CAR-T ανοσοθεραπεια σε ρευματικά νοσήματα

Δαούσης Δημήτρης

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Αντιπρόεδρος (Εκλεγμενος Προεδρος) Ελληνικης Ρευματολογικης Εταιρειας

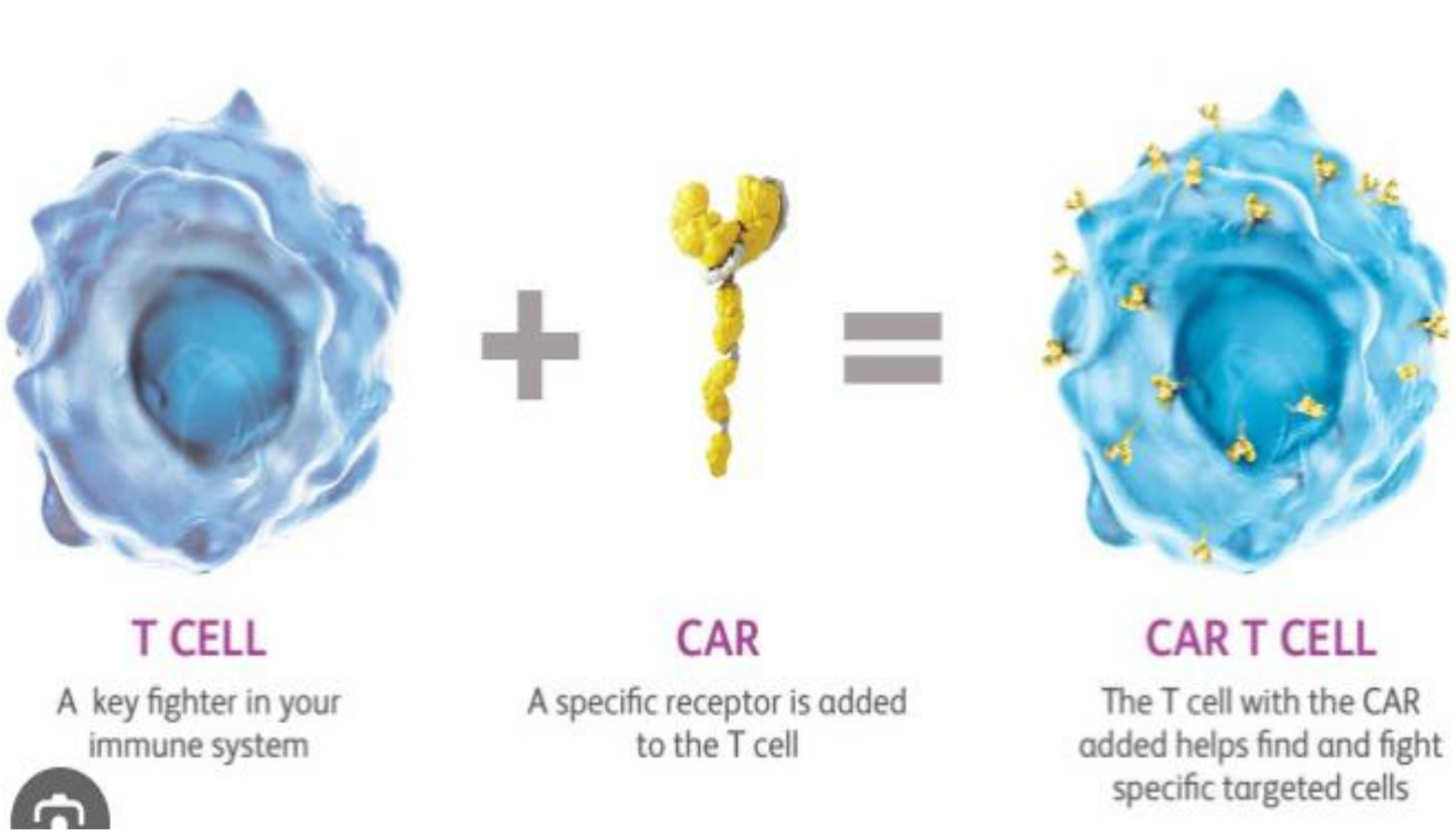
Συνεδριο ΕΠΕΜΥ
Ιωαννινα, Οκτ 2024

Συγκρουση συμφεροντων

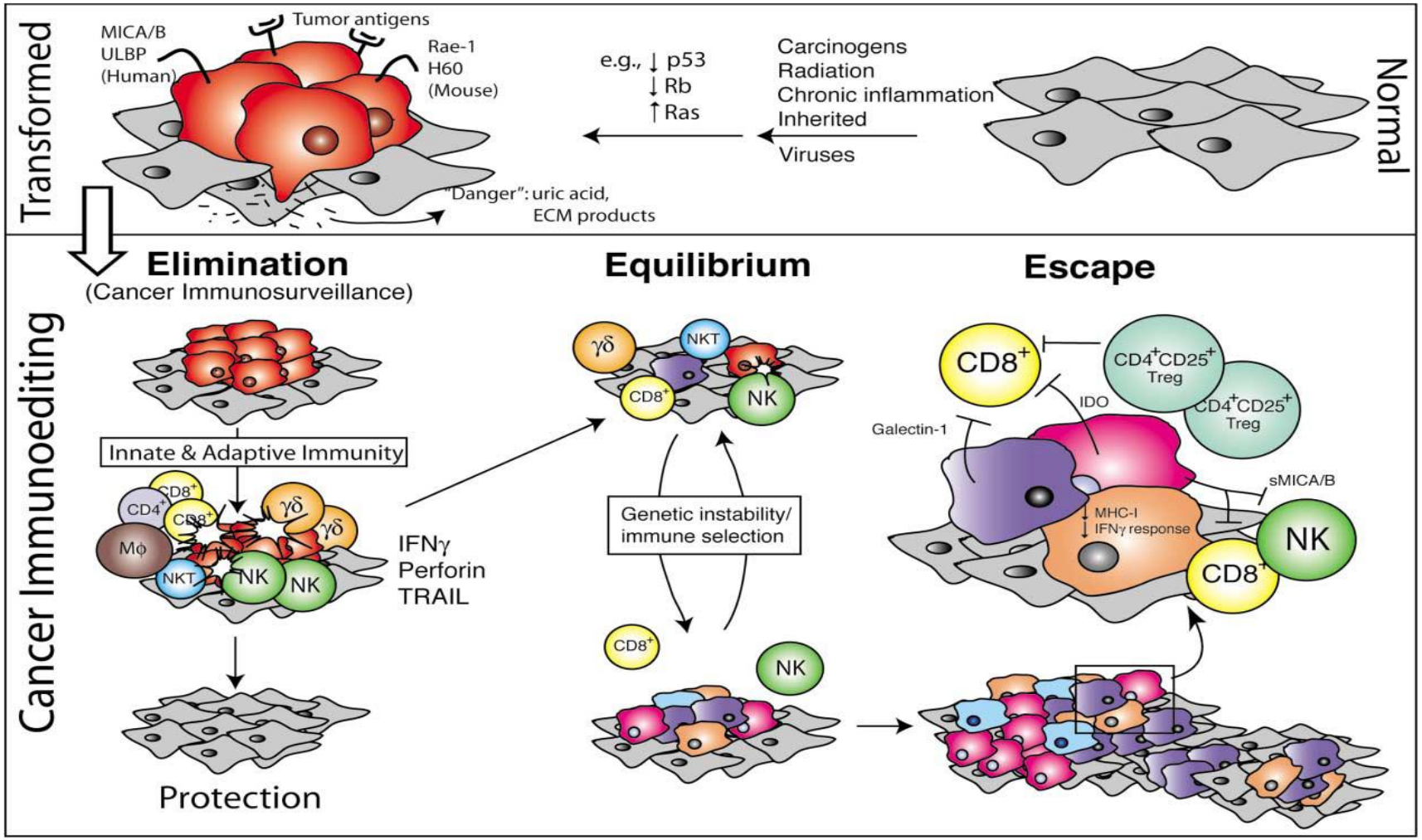
- Καμια για αυτή την παρουσιαση

Από τις στοχευμενες θεραπειες στις κυτταρικες θεραπειες?

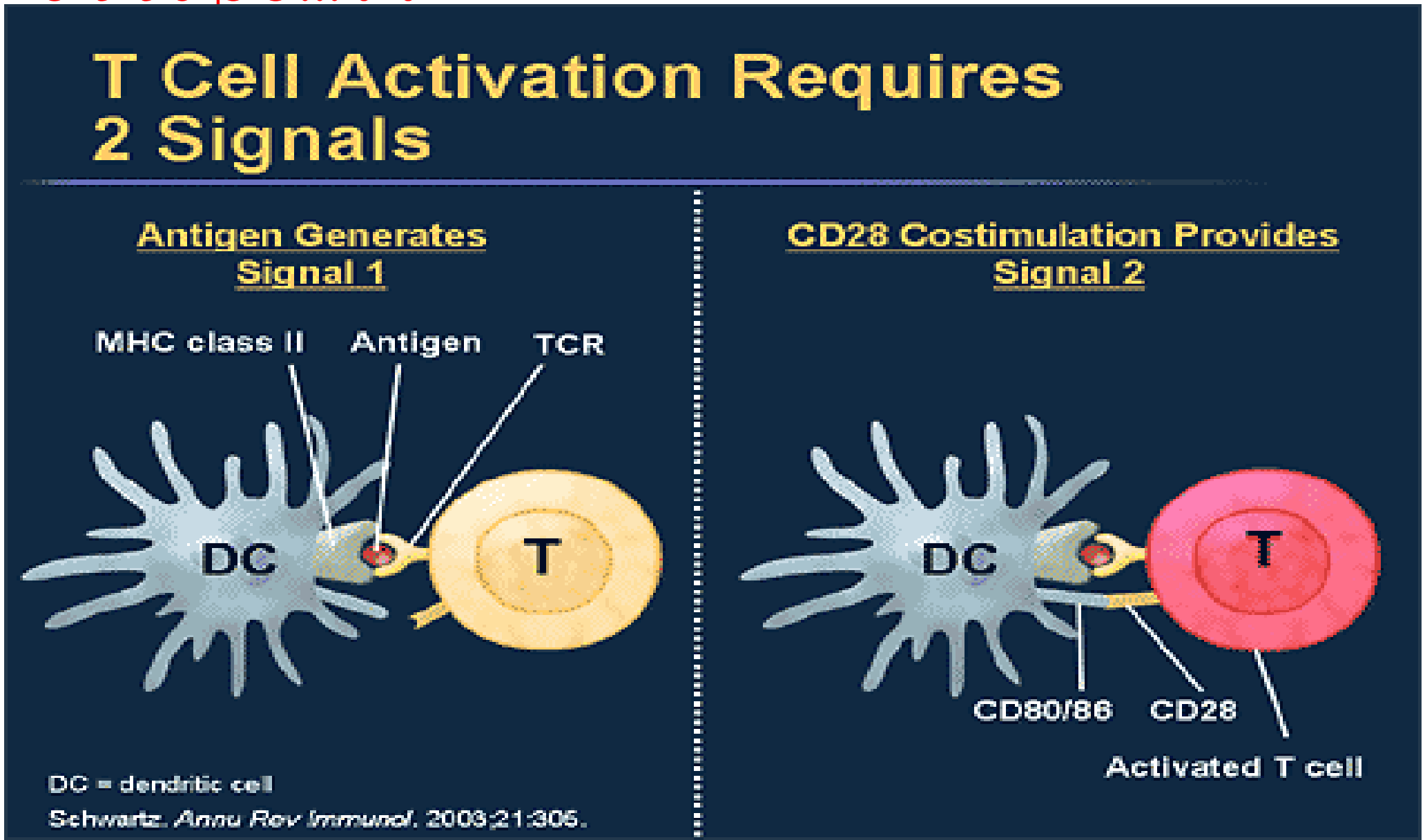
- Οι κυτταρικες θεραπειες αφορουν τροποποιημενα Τ λεμφοκυτταρα
- Χιλιάδες κλινικες μελέτες που στοχεύουν το Τ κύτταρο τρέχουν.....



Οι κυτταρικές θεραπείες ξεκίνησαν από την ογκολογια

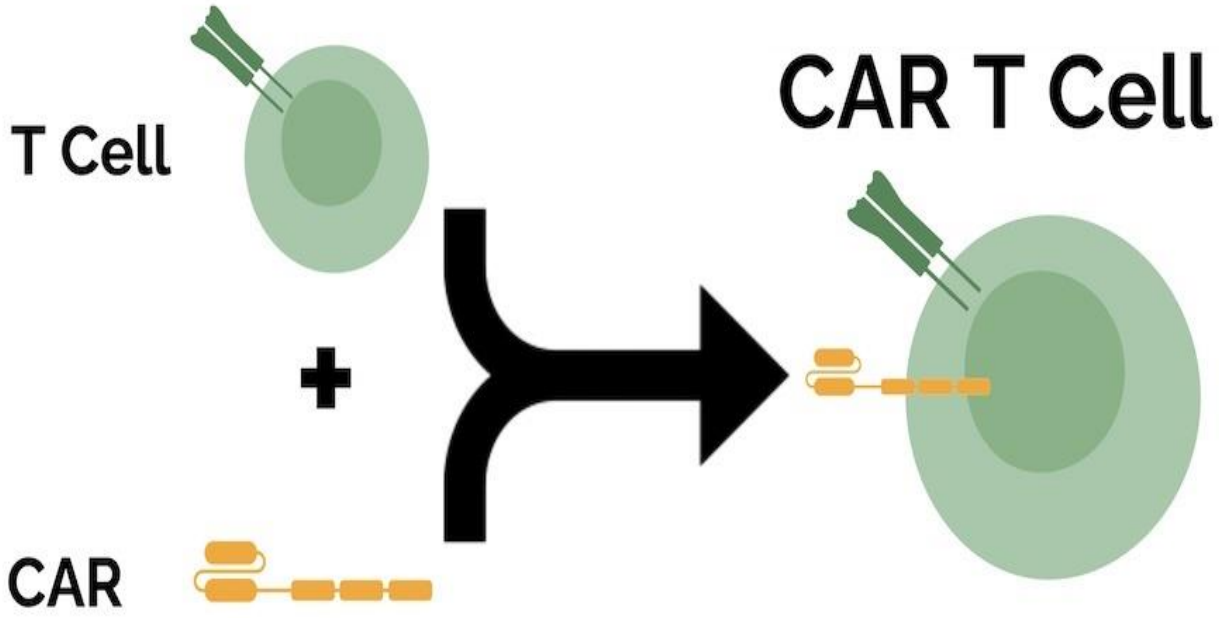


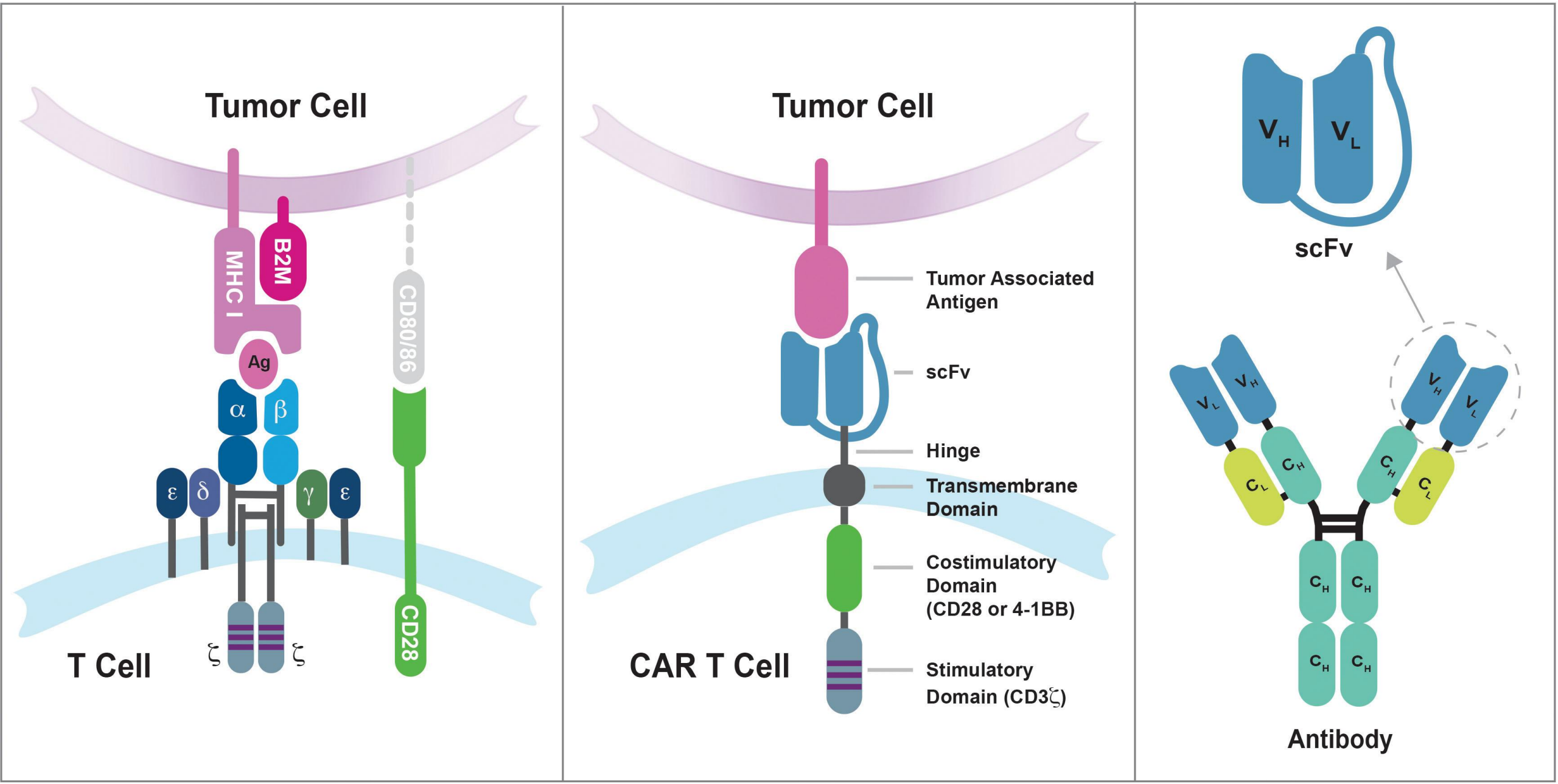
Πως ενεργοποιειται το Τ κυτταρο…..

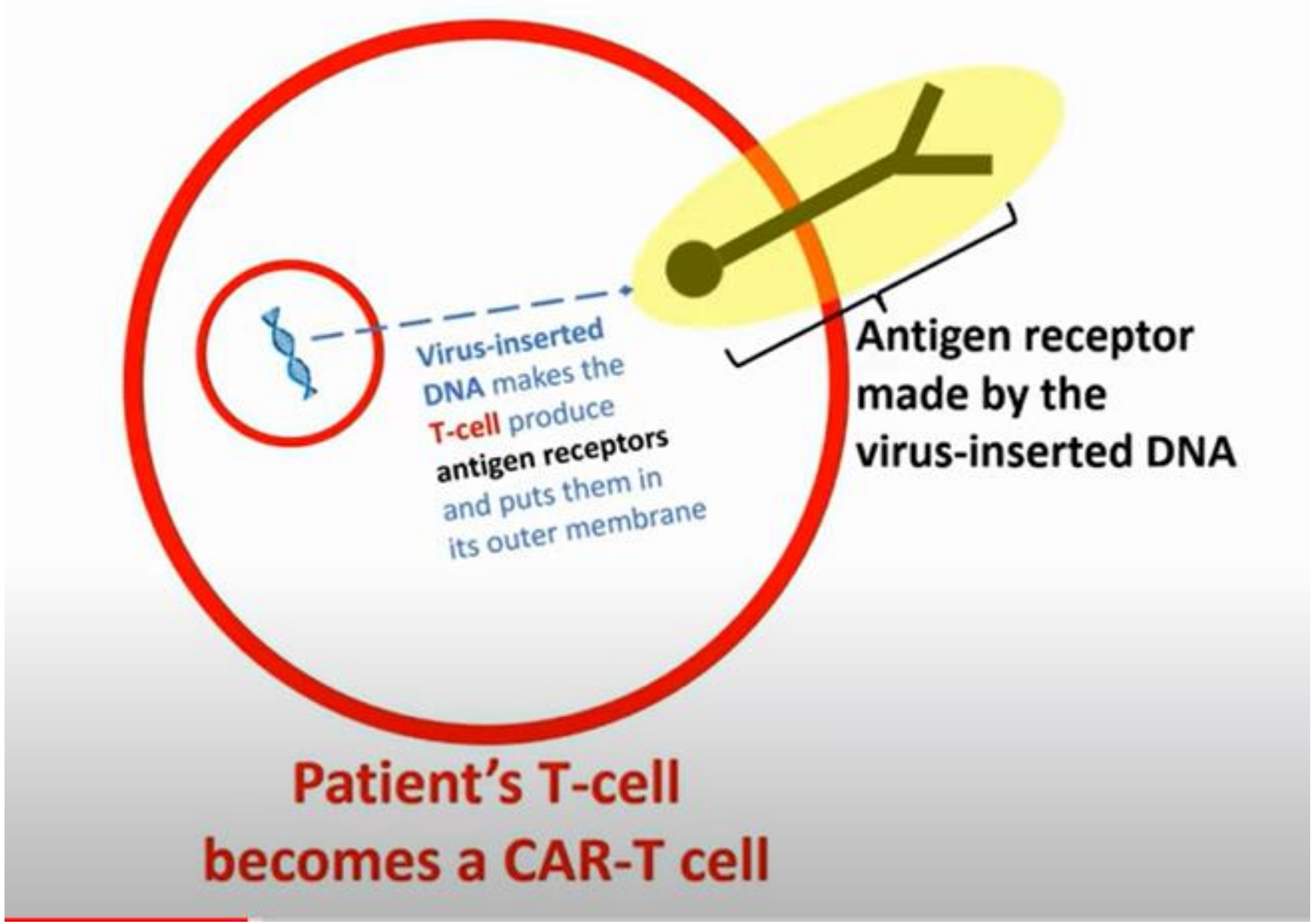


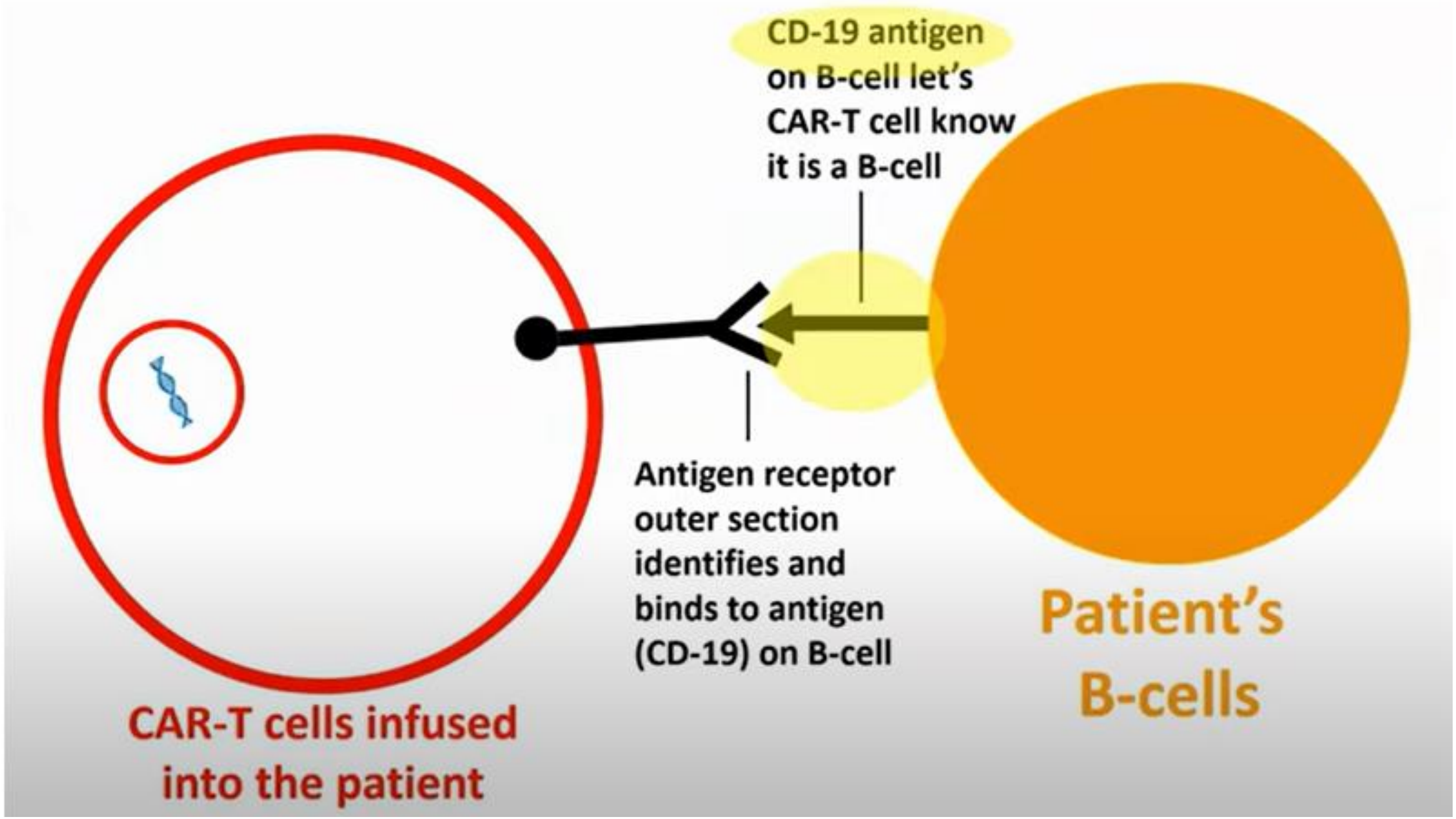
Κατασκευάζοντας το «ιδανικό» Τ λεμφοκύτταρο για κυτταρικη θεραπεια
CAR T cells

- Τι θα θελαμε?
- Πολύ ισχυρη ταση συνδεσης με το αντιστοιχο αντιγονο
- Να διεγειρεται χωρις την συμμετοχη MHC



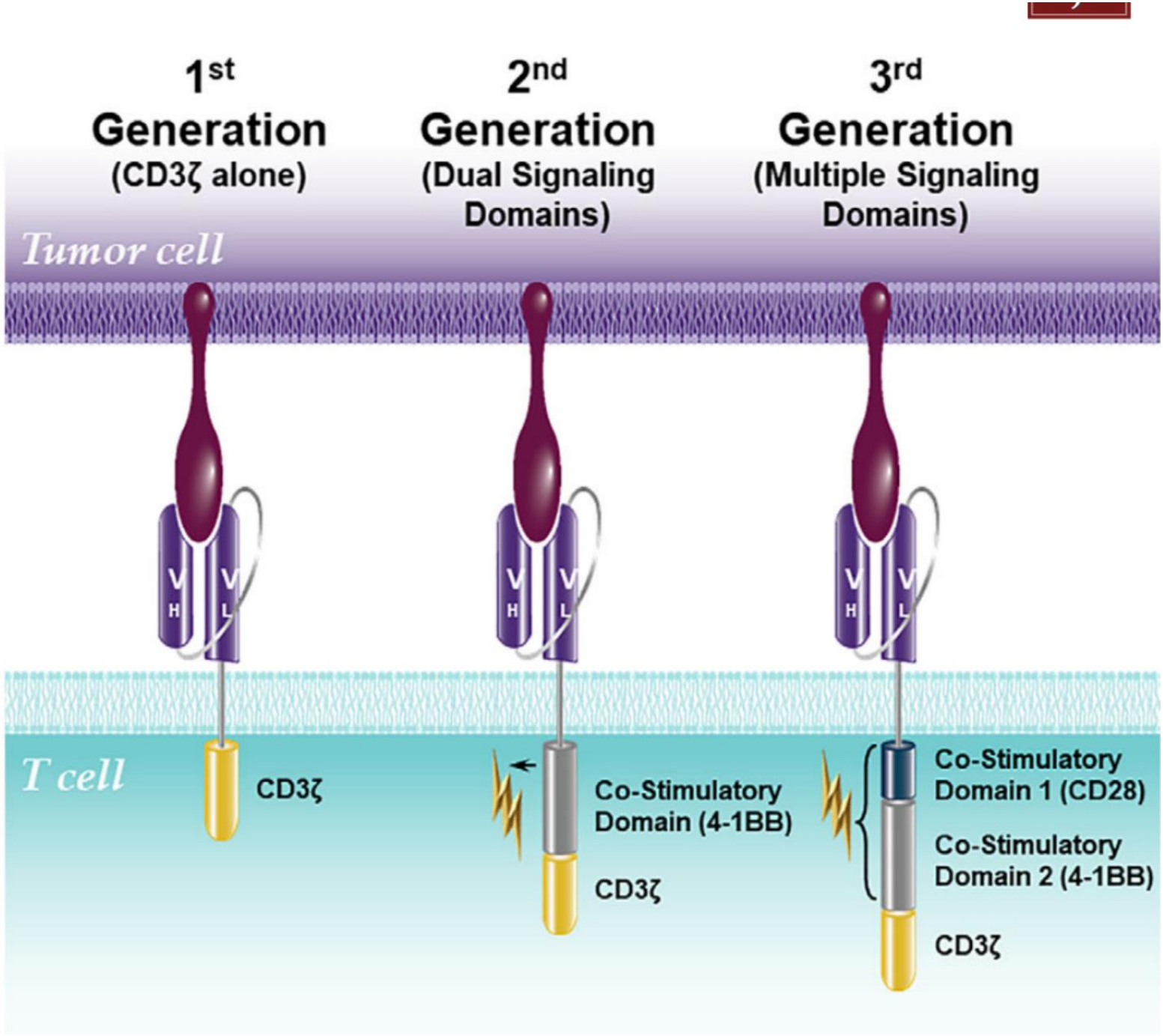

Tumor Cell
MHC I
B2M
Ag
α
β
ε
δ
γ
ε
ζ
ζ
CD80/86
CD28
T Cell
Tumor Cell
Tumor Associated Antigen
scFv
Hinge
Transmembrane Domain
Costimulatory Domain (CD28 or 4-1BB)
Stimulatory Domain (CD3ζ)
CAR T Cell
V_H
V_L
scFv
V_L
V_H
C_L
C_H
C_H
V_H
V_L
C_L
C_H
C_H
C_H
C_H
Antibody


Virus-inserted DNA makes the T-cell produce antigen receptors and puts them in its outer membrane
Antigen receptor made by the virus-inserted DNA
Patient's T-cell becomes a CAR-T cell


CD-19 antigen
on B-cell let's
CAR-T cell know
it is a B-cell
Antigen receptor
outer section
identifies and
binds to antigen
(CD-19) on B-cell
Patient's
B-cells
CAR-T cells infused
into the patient

- Γιατι απετυχε η πρωτη γενια CAR T??

- Ελλειψη συνδιεγερσης

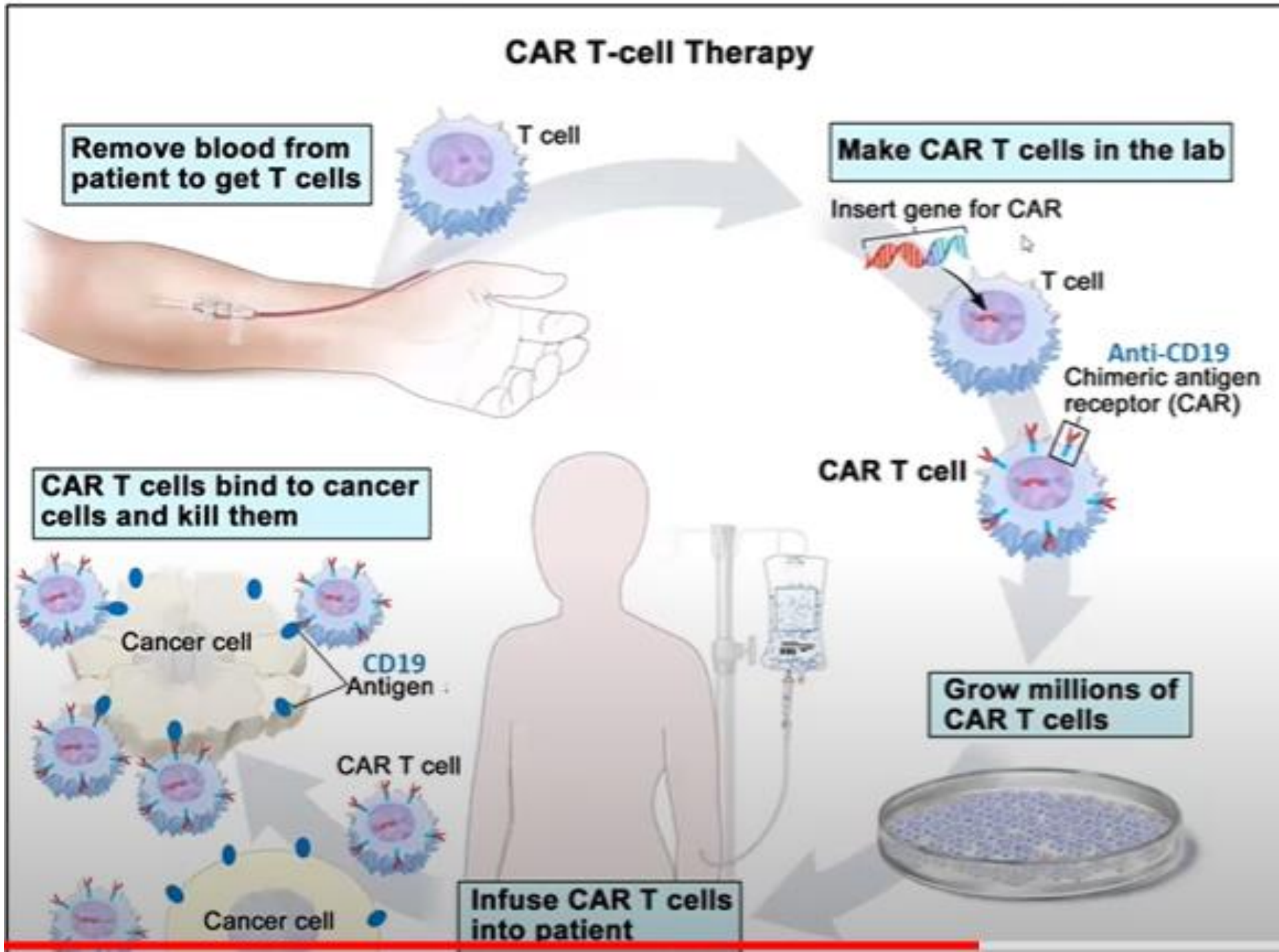


Αποτελεσματικά κυρίως για «ρευστές» κακοηθειες

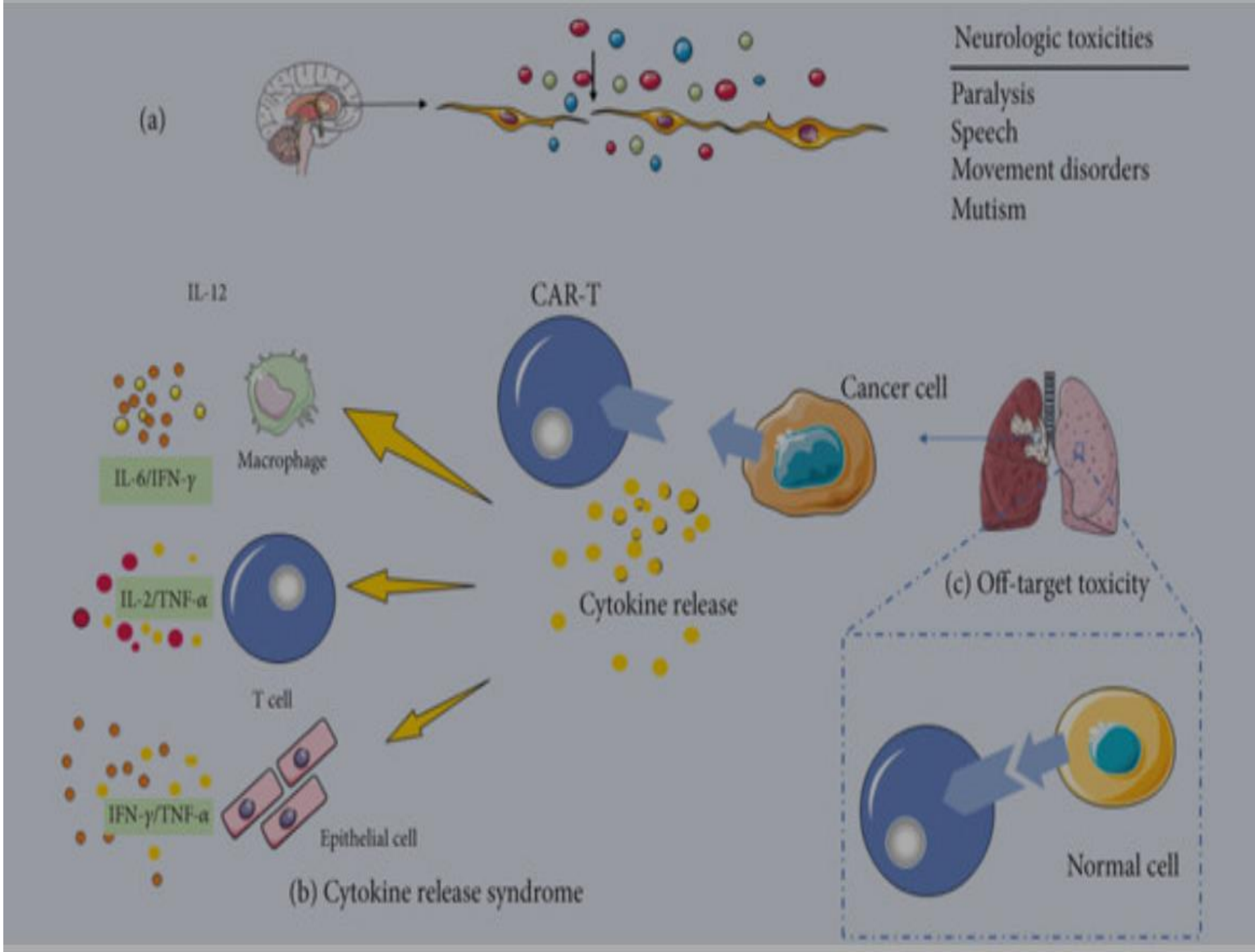
FDA-Approved CAR T-Cell Therapies

Generic Name	Brand Name	Target Antigen	Targeted Disease	Patient Population
Tisagenlecleucel	Kymriah	CD19	B-cell acute lymphoblastic leukemia (ALL)	Children and young adults with refractory or relapsed B-cell ALL
			B-cell non-Hodgkin lymphoma (NHL)	Adults with relapsed or refractory B-cell NHL
Axicabtagene ciloleucel	Yescarta	CD19	B-cell non-Hodgkin lymphoma (NHL)	Adults with relapsed or refractory B-cell NHL
			Follicular lymphoma	Adults with relapsed or refractory follicular lymphoma
Brexucabtagene autoleucel	Tecartus	CD19	Mantle cell lymphoma (MCL)	Adults with relapsed or refractory MCL
			B-cell acute lymphoblastic leukemia (ALL)	Adults with refractory or relapsed B-cell ALL
Lisocabtagene maraleucel	Breyanzi	CD19	B-cell non-Hodgkin lymphoma (NHL)	Adults with relapsed or refractory B-cell NHL
Idecabtagene vicleucel	Abecma	BCMA	Multiple myeloma	Adults with relapsed or refractory multiple myeloma
Ciltacabtagene autoleucel	Carvykti	BCMA	Multiple myeloma	Adults with relapsed or refractory multiple myeloma

Η διαδικασία...



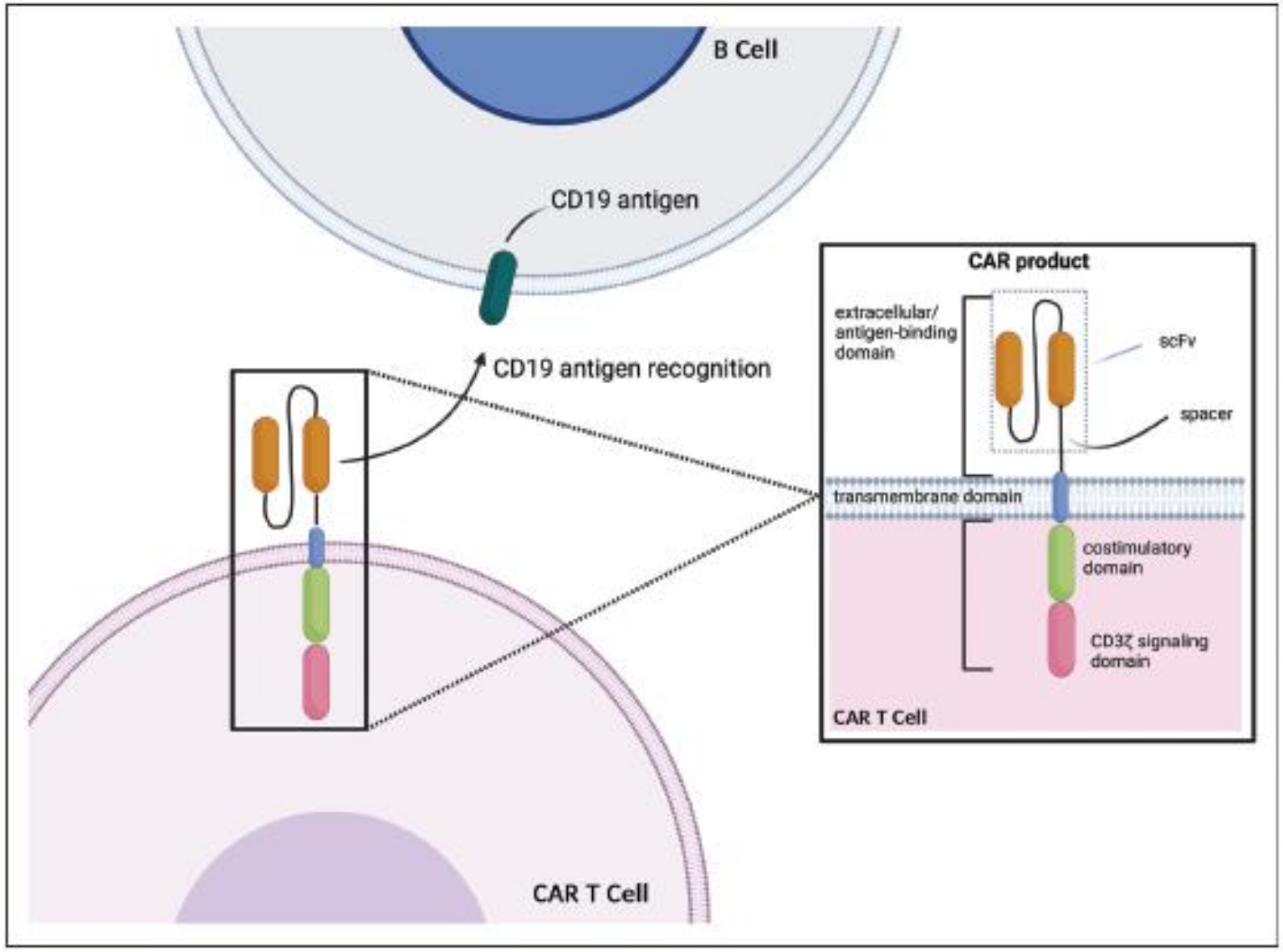
Βασικες παρενεργειες



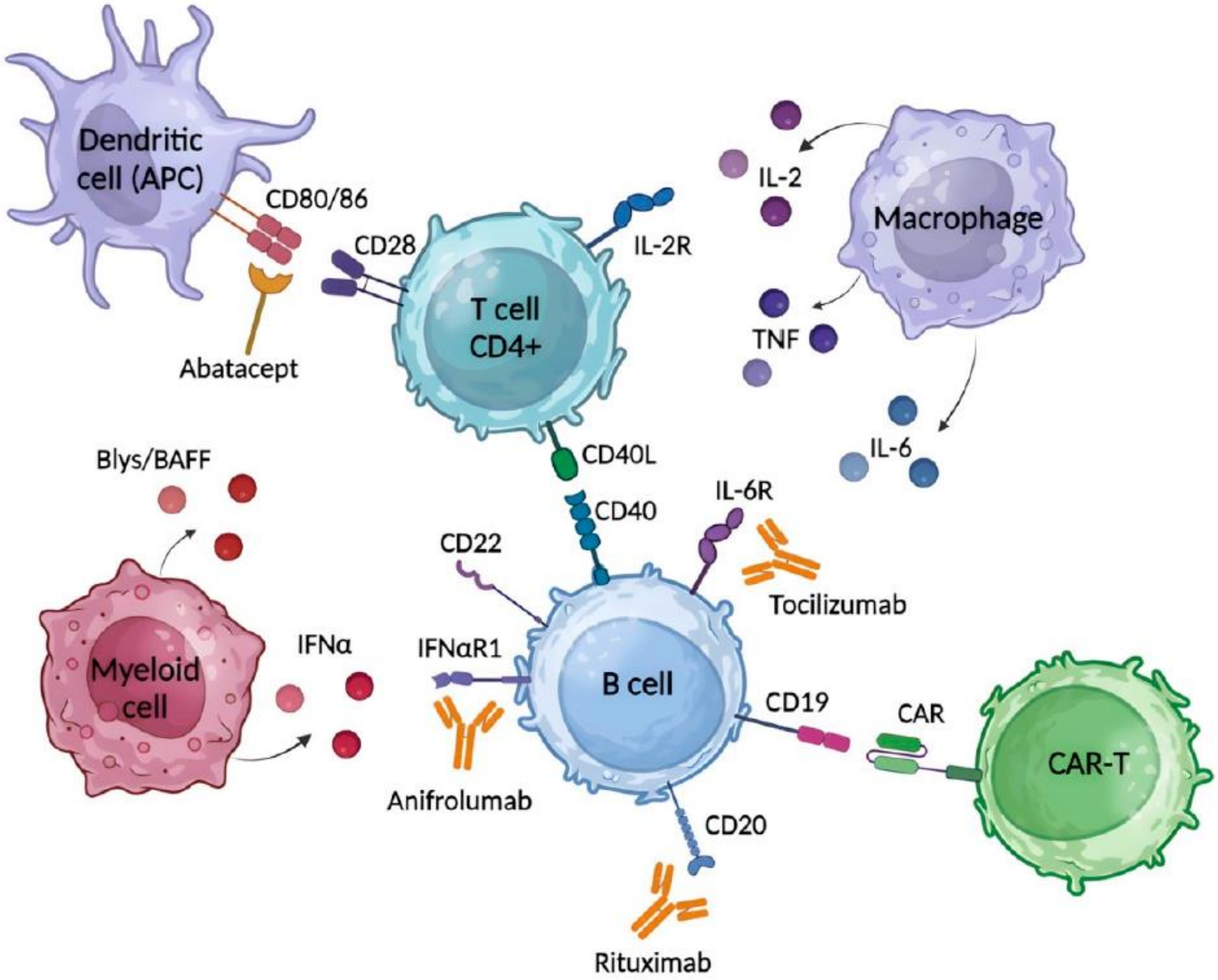
Τα CAR-T σε ρευματικες παθησεις…

- Τι θα μπορουσαν να στοχευσουν?

- **CD19/B λεμφοκυτταρα**



- Το Β λεμφοκυτταρο εχει κεντρικο ρολο στην παθογενεια πολλων αυτοανοσων νοσηματων συνδετικου ιστου

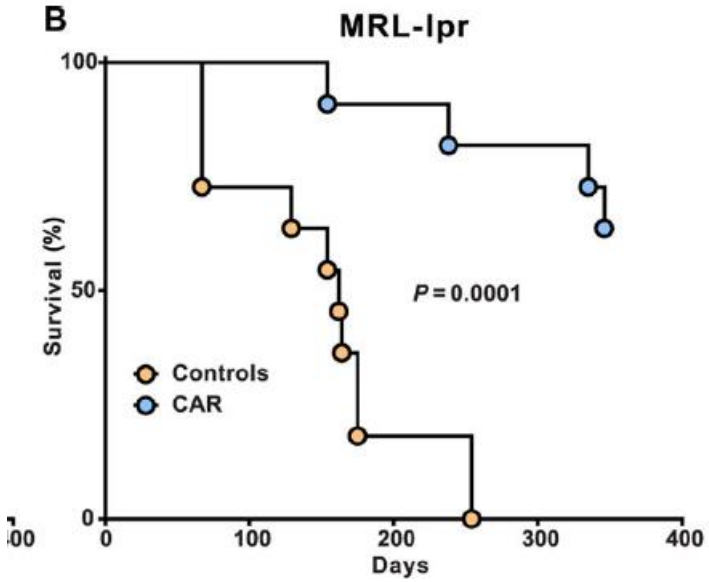


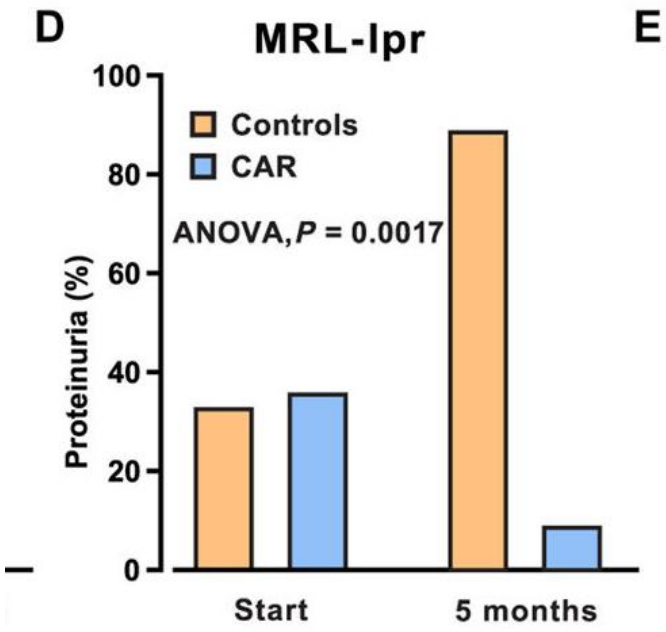
HHS Public Access
Author manuscript
Sci Transl Med. Author manuscript; available in PMC 2021 June 14.

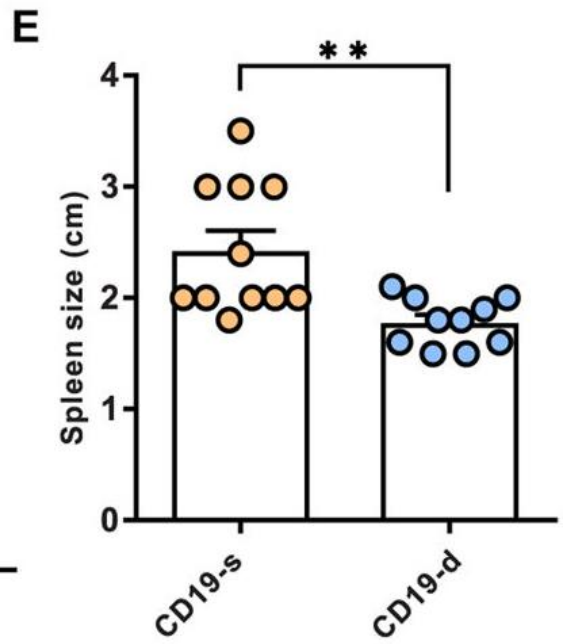
Published in final edited form as:
Sci Transl Med. 2019 March 06; 11(482): . doi:10.1126/scitranslmed.aav1648.

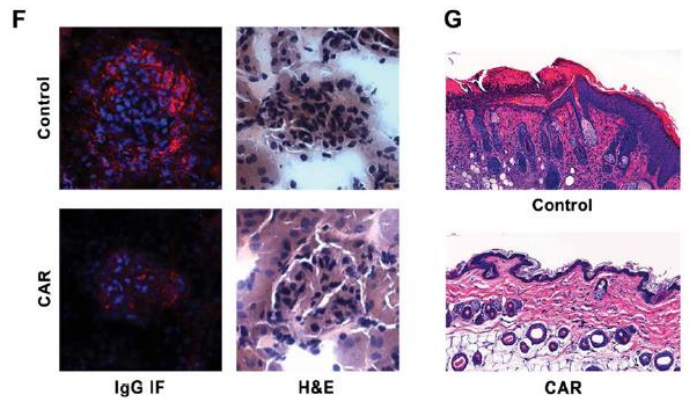
Sustained B cell depletion by CD19-targeted CAR T cells is a highly effective treatment for murine lupus

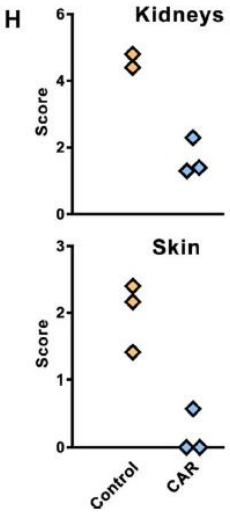
Rita Kansal[1], Noah Richardson[1], Indira Neeli[1], Saleem Khawaja[1], Damian Chamberlain[1], Marium Ghani[1], Qurat-ul-ain Ghani[1], Louisa Balazs[2], Sarka Beranova-Giorgianni[3], Francesco Giorgianni[3], James N. Kochenderfer[4], Tony Marion[1], Lorraine M. Albritton[1], Marko Radic[1,*]











The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 22, 2024 VOL. 390 NO. 8

CD19 CAR T-Cell Therapy in Autoimmune Disease — A Case Series with Follow-up

Fabian Müller, M.D., Jule Taubmann, M.D., Laura Bucci, M.D., Artur Wilhelm, Ph.D., Christina Bergmann, M.D., Simon Völkl, Ph.D., Michael Aigner, Ph.D., Tobias Rothe, Ph.D., Ioanna Minopoulou, M.D., Carlo Tur, M.D., Johannes Knitza, M.D., Soraya Kharboutli, M.D., Sascha Kretschmann, Ph.D., Ingrid Vasova, M.D., Silvia Spoerl, M.D., Hannah Reimann, Ph.D., Luis Munoz, M.D., Roman G. Gerlach, Ph.D., Simon Schäfer, Ph.D., Ricardo Grieshaber-Bouyer, M.D., Anne-Sophie Korganow, M.D., Dominique Farge-Bancel, M.D., Dimitrios Mougiakakos, M.D., Aline Bozec, Ph.D., Thomas Winkler, Ph.D., Gerhard Krönke, M.D., Andreas Mackensen, M.D., and Georg Schett, M.D.

- Οι ασθενεις..

Table 1. Characteristics of 15 Patients with Autoimmune Disease at Baseline.*

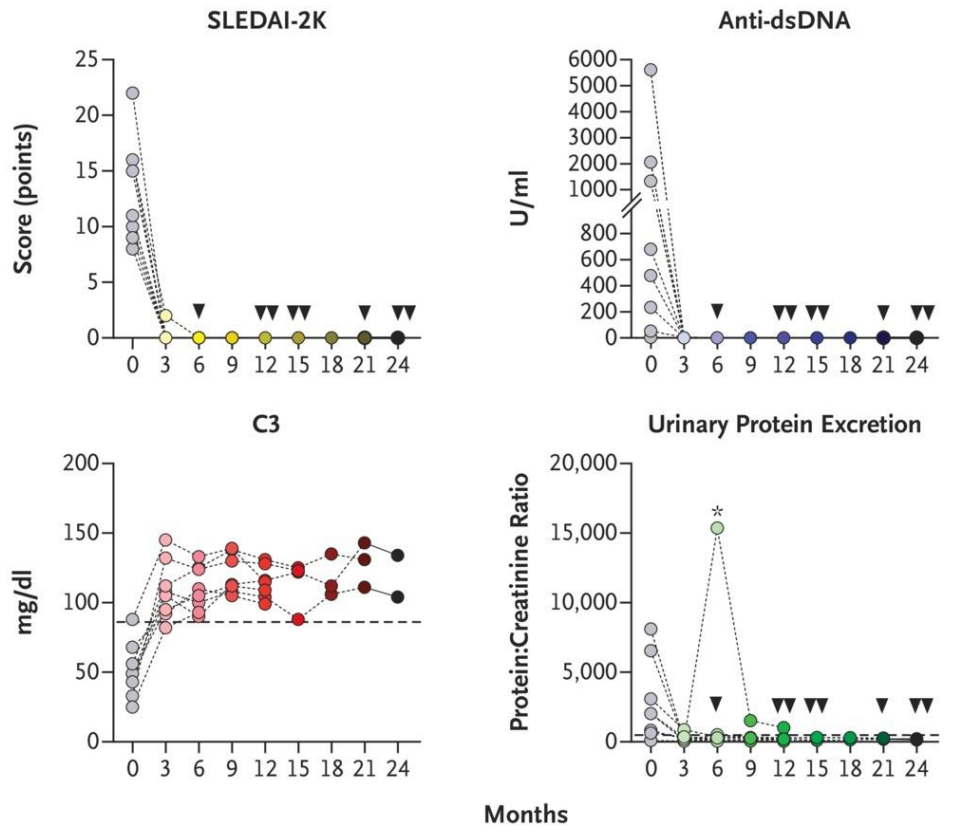
Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13	Patient 14	Patient 15
Age (yr)	20	23	22	24	18	38	33	35	41	43	42	60	36	37	47
Sex	F	M	F	F	F	F	F	F	M	F	M	M	M	F	M
Disease	SLE	SLE	SLE	SLE	SLE	SLE	SLE	SLE	IIM	IIM	IIM	SSc	SSc	SSc	SSc
Disease duration (yr)	4	1	6	9	3	18	1	20	2	5	1	2	2	1	11
Follow-up (mo)	29	25	21	19	15	15	12	6	18	18	5	13	10	7	4
Autoantibodies															
Lead	dsDNA	dsDNA	dsDNA	Sm	dsDNA	dsDNA	dsDNA	dsDNA	Jo-1	Jo-1	PL-7	RNAP III	Scl70	Scl70	Scl70
Co-lead	—	Sm	—	—	Sm	Sm	—	—	—	Pm-Scl100	—	—	—	—	—
Other	—	—	PCNA	Ro60	Ku	Ro52/60	RNP	RNP	—	Ro52	Ro52	—	—	Ro60	—
Organ involvement															
Skin	+	+	+	+	+	+	+	+	+	0	0	+	+	+	+
Kidney	+	+	+	+	+	+	+	+	0	0	0	0	0	+†	0
Nephritis (WHO grade)	III	III	IV	III–V	III–V	IV	IV	IV	0	0	0	0	0	0	0
Lungs	+	0	+	+	0	0	0	+	+	+	+	+	+	+	+
Heart	+	0	0	+	0	0	0	0	0	0	0	+	+	0	0
Bone marrow	+	0	0	0	+	+	0	0	0	0	0	0	0	0	0
Muscles	0	0	0	0	0	0	0	0	+	+	+	0	0	0	0
Joints	0	+	+	+	+	+	0	+	0	+	0	+	+	0	0
Treatments															
Glucocorticoids	+	+	+	+	+	+	+	+	+	+	+	0	+	0	0
HCQ	+	+	+	+	+	+	+	+	0	0	0	0	+	0	0
Mycophenolate	+	+	+	+	+	+	+	+	0	+	0	+	+	+	+
Methotrexate	0	0	0	+	0	+	0	+	0	0	0	+	0	+	0
Azathioprine	0	0	0	+	+	+	0	+	0	0	0	0	0	0	0
CPM	+	+	+	0	0	+	+	0	+	+	+	0	0	0	+
Tacrolimus	+	0	0	0	0	+	+	0	+	+	0	0	0	0	0
Rituximab	+	0	0	0	0	+	+	+	+	+	+	0	0	+	0
Belimumab	+	+	+	+	+	+	+	+	0	0	0	0	0	0	0
IVIG	0	0	0	0	0	0	0	0	+	+	+	0	0	0	0
Other	0	0	0	LEF	0	+‡	0	+§	0	+¶	OCR	0	0	TOC	NIN

* CPM denotes cyclophosphamide, dsDNA double-stranded DNA, HCQ hydroxychloroquine, IIM idiopathic inflammatory myositis, IVIG intravenous immunoglobulins, LEF leflunomide, NIN nintedanib, OCR ocrelizumab, PCNA proliferating-cell nuclear antigen, Pm-Scl100 polymyositis and scleroderma 100, RNAP III RNA polymerase III, RNP ribo-nucleoprotein, Scl70 scleroderma 70, SLE systemic lupus erythematosus, Sm Smith, SSc systemic sclerosis, TOC tocilizumab, and WHO World Health Organization.
† Patient 14 had grade IV chronic kidney insufficiency due to renal crisis.
‡ Patient 6 received leflunomide, bortezomib, upadacitinib, immunoadsorption, and ustekinumab.
§ Patient 8 received photopheresis, lenalidomide, thalidomide, ustekinumab, and interleukin-2.
¶ Patient 10 received tofacitinib, tocilizumab, and ocrelizumab.

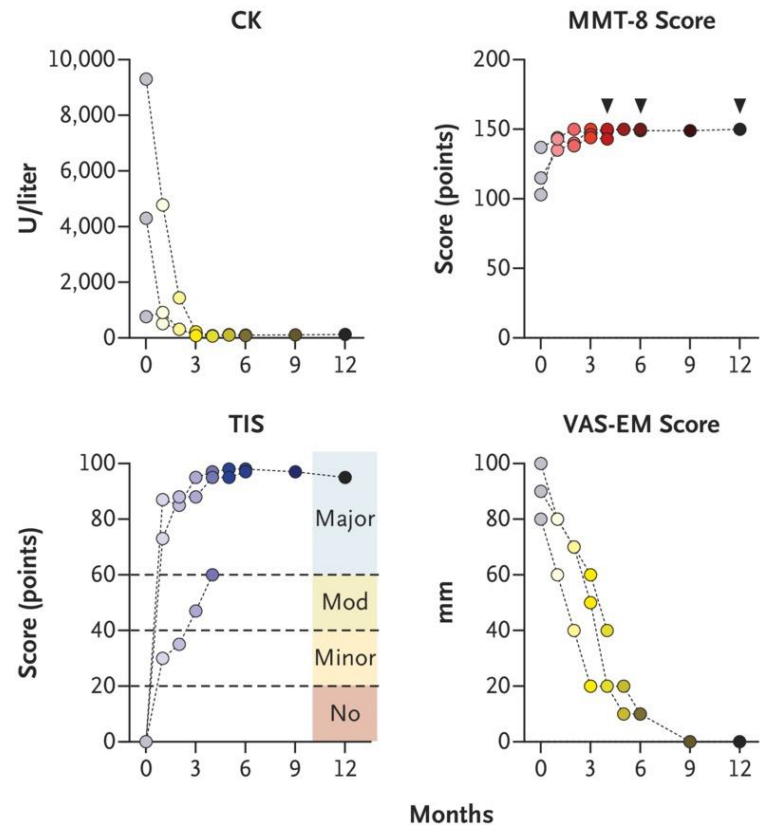
A Short-Term Efficacy of CD19 CAR T-Cell Therapy in Autoimmune Disease

Patient No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Disease	SLE								IIM			SSc			
DORIS Remission	+	+	+	+	+	+	+	+*	N/A			N/A			
LLDAS	+	+	+	+	+	+	+	+*							
SLEDAI-2K Score	0	0	0	0	0	0	0	0							
ACR–EULAR Major Clinical Response	N/A								+	+	+*				
Normalization of CK Level									+	+	+*				
Change in EUSTAR-AI Score									N/A			−2.3	−4.7	−4.3	−1.9*
Change in mRSS												−7	−9	−17	−5*
Glucocorticoid-free State	+	+	+	+	+	+	+	+*	+	+	+*	+	+	+	+*
No Immunosuppressive Drugs	+	+	+	+	+	+	+	+*	+	+	+*	+	+	+	+*

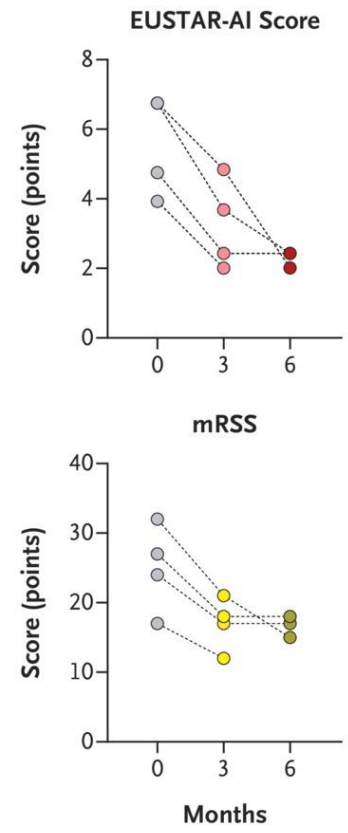
B Long-Term Outcomes in Patients with SLE (N=8)



C Long-Term Outcomes in Patients with IIM (N=3)



D Long-Term Outcomes in Patients with SSc (N=4)



Ανοσολογικο Reset?

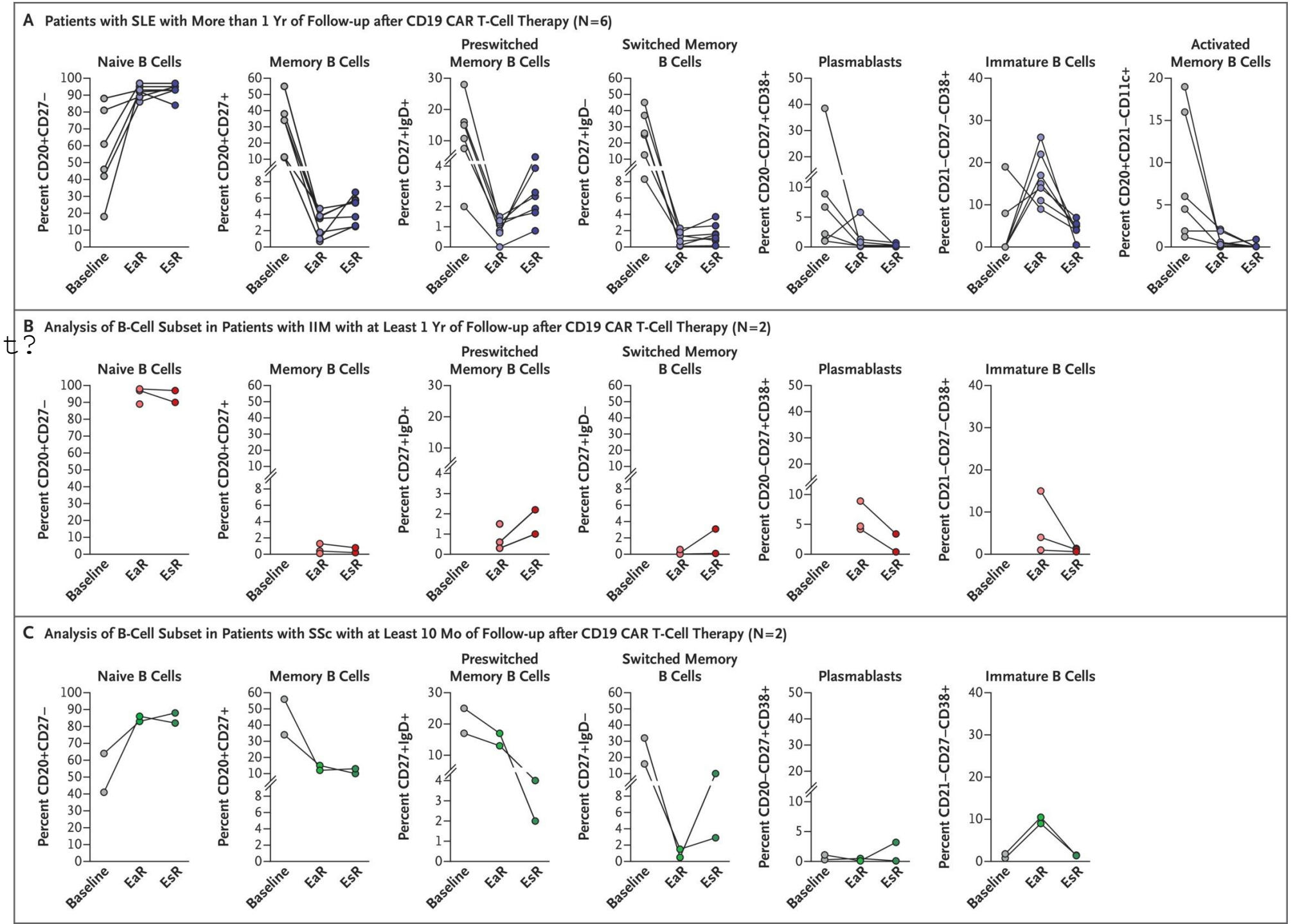


Table 2. Short-Term Safety of CD19 CAR T-Cell Therapy in Autoimmune Disease.*

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13	Patient 14	Patient 15
Disease	SLE	SLE	SLE	SLE	SLE	SLE	SLE	SLE	IIM	IIM	IIM	SSc	SSc	SSc	SSc
CRS (grade)	0	1	1	1	0	1	0	1	1	1	2	1	1	1	0
ICANS (grade)	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
Bone marrow toxicity†	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
TOC treatment	0	0	0	+	0	+	0	+	+	+	+	0	0	0	0
GLC treatment	0	0	0	0	0	0	0	0	0	+	0	0	0	0	0
Low IgG	+	+	+	0	0	0	0	+‡	+‡	0	0	0	0	0	0
IgG substitution	0	+	0	0	0	0	0	+	0	0	0	0	0	0	0

* CAR denotes chimeric antigen receptor, CRS cytokine release syndrome, GLC glucocorticoid, and ICANS immune-effector cell–associated neurotoxicity syndrome.
† Bone marrow toxicity was defined as persisting grade 2 or higher thromocytopenia, leukopenia, or granulocytopenia at or beyond day 28 after CD19 CAR T-cell therapy.
‡ Patients 8 and 9 had preexisting hypogammaglobulinemia due to previous rituximab exposure.

Table 3. Long-Term Safety of CD19 CAR T-Cell Therapy in Autoimmune Disease.*

Patient No.	Disease	<3 Months	3–6 Months	6–12 Months	>12 Months
1	SLE	UTI	0	0	URTI (nonspecified)
2	SLE	0	0	URTI (SARS-CoV-2†)	URTI (nonspecified)
3	SLE	URTI (SARS-CoV-2)	0	URTI (nonspecified)	URTI (SARS-CoV-2) and herpes zoster
4	SLE	0	0	0	Otitis
5	SLE	0	URTI (SARS-CoV-2†)	0	0
6	SLE	0	URTI (SARS-CoV-2† and RSV)	URTI (SARS-CoV-2†)	URTI (nonspecified)
7	SLE	0	0	0	
8	SLE	Pneumonia	0		
9	IIM	0	Enteritis (nonspecified)	0	0
10	IIM	0	Herpes simplex	0	0
11	IIM	URTI (nonspecified)	0		
12	SSc	0	URTI (*Haemophilus influenzae*)	0	0
13	SSc	0	Cellulitis	Herpes zoster	
14	SSc	URTI (SARS-CoV-2†)	0		
15	SSc	0			

* Shown is the infection profile of patients with autoimmune disease undergoing CD19 CAR T-cell therapy. Data are presented chronologically and according to site of infection. RSV denotes respiratory syncytial virus, SARS-CoV-2 severe acute respiratory syndrome coronavirus 2, URTI upper respiratory tract infection, and UTI urinary tract infection.
† The infection was treated with nirmatrelvir–ritonavir (Paxlovid).

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- In this case series, CD19 CAR T-cell transfer appeared to be feasible, safe, and efficacious in three different autoimmune diseases, providing rationale for further controlled clinical trials.

- Οι ασθενείς παραμένουν σε υφεση ΧΩΡΙΣ θεραπεία!!

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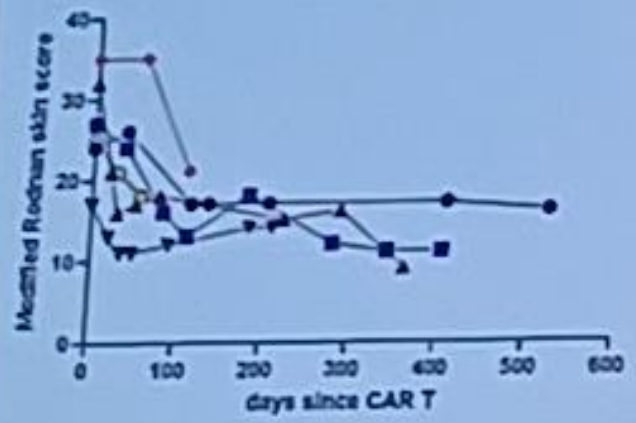
Patient characteristics at baseline

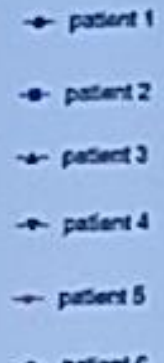
Move to Archive ×

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Demographics						
Age (years)	60	36	37	47	55	29
Sex (female/male)	male	male	female	male	male	female
Disease duration (months)	23	30	15	134	42	47
EUSTAR activity index (0-10)	4.75	9.00	5.25	3.93	7.75	4.00
Laboratory values						
Baseline ANA (titre)	1:320	1:10,000	1:10,000	1:1000	1:3200	1:3200
Baseline ENA profile	RNAP-III	Scl70	Scl70	Scl70	Scl70	Scl70
Skin involvement						
mRSS (0-51)	24	27	32	17	35	25
Tendon friction rubs	√	√	-	-	-	-
Digital ulcerations	-	√	√	-	√	-
Lung involvement						
	√	√	√	√	√	√
Pulmonary hypertension	√	-	-	√	-	-
Heart involvement						
	√	√	-	-	√	-
Kidney involvement						
Renal crisis	-	-	√	-	-	-
Treatments						
Failed treatment	MMF, MTX	MMF, Prednisolone, Hydroxychloroquine	MMF, MTX, Tocilizumab, Rituximab	MMF, Cyclophosphamid	MMF, MTX, Prednisolone, Rituximab, Cyclophosphamid	MMF, MTX, Rituximab

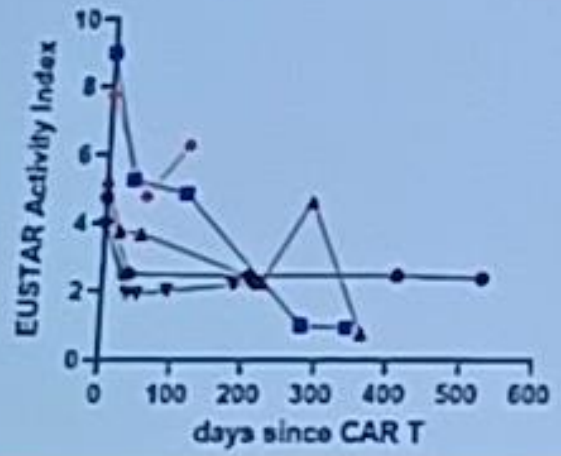
Skin involvement and disease activity

Modified Rodnan Skin Score (mRSS)

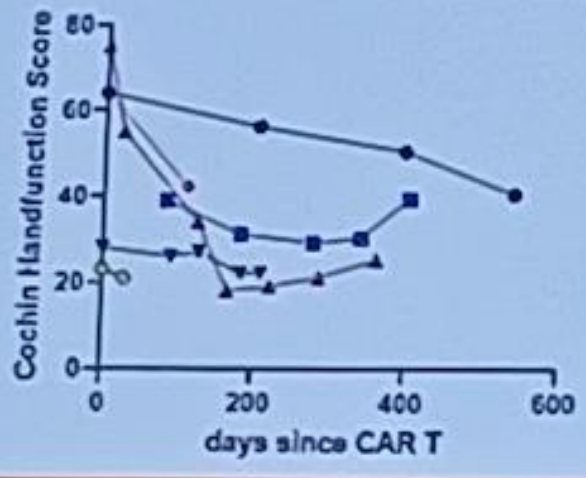




EUSTAR Activity Index



Cochin Hand Function Scale



Digital ulcerations

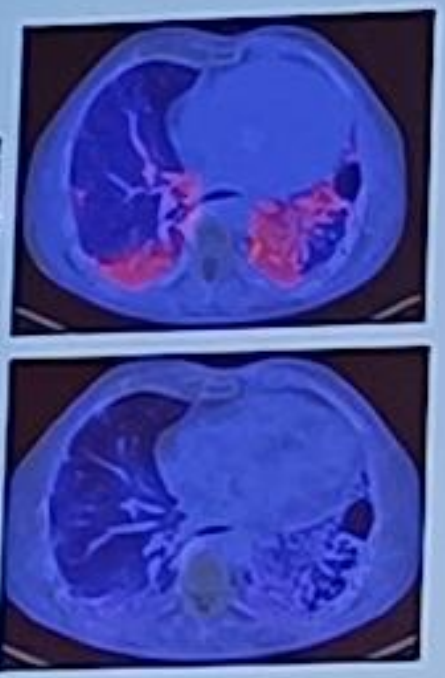
Patient 3

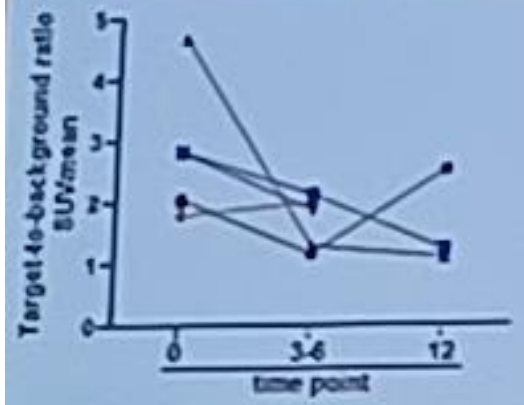
before CAR T therapy

4 weeks after CAR T therapy

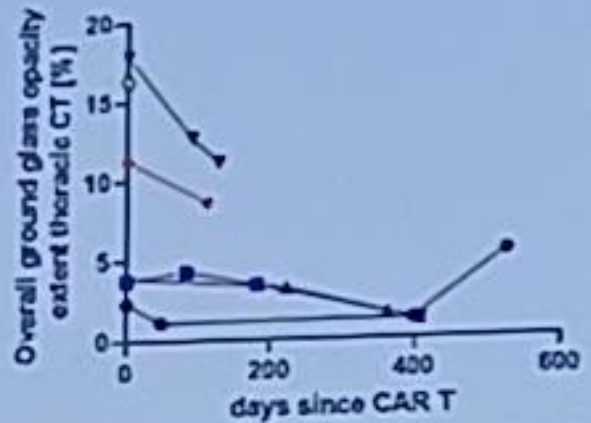
Lung involvement

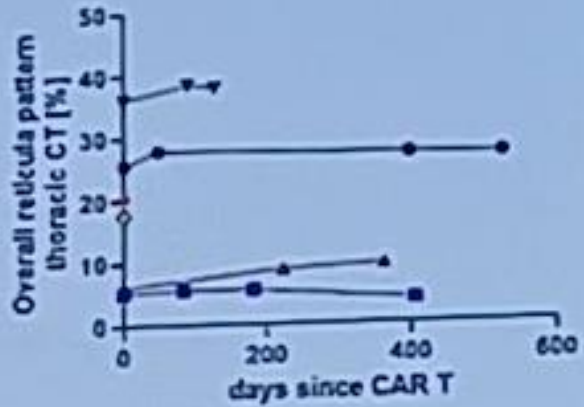
^{68}Ga-FAPI-04-PET-CT



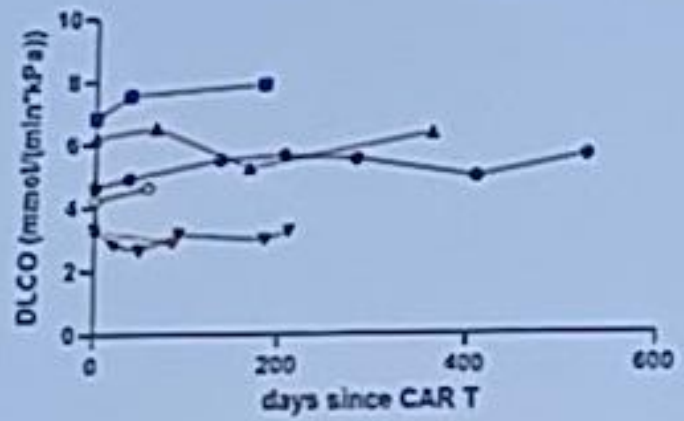


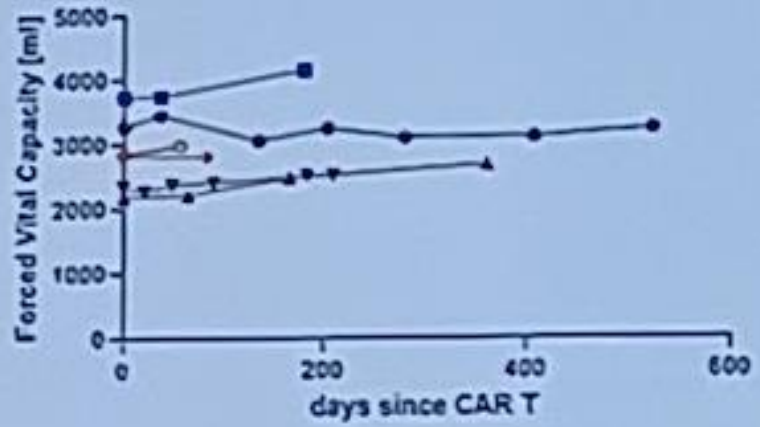
Thoracic CT



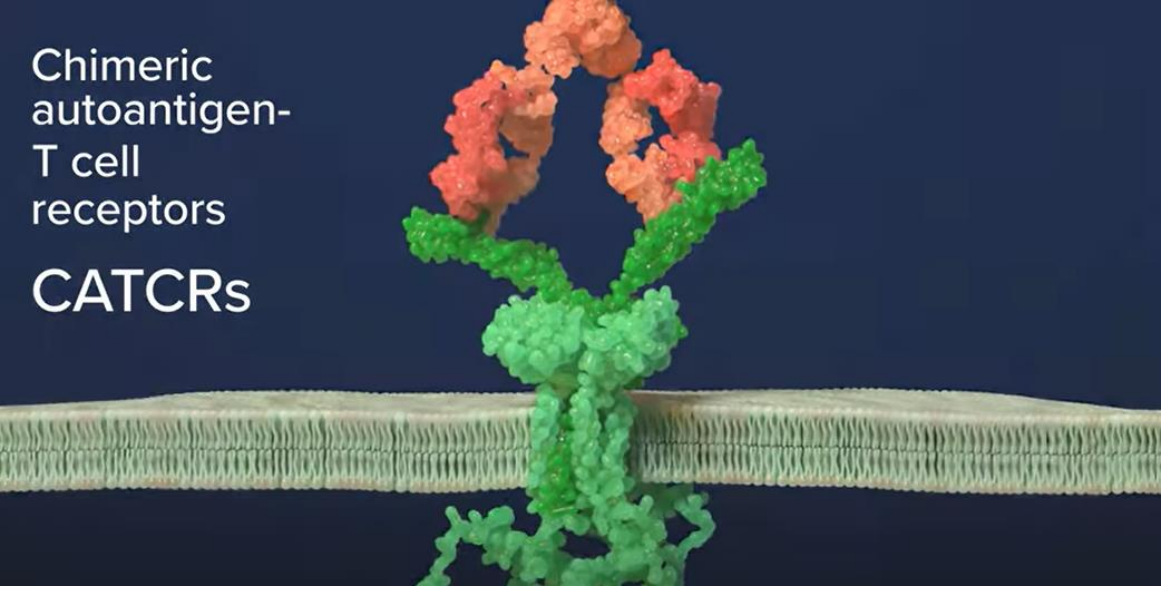


Pulmonary function





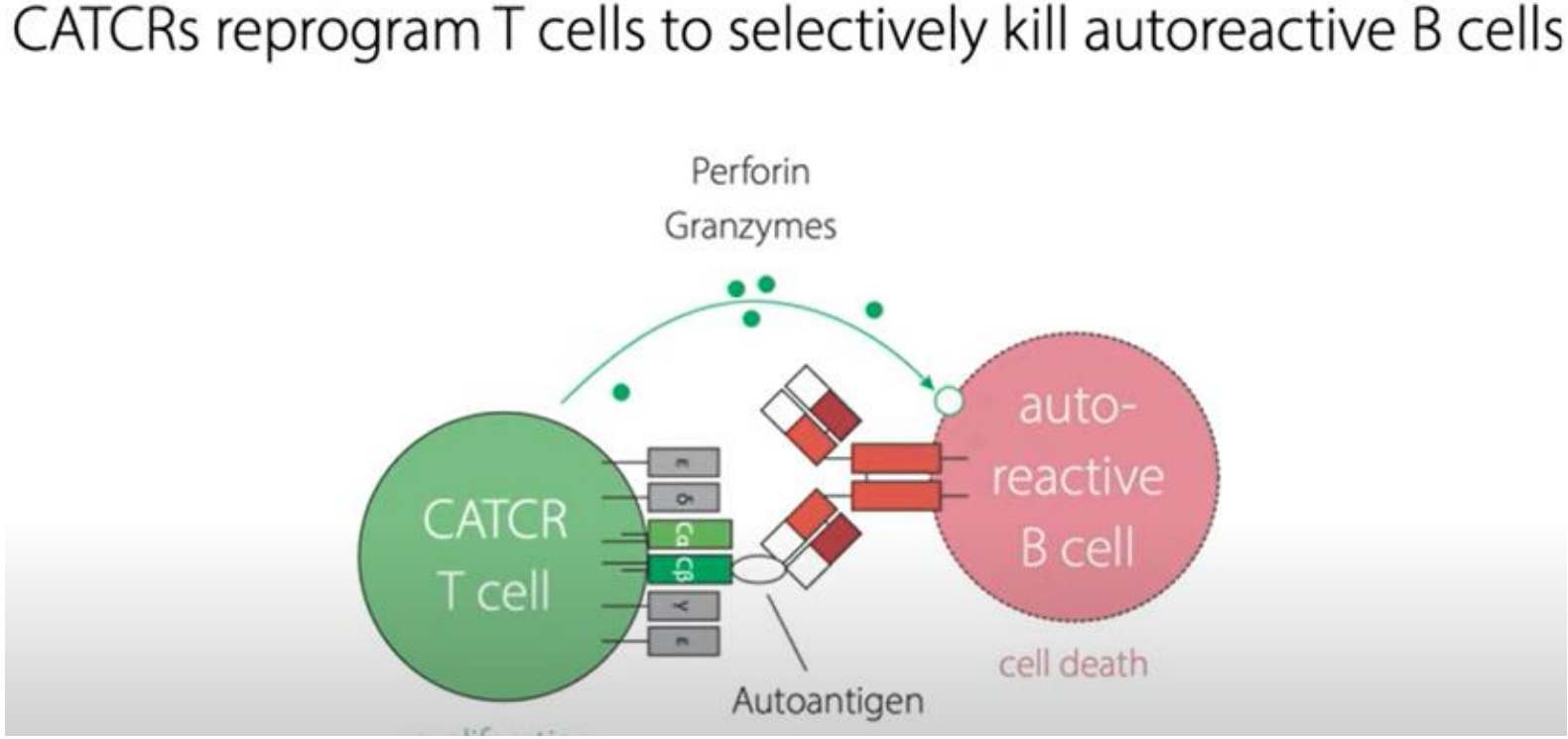
patient 1 patient 2 patient 3 patient 4 patient 5 patient 6

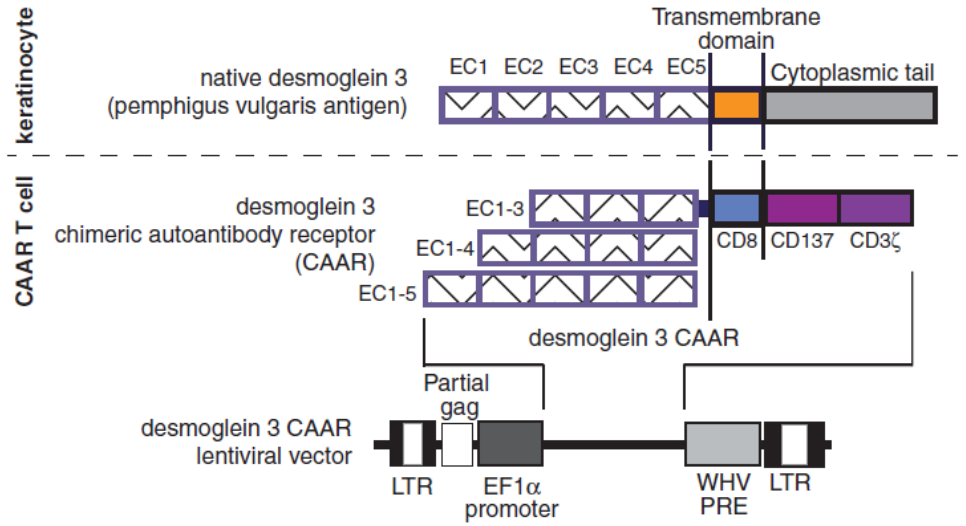


CAAR T. Η εξελιξη…

- Το ιδανικο σε αυτοανοσα νοσηματα

- Να στοχευσεις μονο τα αυτοαντιδραστικα Β λεμφοκυτταρα

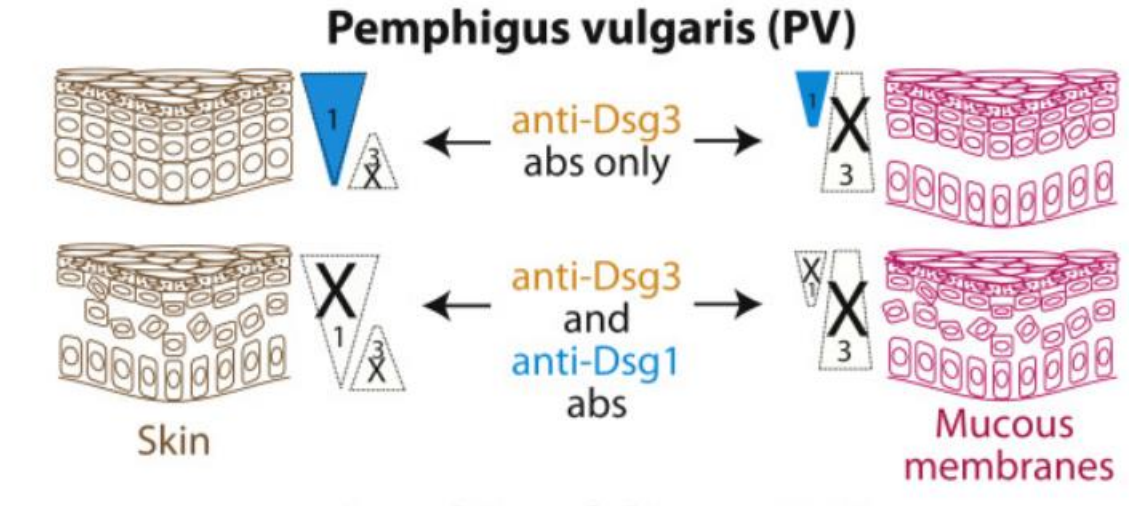


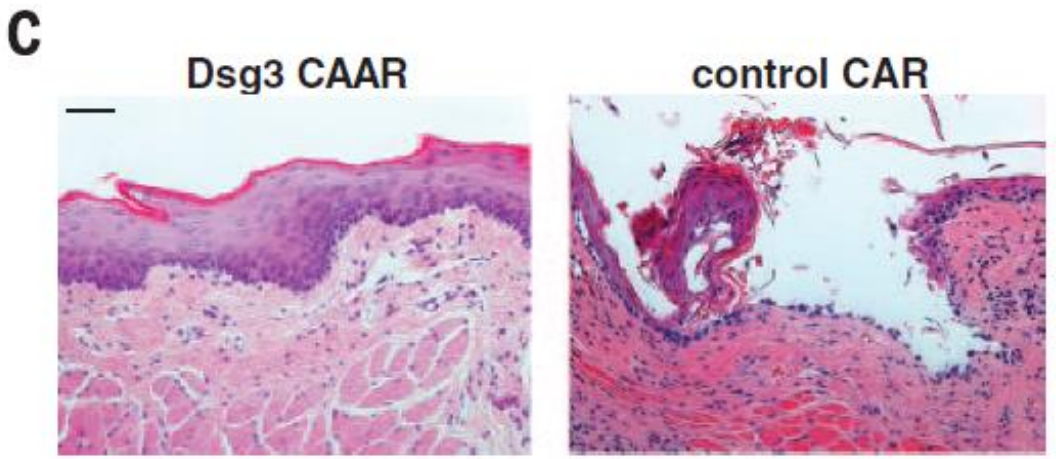


IMMUNOTHERAPY

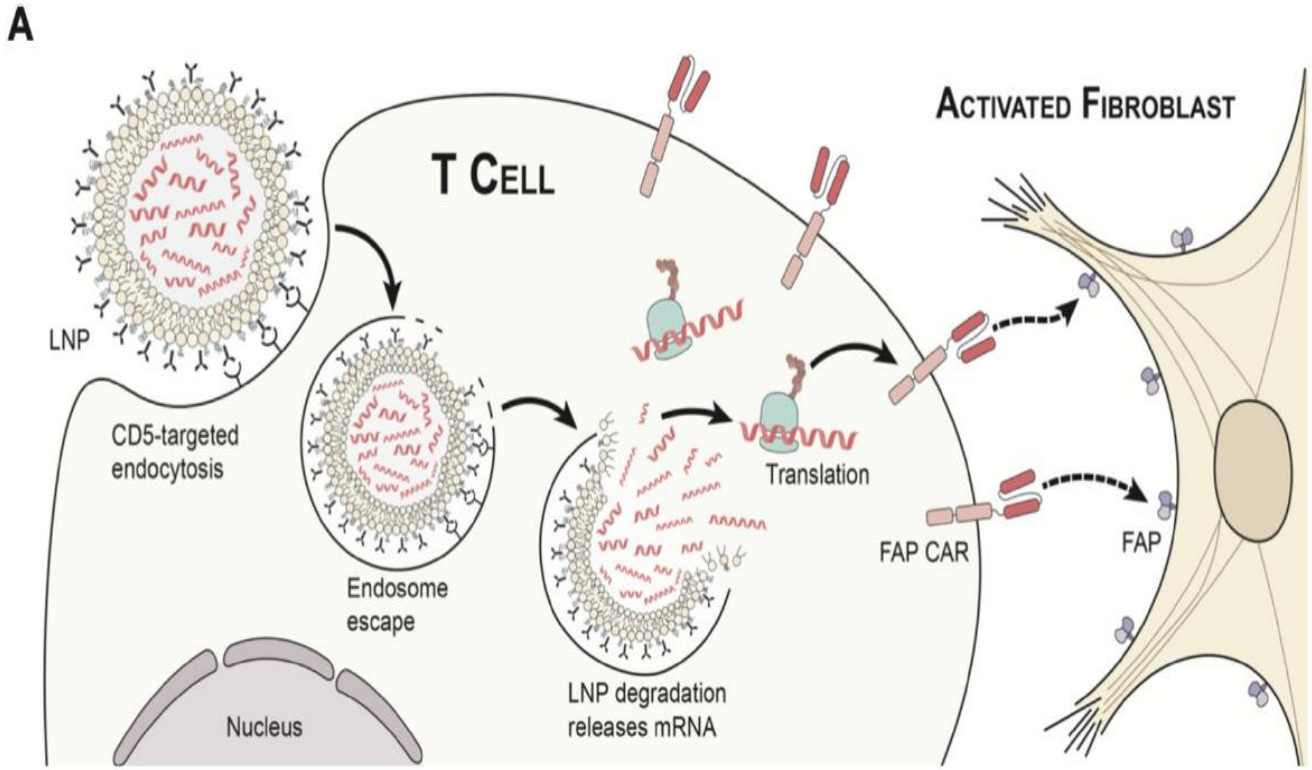
Reengineering chimeric antigen receptor T cells for targeted therapy of autoimmune disease

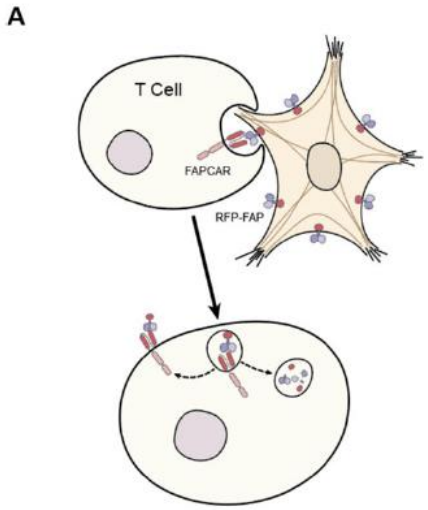
Christoph T. Ellebrecht,[1] Vijay G. Bhoj,[2] Arben Nace,[1] Eun Jung Choi,[1] Xuming Mao,[1] Michael Jeffrey Cho,[1] Giovanni Di Zenzo,[3] Antonio Lanzavecchia,[4] John T. Seykora,[1]

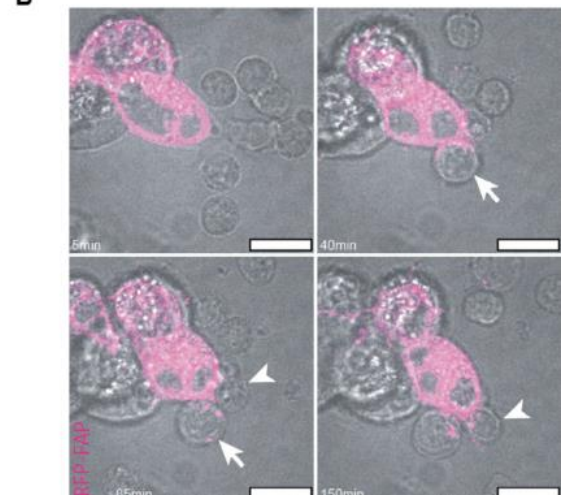


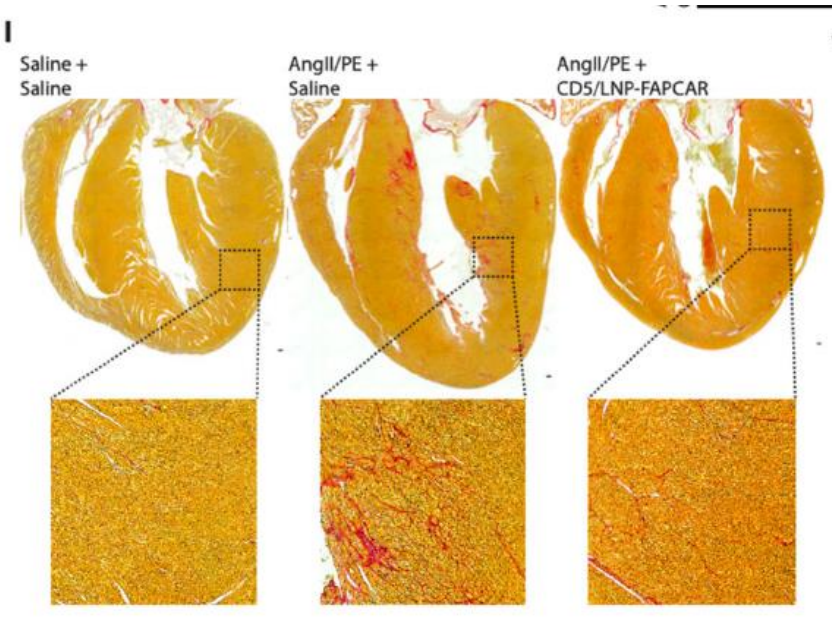


CAR T in vivo???









Published in final edited form as:
Science. 2022 January 07; 375(6576): 91–96. doi:10.1126/science.abm0594.

CAR T cells produced *in vivo* to treat cardiac injury

HHS Public Access
Author manuscript
N Engl J Med. Author manuscript; available in PMC 2020 August 06.

Published in final edited form as:
N Engl J Med. 2020 February 06; 382(6): 545–553. doi:10.1056/NEJMoa1910607.

Use of CAR-Transduced Natural Killer Cells in CD19-Positive Lymphoid Tumors

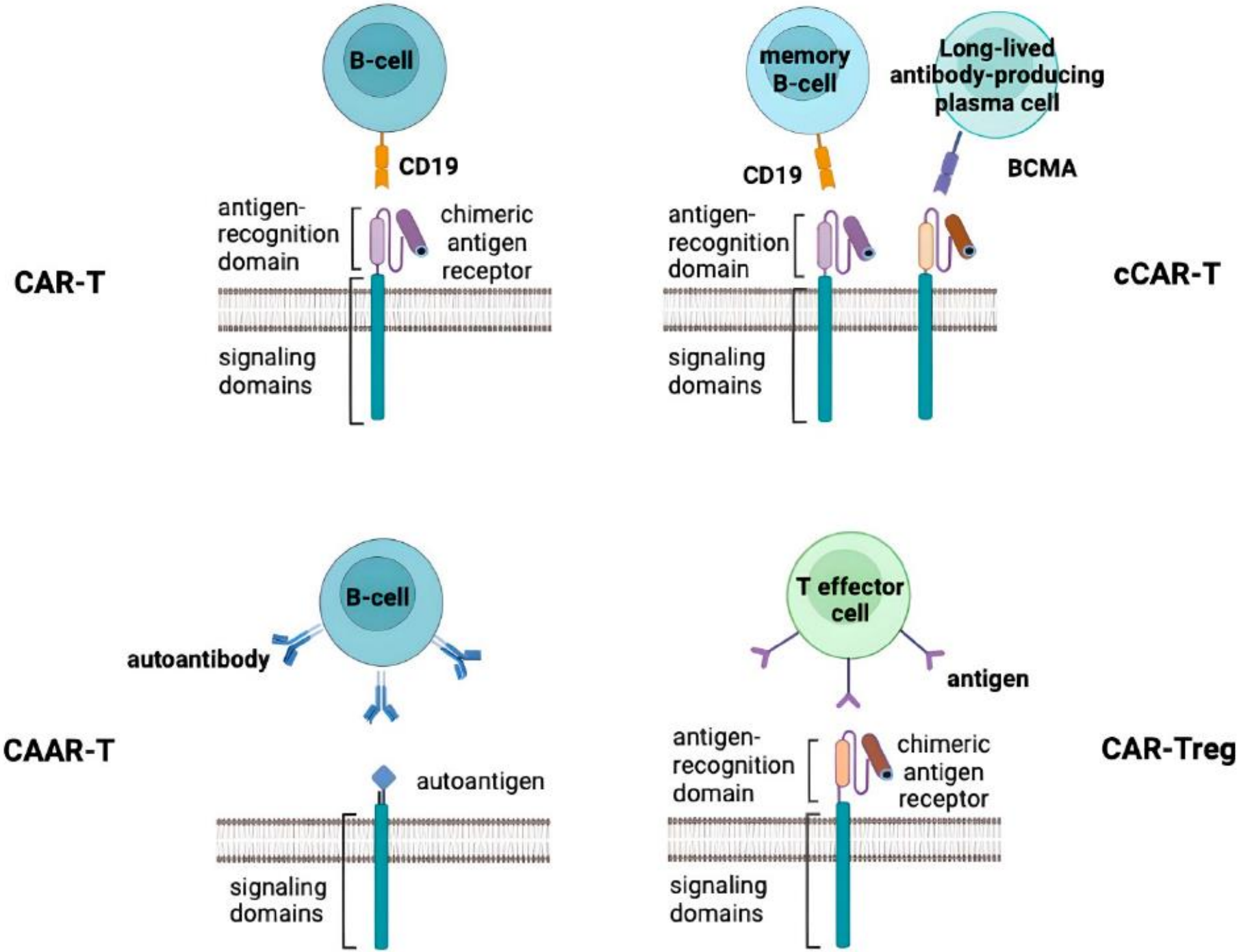
- Μεγαλη προσπαθεια να κατασκευαστουν CAR από αλλα κυτταρα πλην Τ κυτταρων
  - ΝΚ
  - Μακροφαγα…
- Καλυτερη ιστικη διεισδυση?
- Δυνατοτητα ετερολογης χρησης? (πχ από δοτες). Σημαντικα πλεονεκτηματα λογω χαμηλοτερου κοστους και ευκολιας χρησης

Που καταληγουμε?

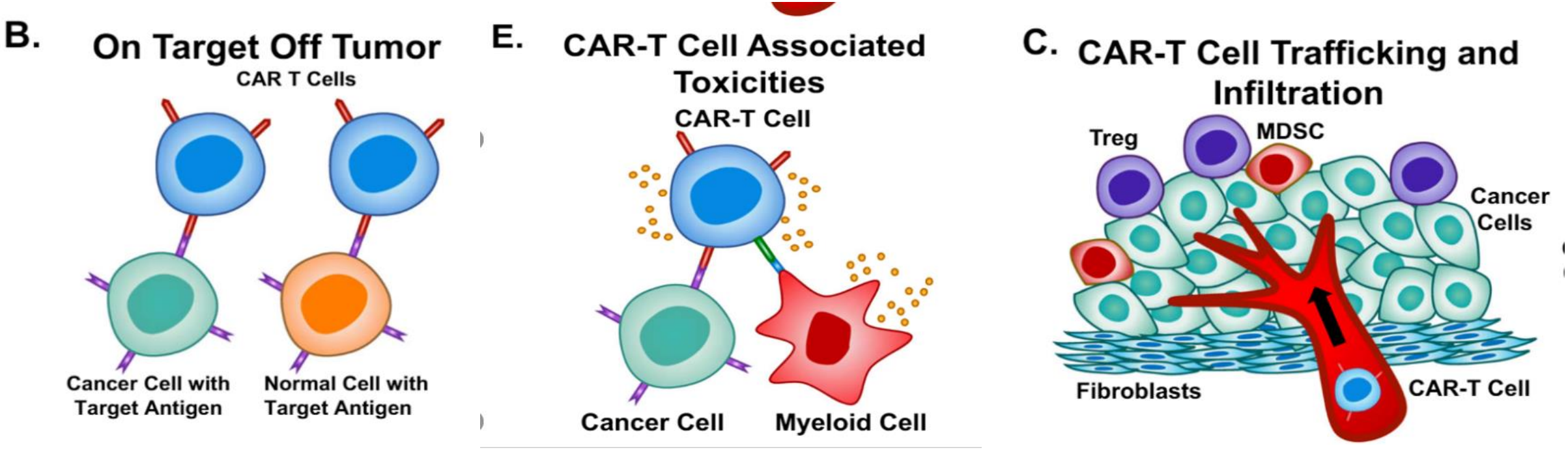
- Φαινεται να είναι αποτελεσματικα σε CTDs με ανεκτο προφιλ ασφαλειας
- Υπερβολικα αισιόδοξο να πιστέψει καποιος σε «ιαση» (ακομη και η κλασσικη μεταμοσχευση αρχεγονων αιμοποιητικων κυτταρων δεν ηταν θεραπευτικη…)
- Σε αναμονη για τυχαιοποιημενες μελετες

- **Πρεπει να μαθουμε καλυτερη Βιολογια και Ανοσολογια!!!**

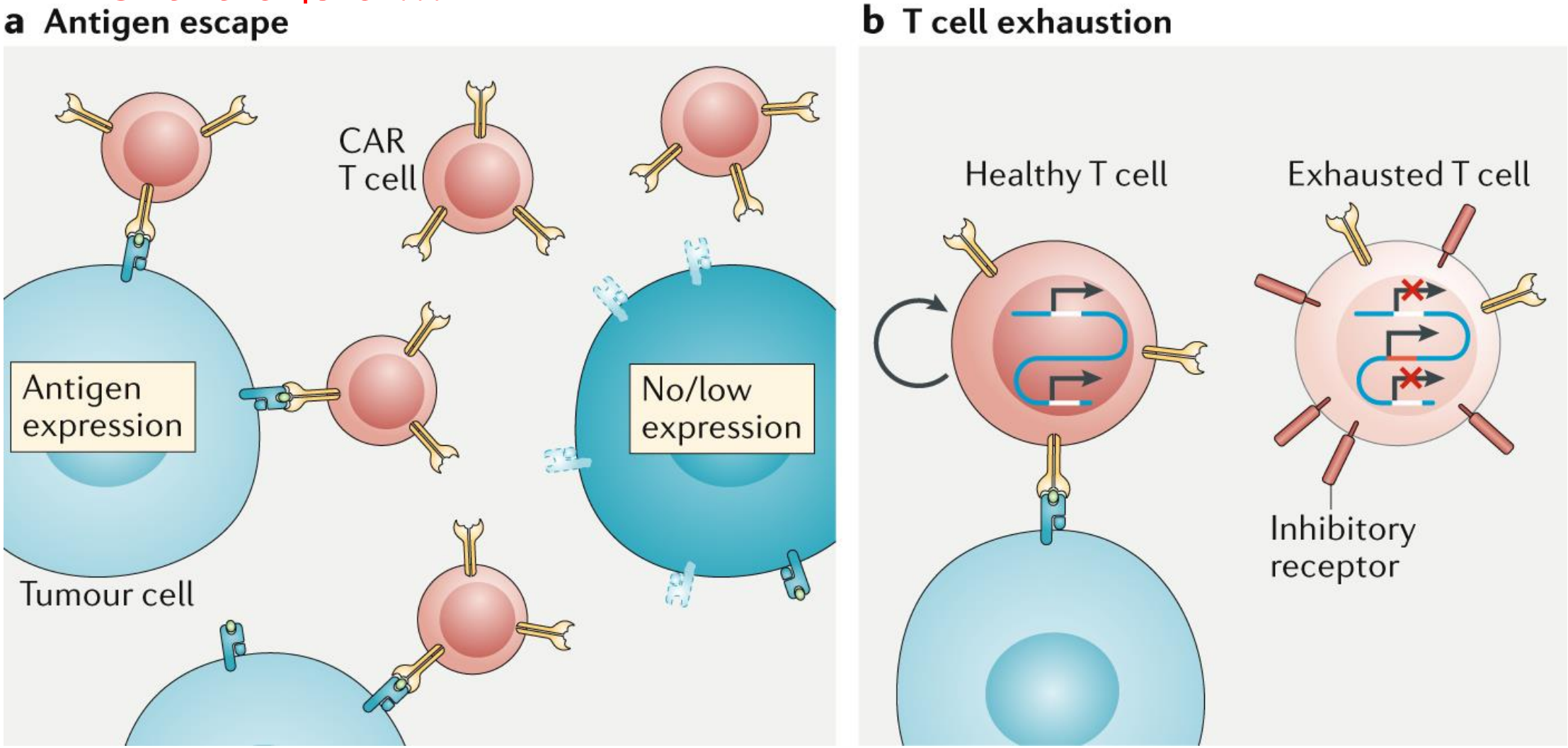
Email: jimdaoussis@hotmail.com

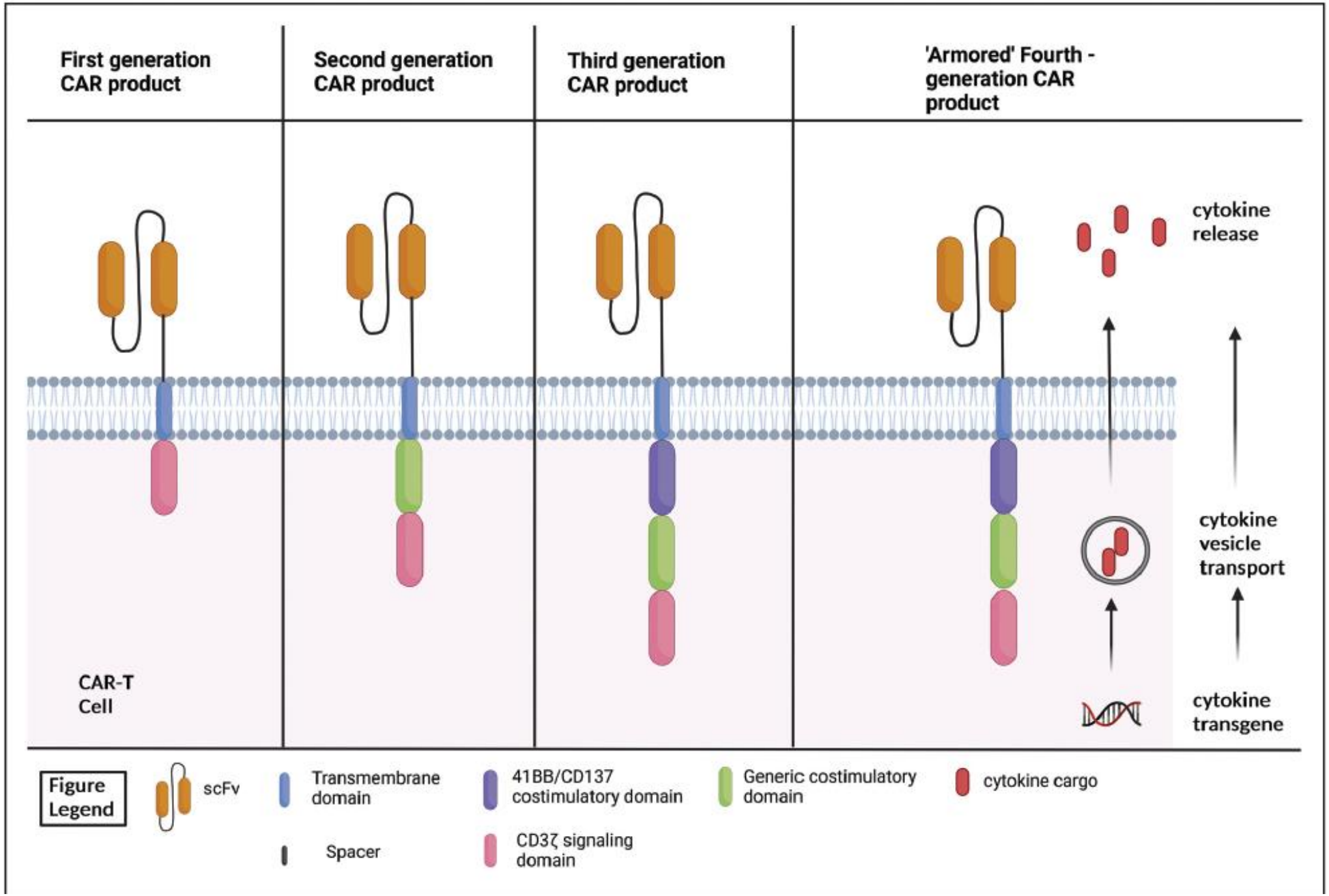

CAR-T
B-cell
CD19
antigen-recognition domain
chimeric antigen receptor
signaling domains
cCAR-T
memory B-cell
Long-lived antibody-producing plasma cell
CD19
BCMA
antigen-recognition domain
signaling domains
CAAR-T
B-cell
autoantibody
autoantigen
signaling domains
CAR-Treg
T effector cell
antigen
antigen-recognition domain
chimeric antigen receptor
signaling domains

Προβλήματα με την CAR T ανοσοθεραπεία



Πως αμύνονται τα καρκινικά κύτταρα…




First generation CAR product
Second generation CAR product
Third generation CAR product
'Armored' Fourth - generation CAR product
cytokine release
cytokine vesicle transport
cytokine transgene
CAR-T Cell
Figure Legend
scFv
Transmembrane domain
41BB/CD137 costimulatory domain
Generic costimulatory domain
cytokine cargo
Spacer
CD3ζ signaling domain

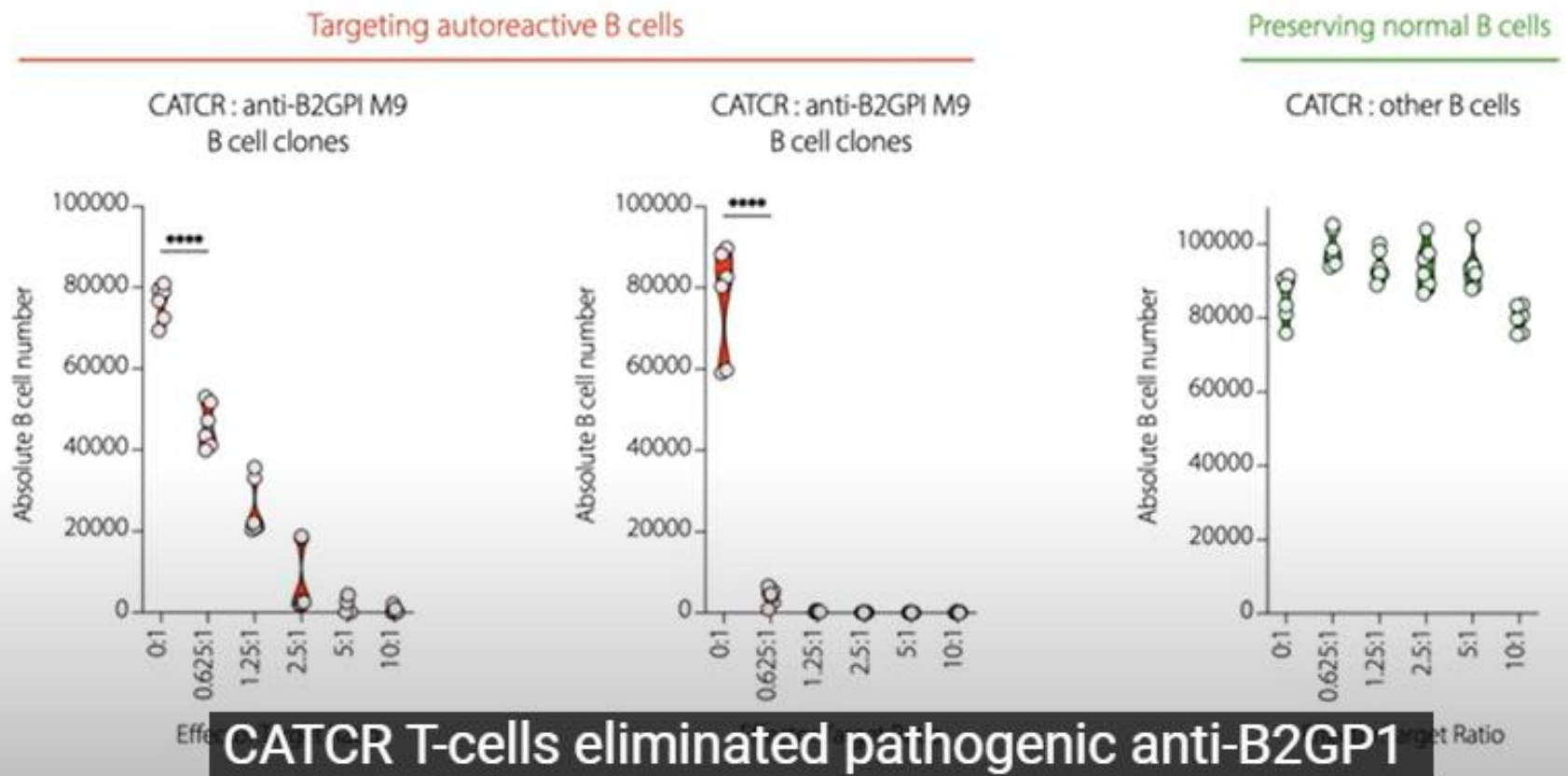
Is CAR-T worth it in AI diseases?

Should CAR-T therapies be restricted to those unlikely to cause CAR-T lymphoma?

Cartesian's Descartes-08 RNA BCMA CAR-T
Doesn't rely on multiplication of CAR-Ts in the body
The RNA BCMA CAR-T cells disappear

Downside: treatments need repeated

CATCR-T cells eliminate anti-B2GPI DI B cells



CATCR T-cells eliminated pathogenic anti-B2GP1

The Journal of Immunology

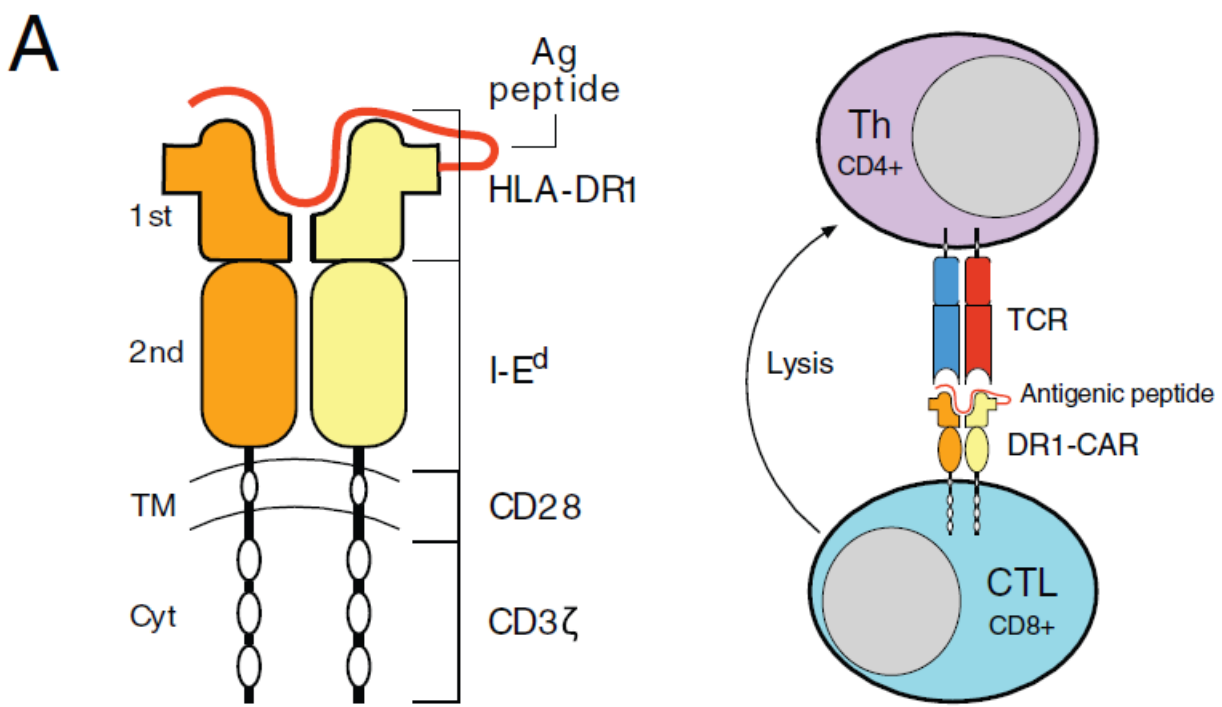
RESEARCH ARTICLE | JANUARY 01 2022

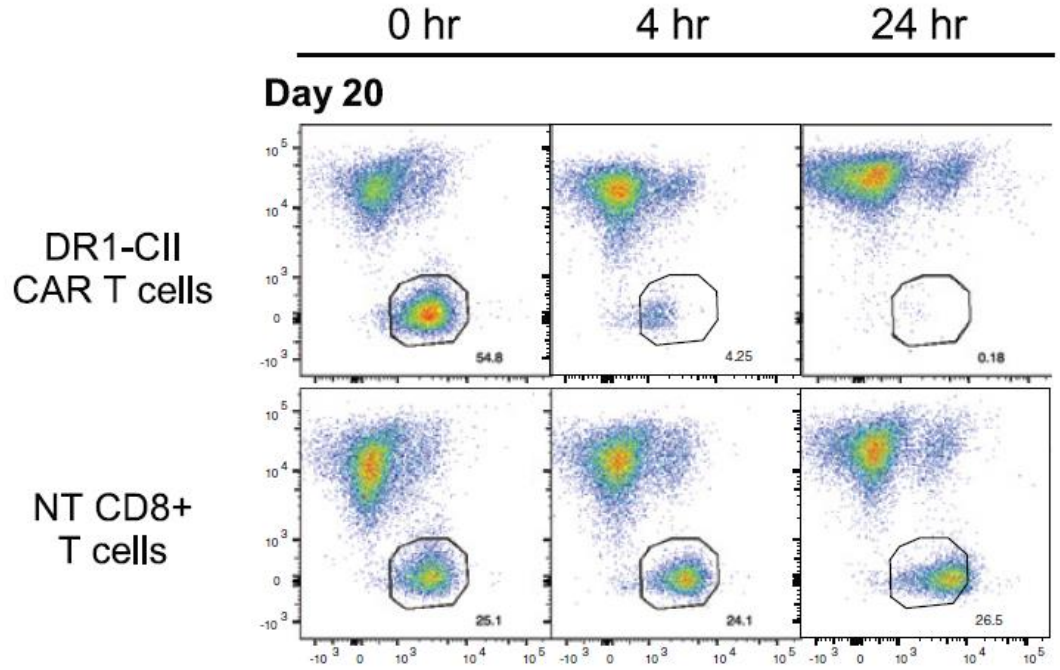
CD8+ T Cells Expressing an HLA-DR1 Chimeric Antigen Receptor Target Autoimmune CD4+ T Cells in an Antigen-Specific Manner and Inhibit the Development of Autoimmune Arthritis

Karen B. Whittington; ... et. al

J Immunol (2022) 208 (1): 16–26.

https://doi.org/10.4049/jimmunol.2100643



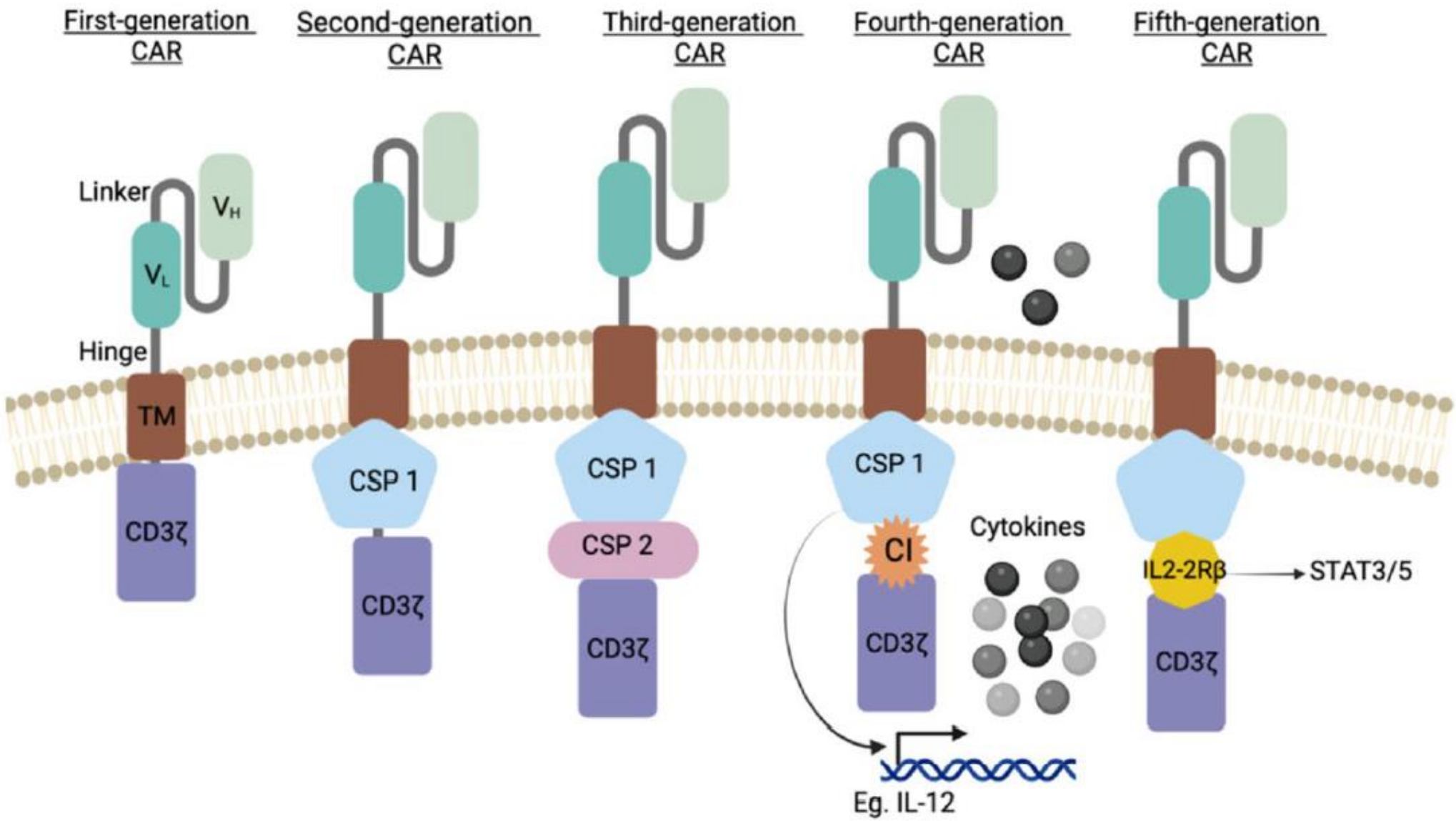


nature communications

Article

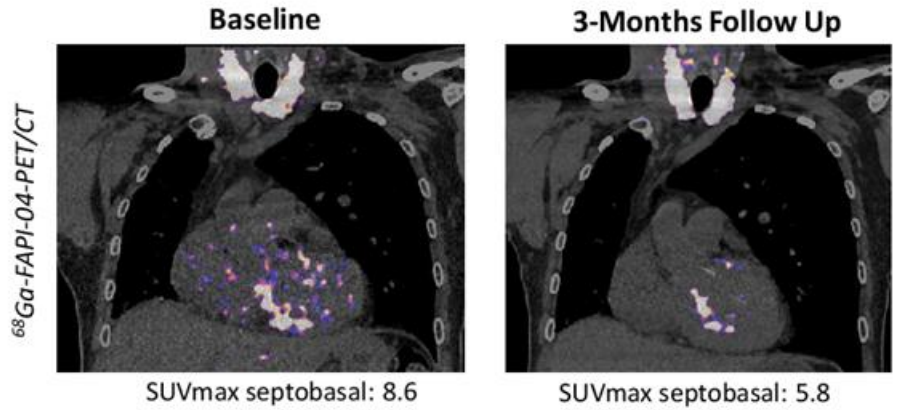
https://doi.org/10.1038/s41467-024-46448-9

Regulatory T cells expressing CD19-targeted chimeric antigen receptor restore homeostasis in Systemic Lupus Erythematosus


First-generation CAR
Second-generation CAR
Third-generation CAR
Fourth-generation CAR
Fifth-generation CAR
Linker
V_H
V_L
Hinge
TM
CD3ζ
CSP 1
CD3ζ
CSP 1
CSP 2
CD3ζ
CSP 1
CI
CD3ζ
Cytokines
Eg. IL-12
IL2-2Rβ
STAT3/5
CD3ζ

Treatment of a patient with severe systemic sclerosis (SSc) using CD19-targeted CAR T cells

D



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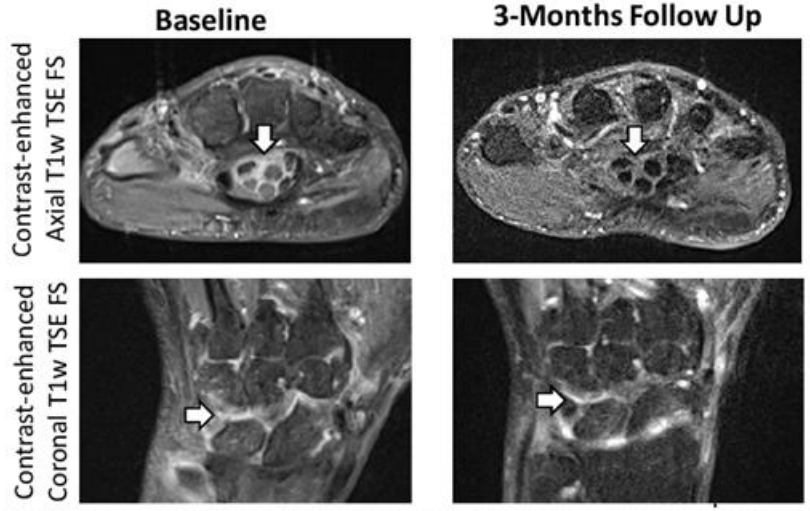

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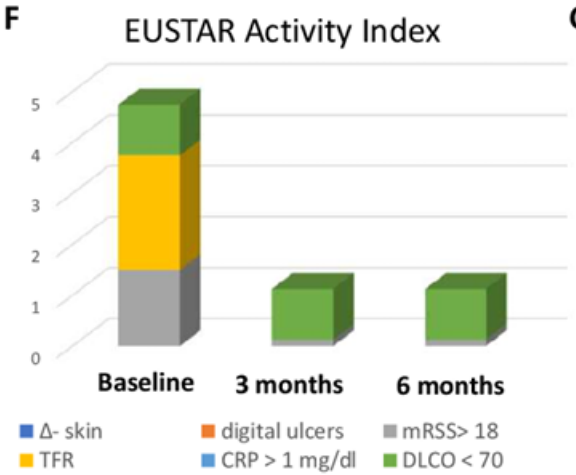

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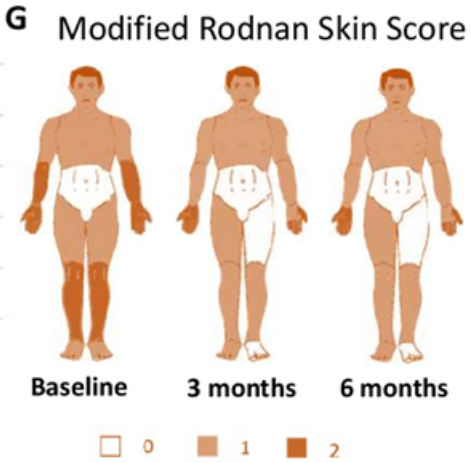

H

PFT

	Baseline	3 months follow-up	6 months follow up
FVC	3,27 l (73% pred.)	3,45 l (77% pred.)	3,21 (72% pred.)
DLCO	49 mmol/(min*kPa)	52 mmol/(min*kPa)	59 mmol/(min*kPa)
KCO	58 mmol/(min*kPa*l)	68 mmol/(min*kPa*l)	80 mmol/(min*kPa*l)

I

TTE

	Baseline		6 months follow up
EF	55-60%		55-60%
PASP	27 mmHg		20 mmHg
RA area	31 cm^2		17 cm^2