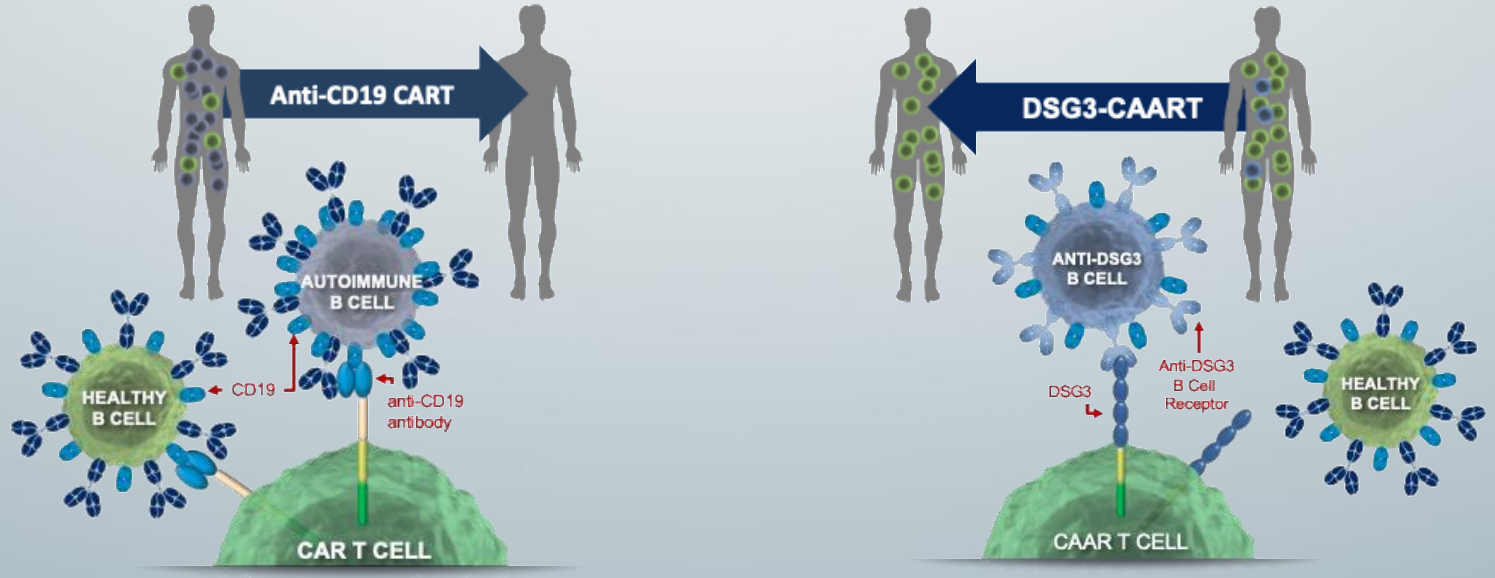
Engineered T cell therapies for autoimmunity: the next frontier



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COLUMBIA | COLUMBIA UNIVERSITY IRVING MEDICAL CENTER

Disclosures

• Cabaletta Bio (equity, payments, grants, patent licensing) • Janssen, Sanofi, BMS, Avilar (consulting)

Unleashing immune cells on autoimmune disease

Science magazine's 2024 runner-up for Breakthrough of the Year

Number of global trials studying CAR T cell therapies for cancer initiated each year

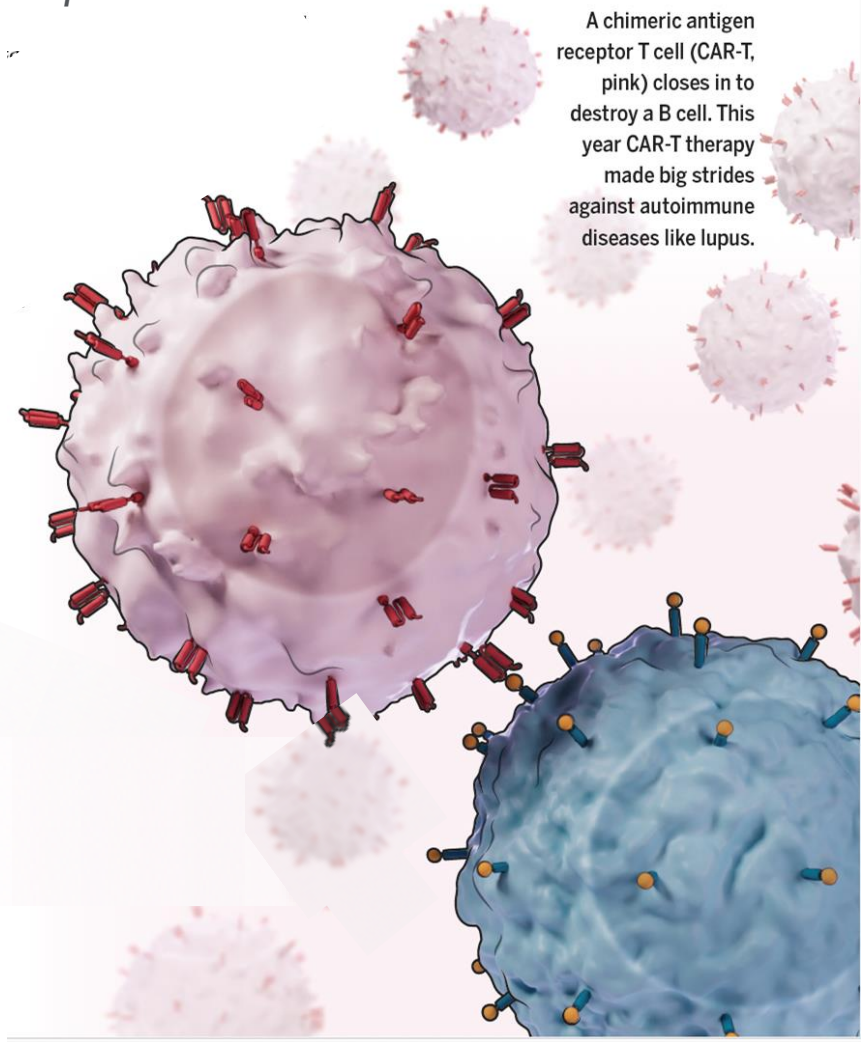
2011: First case report of complete remission of B cell leukemia with CAR T cells

- 2012: 8
- 2016: 75
- 2020: 181
- 2024: 250

Number of global trials studying CAR T cell therapies for autoimmune disease initiated each year

2021: First case report of complete remission of SLE with CAR T cells

- 2022: 5
- 2023: 14
- 2024: 67

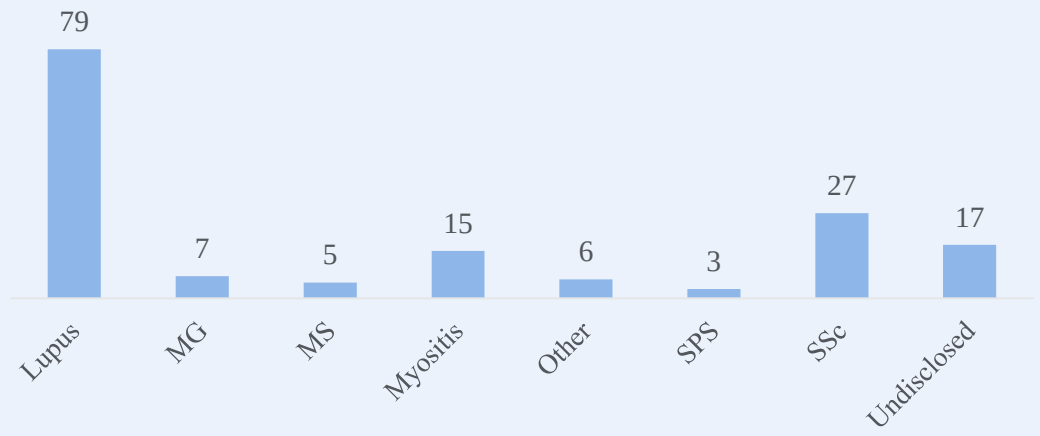


A chimeric antigen receptor T cell (CAR-T, pink) closes in to destroy a B cell. This year CAR-T therapy made big strides against autoimmune diseases like lupus.

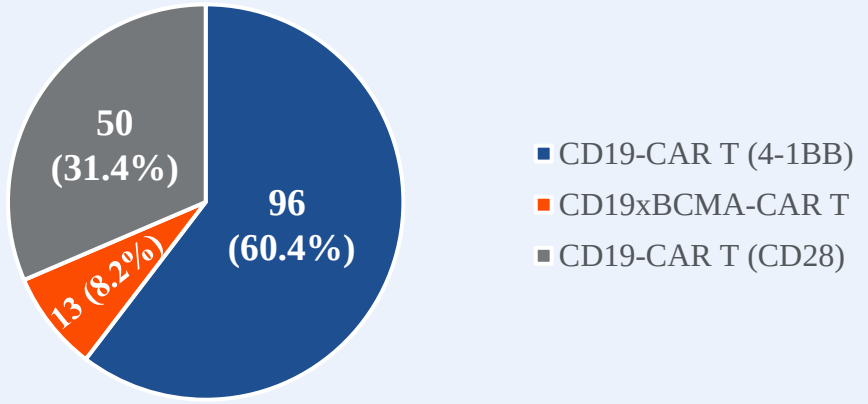
Porter et al, NEJM 2011; Mougiakakos, NEJM 2021; clinicaltrials.gov – search criteria " "cancer" or "autoimmune disease" and "CAR-T cell"
Illustration adapted from N. Burgess/Science; Graphic adapted from Catalyst Healthcare Consulting

Autologous anti-CD19 CART outcomes in autoimmunity[1]

Patients Treated (by Disease)



Type of CAR T Construct



Safety Observations

- **CRS/ICANS less frequent/severe** in autoimmune compared to cancer patients
  - **<2% Gr 3+ CRS & Gr 3+ ICANS** events across >150 autoimmune patients dosed with cell therapy
- **Vaccine titers stable** with anti-CD19-CART therapy
  - Insufficient data on CD19xBCMA-CAR T

Efficacy Observations

- **Clinical responses off immunosuppressants** observed across many autoimmune diseases, **up to ~4 years** of durability
- **Clinical relapses observed in <5%** of treated patients
  - SLE patient with BMI>40 and $5x10^7$ CART dose (CD28 co-stim)
  - IIM patient relapsed after 12 mos drug-free remission (4-1BB co-stim)
    - BCMA-CAR T treatment led to subsequent remission[2]

IIM – idiopathic inflammatory myopathy; MG – Myasthenia gravis; MS – Multiple sclerosis; SPS – Stiff person syndrome; SSc – Systemic sclerosis.
Note: 'Other' indications includes CIDP, IgG4-related disease, ANCA-associated vasculitis, NMOSD, Lambert Eaton myasthenic syndrome, autoimmune encephalitis.

1. Data as of November 2024 based on Cabaletta Bio literature review
2. Abstract 1749: Safety and Long-term Efficacy of CD19-CAR T-cell Therapy in 30 Patients with Autoimmune Disease. ACR Convergence 2024

Baseline Characteristics: 1st 10 Patients in RESET™ Program

All patients had active, refractory disease and most had failed B cell-targeting therapies

	RESET-Myositis™			RESET-SLE™						RESET-SSc™
Patient / Cohort	**IMNM-1**	**IMNM-2**	**DM-1**	**SLE-1†** Class V LN	**SLE-2**	**SLE-3**	**SLE-4**	**LN-1**	**LN-2**	**SSc-Skin-1** Severe skin cohort
Age, sex	33 M	60 M	57 M	26 M	36 F	44 F	37 F	24 F	35 F	66 F
Disease duration (y)	~2	~4	~4	~6	~17	~9	~10	~2	~8	~2
Autoantibodies	SRP	HMGCR	SAE	dsDNA	dsDNA	dsDNA	dsDNA	dsDNA	dsDNA	RNA P III
Baseline Disease activity*	**MMT-8**			**SLEDAI-2K**						**mRSS**
	130	126	131	26	10	8	8	22	14	42
	CK (U/L)			**UPCR (mg/mg)**						
	617	4725	94	1.08†	n/a	n/a	n/a	7.22	4.85	
Therapies at Screening	GC, MTX	GC, IVIG	GC, MMF, HCQ	HCQ, GC, MMF	GC, AZA	HCQ, MMF, BEL	HCQ‡	HCQ, GC, MMF, ANI, VOC	MMF	MMF, BRX
Other prior therapies	RTX, IVIG	RTX, MMF, MTX	IVIG	CYC, BEL, VOC, TAC	HCQ, MTX, ANI, BEL, MSC, RTX, ADA	GC, MTX	MTX, BEL	BEL, LEF	HCQ, GC, AZA, RTX	HCQ
GC dose at Screening (mg/day)#	5	5	20	10	7	n/a	n/a‡	20	N/A	N/A

*Baseline disease activity = activity before preconditioning. #Prednisone/prednisone equivalent dose
†SLE-1 had class V LN; inclusion criteria for LN cohort requires class III/IV LN. ‡SLE-4 initiated 20 mg/day of prednisone after screening and before leukapheresis, tapered to 2.5mg by latest follow-up of week 8 and discontinued as of data cut.
ADA, adalimumab; ANI, anifrolumab; AZA, azathioprine; BEL, belimumab; BRX, brentuximab vedotin; CK, creatinine kinase; CYC, cyclophosphamide; DM, dermatomyositis; dsDNA, double-stranded DNA; GC, glucocorticoid; HCQ, hydroxychloroquine; HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; IMNM, immune-mediated necrotizing myopathy; IVIG, intravenous immunoglobulin; LEF, leflunomide; LN, lupus nephritis; MMF, mycophenolate mofetil; MMT-8, manual muscle testing 8; mRSS, modified Rodnan skin score; MSC, mesenchymal stem cell; MTX, methotrexate; RESET, REstoring SElf-Tolerance; RNA P III, RNA polymerase III; RTX, rituximab; SAE, small ubiquitin-like modifier activating enzyme; SLE, systemic lupus erythematosus; SLEDAI-2K, SLE disease activity index 2000; SRP, signal recognition particle; SSc, systemic sclerosis; TAC, tacrolimus; U/L, units per liter; UPCR, urinary protein-to-creatinine ratio; VOC, voclosporin, y, years.
Cabaletta Bio: Data on file.

Incidence and Severity of Adverse Events*

	RESET-Myositis™			RESET-SLE™						RESET-SSc™
Cohort	**IMNM**		**DM**	**Non-renal SLE**				**LN**		**Severe Skin**
Patient	**IMNM-1**	**IMNM-2**	**DM-1**	**SLE-1**	**SLE-2**	**SLE-3**	**SLE-4**	**LN-1**	**LN-2**	**SSc-Skin-1**
CRS†	None	None	None	None	Grade 1	None	None	Grade 1	None	Grade 2
ICANS†	None	None	None	None	None	None	None	Grade 4	None	None
Serious infections‡	None	None	None	None	None	None	None	None	None	None
Hypogamma-globulinemia	None	None	None	None	None	None	None	Grade 2	None	None
Related SAEs (Grade)§ (excluding CRS and ICANS)	None	None	None	None	None	None	None	Fever (1) Neutropenic fever (1) Pancytopenia¶ (4)	None	None
Unrelated SAEs (Grade)§	None	Back pain (3) PE# (4)	None	None	None	None	None	None	None	Neutropenia (4) (FLU/CY related)

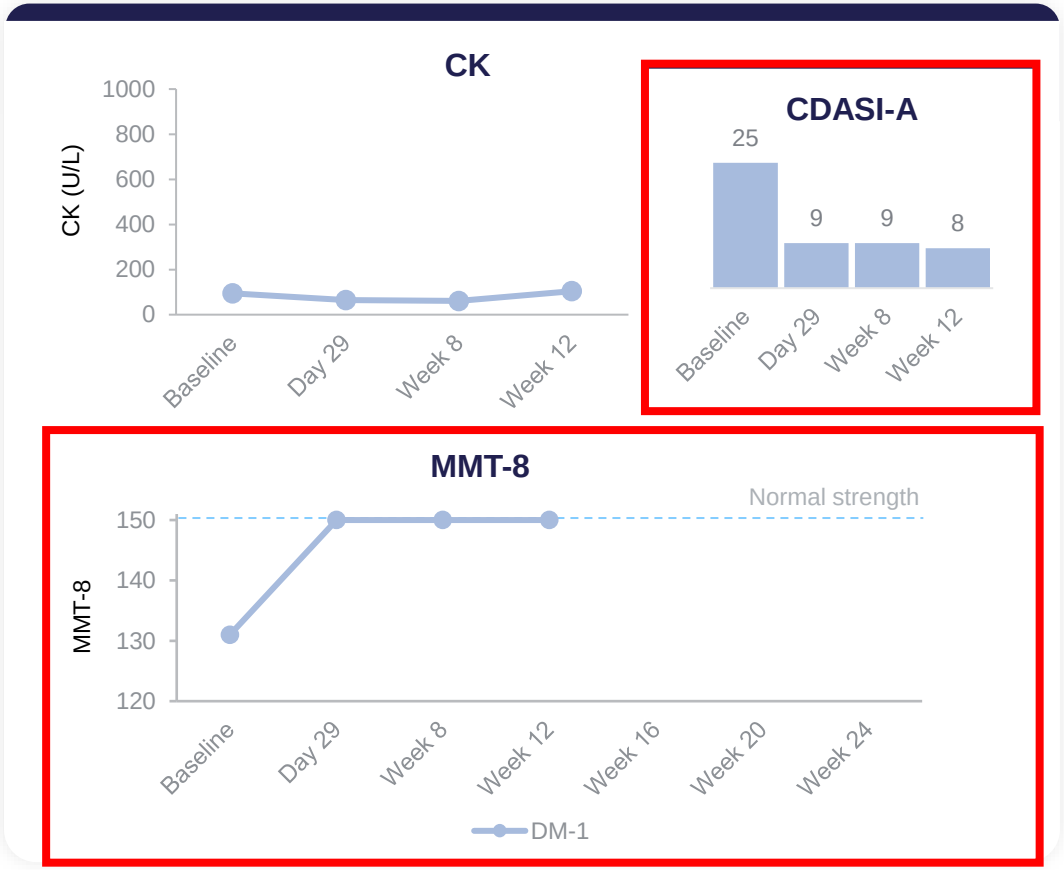
*As of Jan 8, 2025; Primary endpoint is incidence and severity of adverse events through Day 29. †Graded per ASTCT Consensus Grading Criteria. Of these patients, DM-1, SLE-2, SLE-3, SLE-4, LN-2, and SSc-Skin-1 **received** medication for seizure prophylaxis. Tocilizumab was **not** administered for any cases of CRS. ‡Coded in System Organ Class of Infections and Infestations and meets seriousness criteria. §As assessed per FDA guidelines.

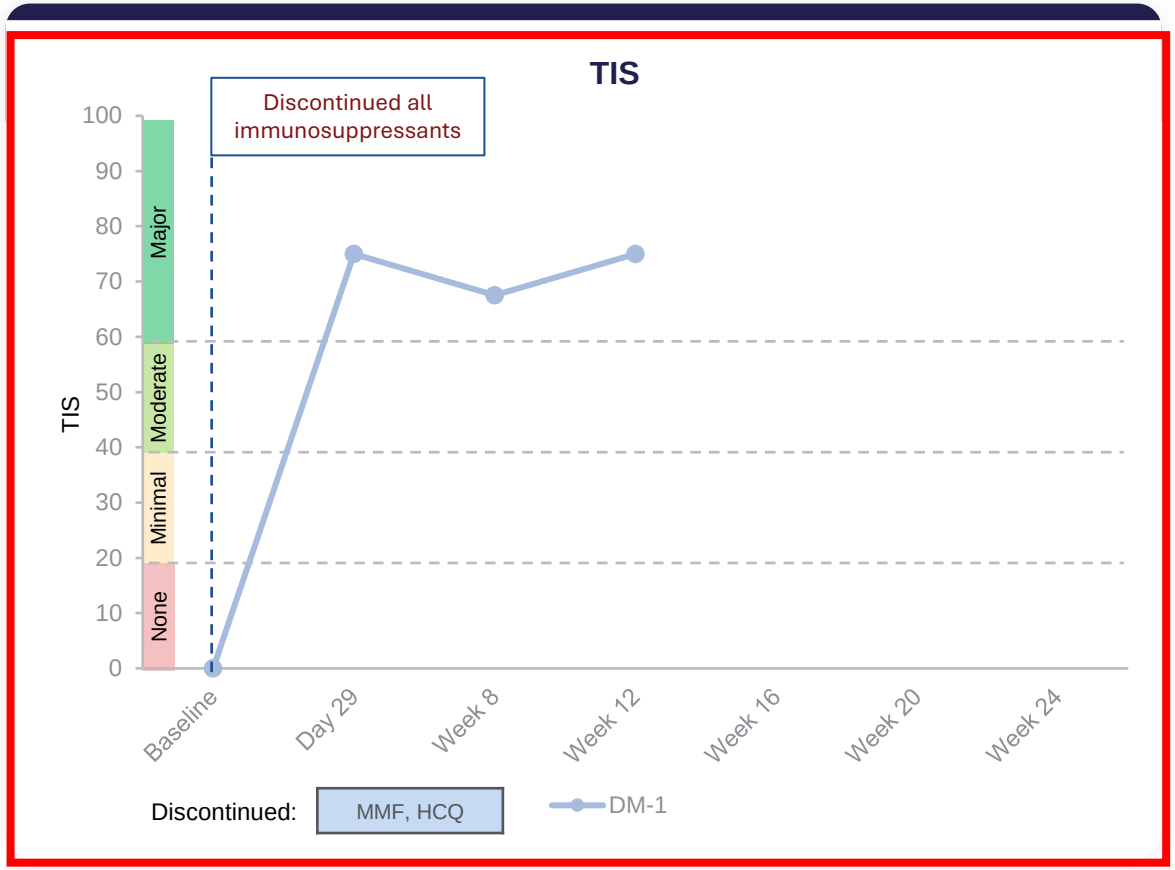
#Patient with Factor V Leiden heterozygosity (increased risk for thrombosis), recent intravenous immunoglobulin treatment, history of myocardial infarction, recent hospitalization for back pain & fatigue with decreased mobility. Undetectable CABA-201 levels since Day 22. Event occurred at Day 38 and was reported as PE leading to cardiac arrest, followed by successful pulmonary artery thrombectomy.
¶Consistent with "Prolonged Cytopenias," which is a labeled warning and precaution for approved oncology CAR T products.

ASTCT, American Society for Transplantation and Cellular Therapy; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; CY, cyclophosphamide; DM, dermatomyositis; FLU, fludarabine; ICANS, immune effector cell-associated neurotoxicity syndrome; IMNM, immune-mediated necrotizing myopathy; LN, lupus nephritis; PE, pulmonary embolism; SAE, serious adverse event; RESET, REstoring SElf-Tolerance; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.
Cabaletta Bio: Data on file.

RESET-Myositis™: Early Efficacy Data Following Rese-cel Infusion

First known adult DM patient dosed with CAR T demonstrated compelling early clinical response off immunosuppressants*





Maintenance of major response to treatment (TIS) in DM-1 shows promise for achieving drug-free remission in patients with refractory myositis

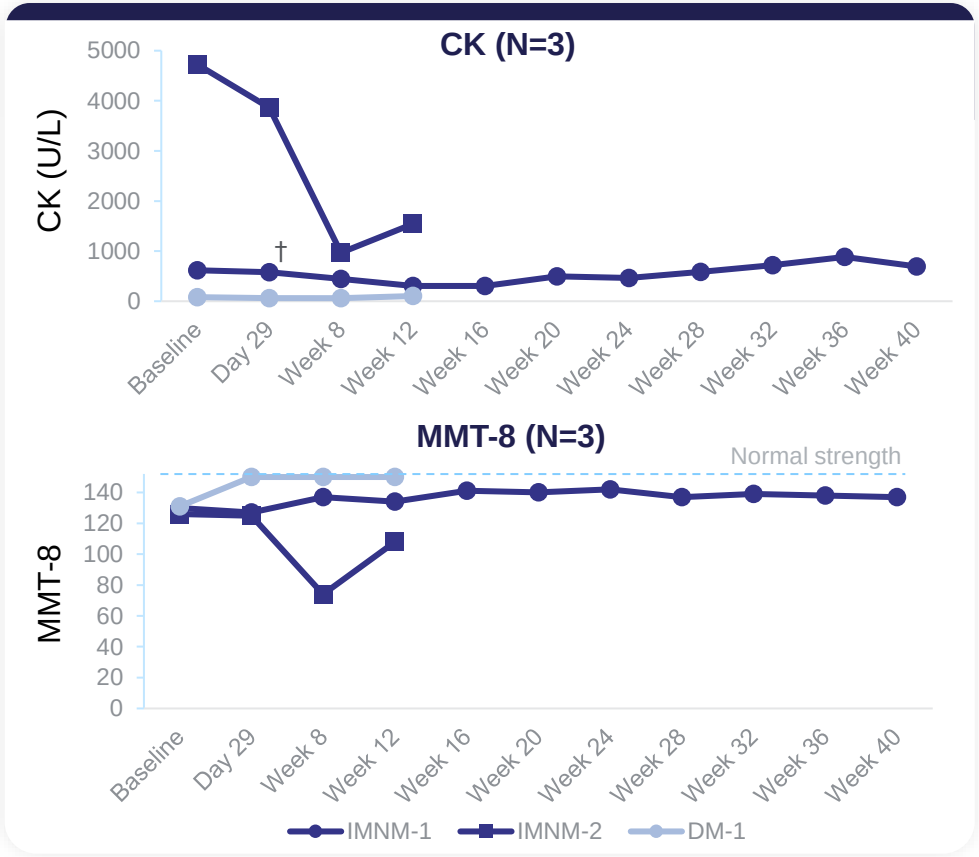
*As of Jan 8, 2025.

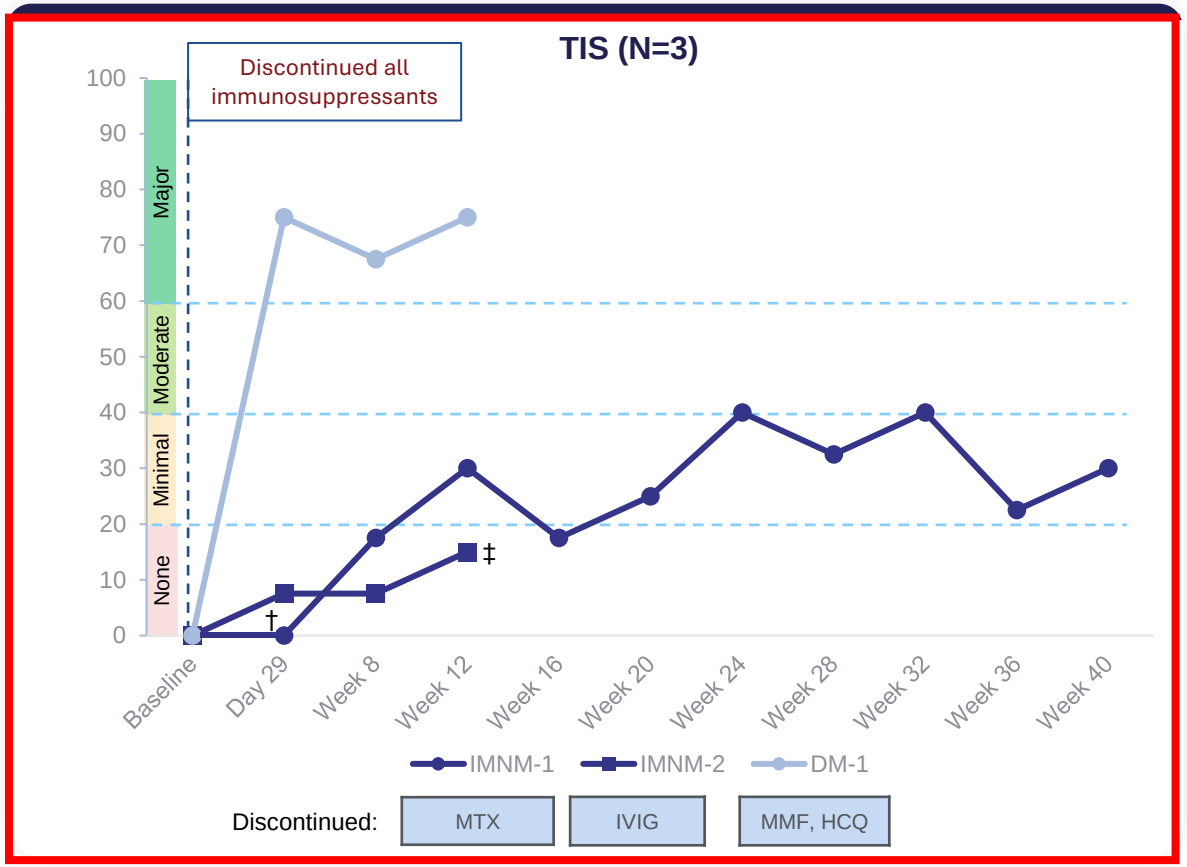
CAR, chimeric antigen receptor; CDASI-A, Cutaneous Dermatomyositis Disease Area and Severity Index – Activity; CK, creatinine kinase; DM, dermatomyositis HCQ, hydroxychloroquine; MMF, mycophenolate mofetil; MMT-8, manual muscle testing 8; rese-cel, resecabtagene autoleucel; RESET, REstoring SElf-Tolerance; TIS, total improvement score; U/L, units per liter.

Cabaletta Bio: Data on file.

RESET-Myositis™: Early Efficacy Data Following Rese-cel Infusion[1]

First IMNM patient with longer follow up demonstrated continuing clinical response off immunosuppressants without flares*





Initial clinical responses in IMNM are consistent with published data;[2] response kinetics may differ among myositis subtypes

*As of Jan 8, 2025. †IMNM-1 Day 29 CK measurement was unavailable; Day 22 used. ‡IMNM-2 developed a PE at Day 38 with a prolonged hospitalization and recovery and received IVIG just after Week 12 visit and increased prednisone from 5 mg to 20 mg 2 weeks later. CK, creatinine kinase; DM, dermatomyositis; HCQ, hydroxychloroquine; IMNM, immune-mediated necrotizing myopathy; IVIG, intravenous immunoglobulin; MTX, methotrexate; MMF, mycophenolate mofetil; MMT-8, manual muscle testing 8; rese-cel, resecabtagene autoleucel; RESET, REstoring SElf-Tolerance; TIS, total improvement score; U/L, units per liter.

1. Cabaletta Bio: Data on file. 2. Schett, G. 'CAR-T Cell Therapy: "The Future is Now."' 5th Global Conference on Myositis. iMyoS. Pittsburgh, PA.

RESET-SLE™: Efficacy Data Following Rese-cel Infusion*

3 of 4 SLE patients have achieved DORIS remission and 1st LN patient achieved CRR; deepening responses over time

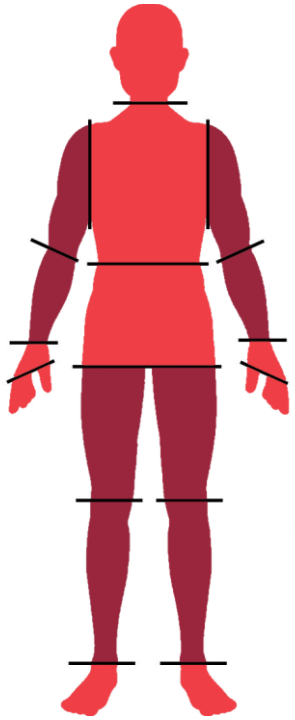
	SLE				LN	
Patient	**SLE-1†**	**SLE-2**	**SLE-3**	**SLE-4**	**LN-1**	**LN-2**
Latest follow-up (weeks)	36	16	8	8	24	4
DORIS remission (at latest follow-up)	–	✓	✓	✓	–	–
LLDAS (at latest follow-up)	–	✓	✓	✓	✓	–
SLEDAI-2K score‡ (baseline to latest follow-up)	26⟶8	10⟶0	8⟶2	8⟶2	22⟶2	14⟶11
UPCR (baseline to latest follow-up)	1.08⟶0.55	N/A	N/A	N/A	7.22⟶0.45	4.85⟶2.56
Complete renal response (CRR) (at latest follow-up)	–	N/A	N/A	N/A	✓	–
Glucocorticoid-free	✓	✓	✓	✓	✓	✓
Immunosuppressant-free	✓	✓	✓	✓	✓	✓

*As of Jan 8, 2025
† Enrollment in the LN cohort requires class III/IV +/- V LN. SLE-1 had isolated class V LN and extra-renal SLE disease activity that met inclusion criteria for the non-renal cohort. Proteinuria contributed 4 SLEDAI-2K points at all assessments.
‡ SLEDAI-2K components at latest follow up: SLE-1: proteinuria-4, complement-2, dsDNA-2; SLE-3: dsDNA-2; SLE-4: dsDNA-2; LN-1: rash-2; LN-2: proteinuria-4, leukopenia-1, alopecia-2, complement-2, dsDNA-2
# SLE-4 and LN-1 had discontinued GC as of the data cut; as of the latest follow up SLE-4 was on 2.5mg/d of prednisone (week 8) and LN-1 was on 7mg/d of prednisone (week 24)
DORIS, definition of remission in SLE; LLDAS, lupus low disease activity state; LN, lupus nephritis; N/A, not applicable; rese-cel, resecabtagene autoleucel; RESET, REstoring SElf-Tolerance; SLE, systemic lupus erythematosus; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; UPCR, urine protein-creatinine ratio.
Cabaletta Bio: Data on file

RESET-SSc™: SSc-Skin-1 Efficacy Data Following Rese-cel Infusion[1]

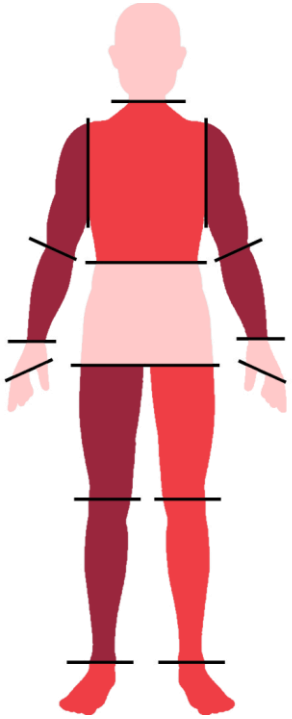
Skin improvements across multiple body areas, and improvement in lung function, after discontinuing immunosuppressants*

Baseline mRSS score by body area



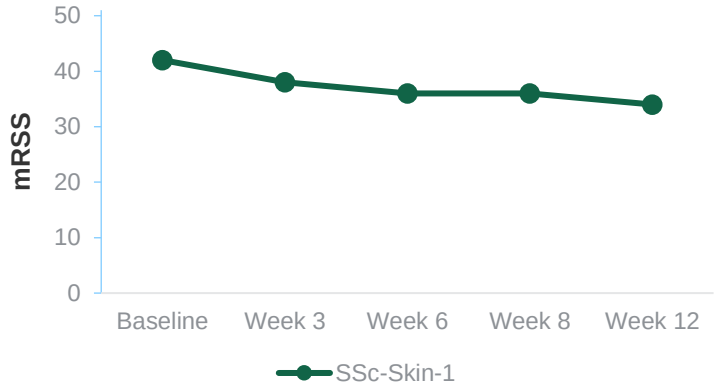
0	None
1	Mild
2	Moderate
3	Severe

Week 12 mRSS score by body area



0	None
1	Mild
2	Moderate
3	Severe

Overall mRSS score



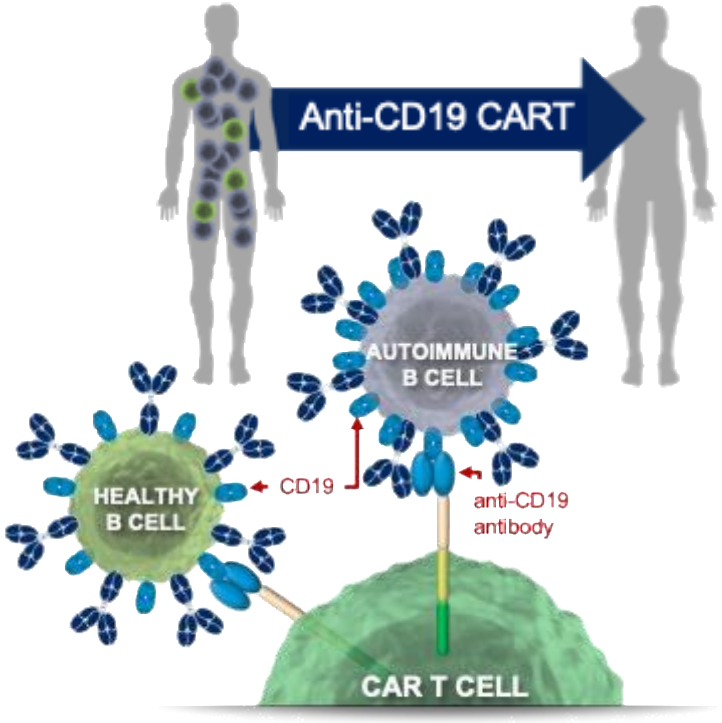
Pulmonary function tests

	Baseline	Week 12
DLCO	70%	85%
FVC	91%	97%

Early clinical data indicate emergence of a drug-free clinical response*

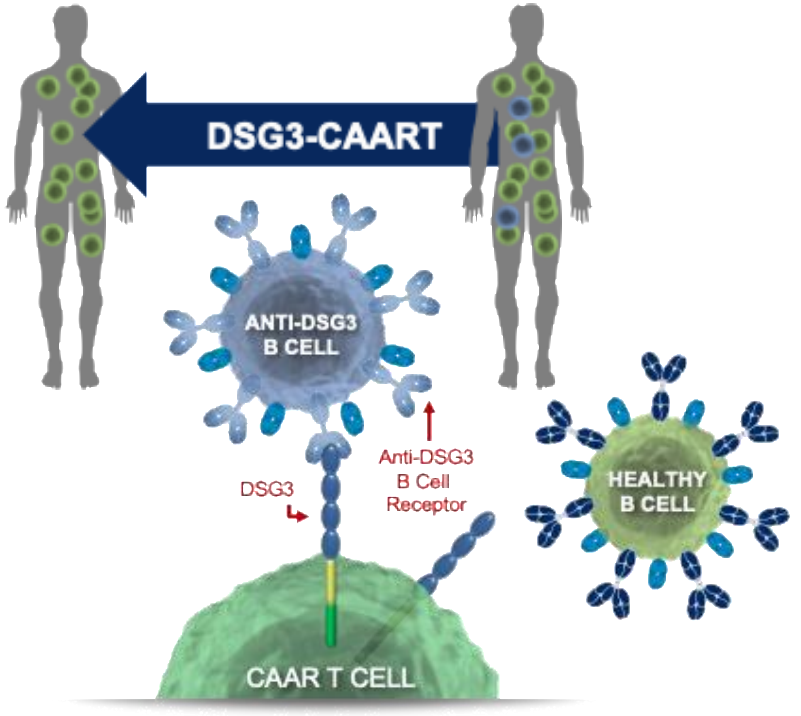
*As of Jan 8, 2025 patient is not taking immunosuppressants or steroids.
DLCO, % predicted diffusing capacity for carbon monoxide; FVC, % predicted forced vital capacity; mRSS, modified Rodnan Skin Score (measure of skin thickness in SSc across 17 body areas, with a maximum score of 51. Used as an outcome measure in SSc clinical trials as a surrogate for disease activity, severity, and mortality)2; rese-cel, resecabtagene autoleucel; RESET, REstoring SElf-Tolerance; SSc, systemic sclerosis.
1. Cabaletta Bio: Data on file. 2. Khanna D, et al. J Scleroderma Relat Disord. 2017;2(1):11–18.

Can a targeted cellular immunotherapy lead to safe and durable autoimmune disease remission?



Chimeric **A**ntigen **R**eceptor T Cell

Global but transient B cell depletion



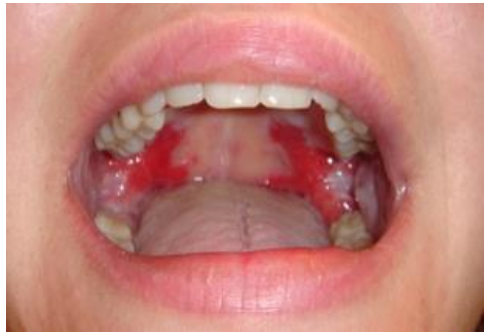
Chimeric **A**uto**A**ntibody **R**eceptor T Cell

Antigen-specific B cell depletion

Ellebrecht et al, Science 2016; Lee et al, JCI 2020

Evaluating CAART technology in first-in-human trials

NCT04422912



Mucosal pemphigus vulgaris

- Blistering of mucosa due to IgG4 autoantibodies that disrupt cell adhesion
- Target antigen: desmoglein 3 (DSG3)
- Standard of care: B cell depletion therapy
- 4-9% annual rate of serious infections

NCT05451212

MuSK myasthenia gravis

- Muscle weakness due to IgG4 autoantibodies that disrupt neuromuscular junction signaling
- Target antigen: muscle-specific tyrosine kinase (MuSK)
- Standard of care: B cell depletion therapy

https://www.nhs.uk/conditions/pemphigus-vulgaris/; https://www.chop.edu/conditions-diseases/myasthenia-gravisl; Joly et al, NEJM 2017; Werth et al, NEJM 2021

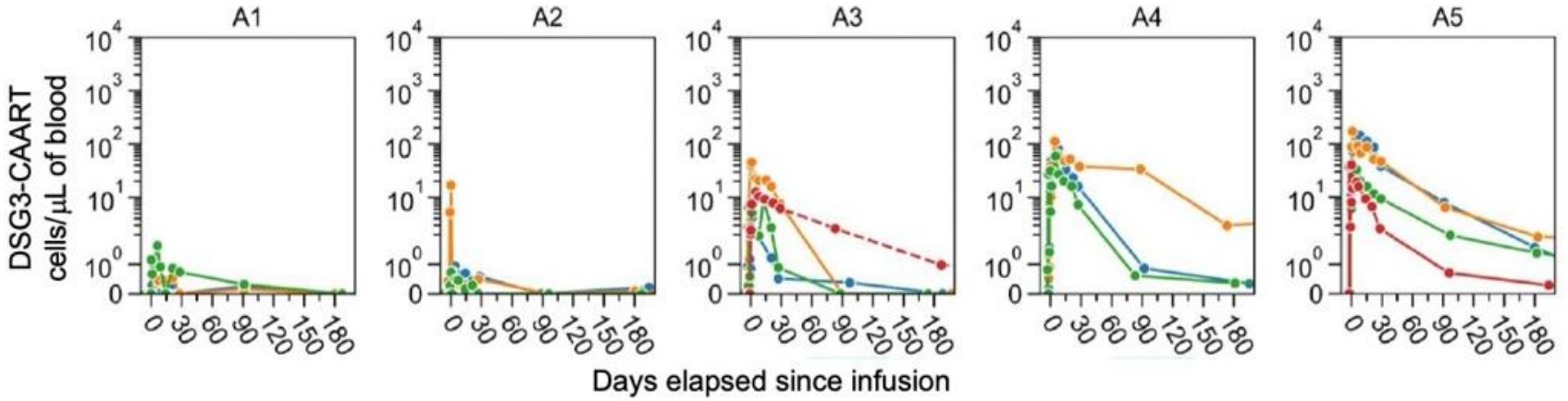
CAART clinical outcomes: persistence

DSG3-CAART persistence

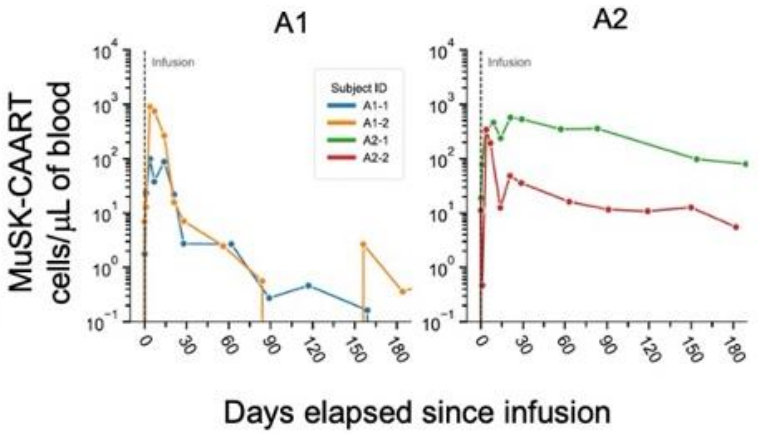
MuSK-CAART persistence

Dose: CAAR+ cells

2 x 10^7 | **1 x 10^8** | **5 x 10^8** | **2.5 x 10^9** | **5-7.5 x 10^9**



5 x 10^8 | **2.5 x 10^9**



Higher peak and long-term persistence with MuSK-CAART

CAART clinical outcomes: efficacy and safety

DSG3-CAART efficacy

- **No consistent pattern of improvement** in clinical or serologic disease measures

MuSK-CAART efficacy

- **1 of 2 subjects in first cohort** with 2+ point MG-ADL improvement
- **3 of 4 subjects in second cohort** with 2+ point MG-ADL improvement

DSG3-CAART safety

- **Well-tolerated**; 1 of 23 subjects with grade 1 CRS

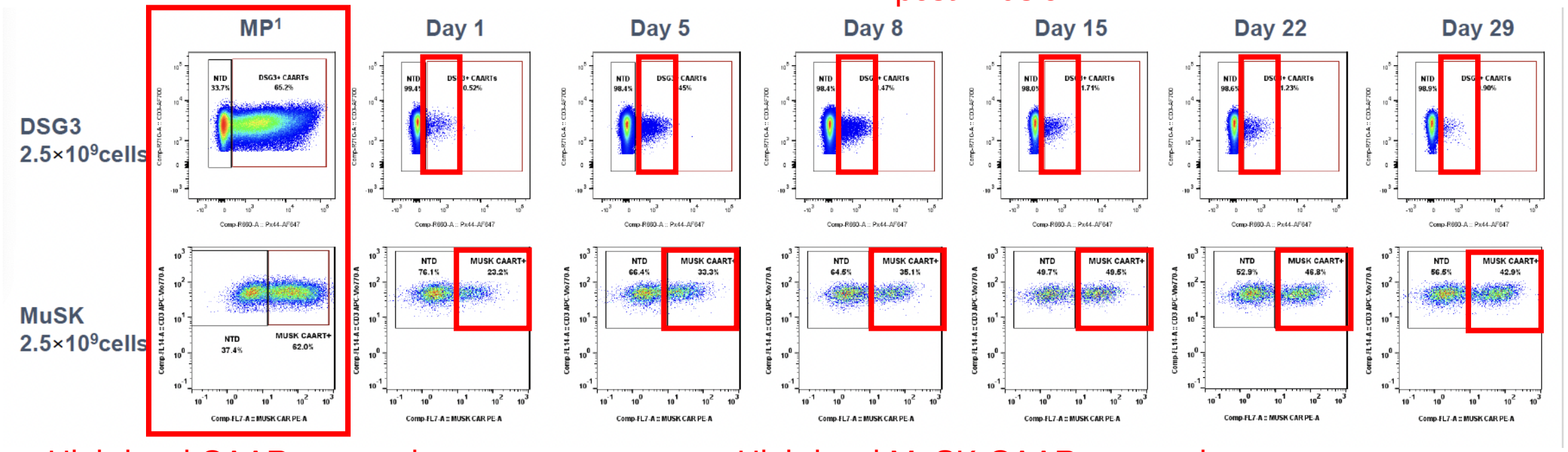
MuSK-CAART safety

- **2 subjects with grade 1-2 CRS**
- **1 subject with grade 4 HLH**

➢ **Ongoing studies to identify a favorable therapeutic index**

Downregulation of DSG3- but not MuSK-CAAR post-infusion

Low-level DSG3-CAAR expression post-infusion



High-level CAAR expression pre-infusion → High-level MuSK-CAAR expression post-infusion

- **Leading hypothesis: DSG3 CAAR downregulation or inhibition by soluble autoantibody causes poor killing activity and correlates with lack of CAART activation in vivo**

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CHOP Vector Core
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Olga Zelenaia

CAROT Vector Core
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Jenell Volkov
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Larissa Ishikawa
Justin Cicarelli
Quynh Lam
Claire Miller
Kate Sheipe
David Heilig
Raj Tummala
Carl DiCasoli
Jinmin Lee
Yan Li
Chien-Chung Chen
Arun Das
Steven Nichtberger

The war on cancer has brought cures to patients

NIH NATIONAL CANCER INSTITUTE

President Richard Nixon signing the National Cancer Act of 1971.

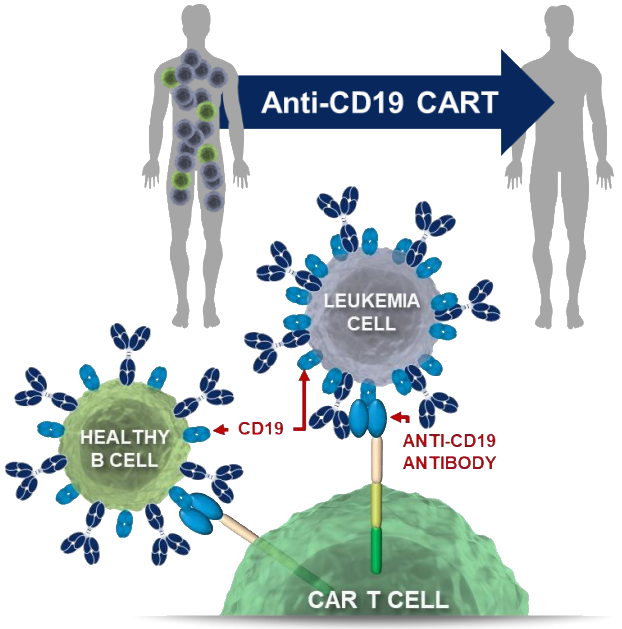
Credit: National Cancer Institute

CANCER MOONSHOT

INITIATIVES 2017–2020

OVER **70** CONSORTIUMS OR PROGRAMS

OVER **240** RESEARCH PROJECTS



Chimeric **A**ntigen **R**eceptor **T** cell

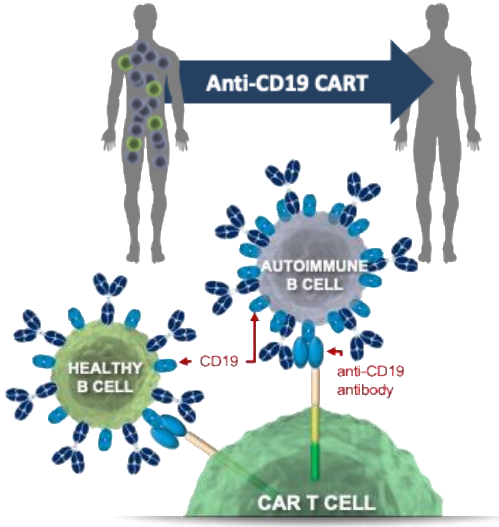
The war on cancer has brought cures to patients

	Cancer
Prevalence	9 million
Annual direct healthcare costs	$80 billion
NIH research funding (2023)	$8 billion

https://www.cancer.org/cancer/cancer-basics/cancer-prevalence.html; https://www.cancer.org/cancer/cancer-basics/economic-impact-of-cancer.html; https://report.nih.gov/funding/categorical-spending#/; Progress in Autoimmune Diseases Research, NIH ADCC report, 2005; The Cost Burden of Autoimmune Disease, AARDA/NCAPG report, 2011

The war on autoimmunity is just beginning

	Cancer	Autoimmune disease
Prevalence	9 million	24 million
Annual direct healthcare costs	$80 billion	$100 billion+
NIH research funding (2023)	$8 billion	$1 billion



Science, doi: 10.1126/science.zi1u1rx

https://www.cancer.org/cancer/cancer-basics/cancer-prevalence.html; https://www.cancer.org/cancer/cancer-basics/economic-impact-of-cancer.html; https://report.nih.gov/funding/categorical-spending#/; Progress in Autoimmune Diseases Research, NIH ADCC report, 2005; The Cost Burden of Autoimmune Disease, AARDA/NCAPG report, 2011