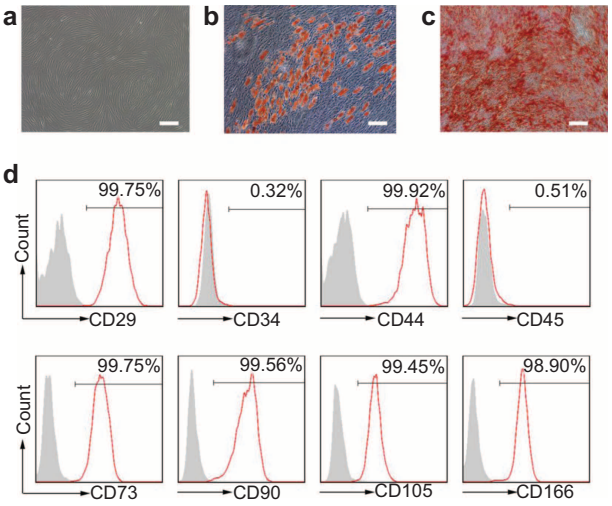
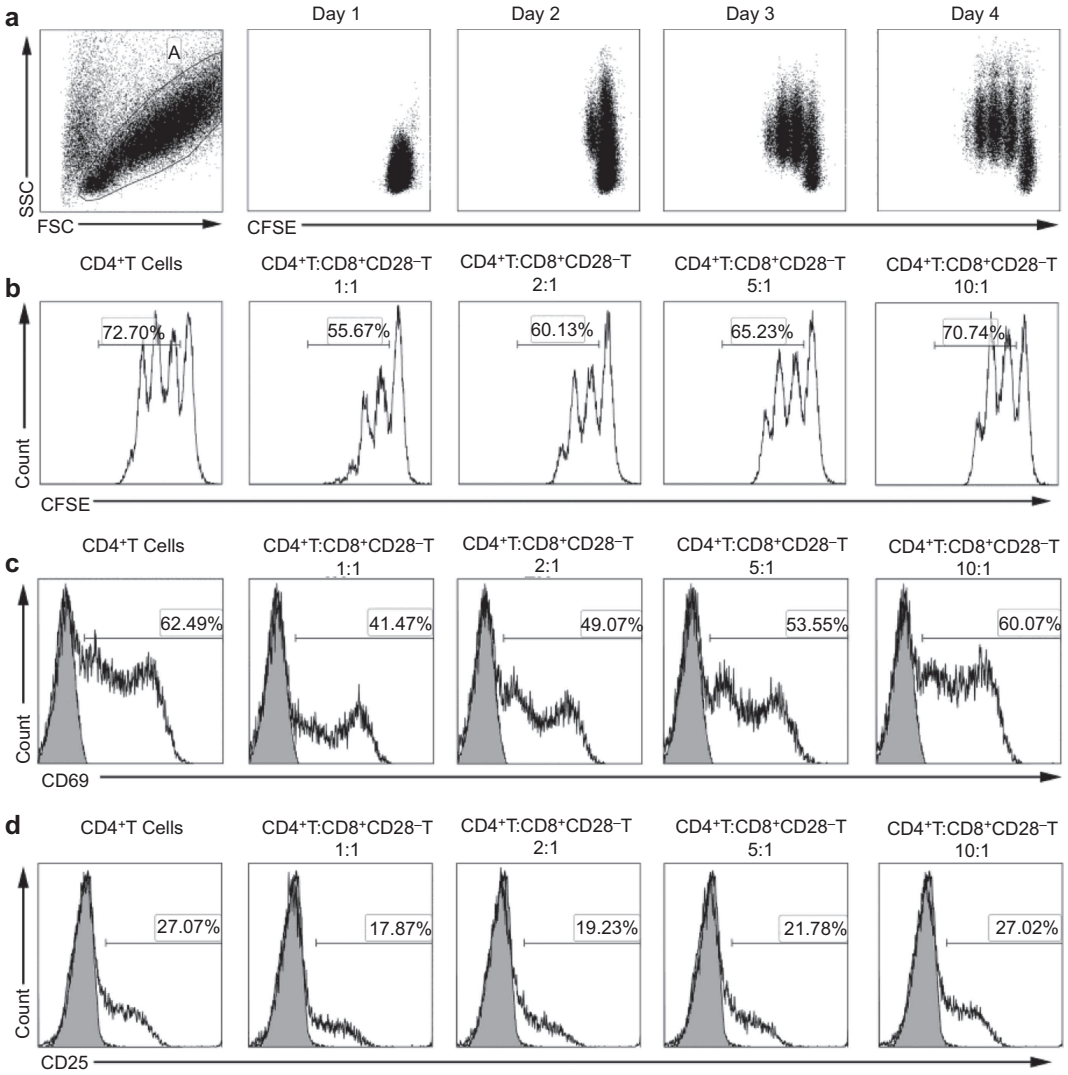
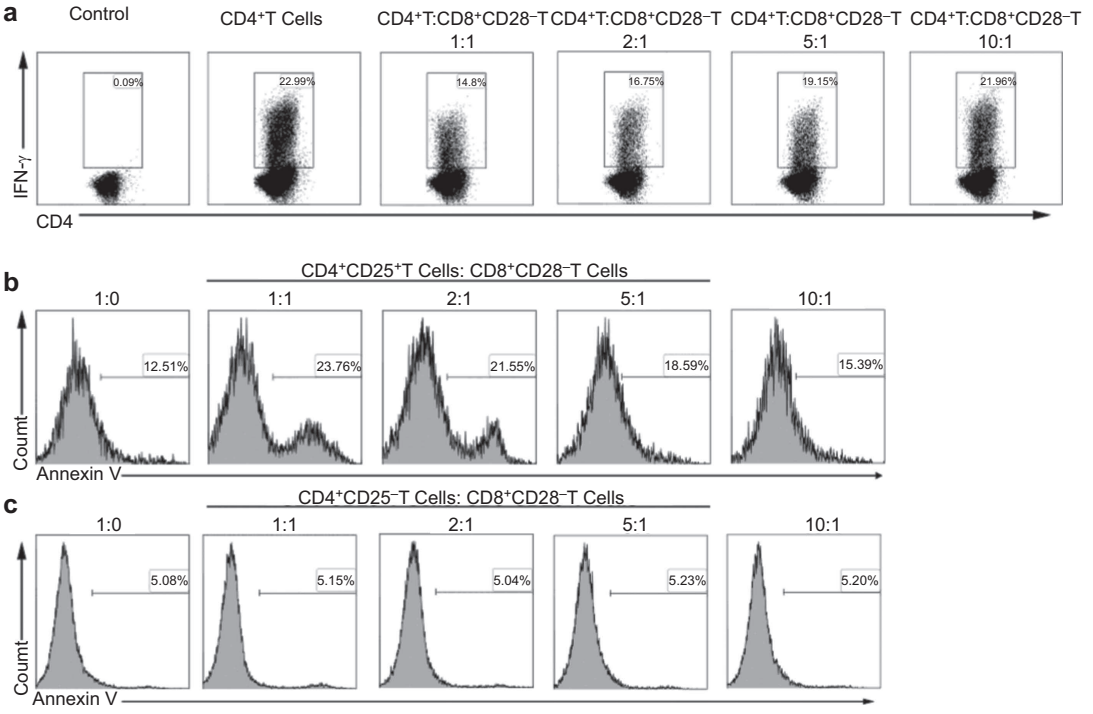


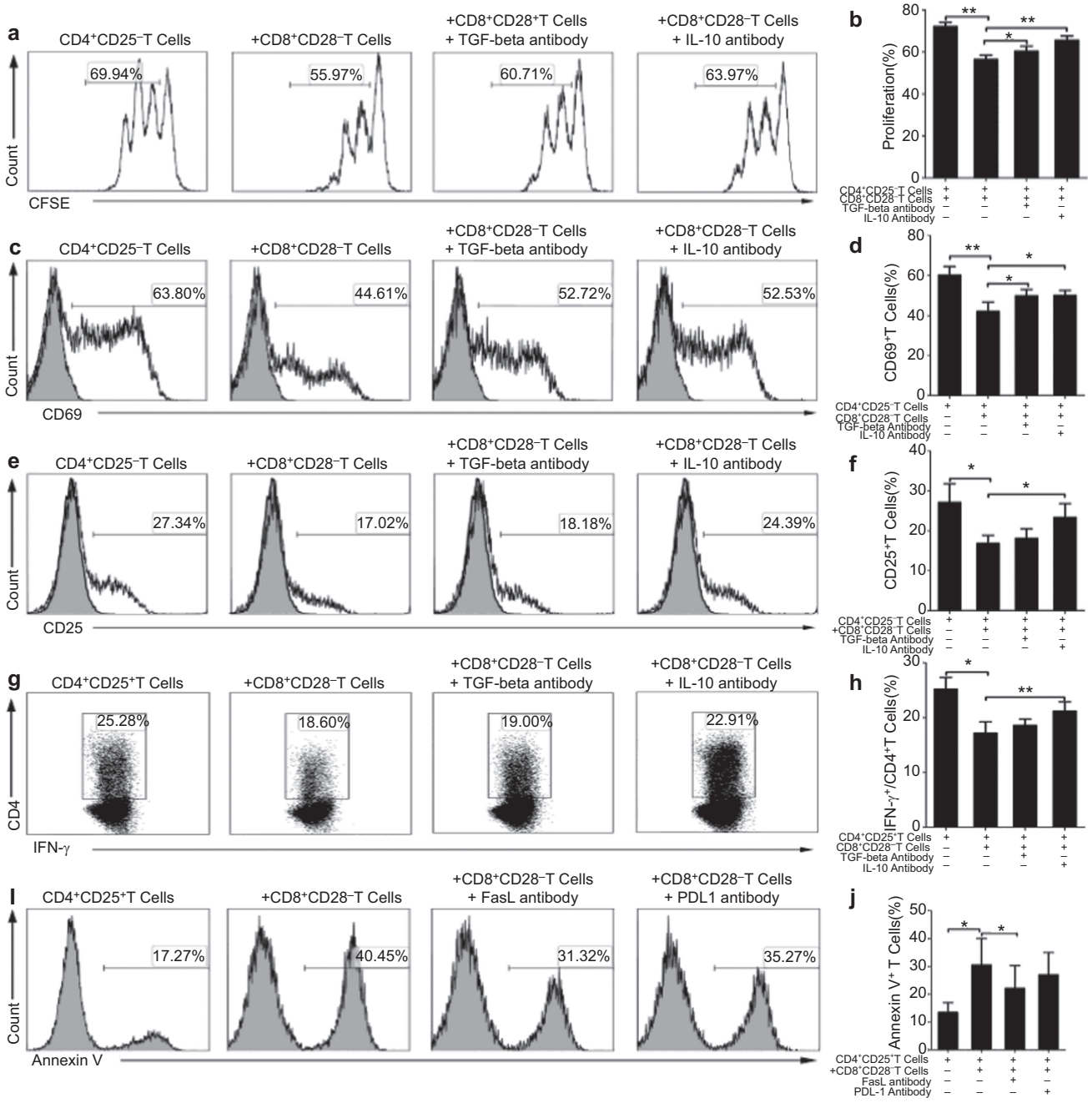
Supplemental Figure 1 Characterization of healthy donor-derived MSCs. The morphology of human MSCs (passage 5) was revealed by phase contrast microscopy (**a**). The adipogenic and osteogenic differentiation of the human MSCs were shown by oil red O staining (**b**) and Alizarin red S staining (**c**). Cell surface markers of human MSCs were detected by flow cytometry (**d**). Scale bar=200 μM.



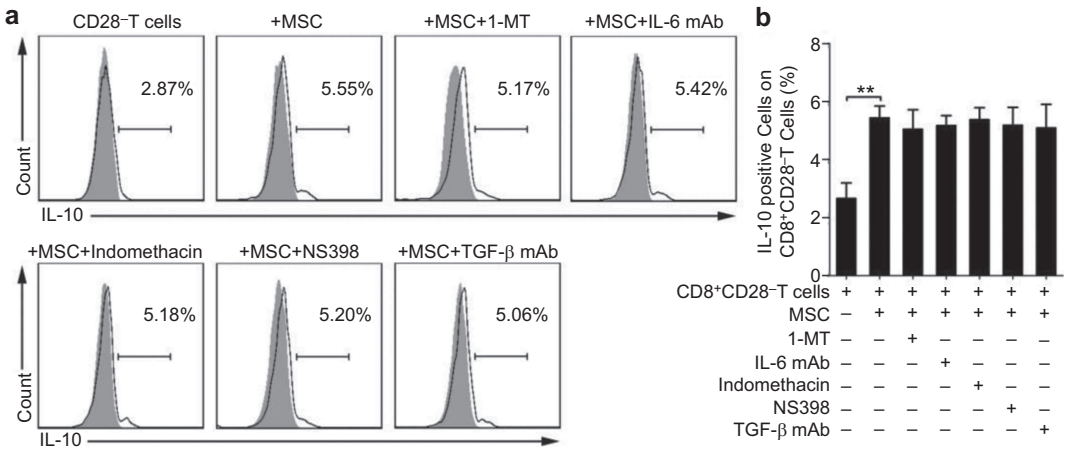
Supplemental Figure 2 The proliferation and activation of naive $CD4^+$ T cells are dose dependently inhibited by the $CD8^+CD28^-$ T cells. The T cell proliferative response was evaluated by the dilution of the CFSE expression. Representative experiments are depicted (**a**). The regulation effects of $CD8^+CD28^-$ T cells on T-cell proliferation were evaluated by coculturing with different ratios of $CD4^+$ T cells (**b**). The regulation effects of $CD8^+CD28^-$ T cells on T-cell activation were evaluated by the expression of CD69 (**c**) and CD25 (**d**) on naive $CD4^+$ T cells that cocultured with different ratios of $CD8^+CD28^-$ T cells in the presence of a stimulus for 24 h. The gray histograms correspond to the isotype controls.



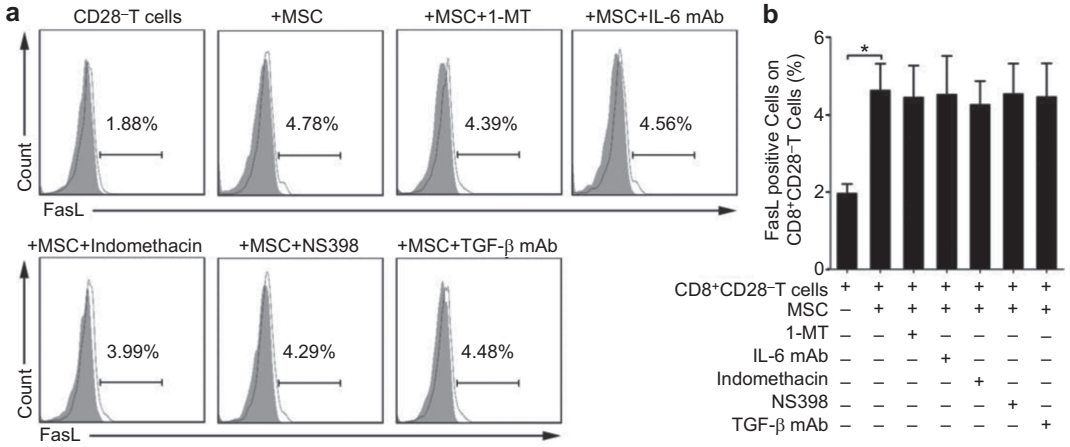
Supplemental Figure 3 $CD8^+CD28^-$ T cells dose-dependently inhibit IFN-γ production by responder $CD4^+$ T cells and induce activated $CD4^+$ T cells apoptosis. The indicated cells were cocultured at ratios of 0 : 1, 1 : 1, 2 : 1, 5 : 1 and 10 : 1 for 3 days, and the effects on regulating the production of IFN-γ expressed by $CD4^+$ T cells were assessed by intracellular cytokine staining (**a**). The isolated $CD4^+CD25^+$ T cells (activated) (**b**) and $CD4^+CD25^-$ T cells (non-activated) (**c**) were respectively cocultured with $CD8^+CD28^-$ T cells for 6 h at ratios of 0 : 1, 1 : 1, 2 : 1, 5 : 1 and 10 : 1. The percentage of Annexin V-positive cells within the total $CD4^+$ T-cell population was then analyzed by flow cytometry.



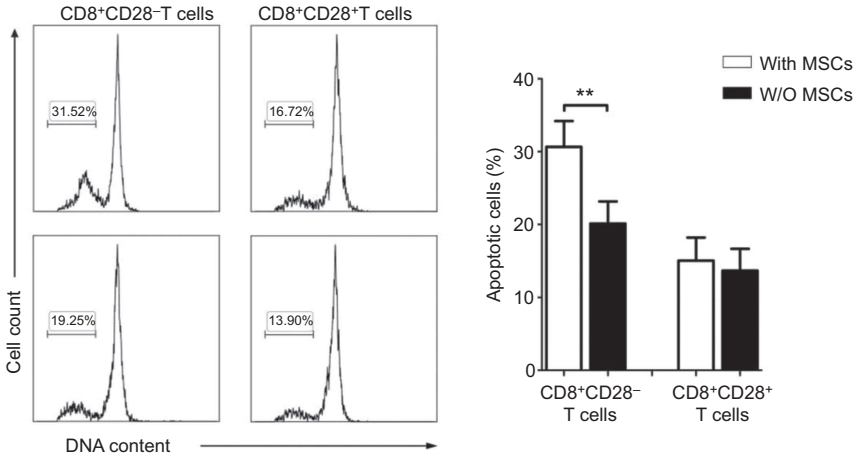
Supplemental Figure 4 $CD8^+CD28^-$ T cells exert the immunomodulatory function through TGF-β, IL-10 or FasL. The $CD8^+CD28^-$ T cells were cocultured with naive $CD4^+$ T cells at a ratio of 1 : 1. Anti-TGF-β and IL-10 neutralizing antibodies were added to the coculture system, and their affection in the regulation of $CD8^+CD28^-$ T cells on $CD4^+$ T cells were evaluated, including on proliferation (**a**, **b**), activation (**c**–**f**) and IFN-γ production (**g**, **h**) of $CD4^+$ T cells. Similarly, anti-FasL and anti-PD-L1 neutralizing antibodies were added, and the Annexin V-positive $CD4^+$ T cells were less, efficiently inhibited by FasL neutralization (**i**, **j**). The results are representative of three independent experiments. The bar graphs indicate the means±s.d. Statistically significant differences are indicated as follows: $*P<0.05$ and $**P<0.01$.



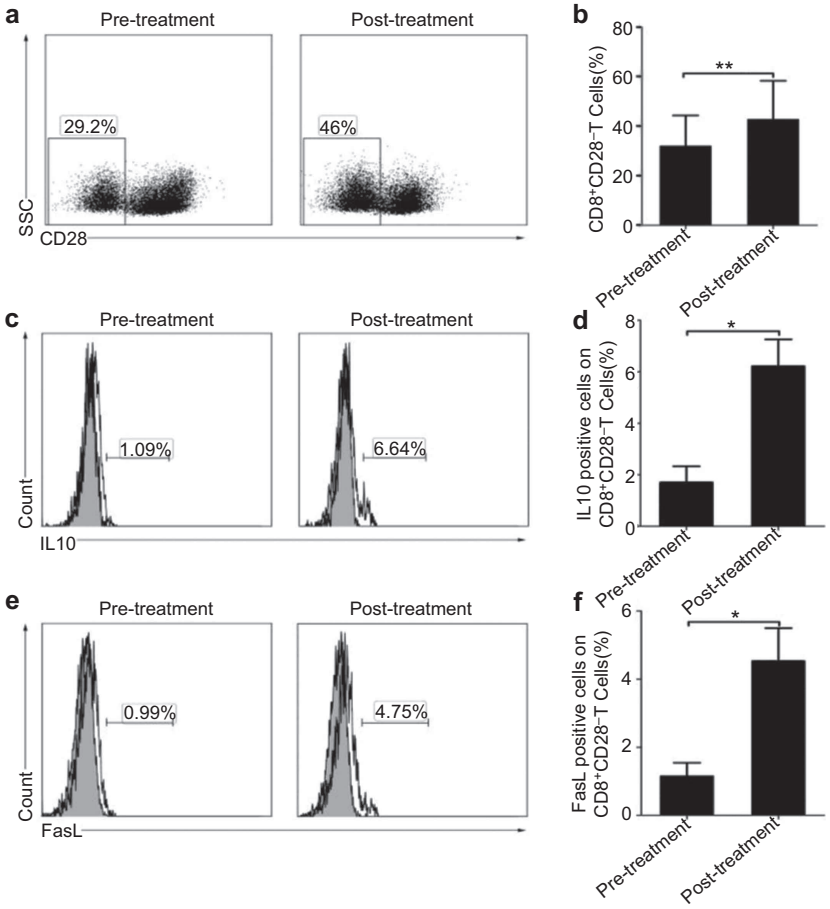
Supplemental Figure 5 The mechanisms of MSCs affect the IL-10 expression on $CD8^+CD28^-$ T cells. The expression of IL-10 on $CD8^+CD28^-$ T cells from healthy donors increased after the cocultured with MSCs. Neither inhibitors nor neutralization antibodies could reverse the expression of IL-10 (**a**, **b**). The gray histograms correspond to the isotype controls. Data are representative of three experiments. The bar graphs indicate the means±s.d. Statistically significant differences are indicated as follows: $^{**}P<0.01$.



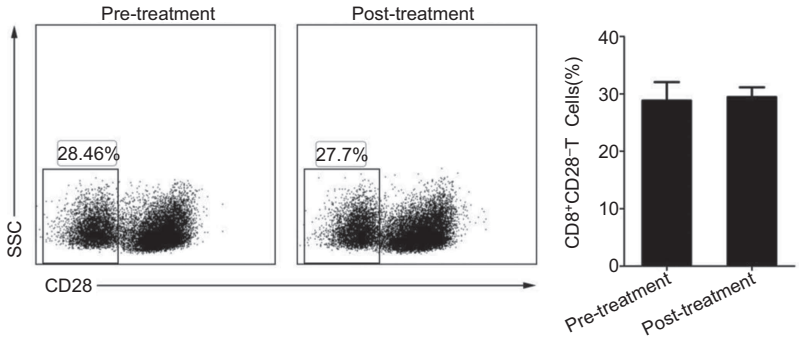
Supplemental Figure 6 The mechanisms of MSCs affect the FasL expression on $CD8^+CD28^-$ T cells. The expression of FasL on $CD8^+CD28^-$ T cells from healthy donors increased after the cocultured with MSCs. Neither inhibitors nor neutralization antibodies could reverse the expression of FasL (**a**, **b**). The gray histograms correspond to the isotype controls. Data are representative of three experiments. The bar graphs indicate the means±s.d. Statistically significant differences are indicated as follows: $*P<0.05$.



Supplemental Figure 7 MSCs inhibit $CD8^+CD28^-$ T cells apoptosis. $CD8^+CD28^-$ T cells and $CD8^+CD28^+$ T cells were respectively cocultured with MSCs at a ratio of 5 : 1 (T cells : MSCs), and T cells were harvested at the indicated time points, then permeabilized and stained with propidium iodide to reveal hypodiploid peaks characteristic of apoptotic cells. MSCs significantly decreased the apoptosis of $CD8^+CD28^-$ T cells, but not obviously affect the $CD8^+CD28^+$ T cells. Data are representative of three experiments. The bar graphs indicate the means±s.d. Statistically significant differences are indicated as follows: $^{**}P<0.01$.



Supplemental Figure 8 MSCs increase the percentage and function of $CD8^+CD28^-$ T-cell subset in CR/PR cGVHD patients. The flow cytometry plots represented the percentage of $CD28^-$ T cells by gating on $CD3^+CD8^+$ T cells in the peripheral blood from CR/PR cGVHD patients pre-MSC treatment and post-MSC treatment (**a**). CR/PR patients (n=10) had significantly higher frequency of $CD8^+CD28^-$ T cells post-MSCs treatment (**b**). The expression of IL-10 and FasL on $CD8^+CD28^-$ T cells were increased post-MSC treatment in CR/PR patients (n=3) (**c**–**f**). The gray histograms correspond to the isotype controls. The bar graphs indicate the means±s.d., n=10; statistically significant differences are indicated as follows: *P<0.05 and **P<0.01.



Supplemental Figure 9 No change in the percentage of $CD8^+CD28^-$ T cells was observed in cGVHD patients that non-response to MSC treatment. The flow cytometry plots represented the percentage of $CD28^-$ T cells by gating on $CD3^+CD8^+$ T cells in the peripheral blood from NR cGVHD patients pre-MSCs treatment and post-MSCs treatment. NR patients (n=3) had no change in frequency of $CD8^+CD28^-$ T cells post-MSC treatment. The bar graphs indicate the means±s.d.

Supplemental Table 1 Clinical characteristics of cGVHD patients

	Sex	Age	Disease	Time post-HSCT (day)	Source of graft	HLA matching	Grade of cGVHD	Organ involvement	Response to MSC infusion
1	Male	34	ANLL	107	Peripheral blood	Matched, related	Moderate	Skin, oral mucosa	CR
2	Female	23	ALL	313	Peripheral blood	Matched, related	Moderate	Oral mucosa, eyes, lung	PR
3	Male	22	ALL	157	Peripheral blood	Matched, related	Severe	Skin, oral mucosa, eyes, lung	PR
4	Male	25	CML	126	Peripheral blood	Matched, related	Severe	Skin, oral mucosa, GI	PR
5	Male	27	NHL	705	Peripheral blood	Matched, related	Severe	Skin, oral mucosa, joint	NR
6	Male	21	ALL	143	Peripheral blood	Matched, related	Severe	Skin, eyes, GI, lung, joint	PR
7	Male	23	ANLL	106	Peripheral blood	Matched, related	Moderate	Skin, oral mucosa, GI, liver	CR
8	Female	41	CML	121	Peripheral blood	Matched, related	Severe	Skin, GI, lung, joint	NR
9	Male	18	ANLL	115	Peripheral blood	Mismatched	Severe	Skin, liver	PR
10	Male	32	ALL	151	Peripheral blood	Matched, related	Severe	Skin, eyes, GI, liver, joint	PR
11	Male	28	ALL	325	Peripheral blood	Matched, related	Severe	Skin, oral mucosa, eyes, liver	CR
12	Female	41	ANLL	293	Peripheral blood	Matched, related	Moderate	Skin, oral mucosa, eyes, GI,	NR
13	Male	36	CML	840	Bone marrow	Matched, related	Severe	Skin, oral mucosa, eyes, liver, joint	PR

Abbreviations: ALL, acute lymphoblastic leukemia; ANLL, acute non-lymphocytic leukemia; cGVHD, chronic graft-*versus*-host disease; CML, chronic monocytic leukemia; CR, complete response; GI, gastrointestinal; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplantation; MSC, mesenchymal stromal cells; NHL, non-Hodgkin's lymphoma; NR, non-response; PR, partial response.