Szemelvények a reumatológiai kutatás és gyógyszerfejlesztés aktualitásaiból

Dr. Balog Attila
Szegedi Tudományegyetem, Reumatológiai és Immunológiai Klinika

Clinical Reasoning and Knowledge Assessment of Rheumatology Residents Compared to AI Models: A Pilot Study

History

AI is showing potential in clinical decision-making.

Alan Turing's 1950 research established the foundational concept of electronic decision-making systems [1]. Over time, Turing's model advanced into diverse subfields including machine learning, deep learning, natural language processing, and computer vision.

In medicine, AI is utilized across multiple domains, such as data collection and management, imaging methods, and treatment recommendations.

Erdogan EK Clin. Med. 2024. https://doi.org/10.3390/jcm13237405

Clinical Reasoning and Knowledge Assessment of Rheumatology Residents Compared to AI Models: A Pilot Study

History

One of the earliest AI applications in healthcare was MYCIN, a backward chaining artificial intelligence system developed in the early 1970s. MYCIN was able to provide a list of potential bacterial pathogens according to patient information and recommend an appropriate treatment

A consultation system for glaucoma was developed using the CASNET model and was officially demonstrated at the meeting of the Academy of Ophthalmology in 1976. This model was able to apply knowledge about a particular disease to individual patients and advise physicians on management.

A landmark moment in the use of AI in medicine occurred in 2017, with the Food and Drug Administration's approval of Artery, the first deep learning based application. Artery's initial deployment, CardioAI, focused on analyzing cardiac magnetic resonance imaging, followed by extensions into liver, lung, and musculoskeletal imaging

Erdogan EK Clin. Med. 2024. https://doi.org/10.3390/jcm13237405

Clinical Reasoning and Knowledge Assessment of Rheumatology Residents Compared to AI Models: A Pilot Study

AI is showing potential in clinical decision-making.

This study aimed to compare clinical decision making approaches of junior rheumatology residents with both trained and untrained AI models in clinical reasoning, pre-diagnosis, first-line, and second-line management stages.

Ten junior rheumatology residents and two GPT-4 models (trained and untrained) responded to 10 clinical cases, encompassing diagnostic and treatment challenges in inflammatory arthritis.

The cases were evaluated using the Revised-IDEA (R-IDEA) scoring system and additional case management metrics.

Strongly, Disagree, Disagree, Neutral, Agree, Strongly Agree

Erdogan EK Clin. Med. 2024. https://doi.org/10.3390/jcm13237405

Clinical Reasoning and Knowledge Assessment of Rheumatology Residents Compared to AI Models: A Pilot Study

Trained GPT-4 outperformed residents across all stages, achieving significantly higher median R-IDEA scores and superior performance in prediagnosis, first-line, and second-line management phases.

Table 1. Summary of R-IDEA, R-IDEA binary, pre-diagnosis, first-line, and second-line treatment scores.

Variable	Human (N = 100)	Trained GPT-4 (N = 10)	GPT-4 (N = 10)	Total (N = 120)	*p*-Value
R-IDEA					<0.001
Median (25–75th)	7.0 (6.5–7.5)	8.5 (8.1–9.4)	7.5 (7.5–7.5)	7.0 (6.5–7.5)	
Range	3.5–9.0	8.0–10.0	6.5–8.0	3.5–10.0	
R-IDEA * (cut of 7)					0.047
Low	36 (36.0%)	0 (0.0%)	2 (20.0%)	38 (31.7%)	
High	64 (64.0%)	10 (100.0%)	8 (80.0%)	82 (68.3%)	
Pre-diagnosis					<0.001
Median (25–75th)	3.8 (3.3–4.1)	5(4.8–5.0)	4.5 (4.5–4.7)	4.0 (3.5–4.3)	
Range	2.8–4.8	4.5–5.0	4.0–5.0	2.8–5.0	
First-line					<0.001
Median (25–75th)	4.0 (3.6–4.0)	4.8 (4.5–4.9)	4.1 (3.8–4.5)	4.0 (3.7–4.3)	
Range	1.5–4.8	4.3–5.0	3.4–5.0	1.5–5.0	
Second-line					<0.001
Median (25–75th)	4.0 (3.5–4.3)	4.9 (4.5–5.0)	4.5 (4.4–4.7)	4.0 (3.5–4.5)	
Range	1.0–5.0	4.1–5.0	4.0–4.7	1.0–5.0	

R-IDEA: Revised IDEA. * "high" (≥7) or "low" (<7).

Erdogan EK Clin. Med. 2024. https://doi.org/10.3390/jcm13237405

Clinical Reasoning and Knowledge Assessment of Rheumatology Residents Compared to AI Models: A Pilot Study

Psychological benefits of AI integration for junior residents, including perceived reductions in fatigue and burnout, as well as improvements in confidence and learning.

These findings position AI tools as valuable adjuncts for medical education and clinical practice, particularly in early-stage training.

Erdogan EK Clin. Med. 2024. https://doi.org/10.3390/jcm13237405

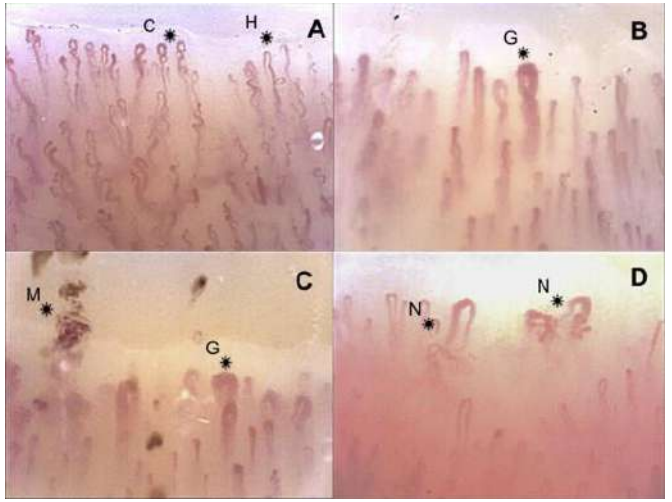

AFP

Automatic assessment of nailfold capillaroscopy software: a pilot study

The study was based on the assessment of 200 capillaroscopic images obtained from patients suffering from systemic sclerosis or scleroderma spectrum diseases and healthy people.

Each image was analysed manually and described using working software.
The neural network was trained using the fast ai library (based on PyTorch).

The ResNet-34 deep residual neural network was chosen;
10-fold cross-validation with the validation and test set was performed, using the Darknet-YoloV3 state of the art neural network in a GPU-optimized (P5000 GPU) environment.



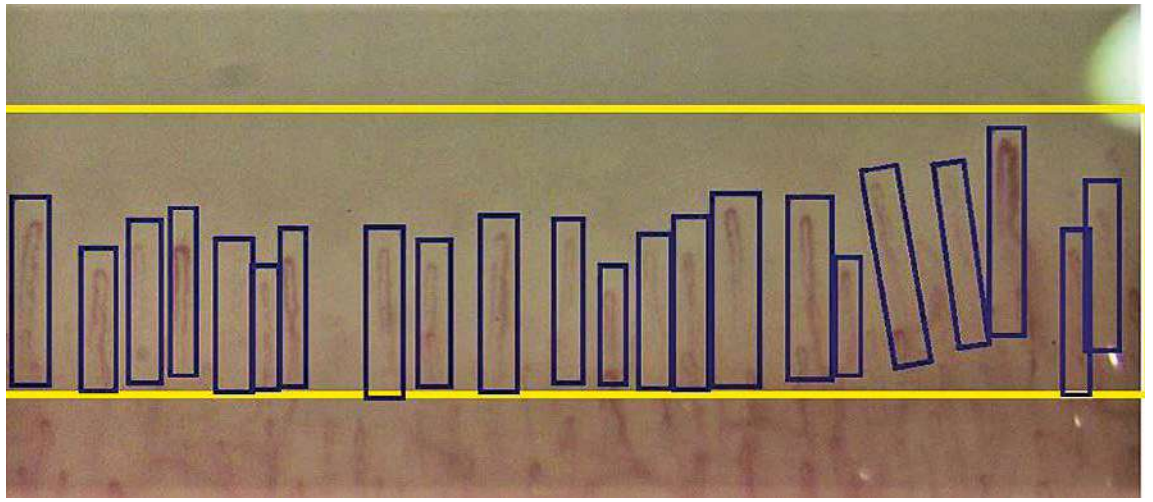
Brzezińska OE et al. Reumatologia 2024; DOI:https://doi.org/10.5114/reum/194040

Automatic assessment of nailfold capillaroscopy software: a pilot study

The results obtained under neural network training were compared to the results obtained in manual analysis.

The sensitivity of the automatic tool relative to manual assessment in classification of correct vs. pathological images was 89.0%, specificity 89.4% for the training group, in validation 89.0% and 86.9% respectively

For the average number of capillaries in 1 mm the precision of real images detected within the region of interest was 96.48%.

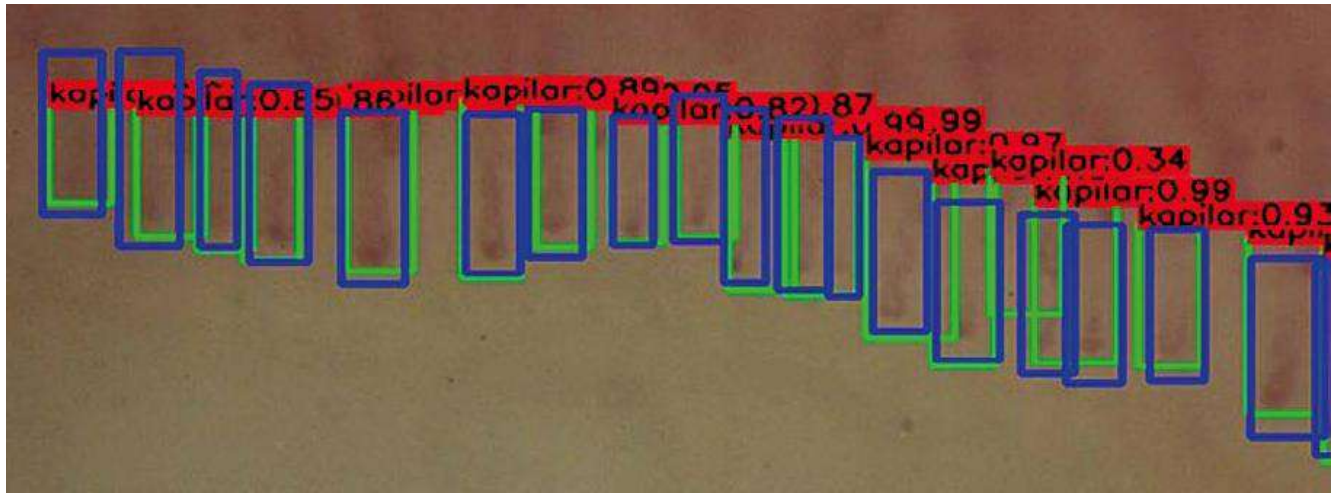


Brzezińska OE et al. Reumatologia 2024; DOI:https://doi.org/10.5114/reum/194040

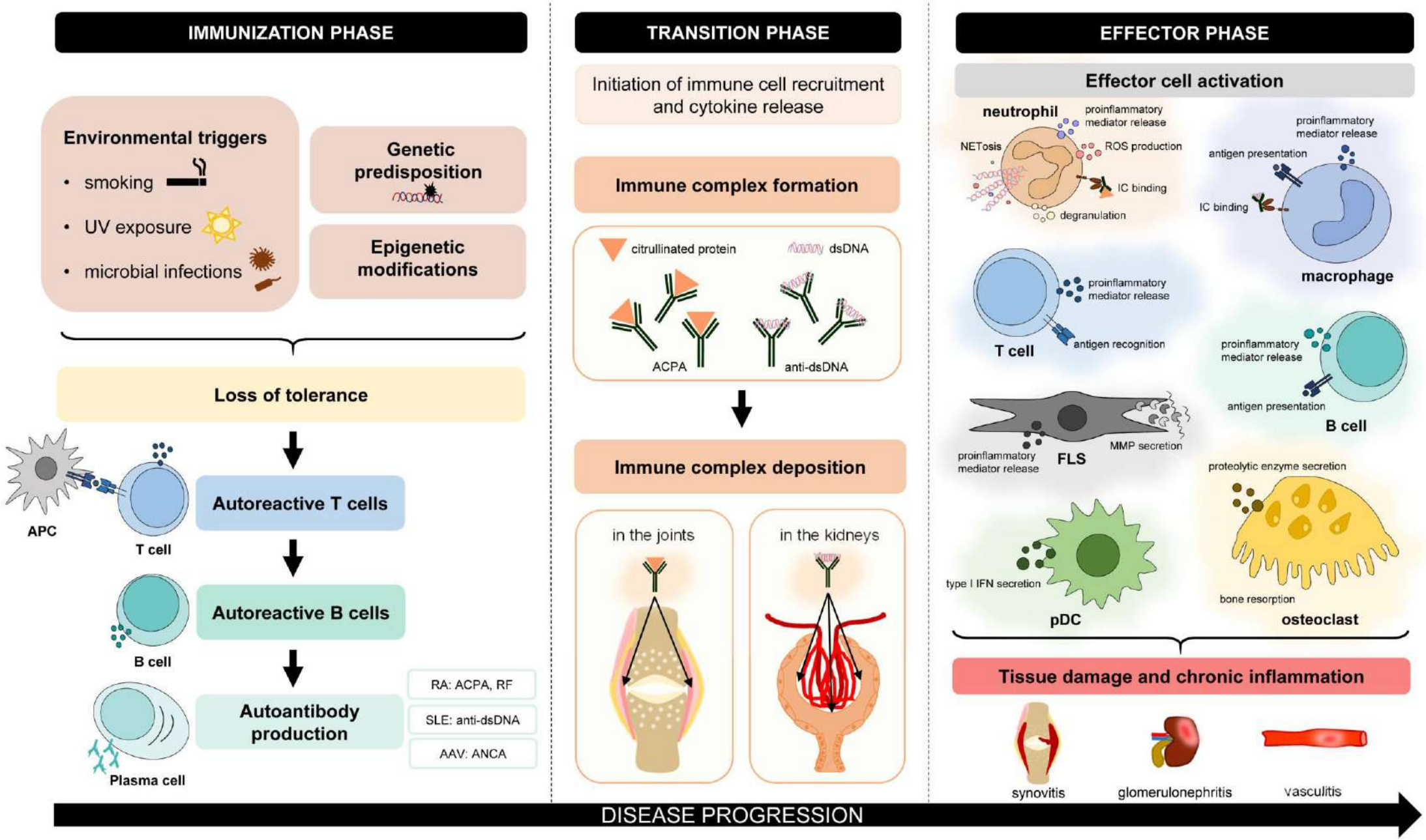
Automatic assessment of nailfold capillaroscopy software: a pilot study

The pilot software for fully automatic capillaroscopic image assessment can be a useful tool for the rapid classification of a normal and altered capillaroscopy pattern. In addition, it allows one to quickly calculate the number of capillaries.

SSc like RA, pSS, and also DM, APS or AH.



Brzezińska OE et al. Reumatologia 2024; DOI:https://doi.org/10.5114/reum/194040



Balog L Novel and potential future therapeutic options in systemic autoimmune diseases. Front. Immunol. doi: 10.3389/fimmu.2024.1249500

Newly approved drugs and some selected promising candidates from phase 2 or 3 trials.

Drug	Target	Status (approved or clinical study phase)	Disease	Refs.
Anifrolumab	Type I interferon receptor subunit 1	Approved (FDA, EMA) Phase 2 Phase 3	SLE Sjögren's syndrome SSc	(5) NCT05383677 NCT05925803
Voclosporin	Calcineurin	Approved (FDA, EMA)	SLE	(6)
Belimumab	BAFF/BLyS	Approved (FDA, EMA) Phase 2 Phase 2	SLE SSc Sjögren's syndrome	(7, 8) NCT01670565, NCT03844061 (9, 10)
Sifalimumab	Interferon-α	Phase 2	SLE	(11, 12)
Obinutuzumab	CD20	Phase 3	SLE	NCT04963296
Telitacicept	BAFF/BLyS and APRIL	Phase 3	SLE	(13, 14)
Atacicept		Phase 2	SLE	(15)
Ianalumab	BAFF receptor	Phase 3	SLE Sjögren's syndrome	(16), NCT05639114, NCT05349214
Daratumumab	CD38	Phase 2	SLE	(17, 18) NCT04810754
Litifilimab	BDCA-2	Phase 3	SLE, CLE	(19, 20)
Low-dose IL-2	regulatory T cells	Phase 2	SLE	(21, 22)
Filgotinib	JAK1	Approved (EMA)	RA	(23–25)
Upadacitinib		Phase 2 Phase 3	SLE Takayasu's arteritis, GCA	NCT03978520 NCT04161898, NCT03725202
Peficitinib	All JAKs	Approved (South Korea, Japan)	RA	(26, 27)

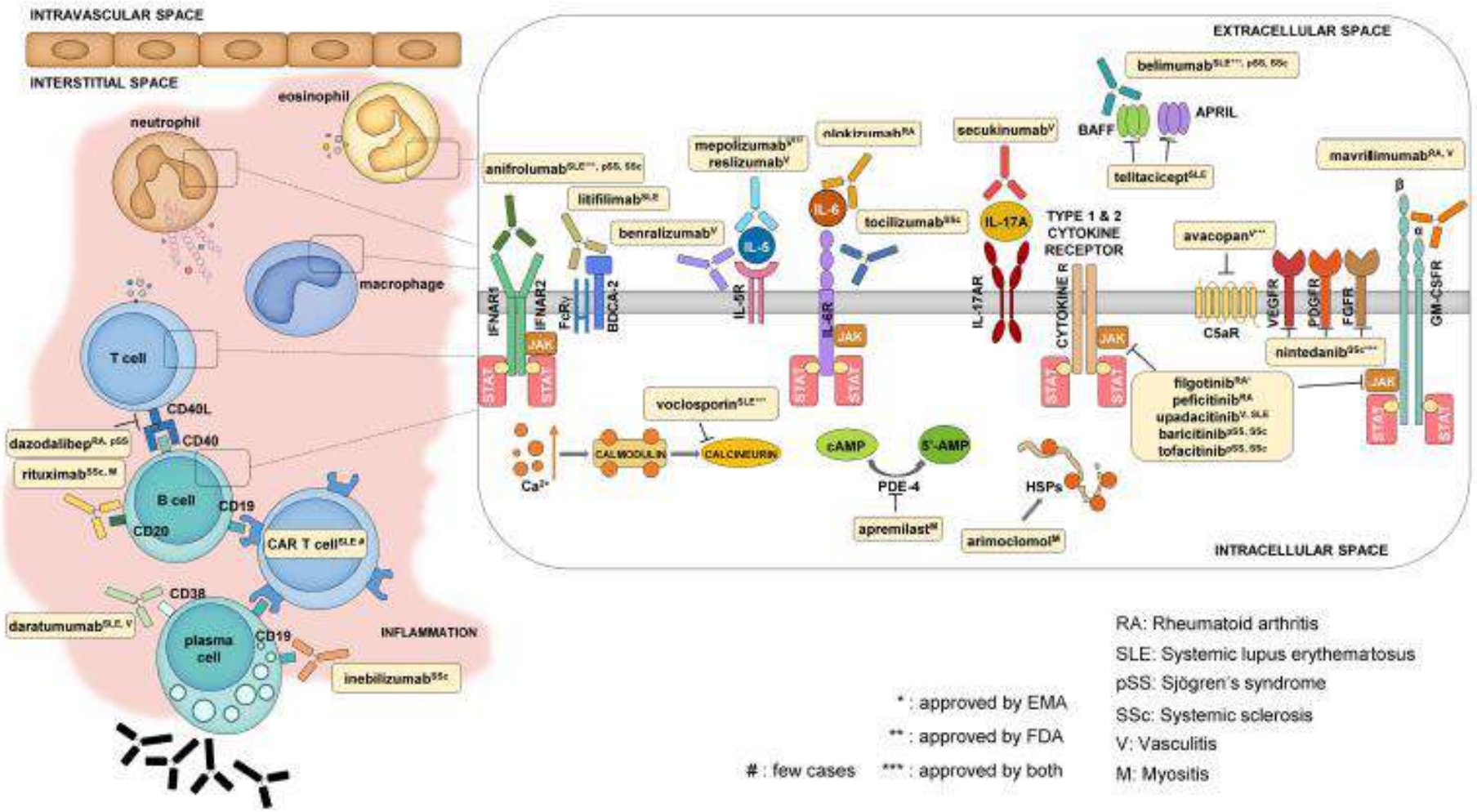
Balog L Novel and potential future therapeutic options in systemic autoimmune diseases. Front. Immunol. doi: 10.3389/fimmu.2024.1249500

Newly approved drugs and some selected promising candidates from phase 2 or 3 trials.

Mavrilimumab	GM-CSFR	Phase 2	RA, GCA	(28, 29)
Dazodalibep	CD40L	Phase 2 Phase 3	RA Sjögren's syndrome	(30–32), NCT06104124
Olokizumab	IL-6	Phase 3	RA	(33–35)
Baricitinib	JAK1 and JAK2	Phase 2 Phase 4	Sjögren's syndrome SSc	NCT05016297 NCT05300932
Nintedanib	VEGFR, PDGFR, FGFR	Approved (FDA, EMA)	SSc	(36)
Tocilizumab	IL-6R	Phase 3	SSc	(37)
Brodalumab	IL-17A receptor	Phase 3	SSc	(38)
Tofacitinib	JAK1 and JAK3	Phase 2	Sjögren's syndrome SSc	NCT04496960 (39)
Inebilizumab	CD19	Phase 3	SSc	NCT05198557
Secukinumab	IL-17A	Phase 2	GCA	(40)
Avacopan	C5a receptor	Approved (FDA, EMA)	GPA, MPA	(41, 42)
Mepolizumab	IL-5	Approved (FDA, EMA)	EGPA	(43–45)
Reslizumab		Phase 2	EGPA	(46)
Benralizumab	IL-5R	Phase 3	EGPA	(47) NCT04157348
IVIG	?	Phase 3	DM	(48)
Apremilast	PDE-4	Phase 2	DM	(49)

Balog L Novel and potential future therapeutic options in systemic autoimmune diseases. Front. Immunol. doi: 10.3389/fimmu.2024.1249500

Mechanism of action of some selected newly approved therapies and promising drug candidates.



Balog L Novel and potential future therapeutic options in systemic autoimmune diseases. Front. Immunol. doi: 10.3389/fimmu.2024.1249500

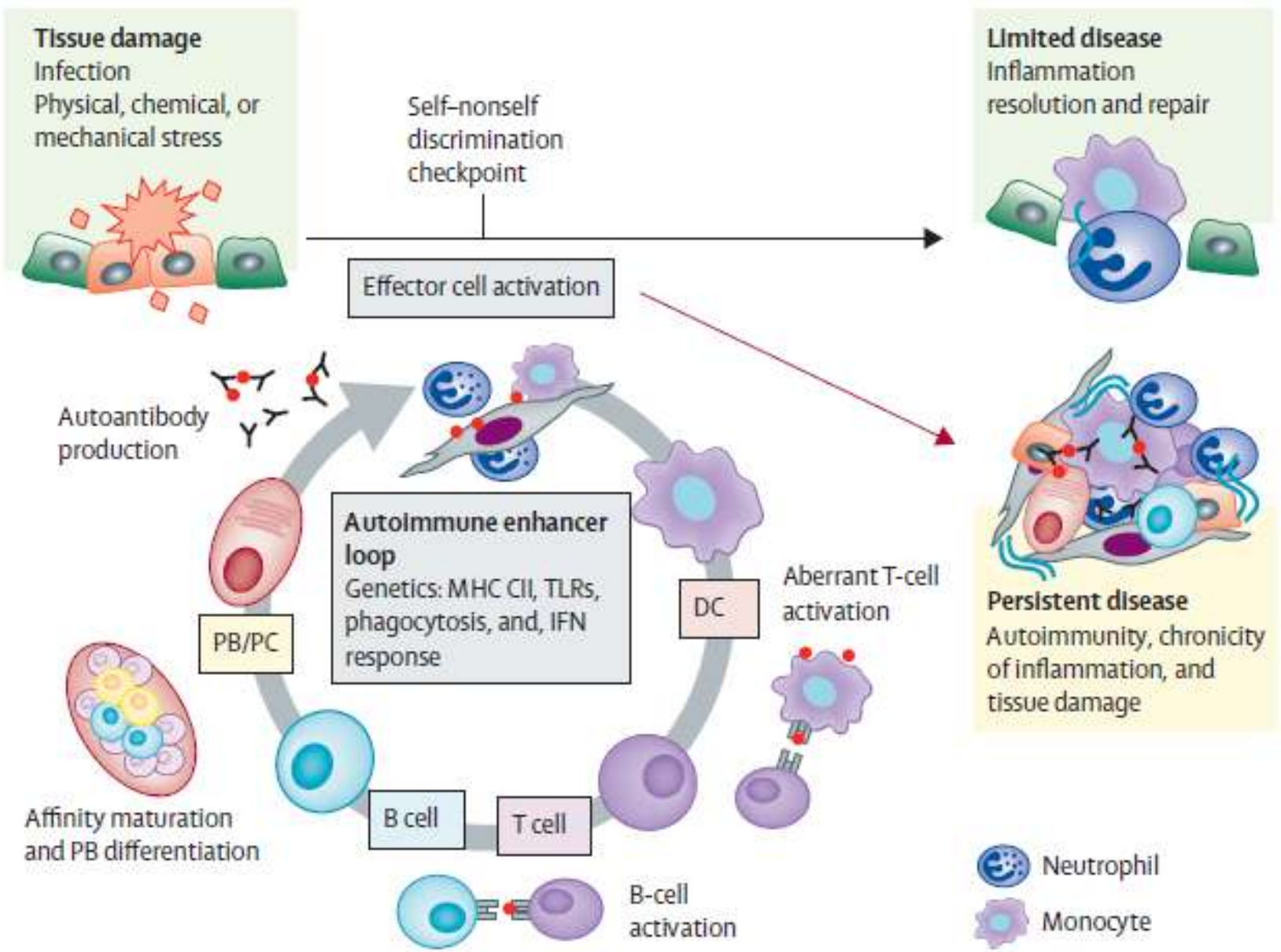
TABLE 2 Common drug targets and similarities.

Target	SLE	RA	pSS	SSc	LVV	AAV	IIM
Type I IFN/IFNR	✓		✓	✓			
IL-17/IL-17R				✓	✓		
GM-CSFR		✓			✓		
BAFF/BAFF receptor	✓		✓	✓			
CD40/40L	✓	✓	✓				
JAK/STAT	✓	✓	✓	✓	✓	✓	✓
IL-6/IL-6R		✓		✓			
CD20	✓	✓	✓	✓	✓	✓	✓
CD19	✓			✓			✓
CD38	✓					✓	

AAV, ANCA-associated vasculitis; GM-CSFR, GM-CSF receptor; IFNR, interferon receptor; IL-6R, IL-6 receptor; IL17R, IL-17 receptor; IIM, idiopathic inflammatory myopathy; LVV, large-vessel vasculitis; pSS, primary Sjögren's syndrome; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.

Balog L Novel and potential future therapeutic options in systemic autoimmune diseases. Front. Immunol. doi: 10.3389/fimmu.2024.1249500

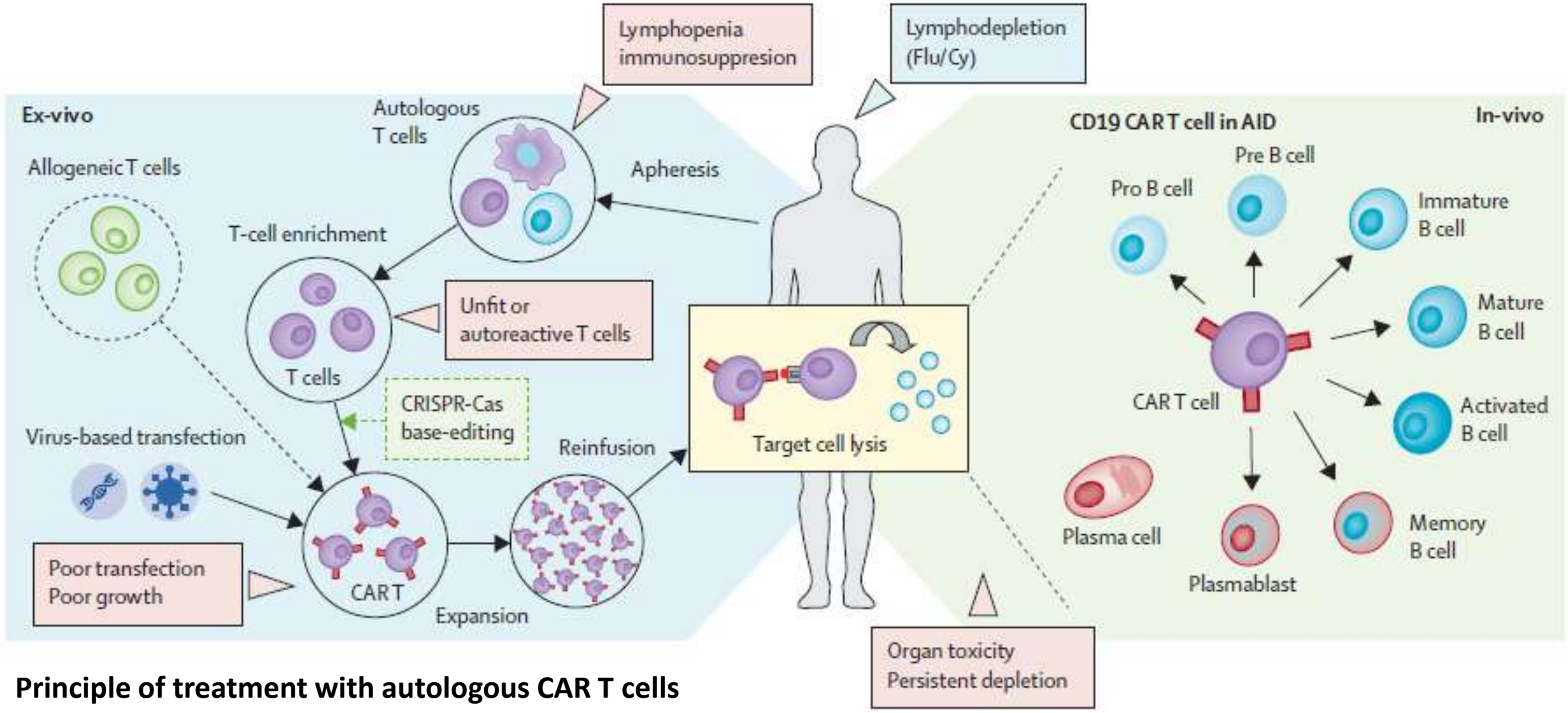
CAR T cell therapy



Schett G CAR T-cell therapy in autoimmune diseases *Lancet* https://doi.org/10.1016/ S0140-6736(23)01126-1

Autoimmune loop of triggering chronic inflammation and tissue damage

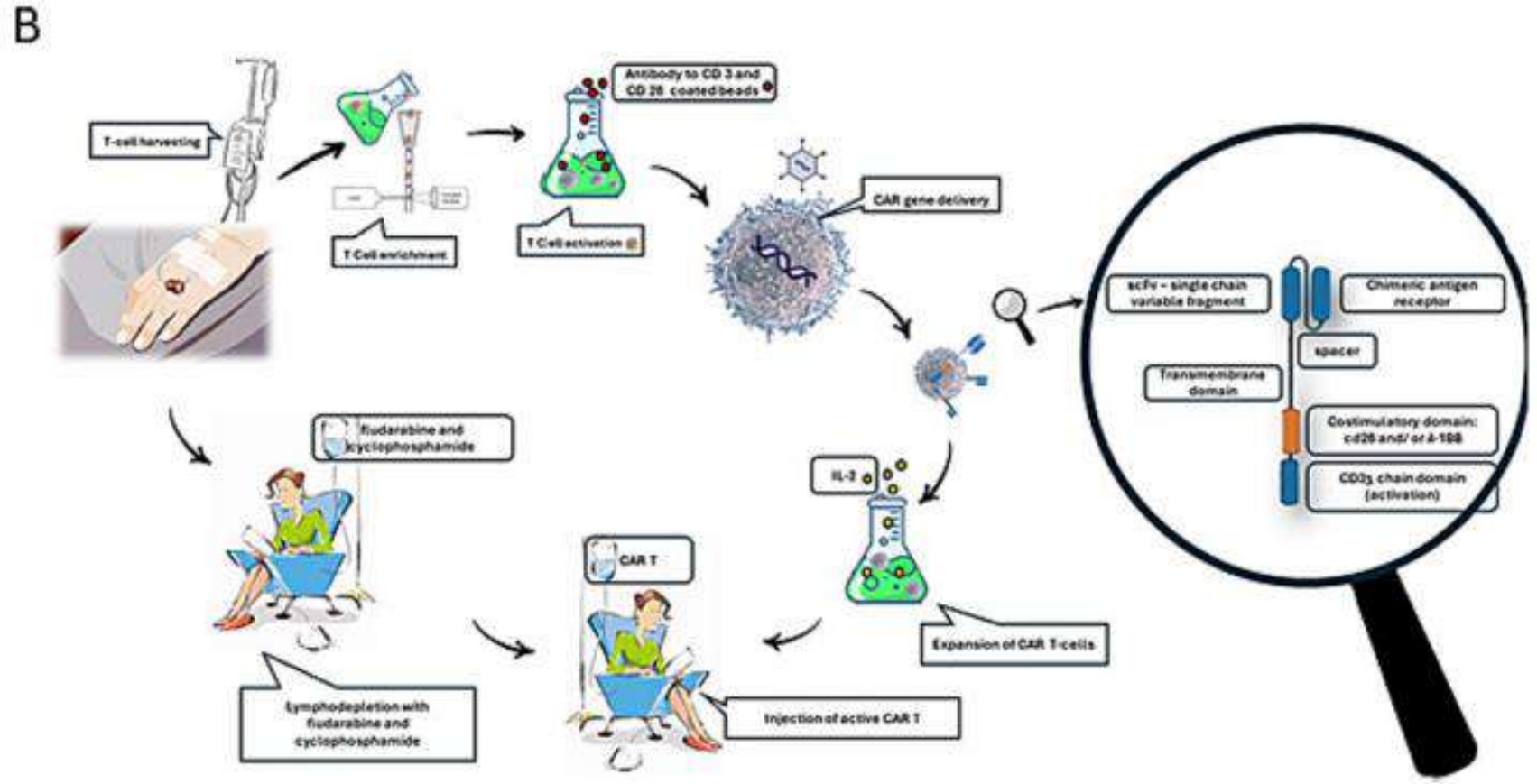
In case of sensitisation to self, an autoimmune loop starts that is characterised by auto-antigen presentation by dendritic cells, auto-reactive T-cell activation, affinity maturation of B cells, and plasmablast-mediated autoantibody production.



Principle of treatment with autologous CAR T cells

Avoid possible dysfunctions of the donor T cells (eg, chemotherapy-induced toxicity, or autoreactive clones), allogeneic off-the-shelf concepts are currently being developed

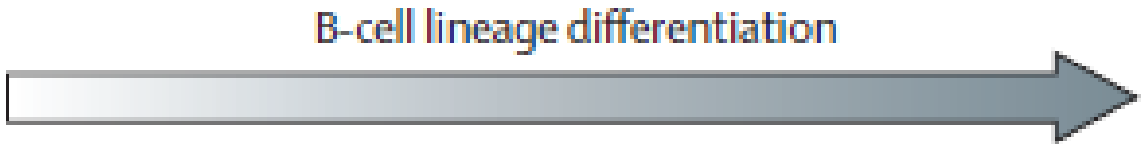
Schett G CAR T-cell therapy in autoimmune diseases *Lancet* https://doi.org/10.1016/ S0140-6736(23)01126-1



Principle of treatment with autologous CAR T cells

Lymphocytes are isolated from the peripheral blood (PB) through leukapheresis. Cell enrichment is done by density gradient separation. T-cells are activated using CD3 and CD28 coated beads. Clinically applied CD19-specific CARs are generated by the fusion of a scFv, derived from an anti-CD19 monoclonal antibody. CAR gene is then delivered to T-cells using lentiviral vector. Expansion of CAR T cells is induced by interleukin 2 (IL-2). Finally, the patient is treated with cyclophosphamide and fludarabine to achieve lymphodepletion before the activated CAR T cells are injected back to the patient.

Alsuliman T Harnessing the potential of CAR-T cell in lupus treatment: From theory to practice. Autoimmunity Reviews 23 (2024) 103687



Tumour cells antigen	Pro B cell	Prä B cell	Imm B B cell	Mature B cell	Memory B cell	Plasma blast	Plasma cell	Target
CD19								B cell
CD20								Bcell
CD22								B cell
BCMA								PC
CD38								PC
CD138								PC

Surface antigen expression of the B-cell lineage

B-cell lineage differentiation from early-stage (left) to late-stage cells (right). Expression of respective markers is indicated by the coloured rectangle. BCMA=B-cell maturation antigen. Imm=immature. PC=plasma cell

Schett G CAR T-cell therapy in autoimmune diseases *Lancet* https://doi.org/10.1016/ S0140-6736(23)01126-1

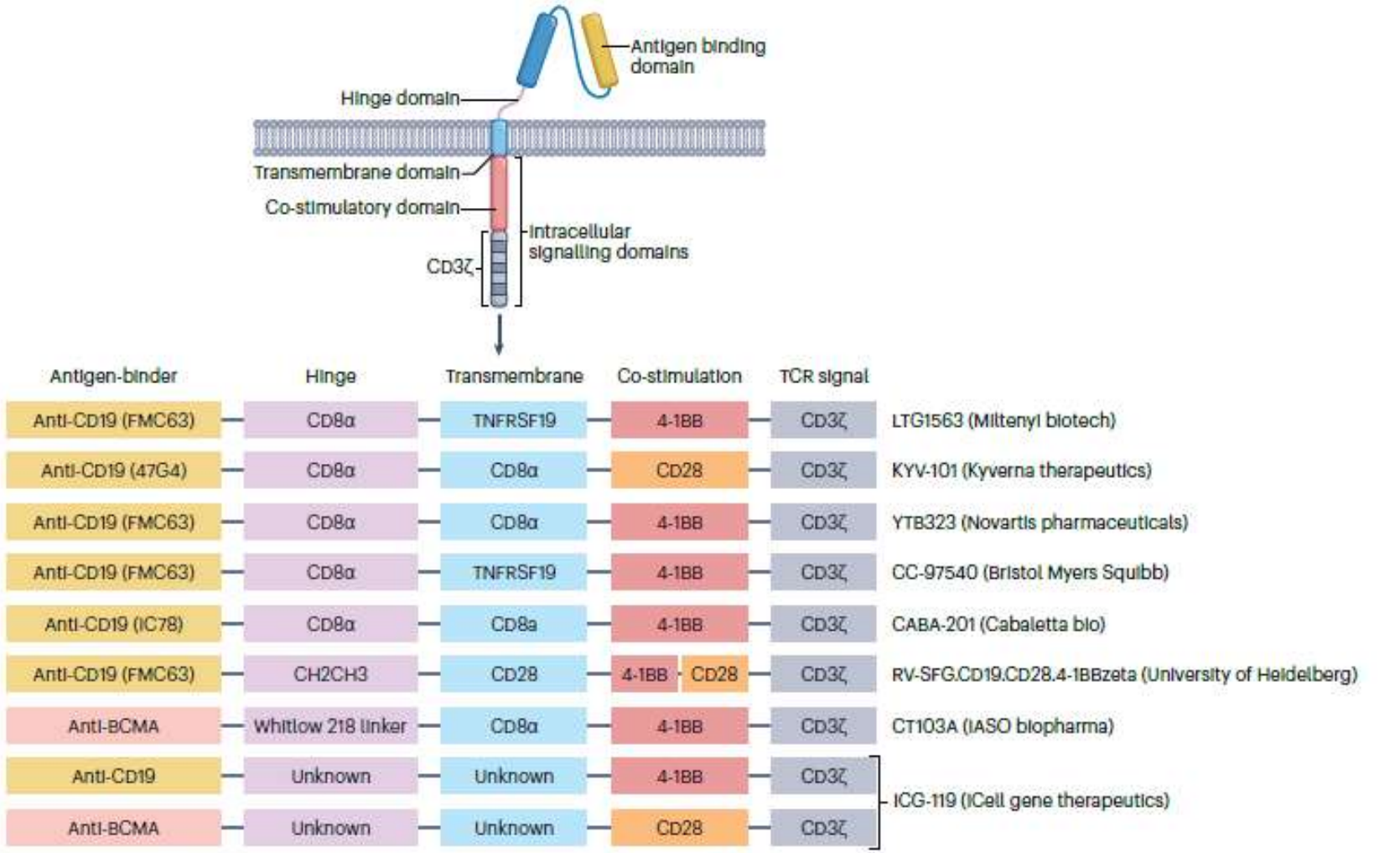
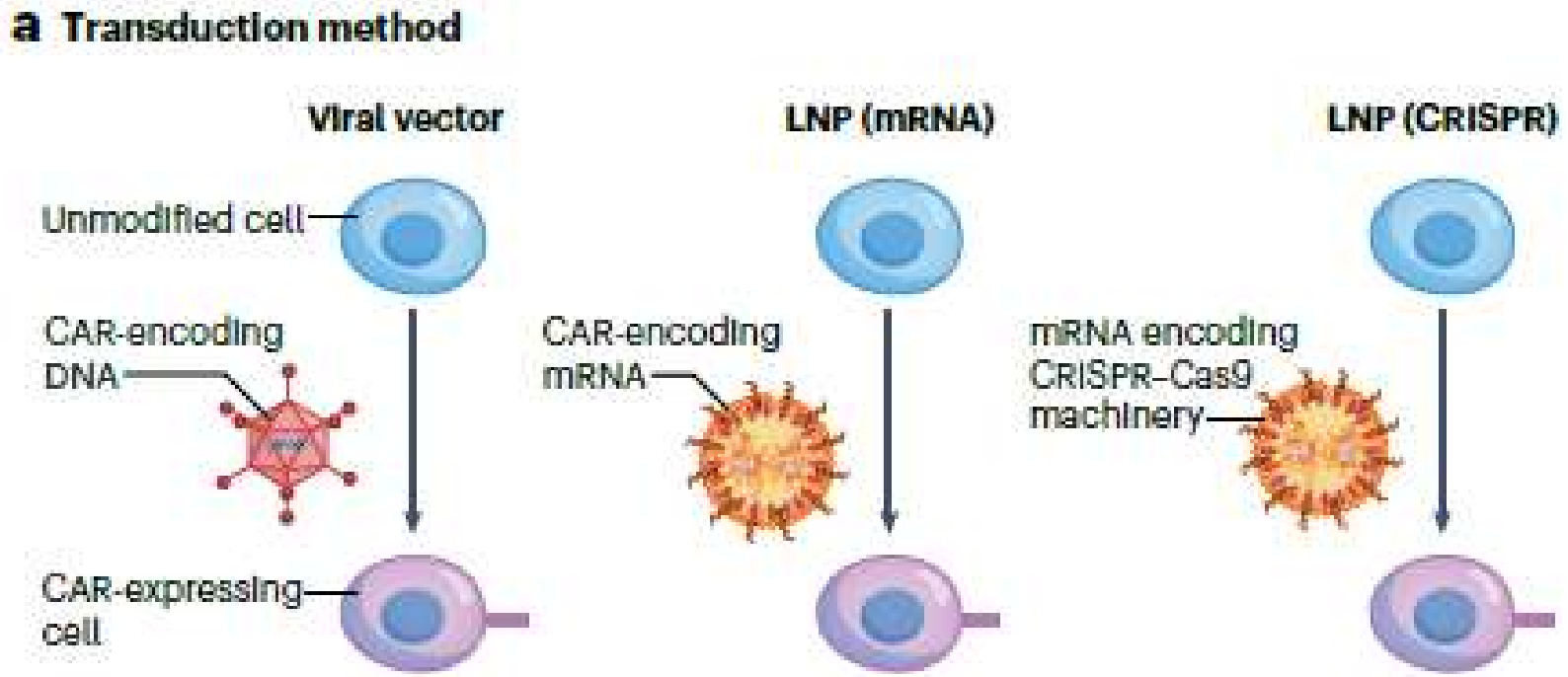


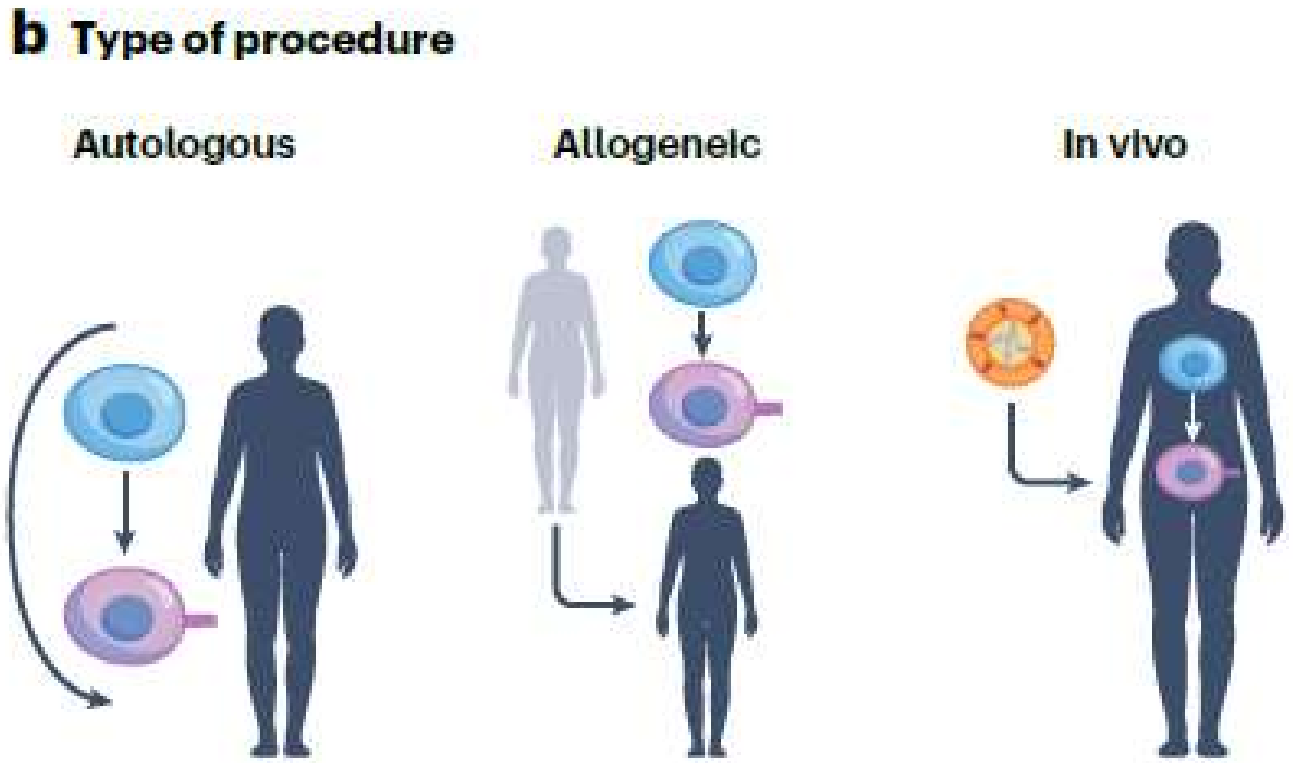
Fig. 1 | Vector constructs used for CAR T cell generation in autoimmune disease. Overview of the current lentiviral-based vector constructs used for the generation of CD19-targeted or B cell maturation antigen (BCMA)-targeted chimeric antigen receptor (CAR) T cells. CH2CH3, domain of the heavy chain of immunoglobulin G1; TCR, T cell receptor.

Schett G Advancements and challenges in CAR T cell therapy in autoimmune diseases. **nature reviews** rheumatology https://doi.org/10.1038/s41584-024-01139-z



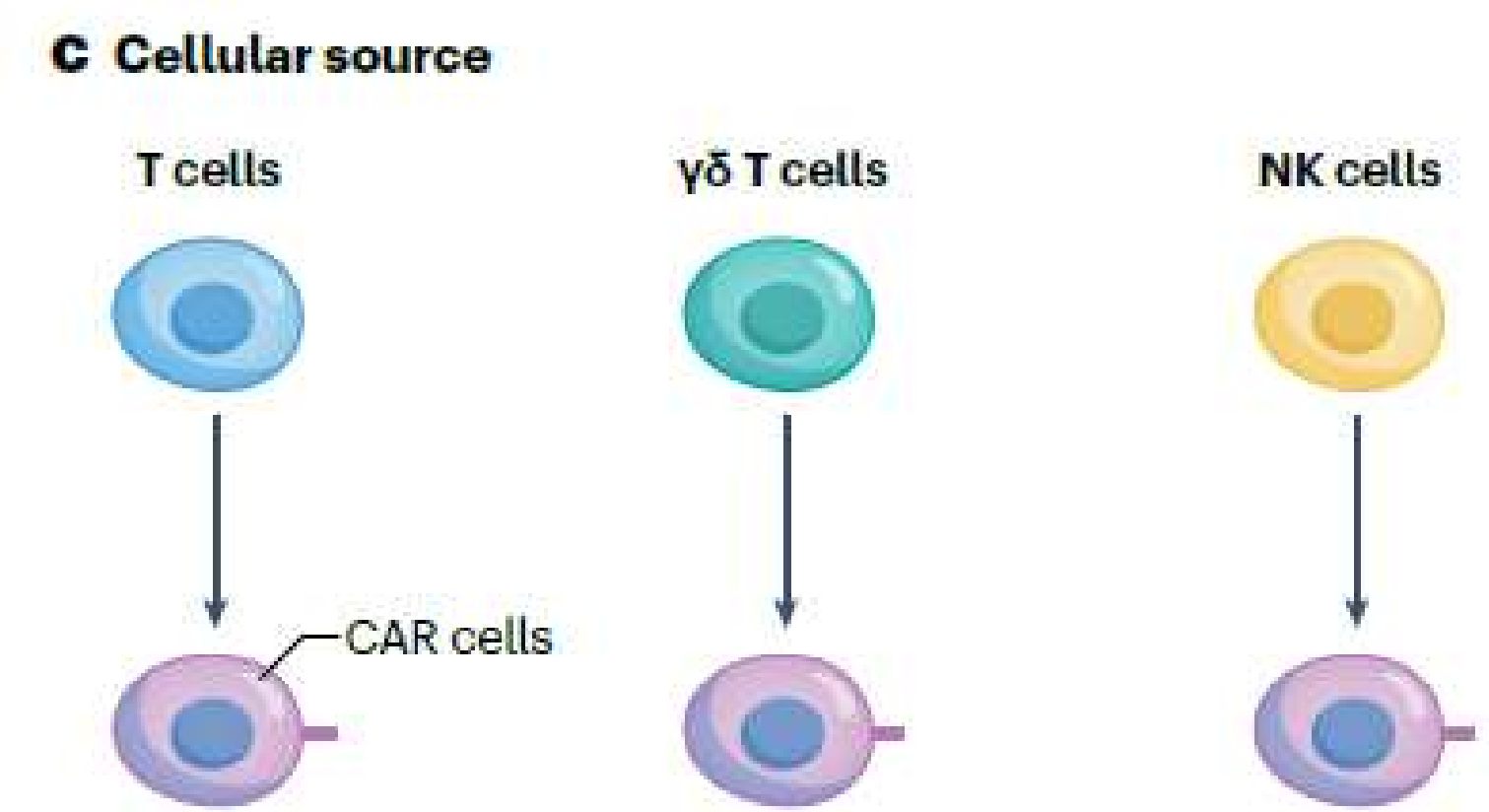
Various transduction methods are used to introduce genetic information of the CAR into activated cells, including viral vectors, lipid nanoparticles (LNPs) and gene editing by CRISPR–Cas9 (which usually also requires LNPs for cell delivery).

Schett G Advancements and challenges in CAR T cell therapy in autoimmune diseases. **nature reviews** rheumatology https://doi.org/10.1038/s41584-024-01139-z



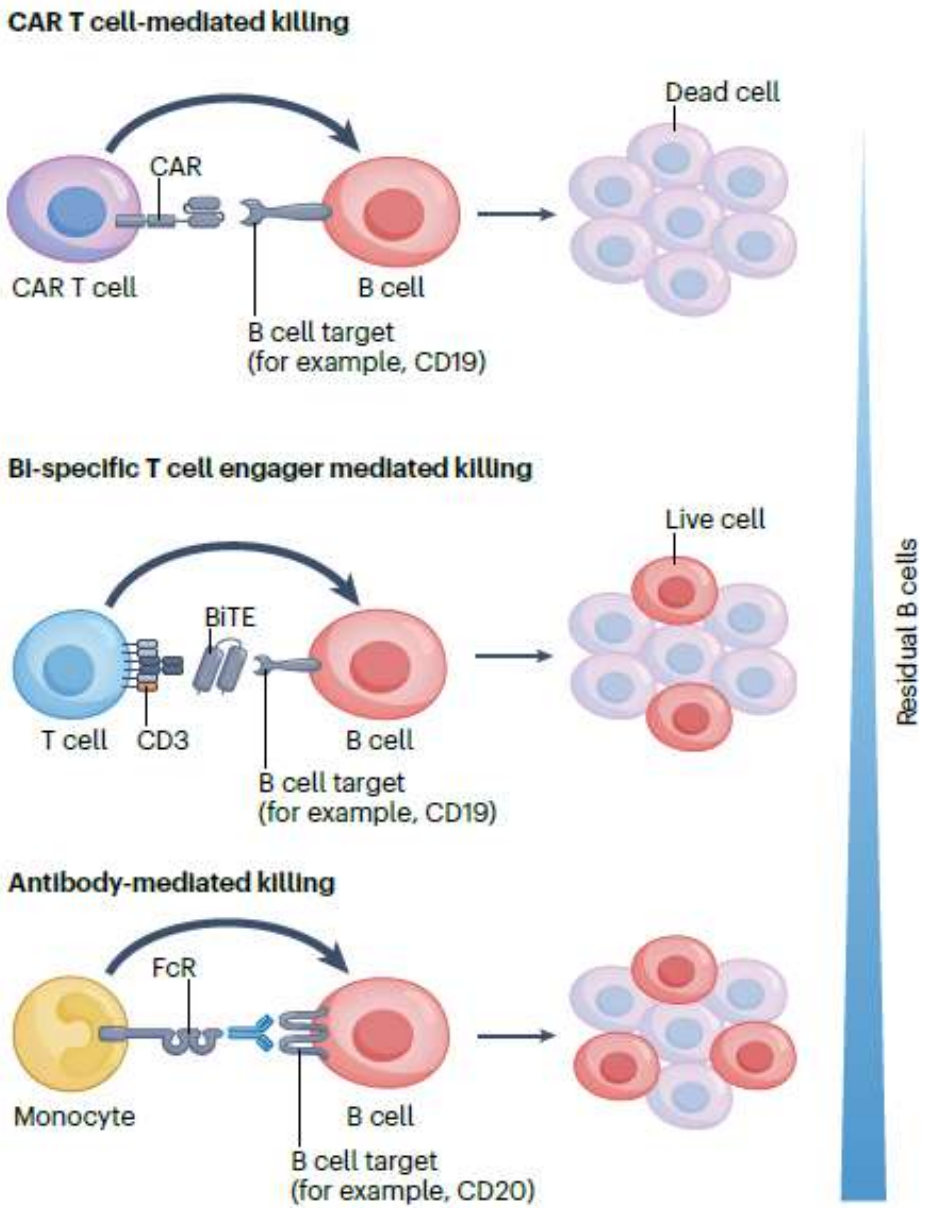
The type of procedure can also vary. Autologous and allogenic CAR T cell therapy require ex vivo transduction of cells, whereas in vivo CAR T cell therapy involves in vivo transduction of cells.

Schett G Advancements and challenges in CAR T cell therapy in autoimmune diseases. **nature reviews** rheumatology https://doi.org/10.1038/s41584-024-01139-z



Although CAR T cells are most commonly used in CAR-based strategies, other cellular sources are also under investigation, including γδ T cells and natural killer (NK) cells.

Schett G Advancements and challenges in CAR T cell therapy in autoimmune diseases. **nature reviews** rheumatology https://doi.org/10.1038/s41584-024-01139-z



Methods of therapeutic B cell depletion and functional consequences.

B cells can be depleted using different therapeutic methods that yield a variable depth of B cell depletion in the body. Therapeutic B cell depletion inhibits several key immune functions that contribute to autoimmune diseases.

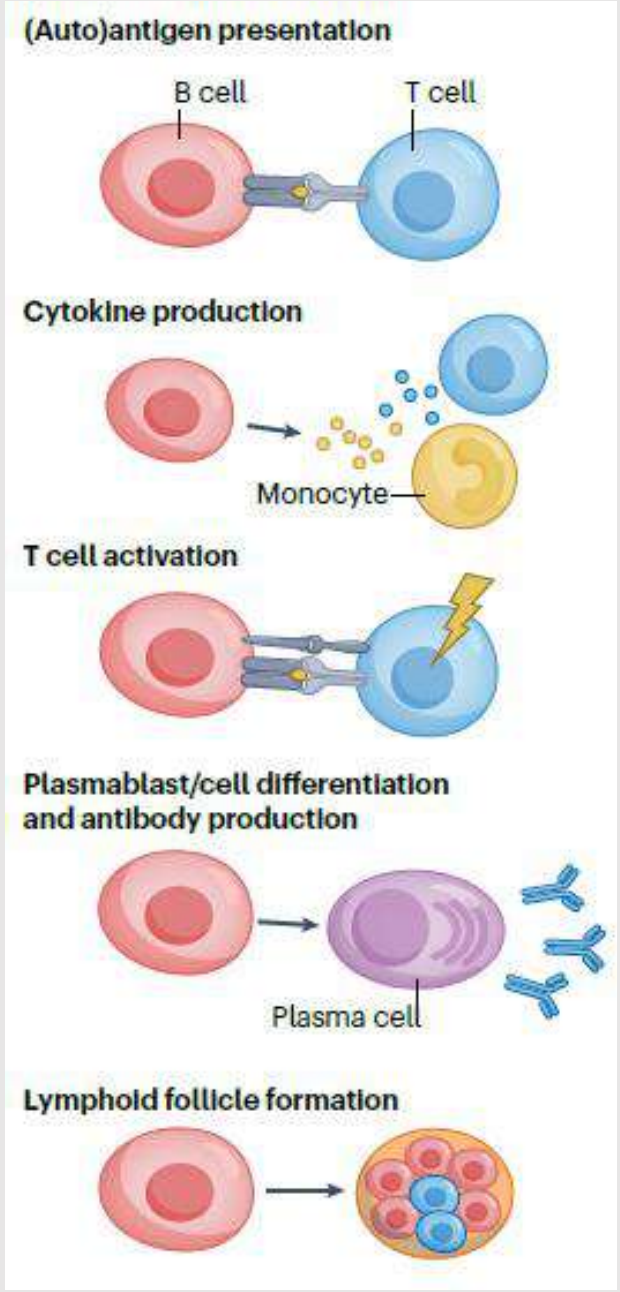
a, Chimeric antigen receptor (CAR)-expressing T cells designed to target surface molecules on B cells (for example, CD19, as shown here) are capable of effectively depleting B cells.

Bi-specific T cell engagers (BiTEs, a class of bi-specific antibodies) that target CD19 on B cells and CD3 on T cells bring both cells together and enable T cell-directed cytotoxic killing of the B cells.

Finally, antibodies against molecules expressed on B cells (such as CD20, as shown here) induce antibodydependent cellular cytotoxicity via activation of the Fc receptor.

<u>The depth of B cell depletion can vary by method, with CAR T cells achieving the most complete depletion.</u>

Schett G Advancements and challenges in CAR T cell therapy in autoimmune diseases. **nature reviews** rheumatology https://doi.org/10.1038/s41584-024-01139-z



B cell depletion can affect various B cell functions, including antigen presentation, cytokine production, T cell activation, plasmablast or plasma cell differentiation, antibody production and lymphoid follicle formation by B cells.

Schett G Advancements and challenges in CAR T cell therapy in autoimmune diseases. **nature reviews** rheumatology https://doi.org/10.1038/s41584-024-01139-z

CAR T sejtes terápia autoimmun kórképekben

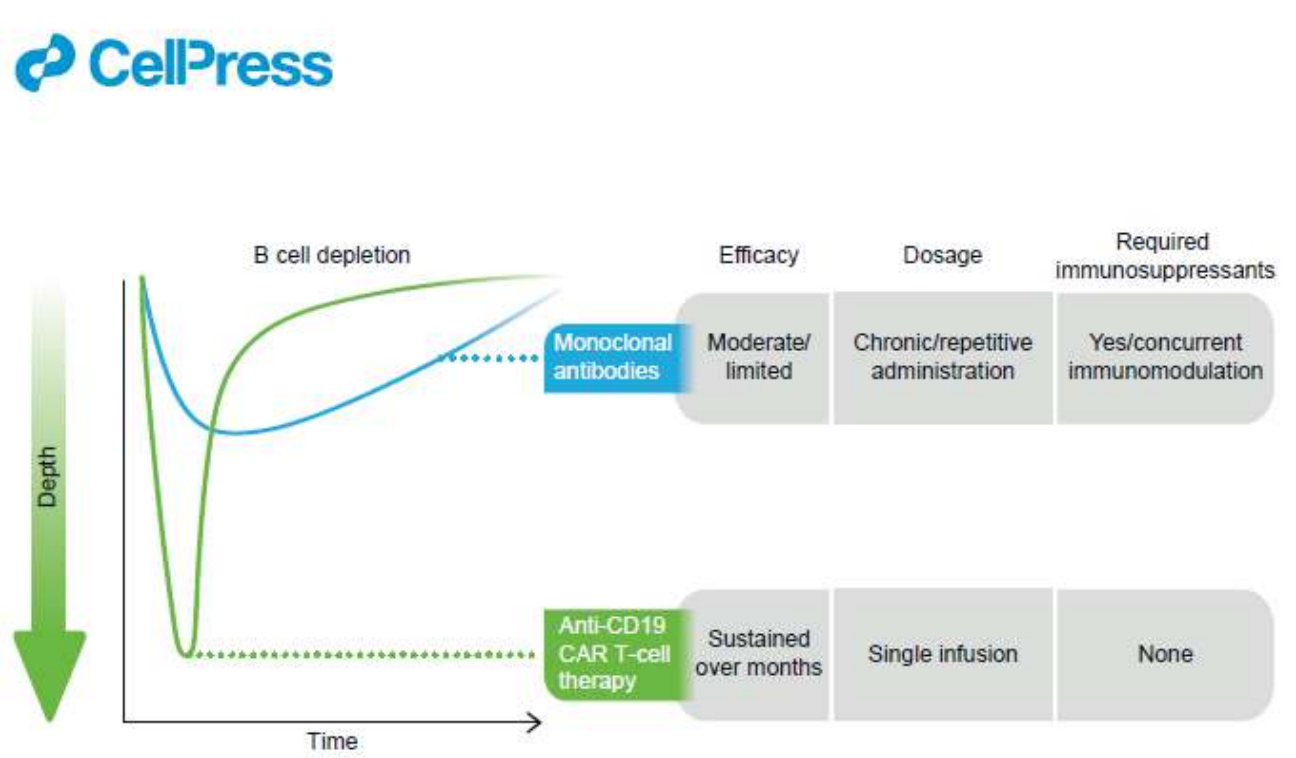
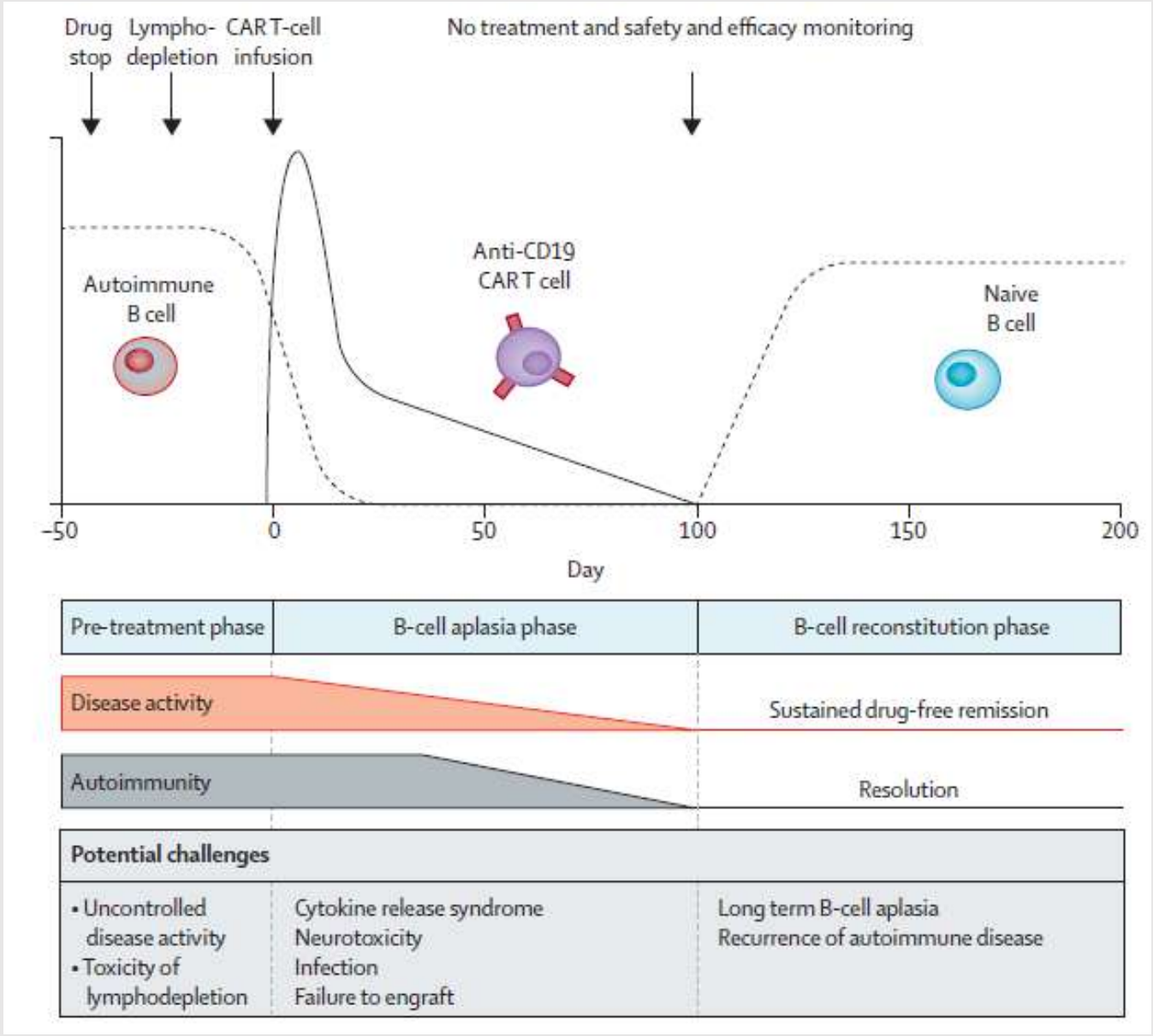


Figure 1. Compared to chronic administration of monoclonal antibodies, a single infusion of anti-CD19 CAR T cells allows for deeper and transient depletion of B cells

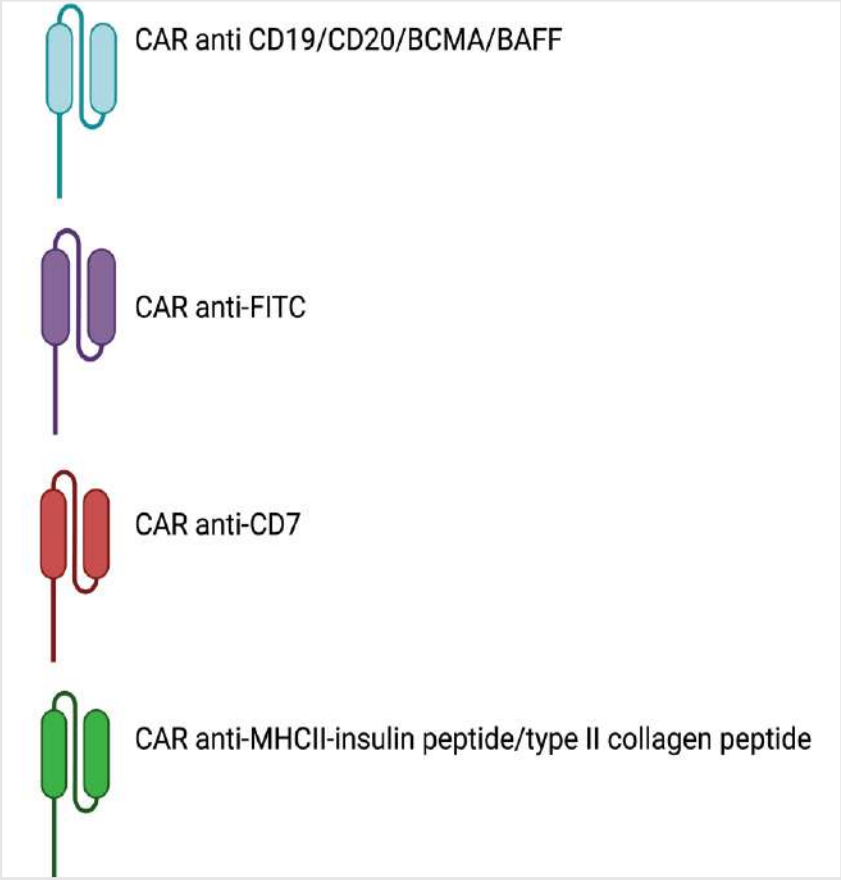
Schett G: CAR T cells in autoimmune disease: On the road to remission Cell Press https://doi.org/10.1016/j.immuni.2024.10.011



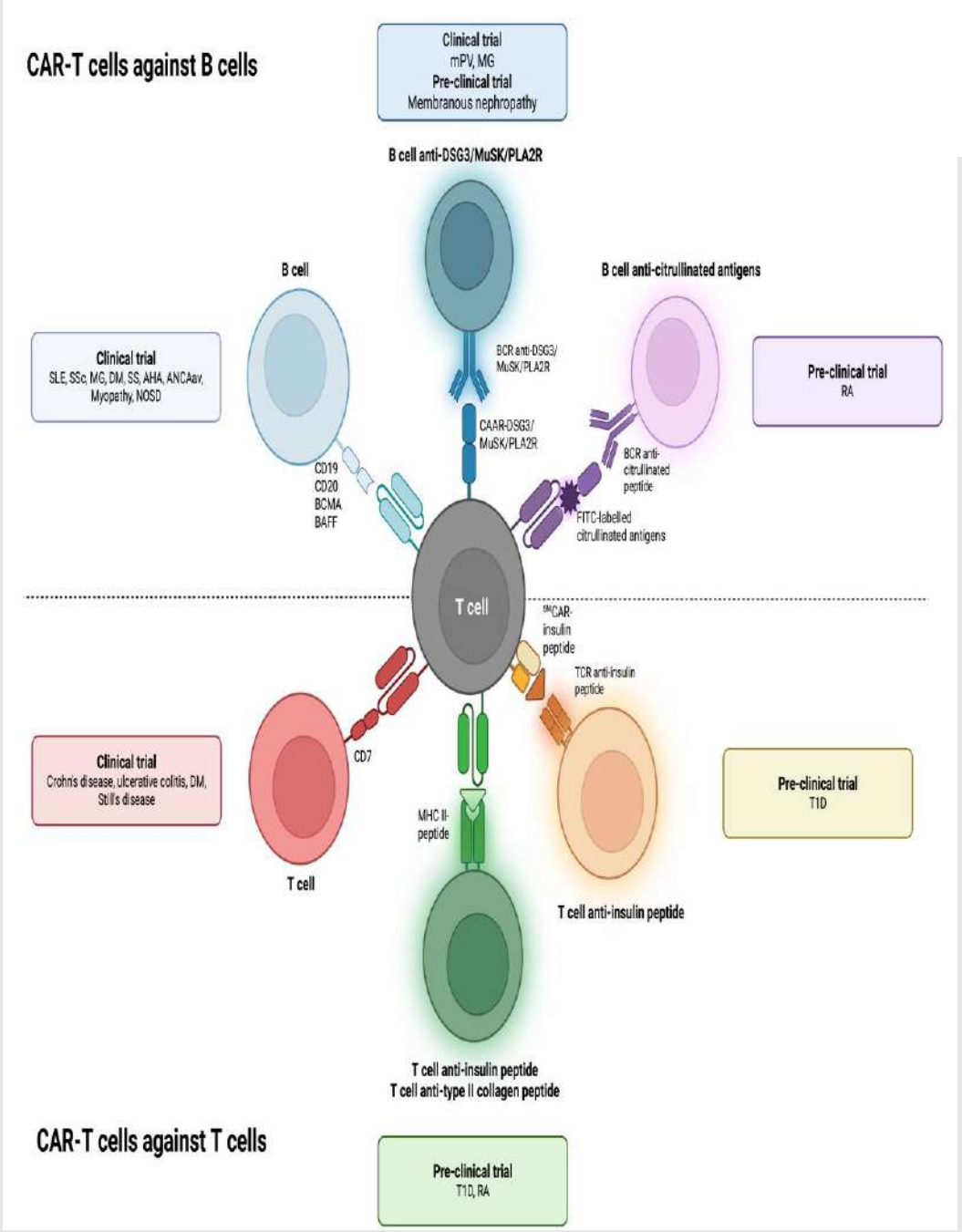
Phases and challenges of treatment with autologous CAR T cells in autoimmune diseases

Schett G CAR T-cell therapy in autoimmune diseases *Lancet* https://doi.org/10.1016/ S0140-6736(23)01126-1

CAR T cells against B cells



Cael B:CAR-T cell therapy : recent updates and challenges in autoimmune diseases. *Journal of Allergy and Clin Immun.* https://doi.org/10.1016/j.jaci.2024.12.1066



Cael B:CAR-T cell therapy : recent updates and challenges in autoimmune diseases. *Journal of Allergy and Clin Immun.* https://doi.org/10.1016/j.jaci.2024.12.1066

TABLE 2 Published clinical results for CAR T cell therapies in autoimmunity.

Institution	Target Antigen	Indication(s)	Pts #	Key Clinical Results	Reference
Ruhr-University Bochum	CD19	Myasthenia Gravis, Lambert Eaton Myasthenic Syndrome	2	Full mobility restored at 4- and 6-months post-CAR T	(57)
Otto-von-Guericke University	CD19	Myasthenia Gravis	1	Restoration of mobility at 62 days post-CAR T	(58)
Friedrich-Alexander University	CD19	Antisynthetase syndrome	1	Drug-free remission at 150 days follow up post-infusion	(59)
University Medical Center Hamburg-Eppendorf	CD19	Multiple Sclerosis	2	EDSS score decreased from 4.5 to 4 at 100 days follow up (n=1) or remained stable at day 28 follow up (n=1)	(60)
Friedrich-Alexander University	CD19	SLE	5	Drug-free remission maintained to median 12 month follow up in all patients	(61)
	CD19	SLE	8 (follow-up study)	100% of patients reached complete remission, with disease activity absent up to 29 months post-CAR T	(62)
	CD19	Idiopathic inflammatory myositis	3	Normalized muscular function	(62)
	CD19	Systemic Sclerosis	4	EUSTAR activity index decreased at 6 months post CAR T	(62)
	CD19	Systemic Sclerosis	1	Reduced disease activity indicated by EUSTAR activity index maintained through 6 month follow up	(63)
University Hospital Tübingen	CD19	Anti-synthetase Syndrome	1	Significant decrease in physician's global assessment of disease activity at 150 days follow up.	(64)
Shanghai Jiao Tong University	CD19	Sjogren's Syndrome with concurrent diffuse large B-cell lymphoma	1	Normal levels of ANA, anti-Ro-52, and cytokines and the improvement of dry mouth symptoms, without the use of glucocorticoids or tocilizumab	(65)
Shanghai Changzheng Hospital	CD19 (allogeneic)	Myositis and systemic sclerosis	3	Complete remission at 6 months follow-up in 3/3 pts	(66)
Huazhong University of Science and Technology	BCMA	Anti-SRP necrotizing myopathy	1	Disease improvement maintained at 18 months	(67)
	BCMA	Neuromyelitis optica spectrum disorder	12	92% drug-free remission with 11/12 patients relapse-free at median follow-up of 5.5 months	(68)
Zhongshan City People's Hospital	BCMA-CD19	SLE + lupus nephritis	13	Symptom and medication-free remission maintained at 46 months for 10/10 evaluable patients	(69)

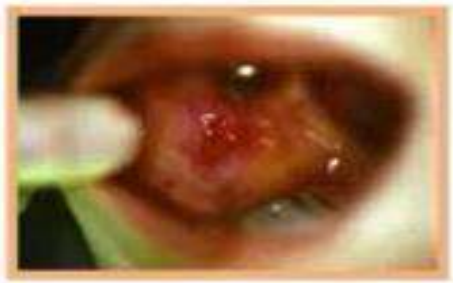
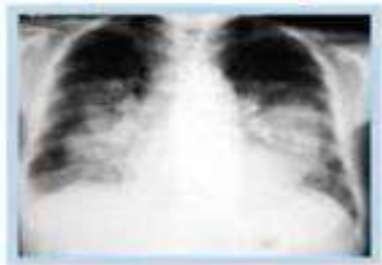
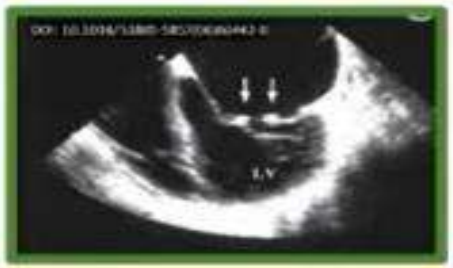
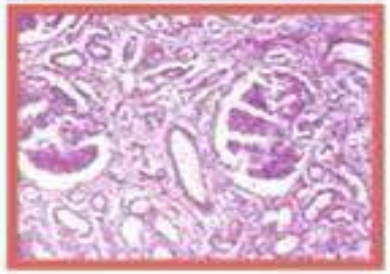
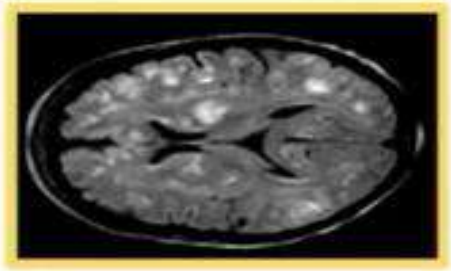
EDSS, expanded disability status scale; EUSTAR, European scleroderma trials and research group. Pts #, number of patients reported.

Bulliard Y: From promise to practice: CAR T and Treg cell therapies in autoimmunity and other immune-mediated diseases. Front. Immunol.doi: 10.3389/fimmu.2024.1509956

Rationale for using CD19 CAR T cells for the treatment of autoimmune diseases – 1 –

Disease model: SLE

- severe autoimmune disease characterized by formation of autoantibodies & immune complex-mediated inflammation & organ damage
- auto-reactive B-cells play a key role in the pathogenesis of SLE
- limited efficacy of B-cell depleting mAbs due to persistence of autoreactive B cells in lymphatic organs & inflamed tissues

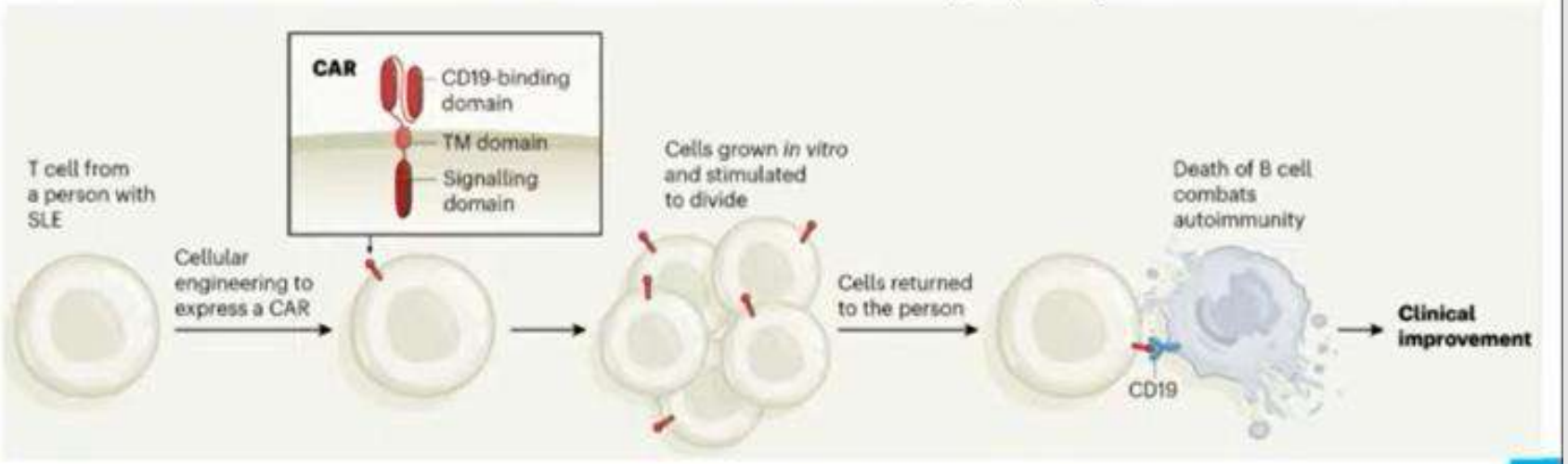
FAU Friedrich-Alexander Universität Erlangen-Nürnberg

Universitätsklinikum Erlangen

[CAR T cells in autoimmune diseases (Georg Schett | Andreas Mackensen)]

Rationale for using CD19 CAR T cells for the treatment of autoimmune diseases – 2 –

- CAR T cells may be more potently depleting target cells than monoclonal antibodies due to better tissue penetration
- Preclinical data showed that CD19 CAR T-cells were capable of reversing SLE manifestations in two murine SLE models *(R. Kansal et al. Sci Transl Med. 2019;11(482))*

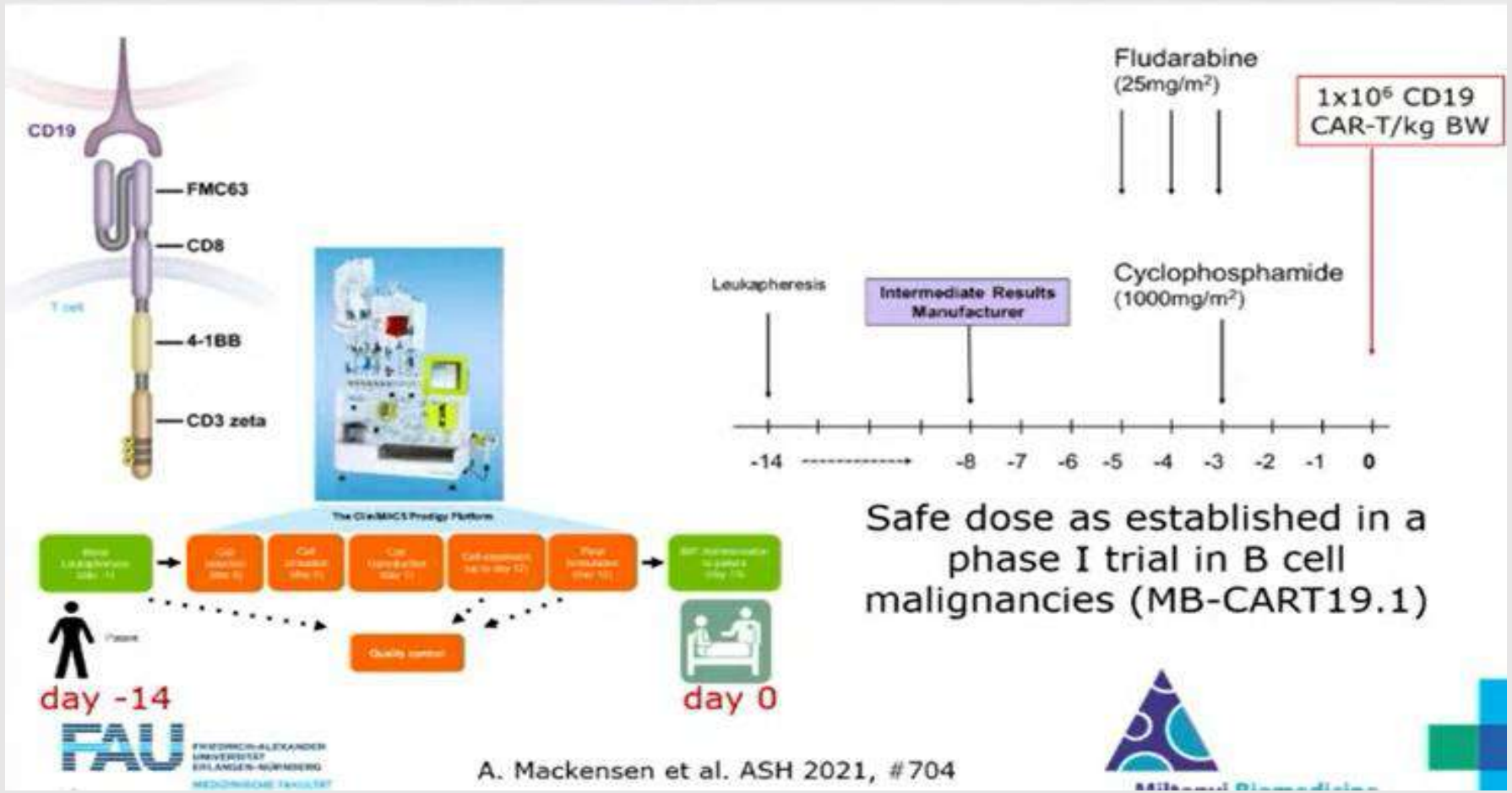


From Tsokos GC., Nature. 2022 Nov;611(7936):456-458.

Universitätsklinikum Erlangen

CAR T cells in autoimmune diseases (Georg Schett | Andreas Mackensen)

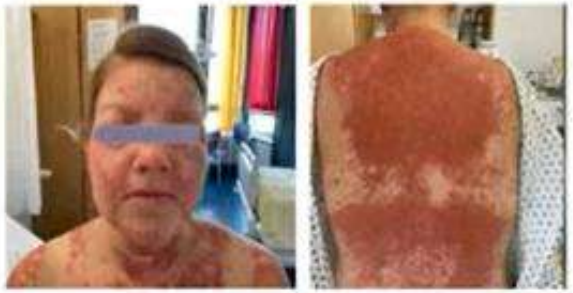
CD19-Targeted CAR T Cells in Refractory Autoimmune Disease - *Intervention schedule*



CAR T cells in autoimmune diseases (Georg Schett | Andreas Mackensen)

B-cell mediated autoimmune diseases treated with CD19 CAR-T cells

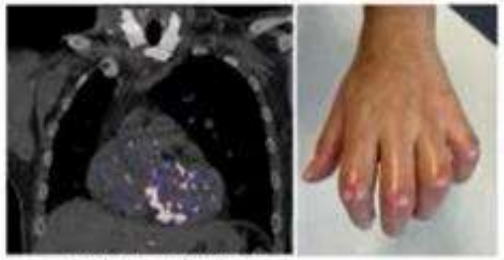
Systemic Lupus Erythematosus (SLE)



Kidney, Skin, Lung, Heart, Brain

Mougiakakos et al. NEJM, 2021
Mackensen et al. Nat Med. 2022

Systemic Sclerosis (SSc)

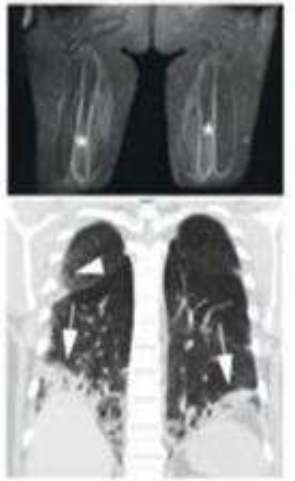


SUVmax septobasal: 8.6

Skin, Lung, Heart, Kidney

Bergmann et al. Annals Rheum. Dis. 2023

Idiopathic Inflammatory myositis (IIM)



Skeletal Muscle, Lung, Heart

Müller et al. Lancet 2023

We report on:

✓ the first 15 patients with longer follow-up

✓ growing understanding of B-cell biology post CD19 CAR-T

FAU Friedrich-Alexander Universität Erlangen-Nürnberg

Universitätsklinikum Erlangen

[CAR T cells in autoimmune diseases (Georg Schett | Andreas Mackensen)]

Patient characteristics at baseline

- n= 15 patients
- Disease type: 8x SLE, 3x IIM, 4x SSc
- Median age (y): 36 (18-60)
- Median disease duration: 4 years (1-20)
- Median previous treatments: 5 (2-14)
- Median follow-up (mo): 15 months (4-29)
- Auto-antibodies present: 15/15
- Organ involvement: (at least 2) 13 skin, 11 lung, 9 kidney, 9 joints, 4 heart, 3 muscle

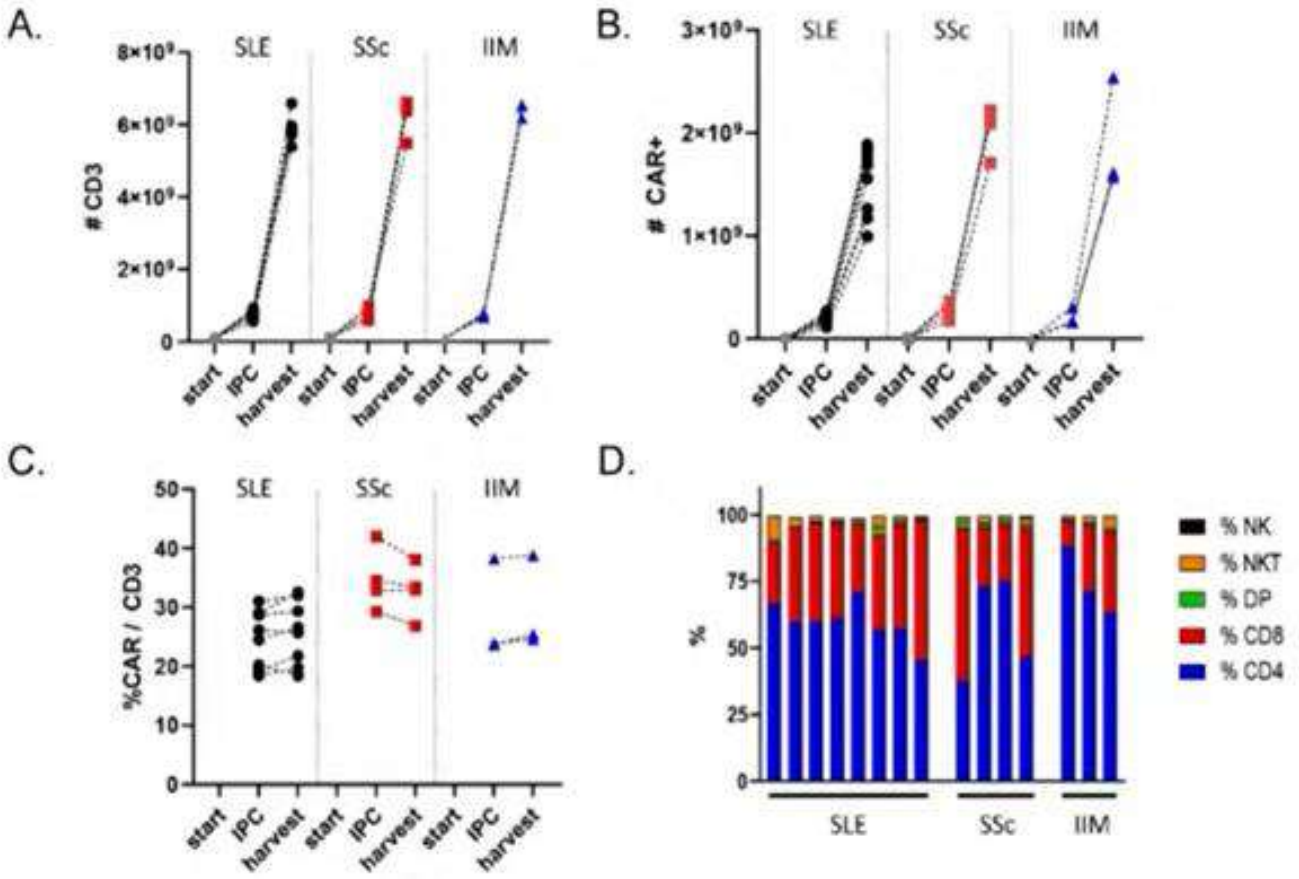
Heavily pretreated, active & progressive disease at time of indication

FAU Friedrich-Alexander Universität Erlangen-Nürnberg

Universitätsklinikum Erlangen

CAR T cells in autoimmune diseases (Georg Schett | Andreas Mackensen)

Successful generation of CD19 CAR T Cells from patients with advanced autoimmune disease

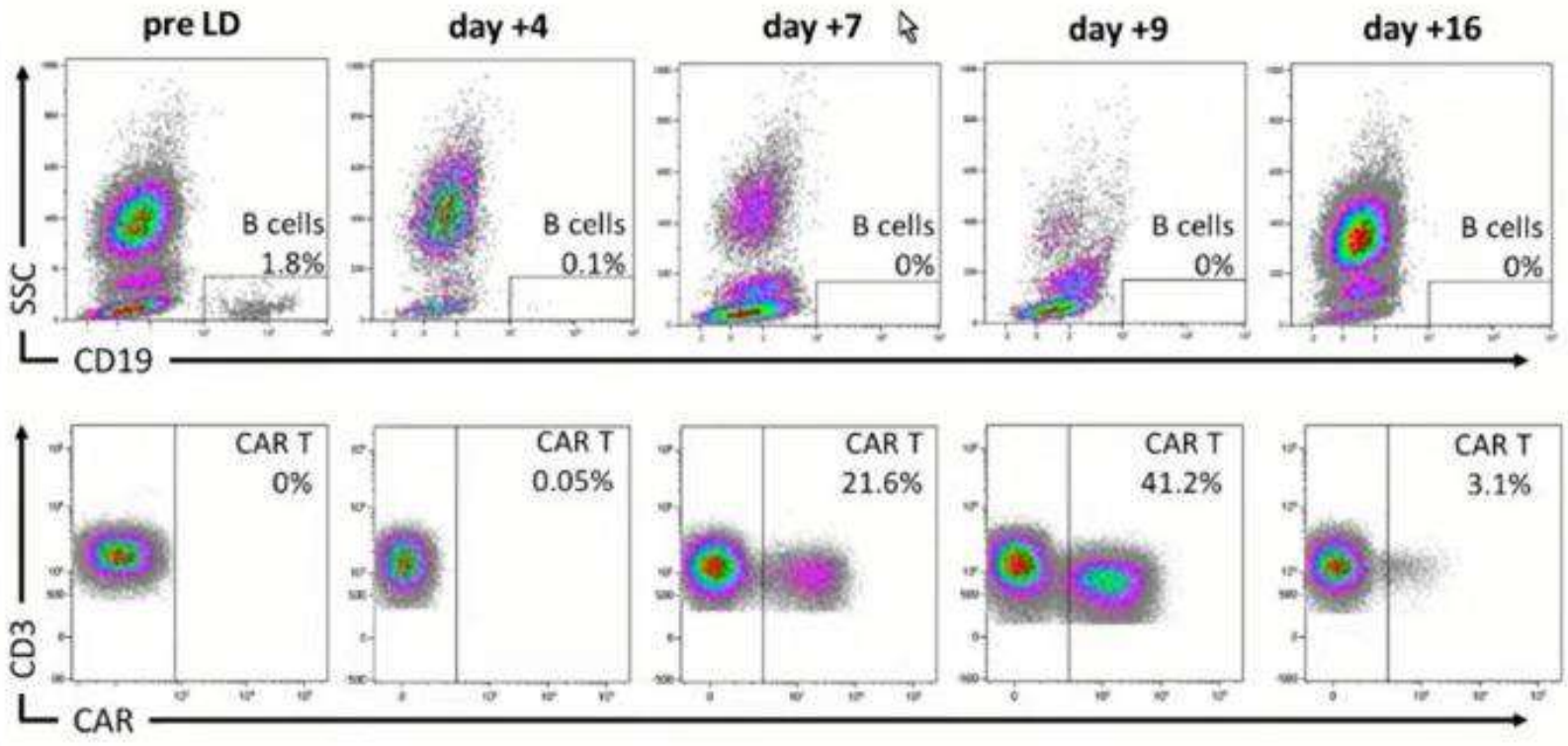


F. Müller et al. N Engl J Med. 2024 Feb 22;390(8):687-700.

Universitätsklinikum Erlangen

CAR T cells in autoimmune diseases (Georg Schett | Andreas Mackensen)

Circulating CD19 CAR T cell expansion and B-Cell depletion after CAR T-cell infusion *(Pat. 02)*



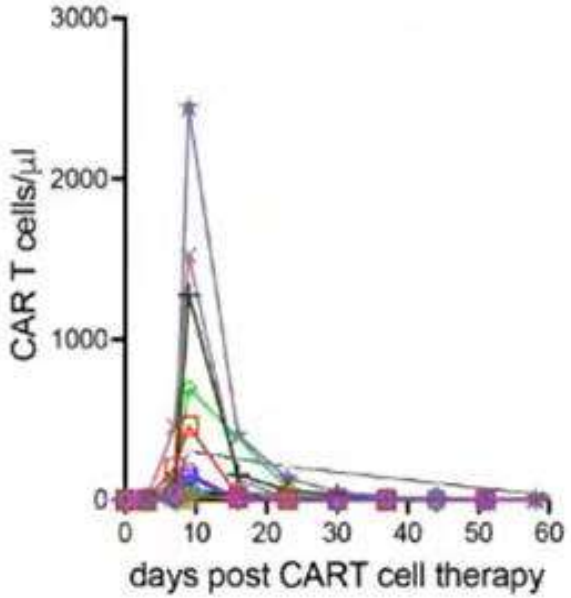
FAU Friedrich-Alexander Universität Erlangen-Nürnberg Medizinische Fakultät

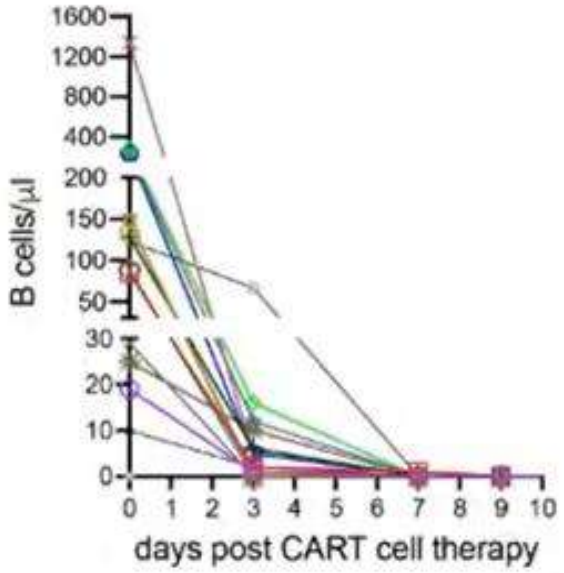
Universitätsklinikum Erlangen

14

[CAR T cells in autoimmune diseases (Georg Schett | Andreas Mackensen)]

Expansion of CAR T cells preceded complete depletion of circulating B cells





- CAR-T cells expand as expected reaching their peak at day 9
- Height of the peak is comparable to those in malignant disease
- Complete and sustained depletion of circulating B cells

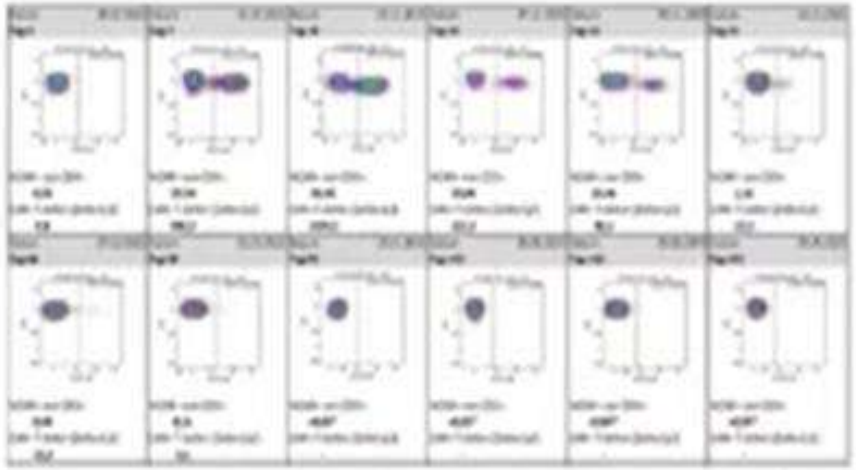
FAU

Universitätsklinikum Erlangen

[CAR T cells in autoimmune diseases (Georg Schett | Andreas Mackensen)]

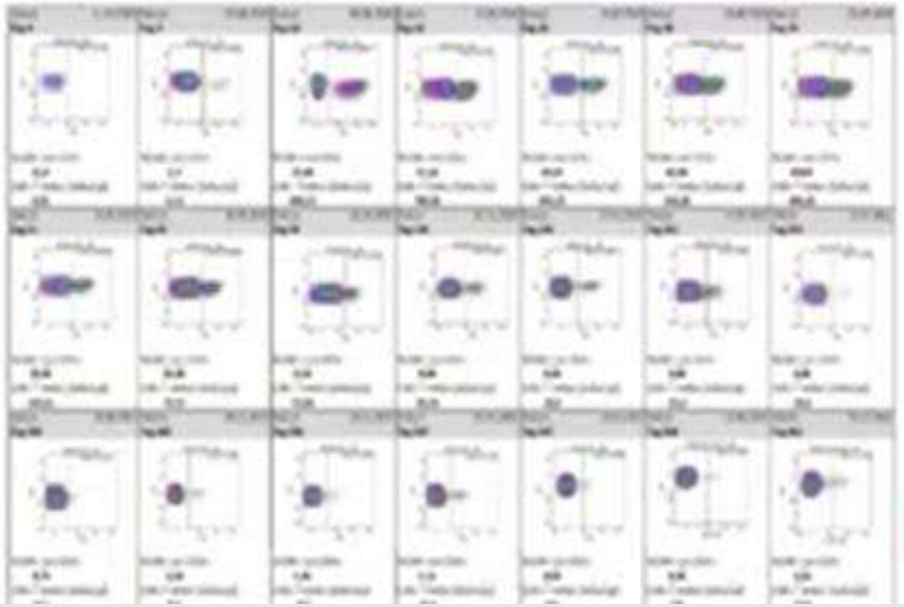
CAR-T cell expansion/persistance (AID vs. Lymphoma)

Autoimmune disease (SLE)



56. napra a CAR-T eltűnik

Lymphoma (DLBCL)



860. Napon (>2év) érdemi CAR-T jelenlét

FAU

16

CAR T cells in autoimmune diseases (Georg Schett | Andreas Mackensen)

The start in 2021

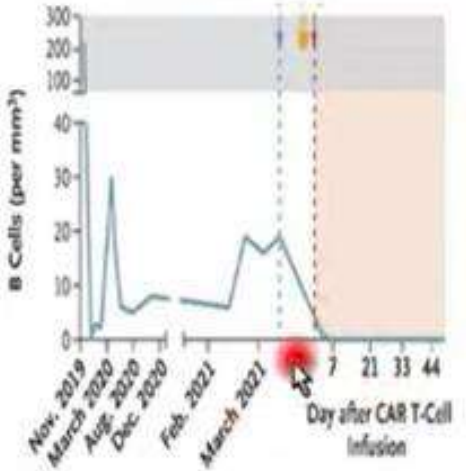
Nephritis, Pleurisy, Endocarditis, Arthritis, Fatigue, Rash

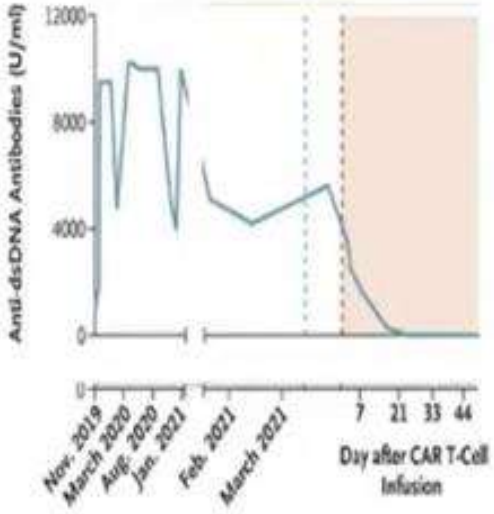
Hydroxychloroquin,myco-phenolate, tacrolimus, cyclophosphamid, beli-mumab, rituximab

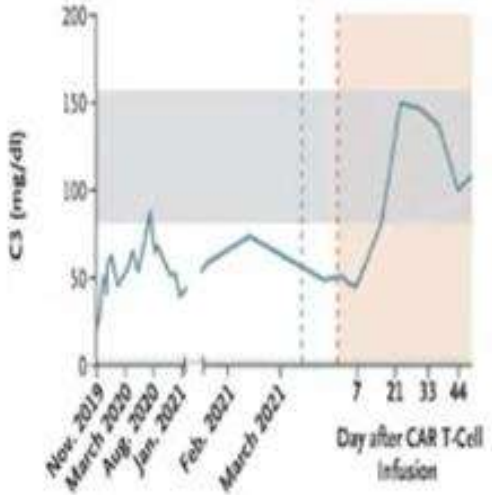
Anti-dsDNA antibodies: 8000-12000 units/ml (normal < 4U/mL); Proteinuria 4-6 g/day (normal <0.15 g/day)

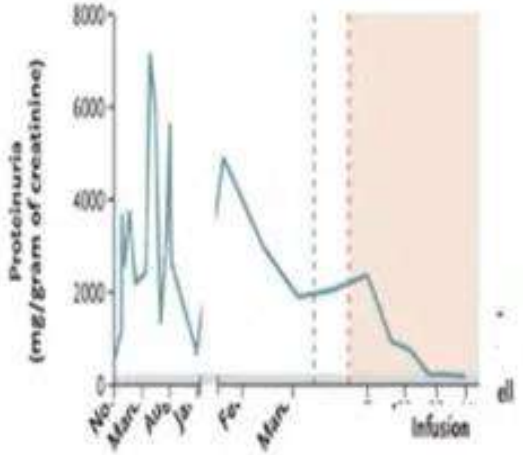
Mougiakakos D et al., N Engl J Med 2021, Mackensen A et al., Nat Med 20222

SLE resolved...









Rapid loss of circulating B cells after CAR T cell exposure

Fast decrease of anti-dsDNA antibodies and sero**conversion later on**

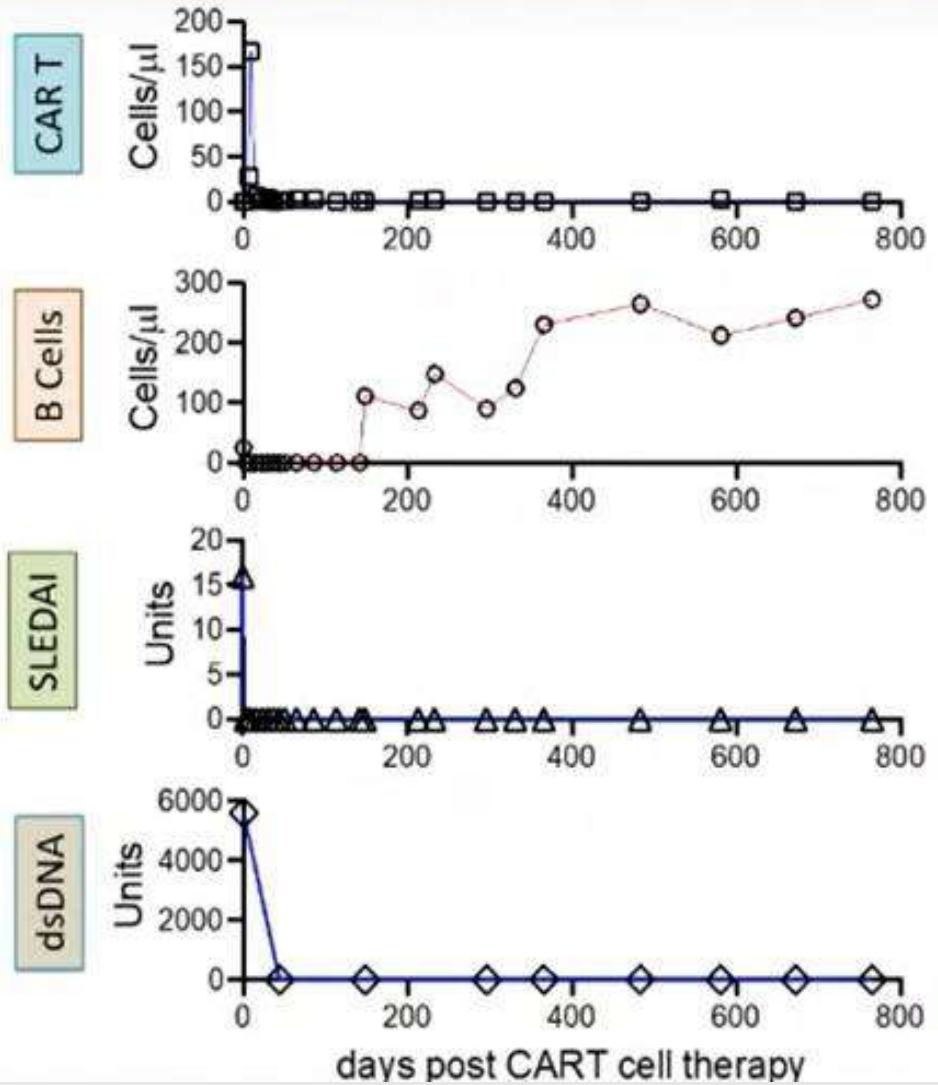
Normalization of complement factor C3 and C4 levels

Regression of proteinuria and complete resolution after 30 days

[CAR T cells in autoimmune diseases (Georg Schett | Andreas Mackensen)]

...and did not come back

3 years healthy
No Treatment, No Signs
of Autoimmunity
Normal Life



[CAR T cells in autoimmune diseases (Georg Schett | Andreas Mackensen)]

Short-Term Efficacy of CD19 CAR T cell therapy in autoimmune disease

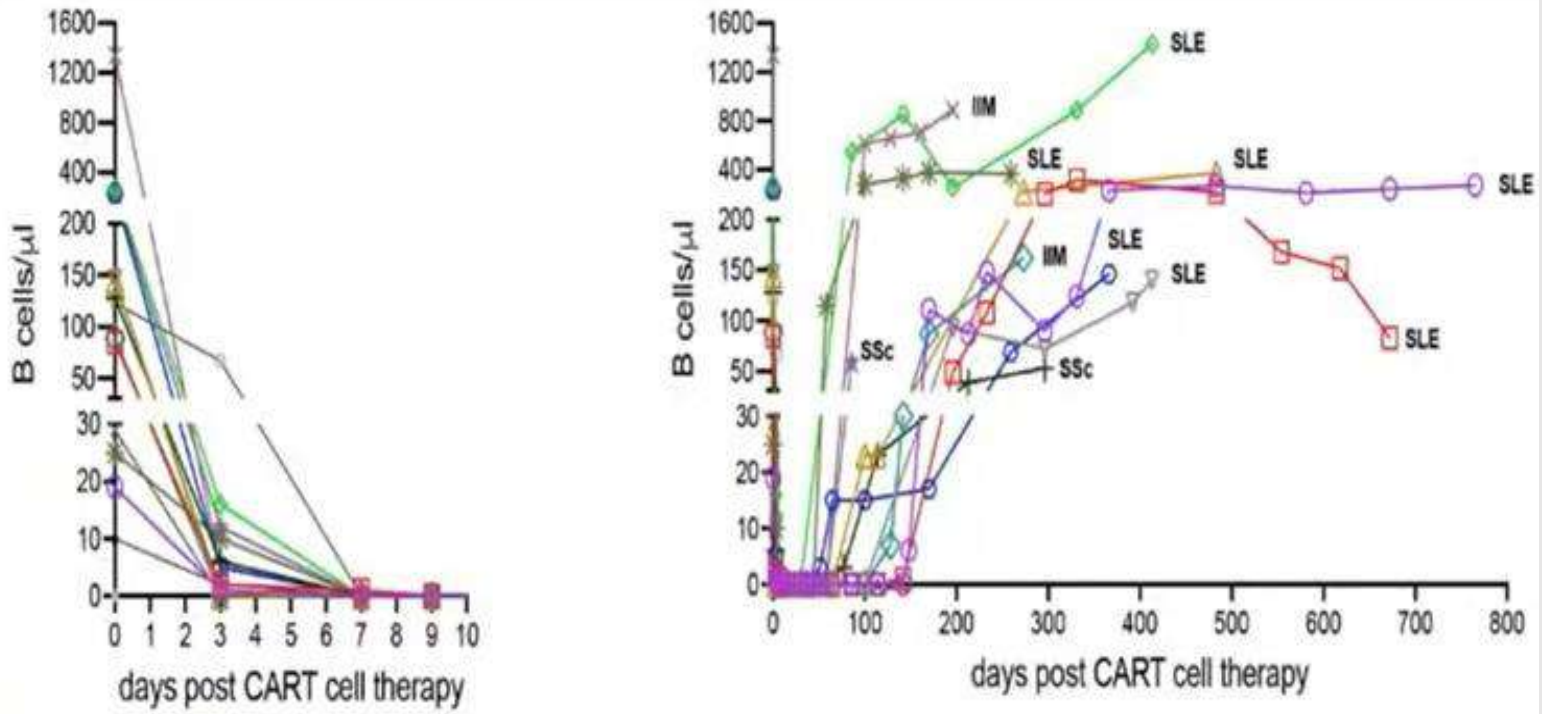
Patient #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Disease	SLE	SLE	SLE	SLE	SLE	SLE	SLE	SLE	IIM	IIM	IIM	SSc	SSc	SSc	SSc
DORIS Remission	+	+	+	+	+	+	+	+*	n/a	n/a	n/a	n/a	n/a	n/a	n/a
LLDAS	+	+	+	+	+	+	+	+*	n/a	n/a	n/a	n/a	n/a	n/a	n/a
SLEDAI	0	0	0	0	0	0	0	0	n/a	n/a	n/a	n/a	n/a	n/a	n/a
ACR/EULAR Major improvement	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	+	+	+*	n/a	n/a	n/a	n/a
CK Normalization	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	+	+	+*	n/a	n/a	n/a	n/a
EUSTAR AI Improvement	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	-3,6	-4.3	-4.3	#
mRSS Improvement	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	-7	-9	-11	#
Glucocorticoid-free state	+	+	+	+	+	+	+	+*	+	+	+*	+	+	+	+**
No Immunosuppressive Drugs	+	+	+	+	+	+	+	+*	+	+	+*	+	+	+	+**

DORIS, Definition Of Remission In SLE; EUSTAR-AI, European Scleroderma Trials and Research Group Activity Index; IIM, idiopathic inflammatory myopathy; LLDAS, Lupus Low Disease Activity State ; mRSS, modified Rodnan skin score; SLE, systemic lupus erythematosus; SLEDAI, SLE Disease Activity Index; SSc, systemic sclerosis; * based on 3 months data**based on 2 months data; # short observation <3 months;

SSc: bőr, ILD

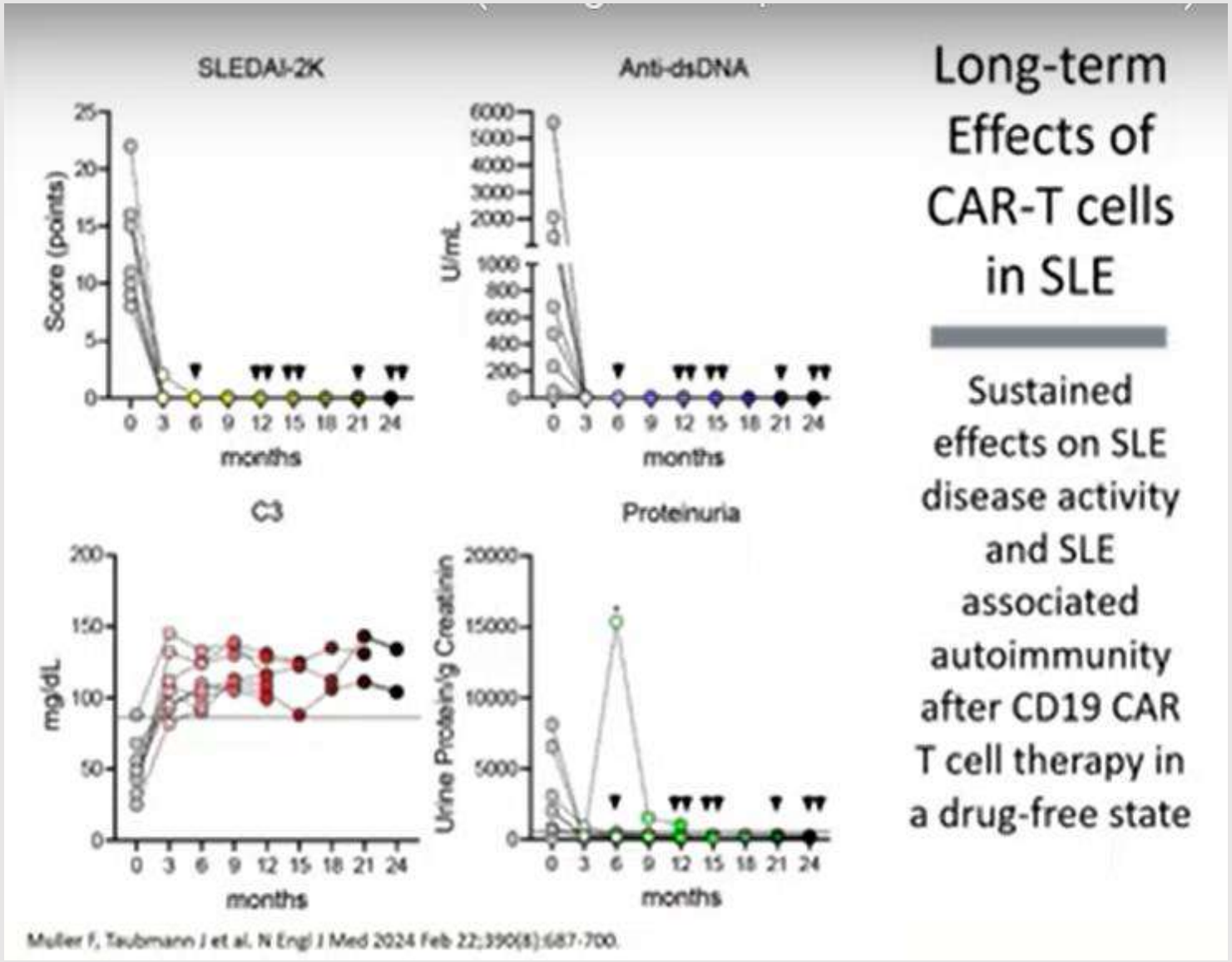
[CAR T cells in autoimmune diseases (Georg Schett | Andreas Mackensen)]

B cell recovery after CAR T cell therapy

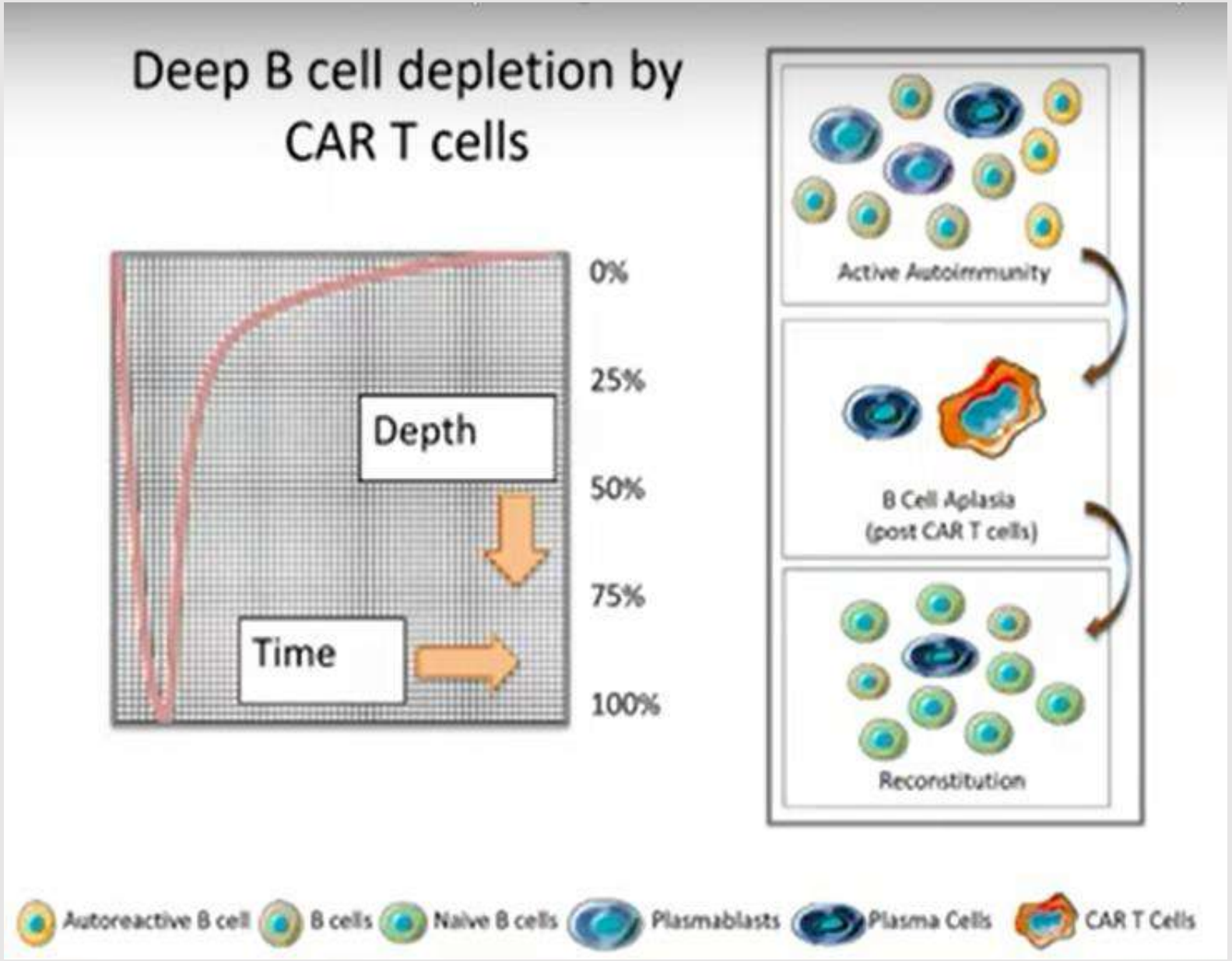


Data of 15 patients with autoimmune disease (8 SLE, 3 IIM, 4 SSc) treated with CD19 CAR T cells. B cell counts are shown in Y axis. X axis shows the days after CAR T cell therapy (0-800). Left graph shows the short time effects in the first 10 days with fast depletion of B cells. B cell recur between 50 and 150 days after the CAR T cell infusion.

CAR T cells in autoimmune diseases (Georg Schett | Andreas Mackensen)

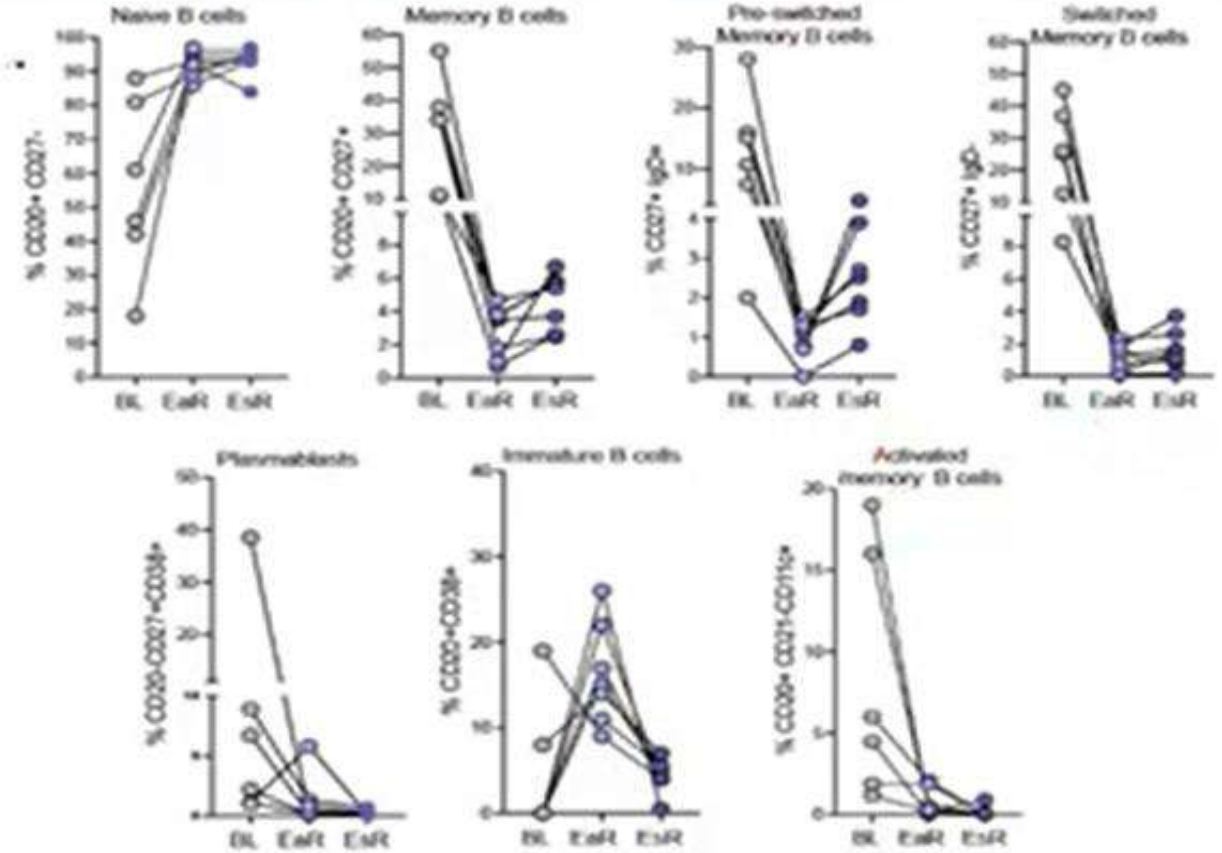


[CAR T cells in autoimmune diseases (Georg Schett | Andreas Mackensen)]



[CAR T cells in autoimmune diseases (Georg Schett | Andreas Mackensen)]

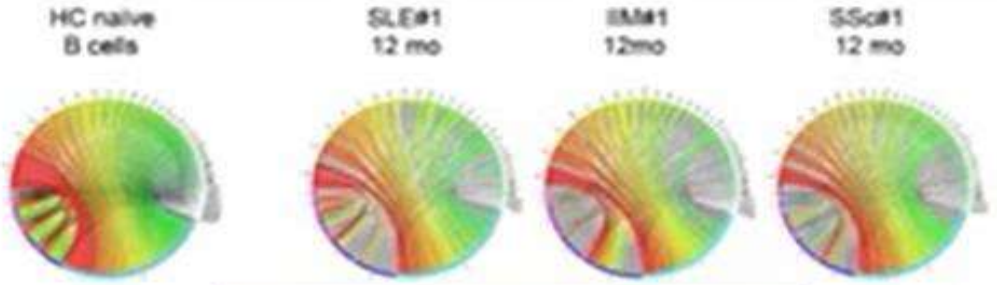
Analysis of memory B cells and plasmablasts in early and established reconstitution of B cells



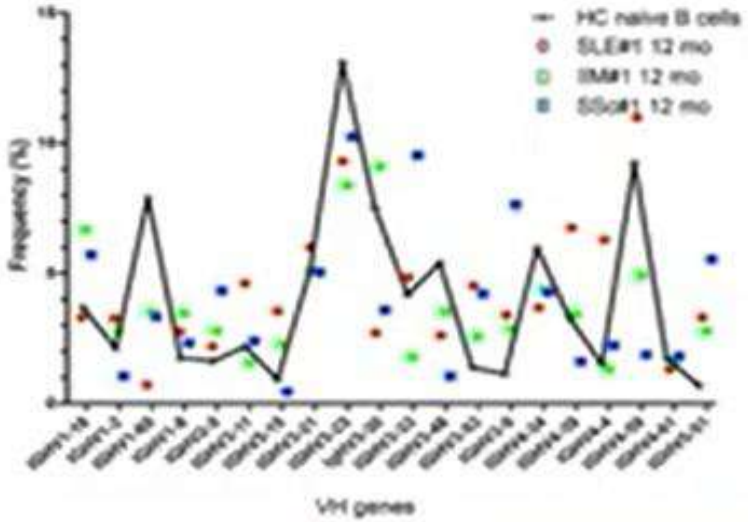
Muller F, Taubmann J et al. N Engl J Med 2024 Feb 22;390(8):687-700.

[CAR T cells in autoimmune diseases (Georg Schett | Andreas Mackensen)]

Next-generation sequencing (NGS) of the V_H gene repertoire



VJ recombination in naïve B cells

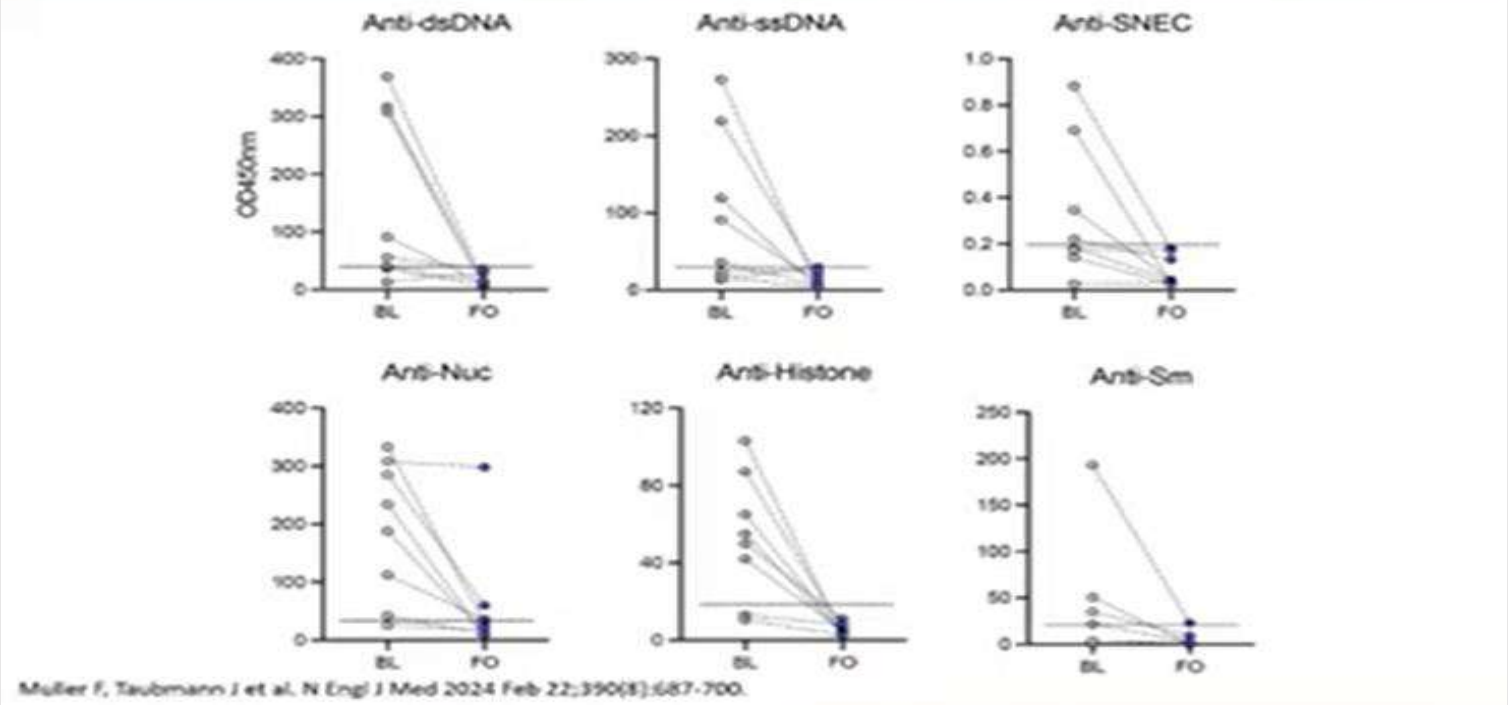


Broad and balanced $V_H - J_H$ usage and a normal naïve V_H repertoire in SLE, IIM and SSc patients treated with CAR-T cells very similar to a normal B cell repertoire of naïve B cells from healthy control donors

V_H gene usage of top 20 most frequent V_H genes in the human repertoire.

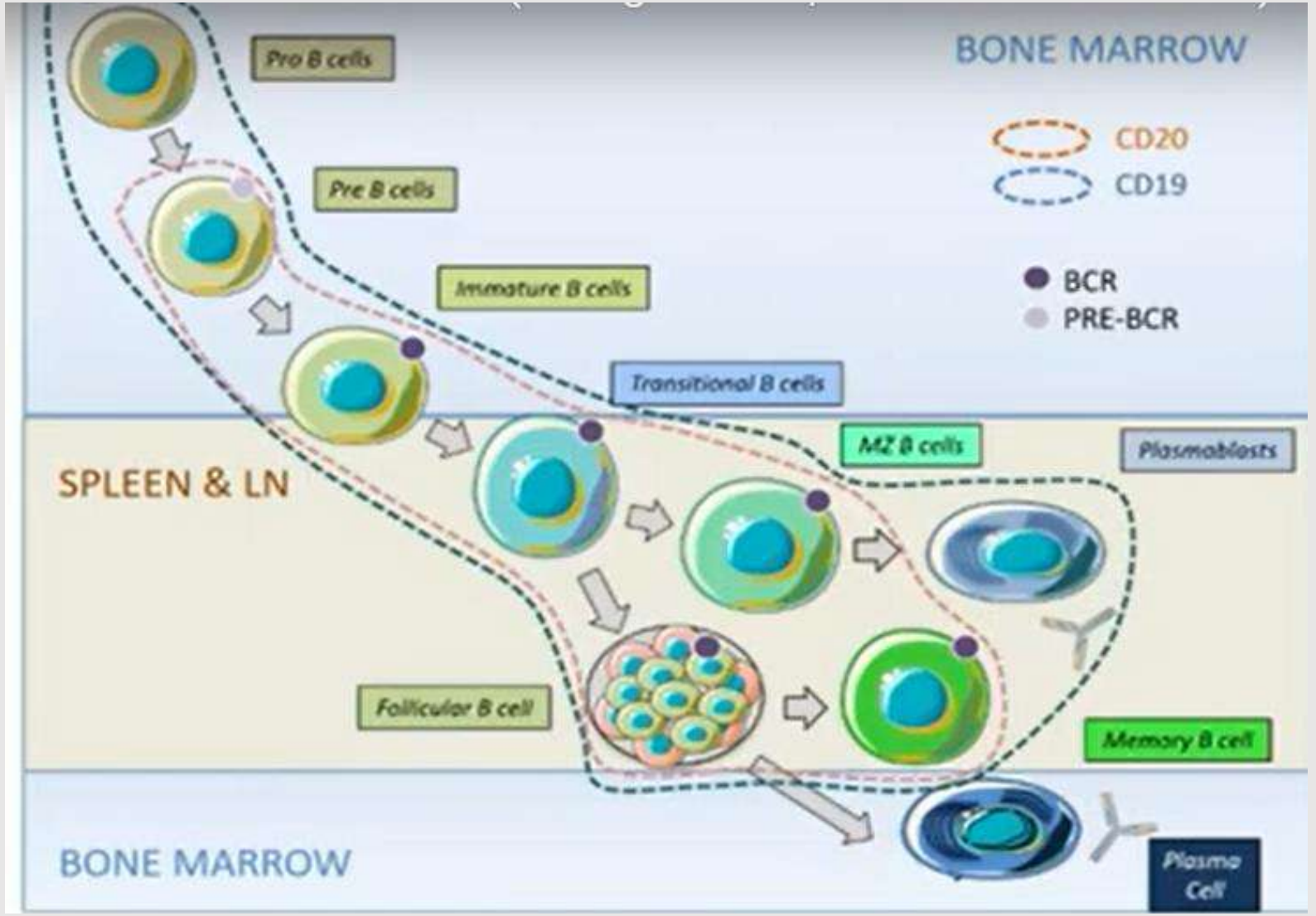
CAR T cells in autoimmune diseases (Georg Schett | Andreas Mackensen)

Seroconversion of SLE-associated autoantibodies



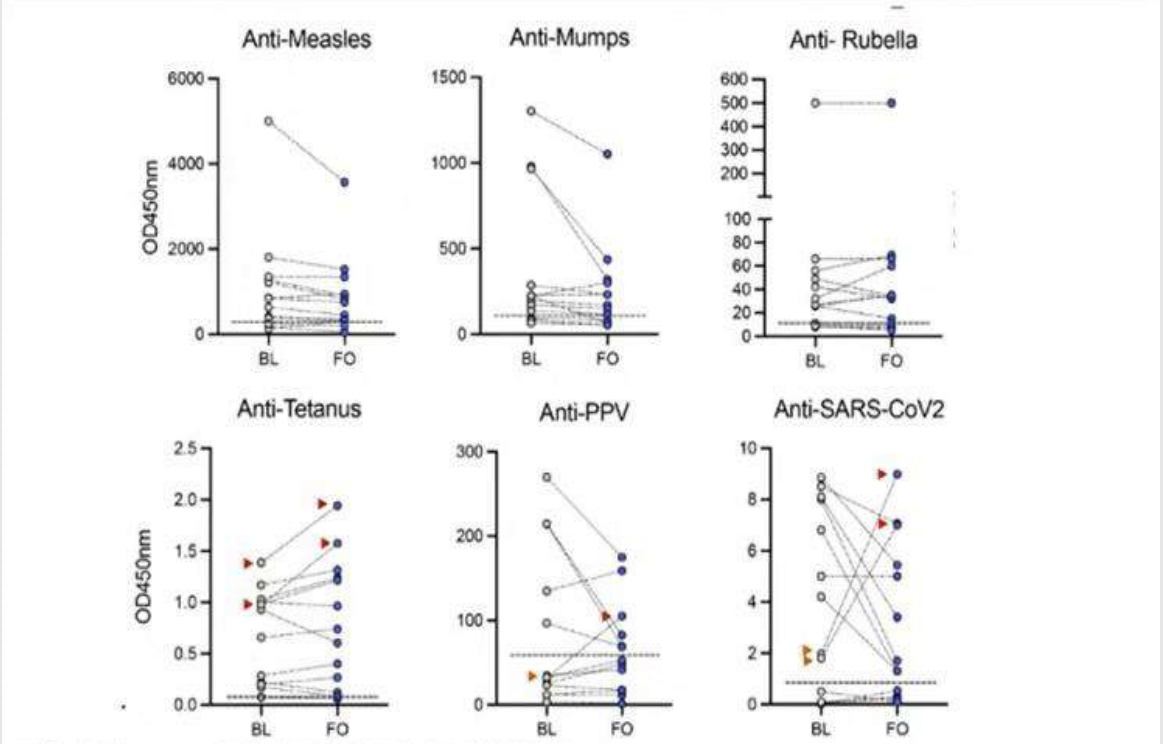
Muller F, Taubmann J et al. N Engl J Med 2024 Feb 22;390(8):687-700.

[CAR T cells in autoimmune diseases (Georg Schett | Andreas Mackensen)]



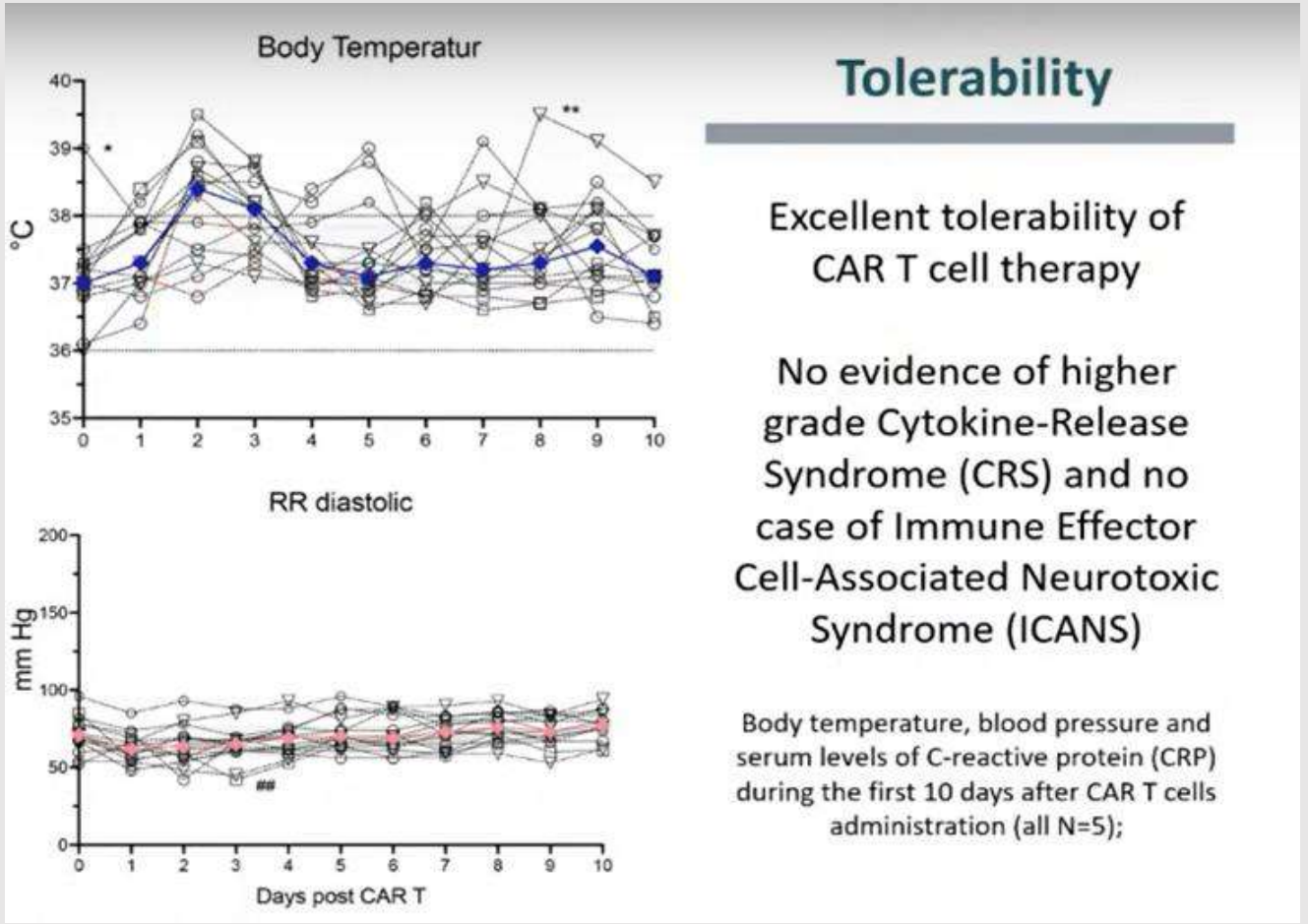
CAR T cells in autoimmune diseases (Georg Schett | Andreas Mackensen)

Vaccination-related antibodies

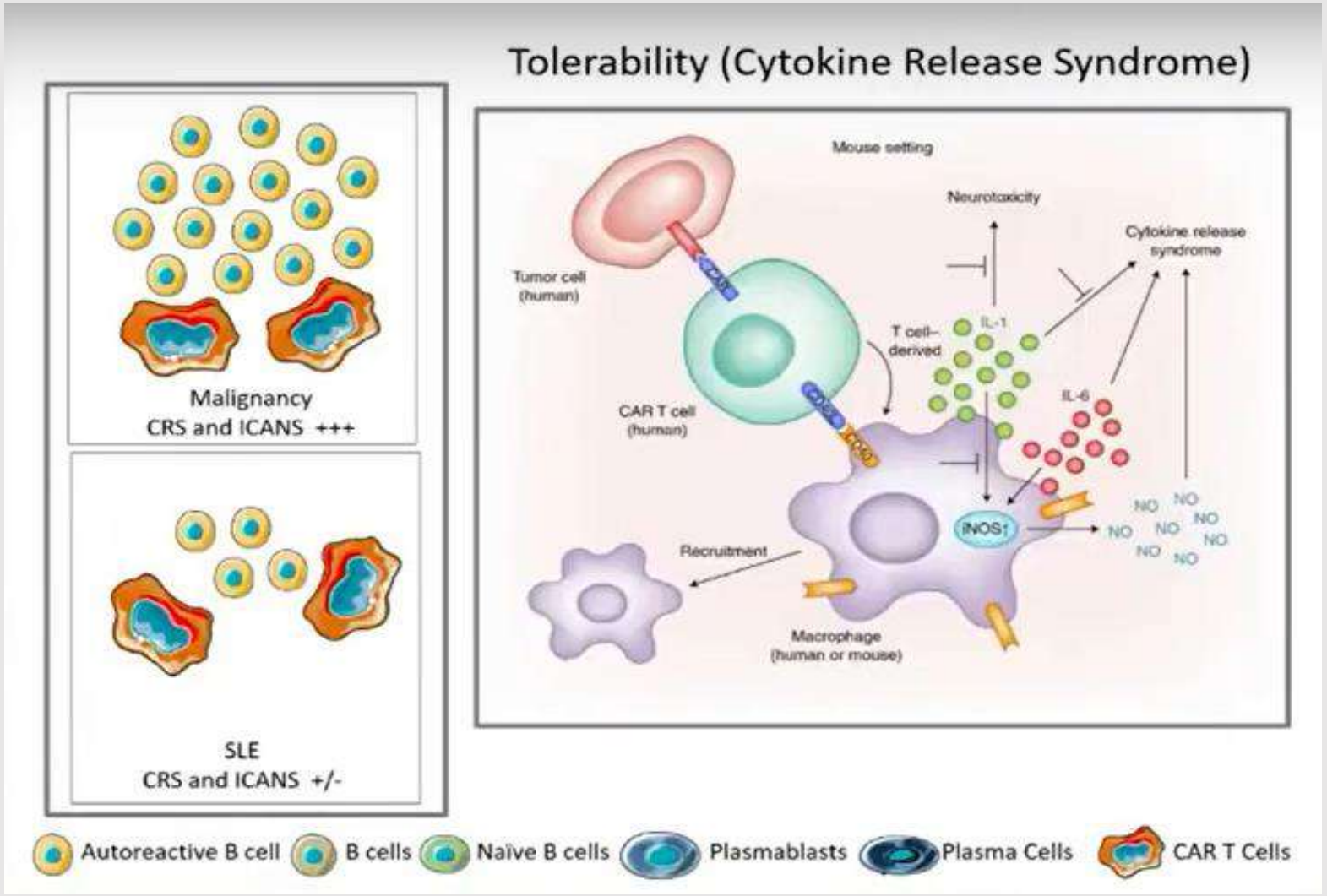


Muller F, Taubmann J et al. N Engl J Med 2024 Feb 22;390(8):687-700.

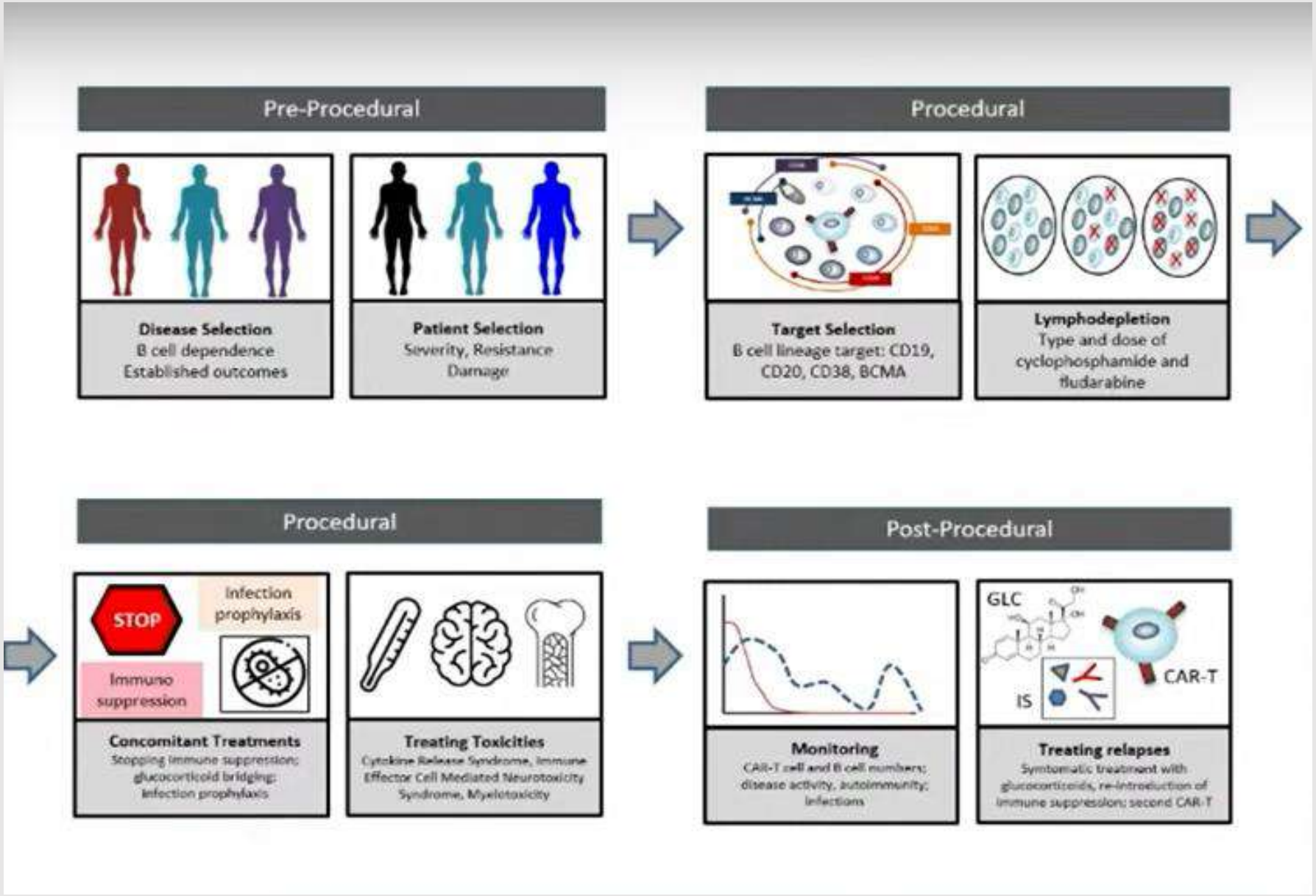
[CAR T cells in autoimmune diseases (Georg Schett | Andreas Mackensen)]



[CAR T cells in autoimmune diseases (Georg Schett | Andreas Mackensen)]



[CAR T cells in autoimmune diseases (Georg Schett | Andreas Mackensen)]



[CAR T cells in autoimmune diseases (Georg Schett | Andreas Mackensen)]

Köszönöm a figyelmet!