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Current and Future Roles of Chimeric Antigen Receptor T-Cell Therapy in Neurology
A Review

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IMPORTANCE Advancements in molecular engineering have facilitated the creation of engineered T cells that express synthetic receptors, termed *chimeric antigen receptors* (CARs). This is promising not only in cancer treatment but also in addressing a spectrum of other conditions. This review provides a comprehensive overview of the current approaches and future potential of CAR T-cell therapy in the field of neurology, particularly for primary brain tumors and autoimmune neurological disorders.

OBSERVATIONS CAR T-cell therapy for glioblastoma is promising; however, first-in-human trials did not yield significant success or showed only limited success in a subset of patients. To date, the efficacy of CAR T-cell therapies has been demonstrated in animal models of multiple sclerosis, but larger human studies to corroborate the efficacy remain pending. CAR T cells showed efficacy in treatment of patients with relapsed or refractory aquaporin 4–immunoglobulin G–seropositive neuromyelitis optica spectrum disorders. Further studies with larger patient populations are needed to confirm these results. Success was reported also for treatment of cases with generalized myasthenia gravis using CAR T cells. Chimeric autoantibody receptor T cells, representing a modified form of CAR T cells directed against autoreactive B cells secreting autoantibodies, were used to selectively target autoreactive anti-*N*-methyl-D-aspartate B cells under in vitro and in vivo conditions, providing the basis for human studies and application to other types of autoimmune encephalitis associated with neuronal or glial antibodies.

CONCLUSIONS AND RELEVANCE CAR T cells herald a new era in the therapeutic landscape of neurological disorders. While their application in solid tumors, such as glioblastoma, has not universally yielded robust success, emerging innovative strategies show promise, and there is optimism for their effectiveness in certain autoimmune neurological disorders.

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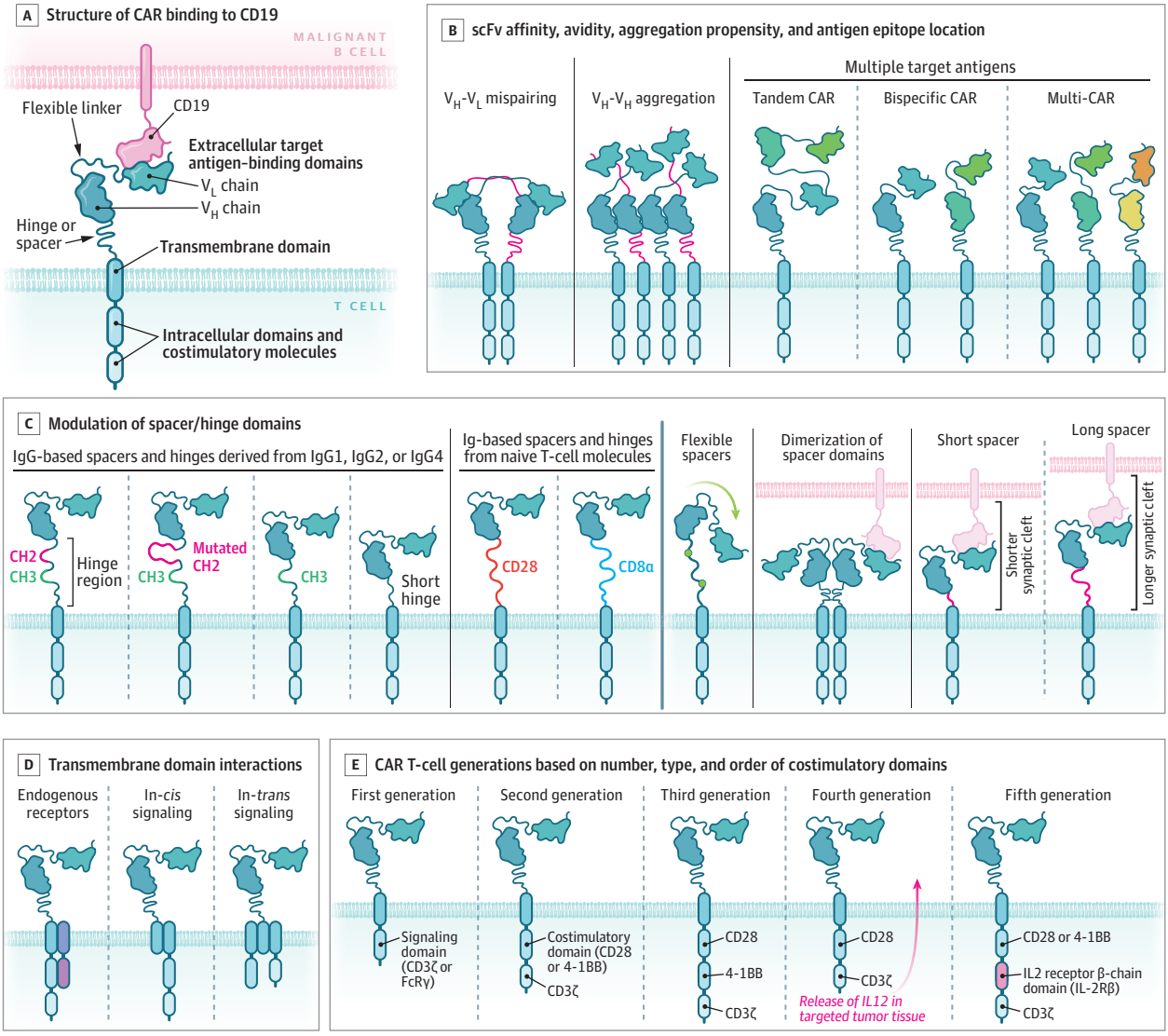
In recent years, the field of medicine has experienced significant progress, marked by breakthroughs in treating diverse diseases that were previously deemed incurable.[1,2] Central to these advancements is the emergence of innovative therapies strategically designed to selectively modulate the immune system. The immune system plays a pivotal role in preventing and combating tumor development and infection.[3] However, when dysregulated, it can instigate severe autoimmune diseases.

T cells, instrumental in adaptive immune responses, have consequently become a key target in the realm of immunotherapy. Various approaches have been explored to enhance the efficacy of immunotherapy, including immune checkpoint inhibition therapy[4-6] and vaccines.[7-11] Furthermore, advancements in molecular engineering have facilitated the creation of novel generations of engineered T cells that express synthetic receptors, termed *chimeric antigen receptors* (CARs). This innovation enables selective targeting and elimination of tumor cells, which has resulted in a paradigm shift in the treatment of previously incurable hematologic cancers.[12-17] Looking ahead, there is a growing body of evidence from both clinical and preclinical studies indicating the potential of CAR T-cell therapy not only in cancer treatment but also in addressing a spectrum of other conditions, including autoimmune disorders, chronic infections, fibrosis diseases (eg, cardiac fibrosis), and senescence-associated diseases.[18-20] This review aims to provide a comprehensive overview of the current approaches and future potential of CAR T-cell therapy in the field of neurology, particularly in relation to primary brain tumors and autoimmune neurological disorders.

CAR T-Cell Therapy

The historical aspects, definition, mechanisms, production, and adverse effects of CAR T-cell therapy, its application for hematological malignancies, solid tumors, and autoimmune diseases, and chimeric autoantibody receptor (CAAR) T-cell therapy are

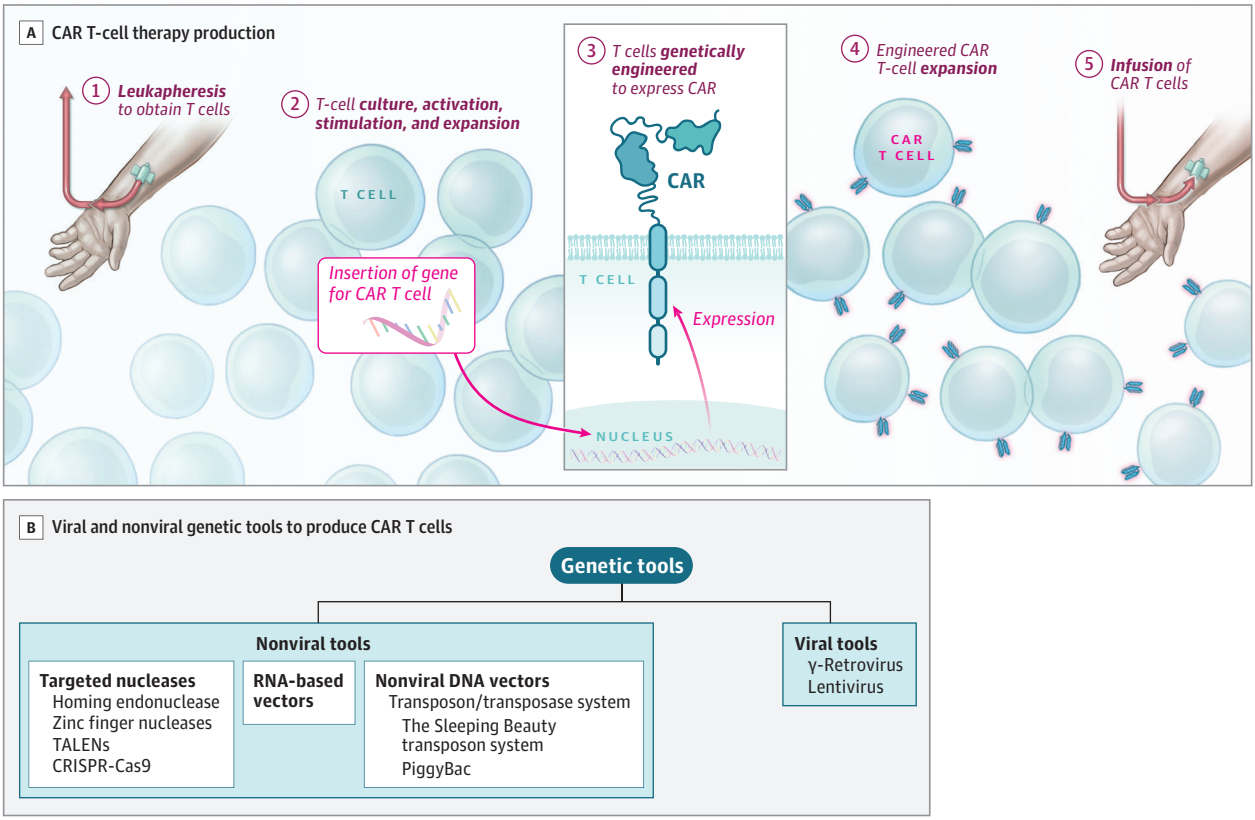
Figure 1. Modulation and Fine-Tuning of Chimeric Antigen Receptor (CAR) Designs Affecting CAR T-Cell Functionality



A, Structure of CAR binding to CD19, a cell biomarker expressed on the surface of B cells at most stages of B-cell differentiation (until downregulation of expression during terminal plasma cell differentiation) and on most B-cell malignant neoplasms. CD19 is a type I transmembrane glycoprotein, part of the immunoglobulin superfamily. CD19 acts as a dominant, critical player in a multimolecular signaling complex on B cells, regulating development, activation, and differentiation of B cells and maintaining the balance between humoral immune response and immune tolerance. CARs typically comprise 4 main components: an extracellular target antigen-binding domain, a hinge or spacer region, a transmembrane domain, and 1 or more intracellular signaling domains and costimulatory molecules. The antigen-binding domains, derived from the variable heavy (V_H) and light (V_L) chains of monoclonal antibodies, are connected via a flexible linker, forming a single-chain variable fragment (scFv). B, Modulation of scFv affinity, avidity, aggregation propensity (eg, V_H-V_L mispairing or V_H-V_H aggregation), and antigen epitope location led to improved CAR T-cell functionality and reduction of adverse effects, such as on-target, off-tumor toxic effects. CAR T-cell approaches targeting multiple antigens have been developed to overcome antigen heterogeneity by engineering CARs with 2 ligand-binding domains in a single receptor (single-chain bispecific or tandem CAR) or by coexpressing 2 (bispecific) or more receptor chains (multi-CAR) in a single T cell. C, Spacer or hinge design with regard to spacer length (short vs long) can regulate intercellular synaptic cleft distances, affecting function of CD45 phosphatases and further immunological signaling. A flexible spacer design can provide access to sterically hindered epitopes. Modulation of immunoglobulin G (IgG)–based spacers, eg, through introducing mutation, can diminish nonspecific innate immune responses. Non–IgG-based spacers from naive T-cell molecules, such as CD8α and CD28, showed equal efficacy in clinically approved CAR T-cell therapies. Dimerization of spacer domains allowed increased activation. D, Transmembrane domain interactions with endogenous receptors or multichain transmembrane interactions lead to novel CAR designs, such as split CAR systems, to initiate in-*cis* and in-*trans* signaling mechanisms. E, CAR T-cell generations are classified based on number, type, and order of costimulatory domains resulting in different effects. IL indicates interleukin.

described in the eAppendix in the Supplement. The eFigure in the Supplement shows therapeutic T-cell engineering for cancer and autoimmune diseases. **Figure 1** shows the modulation and fine-tuning of CAR designs affecting CAR T-cell functionality. **Figure 2** provides an overview of the basic steps of CAR T-cell therapy production using viral and nonviral genetic engineering tools. The **Box** lists complications following CAR T-cell therapy.

Figure 2. Overview of the Basic Steps of Chimeric Antigen Receptor (CAR) T-Cell Therapy Production Using Viral and Nonviral Genetic Engineering Tools



A, First, leukapheresis is performed to collect T cells from patients, followed by in vitro culturing and stimulation using beads, antibodies, or artificial antigen-presenting cells. T cells are genetically engineered to express CAR by gene insertion. B, Viral- and nonviral-based genetic engineering tools have been applied to generate CAR T cells, resulting in permanent or transient expression of therapeutic genes. CAR T cells are expanded to a significant population size in vitro. A lymphodepleting chemotherapy is usually performed before CAR T-cell infusion. CRISPR indicates clustered regularly interspaced short palindromic repeats; TALENs, transcription activator-like effector nucleases.

CAR and CAAR T-Cell Therapy in Neurological Diseases

Despite the tremendous progress in the clinical management of neurological diseases, many patients still face unsatisfactory outcomes due to the limited efficacy or intolerable adverse effects of existing therapies. The revolutionary technology of CAR and CAAR T cells can open new perspectives. Herein, we review the use of CAR and CAAR T cells in neurology, focusing on primary brain tumors and autoimmune neurological diseases[21-39] (**Table**).

Primary Brain Tumors

Malignant neoplasms of the central nervous system (CNS), such as glioblastoma (GBM; characterized as the most prevalent and aggressive primary brain tumor with glial origin in adults) or diffuse midline gliomas, remain incurable so far and pose a formidable therapeutic challenge.[40] Despite advancements in maximal safe resection and adjuvant radiotherapy and chemotherapy, GBM remains incurable, with an average survival period of 14 to 16 months under standard therapy and depending on tumor molecular markers, such as *MGMT* (O6-methylguanine-DNA methyltransferase) promoter methylation, as a more favorable factor for survival time.[41,42] Therefore, novel innovative therapeutic strategies are urgently needed. The recent success observed in CAR T-cell therapy across various malignancies has instigated the initiation of preclinical and clinical investigations of CAR T-cell therapy mainly for GBM (Table). In this context, several tumor antigens have been evaluated, including interleukin 13 (IL-13) receptor subunit α 2 (IL-13Rα2), epidermal growth factor receptor (EGFR) variant III (EGFRvIII), human epidermal growth factor receptor 2 (HER2), erythropoietin-producing hepatocellular carcinoma A2 receptor (EphA2), NKG2D ligands, B7 homolog 3/CD276, disialoganglioside 2 (GD2), CD70, and CD133.[21-24,43-49] Initial investigations focused on IL-13Rα2, which is expressed in more than 75% of GBMs and is associated with tumor aggressiveness and poor prognosis. Preclinical study details are included in the eAppendix in the Supplement.[49-51] The first-in-human pilot safety and feasibility trial, published in 2015,[25] evaluated $CD8^+$ CAR T cells targeting IL-13Rα2 for the treatment of recurrent GBM in 3 patients. Intracranial delivery of CAR T cells into the resection cavity of the patients showed an acceptable safety profile of the therapy. A transient antiglioma response was observed in 2 of the patients, and analysis of tumor tissue from 1 patient demonstrated reduced overall IL-13Rα2 expression. Nevertheless, GBM recurrence was detected in all treated patients.[25] In another study,[21] a patient with recurrent multifocal GBM was treated with multiple infu-

Box. List of Complications Following Chimeric Antigen Receptor (CAR) T-Cell Therapy

Cytokine Release Syndrome
- Fever
- Hypotension
- Tachycardia, tachypnea
- Potential progress to hemodynamic instability with end-organ injury, hypoxia

Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome
- Elevated serum ferritin concentration
- Hemophagocytosis in the bone marrow or other organs
- Liver toxic effects
- Kidney failure
- Splenomegaly
- Pulmonary edema

Immune Effector Cell–Associated Neurotoxicity Syndrome
- Headache
- Attention deficits
- Aphasia, dysphasia
- Confusion, hallucinations
- Apraxia, ataxia, tremor, dysgraphia
- Focal neurological deficits
- Encephalopathy
- Seizures
- Coma
- Fatal cerebral edema

Movement and Neurocognitive Toxic Effects
- Progressive movement disorder with features of parkinsonism
- Neurocognitive disorder

Other (Late) Neurological or Psychiatric Events
- Cerebrovascular accidents, such as transient ischemic attack or stroke
- Peripheral neuropathy, Guillain-Barré–like syndrome
- Dementia
- Mood disorders (new or exacerbated)

Tumor Lysis Syndrome
- Hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia
- Acute kidney injury
- Arrhythmias
- End-organ injury

Early and Late Infections
- Bacterial, viral (eg, progressive multifocal leukoencephalopathy), fungal

Late Autoimmune Reactions
- Lymphocytic alveolitis
- Persistent skin rash
- Eosinophilic pneumonia
- Pneumonitis (not specified)
- Granulomatous disease (not specified)
- Persistent flulike syndrome
- Collagenous colitis
- Autoimmune thyroiditis

Cardiovascular Toxic Effects
- Arrhythmias, including bradycardia

(continued)

Box. (continued)
- Pulseless electrical activity
- Pleural effusion
- Cardiotoxic effects, including reduction in left ventricular ejection fraction
- Cardiorespiratory arrest
- Acute myocardial infarction

Secondary Malignant Neoplasms
- T-cell malignant neoplasms, including CAR-positive lymphoma
- Other hematological malignant neoplasms
- Solid tumors

Hematological Complications
- (Prolonged) cytopenia
- B-cell aplasia and hypogammaglobulinemia

Other Complications
- Allergic reactions or anaphylaxis

sions of CAR T cells targeting IL-13Rα2 through 2 intracranial delivery routes, including infusions into the resected tumor cavity followed by infusions into the ventricular system. No toxic effects of grade 3 or higher were associated with the CAR T-cell therapy. A clinical response with regression of all intracranial and spinal tumors was detected and continued for 7.5 months after the initiation of the CAR T-cell therapy.

Brown et al[26] recently published findings from a completed phase 1 trial that evaluated the safety and efficacy of CAR T-cell therapy targeting IL-13Rα2 in 65 patients with recurrent high-grade glioma, predominantly recurrent GBM. The study found that locoregional (intertumoral or intraventricular) delivery of IL-13Rα2-targeted CAR T cells is safe and shows promising clinical activity in a subset of patients (eAppendix in the Supplement).[26]

Beyond that, in another study, off-the-shelf, healthy donor-derived, steroid-resistant IL-13Rα2–targeting CAR T cells were investigated after intracranial administration in combination with recombinant human IL-2 and systemic dexamethasone in a phase 1 trial in 6 patients with recurrent GBM. The therapy was well tolerated, and transient tumor reduction and/or tumor necrosis at the site of T-cell infusion was observed in 4 of the 6 treated patients. Also in this study, all patients had GBM recurrence in the further course.[27]

EGRFvIII is a mutated EGFR and represents the most common variant of this receptor in cancer, with approximately 50% of patients with EGFR-amplified GBM exhibiting its expression.[44,49] In several preclinical studies, an excellent reduction of tumor growth was observed.[44,49] However, clinical efficacy of CAR T cells specific to EGFRvIII in patients with GBM has been found to be limited.[22,28] In the pioneering study by O'Rourke et al,[22] the first-in-human exploration involved intravenous delivery of a single dose of CAR T cells targeting EGFRvIII in 10 patients with recurrent GBM. The median overall survival was approximately 8 months, with 1 patient exhibiting a residual stable disease lasting longer than 18 months in follow-up. Notably, trafficking of CAR T–EGFRvIII cells to active GBM regions was observed, accompanied by antigen decrease in 5 of 7 patients. Importantly, no off-tumor toxic effects or cytokine release syndrome were reported.[22] Goff et al[28] used a third-generation EGFRvIII-CAR construct with a CD28 and 4-1BB costimulatory domain, along with IL-2 application after transfer, administered

Table. Summary of Published Clinical Studies Using Chimeric Antigen Receptor (CAR) T Cells for the Treatment of Primary Brain Tumors, Including Glioblastoma or Gliomas and Autoimmune Neurological Diseases

Source	Target antigen	Conditions	T-cell type	ClinicalTrials.gov identifier	Phase
Primary brain tumors, including glioblastoma and gliomas					
Brown et al,[25] 2015	IL13-Rα2	Recurrent or refractory unifocal supratentorial WHO grade III or IV glioma	CAR T	NCT00730613	NA (pilot study)
Brown et al,[21] 2016	IL13-Rα2	Recurrent multifocal glioblastoma	CAR T	NCT02208362	1
Brown et al,[27] 2022	IL13-Rα2	Progressive or recurrent WHO grade III or IV malignant glioma	CAR T	NCT01082926	1
Brown et al,[26] 2024	IL13-Rα2	Recurrent high-grade glioma, predominantly recurrent glioblastoma	CAR T	NCT02208362	1
Bagley et al,[30] 2024	IL13-Rα2 and EGFR (bivalent)	Recurrent glioblastoma	CAR T	NCT05168423	1
O'Rourke et al,[22] 2017	EGFRvIII	Recurrent glioblastoma	CAR T	NCT02209376	1
Goff et al,[28] 2019	EGFRvIII	Recurrent glioblastoma	CAR T	NCT01454596	1
Choi et al,[29] 2024	EGFRvIII and EGFR	Recurrent glioblastoma	CAR T	NCT05660369	NA (investigator-initiated, open-label study)
Ahmed et al,[23] 2017	HER2	Progressive recurrent glioblastoma, WHO grade IV glioma	CAR T	NCT01109095	1
Lin et al,[37] 2021	EphA2	Recurrent glioblastoma	CAR T	NCT03423992	NA (pilot study)
Majzner et al,[24] 2022	GD2	Diffuse intrinsic pontine glioma, spinal cord diffuse midline glioma	CAR T	NCT04196413	1
Liu et al,[38] 2023	GD2	Recurrent or progressive glioblastoma	CAR T	NCT03170141	1
Autoimmune neurological diseases					
Qin et al,[34] 2023	BCMA	Relapsed or refractory AQP4-IgG–seropositive NMOSD	CAR T	NCT04561557	1
Cabrera-Maqueda et al,[39] 2024	CD19	Refractory MOGAD	CAR T	NA	NA (single case report)
Granit et al,[35] 2023	BCMA	Generalized myasthenia gravis and required immunosuppression	CAR T	NCT04146051	1b/2a
Haghikia et al,[32] 2023	CD19	Severe, treatment-refractory, anti-AchR-positive generalized myasthenia gravis	CAR T	NA	NA (single case report)
Motte et al,[36] 2024	CD19	Severe concomitant anti-AchR-positive generalized myasthenia gravis and anti-VGCC (N-type) positive Lambert-Eaton myasthenic syndrome	CAR T	NA	NA (2 case reports)
Fischbach et al,[31] 2024	CD19	Progressive multiple sclerosis	CAR T	NA	NA (2 case reports)
Faissner et al,[33] 2024	CD19	Severe treatment-refractory anti-GAD65-positive stiff person syndrome	CAR T	NA	NA (single case report)

Abbreviations: AChR, acetylcholine receptor; AQP4, aquaporin 4; BCMA, B-cell maturation antigen; EGFR, epidermal growth factor receptor; EGFRvIII, epidermal growth factor receptor variant III; EphA2, erythropoietin-producing hepatocellular carcinoma A2 receptor; GAD65, glutamic acid decarboxylase 65; GD2, disialoganglioside 2; HER2, human epidermal growth factor receptor 2; IgG, immunoglobulin G; IL-13Rα2, interleukin 13 receptor subunit α 2; MOGAD, myelin oligodendrocyte glycoprotein antibody–associated disease; NA, not applicable; NMOSD, neuromyelitis optica spectrum disorder; VGCC, voltage-gated calcium channel; WHO, World Health Organization.

intravenously in 18 patients with recurrent GBM. Median overall survival was 6.9 months; 2 patients survived longer than 1 year, and a third patient was alive at 59 months. Regarding adverse events, severe hypoxia occurred in 2 patients, including 1 treatment-related mortality, most likely due to pulmonary edema after congestion of the pulmonary vasculature from activated T cells. Most patients had a progressive disease with a median progression-free survival of 1.3 months.

To address the challenge of recurrent tumor cells expressing wild-type EGFR protein in EGFRvIII CAR T-cell therapy, Choi et al[29] conducted a first-in-human, open-label study involving 3 patients with recurrent GBM. They used intraventricular administration of an

engineered T-cell product (CARv3-TEAM-E) that targets EGFRvIII through a second-generation CAR and secretes T-cell–engaging antibody molecules (TEAMs) against wild-type EGFR, a protein typically absent in healthy brain tissue but commonly expressed in GBM. Despite initial reductions in tumor contrast enhancement suggesting a radiographic response shortly after treatment, tumor progression occurred in 2 of the 3 participants, likely due to limited persistence of the CARv3-TEAM-E T cells (eAppendix in the Supplement). This study indicates that CARv3-TEAM-E may enable safe and localized targeting of wild-type EGFR in the CNS.[29]

Bagley et al[30] presented preliminary findings from a phase 1 trial that assessed the safety and determined the maximum tolerated dose of intrathecally administered bivalent or bispecific CAR T cells targeting EGFR and IL-13Rα2 in 6 patients with recurrent GBM. Early magnetic resonance imaging showed reductions in enhancement and tumor size in all patients, with substantial CAR T-cell presence and cytokine release in the cerebrospinal fluid (CSF) within the first 4 days. However, none of the patients met the modified Response Assessment in Neuro-Oncology response criteria, which require at least a 50% decrease in the sum of the products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks (eAppendix in Supplement).[30]

Additionally, study details on HER2-, EphA2- and GD2-targeting CAR T cells are included in the eAppendix in the Supplement.[37,38]

CAR T-cell therapy for GBM is promising; however, first-in-human trials did not yield significant success. CAR T-cell therapy needs to overcome several challenges, such as T-cell exhaustion and the absence of ideal target antigens. Ideal CAR T-cell target antigens would be GBM surface antigens that are truly tumor specific and uniformly expressed throughout the tumor tissue to minimize the risks of off-tumor toxic effects and regrowth of GBM cells that do not express the target antigen. To date, there is no such ideal surface antigen for GBM. While the previously mentioned antigens, in particular EGFRvIII, represent GBM-specific surface antigens, their expression is heterogeneous within each tumor. On the other hand, nonmutant cell-surface glioma-associated antigens (GAAs), including EphA2 and IL-13Rα2, are expressed in the vast majority of GBM cells but have imperfect specificity, as they are expressed at low levels in some nontumor, nonbrain tissues. As a result, targeting tumor-associated antigens by genetically engineered cell therapy, such as CAR T-cell therapy, can cause life-threatening off-tumor toxic effects.[52]

Recently, it has been found that chimeric forms of Notch, a type 1 transmembrane protein, in which both the extracellular sensor module and the intracellular transcriptional module are replaced with heterologous protein domains can serve as a general platform for generating novel cell-cell contact signaling pathways (synthetic Notch [synNotch]), such as induced expression of a CAR (synNotch-CAR).[53,54]

To safely and effectively target GAAs, Choe et al[54] have adopted the synNotch-CAR system and developed innovative T-cell circuits that recognize tumor cells based on the prime-and-kill strategy. In this system, the first antigen, which is expressed exclusively on brain or GBM cells, primes the T cells to induce expression of a CAR that recognizes, for example, IL-13Rα2 and EphA2, thereby eradicating GBM cells expressing either EphA2 or IL-13Rα2. EGFRvIII-synNotch–primed EphA2/IL-13Rα2 CAR (E-SYNC) are effectively but restrictedly activated by EGFRvIII as the GBM-specific signal, thereby leading to the complete eradication of patient-derived xenografts with heterogeneous EGFRvIII expression, importantly without attacking EphA2- or IL-13Rα2–positive cells outside the CNS. Beyond that, high fractions of T cells engineered with synNotch-CAR circuits showed a stem or naive cell state, which was associated with excellent in vivo persistence.[54] These findings instill optimism for the auspicious application of synNotch-CAR T cells in GBM and have led to the initiation of the currently ongoing first-in-human trial.[55] A comprehensive summary of both completed and ongoing clinical trials using CAR T cells for glioma is provided in the eTable in the Supplement.

Autoimmune Neurological Diseases

Multiple Sclerosis

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the CNS with an autoimmune origin.[56,57] The pathophysiology of MS comprises a wide range of mechanisms, such as activation of self-reactive lymphocytes, antigen presentation, and impaired peripheral tolerance, eg, through the reduced function of regulatory T (Treg) cells and CNS immune invasion.[56-58] The role of B cells in MS is emphasized by the high efficacy of B-cell–depleting therapies for this condition (details on the pathophysiology of MS are described in the eAppendix in the Supplement).[59-61]

Owing to the intricate mechanisms of immunopathogenesis implicated in the pathology of MS, different immunotherapies are at disposal, albeit lacking specificity. Therefore, the CAR T-cell approach depleting B cells in peripheral tissues and in the CNS provides a new direction for targeted MS therapy. To date, the efficacy of CAR T-cell intervention has been demonstrated in animal models of MS, and only 2 patients with MS receiving CAR T-cell therapy were reported.[31,48,62-65] Larger human studies to corroborate these effects remain pending.

In the murine experimental autoimmune encephalomyelitis (EAE) model of MS, $CD4^+$ T cells were transduced using a lentiviral vector system encoding the myelin oligodendrocyte glycoprotein (MOG) CAR gene and FoxP3 gene that drives Treg-cell differentiation.[63] Treg cells have been demonstrated to play a critical role in the protection and recovery of the EAE model of MS. Following this, the main role of MOG CAR Treg cells is to localize and bind to MOG-positive oligodendrocytes in the CNS to prevent immune attacks against these cells. In mice treated with CAR Treg cells, recovery was confirmed (eAppendix in the Supplement). Symptom-free mice were rechallenged with a second EAE-inducing inoculum and were protected against the EAE inflammation, confirming the sustained effect of engineered Treg cells. These findings demonstrated that MOG CAR Treg cells could treat all the mice with EAE.[63] In another study, human Treg cells were transduced to express CARs with single-chain variable antibody fragments that recognized myelin basic protein or MOG.[64] Treg cells require the transcriptional factors FoxP3 and Helios for the maintenance of their regulatory capacity. Following this, a significant amount of FoxP3 and Helios expression was observed in the transduced CAR Treg cells after long-term culture compared with the reference control. Adoptive transfer of a mixture containing an equal number of MOG- and myelin basic protein–recognizing CAR human Treg cells into pMOG35-55–immunized mice suppressed EAE progression.[64] Another study investigated MOG35-55 peptide–major histocompatibility com-

plex class II (pMHCII)–CAR–expressing CD8$^+$ T cells in mice to specifically eliminate pathogenic or autoreactive T cells.[66] Both naive and activated T-cell receptor–specific, higher-affinity CD4$^+$ T cells were efficiently depleted in vivo using pMHCII-CAR T cells, preventing the initiation of EAE.[66] Modifications of the pMHCII-CAR construct led to elimination of lower-affinity autoreactive T cells with attenuation of disease progression. It was concluded that higher-affinity T cells can induce CNS autoimmunity, whereas lower-affinity T cells are required for the maintenance of ongoing autoimmunity.[66]

An additional study explored the application of anti-CD19 CAR T cells in the spontaneous model of EAE, the opticospinal encephalomyelitis mouse model. In this model, both T cells and B cells express a MOG-specific antigen receptor, and there is a notable abundance of meningeal B-cell aggregates (MEBAGs).[62] MEBAGs have been found in autopsy material of patients with chronic MS and correlated with worse disease course. Anti-CD19 CAR T-cell intervention eliminated MEBAGs but also caused massive infiltrates of T cells and macrophages both in the meningeal compartment and deep in the spinal cord white matter, contributing to more widespread demyelination and axonal loss (eAppendix in the Supplement). In summary, anti-CD19 CAR T-cell treatment reduced the size of MEBAGs but exacerbated clinical disease.[62] In contrast to these data, a recent study demonstrated that anti-CD19 CAR T cells ameliorated EAE and thoroughly depleted B cells in the periphery and within the CNS (eAppendix in the Supplement).[65]

In 2024, the first report of individual treatment with a fully human CD19 CAR T-cell therapy (KYV-101) in 2 patients with progressive MS (despite previous immunomodulating therapy) was published.[31] Previous findings of KYV-101 in a phase 1 clinical trial of 20 patients with B-cell lymphoma and a clinical case study in a patient with myasthenia gravis showed good safety and efficacy.[32,67] Recently, the successful use of KYV-101 in a patient with treatment-refractory stiff person syndrome was reported.[33] In the MS cases, each patient was administered a single dose of 1×10^8 second-generation CD19 CAR T cells (KYV-101) after lymphodepletion with fludarabine and cyclophosphamide.[31] In both patients, the CD19 CAR T-cell therapy had tolerable short-term safety profiles. CAR T-cell expansion was detected in the CSF without clinical signs of neurotoxic effects or immune effector cell–associated neurotoxicity syndrome. Reduced intrathecal antibody production was observed after CAR T-cell infusion in 1 patient, indicating CAR T-cell effects on CD19$^+$ target cells in the CNS. However, 1 new T2 lesion without contrast enhancement was described during magnetic resonance imaging follow-up. In the other patient, the intrathecal antibody production was not altered, and the lesions remained unchanged on magnetic resonance imaging.[31]

In conclusion, further experimental and future clinical studies are needed to confirm the efficacy and safety of CAR T cells in MS treatment. In recent years, many new approved MS drugs with long-term efficacy and safety, including reduced adverse effects, have become available.[68,69] In contrast, CAR T-cell therapy could represent an even more personalized treatment option for MS and enable deeper elimination of B cells, particularly in the meninges, which are difficult to access for monoclonal antibodies. CAR T cells have shown the ability to penetrate tissues more thoroughly than monoclonal antibodies, although they harbor other complications (Box). Several cases of progressive multifocal leukoencephalopathy (PML), a life-threatening brain infection caused by the reactivation of JC virus in immunocompromised patients, were reported as a complication after anti-CD19 CAR T-cell therapy in patients with hematological malignancies.[70-75] It is well known that disease-modifying therapies including monoclonal antibodies, such as natalizumab, have been associated with cases of PML in patients with MS.[76] Therefore, the significant risks of the CAR T-cell therapies to cause PML and other complications in patients with MS where highly effective treatments already exist could be a major barrier to future clinical use.

Neuromyelitis Optica Spectrum Disorder

Neuromyelitis optica spectrum disorder (NMOSD) is a severe inflammatory autoimmune disease of the CNS mediated by serum aquaporin 4 (AQP4)–immunoglobulin G (IgG) antibodies (details on pathophysiology and treatment are provided in the eAppendix in the Supplement).[77-82] Despite the existing treatment options, 25% to 60% of patients have further recurrent episodes. Therefore, novel therapeutic approaches are needed. In 2023, the first investigator-initiated, open-label, single-arm, phase 1 clinical trial with a CAR construct targeting B-cell maturation antigen (BCMA; CT103A) in patients with relapsed or refractory AQP4-IgG–seropositive NMOSD was published.[34] Clinical improvement was demonstrated in all patients from baseline at last follow-up (eAppendix in the Supplement).[34]

Another study performed single-cell analysis of the anti-BCMA CAR T cells on CSF and blood samples from 5 trial patients with NMOSD who previously received anti-BCMA CAR T-cell therapy, aiming to provide mechanistic insights into in vivo CAR T-cell function.[34,83] Cytotoxic-like CD8$^+$ CAR T-cell clones were detected as predominant players in autoimmunity. Anti-BCMA CAR T cells with enhanced chemotaxis properties and increased CXCR3 expression efficiently crossed the blood-CSF barrier to eliminate plasmablasts and plasma cells in the CSF, contributing to reduction of neuroinflammation in patients with NMOSD.[83]

In conclusion, CAR T cells showed efficacy in the treatment of patients with relapsed or refractory AQP4-IgG–seropositive NMOSD.[34,39] Adverse events were reported, but all were manageable. Further studies with larger patient populations are needed to confirm the results of this first-in-human clinical study in NMOSD.

Autoimmune Encephalitis

Antibody-associated autoimmune encephalitis is a group of inflammatory brain diseases associated with antibodies against neuronal cell-surface (eg, ion channels, receptors) or intracellular neuronal proteins.[84-86] The list of antibodies associated with neurological syndromes continues to grow, and intensive research is being carried out to better understand the underlying pathomechanisms (details on pathophysiology are provided in the eAppendix in the Supplement).[84,87,88]

Anti–*N*-methyl-D-aspartate receptor (NMDAR) encephalitis represents the most common form of autoimmune encephalitis (details on pathophysiology and treatment are provided in the eAppendix in the Supplement).[89] In a recent study from 2023,[90] NMDAR-specific CAAR (NMDAR-CAAR) T cells were developed to avoid chronic immunosuppression due to current unselective treatments and to achieve the selective depletion of NMDAR antibody-producing B cells with an increase in treatment efficacy. In sum-

mary, NMDAR-CAAR T cells selectively target autoreactive anti-NMDAR B cells under in vitro and in vivo conditions (eAppendix in the Supplement).[90] This preclinical study provides the basis for clinical, in-human studies. Moreover, the CAAR T-cell approach may also be applicable to other types of autoimmune encephalitis with antibodies directed against cell-surface proteins, such as LGI1, CASPR2, and GABAA/BR, because the direct pathogenicity of these antibodies suggests the indication for selective depletion of disease-driving B cells.

Myasthenia Gravis

Myasthenia gravis is a chronic autoimmune disease caused by specific, pathogenic IgG antibodies against the acetylcholine receptor (AChR), muscle-specific kinase (MuSK), and lipoprotein receptor–related protein 4 in the postsynaptic membrane at the neuromuscular junction, leading to fluctuating, life-threatening muscle weakness.[91] Standard therapies for myasthenia gravis include acetylcholinesterase inhibitors, steroids, steroid-sparing immunosuppressants, and thymectomy. Recently, targeted immunotherapy with C5 and neonatal Fc receptor inhibitors has been developed.[92] Despite the implementation of various therapeutic interventions, comprehensive disease control is discerned solely within a subset of patients. For instance, only a limited number of patients attain complete remission, with the majority failing to achieve full pharmacologic remission.[91] The disease-inducing antibodies are well characterized, but the available therapies are not immunospecific. Therefore, new targeted or precision immunotherapies with increased efficacy and safety are needed for complete elimination of the pathogenic antibodies. Although antibody-producing plasma cells are involved as key players in the pathophysiology of myasthenia gravis, the focus of available therapies is not adequately or specifically on plasma cells.[93] However, the specific expression of BCMA on the surface of mature plasma cells offers novel opportunities. In 2023, the first preclinical data of CAR T-cell therapy application in myasthenia gravis with MuSK antibodies were published.[94] Treatment with MuSK-CAAR T cells led to MuSK-specific B-cell depletion (eAppendix in the Supplement).[94]

In 2023, T cells with autologous RNA chimeric antigen receptor (rCAR), rather than the conventional DNA approach, were engineered to target B-cell maturation antigen BCMA, which is expressed on plasma cells. These were tested for the first time in a prospective, open-label, multicenter, nonrandomized, phase 1b/2a trial evaluating the safety and clinical activity of Descartes-08, an anti-BCMA rCAR T-cell therapy, in adults with generalized myasthenia gravis receiving a background therapy of prednisone, steroid-sparing immunosuppressants, or both.[35] In summary, treatment with Descartes-08 was well tolerated and led to clinically meaningful decreases on myasthenia gravis severity scales (eAppendix in the Supplement). However, these results need to be confirmed in randomized, double-blinded, placebo-controlled trials with larger patient populations. Nevertheless, CAR T-cell therapy can provide a basis for a future therapy option in myasthenia gravis.[35,95] Recently, the first case of successful treatment of a patient with severe, treatment-refractory, anti-AchR-positive generalized myasthenia gravis using fully human autologous anti-CD19 CAR T cells was reported.[32] Moreover, 2 patients with concomitant myasthenia gravis and Lambert-Eaton myasthenic syndrome had rapid clinical recovery accompanied by profound B-cell depletion and substantial reduction and final normalization of AChR and voltage-gated calcium channel N-type antibody levels after autologous anti-CD19 CAR T-cell treatment.[36] Also, the successful use of bispecific anti-BCMA/CD19 CAR T cells in refractory myasthenia gravis was reported.[96] Anti-CD19 CAR constructs were previously administered in patients with lymphoma and autoimmune rheumatic disease and might represent a new treatment option in neurological diseases with involvement of autoreactive B cells and autoantibodies, such as myasthenia gravis.

Conclusions

CAR T cells herald a new era in the therapeutic landscape of neurological disorders, offering a targeted approach that ensures the safeguarding of healthy tissues and imposes limited toxic effects. While their application in solid tumors, such as GBM, has not universally yielded robust success, emerging innovative strategies show promise. Additionally, there is optimism for their effectiveness in certain autoimmune neurological disorders. This underscores the potential of CAR T-cell therapy as a transformative avenue in neurology.

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