Chimeric antigen receptor (CAR) and chimeric autoantibody receptor T-cell therapy hold great promise in the treatment of cancer and autoimmune disease, respectively. This powerful technique involves genetically engineering T lymphocytes to enable selective destruction of disease-causing cells. In the current approach, a patient’s T cells are genetically engineered to express an antigen-specific antibody fragment fused to activating cytoplasmic T-cell signaling domains. After ex vivo activation and genetic modification of a patient’s own T cells, the individually tailored CAR T cells are then infused into the patient for the selective destruction of cells bearing the targeted antigen. CAR T cells directed against the CD19 antigen expressed on B lymphoma cells have shown remarkable clinical efficacy in the treatment of refractory lymphoma, with two anti-CD19 CAR-T products recently gaining approval from the US Food and Drug Administration. For dermatological disease, preliminary studies have shown efficacy of CAR T cells in targeting melanoma cells and the pathogenic B cells in pemphigus vulgaris. Despite its great promise, current clinical CAR T-cell (or CAR-T) therapy carries a high risk of cytokine release syndrome, a potentially fatal systemic inflammatory response that can be manifest in cutaneous findings. For the dermatologist, the rapid clinical emergence of CAR-T therapy promises to treat and cure a variety of dermatological conditions, but it also requires an astute awareness of potential cutaneous complications in the increasing number of patients undergoing CAR-T therapy.

INTRODUCTION
Chimeric antigen receptors (CARs) are fusion proteins consisting of an antigen-recognition domain and T-cell intracellular signaling domains. Typically, the CAR antigen-recognition domain is an antibody single-chain variable fragment derived from a monoclonal antibody specific for a target antigen such as CD19 (Levine et al., 2017). The CAR intracellular portion contains T-cell signaling domains that activate and potentiate the T-cell response. When the CAR T cell’s antigen-recognition domain interacts with an antigen-
**What are the domains of a chimeric antigen receptor?**

CARs are made of three domains:

1. The extracellular portion contains the antigen-recognition domain. The antigen-recognition domain is typically an single-chain variable fragment antibody fragment or another peptide that recognizes autoantibodies, such as with Dsg3 CAAR T cells recognizing the anti-Dsg3 BCR on B cells.

2. A transmembrane domain that anchors the CAR to the cell membrane.

3. The intracellular domain that contains a CD3ζα signaling domain and costimulatory domains that enhance T-cell proliferation, cytokine release, and killing activity after antigen binding.

**What are the major potential advantages of CAR T-cell therapy in melanoma and pemphigus vulgaris?**

**Melanoma:** In melanoma, CAR T-cell therapy in combination with TCRs through the use of T cells co-expressing TCR and CAR for different melanoma antigens may help reduce tumor evasion of the immune response and reduce likelihood of recurrence.

**Pemphigus vulgaris:** In PV, CAAR T-cell therapy may provide a strategy to eliminate self-reactive B cells without systemic immunosuppression. Specifically, CAAR T cells expressing desmoglein 3 recognize and interact with anti-desmoglein 3 on pathogenic B cells without inducing off-target effects. Preliminary data in cell cultures and animal models have shown this strategy to successfully eliminate B cells carrying the B-cell receptor against desmoglein 3.

**CAR T-cell production**

After designing the CAR construct, the CAR elements are cloned into a lentiviral or retroviral backbone plasmid using standard molecular cloning techniques. The CAR and viral enzyme plasmids are transfected into a packaging cell line (e.g., 293T cells) that can generate large titers of CAR-bearing virus. Peripheral blood mononuclear cells derived from the patient by leukapheresis are then stimulated with anti-CD3/CD28 beads to activate and expand T cells. During CD3/CD28 activation, the patient’s T cells are transduced with the CAR-bearing retro or lentivirus to produce CAR T cells containing a stably integrated and expressed CAR. Experimentally, successfully transduced T cells may be further enriched using markers such as GFP or human CD34 fused to the CAR and introduced during transduction. After continued expansion ex vivo, highly enriched CAR T cells undergo washing, concentration, and cryopreservation for future transfer into the patient (Levine et al., 2017) (Figure 2).

**DERMATOLOGIC APPLICATIONS OF CAR T CELLS**

**Melanoma**

Melanomas often develop resistance to targeted therapy through antigen down-regulation or activation of compensatory signaling pathways (Sullivan and Flaherty, 2013). Taking advantage of the T cells' ability to reliably recognize melanomas, Rosenberg et al. (2008, 2011) used adoptive cell therapy to treat melanoma patients. In adoptive cell therapy, patient T cells with antitumor activity are expanded ex vivo and reinfused into the patient, with significant clinical success (Lu et al., 2017). Although adoptive cell therapy uses a single T-cell clone expressing a single TCR (Uslu et al., 2016), developed as a multi-hit therapy to use T cells expressing both a TCR and a CAR, known as TETARs (i.e., T cells Expressing Two Additional Receptors). They found that co-expressing CAR and TCR in a single T cell can have stronger cytotoxic capability than providing a mixture of T cells expressing a single receptor. In particular, CARs targeting gp100, an
immunogenic antigen present in over 90% of melanomas, are very promising (Zhang et al., 2014).

Pemphigus vulgaris

Pemphigus vulgaris (PV) is a blistering autoimmune disease caused by the production of autoantibodies against desmoglein 3 (Dsg3), a desmosome and critical component of cell-cell junctions. PV is typically managed with systemic immunosuppressants, including rituximab, a monoclonal antibody targeting CD20\(^+\) B cells. However, such therapies may have limited efficacy and severe adverse effects.

In preclinical models of PV, Ellebrecht et al. (2016) showed that engineered T-cell therapy may be used to specifically eliminate pathogenic antibody-producing B cells without suppressing healthy B cells. The authors generated T cells expressing a chimeric autoantibody receptor (CAAR) selective for antibody-producing B cells. This CAAR consists of a PV autoantigen (Dsg3) fused to a CD137/CD3\(\zeta\) signaling domain. In vivo, Dsg3 CAAR T cells selectively eliminated B cells expressing the anti-Dsg3 BCR, offering the potential for a targeted treatment approach.

To identify an antigen-recognition domain with therapeutic potential, different truncated Dsg3 fragments were engineered as the CAAR extracellular domain. Two Dsg3 fragment-expressing CAAR constructs selectively killed anti-Dsg3 BCR-expressing B cells in vitro. In vivo, Dsg3 CAAR cells eliminated anti-Dsg3 BCR-expressing B cells in preclinical mouse models using human PV-causing anti-Dsg3 B cells, prevented blistering, and produced no major off-target toxicity (Ellebrecht et al., 2016; Ellebrecht and Payne, 2017). The use of CAAR T-cell therapy in PV may thus be a potential future clinical option for selectively removing self-reactive B cells without systemic immunosuppression. Broadly, Ellebrecht et al.’s study shows the potential to re-engineer the CAR-T concept to target autoantibody-expressing cells pathogenic in autoimmune disease (i.e., CAAR T cells).

CURRENT AND FUTURE DIRECTIONS

CAR T-cell therapy represents a powerful therapeutic approach to multiple diseases in oncology, dermatology, and other fields. Although clinical trials have shown durable tumor remission in refractory B-cell malignancies, CAR-T therapy for cutaneous cancers and autoimmune diseases remain in preclinical testing. The density of solid tumors and non-hematopoietic organs such as the skin may complicate CAR T-cell tissue penetration and efficacy (Jin et al., 2016). For this reason, novel approaches to CAR T-cell engineering and/or adjunctive therapy to increase therapeutic efficacy against solid tumors need exploration.

With increasing clinical use, the CAR-T therapy’s efficacy and potential toxicities are becoming more apparent. CAR T cells induce high levels of inflammatory cytokines, which can lead to cytokine release syndrome, a potentially fatal condition associated with severe hypotension/tachycardia, capillary leak, and disseminated intravascular coagulation (Bonifant et al., 2016). CAR T cells have also been reported to cause a spectrum of skin changes including rashes associated with and independent of cytokine release syndrome. One case series reported CAR T-cell therapy—associated Merkel
In summary, CAR and CAAR technology promises to efficiently treat and potentially cure various hematologic malignancies, solid tumors, autoimmune diseases, and inflammatory skin conditions. Although CAR therapy is in its clinical infancy, preclinical advances are occurring rapidly. With increasing translation to the clinic, dermatologists are likely to see and treat cutaneous toxicities related to CAR therapy while providing unique insights into the relationship between the skin and the immune system.

CONFLICT OF INTEREST
Karl Staser is a co-inventor on a pending patent related to CART technology. The other authors state no conflict of interest.

ACKNOWLEDGMENTS
KWS would like to acknowledge his funding sources: the Dermatologist Research Investigator Fellowship (Dermatology Foundation), the Loan Repayment Program (NIH), and the Gabrielle’s Angel Cancer Research Award.

SUPPLEMENTARY MATERIAL
Supplementary material is linked to this paper. Teaching slides are available as supplementary material.

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Uslu U, Gerer K, Dorrie J, Schaft N. Combining a chimeric antigen receptor and a conventional T-cell receptor to generate T cells expressing two additional receptors (TETARs) for a multi-hit immunotherapy of melanoma. Exp Dermatol 2016;25:872–9.
1. There are three generations of CARs. The generation of a CAR is defined by which of the following?

Correct answer: C. Number of signaling domains

The chimeric antigen receptor typically consists of three domains: an ectodomain, transmembrane domain, and endodomain. CARs are classified into three generations depending on the number of signaling domains in the CAR endodomain. First-generation CARs contain one signaling domain, second-generation CARs contain two, and third-generation CARs contain three.

2. What is the main role of CD3ζ in a CAR?

Correct answer: D. T-cell activation

The endodomain of CAR T cells consists of a CD3ζ derived signaling domain along with co-stimulatory domains to enhance T-cell activity after antigen binding, potentiating T-cell proliferation, cytokine production, and cell killing.

3. What is the source of T cells used in US Food and Drug Administration—approved CAR T-cell therapies?

Correct answer: C. Patient’s peripheral blood

In currently US Food and Drug Administration—approved CAR T-cell therapies, the patient’s blood serves as the source for generating CAR T cells. Peripheral blood mononuclear cells are isolated by leukapheresis, T cells purified and virally transduced, amplified, and then infused back into the patient.

4. Which of the following targets would make a logical choice for highly selective CAAR T-cell therapy in pemphigus vulgaris?

Correct answer: B. All B cells expressing anti-desmoglein-3 receptors

Pemphigus vulgaris is an autoimmune blistering disease resulting from autoantibodies against desmoglein 3. A recent study (Ellebrecht et al., 2016) showed that chimeric autoantibody receptor (CAAR) T cells expressing a Dsg3 fragment could selectively target B cells expressing an anti-desmoglein-3 receptor. Conversely, CD19 is expressed on nearly all B cells, CD30 is expressed on CD30⁺ lymphoproliferative disorders, and CD52 is expressed on all leukocytes.

5. Which of the following cutaneous toxicities has been described after CAR T-cell therapy for hematologic malignancy?

Correct answer: B. An eruption mimicking the rash of lymphocyte recovery

The characterization of cutaneous toxicities from CAR T-cell therapy is in its early stages. However, a diffuse macular eruption with clinical and histopathologic features similar to the rash of lymphocyte recovery seen in individuals after hematopoietic stem cell transplantation has been reported after the use of CAR T-cell therapy. Further work is needed to fully characterize the spectrum of dermatologic manifestations from this new treatment.