elevated levels of a nuclear factor kappa B subunit 1 (NFκB1) polypeptide, a Jun proto-oncogene (JUN) polypeptide, a transcription factor RelB (RELB) polypeptide, an interferon regulatory factor 1 (IRF1) polypeptide, a tumor necrosis factor (TNF) α polypeptide, an interleukin (IL)-10 polypeptide, a fibroblast growth factor (FGF)-2 polypeptide, a granulocyte colony stimulating factor (G-CSF) polypeptide, a granulocyte-macrophage colony-stimulating factor (GM-CSF) polypeptide, an eotaxin polypeptide, a galectin 9 (Gal-9) polypeptide, a programmed cell death protein 1 (PD-1) polypeptide, a T-cell immunoglobin mucin-3 (TIM-3) polypeptide, a CXC chemokine receptor (CXCR) 3 polypeptide, and/or a CXCR4 polypeptide exhibited both enhanced immunosuppression and enhanced homing capacity to sites of inflammation. Also as demonstrated herein, CAR-MSCs having elevated levels of a cytotoxic T-lymphocyte-associated-protein 4 (CTLA4) polypeptide, a toll-like receptor (TLR) 3 polypeptide, a TLR4 polypeptide, a TLR9 polypeptide, and/or a TNF receptor 2 (TNFR2) polypeptide exhibited both enhanced immunosuppression and enhanced homing capacity to sites of inflammation.

In general, one example of this document features a MSC including (1) exogenous nucleic acid encoding a CAR targeting an epithelial-specific antigen, where the MSC expresses the CAR, and (2) an elevated level of a polypeptide selected from the group consisting of a NFκB1 polypeptide, a JUN polypeptide, a RELB polypeptide, an IRF1 polypeptide, a TNFα polypeptide, an IL-10 polypeptide, a FGF-2 polypeptide, a G-CSF polypeptide, a GM-CSF polypeptide, an eotaxin polypeptide, a Gal-9 polypeptide, a PD-1 polypeptide, a TIM-3 polypeptide, a CXCR3 polypeptide, a CXCR4 polypeptide, a CTLA4 polypeptide, a TLR3 polypeptide, a TLR4 polypeptide, a TLR9 polypeptide, and a TNFR2 polypeptide. The MSC can be a human MSC. The MSC can be an adipose derived-MSC. The epithelial-specific antigen can be E-cadherin (Ecad). The polypeptide can be the NFκB1 polypeptide, the JUN polypeptide, the RELB polypeptide, or the IRF1 polypeptide. The MSC can include exogenous nucleic acid encoding the NFκB1 polypeptide, where the MSC expresses the NFκB1 polypeptide. The MSC can include exogenous nucleic acid encoding the JUN polypeptide, where the MSC expresses the JUN polypeptide. The MSC can include exogenous nucleic acid encoding the RELB polypeptide, where the MSC expresses the RELB polypeptide. The MSC can include exogenous nucleic acid encoding the IRF1

polypeptide, where the MSC expresses the IRF1 polypeptide. The polypeptide can be the CXCR3 polypeptide or the CXCR4 polypeptide. The MSC can include exogenous nucleic acid encoding the CXCR3 polypeptide, where the MSC expresses the CXCR3 polypeptide. The MSC can include exogenous nucleic acid encoding the CXCR4 polypeptide, where the MSC expresses the CXCR4 polypeptide. The polypeptide can be the PD-1 polypeptide, the Gal-9 polypeptide, or the TIM-3 polypeptide. The MSC can include exogenous nucleic acid encoding the PD-1 polypeptide, where the MSC expresses the PD-1 polypeptide. The MSC can include exogenous nucleic acid encoding the Gal-9 polypeptide, where the MSC expresses the Gal-9 polypeptide. The MSC can include exogenous nucleic acid encoding the TIM-3 polypeptide, where the MSC expresses the TIM-3 polypeptide. The polypeptide can be the TNFα polypeptide, the IL-10 polypeptide, or the FGF-2 polypeptide. The MSC can include exogenous nucleic acid encoding the TNFα polypeptide, where the MSC expresses the TNFα polypeptide. The MSC can include exogenous nucleic acid encoding the IL-10 polypeptide, where the MSC expresses the IL-10 polypeptide. The MSC can include exogenous nucleic acid encoding the FGF-2 polypeptide, where the MSC expresses the FGF-2 polypeptide. The CAR can include a heavy chain comprising the CDRs set forth in SEQ ID NO:1, and a light chain comprising the CDRs set forth in SEQ ID NO:2. The heavy chain can include an amino acid sequence set forth in SEQ ID NO:1, and where the light chain can include an amino acid sequence set forth in SEQ ID NO:2. The CAR can include a heavy chain comprising the CDRs set forth in SEQ ID NO:3, and a light chain comprising the CDRs set forth in SEQ ID NO:4. The heavy chain can include an amino acid sequence set forth in SEQ ID NO:3, and where the light chain can include an amino acid sequence set forth in SEQ ID NO:4.

In one aspect, the present disclosure refers to a mesenchymal stromal cell (MSC) comprising:

(1) exogenous nucleic acid encoding a chimeric antigen receptor (CAR) targeting an epithelial-specific antigen, wherein said MSC expresses said CAR, and

(2a) an elevated level of a polypeptide selected from the group consisting of a nuclear factor kappa B subunit 1 (NFκB1) polypeptide, a Jun proto-oncogene (JUN) polypeptide, a transcription factor RelB (RELB) polypeptide, an interferon regulatory factor 1 (IRF1) polypeptide, a tumor necrosis factor (TNF) α polypeptide, an interleukin (IL)-10 polypeptide, a fibroblast growth factor (FGF)-2 polypeptide, a granulocyte colony stimulating factor (G-CSF) polypeptide, a granulocyte-macrophage colony-stimulating factor (GM-CSF) polypeptide, an eotaxin polypeptide, a galectin 9 (Gal-9) polypeptide, a programmed cell death protein 1 (PD-1) polypeptide, a T-cell immunoglobin mucin-3 (TIM-3) polypeptide, a CXC chemokine receptor (CXCR) 3 polypeptide, and a CXCR4 polypeptide, or

(2b) an elevated level of a polypeptide selected from the group consisting of a NFκB1 polypeptide, a JUN polypeptide, a RELB polypeptide, an IRF1 polypeptide, a TNFα polypeptide, a cytotoxic T-lymphocyte-associated-protein 4 (CTLA4), a toll-like receptor 3 (TLR3), a toll-like receptor 4 (TLR4), a toll-like receptor 9 (TLR9), a tumor necrosis factor receptor 2 (TNFR2) polypeptide, an IL-10 polypeptide, a FGF-2 polypeptide, a G-CSF polypeptide, a GM-CSF polypeptide, an eotaxin polypeptide, a Gal-9 polypeptide, a PD-1 polypeptide, a TIM-3 polypeptide, a CXCR3 polypeptide, and a CXCR4 polypeptide.

In another example, this document features compositions including a MSC including (1) exogenous nucleic acid encoding a CAR targeting an epithelial-specific antigen, where the MSC expresses the CAR, and (2) an elevated level of a polypeptide selected from the group consisting of a NFκB1 polypeptide, a JUN polypeptide, a RELB polypeptide, an IRF1 polypeptide, a TNFα polypeptide, an IL-10 polypeptide, a FGF-2 polypeptide, a G-CSF polypeptide, a GM-CSF polypeptide, an eotaxin polypeptide, a Gal-9 polypeptide, a PD-1 polypeptide, a TIM-3 polypeptide, a CXCR3 polypeptide, a CXCR4 polypeptide, a CTLA4

polypeptide, a TLR3 polypeptide, a TLR4 polypeptide, a TLR9 polypeptide, and a TNFR2 polypeptide.

In one aspect, the present disclosure refers to a composition comprising a MSC comprising:

(1) exogenous nucleic acid encoding a CAR targeting an epithelial-specific antigen, wherein said MSC expresses said CAR, and

(2a) an elevated level of a polypeptide selected from the group consisting of a NFκB1 polypeptide, a JUN polypeptide, a RELB polypeptide, an IRF1 polypeptide, a TNFα polypeptide, an IL-10 polypeptide, a FGF-2 polypeptide, a G-CSF polypeptide, a GM-CSF polypeptide, an eotaxin polypeptide, a Gal-9 polypeptide, a PD-1 polypeptide, a TIM-3 polypeptide, a CXCR 3 polypeptide, and a CXCR4 polypeptide, or

(2b) an elevated level of a polypeptide selected from the group consisting of a NFκB1 polypeptide, a JUN polypeptide, a RELB polypeptide, an IRF1 polypeptide, a TNFα polypeptide, a CTLA4, a TLR3, a TLR4, a TLR9, a TNFR2 polypeptide, an IL-10 polypeptide, a FGF-2 polypeptide, a G-CSF polypeptide, a GM-CSF polypeptide, an eotaxin polypeptide, a Gal-9 polypeptide, a PD-1 polypeptide, a TIM-3 polypeptide, a CXCR3 polypeptide, and a CXCR4 polypeptide.

In another aspect, the present disclosure refers to use of a MSC or a composition comprising said MSC, wherein said MSC comprises:

(1) exogenous nucleic acid encoding a CAR targeting an epithelial-specific antigen, wherein said MSC expresses said CAR, and

(2a) an elevated level of a polypeptide selected from the group consisting of a NFκB1 polypeptide, a JUN polypeptide, a RELB polypeptide, an IRF1 polypeptide, a TNFα polypeptide, an IL-10 polypeptide, a FGF-2 polypeptide, a G-CSF polypeptide, a GM-CSF polypeptide, an eotaxin polypeptide, a Gal-9 polypeptide, a PD-1 polypeptide, a TIM-3 polypeptide, a CXCR 3 polypeptide, and a CXCR4 polypeptide, or

(2b) an elevated level of a polypeptide selected from the group consisting of a NFκB1 polypeptide, a JUN polypeptide, a RELB polypeptide, an IRF1 polypeptide, a TNFα polypeptide, a CTLA4, a TLR3, a TLR4, a TLR9, a TNFR2 polypeptide, an IL-10 polypeptide, a FGF-2 polypeptide, a G-CSF polypeptide, a GM-CSF polypeptide, an eotaxin polypeptide, a Gal-9 polypeptide, a PD-1 polypeptide, a TIM-3 polypeptide, a CXCR3 polypeptide, and a CXCR4 polypeptide,

in the manufacture of a medicament for (a) treating a mammal having graft versus host disease (GVHD), (b) suppressing an immune response within a mammal, or (c) reducing the number of activated T cells within a mammal.

In another example, this document features methods for treating a mammal having GVHD. The methods can include, or consist essentially of, administering to a mammal having GVHD a MSC including (1) exogenous nucleic acid encoding a CAR targeting an epithelial-specific antigen, where the MSC expresses the CAR, and (2) an elevated level of a polypeptide selected from the group consisting of a NFκB1 polypeptide, a JUN polypeptide, a RELB polypeptide, an IRF1 polypeptide, a TNFα polypeptide, an IL-10 polypeptide, a FGF-2 polypeptide, a G-CSF polypeptide, a GM-CSF polypeptide, an eotaxin polypeptide, a Gal-9 polypeptide, a PD-1 polypeptide, a TIM-3 polypeptide, a CXCR3 polypeptide, a CXCR4 polypeptide, a CTLA4 polypeptide, a TLR3 polypeptide, a TLR4 polypeptide, a TLR9 polypeptide, and a TNFR2 polypeptide. The mammal can be a human. The symptom of the GVHD can be reduced at least 10 percent. The number of Tregs within the mammal can be increased at least 10 percent.

In another example, this document features methods for suppressing an immune response within a mammal. The methods can include, or consist essentially of, administering to a mammal a MSC including (1) exogenous nucleic acid encoding a CAR targeting an epithelial-specific antigen, where the MSC expresses the CAR, and (2) an elevated level of a polypeptide selected from the group consisting of a NFκB1 polypeptide, a JUN polypeptide, a RELB polypeptide, an IRF1 polypeptide, a TNFα polypeptide, an IL-10 polypeptide, a FGF-2 polypeptide, a G-CSF polypeptide, a GM-CSF polypeptide, an eotaxin polypeptide, a Gal-9 polypeptide, a PD-1 polypeptide, a TIM-3 polypeptide, a CXCR3 polypeptide, a CXCR4 polypeptide, a CTLA4 polypeptide, a TLR3 polypeptide, a TLR4 polypeptide, a TLR9 polypeptide, and a TNFR2 polypeptide. The mammal can be a human. The number of activated T cells within the mammal can be reduced at least 10 percent. The number of Tregs within the mammal can be increased at least 10 percent.

In another example, this document features methods for reducing the number of activated T cells within a mammal. The methods can include, or consist essentially of, administering to a mammal a MSC including (1) exogenous nucleic acid encoding a CAR targeting an epithelial-specific antigen, where the MSC expresses the CAR, and (2) an

elevated level of a polypeptide selected from the group consisting of a NFκB1 polypeptide, a JUN polypeptide, a RELB polypeptide, an IRF1 polypeptide, a TNFα polypeptide, an IL-10 polypeptide, a FGF-2 polypeptide, a G-CSF polypeptide, a GM-CSF polypeptide, an eotaxin polypeptide, a Gal-9 polypeptide, a PD-1 polypeptide, a TIM-3 polypeptide, a CXCR3 polypeptide, a CXCR4 polypeptide, a CTLA4 polypeptide, a TLR3 polypeptide, a TLR4 polypeptide, a TLR9 polypeptide, and a TNFR2 polypeptide. The mammal can be a human. The number of activated T cells within the mammal can be reduced at least 10 percent. The number of Tregs within the mammal can be increased at least 10 percent.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure pertains. Although methods and materials similar or equivalent to those described herein can be used to practice the disclosure, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

The details of one or more examples of the disclosure are set forth in the accompanying drawings and the description below. Other features, objects, and advantages of the disclosure will be apparent from the description and drawings, and from the claims.

DESCRIPTION OF THE DRAWINGS

Figures 1A-1J show that MSCs are stably transduced to express CAR and that EcCAR-MSCs exhibit superior T cell suppression compared to untransduced (UTD) MSCs. Figure 1A is a representative flow cytometry plot depicting the expression of CAR19 as detected by goat anti-mouse IgG (y-axis) following transduction of MSCs with VSV-γ lentiviral particles with increasing concentration of protamine sulfate enhancer (50 μg/mL and 100 μg/mL). Data are representative of >3 independent experiments using 5 different biological MSC donors. Figure 1B is a histogram showing CAR expression of anti-Ecad CAR-MSC (EcCAR-MSC), anti-CD103 T cell integrin CAR-MSC (CD103CAR-MSC), and anti-CD19 CAR MSC (CD19CAR-MSC) positive control as detected by flow cytometry