

Synthetic Cell-Based Immunotherapies for Neurologic Diseases

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Abstract

The therapeutic success and widespread approval of genetically engineered T cells for a variety of hematologic malignancies spurred the development of synthetic cell-based immunotherapies for CNS lymphoma, primary brain tumors, and a growing spectrum of nononcologic disease conditions of the nervous system. Chimeric antigen receptor effector T cells bear the potential to deplete target cells with higher efficacy, better tissue penetration, and greater depth than antibody-based cell depletion therapies. In multiple sclerosis and other autoimmune disorders, engineered T-cell therapies are being designed and currently tested in clinical trials for their safety and efficacy to eliminate pathogenic B-lineage cells. Chimeric autoantibody receptor T cells expressing a disease-relevant autoantigen as cell surface domains are designed to selectively deplete autoreactive B cells. Alternative to cell depletion, synthetic antigen-specific regulatory T cells can be engineered to locally restrain inflammation, support immune tolerance, or efficiently deliver neuroprotective factors in brain diseases in which current therapeutic options are very limited. In this article, we illustrate prospects and bottlenecks for the clinical development and implementation of engineered cellular immunotherapies in neurologic diseases.

Introduction

Progress in research and treatment development over the past 3 decades culminated in remarkable improvements in managing immune-mediated neurologic diseases. To date, the available arsenal to treat people with multiple sclerosis (MS) covers more than 20 drugs, and the aim of treatment has changed from simply reducing relapse rates to achieving complete and durable disease control.¹ In particular, antibody (Ab)-based therapeutics evolved as important tools in treating patients with MS and other autoimmune disease conditions such as neuromyelitis optica spectrum disorders (NMOSD) or myasthenia gravis (MG), and the spectrum of diseases targeted by Ab-based treatment platforms continues to grow.² Although disease activity is controlled by high-efficacy monoclonal Ab therapies in most patients with autoimmune neurologic diseases, a not negligible proportion of the cases fails to respond to treatment.³ As an example, evidence for ongoing disease activity defined by presence of clinical relapses, disability worsening, or signs of inflammatory activity at brain MRI has been observed in more than half of the patients with MS receiving high-efficacy monoclonal Ab therapies as reported in pivotal phase 3 clinical trials.³ Monoclonal Ab-based therapies are being evaluated and increasingly used to treat various brain tumors, but the blood-brain barrier (BBB) limits their bioavailability and efficacy within the CNS. Synthetic cell-based immunotherapies, such as chimeric antigen receptor (CAR) T cells, combine the biology of antibodies in targeting specific molecules with powerful immunologic functions of T cells or natural killer (NK) cells as outlined below.⁴

The initial development of CAR T-cell therapies focused on the most common cancer in children, acute lymphoblastic leukemia (ALL). One of the significant obstacles to the cure ALL is its propensity to relapse despite or being refractory to initial chemotherapy or hematopoietic

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Glossary

Ab = antibody; **A β** = amyloid beta; **AD** = Alzheimer disease; **ALL** = acute lymphoblastic leukemia; **BBB** = blood-brain barrier; **BCMA** = B-cell maturation antigen; **CAAR** = chimeric autoantibody receptor; **CAR** = chimeric antigen receptor; **CRS** = cytokine release syndrome; **EAE** = experimental autoimmune encephalomyelitis; **HER2** = human epidermal growth factor receptor 2; **HLA** = human leukocyte antigen; **FDA** = Food and Drug Administration; **ICANS** = immune effector cell-associated neurotoxicity syndrome; **MS** = multiple sclerosis; **MG** = myasthenia gravis; **NMOSD** = neuromyelitis optica spectrum disorders; **NK** = natural killer; **scFv** = single-chain fragment domain; **SLE** = systemic lupus erythematosus; **TCR** = T-cell receptor; **TME** = tumor microenvironment; **Treg** = regulatory T cell.

stem-cell transplantation, which occurs in approximately 10%–15% of cases. In patients with relapsed or refractory ALL and other B-lineage cell-derived blood cancers, CAR T-cell therapies have the potential to induce sustained remission.⁵ So far, 6 CAR T-cell therapies have been approved by the Food and Drug Administration (FDA) and the European Medicines Agency^{4,5} for the treatment of relapsed or refractory blood cancers, including lymphomas, some forms of leukemia, and, most recently, multiple myeloma.⁴⁻⁶

The unprecedented therapeutic success seen with CAR T-cell therapies against hematologic malignancies has attracted interest in developing such therapies for solid tumors, including brain tumors, for which current therapeutic opportunities are very limited. Case series demonstrated durable disease remission in patients with B-cell–driven autoimmune disease refractory to standard Ab-based therapies.⁷ These data, together with recent progress in engineering synthetic cell-based immunotherapies, spurred the interest in harnessing these platforms to achieve better outcomes for patients with difficult-to-treat neurologic diseases.

Biology of Synthetic Cell-Based Immunotherapies

Engineered cell-based immunotherapies were initially developed by integrating exogenous cancer cell-targeting T-cell receptors (TCRs) into cancer patients' autologous T cells and first successfully tested in patients with metastatic melanoma.⁸ The requirement to match the exogenous TCR with human leukocyte antigen (HLA) molecules of the recipient limited the wider use of these approaches. CARs consist of an extracellular Ab-based single-chain fragment domain (scFv) which recognizes the antigen in a major histocompatibility complex-independent manner (Figure 1).

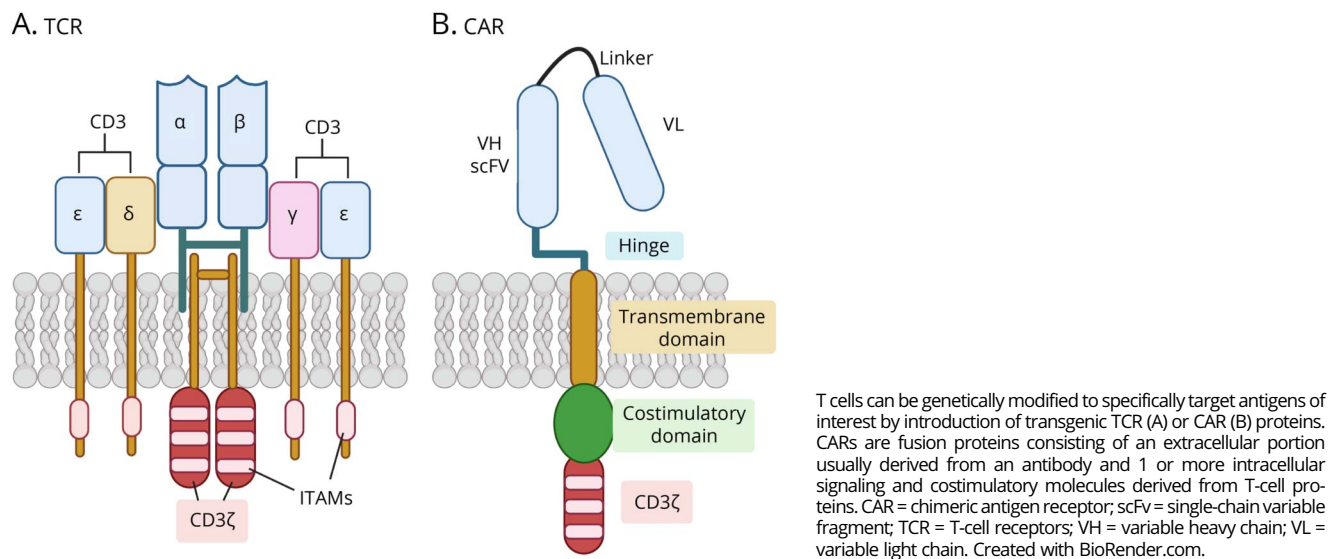
The development of efficient gene transfer platforms to reprogram primary human T cells has provided opportunities to rapidly produce therapeutic T-cell products with desired specificity and function (Figure 2). Although retroviral and lentiviral gene transfer is currently most commonly used in the clinical setting, nonviral gene transfer technologies provide exciting new opportunities to prepare engineered T-cell products *in vitro* and, most remarkably, also *in vivo*.⁹⁻¹¹ Although

malignant transformation due to insertional mutagenesis of retroviral and lentiviral gene delivery has been seen with gene-engineered stem cells, mature T cells are far less susceptible to genome toxicity and malignant T-cell tumors have not been observed in the very large number of patients treated with gene-engineered T cells.

To program the specificity of engineered T cells, CARs and TCRs have been exploited extensively.^{4,12,13} CARs provide engineered T cells with the specificity of an Ab by creating a synthetic receptor consisting of the scFv of an Ab, a linker sequence, a transmembrane, and an intracellular portion, which enables the expression of synthetic CAR molecules on the surface of T cells (Figure 1). The intracellular portion of CARs can further be engineered to contain signaling domains required for T-cell activation, most commonly the immunoreceptor tyrosine-based activation motifs of CD3 zeta, and costimulation derived from CD28, CD137, OX40, and others. The advantage of this modular design is that CAR binding to its target antigen delivers multiple signals required for T-cell activation, proliferation, effector function, persistence, and memory development. The disadvantage is that CARs can be less efficient than TCRs in triggering T-cell activation and effector functions.^{14,15}

In contrast to CARs, TCRs are natural receptors that have evolved to orchestrate antigen-specific T-cell immunity, including long-term memory. However, the introduction of antigen-specific TCRs into primary T cells can result in the mispairing with endogenous TCR chains, which can create autoreactive TCRs that were found to cause substantial toxicity in murine models, although similar toxicities have not been seen in humans.¹⁶ Various engineering technologies have been developed to reduce TCR mispairing, and more recently, clustered regularly interspaced short palindromic repeats-mediated deletion of endogenous TCRs has completely removed the risk of mispairing.¹⁷ Although HLA-restricted antigen recognition by TCRs limits the technology to treatment of patients with defined HLA types, a limitation that does not apply to CARs, it also provides a substantial advantage of TCRs over CARs. HLA-presented peptide antigens can be derived from any cellular protein, enabling TCRs to recognize intracellular and cell surface proteins.¹⁸ Considering that approximately 80% of cellular proteins reside inside the cell,¹⁹ the range of TCR target antigens is dramatically greater than the surface proteins that are accessible to CARs.

Figure 1 Engineering T Cells



Engineered T-Cell Therapies for Brain Tumors

Based on their efficacy to eradicate advanced refractory/relapsed leukemias and lymphomas, 6 CAR T-cell therapies have been approved by the FDA for the treatment of hematologic cancers. Clinical benefit notwithstanding the side effect profile of CAR T therapy, namely, cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), affecting up to two thirds of the patients, presents a clinical challenge.¹² CRS is characterized by an increase of proinflammatory cytokines resulting in endothelial activation and diffuse capillary leakage translating into a sepsis-like phenotype including fever, hypotension, and eventually multiorgan dysfunction.¹² ICANS presents with clinical symptoms that vary in severity ranging from headaches, fatigue, and mild aphasia to seizures, localizing neurologic deficits, and potentially fatal cerebral edema.¹² The underlying pathophysiologic mechanisms remain largely elusive but may include IL-1–mediated and IL-6–mediated systemic inflammation, BBB disruption followed by neuroinflammation, and endothelial activation and neuroaxonal damage.¹²

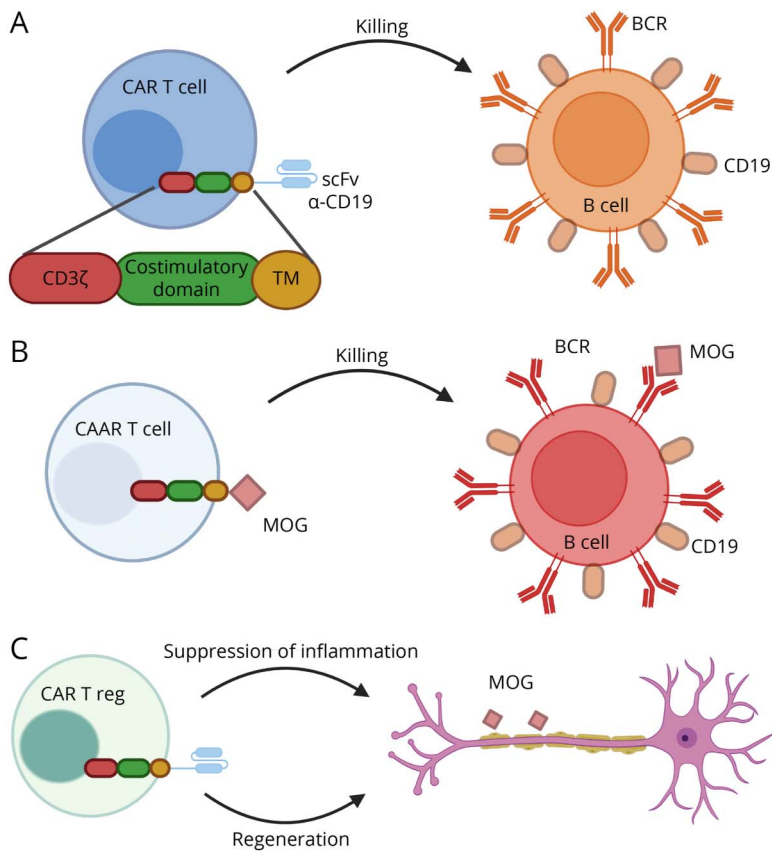
Most pioneering clinical studies on CD19 CAR T cells have excluded patients with CNS involvement because of concerns for potentially fatal neurotoxicity. Current early clinical data, however, suggest an acceptable safety profile with incidences and grades of adverse effects in CNS lymphoma patients similar to patients with systemic lymphoma.^{20,21} In addition, the antitumor response resembled that observed in patients without CNS disease, and durable remissions have been reported.²² Of importance, IV CAR T application was also effective in patients

in the absence of systemic lymphoma manifestation.^{20,21} Small patient numbers and limited follow-up, however, caution the strength of conclusion from these early studies regarding the comparison with other treatment options in the relapsed and refractory setting and for the application to clinical practice in patients with CNS lymphoma.

With its achievements in hematologic cancers, the therapeutic efficacy of CAR T-cell therapy has also been investigated in solid malignancies including brain tumors. CAR T cells targeting various tumor antigens have been evaluated in pre-clinical studies.²³ The most common include interleukin 13 receptor subunit alpha 2, epidermal growth factor receptor variant III, human epidermal growth factor receptor 2 (HER2), *B7 Homolog 3/CD276*, disialoganglioside 2, and CAR T cells that directed against these antigens have been tested in small phase I clinical trials (eTable 1, [links.lww.com/NXI/A877](https://www.lww.com/NXI/A877)). Research is still in its early stages and no conclusion can yet be drawn for clinical practice.²⁴⁻²⁸ Further studies comprising high-grade gliomas, medulloblastoma, atypical rhabdoid teratoid tumors, and ependymomas targeting published and several new antigens are currently recruiting (eTable 1).

Collectively, published clinical data suggest an overall acceptable safety profile and preliminary evidence of clinical activity for CAR T-cell therapy of brain tumors. IV, intraventricular, and intracavitary CAR T administration routes have been applied, with all of them proving feasible and safe. IV injection is less invasive; however, the blood-brain barrier may impede lymphocyte trafficking to the tumor site, and locoregional delivery therefore presumably provides higher efficiency and less systemic toxicities. So far,

Figure 2 CAR T-Cell Therapy: Procedure

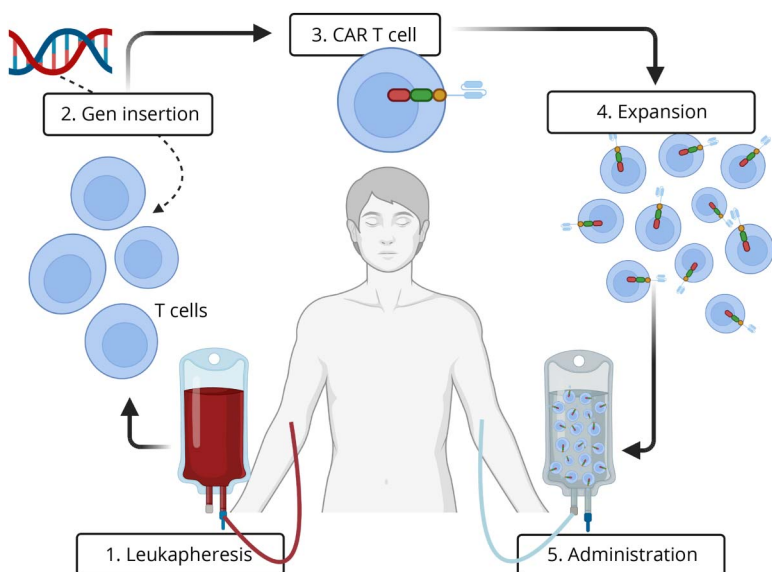


Patients' T cells are collected by leukapheresis and genetically modified to express the CAR of interest. Subsequently, CAR T cell as expanded and readministered to the patient. A conditioning chemotherapy is usually performed before CAR T-cell administration. The procedure as outlined is usually performed within 4-5 weeks. CAR = chimeric antigen receptor; scFv = single-chain variable fragment; Created with BioRender.com.

there is no evidence on the optimal approach, and studies comparing different applications routes have not yet been performed.

Compared with the efficacy of CAR T cells in the treatment of hematologic malignancies, the antitumor effect in brain tumors seems to be modest and short-lived. Disease recurrence was

Figure 3 Synthetic Cell-Based Immunotherapy Platforms



(A) CAR T cells comprising costimulatory signaling domains and CD3 zeta chain and specific for B-cell lineage molecules such as CD19 efficiently deplete target cells. (B) CAAR T cells expressing extracellular domain autoantigen, such as myelin oligodendrocyte glycoprotein, recognize and eliminate B cells specific for that autoantigen. (C) CAR Tregs designed to recognize CNS antigen have the potential to support tissue protection and repair. CAR = chimeric antigen receptor; CAAR = chimeric autoantibody receptor; scFv CD19 = single-chain variable fragment specific for CD19; TM = transmembrane domain. Created with BioRender.com.

inevitable in all patients, and no lasting remissions have been published. The key challenges that could be identified are (1) the heterogeneous intertumoral and intratumoral expression of target antigens in brain tumors,^{23,29} (2) a highly variable expansion and trafficking of CAR T cells in the CNS,²⁷ (3) a strong immunosuppressive response raised by the tumor microenvironment (TME) potentially resulting in CAR T exhaustion and impaired CAR T persistence,^{23,25} and (4) comparatively short-lived clinical remissions with antigen loss in posttherapy recurrent tumors.²⁴⁻²⁶ Retrieving T cells at quantities and qualities required for the generation of synthetic cell-based immunotherapies from patients who underwent multiple rounds of chemotherapy might be challenging in individual cases. The use of allogeneic CAR T-cell products, cryopreserved and available of the shelf, could potentially overcome such limitations.³⁰ Hence, developing strategies to overcome these challenges are necessary to improve the therapeutic success of the CAR T approach for brain tumors.

As the activation of the immune checkpoints through the TME confers to CAR T-cell exhaustion,³¹ combining immune checkpoint blockade with CAR T-cell therapy is expected to enhance therapeutic efficacy. There are several potential methods to achieve this, including coadministration of immune checkpoint inhibitors, engineering CAR T cells to secrete monoclonal checkpoint inhibiting antibodies or scFv fragments,³² gene editing,³³ and gene silencing of the immune checkpoint receptors.³⁴ Clinical trials are currently exploring the combination of immune checkpoint blockade and CAR T cells (NCT03726515, NCT04003649, NCT02873390, and NCT03182816) as well as the safety and efficacy of PD-1-Ab-expressing CAR T cells in EGFR-expressing advanced solid malignancies including glioblastoma multiforme (NCT02873390).

The development of CARs on immune cells beyond T cells is an expanding area of research. One promising avenue is the use of CAR NK cells, which offer unique biological features and may serve as an alternative to T cells. CAR NK cells are believed to produce fewer side effects than CAR T cells, likely due to their lower propensity to trigger cytokine storms. In addition, the short lifespan of NK cells in circulation reduces the risk of on-target/off-tumor toxicity, although this may also limit their effectiveness. A clinical trial on HER2-directed CAR NK cells for glioblastoma has been launched (NCT03383978). In addition to NK cells, macrophages have been investigated as a CAR platform.³⁵

In conclusion, both preclinical and clinical investigations on the use of CAR T cells for treating brain tumors have indicated promising antitumor effects and acceptable safety profiles. However, limited CAR T-cell activation and persistence as well as antigen depletion currently limit their effectiveness. The field of CAR T engineering, however, continues to evolve to address these obstacles and to release the full therapeutic efficiency of CAR T cells in the treatment of brain tumors.

Synthetic Cell-Based Immunotherapies for Neurologic Autoimmune Diseases

Research and pivotal clinical trials performed over the past 2 decades identified B-lineage cells as important contributors to several autoimmune neurologic diseases including MS and NMOSD. However, despite the convincing efficacy of B-cell-depleting therapeutic antibodies targeting CD19 and CD20, a substantial fraction of patients treated with these compounds continue to experience disease activity. As an example, no evidence for MS disease activity (NEDA-3, as defined by absence of relapses, Expanded Disability Status Scale score worsening, and MRI activity) could only be achieved for 48% for ocrelizumab-treated and for 32% for alemtuzumab-treated patients at year 2 based on data obtained clinical trials, which led to the approval of these therapies (i.e., OPERA I-II and CARE-MS I-II).^{36,37}

CD20-targeting monoclonal antibodies do not thoroughly deplete B cells in tissues such as lymphoid organs in which most B cells reside.³⁸ In line with these reports, we and others observed persistence of pathogenic clonal B-cell expansions despite efficient depletion of circulating blood B cells after rituximab therapy,³⁹ indicating that a considerable number of B cells, including pathogenic B cells, escape depletion by CD20-targeting Ab therapy.

An important advantage of CAR T cells during the antitumor immune response is their efficient migration and ability to stay in tissues, including immunologic niches, where they can kill target cells.¹ It was recently reported that anti-CD19 CAR T-cell therapy resulted in drug-free disease remission in a case series of 5 patients with systemic lupus erythematosus (SLE) previously refractory to several immunosuppressive treatments.⁷ In these patients, B-cell reconstitution occurred about 3 months after CAR T-cell therapy with disappearance of previously enriched B-cell receptor clonotypes and repopulation with naïve and non-class-switched B cells.⁷ Thus, anti-CD19 CAR T cells have the potential to reach an unprecedented depth of B-cell depletion including efficient depletion of autoreactive species, leading to immune reconstitution and sustained clinical improvement in patient with SLE. CAR T-cell treatment in the aforementioned study was well tolerated with occurrences of only mild cytokine release syndromes.⁷ The efficacy of anti-CD19 CAR T-cell therapy to deplete B cells in peripheral tissues and in the CNS has recently been demonstrated in animal models of MS, i.e., experimental autoimmune encephalomyelitis (EAE).^{40,41} Case reports or series on anti-CD19 CAR T-cell therapies in patients with MS have, so far, not been reported. China's National Medical Products Administration recently approved a pulsed CAR T-cell therapy targeting the B-cell maturation antigen (BCMA), expressed on subsets of B cells and plasma cells, for the treatment of NMOSD (Acceptance No. CXSL2200233 and CXSL2200234). Although the approval is said to be based on an investigator-initiated open-label, multicenter, single-arm phase I/II study enrolling 12 patients with aquaporin 4-Ab-positive NMOSD and poor symptom control

under standard immunotherapy (iasobio.com/info.php?id=188), clinical trial data have so far not been made publicly accessible. Deep and sustained depletion of pathogenic B-lineage cells through synthetic cell-based immunotherapies targeting CD19 or other B-cell lineage molecules such as BCMA might be a feasible, tolerable, and effective therapeutic option for patients with other B-cell-driven neurologic diseases poorly responding to standard therapy (Figure 3).

In B-cell or Ab-mediated autoimmune diseases with a limited number of better defined target antigens, synthetic cell-based immunotherapy technology can also be harnessed to specifically deplete pathogenic autoreactive cells. To this end, T cells can be engineered to express a chimeric autoantibody receptor (CAAR), consisting of the autoantigen fused to signaling domains⁴² (Figure 3). These modified CAAR T cells are designed to identify and kill B cells expressing the receptor for the autoantigen. A growing spectrum of neurologic disorders is characterized by immune response targeting defined antigens expressed in central or peripheral nervous system and the neuromuscular junction, those disease conditions include MG, NMOSD including myelin oligodendrocyte glycoprotein-Ab-associated diseases, and autoimmune encephalitides.⁴³ Ab responses toward associated neuronal, glial, or neuromuscular antigens are likely pathogenic because adoptive transfer of Abs from patients into susceptible rodents can recapitulate features of the human disease.⁴³ Depleting B-lineage cells specific for these antigens is, therefore, a valid therapeutic strategy. A preclinical study in animal models of an antigen-driven autoimmune skin disease, i.e., pemphigus vulgaris, demonstrated feasibility and efficacy of this therapeutic approach,^{42,44} and first in human, CAAR T-cell therapies are currently developed for evaluation in clinical trials in patients with pemphigus vulgaris (NCT04422912), MuSK-Ab-positive MG (NCT05451212), and NMDA receptor-Ab-positive autoimmune encephalitis (ascension.de/en/technology-offers/nmdar-targeted-caar-t-cell-therapy-6684).

The success of T-cell engineering in oncology has also triggered an interest applying the engineering technology to foster regulatory and tissue-regenerative immune functions. Regulatory T cells, or Tregs, are critical in maintaining tolerance in humans, as evidenced by the severe autoimmune conditions seen in patients with inherited defects that result in a lack of Tregs. The introduction of antigen-specific TCRs or CARs into Tregs provides the exciting opportunity to achieve immune suppression at a pathologic site where the TCR/CAR antigen is expressed, without decreasing immune responses elsewhere in the body⁴⁵ (Figure 3). Engineered Treg cells (CAR or TCR) seem to be superior to polyclonal Tregs in their efficacy to treat autoimmune diseases and transplantation rejection.⁴⁶ Antigen-specific Treg cells can be generated either from redirecting regulatory T cells using synthetic receptors on the one hand or by converting antigen-specific effector T cells into regulatory T cells using overexpression of the Treg master transcription factor forkhead box P3. Several preclinical studies performed in various autoimmune disease conditions including EAE

demonstrated that therapeutic transfer of disease antigen-specific Tregs can completely abrogate disease activity after onset and that genetically modified antigen-specific Tregs maintain their immunosuppressive capacities *in vivo*.^{47,48} Although both CAR-based and TCR-based constructs are available for Treg redirection, CAR constructs have mainly been used, and the clinical development of synthetic Treg-based immunotherapies for autoimmune disease is still in early development. A key issue that remains to be better understood and carefully investigated is the stability of Treg phenotypes after transfer in humans because CAR Tregs could potentially acquire effector cell functions, resulting in further tissue injury. In addition, functional exhaustion of Tregs might limit their immunosuppressive capacity. Although most of the studies on CAR Tregs used second-generation CARs containing a CD28 costimulatory domain, some studies reported that CARs with CD137 costimulation or equipped with the interleukin-2 receptor beta-chain limit T-cell exhaustion and improve CAR T-cell persistence.⁴⁹⁻⁵¹

Moreover, difficult isolation and expansion of Treg cells to numbers required for achieving desired therapeutic effects might limit the potential for clinical application. The first in human studies with redirected CAR Treg cells are currently investigating the safety and tolerability of HLA-A2-specific CAR Treg cells after transplantation of A2-positive organs in A2-negative individuals (NCT04817774; NCT05234190). These studies will likely provide important safety and efficacy data in man, guiding the further development of synthetic Treg therapies.

Emerging Fields

The power and versatility of engineered T-cell therapies could potentially be harnessed for a broad spectrum of neurologic diseases for which current therapeutic options are very limited. Accumulation of aggregate-prone proteins is a pathologic hallmark of many neurodegenerative diseases, and aggregation of the amyloid β -protein ($A\beta$) peptide is one of the primary features of Alzheimer disease (AD). $A\beta$ -reactive T cells can directly facilitate the clearance of $A\beta$, and vaccination against $A\beta$ reduces neurotoxicity in mouse models of AD.⁵² Additional evidence for beneficial functions of T cells in brain diseases has been obtained in experimental models of brain trauma,⁵³ stroke,⁵⁴ and CNS autoimmunity and neurodegeneration.⁵⁵ Here, T cells were shown to foster a proregenerative environment through either release of cytokines or interaction with CNS-resident immune cells such as microglia. T cells genetically engineered to support clearance of protein aggregates, regulatory immune functions, and repair processes are currently being explored for their potential therapeutic merit in preclinical models of aforementioned disease conditions (e.g., aztherapies.com/our-science/car-treg/).

Summary and Outlook

The unprecedented success of autologous T cells engineered to recognize and destroy cancerous cells and the potential of synthetic cell-based immunotherapies in managing otherwise

difficult-to-treat disease conditions are some of the most exciting new developments in clinical medicine.

Challenges currently limiting the therapeutic efficacy of engineered T cells in oncology include off-target life-threatening toxicities, including the usually transient ICANS and limited antitumor activity in solid cancers. Getting CAR T cells to traffic to and infiltrate malignantly transformed tissue in the CNS and to additionally unleash T-cell activity within an immunosuppressive microenvironment is even more complex and requires further development.

Advances in immunology and molecular engineering have facilitated the engineering of next-generation CAR T cells equipped with additional molecular mechanisms to improve clinical efficiency. These include the addition of costimulatory domains (third-generation CAR T)²³ and the expression of inducible transgenic cytokines that are released on CAR signaling thereby combining direct antitumor attack with the immune-modulating properties of the released cytokine (fourth-generation CAR T).⁵⁶ In addition, to mitigate potential antigen loss and intratumoral heterogeneity, bivalent and trivalent CAR T cells have been designed to direct T cells against more than a single antigen.⁵⁷ The addition of multiantigen prime-and-kill recognition circuits through a synthetic Notch design may potentially improve the specificity and persistence and reduce the toxicity of T cells in brain tumors.⁵⁸

The adaption of protocols established for depletion of malignant B cells for the management of difficult-to-treat B-cell-driven neuroinflammatory diseases seems to be feasible and within reach. Here, engineered T cells administered as pulsed on-off therapy similar to classic immune-reconstitution therapies⁵⁹ have the potential to allow for renewal of adaptive immune features, possibly resulting in sustained disease remission. Carefully performed case series of patients with autoimmune disease efficiently treated with CAR T-cell therapies as reported by Mackensen et al.⁷ for patients with refractory SLE provide important information on safety and efficacy relevant for regulatory agencies and form the basis for designing clinical trials to treat autoimmune disease conditions. New developments allowing for antigen-specific depletion of autoreactive CD4⁺ T cells using peptide, major histocompatibility complex class II CAR CD8⁺ T cells, shown to strongly inhibit development and progression of EAE,⁶⁰ are alternative approaches to restrain CNS injury in T-cell-driven autoimmune diseases.

The therapeutic potential of CAR Tregs fostering tissue protection and repair is currently evaluated in several preclinical disease models. A better understanding of their safety profile and functional stability in vivo is needed before moving to broader clinical applications, yet they generated great excitement in the field and have the potential to improve outcomes in neurologic diseases in which current therapeutic options are very limited.

Although scientific advances in the development of synthetic cell-based immunotherapies are impressive, many questions related to affordability and access to these therapies, if approved,

remain to be addressed.⁶ Costs and the complexity of manufacture and delivery are barriers for a widespread adoption of this treatment. These limited resources require a rigorous design of representative clinical trials, innovative measures to capture efficacy, and free access for all stakeholders to knowledge resources to guide the development and implementation of engineered T-cell therapies in neurology.

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