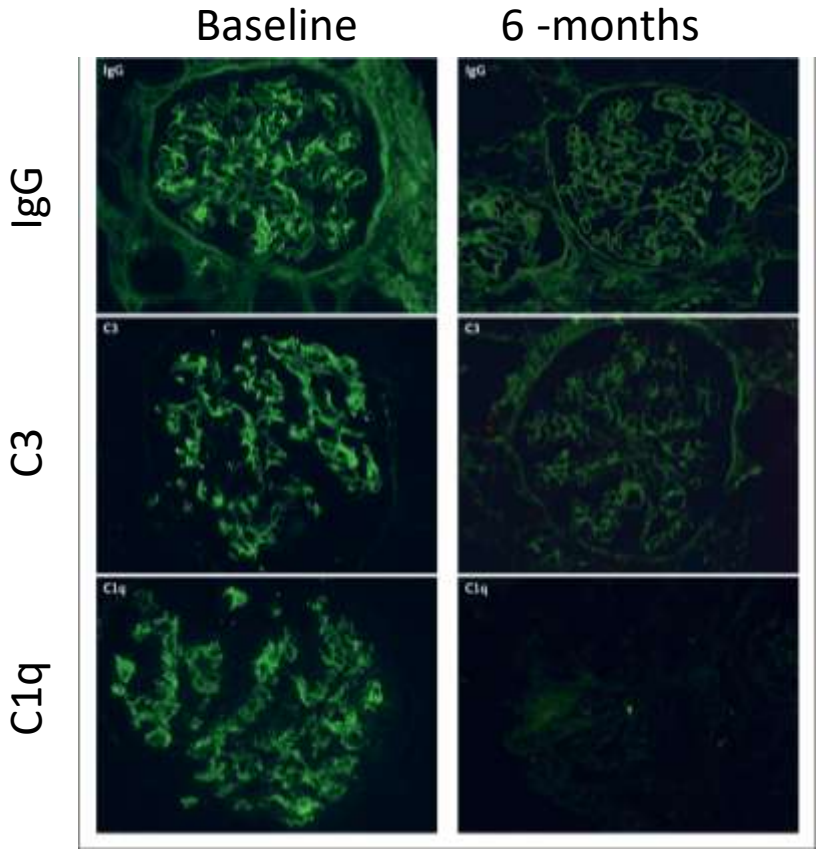
Sustained decrease in infection rates after CAR T-cell therapy



Date from 8 SLE patients with >3 years drug-free remission

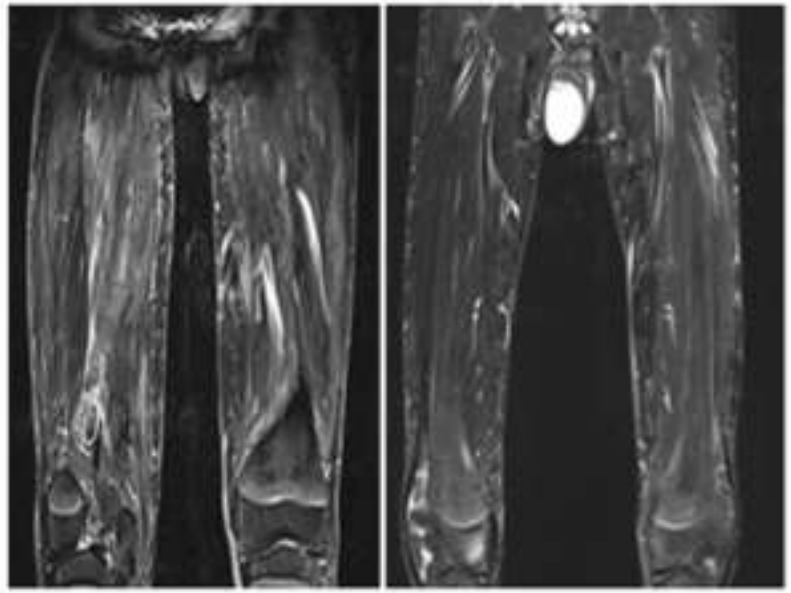
CD19-CAR-T cell therapy in pediatric SLE

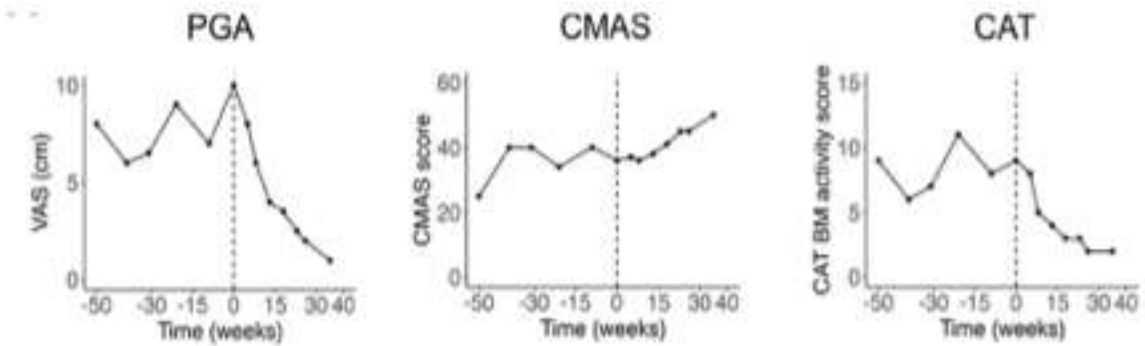




Krickau T, et al.. Lancet. 2024; 403:1627-1630; De Benedetti F, Diomedi Camassei F, Locatelli F. N Engl J Med. 2024 May 2;390(17):1629.Becilli M, et al Nature Medicine 2026, in press

CAR T Cell therapy in a Patient With Juvenile Dermatomyositis

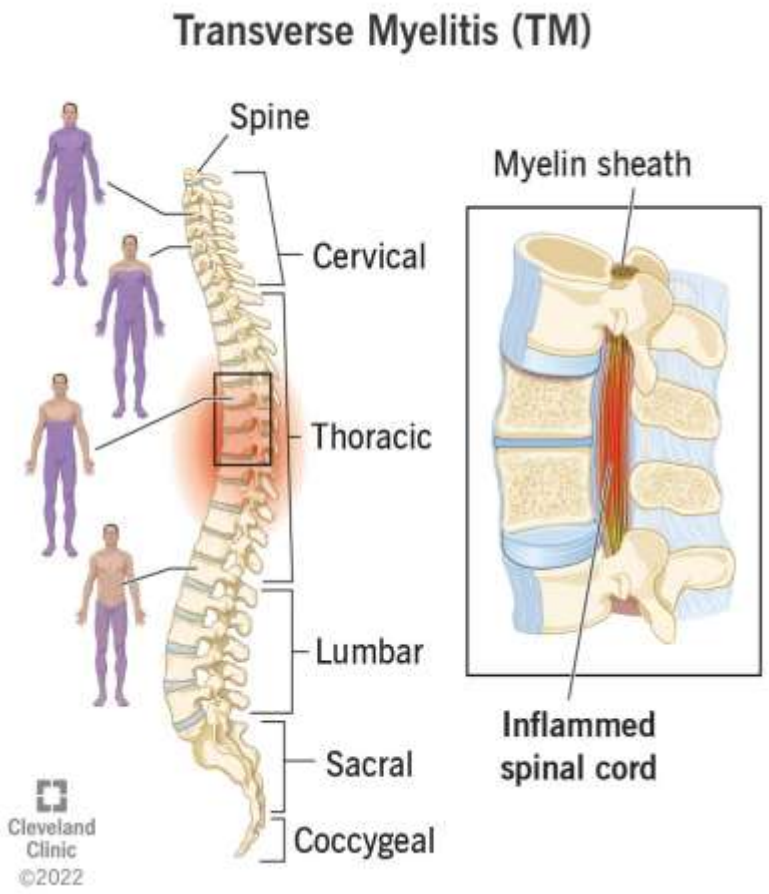




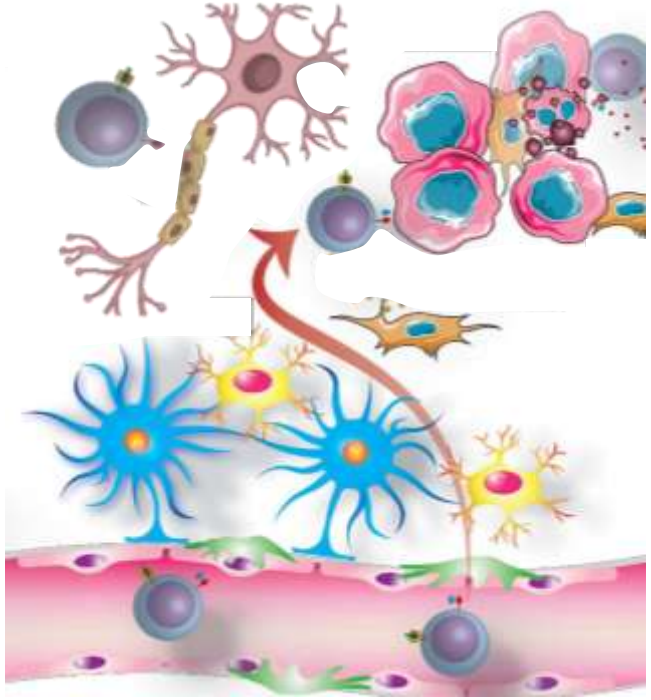
Physician Global Assessment the Childhood Myositis Assessment Scale (CMAS), and the Cutaneous Assessment Tool Binary Method (CAT BM)

Nicolai R, et al. Arthritis Rheumatol. 2024 Oct;76(10):1560-1565.

Can CAR T-cells affect AID in the CNS?

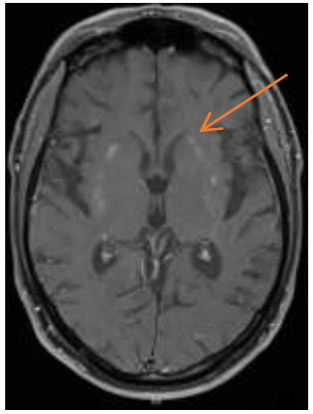


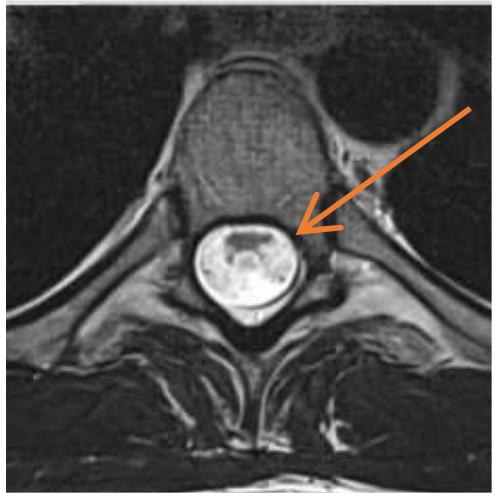
CNS affection in SLE



CAR T-cells have “full access” to the brain and can cross the blood-brain abrrier

20-year old man with SLE and severe CNS involvement with subtotal paraplegia: Progressive course despite HCQ, GLC, MTX, RTX and CYP treatment as well as plasmapheresis



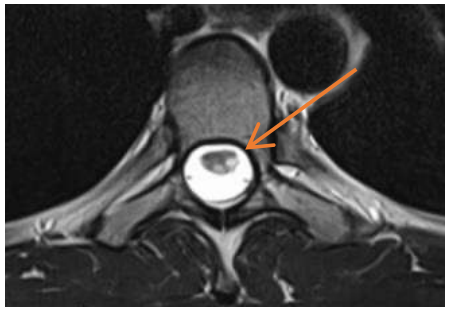


SLEDAI_2K (points)	20
MMT8 (points)	34
VAS_global (mm)	90
HAQ	2,63
FACIT	23

Hagen M et al. , Lancet 2024; 404:2158-2160.

Improvement of neuro- lupus after CAR T-cells

SLEDAI_2K (points)	20	0
MMT8 (points)	34	91
VAS_global (mm)	90	10
HAQ	2,63	2,13
FACIT	23	48



Hagen M et al. , Lancet 2024; 404:2158-2160.

Summary

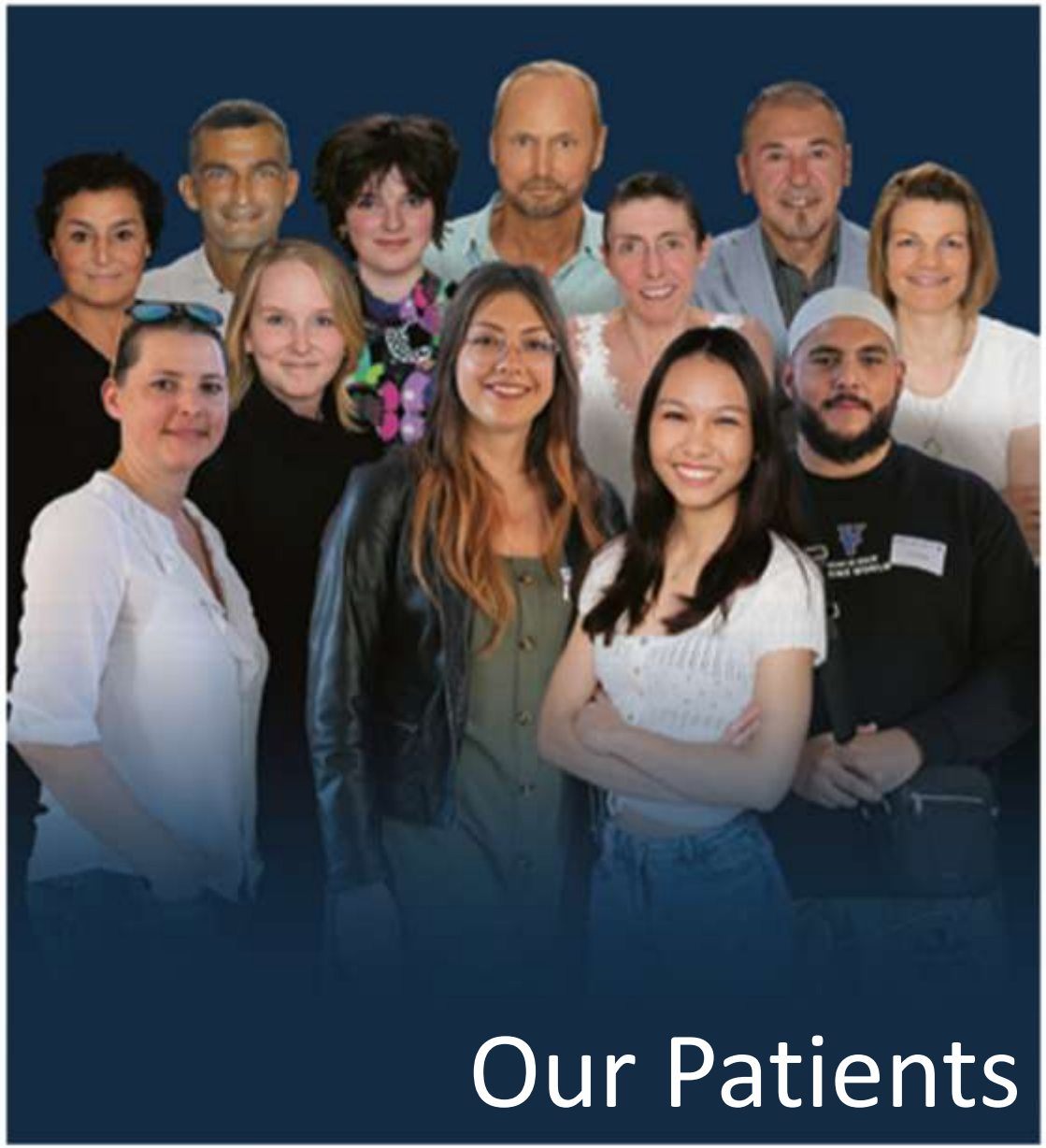
CAR T–cells are represent a inducible and reversible B-cell knockout that allows to **understand**:

- the reconstitution of B-cell memory
- the source of autoantibodies and vaccination-induced antibodies
- the interaction of B-cell with other cells

B-cell depletion and its consequences can be **monitored** very well (CAR T-cell expansion; peripheral B-cell depletion, tissue depletion, autoantibody levels, vaccination-induced antibody levels, immunoglobulin levels).

The methods of CAR T-cell mediated depletion of B-cells **rapidly develop** and may likely improve scalability of this therapeutic approach.

New insights in the pathophysiology of disease and definition of **disease subsets.**



Key People Involved

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Carlo Tur
Maria-Gabriella Raimondo
Laura Bucci
Janina Auth
Christina Bergmann
Jule Taubmann
Luis Muñoz
Tobias Rothe

Aline Bozec
Sebastian Böltz
Panagiotis Garatziotis
Koray Tascilar
Fabian Hartmann
Louis Schuster
Andreas Mackensen
Michael Aigner
Simon Völkl
Fabian Müller

Leibniz Award