CAAR-T Therapy for Autoimmune Diseases

Korea-EU
Horizon Europe
Researchers
Networking Forum
on Advanced Biotechnology

2025.07.01-07.3

Hallym University
South Korea
Sangwook Oh

(swoh@hallym.ac.kr)

Disclosures:
Inventor on patents licensed by Cabaletta Bio

Hallym University & Hallym University Medical Centers

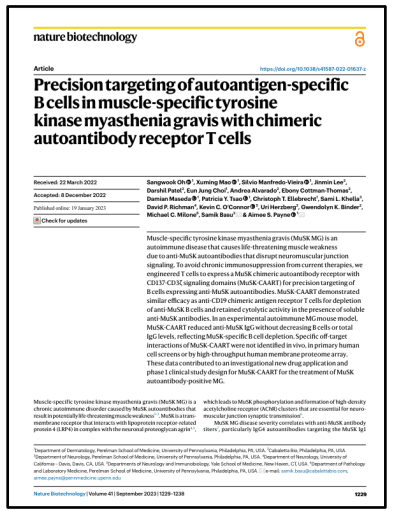
Excellence in Education and Healthcare

- **Hallym University** is a leading private university in Chuncheon, South Korea.
- **Hallym University** operates **6** general hospitals across Korea.
  - **Sacred Heart Hospital (Anyang)** – Flagship hospital with top medical services.
  - **Kangnam Sacred Heart Hospital (Seoul)** – Located in central Seoul, strong in surgery and emergency care.
  - **Chuncheon Sacred Heart Hospital** – Connected to the university, offers training and local care.
  - **Dongtan Sacred Heart Hospital** – High-tech smart hospital in a growing city.
  - **Hangang Sacred Heart Hospital (Seoul)** – Nationally recognized for burn and trauma care.
  - **Kangdong Sacred Heart Hospital (Seoul)** – Focuses on internal medicine, cancer, and patient care.

- **2023-Present:**
  - Assistant professor at Department of Biomedical Science at **Hallym University**
  - Chief Technology Officer (CTO) at **EIONCell INC.**
- **2021-2023**: Senior research Investigator at **University of Pennsylvania**
- **2017-2021**: Postdoc fellow at **University of Pennsylvania**
- **2016-2017**: Senior researcher at **JB Biotech INC**.
- **2000-2016**: BS & Ph.D at **Seoul National University**

- **Current Research Projects**
  - Enhancing Anti-Tumor Activity: **CAR-T.BiTE** strategies for solid tumors.
  - **CAR-Macrophage** Therapy for Neurodegeneration
  - Precision **CAART** Therapy for Autoimmunity
  - AI-Driven **CAR-Treg** Development

- **Achievements:**


nature biotechnology

Article

https://doi.org/10.1038/s41587-022-01637-z

Precision targeting of autoantigen-specific B cells in muscle-specific tyrosine kinase myasthenia gravis with chimeric autoantibody receptor T cells

Received: 22 March 2022

Accepted: 8 December 2022

Published online: 19 January 2023

Check for updates

Sangwook Oh[1], Xuming Mao[1], Silvio Manfredo-Vieira[1], Jinmin Lee[1], Darshil Patel[1], Eun Jung Choi[1], Andrea Alvarado[1], Ebony Cottman-Thomas[1], Damian Maseda[1], Patricia Y. Tsao[1], Christoph T. Ellebrecht[1], Sami L. Khella[2], David P. Richman[3], Kevin C. O'Connor[1], Uri Hershberg[4], Gwendolyn K. Binder[2], Michael C. Milone[1], Samik Basu[1] & Aimee S. Payne[1]

Muscle-specific tyrosine kinase myasthenia gravis (MuSK MG) is an autoimmune disease that causes life-threatening muscle weakness due to anti-MuSK autoantibodies that disrupt neuromuscular junction signaling. To avoid chronic immunosuppression from current therapies, we engineered T cells to express a MuSK chimeric autoantibody receptor with CD137-CD3ζ signaling domains (MuSK-CAART) for precision targeting of B cells expressing anti-MuSK autoantibodies. MuSK-CAART demonstrated similar efficacy as anti-CD19 chimeric antigen receptor T cells for depletion of anti-MuSK B cells and retained cytolytic activity in the presence of soluble anti-MuSK antibodies. In an experimental autoimmune MG mouse model, MuSK-CAART reduced anti-MuSK IgG without decreasing B cells or total IgG levels, reflecting MuSK-specific B cell depletion. Specific off-target interactions of MuSK-CAART were not identified in vivo, in primary human cell screens or by high-throughput human membrane proteome array. These data contributed to an investigational new drug application and phase 1 clinical study design for MuSK-CAART for the treatment of MuSK autoantibody-positive MG.

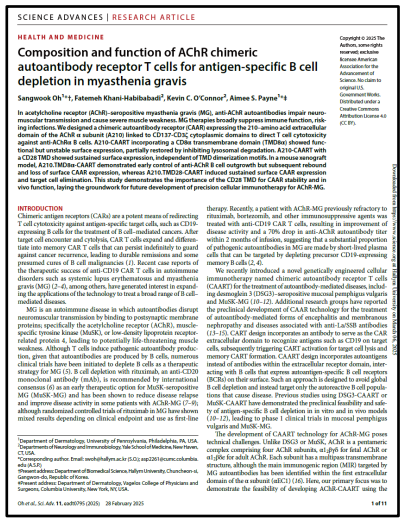
Muscle-specific tyrosine kinase myasthenia gravis (MuSK MG) is a chronic autoimmune disorder caused by MuSK autoantibodies that result in potentially life-threatening muscle weakness[1–3]. MuSK is a transmembrane receptor that interacts with lipoprotein receptor-related protein 4 (LRP4) in complex with the neuronal proteoglycan agrin[4], which leads to MuSK phosphorylation and formation of high-density acetylcholine receptor (AChR) clusters that are essential for neuromuscular junction synaptic transmission[5].

MuSK MG disease severity correlates with anti-MuSK antibody titers[6], particularly IgG4 autoantibodies targeting the MuSK Ig1

Department of Dermatology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA. [2]Cabaletta Bio, Philadelphia, PA, USA. [3]Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA. [4]Department of Neurology, University of California – Davis, Davis, CA, USA. [5]Department of Neurology and Immunobiology, Yale School of Medicine, New Haven, CT, USA. [6]Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA. e-mail: samik.basu@cabalettabio.com; aimee.payne@pennmedicine.upenn.edu

Nature Biotechnology | Volume 41 | September 2023 | 1229–1238 1229

- *Nat Biotech* (2023)
- MuSK-CAART for MG


SCIENCE ADVANCES | RESEARCH ARTICLE

HEALTH AND MEDICINE

Composition and function of AChR chimeric autoantibody receptor T cells for antigen-specific B cell depletion in myasthenia gravis

Sangwook Oh[1]†, Fatemeh Khani-Habibabadi[2], Kevin C. O'Connor[2], Aimee S. Payne[1]*†

Copyright © 2025 The Authors, some rights reserved; exclusive licensee American Association for the Advancement of Science. No claim to original U.S. Government Works. Distributed under a Creative Commons Attribution License 4.0 (CC BY).

In acetylcholine receptor (AChR)–seropositive myasthenia gravis (MG), anti-AChR autoantibodies impair neuromuscular transmission and cause severe muscle weakness. MG therapies broadly suppress immune function, risking infections. We designed a chimeric autoantibody receptor (CAAR) expressing the 210- amino acid extracellular domain of the AChR α subunit (A210) linked to CD137-CD3ζ cytoplasmic domains to direct T cell cytotoxicity against anti-AChRs B cells. A210-CAART incorporating a CD8α transmembrane domain (TMD8α) showed functional but unstable surface expression, partially restored by inhibiting lysosomal degradation. A210-CAART with a CD28 TMD showed sustained surface expression, independent of TMD dimerization motifs. In a mouse xenograft model, A210.TMD8α-CAART demonstrated early control of anti-AChR B cell outgrowth but subsequent rebound and loss of surface CAAR expression, whereas A210.TMD28-CAART induced sustained surface CAAR expression and target cell elimination. This study demonstrates the importance of the CD28 TMD for CAAR stability and in vivo function, laying the groundwork for future development of precision cellular immunotherapy for AChR-MG.

INTRODUCTION

Chimeric antigen receptors (CARs) are a potent means of redirecting T cell cytotoxicity against antigen-specific target cells, such as CD19-expressing B cells for the treatment of B cell–mediated cancers. After target cell encounter and cytolysis, CAR T cells expand and differentiate into memory CAR T cells that can persist indefinitely to guard against cancer recurrence, leading to durable remissions and some presumed cures of B cell malignancies (*1*). Recent case reports of the therapeutic success of anti-CD19 CAR T cells in autoimmune disorders such as systemic lupus erythematosus and myasthenia gravis (MG) (*2*–*4*), among others, have generated interest in expanding the applications of the technology to treat a broad range of B cell–mediated diseases.

MG is an autoimmune disease in which autoantibodies disrupt neuromuscular transmission by binding to postsynaptic membrane proteins; specifically the acetylcholine receptor (AChR), muscle-specific tyrosine kinase (MuSK), or low-density lipoprotein receptor–related protein 4, leading to potentially life-threatening muscle weakness. Although T cells induce pathogenic autoantibody production, given that autoantibodies are produced by B cells, numerous clinical trials have been initiated to deplete B cells as a therapeutic strategy for MG (*3*). B cell depletion with rituximab, an anti-CD20 monoclonal antibody (mAb), is recommended by international consensus (*4*) as an early therapeutic option for MuSK-seropositive MG (MuSK-MG) and has been shown to reduce disease relapse and improve disease activity in some patients with AChR-MG (*5*–*9*), although randomized controlled trials of rituximab in MG have shown mixed results depending on clinical endpoint and use as first-line therapy. Recently, a patient with AChR-MG previously refractory to rituximab, bortezomib, and other immunosuppressive agents was treated with anti-CD19 CAR T cells, resulting in improvement of disease activity and a 70% drop in anti–AChR autoantibody titer within 2 months of infusion, suggesting that a substantial proportion of pathogenic autoantibodies in MG are made by short-lived plasma cells that can be targeted by depleting precursor CD19-expressing memory B cells (*2*, *4*).

We recently introduced a novel genetically engineered cellular immunotherapy named chimeric autoantibody receptor T cells (CAART) for the treatment of autoantibody-mediated diseases, including desmoglein 3 (DSG3)–seropositive mucosal pemphigus vulgaris and MuSK-MG (*10*–*12*). Additional research groups have reported the preclinical development of CAAR technology for the treatment of autoantibody-mediated forms of encephalitis and membranous nephropathy and diseases associated with anti-La/SSB antibodies (*13*–*15*). CAART design incorporates an antibody to serve as the CAR extracellular domain to recognize antigens such as CD19 on target cells, subsequently triggering CART activation for target cell lysis and memory CART formation. CAART design incorporates autoantigens instead of antibodies within the extracellular receptor domain, interacting with B cells that express autoantigen-specific B cell receptors (BCRs) on their surface. Such an approach is designed to avoid global B cell depletion and instead target only the autoreactive B cell populations that cause disease. Previous studies using DSG3-CAART or MuSK-CAART have demonstrated the preclinical feasibility and safety of antigen-specific B cell depletion in in vitro and in vivo models (*10*–*12*), leading to phase 1 clinical trials in mucosal pemphigus vulgaris and MuSK-MG.

The development of CAART technology for AChR-MG poses technical challenges. Unlike DSG3 or MuSK, AChR is a pentameric complex comprising four AChR subunits, αεγδ for fetal AChR or αεδε for adult AChR. Each subunit has a multipass transmembrane structure, although the main immunogenic region (MIR) targeted by MG autoantibodies has been identified within the first extracellular domain of the α subunit (αEC1) (*16*). Here, our primary focus was to demonstrate the feasibility of developing AChR-CAART using the

[1]Department of Dermatology, University of Pennsylvania, Philadelphia, PA, USA. [2]Department of Neurology and Immunobiology, Yale School of Medicine, New Haven, CT, USA.
*Corresponding author. Email: swoh@hallym.ac.kr (S.O.); asp2201@cumc.columbia.edu (A.S.P.)
†Present address: Department of Biomedical Science, Hallym University, Chuncheon-si, Gangwon-do, Republic of Korea.
‡Present address: Department of Dermatology, Vagelos College of Physicians and Surgeons, Columbia University, New York, NY, USA.

Oh et al., Sci. Adv. 11, eadt6795 (2025) 28 February 2025 1 of 11

- *Sci Adv* (2025)
- AChR-CAART for MG


IMMUNE NETWORK

Review Article

Engineering Cell Therapies for Autoimmune Diseases: From Preclinical to Clinical Proof of Concept

Sangwook Oh, Aimee S. Payne

Department of Dermatology, University of Pennsylvania, Philadelphia, PA 19104, USA

OPEN ACCESS

ABSTRACT

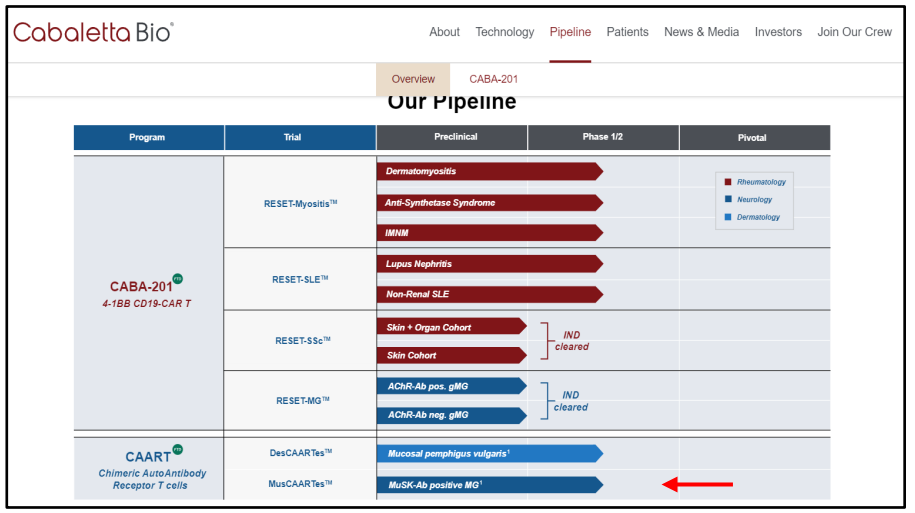
Autoimmune diseases are caused by a dysfunction of the acquired immune system. In a subset of autoimmune diseases, B cells escaping immune tolerance present autoantigen and produce cytokines and/or autoantibodies, resulting in systemic or organ-specific autoimmunity. Therefore, B cell depletion with monoclonal Abs targeting B cell lineage markers is standard care therapy for several B cell–mediated autoimmune disorders. In the last 5 years, genetically-engineered cellular immunotherapies targeting B cells have shown superior efficacy and long-term remission of B cell malignancies compared to historical clinical outcomes using B cell depletion with monoclonal Ab therapies. This has raised interest in understanding whether similar durable remission could be achieved with use of genetically-engineered cell therapies for autoimmunity. This review will focus on current human clinical trials using engineered cell therapies for B cell-associated autoimmune diseases.

Keywords: Autoimmunity; Cell therapy; Chimeric antigen receptor; Clinical trials; Pemphigus; Myasthenia gravis; Lupus; Neuromyelitis optica; Systemic sclerosis; Sjogren's syndrome

INTRODUCTION

Autoimmune diseases are caused by a dysfunction of the acquired immune system, leading T and B lymphocytes to attack normal cells or proteins in the body. Although autoimmune diseases are classified as being predominantly T or B cell–mediated, both T and B cells contribute to pathogenesis in many autoimmune diseases. B cells can contribute to autoimmunity through Ag presentation, cytokine production, and the production of autoantibodies, which normally protect against infection by several mechanisms, such as: 1) direct neutralization to prevent infection; 2) opsonization and phagocytosis to clear pathogens; and 3) Ab-dependent cellular cytotoxicity, and 4) complement-dependent cytotoxicity to lyse bacteria or virus-infected cells. T cells differentiate into several subtypes including: 1) cytotoxic T cells that recognize infected cells and lead to cell death; 2) helper T cells that directly engage and activate B cells or indirectly activate B cells or cytotoxic T cells through cytokine production; and 3) regulatory T cells that suppress a broad range of effector immune functions to maintain homeostasis.

- *Immune Netw* (2022)
- Review: CART for Autoimmune diseases



- **First-in-human clinical trial (2022)**

- **2023-Present:**
  - Assistant professor at Department of Biomedical Science at **Hallym University**
  - Chief Technology Officer (CTO) at **EIONCell INC.**
- **2021-2023**: Senior research Investigator at **University of Pennsylvania**
- **2017-2021**: Postdoc fellow at **University of Pennsylvania**
- **2016-2017**: Senior researcher at **JB Biotech INC**.
- **2000-2016**: BS & Ph.D at **Seoul National University**

- **Current Research Projects**
  - Enhancing Anti-Tumor Activity: **CAR-T.BiTE** strategies for solid tumors.
  - **CAR-Macrophage** Therapy for Neurodegeneration
  - Precision **CAART** Therapy for Autoimmunity
  - AI-Driven **CAR-Treg** Development

- **Achievements:**


nature biotechnology

Article

https://doi.org/10.1038/s41587-022-01637-z

Precision targeting of autoantigen-specific B cells in muscle-specific tyrosine kinase myasthenia gravis with chimeric autoantibody receptor T cells

Received: 22 March 2022

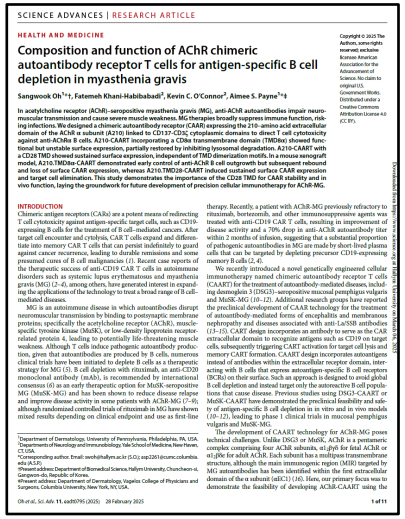
Accepted: 8 December 2022

Published online: 19 January 2023

Check for updates

Sangwook Oh[1], Xuming Mao[1], Silvio Manfredo-Vieira[1], Jinmin Lee[1], Darshil Patel[1], Eun Jung Choi[1], Andrea Alvarado[1], Ebony Cottman-Thomas[1], Damian Maseda[1], Patricia Y. Tsao[1], Christoph T. Ellebrecht[1], Sami L. Khella[1], David P. Richman[2], Kevin C. O'Connor[3], Uri Hershberg[4], Gwendolyn K. Binder[5], Michael C. Milone[1], Samik Basu[1] & Aimee S. Payne[1]

Muscle-specific tyrosine kinase myasthenia gravis (MuSK MG) is an autoimmune disease that causes life-threatening muscle weakness due to anti-MuSK autoantibodies that disrupt neuromuscular junction signaling. To avoid chronic immunosuppression from current therapies, we engineered T cells to express a MuSK chimeric autoantibody receptor with CD137-CD3ζ signaling domains (MuSK-CAART) for precision targeting of B cells expressing anti-MuSK autoantibodies. MuSK-CAART demonstrated similar efficacy as anti-CD19 chimeric antigen receptor T cells for depletion of anti-MuSK B cells and retained cytolytic activity in the presence of soluble anti-MuSK antibodies. In an experimental autoimmune MG mouse model, MuSK-CAART reduced anti-MuSK IgG without decreasing B cells or total IgG levels, reflecting MuSK-specific B cell depletion. Specific off-target interactions of MuSK-CAART were not identified in vivo, in primary human cell screens or by high-throughput human membrane proteome array. These data contributed to an investigational new drug application and phase 1 clinical study design for MuSK-CAART for the treatment of MuSK autoantibody-positive MG.


SCIENCE ADVANCES | RESEARCH ARTICLE

HEALTH AND MEDICINE

Composition and function of AChR chimeric autoantibody receptor T cells for antigen-specific B cell depletion in myasthenia gravis

Sangwook Oh[1,2]†, Fatemeh Khani-Habibabadi[3], Kevin C. O'Connor[3], Aimee S. Payne[1,2]*

In acetylcholine receptor (AChR)–seropositive myasthenia gravis (MG), anti-AChR autoantibodies impair neuromuscular transmission and cause severe muscle weakness. MG therapies broadly suppress immune function, risking infections. We designed a chimeric autoantibody receptor (CAAR) expressing the 210–amino acid extracellular domain of the AChR α subunit (A210) linked to CD137-CD3ζ cytoplasmic domains to direct T cell cytotoxicity against anti-AChRs B cells. A210-CAART incorporating a CD8α transmembrane domain (TMD8α) showed functional but unstable surface expression, partially restored by inhibiting lysosomal degradation. A210-CAART with a CD28 TMD showed sustained surface expression, independent of TMD dimerization motifs. In a mouse xenograft model, A210.TMD8α-CAART demonstrated early control of anti-AChR B cell outgrowth but subsequent rebound and loss of surface CAAR expression, whereas A210.TMD28-CAART induced sustained surface CAAR expression and target cell elimination. This study demonstrates the importance of the CD28 TMD for CAAR stability and in vivo function, laying the groundwork for future development of precision cellular immunotherapy for AChR-MG.


IMMUNE NETWORK

Review Article

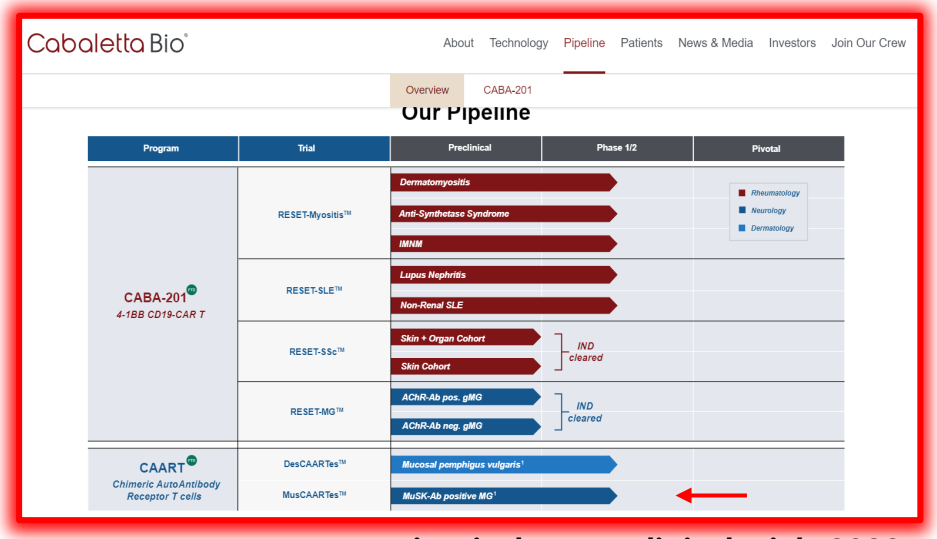
Engineering Cell Therapies for Autoimmune Diseases: From Preclinical to Clinical Proof of Concept

Sangwook Oh, Aimee S. Payne

Department of Dermatology, University of Pennsylvania, Philadelphia, PA 19104, USA

ABSTRACT

INTRODUCTION


Cabaletta Bio

About Technology Pipeline Patients News & Media Investors Join Our Crew

Overview CABA-201

Our Pipeline

Program	Trial	Preclinical	Phase 1/2	Pivotal
CABA-201 4-1BB CD19-CAR T	RESET-Myositis™	Dermatomyositis		Rheumatology, Neurology, Dermatology
		Anti-Synthetase Syndrome		
		IMNM		
	RESET-SLE™	Lupus Nephritis		
		Non-Renal SLE		
	RESET-SSc™	Skin + Organ Cohort	IND cleared	
		Skin Cohort		
	RESET-MG™	AChR-Ab pos. gMG	IND cleared	
		AChR-Ab neg. gMG		
CAART Chimeric AutoAntibody Receptor T cells	DesCAARTes™	Mucosal pemphigus vulgaris[1]		
	MusCAARTes™	MuSK-Ab positive MG[1]		

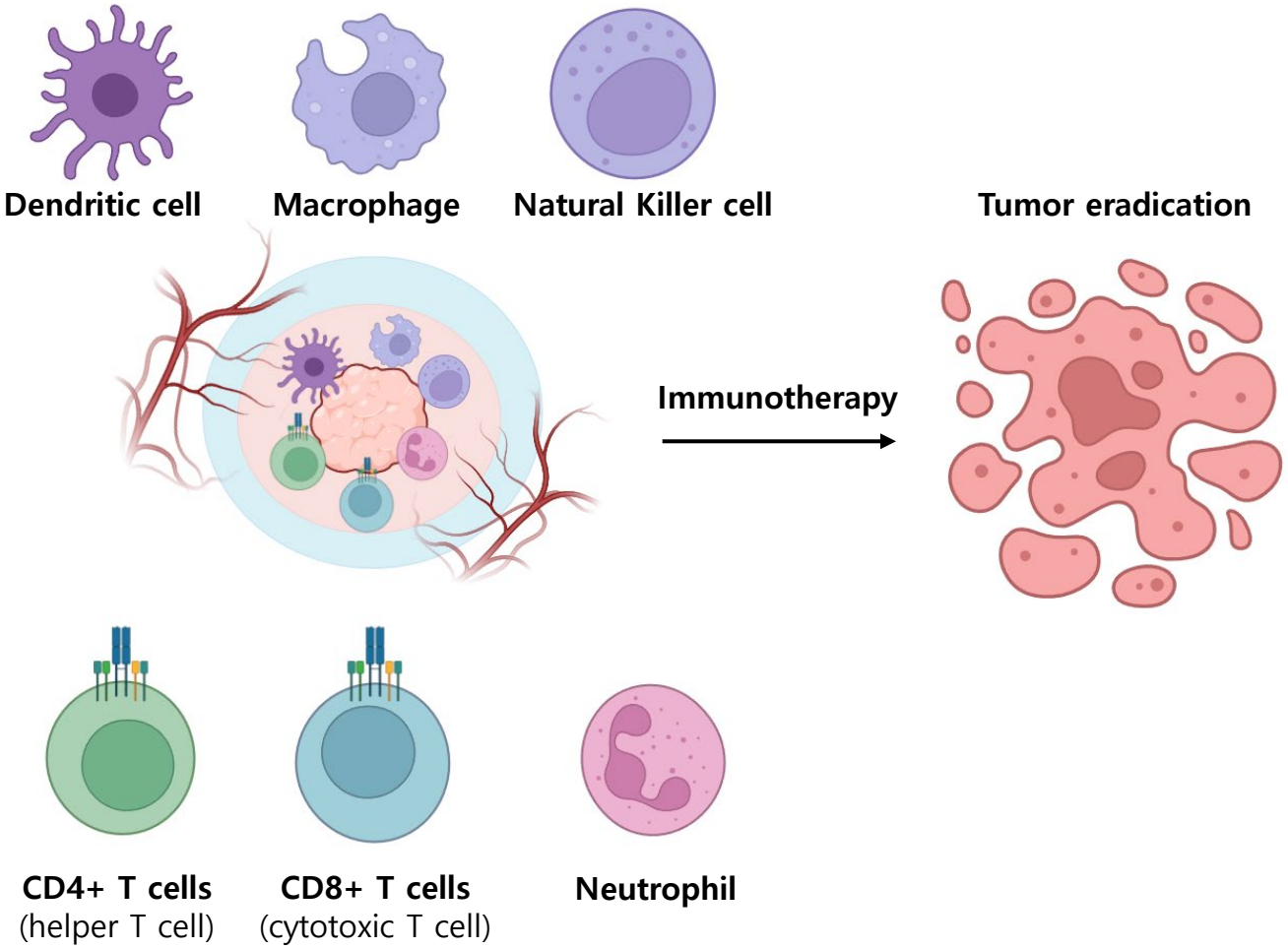
- *Nat Biotech* (2023)
- MuSK-CAART for MG

- *Sci Adv* (2025)
- AChR-CAART for MG

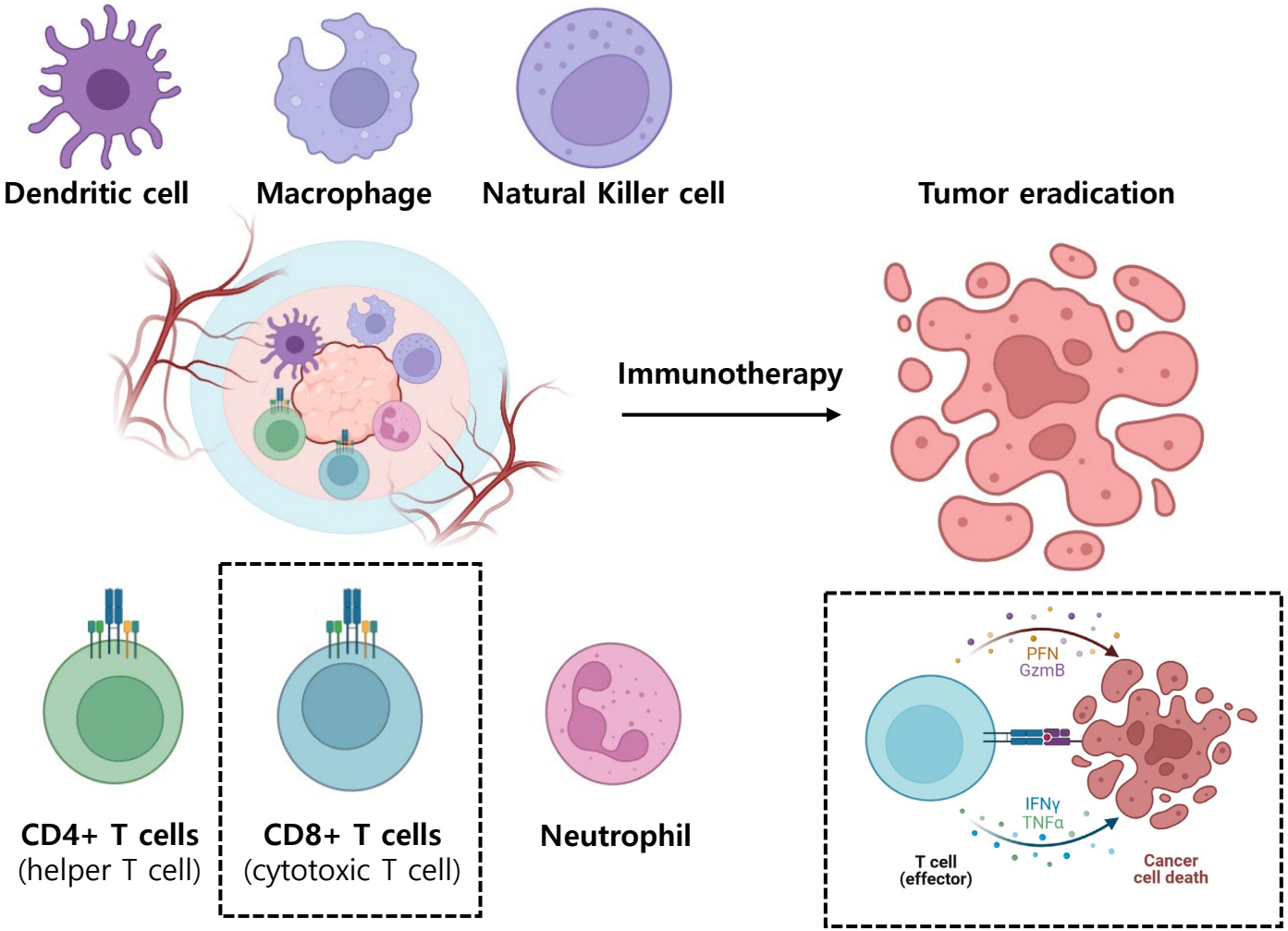
- *Immune Netw* (2022)
- Review: CART for Autoimmune diseases

- First-in-human clinical trial (2022)

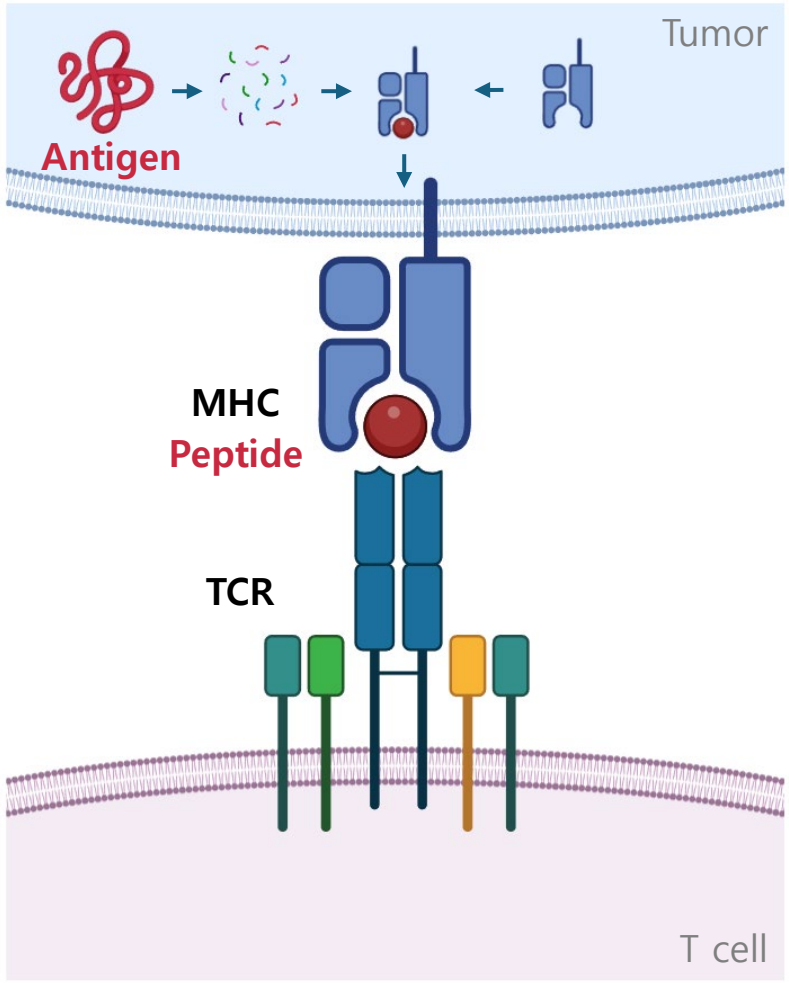
Immune cells and cancer immunotherapy



Immune cells and cancer immunotherapy

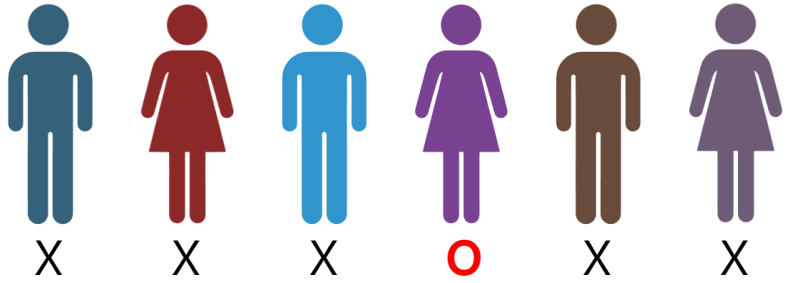


T Cell Therapy is limited by MHC Restriction



MHC – Major histocompatibility complex
TCR – T cell receptor
TSA – Tumor specific antigen

- **TSAs** are presented on **MHC molecules** and recognized by **TCR**s.
- **MHC restriction and polymorphism** create a major barrier, as each person expresses **a unique combination of MHC alleles**.
- As a result, the probability of **MHC matching between patients is less than 10%**.

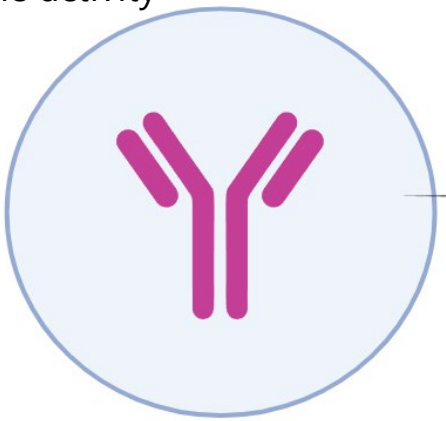


Patients with TSA

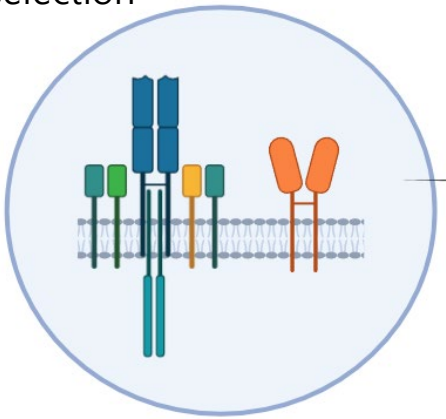
MHC-matched patients (<10%)

Chimeric Antigen Receptor (CAR) T cell

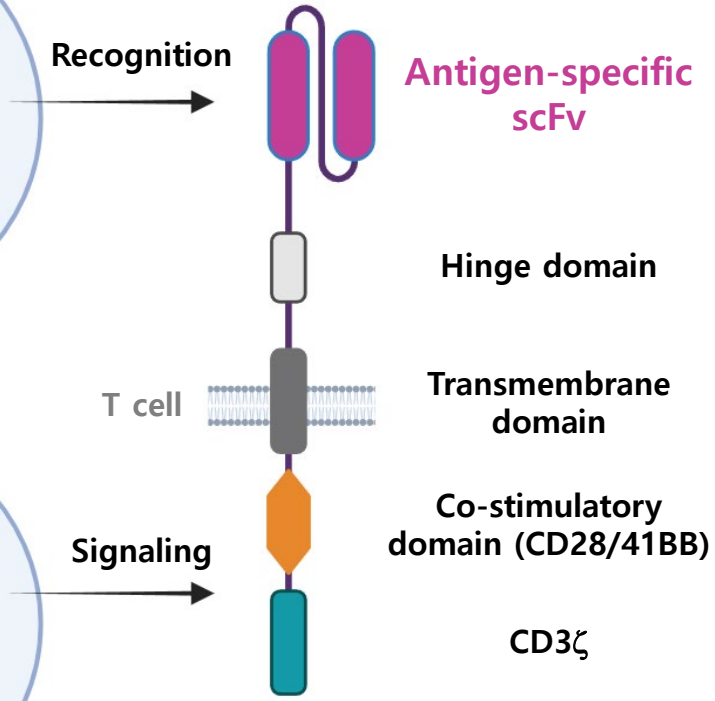
Antibody:
Limited therapeutic activity



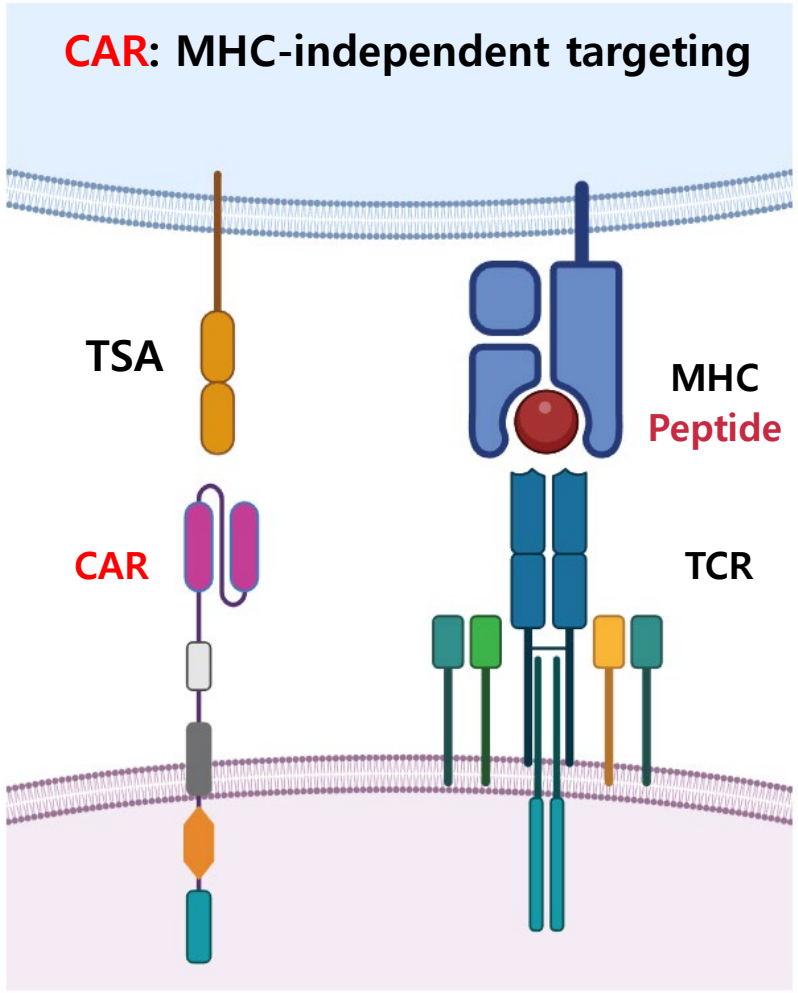
T cell receptor:
Stringent target selection
(MHC-restriction)



CAR-T



- **Living therapy**
- **Breadth of target recognition**

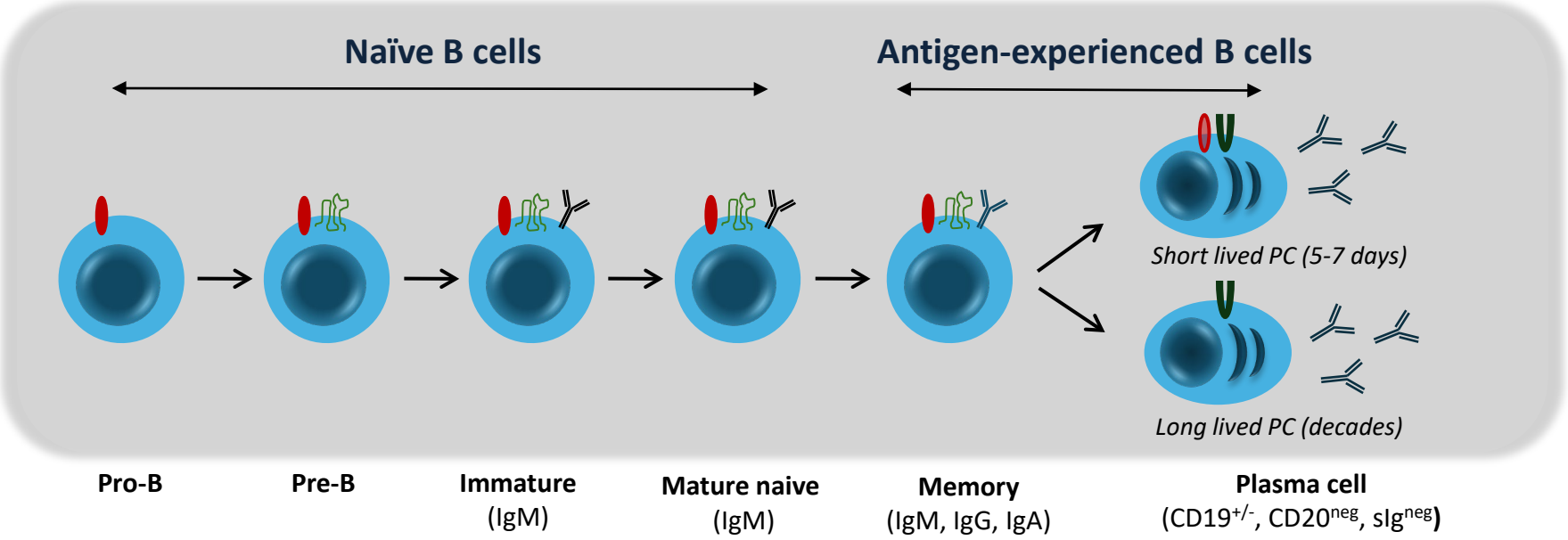


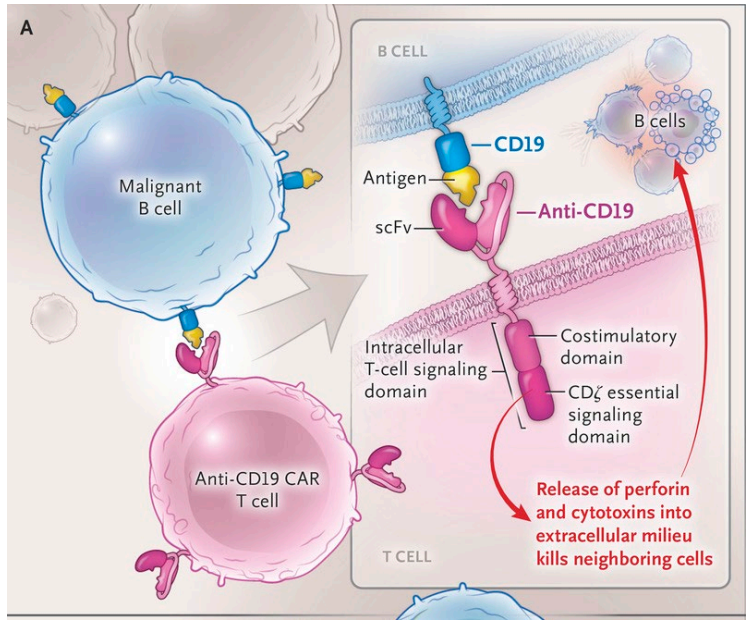
Currently, seven CAR-T therapies have received FDA approval (as of 03/2025)

Generic Name	Brand Name	Target Antigen	Target Disease	Patient Population
Tisagenlecleucel (**Tisa-cel)**	Kymriah (Aug 30, 2017)	CD19 (FMC63)	B-cell acute lymphoblasticleukemia (ALL)	Children and young adults with refractory orrelapsed B-cell ALL
			B-cell non-Hodgkin lymphoma (NHL)	Adults with relapsed or refractory B-cell NHL
Axicabtagene ciloleucel (**Axi-cel**)	Yescarta (Oct 18, 2017)	CD19 (FMC63)	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 (**Brexu-cel**)	Tecartus (July 24, 2020)	CD19 (FMC63)	Mantle cell lymphoma (MCL)	Adults with relapsed or refractory MCL
			B-cell acute lymphoblasticleukemia (ALL)	Adults with relapsed or refractory B-cell NHL
Lisocabtagene maraleucel (**Liso-cel**)	Breyanzi (Feb 5, 2021)	CD19	B-cell non-Hodgkin lymphoma (NHL)	Adults with relapsed or refractory B-cell NHL
Idecabtagene vicleucel (**ide-cel**)	Abecma (Mar 26, 2021)	BCMA	Multiple myeloma	Adults with relapsed or refractory multiple myeloma
Ciltacabtagene autoleucel (**Cilta-cel**)	Carvykti (Feb 28, 2022)	BCMA	Multiple myeloma	Adults with relapsed or refractory multiple myeloma
obecabtagene autoleucel (**Obe-cel**)	AUCATZYL (Nov 8, 2024)	CD19 (CAT)	B-cell acute lymphoblasticleukemia (ALL)	Adults with relapsed or refractory B-cell ALL

- https://www.cancer.gov/about-cancer/treatment/research/car-t-cells

FDA-Approved CAR-T Therapies Target Pan-B Cell Markers





Pan-B cell marker:
Global B cell depletion

- Oh S. and Payne AS, *Immune Network* (2022)
- Masayuki Amagai, *N Engl J Med* (2016)

Remarkable Achievements of CAR T Cell Therapies in B Cell Malignancies

Company name Brand name Generic name	Date of approval	Target antigen/ Antibody	Hinge/ transmembrane	Costimulatory domains	Vector/ promoter	Targeted cancers	Pivotal trial	No. of Patients	Outcomes	References
Novartis Kymriah Tisagenlecleucel	Aug 30, 2017	CD19 Mouse FMC63	CD8α/CD8α	4-1BB + CD3ζ	Lentiviral EF1α	R/R CAYA B-ALL	ELIANA (NCT02228096)	75	81% overall remission rate	(58)
Kite Yescarta Axicabtagene ciloleucel	Oct 18, 2017	CD19 Mouse FMC63	CD8α/CD8α	CD28 + CD3ζ	Gammaretroviral LTR	R/R LBCL	ZUMA-1 (NCT02348216)	108	58% complete response	(59)
Kite Tecartus Brexucabtagene autoleucel	Jul 24, 2020	CD19 Mouse FMC63	CD28/CD28	CD28 + CD3ζ	Gammaretroviral LTR	R/R MCL	ZUMA-2 (NCT02601313)	68	67% complete response	(61)
Juno Breyanzi Lisocabtagene maraleucel	Feb 5, 2021	CD19 Mouse FMC63	IgG4/CD28	4-1BB+ CD3ζ	Lentiviral EF1α	R/R LBCL	Transcend NHL001 (NCT02631044)	269	53% complete response	(60)
Bluebird Abecma Idecabtagene vicleucel	Mar 26, 2021	BCMA Mouse BB2121	CD8α/CD8α	4-1BB+ CD3ζ	Lentiviral MND	R/R MM	KarMMa (NCT03361748)	128	33% complete response	(63)
J&J and Legend Carvykti Ciltacabtagene autoleucel	Feb 28, 2022	BCMA dual camel single-domain antibodies	CD8α/CD8α	4-1BB + CD3ζ	Lentiviral EF1α	R/R MM	CARTITUDE-1 (NCT03548207)	97	82.5% complete response	(64)
Autolus Inc Aucatzyl Obecabtagene autoleucel (obe-cel)	Nov 08, 2024	CD19 CAT (intermediate-affinity)	CD8α + CD8 α	4-1BB + CD3ζ	Lentiviral EF1α	R/R adults with ALL	FELIX (NCT04404660)	65	42% complete response	

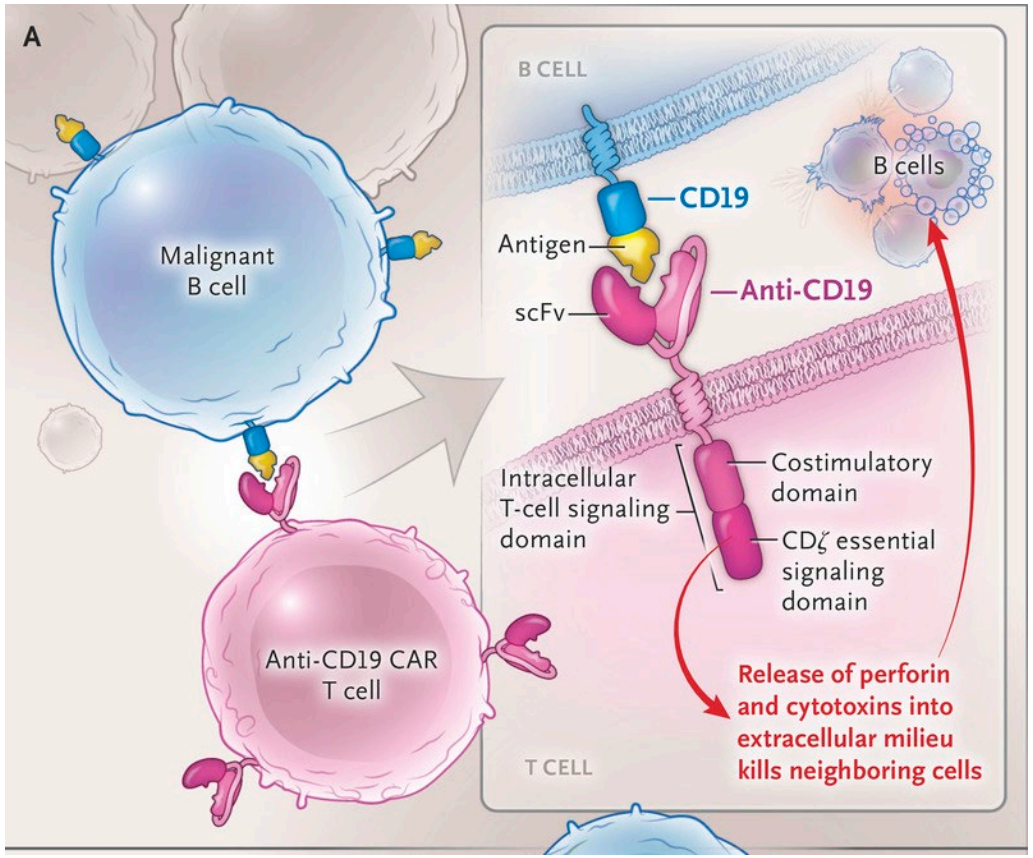
R/R, relapsed or refractory. CAYA, children and young adults. LBCL, large B-cell lymphoma. MCL, mantle cell lymphoma. MM, multiple myeloma.

- Complete responses: 33-82.5% across trials

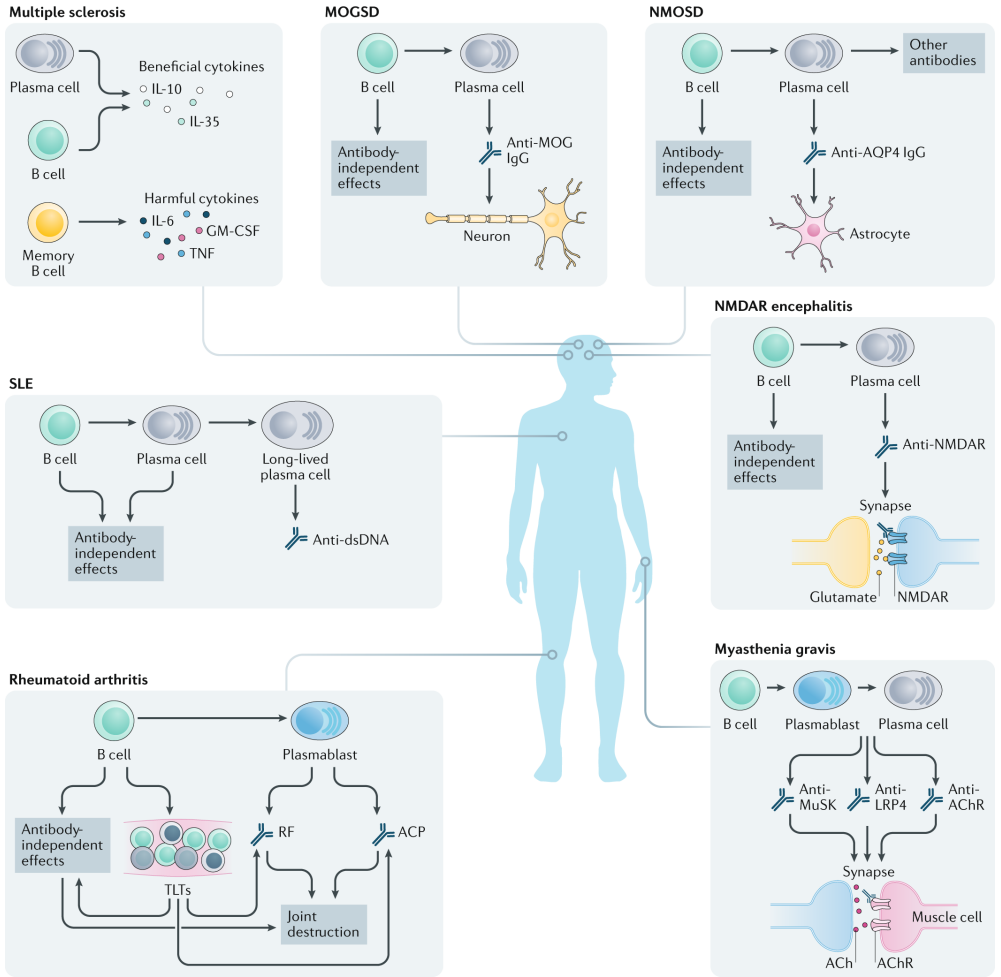
- Mitra A et al, *Front Immunol* (2023)
- https://www.fda.gov/drugs/resources-information-approved-drugs

CAR-T Therapy Beyond Cancers

B cell cancers



B cell-mediated autoimmune diseases



- Masayuki Amagai, *N Engl J Med* (2016)
- Lee et al, *Nature Reviews Drug Discovery* (2021)

Early Clinical Outcomes of CAR-T in Autoimmune Diseases

- Early trial results suggest that **CAR-T therapy** shows **promising efficacy** in various autoimmune diseases.
- Compared to cancer treatment, **a milder side effect profile** is often observed—possibly due to a **lower target cell burden**.

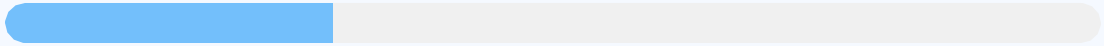
Systemic Lupus Erythematosus (SLE)

→ **Anti-CD19 CAR-T** treatment applied

5/5	5-17
Achieved **drug-free remission**	Follow-up duration (months)

Safety Profile:

- Mild **cytokine release syndrome (CRS)**



- **No ICANS** (immune effector cell-associated neurotoxicity syndrome)

None Mild Moderate Severe

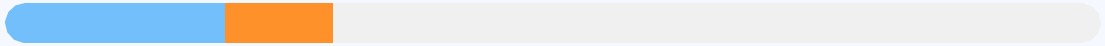
Neuromyelitis Optica Spectrum Disorder (NMOSD)

→ **Anti-BCMA CAR-T** treatment applied

11/12	5.5
Achieved **drug-free remission**	Median follow-up duration (months)

Safety Profile:

- Grade 1 or 2 mild CRS



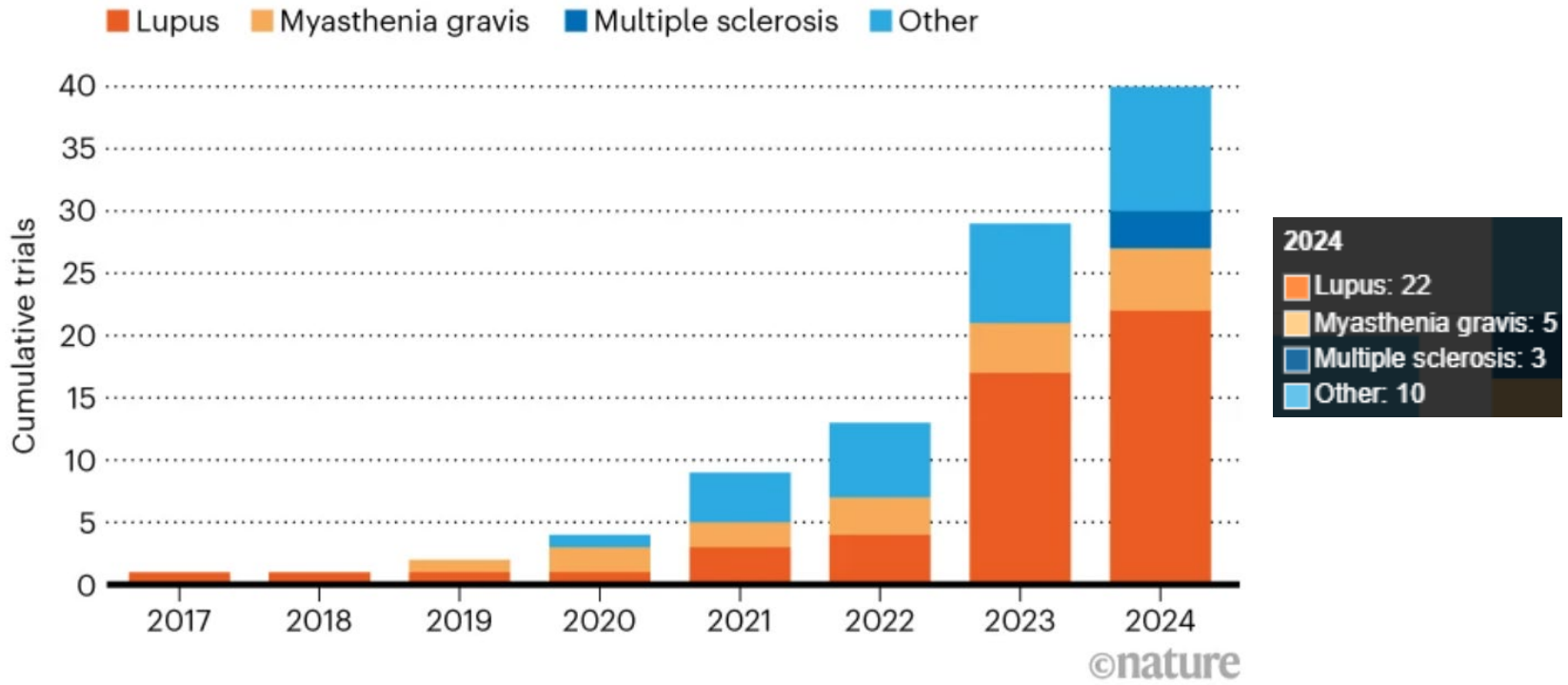
- **No ICANS**

None Mild Moderate Severe

- Nature medicine, 2022
- Sig. Transduc Target Ther, 2022

The Rise of CAR-T Cells in Autoimmune Disease Therapy

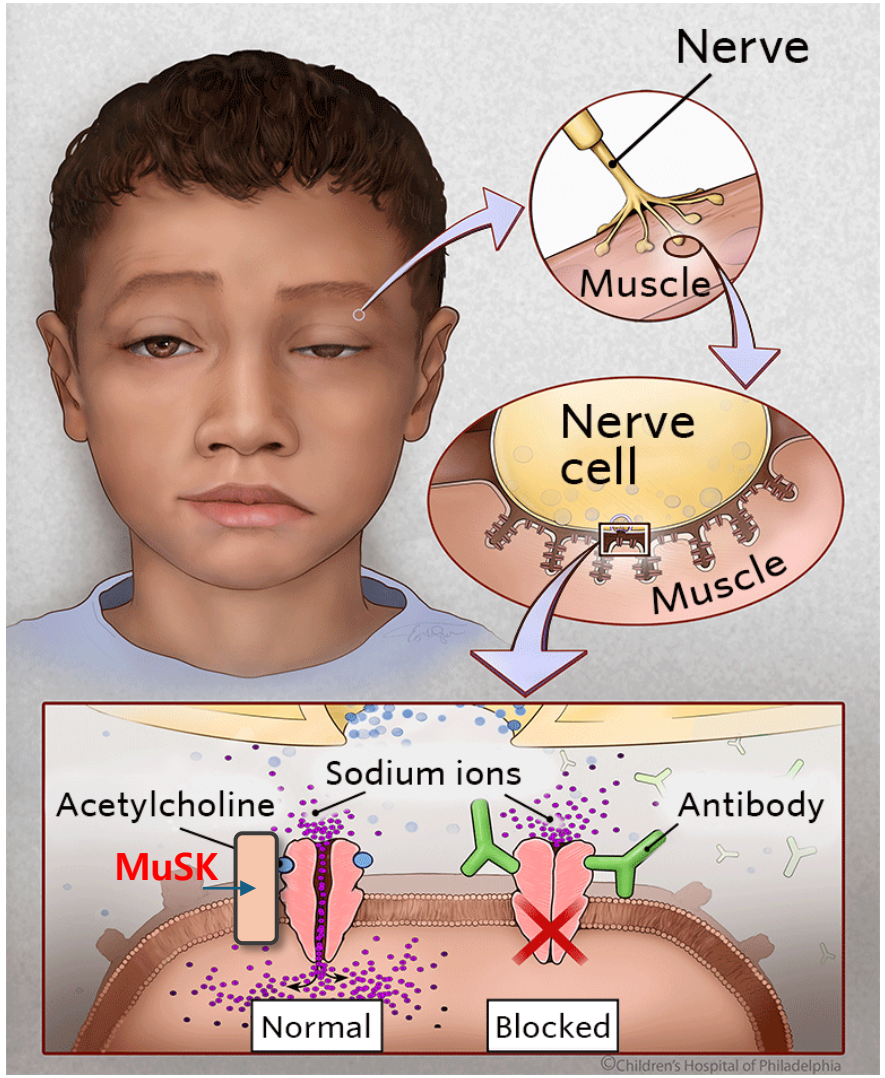
CAR-T trials for lupus dominate, but studies for other autoimmune disease are rapidly increasing



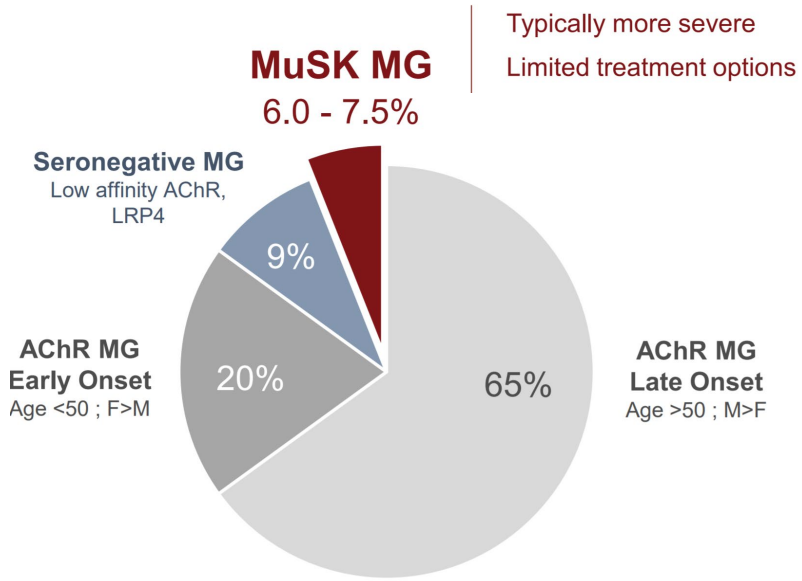
Source: clinicaltrials.gov

- Bone Marrow Transplantation (2024) 08 Oct: Image from https://www.nature.com/articles/d41586-024-00470-5

Myasthenia gravis (MG)



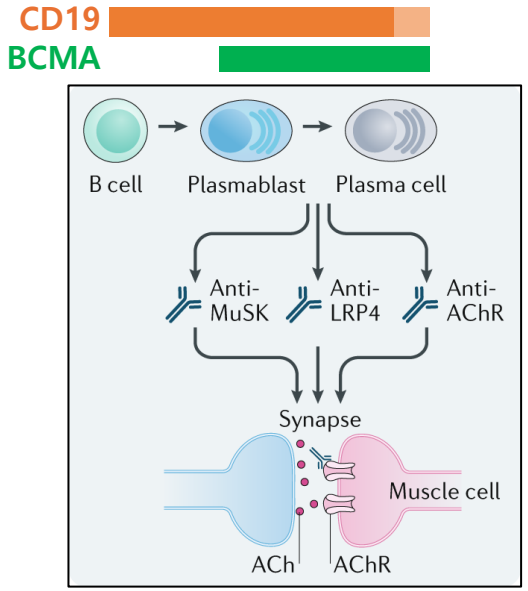
- Autoantibodies bind to post-synaptic proteins (e.g. AChR, MuSK, LRP4 and etc)
- Classification depending on serum autoantibodies



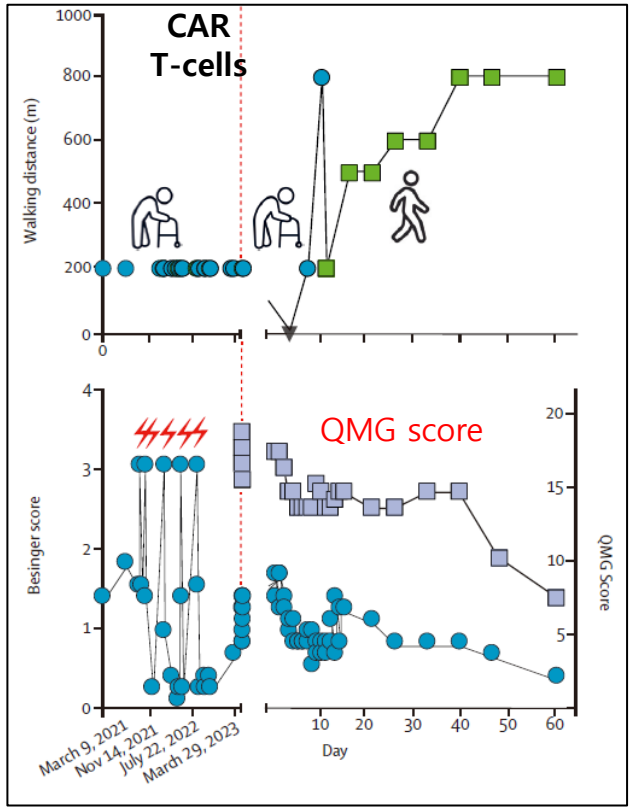
- Image from https://www.chop.edu/conditions-diseases/myasthenia-gravis

B cell-depletion using CAR-T for myasthenia gravis

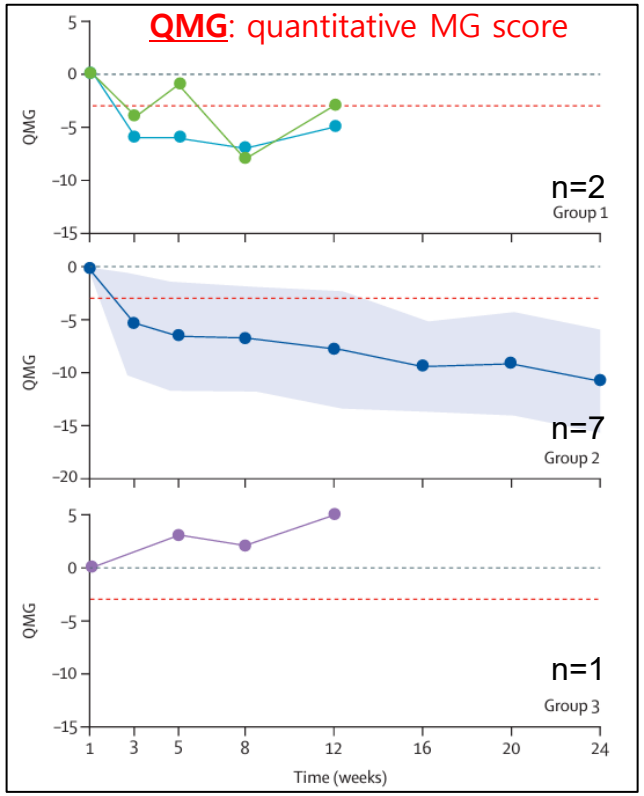
- **Anti-CD19 CAR-T cells** target B cells, plasmablasts, and plasma cells (Haghikia et al., 2023a)
- **Anti-BCMA CAR-T cells** target plasmablasts and plasma cells (Granit et al, 2023b)



Anti-**CD19** CAR-T (case report)



Anti-**BCMA** CAR-T (open-label, phase 1b/2a)



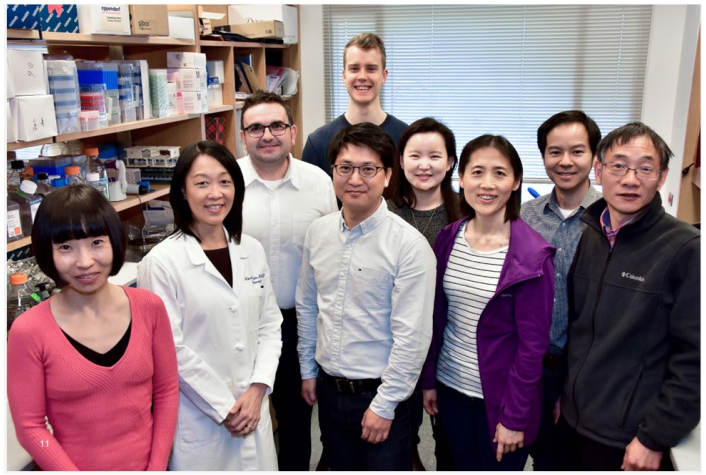
6 doses (mRNA-based CAR)
- Group 1 (n=2): twice a week
- **Group 2 (n=7): once a week**
- Group 3 (n=1): once a month

- *Nature Reviews Drug Discovery* (2021)
- *The Lancet Neurology* (2023)[a,b]

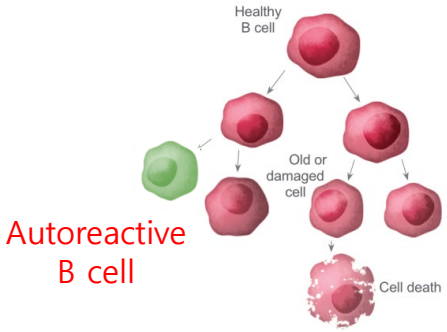
CAR T-cell Therapy for B cell-mediated diseases

Is it possible to selectively remove autoreactive B cells?

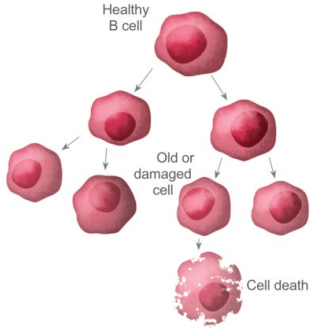
Aimee Payne, MD, PhD, and her quest for precision medicine in the treatment of pemphigus

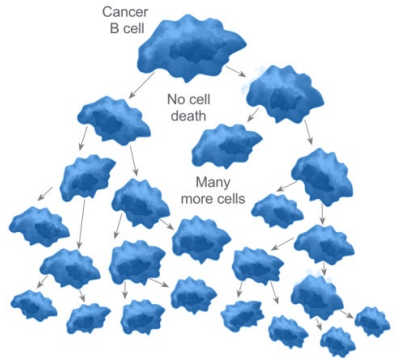


Autoimmunity ← *Health* → *Cancer*



Autoreactive
B cell

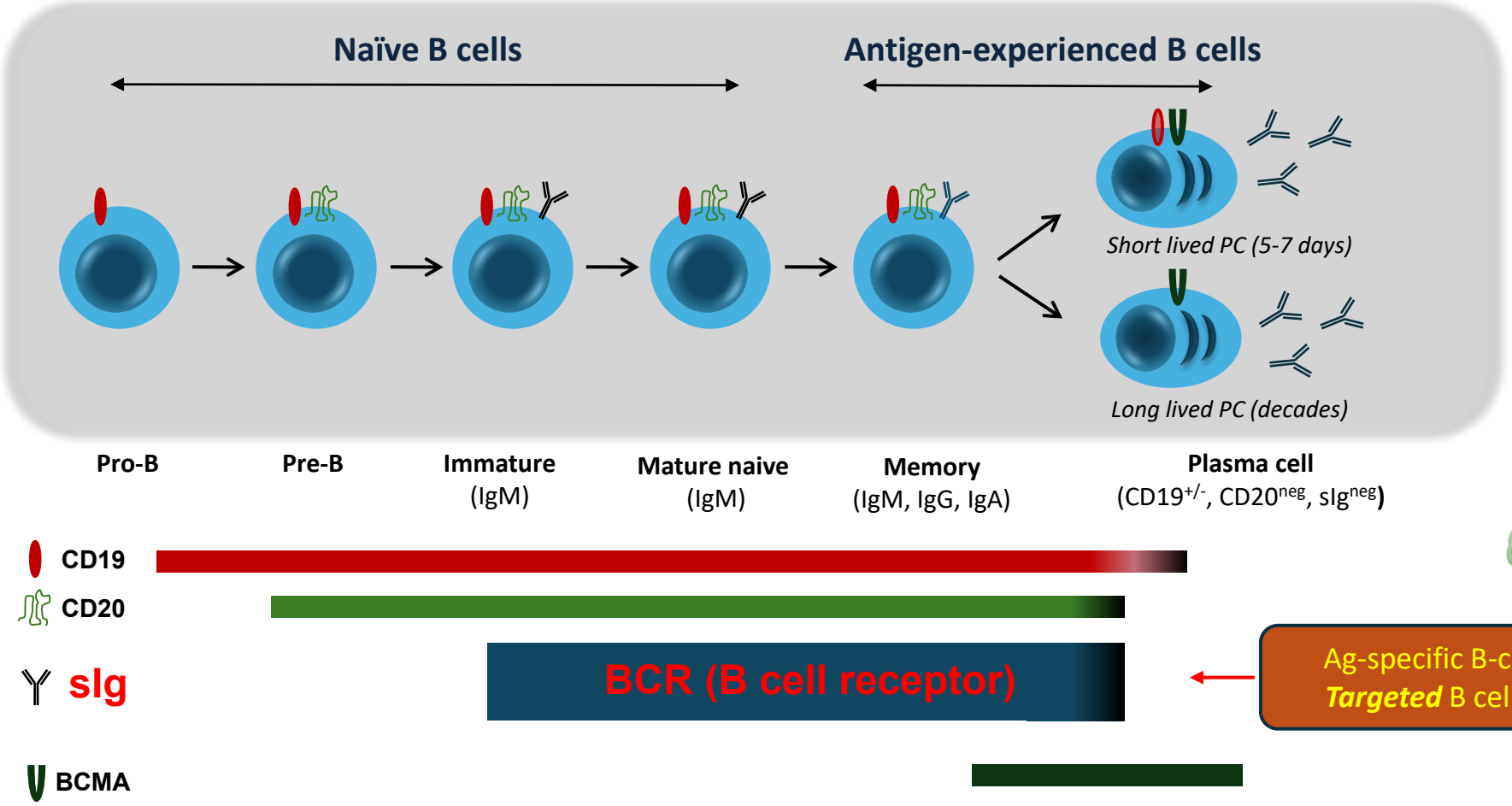




Autoreactive B cells are rare (less than 2% in total B cells)

Most cells are cancerous

Each autoreactive B cell has a unique BCR that recognizes a specific autoantigen

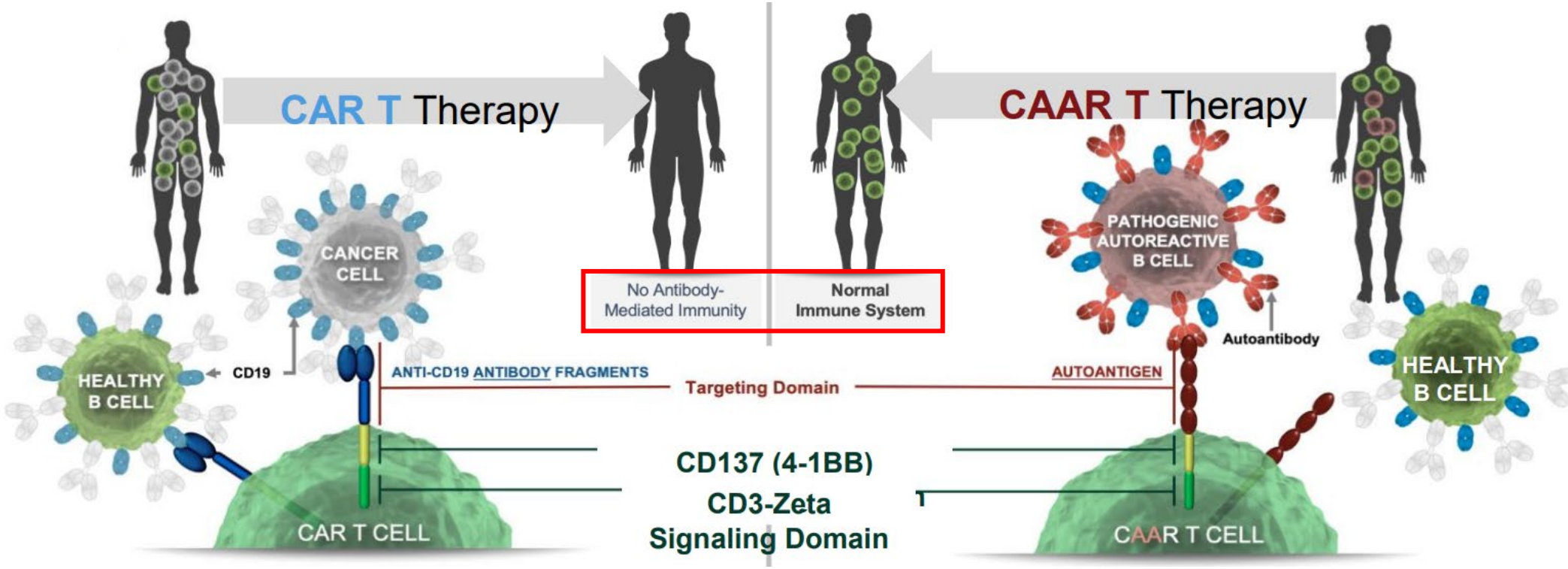


- Oh S. and Payne AS, *Immune Network* (2022)

CAAR-T Platform:

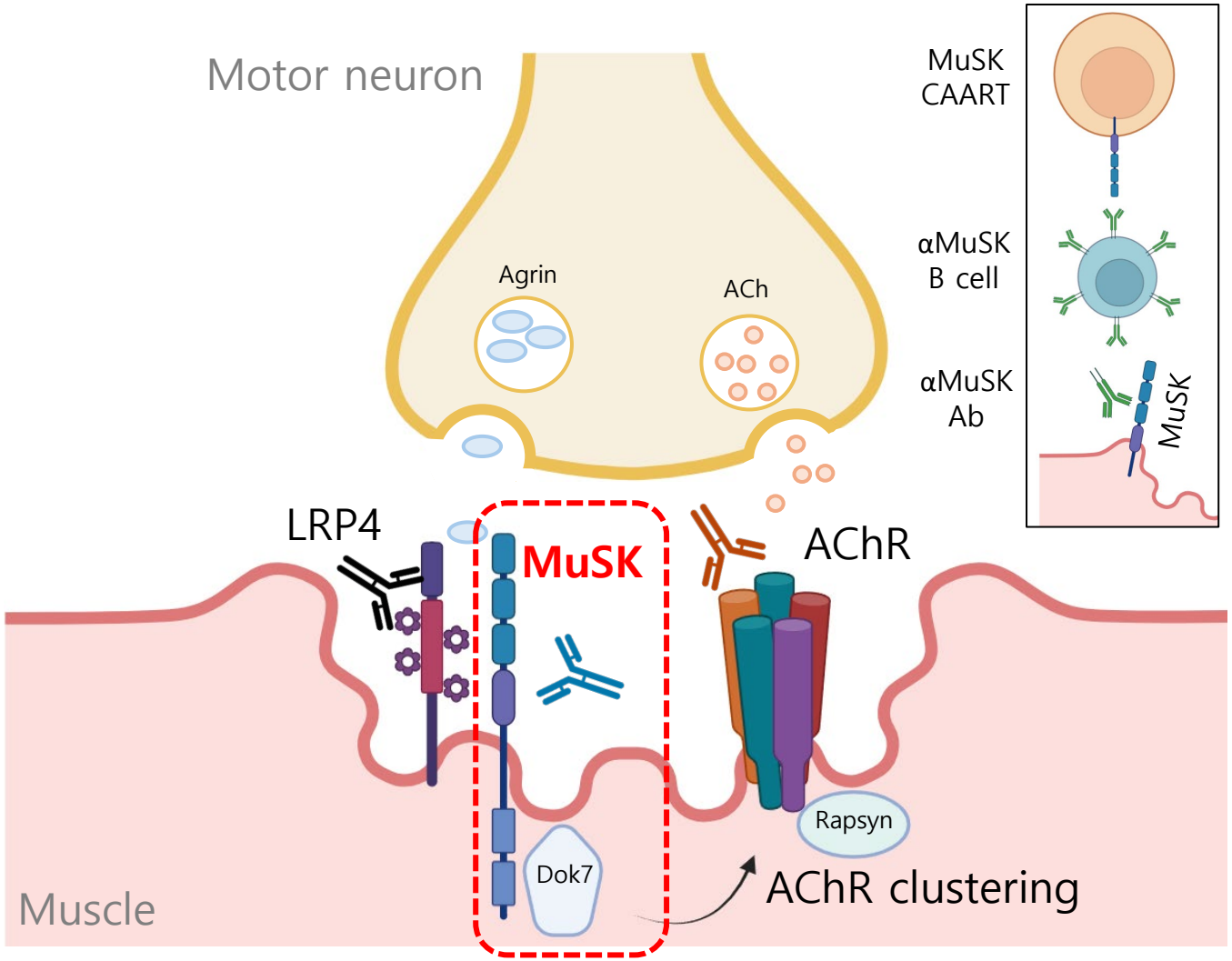
ABCD: Antigen-specific B Cell Depletion

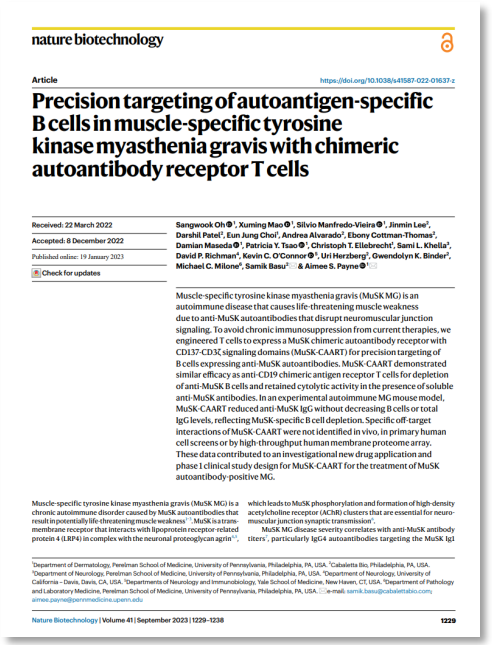
- **CAAR** (chimeric autoantibody Receptor): express **autoantigen** as a receptor domain
  (called a "Double A CAR")



- Image from Cabalettabio.com

Developing MuSK-CAART for MuSK seropositive MG

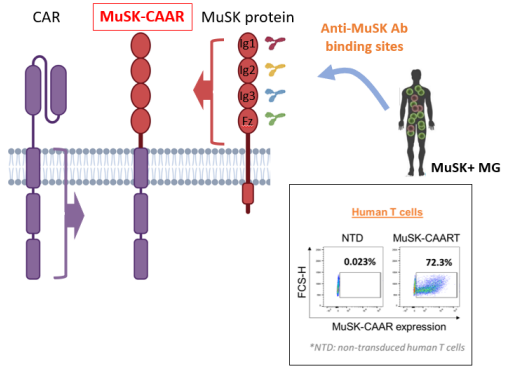


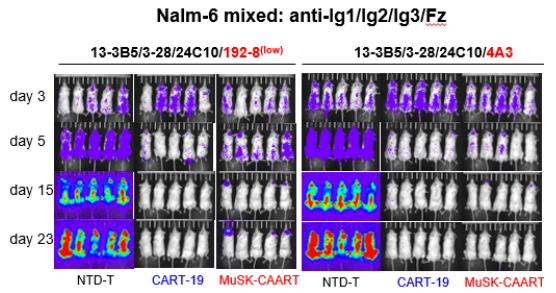


nature biotechnology

Article

Precision targeting of autoantigen-specific B cells in muscle-specific tyrosine kinase myasthenia gravis with chimeric autoantibody receptor T cells





U.S. Food and Drug Administration Grants Cabaletta Bio Fast Track Designation for MuSK-CAART

(Cabaletta Bio, NCT05451212, 2022-2028)

- Oh et al, *Nature Biotechnology* (2023)
- https://clinicaltrials.gov/study/NCT05451212

NSG xenograft mouse model:
Advantages and disadvantages for evaluation of MuSK-CAART

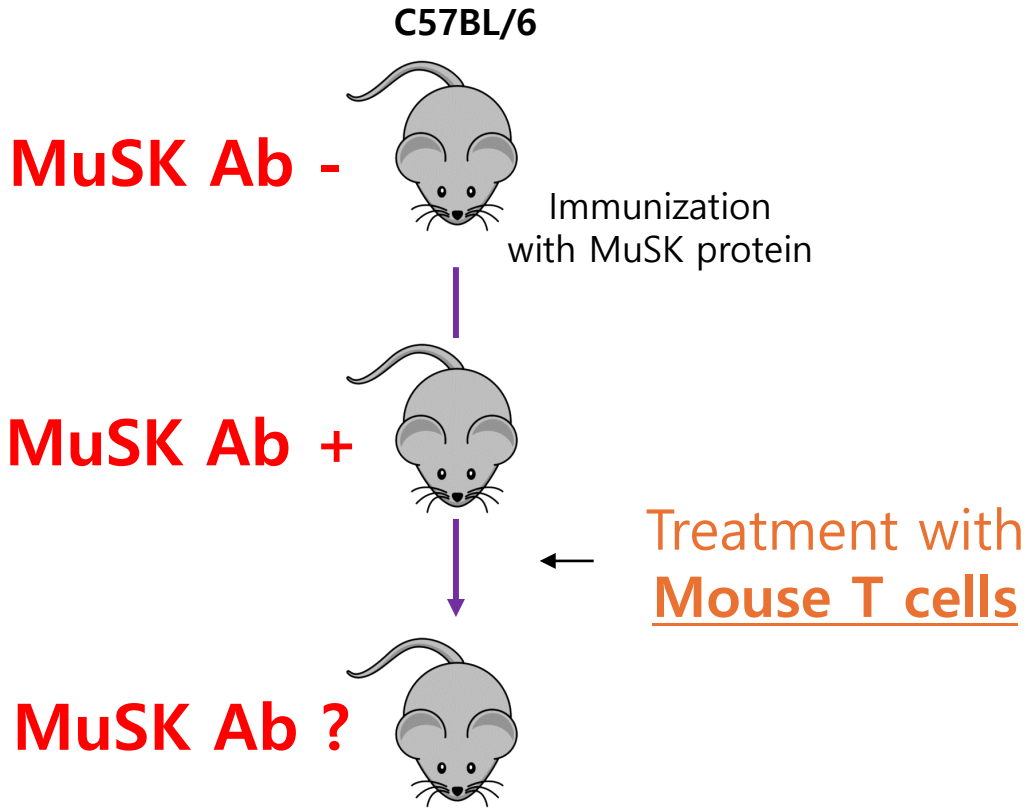
Advantages

- Allows testing of the clinical product, MuSK-CAART
- Anti-MuSK Nalm-6 target cells are similar to those found in MuSK MG patients (epitopes and antibody affinities)
- Circulating anti-MuSK antibodies present
- Sensitive tracking for clone elimination by bioluminescence imaging
- High level of sequence homology between human and mouse MuSK for toxicology studies

Disadvantages

- ***Tumor model*** (rate of CAART cytolysis must exceed the rapid growth of the Nalm6 targets)
- ***100% target cells*** in the model are MuSK-reactive, whereas MuSK-reactive B cells are **rare** in MG

Syngeneic MuSK experimental autoimmune MG (EAMG):
Mimicking autoimmune physiology of MuSK MG patients

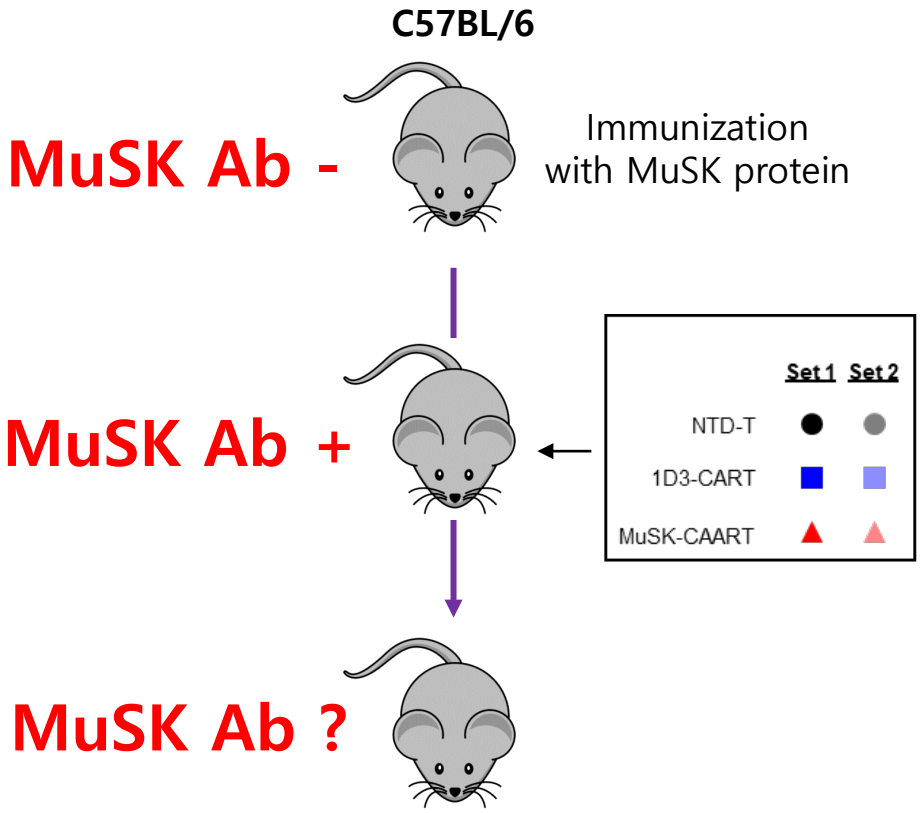


Advantages

- Lower frequency and number of anti-MuSK target cells (**less than 1%**) compared to a tumor model
- Polyclonal serum anti-MuSK antibodies like human MG patients
- Xenogeneic rejection is not expected

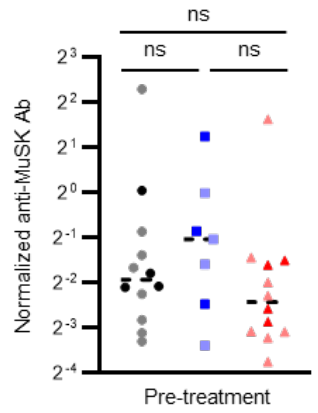
Anti-MuSK antibody titer was specifically decreased in MuSK-CAART treatment

- 1D3 is anti-mouse CD19 clone, targeting CD19+ B cells
- 1D3-CART treated mice (blue) showed decreased serum IgG level as well as decreased anti-MuSK Ab level



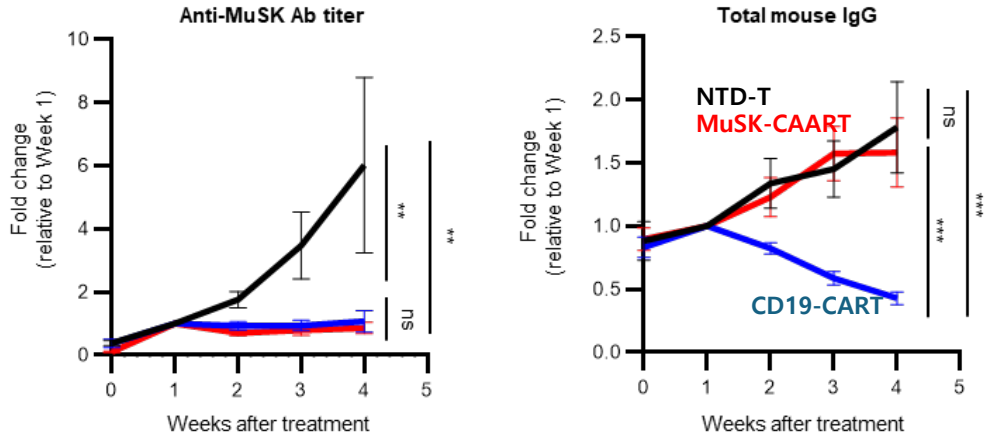
Before treatment

A.



After treatment

B.



- **CD19-CART:** Targeting most B cells expressing CD19 via an anti-CD19 Ab
- **MuSK-CAART:** Specifically targeting anti-MuSK BCR+ B cells using theMuSK autoAg

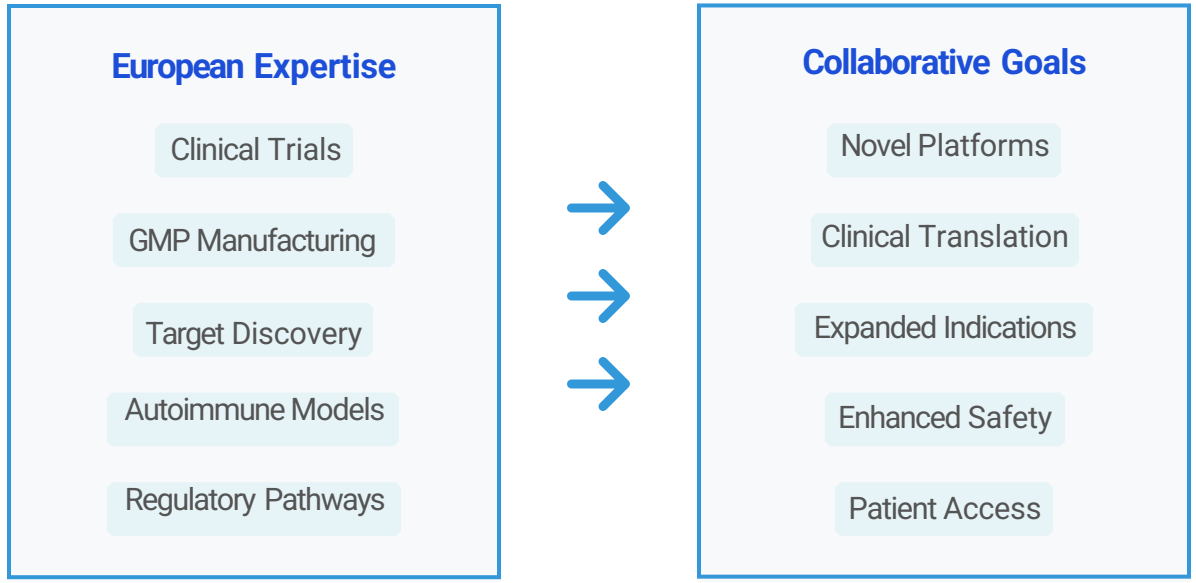
Leveraging European Strengths in CAR-T for Collaborative Innovation

Key European Strengths in CAR-T

- Advanced GMP infrastructure for cell therapy production
- Pioneering autoimmunity clinical trials
- Leading expertise in allogeneic and iPSC approaches
- Sophisticated regulatory frameworks for advanced therapies
- Strong cross-border collaborative networks

Our Research Focus Areas

- **CAR-T.BiTE:** Dual-targeting strategies for enhanced efficacy
- **CAAR-T:** Chimeric autoantibody receptor T cells for autoimmunity
- **CAR-Macrophage:** Innate immune cell engineering for solid tumors
- **AI-driven CAR-Treg:** Machine learning optimization of regulatory T cells



Integrating complementary expertise for accelerated development, regulatory approval, and improved patient outcomes

"We seek partnerships to translate next-gen CAR/CAAR platforms into impactful, patient-centered therapies."

Acknowledgement

ImmunoTherapy Lab (SO Lab)

Seung-A Lee
Sooyeon Lee

Payne Lab

Prof. Aimee S. Payne
Xuming Mao
Eun-Jung Choi
Silvio Manfredo-Vieira
Christoph Ellebrecht
Damian Maseda
Casey Lee
Emma Goodman
Burcin Altun
Insuk Choe

Yale School of Medicine

Prof. Kevin C O'Connor
Fatemeh Khani-Habibabadi

Thank you

Contact: swoh@hallym.ac.kr
Lab Info:
Hallym University
ImmunoTherapy Lab

Fundings: