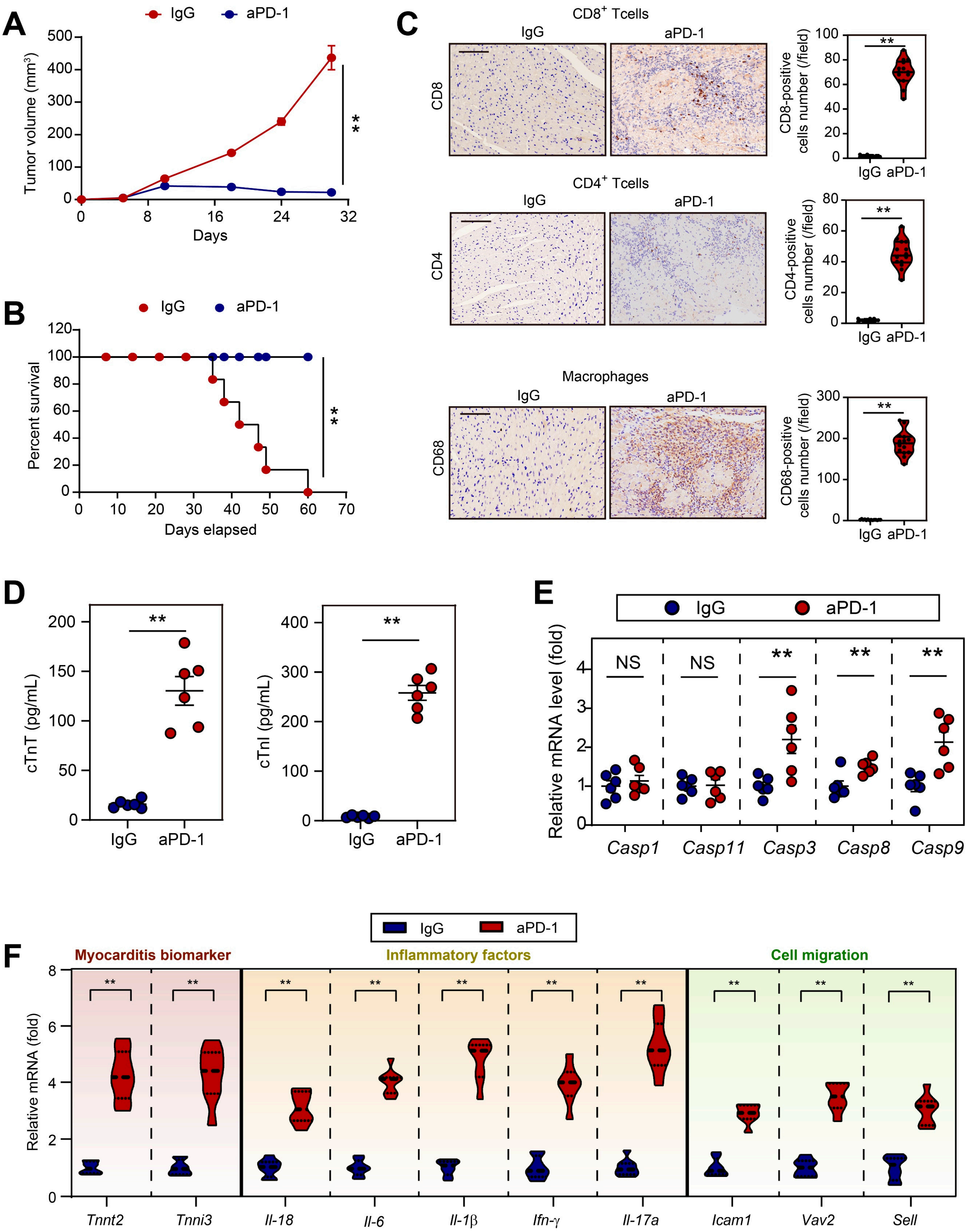
Supplemental Figure 1



Overdose anti-PD-1 (aPD-1) therapy in mice inhibits tumor growth but causes myocardial immune cells infiltration and elevation of blood biomarkers.
(**A**) Tumor size in tumor-bearing mice received overdose aPD-1 therapy or normal IgG**.** *n* = 6 biologically independent experiments.

(**B**) Survival of tumor-bearing mice received overdose aPD-1 therapy or normal IgG**.** *n* = 6 biologically independent experiments.

(**C**) Immunohistochemistry staining of T-cell ($CD8^+$ and $CD4^+$) and macrophages/monocytes ($CD68^+$) in myocardium of mice received overdose aPD-1 therapy or normal IgG**.** *n* = 14 biologically independent experiments.

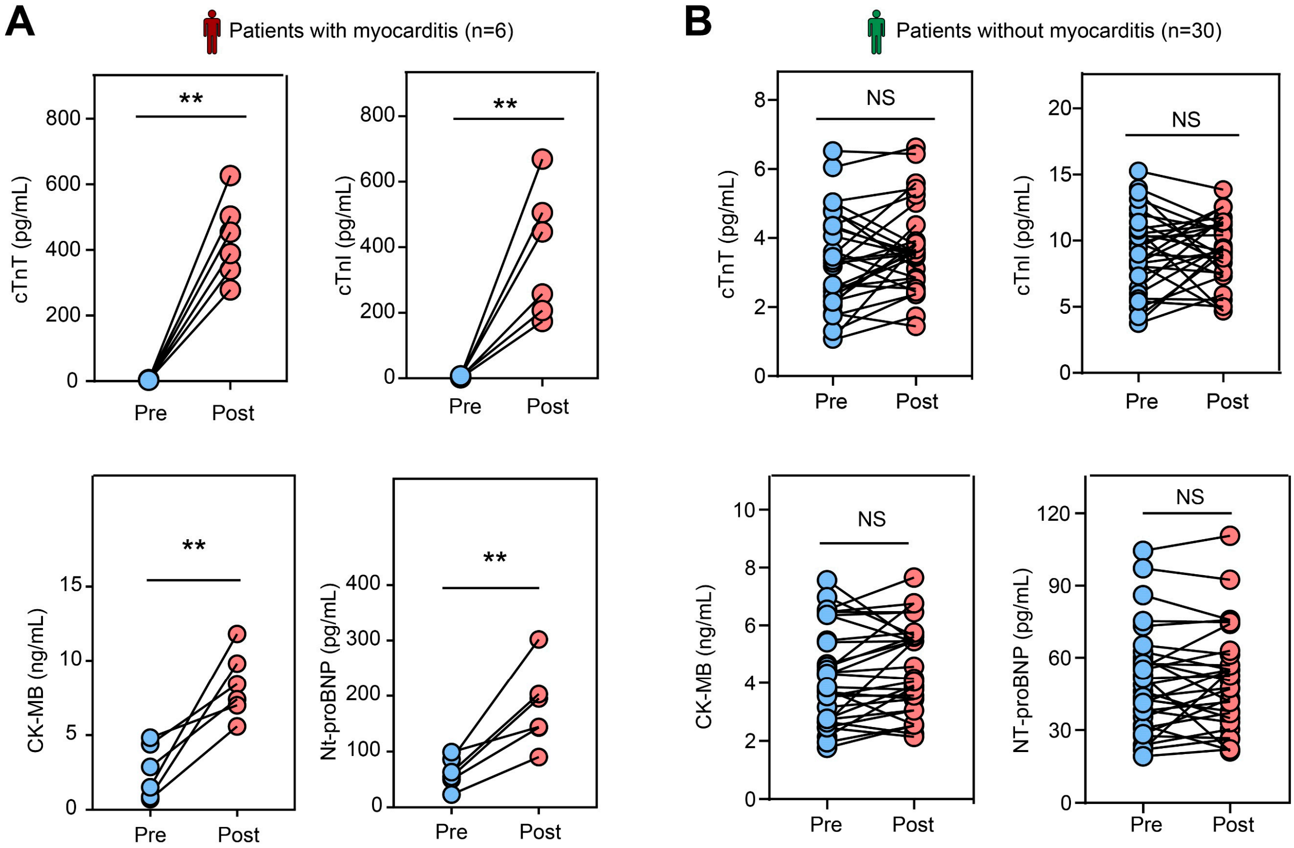
(**D**) Serum levels of cTnT and cTnI in mice received overdose aPD-1 therapy or normal IgG**.** *n* = 6 biologically independent experiments.

(E) Gene expression of *caspase-1, caspase-11, caspase-3, caspase-8* and *caspase-9* in heart of mice received overdose aPD-1 therapy or normal IgG. *n* = 6 biologically independent experiments.

(F) Gene expression of *Tnni3*, *Tnnt2, Il-18, Il-6, Il-1b, Ifn-*γ, *Il-17a, Icam1, Vav2* and *Sell* in heart of mice received overdose aPD-1 therapy or normal IgG. *n* = 8 biologically independent experiments.

The data were presented as means ± SEM and analyzed by Log-Rank test (survival, **B**) and two-sided unpaired Student's t-test (other panels). $^{**}P<0.01$. NS, no significance.

Supplemental Figure 2



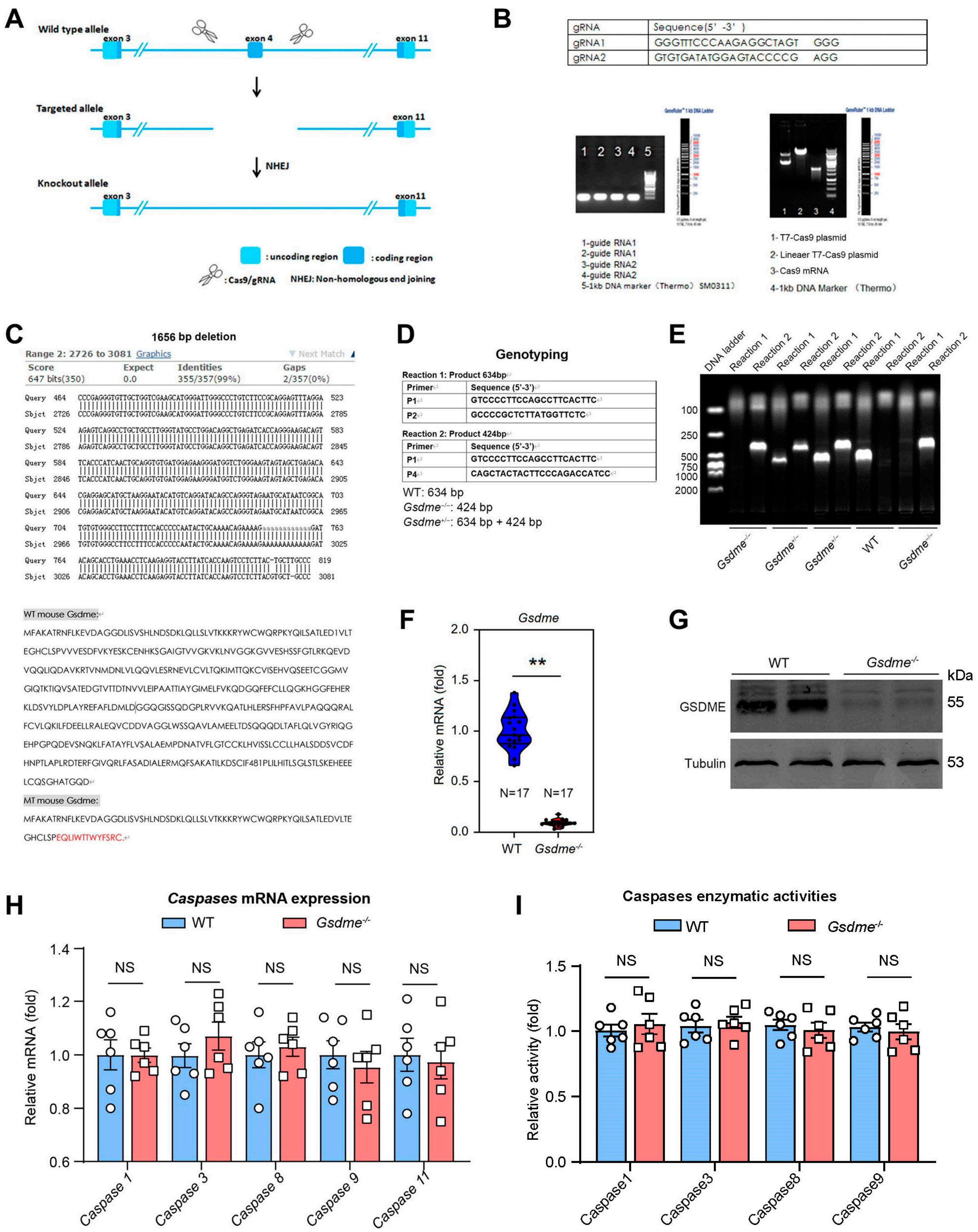
Investigation of serum biomarkers for cardiac injury in patients with aPD-1 therapy-induced myocarditis.

(**A**) Serum biomarkers of cardiac damage (cTnT, cTnI, CK-MB and NT-proBNP) in 6 NSCLC patients with myocarditis (IC-OS 2021 criteria).

(B) Serum biomarkers of cardiac damage (cTnT, cTnI, CK-MB and NT-proBNP) in 30 NSCLC patients without myocarditis (IC-OS 2021 criteria).

The data were analyzed by two-sided paired Student's t-test. $^{**}P<0.01$. NS, no significance.

Supplemental Figure 3



Generation of a mouse strain with globally knockout of GSDME.
(**A**) Schematic diagram showing the knockout strategy in mice by targeting exon 4 of GSDME using CRISPR/CAS9 technology.
(**B**) Design and preparation of gRNAs.
(**C**) Sequencing confirmation of the deletion of 1656 bp in F0 animal.
(**D**) Genotyping primers of genotyping in F1 animals.

(**E**) The representative agarose images in genotyping.

(**F**) The mRNA level of GSDME in WT and *Gsdme*$^{-/-}$ mice. The primers were designed to target the gene sequence within the exon 4 of GSDME. *n* = 17 biologically independent experiments.

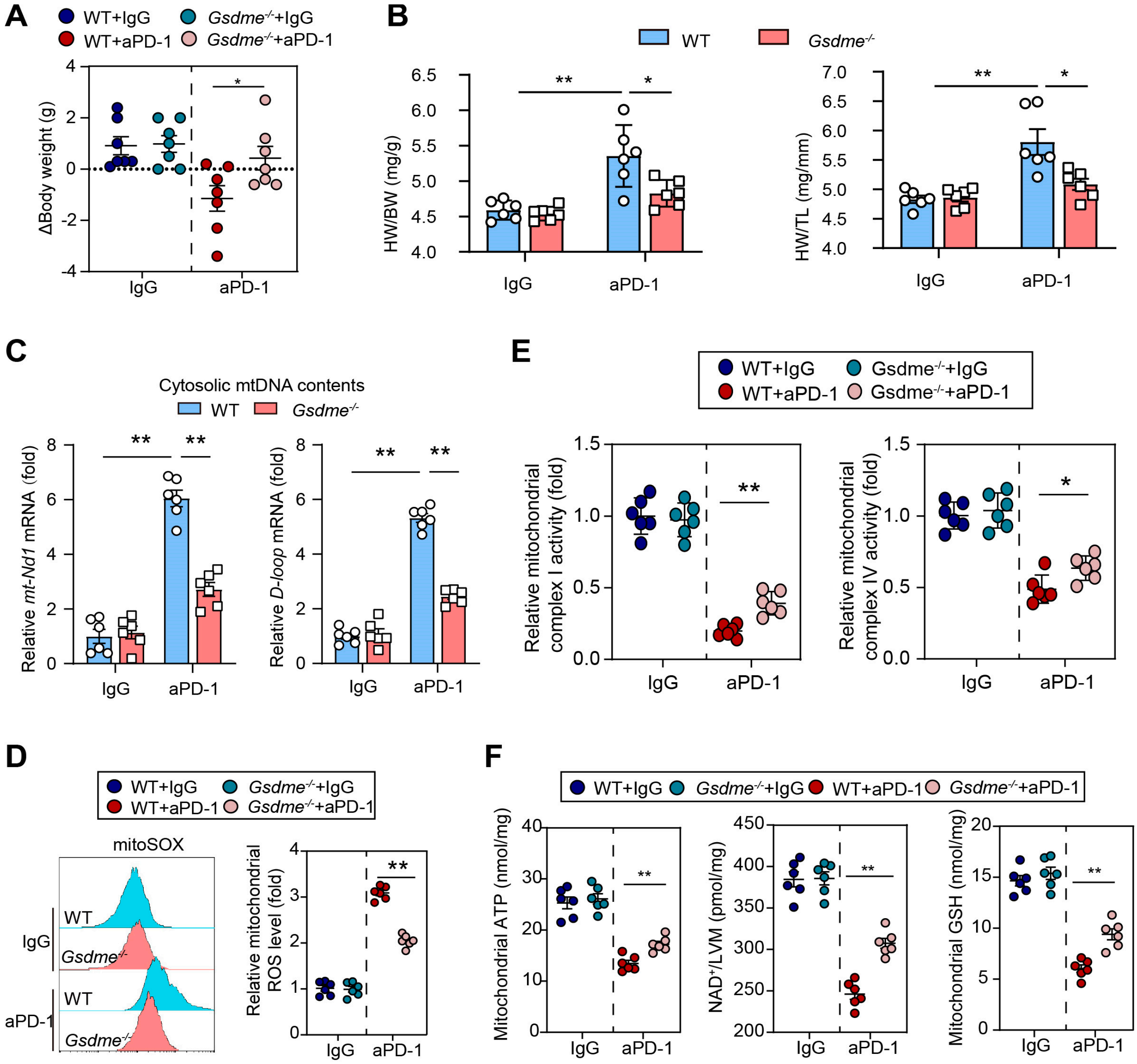
(**G**) Immunoblotting analysis confirmed the successful deletion of GSDME protein in *Gsdme*$^{-/-}$ mice.

(H) The mRNA expression of *caspase 1, caspase 3, caspase 8, caspase 9* and *caspase 11* in hear tissue of WT and *Gsdme*$^{-/-}$ mice. *n* = 6 biologically independent experiments.

(I) The enzymatic activities of Caspase 1, Caspase 3, Caspase 8 and Caspase 9 in heart tissue of WT and *Gsdme*$^{-/-}$ mice. *n* = 6 biologically independent experiments.

The data were presented as means ± SEM and analyzed by two-sided unpaired Student’s t-tests. **P<0.01. NS, no significance.

Supplemental Figure 4



Deletion of GSDME in mice attenuates aPD-1 therapy-induced myocardial damage and mitochondrial dysfunction.

(**A**) The body weight change induced by aPD-1 therapy in WT and *Gsdme*$^{-/-}$ mice. Normal IgG was used as a control. *n* = 7 biologically independent experiments.

(**B**) Heart weight to body weight ratio (HW/BW) and heart weight to tibia length ratio (HW/TL). *n* = 6 biologically independent experiments.

(**C**) Cytosolic mtDNA (*mt-Nd1* and *D-loop*) contents in heart of WT and *Gsdme*$^{-/-}$ mice received aPD-1 therapy or control IgG. *n* = 6 biologically independent experiments.

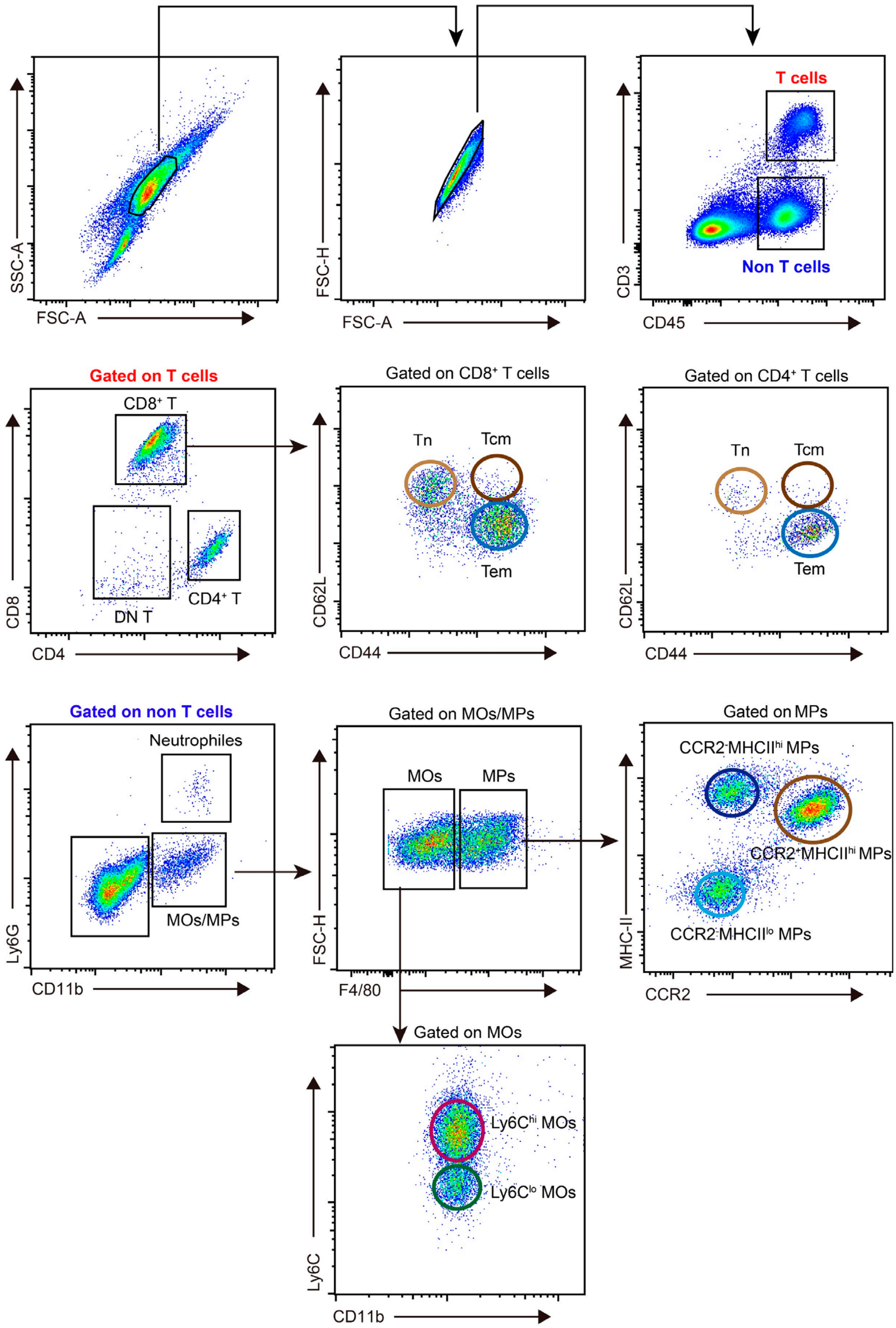
(**D**) Mitochondrial ROS levels were determined using flow cytometry with mitoSOX probe in single cells extracted from heart tissues of WT and *Gsdme*$^{-/-}$ mice after treatment of aPD-1 or normal IgG. *n* = 6 biologically independent experiments.

(**E**) Quantitative analysis of mitochondrial complex I and IV activities in heart of WT and *Gsdme*$^{-/-}$ mice received aPD-1 therapy or control IgG. *n* = 6 biologically independent experiments. *n* = 6 biologically independent experiments.

(**F**) Mitochondrial contents of ATP, NAD^{+} and GSH in mitochondrial fractions extracted from heart tissues of WT and *Gsdme*$^{-/-}$ mice after treatment of aPD-1 or normal IgG. *n* = 6 biologically independent experiments.

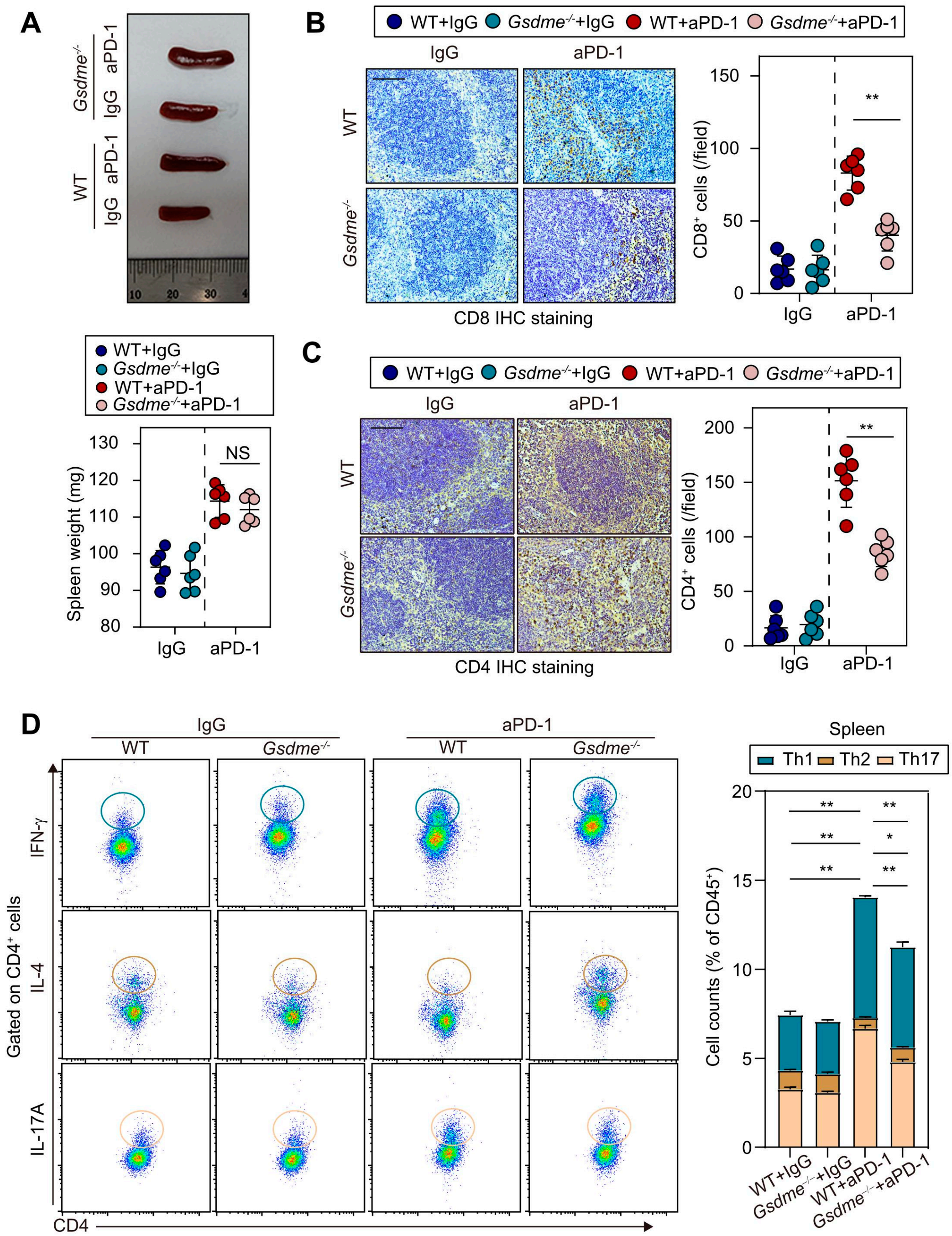
The data were presented as means ± SEM and analyzed by two-sided unpaired Student's t-tests. *P<0.05, **P<0.01. NS, no significance.

Supplemental Fig 5



Gating strategy of flow cytometry. The gating strategy of flow cytometry in cells isolated from hearts of mice received aPD-1 therapy was presented.

Supplemental Fig 6



Deletion of GSDME in mice weakens aPD-1 therapy-induced T-cells activation in spleen

(**A**) Morphology and spleen weight of WT and *Gsdme*$^{-/-}$ mice received aPD-1 therapy or normal IgG.

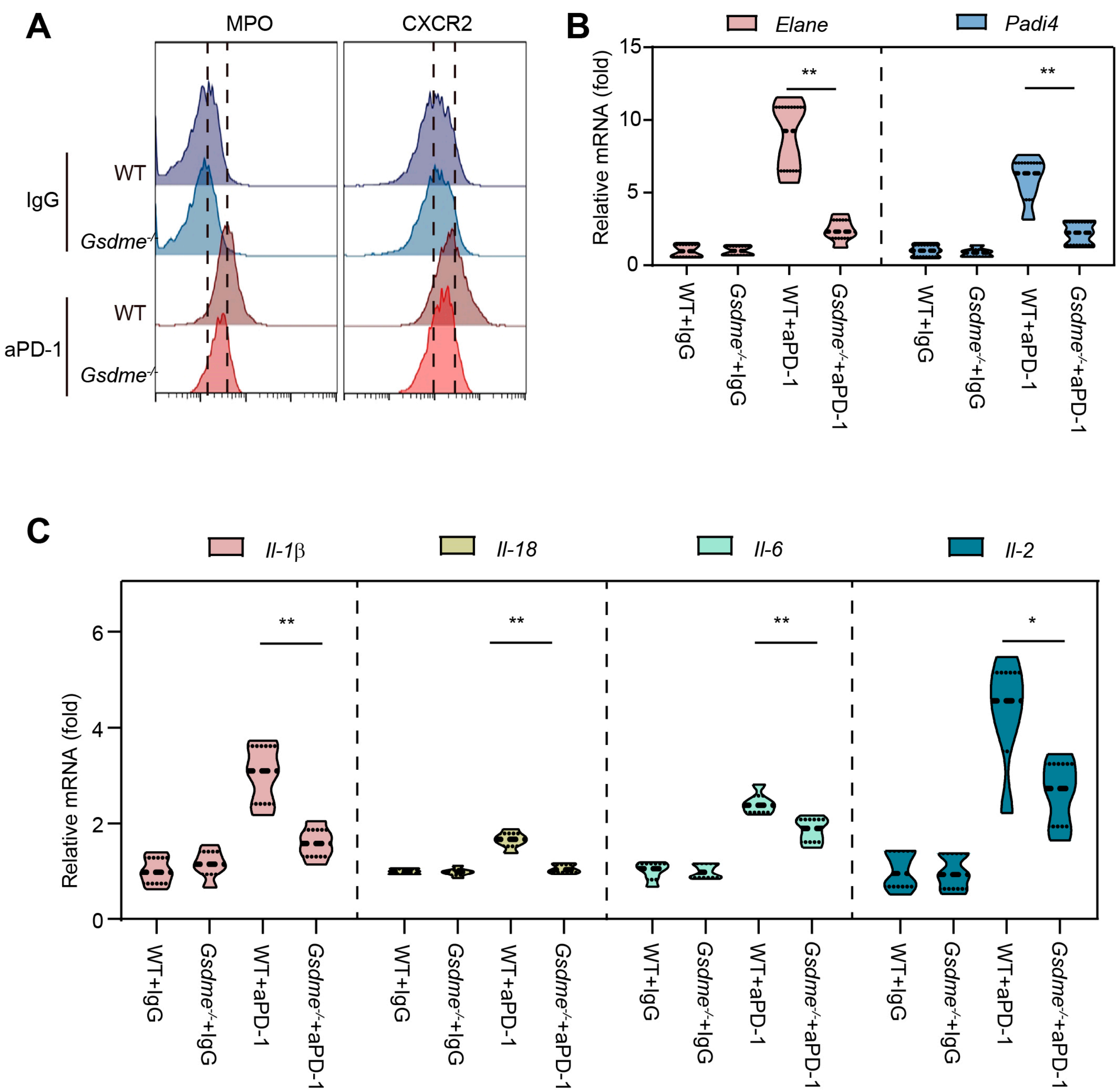
(**B**) Representative immunohistochemistry staining and quantitative analysis of CD8^{+} T-cells in spleen of WT and *Gsdme*$^{-/-}$ mice received aPD-1 therapy or control IgG.

(**C**) Representative immunohistochemistry staining and quantitative analysis of CD4^{+} T-cells in spleen of WT and *Gsdme*$^{-/-}$ mice received aPD-1 therapy or control IgG.

(**D**) Proportions of Th1 (IFN-γ^{+}), Th2 (IL-4^{+}) and Th17 (IL-17A^{+}) cells within CD4^{+} cells in spleens of WT and *Gsdme*$^{-/-}$ mice were determined using flow cytometry analysis.

The data were presented as means ± SEM and analyzed by two-sided unpaired Student's t-tests. *P<0.05, **P<0.01. NS, no significance. n = 6 biologically independent experiments.

Supplemental Figure 7



Deletion of GSDME alleviates aPD-1 therapy-induced myocardial inflammation

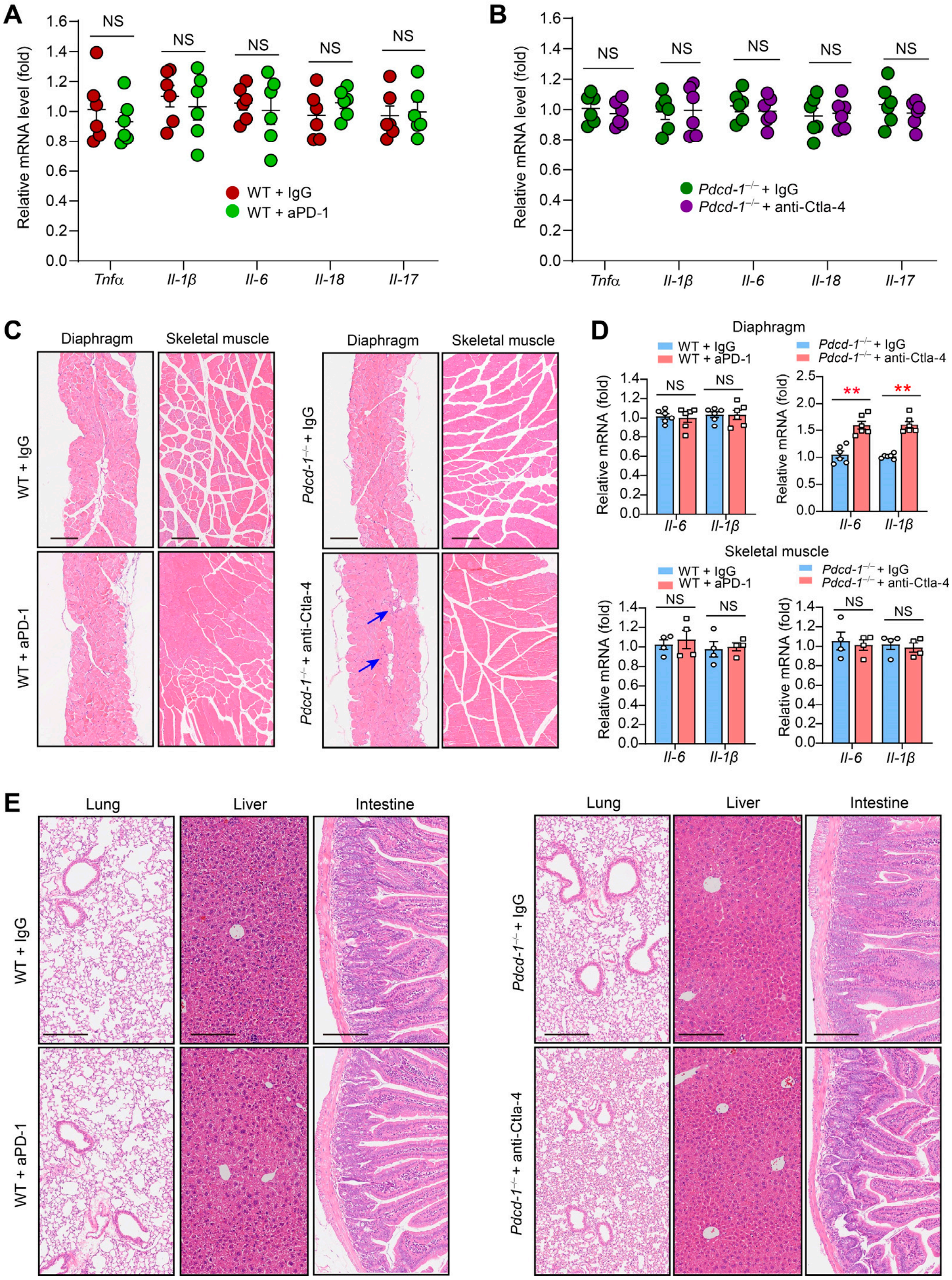
(**A**) Representative flow cytometry plots of MPO and CXCR2 in heart of WT and *Gsdme*$^{-/-}$ mice received aPD-1 therapy or normal IgG. MPO, myeloperoxidase; CXCR2, C-X-C motif chemokine receptor 2.

(**B**) Quantitative PCR analyses of mRNA levels of *Elane* and *Padi4* in heart of WT and *Gsdme*$^{-/-}$ mice received aPD-1 therapy or normal IgG. *Elane,* neutrophil elastase; *Padi4,* peptidyl arginine deiminase, type IV.

(**C**) Quantitative PCR analyses of mRNA levels of *IL-1β, IL-6, IL-18* and *IL-2* in heart of WT and *Gsdme*$^{-/-}$ mice received aPD-1 therapy or normal IgG. *IL-1β,* interleukin-1β; *IL-6,* interleukin-6; *IL-18,* interleukin-18; *IL-2,* interleukin-2.

The data were presented as means ± SEM and analyzed by two-sided unpaired Student's t-tests. *P<0.05, **P<0.01. n = 6 biologically independent experiments.

Supplemental Fig 8



Absence of systemic immune activation in two animal models of ICI-induced myocarditis.

(**A**) The mRNA expression of *Tnfα, Il-1β, Il-6, Il-18* and *Il-17* in PBMCs isolated from WT mice receiving IgG or anti-PD1. *n* = 6 biologically independent experiments.

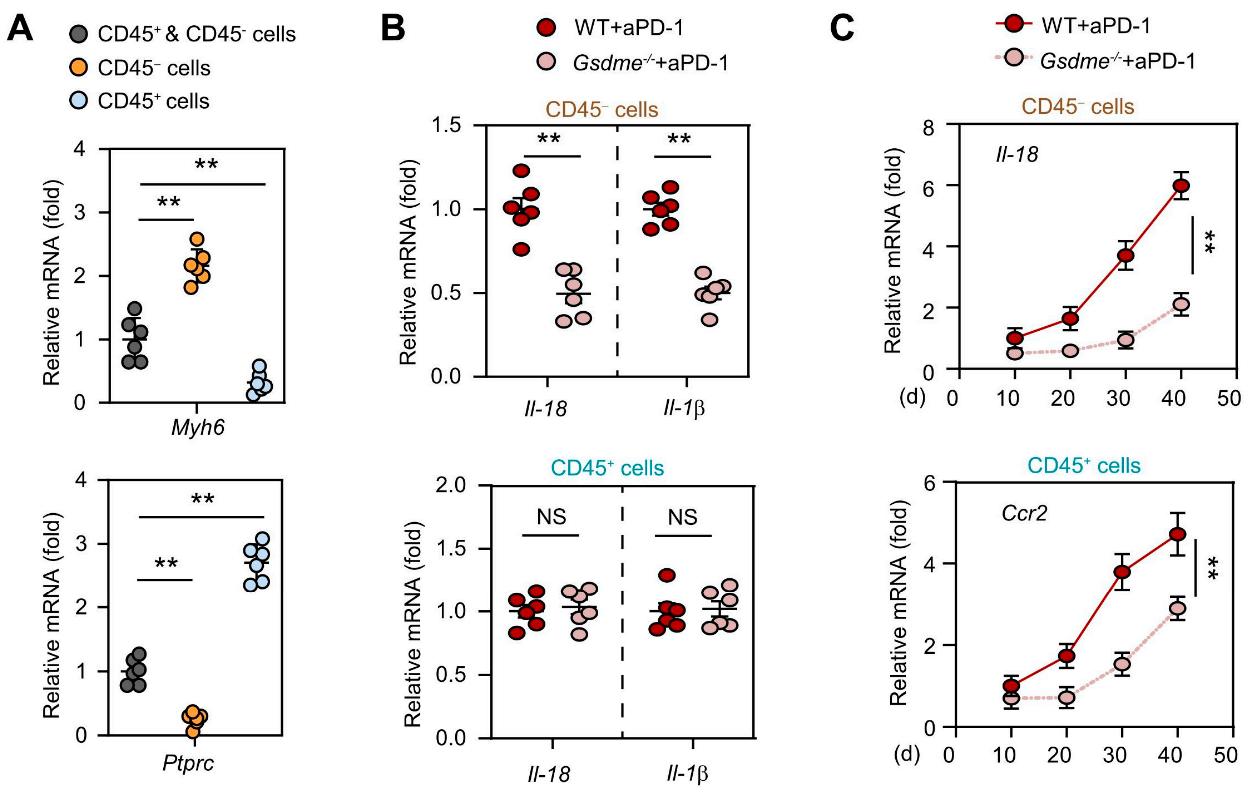
(**B**) The mRNA expression of *Tnfα, Il-1β, Il-6, Il-18* and *Il-17* in PBMCs isolated from $Pdcd1^{-/-}$ mice receiving IgG or anti-Ctla4. *n* = 6 biologically independent experiments.

(**C**) Histological analysis showing the structure of diaphragm and skeletal muscle (quadriceps femoris muscle) of WT mice receiving IgG or anti-PD1, as well as $Pdcd1^{-/-}$ mice receiving IgG or anti-Ctla4. Blue arrows indicate mild immune cell infiltration. *n* = 6 biologically independent experiments.

(**D**) Quantitative analysis by qPCR on the *Il-6* and *Il-1β* in diaphragm (*n* = 6 biologically independent experiments.) and skeletal muscle (*n* = 4 biologically independent experiments.) of WT mice receiving IgG or anti-PD1, as well as $Pdcd1^{-/-}$ mice receiving IgG or anti-Ctla4.

(**E**) Histological analysis showing the structure of lung, liver and intestine of WT mice receiving IgG or anti-PD1, as well as *Pdcd1*$^{-/-}$ mice receiving IgG or anti-Ctla4. *n* = 6 biologically independent experiments.
The data were presented as means ± SEM and analyzed by two-sided unpaired Student's t-tests. **P*<0.05, ***P*<0.01. NS, no significance.

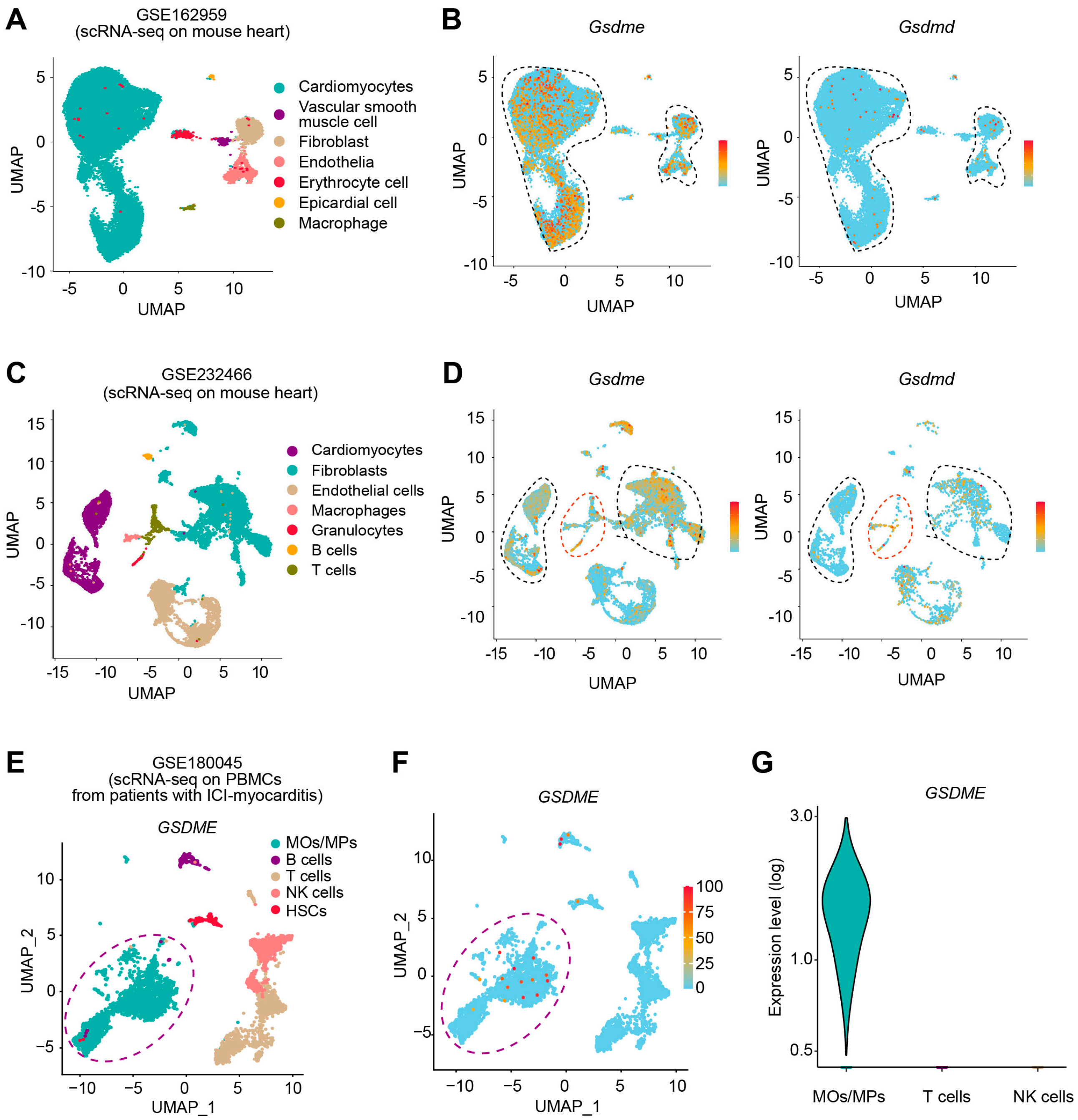
Supplemental Figure 9



Characterization of pyroptosis-related molecules in CD45⁺ and CD45⁻ cells isolated from hearts of WT and Gsdme⁻/⁻ mice received aPD-1 therapy.

(**A**) Determination of signature genes *Myh6* (encoding cardiac α-myosin heavy chain) and *Ptprc* (encoding CD45) expression in CD45⁺ and CD45⁻ cells isolated from hearts of WT and *Gsdme*⁻/⁻ mice received aPD-1 therapy. CD45⁺ and CD45⁻ cells were isolated using sorting flow cytometry.
(**B**) Comparison of pyroptosis-related molecules *Il-18* and *Il-1β* expression in isolated CD45⁻ and CD45⁺ cells respectively between hearts of WT and *Gsdme*⁻/⁻ mice received aPD-1 therapy.
(**C**) Comparison of *Il-18* and *Ccr2* mRNA expression in isolated CD45⁻ and CD45⁺ cells respectively between hearts of WT and *Gsdme*⁻/⁻ mice received aPD-1 therapy.
The data were presented as means ± SEM and analyzed by two-sided unpaired Student's t-tests. **P<0.01. NS, no significance. n = 6 biologically independent experiments.

Supplemental Figure 10



Public single-cell RNA sequencing (scRNA-seq) analysis of Gsdme transcription level in normal mouse heart and peripheral blood mononuclear cells (PBMCs) of patients with ICI-myocarditis.

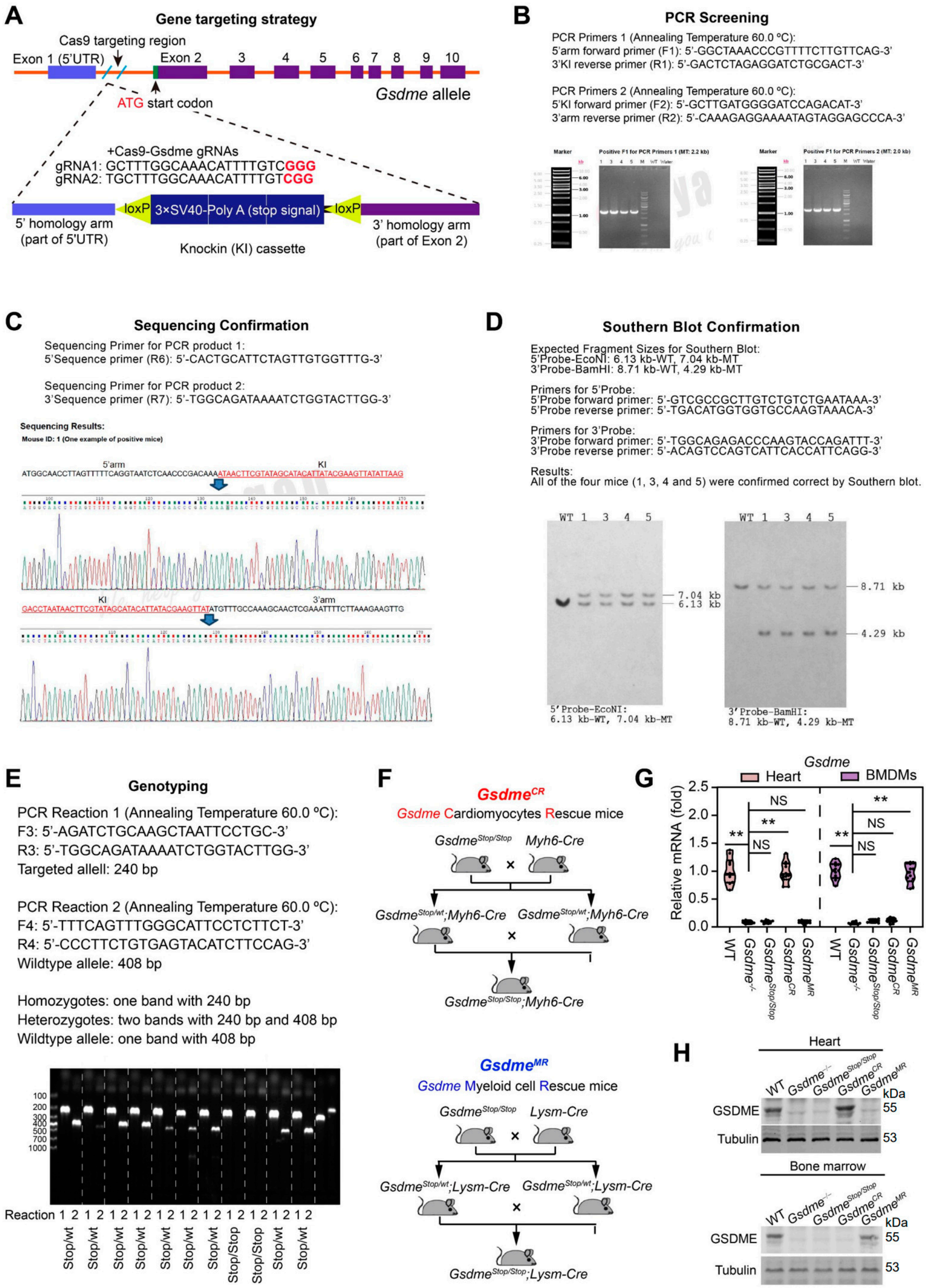
(**A**) UMAP analysis of cells clusters in mouse heart from a public scRNA-seq dataset (GEO Access Numbers: GSE162959).

(**B**) Transcription levels of *Gsdme* and *Gsdmd* in different clusters of cardiac cells. The colors in the expression-level heatmaps (right panel) represent the median intensity values for *Gsdme* or *Gsdmd* gene.

(**C**) UMAP analysis of cells clusters in mouse heart from a public scRNA-seq dataset (GEO Access Numbers: GSE232466).

(**D**) Transcription levels of *Gsdme* and *Gsdmd* in different clusters of cardiac cells. The colors in the expression-level heatmaps (right panel) represent the median intensity values for *Gsdme* or *Gsdmd* gene.
(**E**) UMAP analysis of cells clusters in PBMCs of patients with ICI-myocarditis from a public scRNA-seq dataset (GEO Access Numbers: GSE180045).
(**F**) Transcription levels of *Gsdme* in different clusters of immune cells within PBMCs. The colors in the expression-level heatmaps (right panel) represent the median intensity values for *Gsdme* gene.
(**G**) Violin plot showing the transcription levels of *Gsdme* in MOs/MPs, T cells and NK cells.

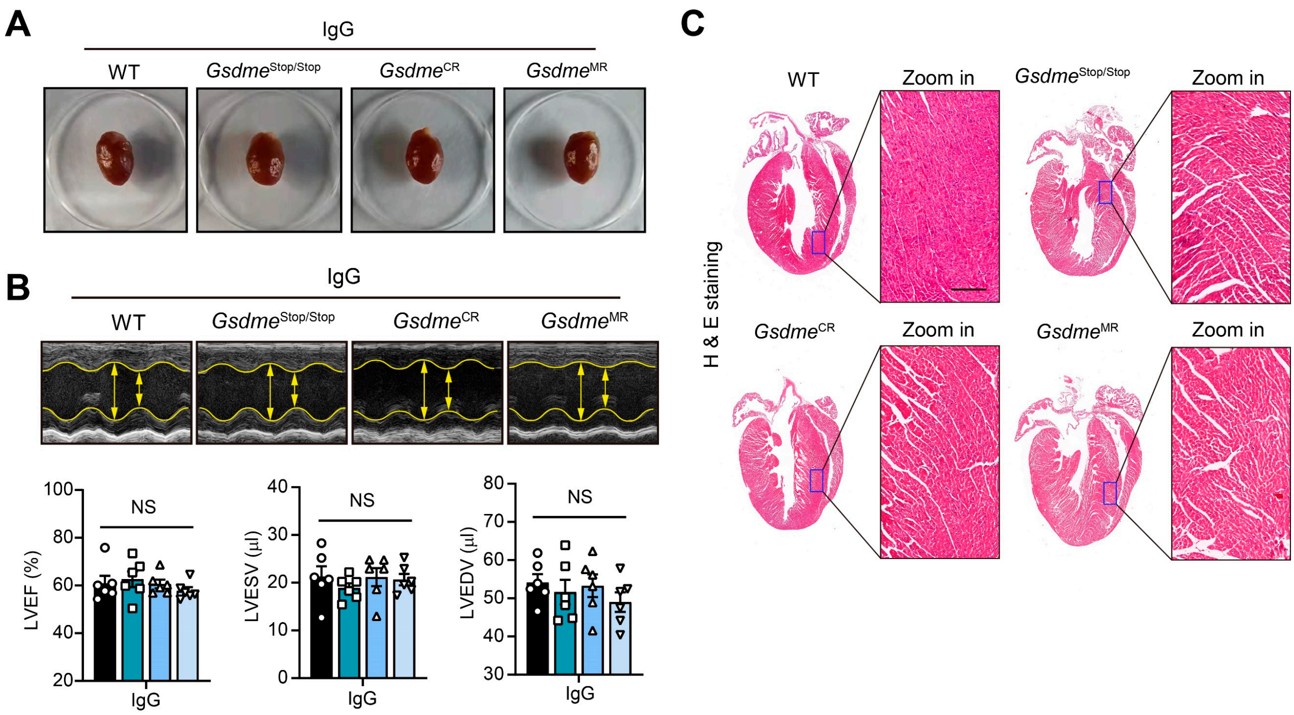
Supplemental Figure 11



Generation of mouse stains with conditional rescue of GSDME in cardiomyocytes and myeloid cells respectively

(**A**) Schematic diagram showing the gene targeting strategy for generation a mouse strain carrying a transcriptional *Stop* element flanked by *loxP* recombination sites (*loxP-Stop-loxP*, LSL) upstream of the ATG start codon of *Gsdme* gene. The gRNA1 and gRNA2 to mouse *Gsdme* gene, the donor vector containing "part of 5'UTR-loxP-3*SV40-Poly A -loxP-part of E2" cassette, and *Cas9* mRNA were co-injected into fertilized mouse eggs to generate targeted conditional knockin offspring (*Gsdme*$^{\text{Stop/Stop}}$). The sequences of gRNA1 and gRNA2 were also shown. The *Stop* element before ATG start codon was expected to terminate the transcription of *Gsdme* gene.
(**B**) The PCR primers and array to identify the positive F1 *Gsdme*$^{\text{Stop/Stop}}$ mice. Four positive F1 *Gsdme*$^{\text{Stop/Stop}}$ mice were identified.
(**C**) One of the positive F1 mice was sequenced to confirm the knockin targeting.
(**D**) Southern blot analysis further confirmed the successful knockin targeting.
(**E**) Genotyping of *Gsdme*$^{\text{Stop/Stop}}$ mice.
(**F**) The *Gsdme*$^{\text{Stop/Stop}}$ mouse strain was crossed with *Myh6*-Cre or *Lysm*-Cre mouse to produce *Gsdme*$^{\text{Stop/Stop}}$;*Myh6*-Cre mouse (cardiomyocyte rescue of GSDME, referred as *Gsdme*^{CR}) or *Gsdme*$^{\text{Stop/Stop}}$;*Lysm*-Cre mouse (myeloid cell rescue of GSDME, referred as *Gsdme*^{MR}). The Cre expression in cardiomyocyte or myeloid cell can delete the *Stop* element in specific tissue to allow GSDME re-expression.
(**G**) Quantitative PCR analysis showing *Gsdme* mRNA level in heart tissue and bone-marrow derived macrophages (BMDMs) from WT, *Gsdme*$^{-/-}$, *Gsdme*$^{\text{Stop/Stop}}$, *Gsdme*^{CR} and *Gsdme*^{MR} mice. n = 10 biologically independent experiments. The data were presented as means ± SEM and analyzed by two-sided unpaired Student's t-tests. **P<0.01. NS, no significance.
(**H**) Immunoblotting analysis of GSDME protein level in heart tissue and bone marrow from WT, *Gsdme*$^{-/-}$, *Gsdme*$^{\text{Stop/Stop}}$, *Gsdme*$^{\text{CR}}$ and *Gsdme*$^{\text{MR}}$ mice. GSDME protein was rescued in heart of *Gsdme*$^{\text{CR}}$ mice and bone marrow of *Gsdme*$^{\text{MR}}$ mice. n = 6 biologically independent experiments.

Supplemental Figure 12



Comparison of cardiac function of WT, Gsdme*$^{Stop/Stop}$*, Gsdme*^{CR} *and Gsdme*^{MR} *mice under normal condition

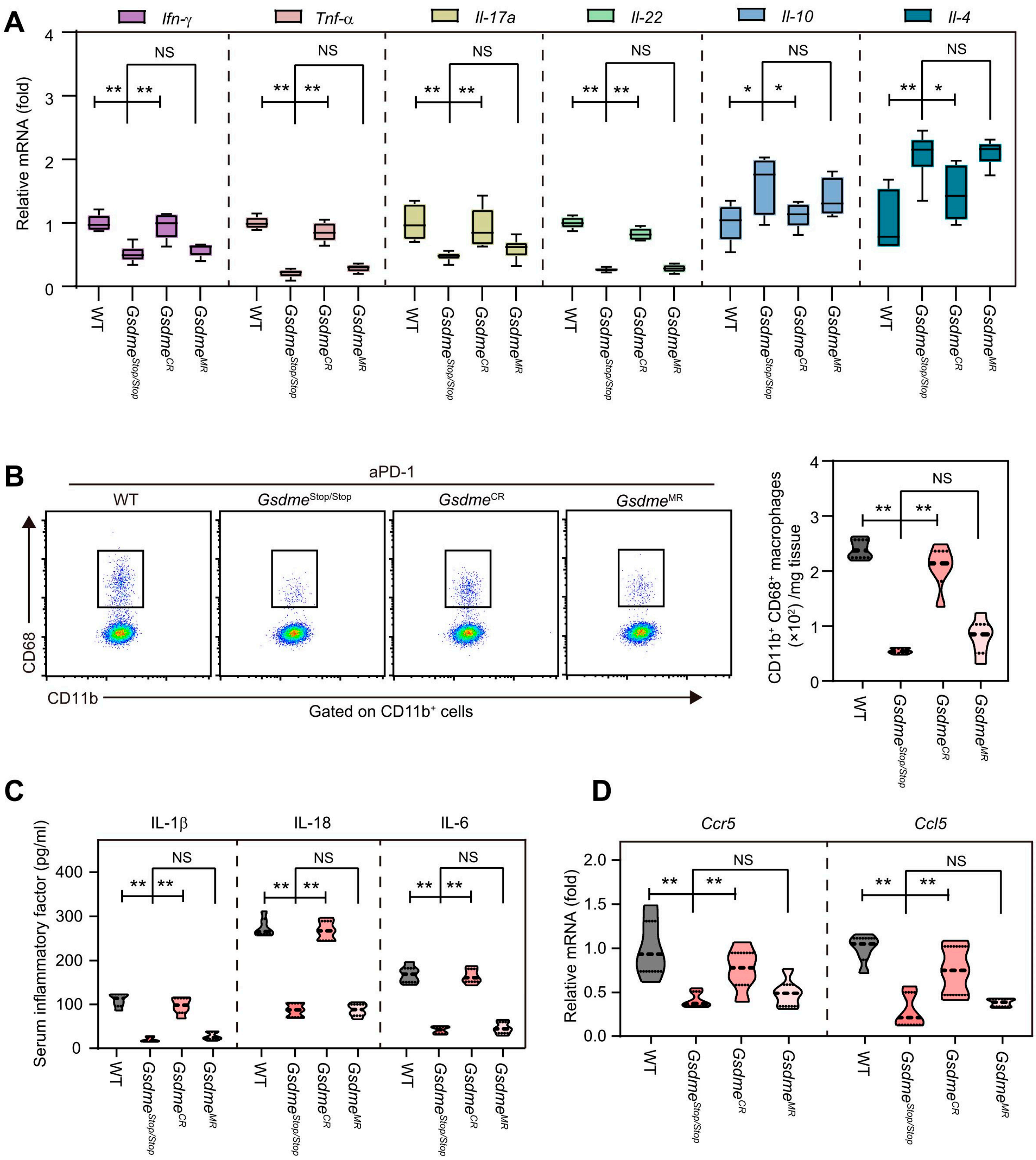
(**A**) Morphology of hearts of WT, *Gsdme*$^{Stop/Stop}$, *Gsdme*^{CR} and *Gsdme*^{MR} mice received control IgG. $n = 6$ biologically independent experiments.

(**B**) Representative echocardiograms in WT, *Gsdme*$^{Stop/Stop}$, *Gsdme*^{CR} and *Gsdme*^{MR} mice received control IgG. $n = 6$ biologically independent experiments.

(**C**) HE staining of hearts of WT, *Gsdme*$^{Stop/Stop}$, *Gsdme*^{CR} and *Gsdme*^{MR} mice received control IgG. $n = 6$ biologically independent experiments.

The data were presented as means ± SEM and analyzed by two-sided unpaired Student's t-tests. NS, no significance.

Supplemental Figure 13



Rescue of GSDME in cardiomyocyte alleviates aPD-1 therapy-associated inflammation.

(**A**) Comparison of mRNA levels of *Ifn-γ, Tnf-α, Il-17a, Il-22, Il-10* and *Il-4* in heart of WT, *Gsdme*$^{\mathrm{Stop/Stop}}$, *Gsdme*$^{\mathrm{CR}}$ and *Gsdme*$^{\mathrm{MR}}$ mice received aPD-1 therapy. *n* = 6 biologically independent experiments.

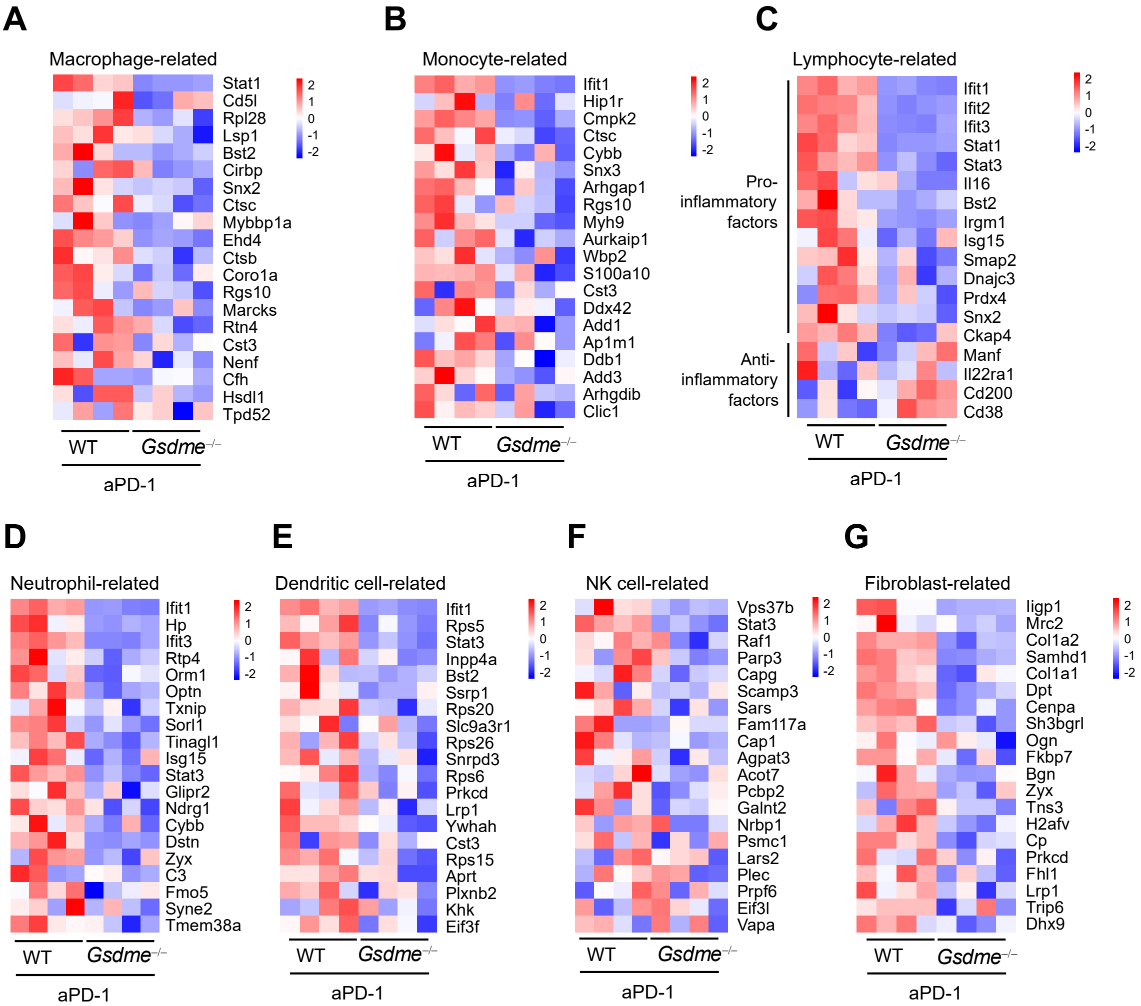
(**B**) Representative flow cytometry plots and quantitative analysis of CD11b$^+$CD68$^+$ monocytes/macrophages (MOs/MPs) in heart of WT, *Gsdme*$^{\mathrm{Stop/Stop}}$, *Gsdme*$^{\mathrm{CR}}$ and *Gsdme*$^{\mathrm{MR}}$ mice received aPD-1 therapy. *n* = 6 biologically independent experiments.

(**C**) ELISA analyses showing the protein levels of pro-inflammatory factors including IL-1β, IL-18 and IL-6 in heart of WT, *Gsdme*$^{\mathrm{Stop/Stop}}$, *Gsdme*$^{\mathrm{CR}}$ and *Gsdme*$^{\mathrm{MR}}$ mice received aPD-1 therapy. *n* = 6 biologically independent experiments.

(**D**) Quantitative PCR analysis showing the mRNA levels of *Ccr5* and *Ccl5* in heart of WT, $Gsdme^{Stop/Stop}$, $Gsdme^{CR}$ and $Gsdme^{MR}$ mice received aPD-1 therapy. $n = 6$ biologically independent experiments.

The data were presented as means ± SEM and analyzed by two-sided unpaired Student's t-tests. *P<0.05, **P<0.01. NS, no significance.

Supplemental Figure 14



Tandem Mass Tagging (TMT)-based multiplexed quantitative proteomics showing the changed protein signatures in immune cells and fibroblasts between WT and Gsdme$^{-/-}$ mice upon aPD-1 therapy

(**A**) Macrophage-related protein signature between heart of WT and *Gsdme*$^{-/-}$ mice upon aPD-1 therapy.

(**B**) Monocyte-related protein signature between heart of WT and *Gsdme*$^{-/-}$ mice upon aPD-1 therapy.

(**C**) Lymphocyte-related protein signature between heart of WT and *Gsdme*$^{-/-}$ mice upon aPD-1 therapy.

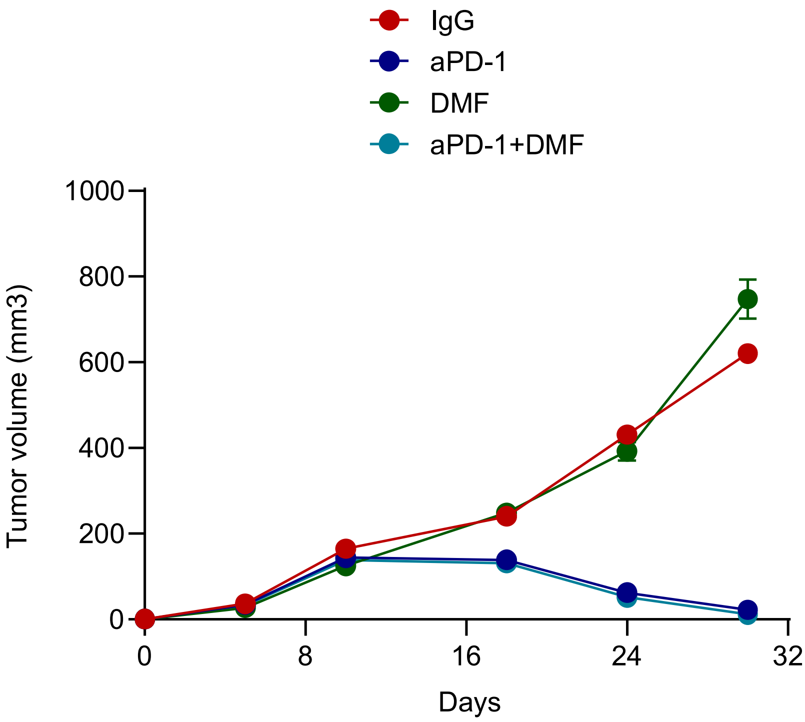
(**D**) Neutrophil-related protein signature between heart of WT and *Gsdme*$^{-/-}$ mice upon aPD-1 therapy.

(**E**) Dendritic cell-related protein signature between heart of WT and *Gsdme*$^{-/-}$ mice upon aPD-1 therapy.

(**F**) NK cell-related protein signature between heart of WT and *Gsdme*$^{-/-}$ mice upon aPD-1 therapy.

(**G**) Fibroblast-related protein signature between heart of WT and *Gsdme*$^{-/-}$ mice upon aPD-1 therapy.

Supplemental Figure 15



Effects of dimethyl fumarate (DMF) on tumor growth in the presence or absence of aPD-1 therapy. The Tumor size in tumor-bearing mice received overdose aPD-1 therapy or normal IgG or DMF or aPD-1+DMF**.** *n* = 6 biologically independent experiments.

Supplemental Table 1

Characteristics of 6 tumor patients with myocarditis after first-course therapy of aPD-1

Case No.	Gender	Tumor type	Age	cTnT baseline (pg/ml)	cTnT elevation (>200 pg/ml)	cTnI baseline (pg/ml)	cTnI elevation (>200 pg/ml)	Major Criterion	Minor Criterion				IC-OS 2021 criteria
								Diagnostic CMR	Suggestive CMR	Clinical syndrome	Decline in cardiac function	Ventricular arrhythmia	
1	M	NSCLC	64	<10	+	<10	+	+	/	+	+	+	Y
2	F	NSCLC	68	<10	+	<10	+	+	/	+	+	+	Y
3	M	Gastric cancer	56	<10	+	<10	+	–	–	+	+	–	Y
4	M	Gastric cancer	59	<10	+	<10	+	–	+	+	–	+	Y
5	F	Melanoma	47	<10	+	<10	+	–	–	+	+	–	Y
6	M	Esophageal cancer	56	<10	+	<10	+	–	–	+	–	+	Y

IC-OS 2021 criteria: troponin elevation + 1 major criterion or troponin elevation + with 2 minor criteria after exclusion of acute coronary syndrome or acute infectious myocarditis based on clinical suspicion. NSCLC, non-small cell lung cancer.

Supplemental Table 2.
Differentially expressed proteins between WT mice (n = 4) and *Gsdme*$^{-/-}$ mice upon aPD-1 therapy in isobaric Tandem Mass Tag multiplexed quantitative proteomics

Protein accession	Protein name	MW [kDa]	Coverage [%]	Peptides	PSMs	Unique peptides	WT +aPD-1	WT +aPD-1	WT +aPD-1	WT +aPD-1	Gsdme$^{-/-}$ +aPD-1	Gsdme$^{-/-}$ +aPD-1	Gsdme$^{-/-}$ +aPD-1	Gsdme$^{-/-}$ +aPD-1	Gsdme$^{-/-}$ +aPD-1 to WT+aPD-1 ratio	P value
Q61941	**Nnt**	113.84	34.8	37	117	37	1.677	1.645	1.637	1.617	0.253	0.272	0.221	0.247	0.151	1.726E-10
Q80TD3	**Fnip2**	122.52	0.7	1	1	1	2.247	2.299	0.880	1.043	0.286	0.288	0.369	0.370	0.203	1.479E-02
Q64282	**Ifit1**	53.74	19.7	7	10	7	1.554	1.701	1.368	1.451	0.488	0.529	0.401	0.371	0.295	1.126E-05
Q60766	**Irgm1**	46.55	21.0	9	13	9	1.649	1.681	1.166	1.085	0.625	0.589	0.536	0.614	0.424	2.243E-03
Q9QZ85	**Iigp1**	47.57	34.4	11	13	11	1.724	1.776	0.965	0.984	0.567	0.623	0.619	0.638	0.449	1.561E-02
Q64112	**Ifit2**	55.02	3.0	1	1	1	1.460	1.405	1.393	1.201	0.627	0.574	0.636	0.663	0.458	1.653E-05
Q9R233	**Tapbp**	49.74	7.1	3	3	3	1.566	1.590	1.150	1.131	0.572	0.568	0.692	0.663	0.459	1.327E-03
Q61646	**Hp**	38.75	34.6	12	16	12	1.618	1.721	0.951	1.047	0.630	0.596	0.701	0.666	0.486	1.310E-02
P42225	**Stat1**	87.20	20.7	13	20	13	1.517	1.410	1.105	1.158	0.627	0.671	0.670	0.696	0.513	7.332E-04
Q8BGV8	**Mief1**	51.18	5.8	2	2	2	1.296	1.321	1.369	1.243	0.621	0.617	0.781	0.751	0.530	1.820E-05
Q64345	**Ifit3**	47.22	7.2	3	3	3	1.282	1.351	1.236	1.154	0.722	0.720	0.707	0.792	0.586	2.705E-05
P01887	**B2m**	13.78	8.4	1	3	1	1.368	1.371	1.082	1.098	0.717	0.751	0.815	0.755	0.618	1.323E-03
Q9ER80	**Rtp4**	28.39	3.6	1	1	1	1.263	1.581	0.921	1.030	0.871	0.616	0.791	0.861	0.655	3.912E-02
Q07797	**Lgals3bp**	64.49	9.9	4	5	4	1.261	1.216	1.079	1.211	0.757	0.817	0.741	0.830	0.660	1.037E-04
P01901	**H2-K1**	41.30	26.0	8	11	5	1.382	1.367	0.987	1.038	0.744	0.770	0.852	0.824	0.668	1.046E-02
P97371	**Psme1**	28.67	57.4	13	25	13	1.338	1.250	1.043	1.121	0.807	0.797	0.804	0.804	0.676	1.098E-03
Q03734	**Serpina3**	47.06	16.0	6	14	2	1.220	1.185	1.163	1.214	0.726	0.683	0.903	0.929	0.678	8.960E-04
O35955	**Psmb10**	29.06	10.6	3	3	3	1.275	1.496	0.968	1.032	0.794	0.731	0.850	0.883	0.683	2.344E-02

P01899	**H2-D1**	40.84	20.4	7	12	3	1.220	1.195	1.153	1.156	0.805	0.783	0.832	0.843	0.691	2.353E-06
Q9QZU9	**Ube2l6**	17.84	9.8	1	1	1	1.215	1.209	1.047	1.172	0.864	0.997	0.746	0.663	0.704	5.945E-03
P36371	**Tap2**	77.44	8.0	5	5	5	1.323	1.267	1.081	1.072	0.733	0.782	0.858	0.972	0.705	5.490E-03
Q8CAS9	**Parp9**	96.66	2.4	2	3	2	1.187	1.248	0.965	1.238	0.821	0.803	0.757	0.939	0.716	5.116E-03
Q99L88	**Sntb1**	58.08	4.1	2	2	2	0.998	1.122	1.264	1.238	0.827	0.839	0.845	0.869	0.731	2.344E-03
Q01149	**Col1a2**	129.56	10.1	12	15	12	1.189	1.129	1.132	1.155	0.835	0.757	0.914	0.903	0.740	2.502E-04
P21958	**Tap1**	78.86	1.9	2	2	2	1.380	1.273	0.914	0.992	0.831	0.833	0.937	0.806	0.747	4.611E-02
Q8BZ20	**Parp12**	79.92	2.0	1	1	1	1.139	1.150	1.255	1.022	0.853	0.926	0.671	0.971	0.749	1.260E-02
Q80SU7	**Gvin1**	280.81	5.9	14	14	14	1.168	1.235	1.137	1.117	0.768	0.813	0.964	0.947	0.750	1.848E-03
P28063	**Psmb8**	30.26	8.0	2	2	2	1.244	1.277	0.958	1.062	0.842	0.820	0.876	0.893	0.756	1.159E-02
Q8VCK3	**Tubg2**	51.12	4.4	2	2	2	1.018	1.128	1.177	1.199	0.934	0.951	0.765	0.784	0.759	5.105E-03
P97372	**Psme2**	27.06	28.9	6	9	6	1.168	1.201	1.047	1.090	0.824	0.824	0.886	0.933	0.769	1.063E-03
Q60710	**Samhd1**	75.89	13.8	8	11	8	1.189	1.167	1.070	1.094	0.843	0.848	0.887	0.908	0.771	2.105E-04
P63078	**Gng8**	7.84	17.1	1	1	1	1.144	1.202	1.081	1.098	0.867	0.698	0.970	0.963	0.773	9.775E-03
Q9CYZ8	**Ssbp2**	37.85	3.6	1	1	1	1.135	0.997	1.076	1.273	0.858	0.946	0.799	0.897	0.781	9.907E-03
Q60590	**Orm1**	23.90	7.7	2	2	2	1.257	1.211	0.947	1.075	0.791	0.774	0.992	0.965	0.784	3.657E-02
Q9ER38	**Tor3a**	43.81	3.1	1	1	1	1.075	1.110	1.196	1.110	0.877	0.828	0.981	0.840	0.785	1.414E-03
Q9Z0E6	**Gbp2**	66.74	15.4	7	8	7	1.210	1.161	1.012	1.048	0.821	0.818	0.855	1.000	0.789	1.014E-02
O70228	**Atp9a**	118.61	1.1	1	1	1	1.084	1.121	1.123	1.150	0.864	0.827	0.983	0.858	0.789	6.791E-04
Q99388	**Csprs**	24.06	4.8	1	1	1	1.109	1.073	1.150	1.138	0.921	0.843	0.781	0.986	0.790	2.721E-03
Q61555	**Fbn2**	313.82	1.3	4	5	1	1.236	1.061	1.113	1.094	0.769	0.731	1.108	0.952	0.790	4.791E-02
Q3UYH7	**Adrbk2**	79.66	1.7	1	1	1	1.047	1.167	1.173	1.067	0.890	0.903	0.894	0.849	0.794	6.033E-04
P17918	**Pcna**	28.79	17.2	3	3	3	1.026	1.306	1.011	1.082	0.878	0.894	0.823	0.942	0.799	2.227E-02
Q8BVK9	**Sp110**	50.14	2.0	1	1	1	1.226	0.874	1.254	1.102	0.918	0.875	0.909	0.876	0.803	4.557E-02
Q3U5Q7	**Cmpk2**	50.04	27.1	9	14	9	1.072	1.123	1.092	1.061	0.876	0.879	0.839	0.904	0.805	3.137E-05

P83882	**Rpl36a**	12.44	17.0	2	2	2	1.050	1.134	1.210	1.031	0.824	1.034	0.737	0.966	0.805	3.379E-02
Q61581	**Igfbp7**	28.97	8.5	2	2	2	1.175	0.936	1.144	1.158	0.996	0.975	0.838	0.751	0.807	3.851E-02
Q61704	**Itih3**	99.36	2.1	2	2	2	1.255	1.078	1.049	1.045	0.900	0.864	0.894	0.914	0.807	5.773E-03
Q9CPQ8	**Atp5mg**	11.42	19.4	2	10	2	1.061	1.007	1.211	1.212	0.891	0.883	0.929	0.929	0.809	7.200E-03
Q61233	**Lcp1**	70.15	27.3	14	18	12	1.130	1.159	1.054	1.056	0.906	0.879	0.886	0.894	0.810	2.543E-04
Q8K3K8	**Optn**	67.02	3.4	2	6	2	1.128	1.030	1.194	1.079	0.901	0.850	0.915	0.928	0.811	1.712E-03
Q9CY57	**Chtop**	26.59	5.2	1	2	1	1.044	1.113	1.186	1.080	0.840	0.894	0.918	0.943	0.813	1.464E-03
Q62351	**Tfrc**	85.73	15.9	12	18	12	1.127	1.085	1.117	1.090	0.910	0.903	0.875	0.913	0.815	5.003E-06
P11087	**Col1a1**	138.03	9.2	12	18	12	1.133	1.162	1.062	1.034	0.798	0.768	1.030	0.984	0.815	3.069E-02
Q8CD91	**Smoc2**	49.89	2.5	1	1	1	1.064	0.973	1.218	1.163	0.867	0.908	0.858	0.974	0.816	1.517E-02
Q9QZZ6	**Dpt**	24.00	23.9	5	6	5	1.139	1.111	1.087	1.061	0.853	0.887	0.914	0.958	0.821	3.969E-04
P32921	**Wars**	54.36	21.4	8	13	8	1.123	1.137	1.066	1.097	0.851	0.834	1.009	0.945	0.823	4.300E-03
Q9EQH2	**Erap1**	106.60	13.8	13	17	13	1.081	1.105	1.049	1.091	0.917	0.918	0.850	0.884	0.825	8.060E-05
O88307	**Sorl1**	247.08	1.0	2	2	2	1.113	1.122	1.190	0.951	0.893	0.970	0.898	0.861	0.828	1.473E-02
P55821	**Stmn2**	20.83	10.6	2	2	1	1.089	1.181	1.064	1.027	1.029	0.829	0.864	0.894	0.829	1.438E-02
Q9D6N5	**Drap1**	22.28	3.9	1	1	1	1.011	0.875	0.834	0.902	1.100	1.160	1.057	1.077	1.213	4.599E-03
Q02013	**Aqp1**	28.79	14.5	3	7	3	0.915	0.882	0.911	0.902	1.120	1.126	1.089	1.047	1.214	6.185E-05
Q8CBE3	**Wdr37**	55.05	10.9	5	6	5	1.030	0.913	0.787	0.868	1.123	0.990	1.199	1.058	1.215	2.898E-02
B1AUE5	**Pex10**	37.16	6.8	2	2	2	0.882	0.853	0.934	0.965	1.178	0.986	1.108	1.146	1.216	7.114E-03
O88456	**Capns1**	28.46	8.9	3	3	3	0.882	0.956	0.914	0.872	1.068	1.104	1.178	1.067	1.219	8.411E-04
Q99M07	**Coa5**	8.36	20.3	1	1	1	0.984	0.727	0.888	1.010	1.205	1.157	0.997	1.044	1.220	4.817E-02
Q8C0Z1	**Fam234a**	60.58	3.4	2	2	2	0.907	0.904	0.890	0.914	1.228	1.011	1.126	1.049	1.221	6.030E-03
P50543	**S100a11**	11.08	20.4	2	3	2	0.923	0.942	0.843	0.888	1.177	1.187	0.984	1.043	1.221	1.089E-02
P09528	**Fth1**	21.07	45.6	6	18	6	0.977	0.858	0.873	0.902	1.079	1.024	1.149	1.165	1.224	2.991E-03
Q9CQF4	**Mtres1**	27.85	12.1	3	5	3	0.873	0.926	0.915	0.923	1.025	1.172	1.100	1.165	1.227	1.298E-03

P15864	**H1-2**	21.27	33.0	8	14	2	0.852	0.811	0.972	0.956	1.205	1.206	0.973	1.028	1.229	2.903E-02
Q9EPX2	**Papln**	138.90	6.8	8	8	8	0.904	0.925	0.912	0.834	1.230	1.152	1.060	0.963	1.232	1.467E-02
Q91WJ7	**Spats2l**	61.67	1.8	1	1	1	0.910	0.901	0.928	0.855	1.078	1.149	1.132	1.086	1.237	9.641E-05
Q80ZM8	**Crls1**	32.50	6.6	1	1	1	0.843	0.950	0.942	0.878	0.930	1.063	1.307	1.180	1.240	4.278E-02
P02798	**Mt2**	6.12	32.8	2	3	1	0.808	0.865	1.007	0.922	1.039	1.051	1.170	1.222	1.244	1.194E-02
O08759	**Ube3a**	99.82	11.4	9	11	9	0.859	0.865	0.873	0.982	1.198	1.093	0.980	1.183	1.244	9.320E-03
Q9D0R4	**Ddx56**	61.21	3.5	2	2	2	0.903	0.886	0.859	0.920	1.063	1.172	1.009	1.219	1.251	4.226E-03
D3Z1D3	**CEFIP**	154.48	1.7	3	3	3	0.850	0.997	0.968	0.748	1.104	1.188	1.066	1.105	1.253	1.156E-02
P53351	**Plk2**	77.81	1.6	1	1	1	0.878	0.960	0.926	0.804	1.111	1.069	1.180	1.124	1.257	1.372E-03
Q9Z319	**Corin**	123.00	1.3	2	2	2	0.822	0.810	1.047	0.875	1.064	1.239	1.131	1.063	1.265	1.387E-02
Q8K212	**Pacs1**	104.83	8.7	6	8	6	0.845	0.838	0.888	0.917	1.253	1.007	1.066	1.099	1.269	5.649E-03
Q923Z3	**Mto1**	74.33	7.3	4	4	4	0.849	0.926	0.785	0.968	1.201	1.090	1.296	0.898	1.271	4.485E-02
P50172	**Hsd11b1**	32.36	8.2	3	3	3	0.912	0.986	0.838	0.799	0.976	1.172	1.216	1.153	1.278	1.055E-02
Q923D3	**Parm1**	30.67	3.0	1	1	1	0.958	0.899	0.831	0.815	1.228	1.205	1.143	0.915	1.282	2.015E-02
Q8BI72	**Cdkn2aip**	59.74	4.1	2	2	2	1.131	0.814	0.847	0.743	1.110	1.026	1.172	1.238	1.286	3.956E-02
Q9QZ49	**Ubxn8**	31.56	2.9	1	2	1	0.978	0.988	0.793	0.723	1.160	1.325	1.022	0.981	1.289	4.927E-02
Q61235	**Sntb2**	56.38	5.8	3	3	3	0.774	0.877	0.985	0.886	1.110	1.095	1.157	1.184	1.291	1.733E-03
Q8CBC4	**Cnst**	76.87	3.0	2	2	2	0.907	0.847	0.927	0.809	1.178	1.175	1.096	1.095	1.302	3.238E-04
Q61585	**G0s2**	11.12	7.8	1	2	1	0.867	0.891	0.820	0.916	1.079	1.144	1.148	1.180	1.303	1.068E-04
Q3V3A7	**Rnf207**	70.76	4.9	3	3	3	0.826	0.927	0.945	0.792	1.057	1.208	1.205	1.089	1.306	2.620E-03
Q8JZL7	**Rasgef1b**	55.27	2.1	1	1	1	0.910	0.974	0.833	0.773	1.122	1.014	1.366	1.077	1.312	2.192E-02
P58308	**Hcrtr2**	52.46	3.5	1	2	1	0.956	0.860	0.784	0.840	1.275	1.273	0.999	0.984	1.317	2.221E-02
Q9D938	**Tmem160**	19.59	6.9	1	1	1	0.955	0.923	0.747	0.847	1.121	1.062	1.269	1.126	1.319	4.916E-03
Q91ZP3	**Lpin1**	102.00	6.8	4	4	4	0.737	0.982	0.878	0.864	1.083	1.054	1.347	1.101	1.325	1.567E-02
Q8VE37	**Rcc1**	44.93	4.5	2	2	2	0.755	0.935	0.872	0.901	1.127	0.921	1.189	1.398	1.338	3.232E-02

Q9DBG7	**Srpra**	69.62	7.2	4	4	4	0.828	0.958	0.754	0.896	0.923	1.042	1.377	1.328	1.359	4.041E-02
Q3THF9	**Coq10b**	27.27	4.2	1	1	1	0.852	0.826	1.019	0.715	1.154	1.221	1.273	1.000	1.362	1.165E-02
Q91VS7	**Mgst1**	17.55	8.4	1	3	1	0.870	0.979	0.776	0.779	1.130	1.094	1.194	1.229	1.365	1.557E-03
P61014	**Pln**	6.09	23.1	2	6	2	0.920	0.944	0.775	0.742	1.106	1.064	1.233	1.229	1.370	3.327E-03
A6BLY7	**Krt28**	50.35	5.2	3	3	1	0.914	0.843	0.789	0.794	0.986	0.891	1.331	1.370	1.371	4.704E-02
Q91WD2	**Trpv6**	87.39	1.6	1	1	1	0.824	0.813	0.873	0.911	0.990	1.073	1.321	1.310	1.372	1.048E-02
Q3U276	**Sdhaf1**	13.14	6.8	1	1	1	0.960	0.877	0.763	0.793	1.212	1.068	1.077	1.299	1.372	4.421E-03
Q9CQ86	**Mien1**	12.30	7.8	1	1	1	0.897	0.851	0.812	0.819	1.220	1.183	1.209	1.036	1.376	5.096E-04
Q91V09	**Wdr13**	53.66	4.7	2	2	2	0.931	0.897	0.725	0.819	1.205	1.177	1.120	1.143	1.378	6.664E-04
Q8R4S0	**Ppp1r14c**	17.75	22.6	2	3	2	0.869	0.786	0.829	0.894	1.117	1.492	1.141	0.904	1.378	4.224E-02
P35505	**Fah**	46.18	16.0	6	8	6	0.885	0.898	0.783	0.841	1.120	1.128	1.232	1.216	1.378	1.698E-04
Q9Z2A9	**Ggt5**	61.67	5.4	4	5	4	0.802	0.771	0.864	0.936	1.381	1.050	1.078	1.150	1.381	8.449E-03
Q8VC19	**Alas1**	71.02	6.4	4	4	4	0.791	0.949	0.760	0.848	1.144	1.331	1.091	1.077	1.387	4.063E-03
P35969	**Flt1**	149.87	0.8	1	1	1	0.955	0.958	0.754	0.687	1.149	1.248	1.222	1.047	1.391	7.437E-03
Q9JIF9	**Myot**	55.32	31.7	14	19	14	0.809	0.843	0.862	0.829	1.226	1.237	1.103	1.096	1.395	1.675E-04
Q6P5D8	**Smchd1**	225.65	1.5	3	3	3	0.804	0.989	0.783	0.761	1.316	1.136	1.086	1.128	1.398	3.908E-03
P59672	**Anks1a**	125.24	3.7	3	4	3	0.685	0.776	0.875	1.001	1.316	1.168	1.120	1.081	1.404	7.445E-03
Q9QYI5	**Dnajb2**	35.59	15.7	5	7	4	0.900	0.765	0.722	0.944	1.372	0.957	1.254	1.137	1.417	1.511E-02
Q3UV17	**Krt76**	62.84	4.2	3	2	1	0.750	0.662	0.813	0.807	1.099	1.106	1.478	1.447	1.692	3.080E-03

Supplemental Table 3. Key Reagents

REAGENT	SOURCE	IDENTIFIER
Antibodies		
Anti-mouse PD-1	BioXcell	Cat#BE0273, RRID:AB_2687796
Anti-mouse Ctla4	BioXcell	Cat #BE0164, RRID:AB_10949609
Anti-normal IgG	BioXcell	Cat#BE0083, RRID:AB_110778
Anti-GSDME	Abcam	Cat#ab215191, RRID:AB_2737000
Anti-GSDME-N terminal	Abcam	Cat#ab222407, RRID:AB_2923216
Anti-GSDMD	Abcam	Cat#ab209845, RRID:AB_2783550
Anti-Caspase-1	Abcam	Cat#ab179515, RRID:AB_2884954
Anti-Caspase-3	Santa Cruz Biotechnolog	Cat#sc-373730, RRID:AB_10918110
Anti-Caspase-8	Cell signaling technology	Cat#4927, RRID: AB_2068301
Anti-Caspase-9	Abcam	Cat#ab202068, RRID: AB_2889070
Anti-Caspase-11	Abcam	Cat#ab180673, RRID:AB_2923217
Anti-Nos2	Cell signaling technology	Cat #13120, RRID:AB_2687529
Anti-IL-1β	Santa Cruz Biotechnology	Cat#sc-52012, RRID:AB_629741
Anti-cGAS	Cell signaling technology	Cat#31659, RRID:AB_2799008
Anti-STING	Cell signaling technology	Cat#13647, RRID:AB_2732796
Anti-IRF3	Cell signaling technology	Cat#4302, RRID:AB_1904036
Anti-p-IRF3	Cell signaling technology	Cat#29047, RRID:AB_2773013
Anti-TBK1	Cell signaling technology	Cat#38066, RRID:AB_2827657
Anti-p-TBK1	Cell signaling technology	Cat#5483, RRID:AB_10693472
Anti-β-Tubulin	Cell signaling technology	Cat#2128, RRID:AB_823664
Anti-CD3	Abcam	Cat#ab16669, RRID:AB_443425
Anti-CD4	Abcam	Cat#ab183685, RRID:AB_2686917
Anti-CD8	Abcam	Cat#ab217344, RRID:AB_2890649
Anti-CD68	Cell signaling technology	Cat#97778, RRID:AB_2928056
Anti-IFN-γ	Thermo Fisher Scientific	Cat#14-7311-81, RRID:AB_468467
Anti-Myh6	Thermo Fisher Scientific	Cat# MA5-27819, RRID:AB_2735280
Anti-IFN-γ-FITC	BioLegend	Cat#505806, RRID:AB_315400

Anti-STING	Novus	Cat#NBP2-24683, RRID: AB_2868483
Anti-MPO-FITC	Thermo Fisher Scientific	Cat#11-1299-42, RRID:AB_10596801
Anti-CXCR2-APC	BioLegend	Cat#149312, RRID:AB_2728185
Anti-CD68-APC	BioLegend	Cat#137008, RRID:AB_10575300
Anti-CD45-PerCP/Cyanine5.5	BioLegend	Cat#103132, RRID:AB_893340
Anti-CD3-FITC	BioLegend	Cat#100204, RRID:AB_312661
Anti-CD4-AF700	BioLegend	Cat#116022, RRID:AB_2715958
Anti-IFN-γ-BV650	BioLegend	Cat#505832, RRID:AB_2734492
Anti-IL-4-BV421	BioLegend	Cat#504119, RRID:AB_10896945
Anti-IL-17A-BV605	BD Biosciences	Cat#564169, RRID:AB_2738640
Anti-CD11b-APC/Fire750	BioLegend	Cat#101261, RRID:AB_2572121
Anti-CD8a-APC/Cyanine7	BioLegend	Cat#100714, RRID:AB_312753
Anti-CD62L-PE/Cyanine7	BioLegend	Cat#104418, RRID:AB_313103
Anti-CD44-PE/Dazzle™ 594	BioLegend	Cat#103056, RRID:AB_2564044
Anti-TCR γ/δ- PE	BioLegend	Cat#118108, RRID:AB_313832
Anti-CD45-BV605	BioLegend	Cat#103139, RRID:AB_2562341
Anti-CD3-APC	BioLegend	Cat#100236, RRID:AB_2561456
Anti-CD11B-BB515	BD Biosciences	Cat#564454, RRID:AB_2665392
Anti-LY6G-BV421	BD Biosciences	Cat#562737, RRID:AB_2737756
Anti-F4/80-APC-R700	BD Biosciences	Cat#565787, RRID:AB_2869711
Anti-CCR2-BV650	BioLegend	Cat#150613, RRID:AB_2721553
Anti-MHC-II-APC/Fire750	BioLegend	Cat#107651, RRID:AB_2616728
Anti-Ly6C-PE	BioLegend	Cat#128007, RRID:AB_1186133
Anti-CD64- PE/Cyanine7	BioLegend	Cat#139314, RRID: AB_2563904
IRDye 800CW Goat anti-Mouse IgG antibody	LI-COR	Cat#926-32210, RRID:AB_621842
IRDye 800CW Goat anti-Rabbit IgG antibody	LI-COR	Cat#925-32211, RRID:AB_2651127
Alexa Fluor 488-conjugated goat anti-rabbit IgG	Thermo Fisher Scientific	Cat#A-11034, RRID:AB_2576217
Alexa Fluor 568-conjugated goat anti-mouse IgG	Thermo Fisher Scientific	Cat#A-21134, RRID:AB_2535773
Biological Samples		
Serum samples cancer patients treated with ICI	Shanghai Changzheng Hospital	Approval number: 2017SL016
Serum samples cancer patients treated with ICI	Shanghai Tenth People's Hospital	Approval number: 2019-K-032
Chemicals, Peptides, and Recombinant Proteins		

TRIzol	Thermo Fisher Scientific	15596026
WGA	Thermo Fisher Scientific	W11261
DAPI	Thermo Fisher Scientific	D1306
PI	Sigma	25535-16-4
MitoSOX	Thermo Fisher Scientific	M36008
Normal Goat Serum	Thermo Fisher Scientific	31872
Sirius Red	Sigma-Aldrich	365548
Prestained Protein Marker	GeneTex	GTX50875
Collagenase II	Worthington	LS004176
RBC lysis buffer	eBiosciences	00-4333-57
DNase I	Sigma	10104159001
DMF	Sigma	242926
Protease and phosphatase inhibitors	Sigma	PPC1010
DL1000 DNA ladder	Takara Bio	3591A
DL2000 DNA ladder	Takara Bio	3427A
PrimeScript™ RT Master Mix	Takara Bio	RR036A
TB Green® Premix Ex Taq™ II	Takara Bio	RR820Q
TransScript ® First-Strand cDNA Synthesis SuperMix	TransGen Biotech	AT301-02
Critical Commercial Assays		
Human/Mouse GSDME ELISA Kit	Adipogen Life Sciences	AG-45B-0024-KI01
Mouse IL-1β ELISA kit	R&D systems	MLB00C
Mouse IL-18 ELISA Kit	R&D systems	7625
Mouse IL-6 ELISA Kit	R&D systems	M6000B
Mouse cTnT ELISA Kit	Sangon Biotech	D721161-0096
Mouse cTnI ELISA Kit	Sangon Biotech	D721149-0096
Mouse CK-MB ELISA Kit	Sangon Biotech	D721065-0096
Mouse Caspase1 ELISA Kit	Beyotime Biotechnology	C1102
Mouse Caspase3 ELISA Kit	Beyotime Biotechnology	C1116
Mouse Caspase8 ELISA Kit	Beyotime Biotechnology	C1152
Mouse Caspase9 ELISA Kit	Beyotime Biotechnology	C1158
Mitochondria isolation Kit	Sigma-Aldrich	MITOISO1

In situ Cell Death Detection Kit,Fluorescein	Merck	11684795910
Mitochondrial complex I ELISA kit	Abcam	ab287847
NAD^+ Assay Kit	Abcam	ab65348
Mitochondrial complex IV ELISA kit	Solarbio	BC0945
ATP assay kit	Solarbio	BC0300
GSH assay kit	Solarbio	BC1175
BCA protein assay kit	Beyotime Biotechnology	P0011
Tandem Mass Tag Multiplexed Labelling System	Thermo Fisher Scientific	N/A
Quant-iT PicoGreen dsDNA Kits	Thermo Fisher Scientific	P11495
Deposited Data		
Tandem Mass Tag Multiplexed quantitative proteomics	iProx database	IPX0004084000
Experimental Models: Organisms/Strains		
Mouse: *Lysm*-Cre: B6.129P2-*Lyz2*$^{tm1(cre)Ifo/}$J	The Jackson Laboratory	JAX stock 004781
Mouse: *Myh6-Cre*: B6.FVB-Tg$^{Myh6\text{-}(cre)2182Mds/}$J	The Jackson Laboratory	JAX stock 011038
Mouse: *Sting*$^{gt/gt}$: C57BL/6J-*Sting1*$^{gt/}$J	The Jackson Laboratory	JAX stock 017537
Mouse: *Gsdme*$^{stop/stop}$	This study	N/A
Mouse: *Gsdme*$^{-/-}$	This study	N/A
Experimental Models: Cell Lines		

Cell: MC38 mouse colon adenocarcinoma cells	Kerafast	N/A
Oligonucleotides		
Primers for mouse *Caspase-1* Forward	This study	AGGCACGGGACCTATGTGAT
Primers for mouse *Caspase-1* Reverse	This study	AGGGCAAAACTTGAGGGTCC
Primers for mouse *Caspase-3* Forward	This study	GAGCTTGGAACGGTACGCTA
Primers for mouse *Caspase-3* Reverse	This study	CCGTACCAGAGCGAGATGAC
Primers for mouse *Caspase-8* Forward	This study	TTCGGAGGCATTTCTGTCCC
Primers for mouse *Caspase-8* Reverse	This study	CGGCTCACAGAGGTTTGCTA
Primers for mouse *Caspase-9* Forward	This study	ACCTTCCCAGGTTGCCAATG
Primers for mouse *Caspase-9* Reverse	This study	GCTGCTAGGAGCATGTTTGC
Primers for mouse *Caspase-11* Forward	This study	GGCTACGATGTGGTGGTGAA
Primers for mouse *Caspase-11* Reverse	This study	AGGCCTGCACAATGATGACT
Primers for mouse *Gsdma* Forward	This study	GCACCCACTAAGCCCATCTC
Primers for mouse *Gsdma* Reverse	This study	CACACATGGGAAGGATCAGACT
Primers for mouse *Gsdmc* Forward	This study	TCGGACCTGCTAAAAGGAAGG
Primers for mouse *Gsdmc* Reverse	This study	AGCCAACCGGGAAGAAGTTT
Primers for mouse *Gsdmd* Forward	This study	GATCAAGGAGGTAAGCGGCA
Primers for mouse *Gsdmd* Reverse	This study	CACTCCGGTTCTGGTTCTGG
Primers for mouse *Gsdme* Forward	This study	GGTGGGATACAGGATACAAGGA
Primers for mouse *Gsdme* Reverse	This study	GCAGCACAGCGAAGAAATAAC
Primers for mouse *Tnnt2* Forward	This study	GTGTGCAGTCCCTGTTCAGA
Primers for mouse *Tnnt2* Reverse	This study	GCTTGGGTTTGGTGTCCTCT
Primers for mouse *Tnni3* Forward	This study	TGTCCTCGCCCCTTATCTCA

Primers for mouse *Tnni3* Reverse	This study	GGTTCCCCAGCCGCATC
Primers for mouse *Icam1* Forward	This study	TTCTCATGCCGCACAGAACT
Primers for mouse *Icam1* Reverse	This study	TCCTGGCCTCGGAGACATTA
Primers for mouse *Vav2* Forward	This study	ACAGAGCAAAGGGATCAGGC
Primers for mouse *Vav2* Reverse	This study	CCCATTTTCATGGGCTGCTG
Primers for mouse *Sell* Forward	This study	GACATGGGTGGGAACCAACA
Primers for mouse *Sell* Reverse	This study	CACTGGACCACTGTGTAGCA
Primers for mouse *Myh6* Forward	This study	ATAAAGGGGCTGGAGCACTG
Primers for mouse *Myh6* Reverse	This study	GCCTCTAGGCGTTCCTTCTC
Primers for mouse *Ptprc* Forward	This study	GGCGCATCAGAAGGGGATAA
Primers for mouse *Ptprc* Reverse	This study	GCTGTTGCAAATGTGCTGCT
Primers for mouse *Cxcl1* Forward	This study	ACTCAAGAATGGTCGCGAGG
Primers for mouse *Cxcl1* Reverse	This study	GTGCCATCAGAGCAGTCTGT
Primers for mouse *Ccr2* Forward	This study	GCCATCATAAAGGAGCCATACC
Primers for mouse *Ccr2* Reverse	This study	ATGCCGTGGATGAACTGAGG
Primers for mouse *Cxcr2* Forward	This study	CTCTGCTCACAAACAGCGTC
Primers for mouse *Cxcr2* Reverse	This study	TCTCTGAGTGGCATGGGACA
Primers for mouse *α-SMA* Forward	This study	GTACCCAGGCATTGCTGACA
Primers for mouse *α-SMA* Reverse	This study	GCTGGAAGGTAGACAGCGAA
Primers for mouse *mt-Nd1* Forward	This study	CACCCAAGAACAGGGTTTGT
Primers for mouse *mt-Nd1* Reverse	This study	TGGCCATGGGTATGTTGTTAA
Primers for mouse *D-loop* Forward	This study	CTATCACCCTATTAACCACTCA
Primers for mouse *D-loop* Reverse	This study	TTCGCCTGTAATATTGAACGTA

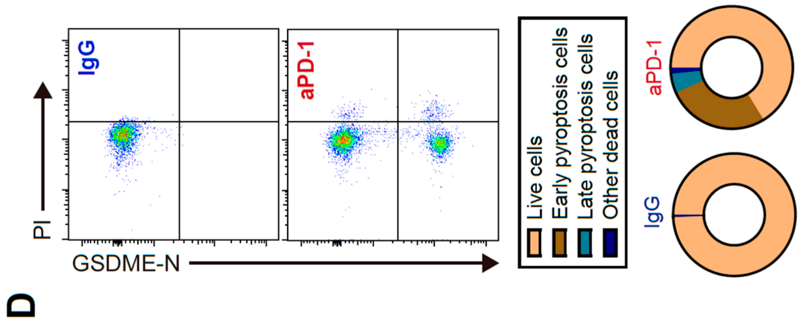
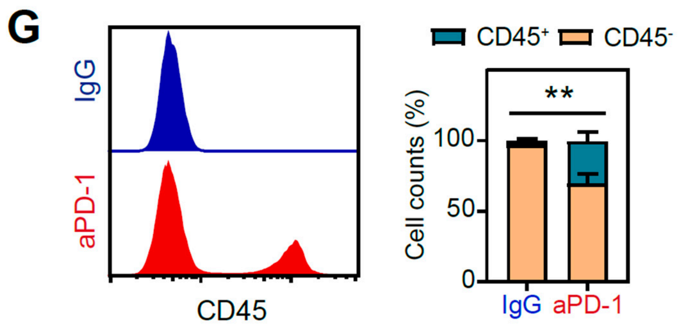
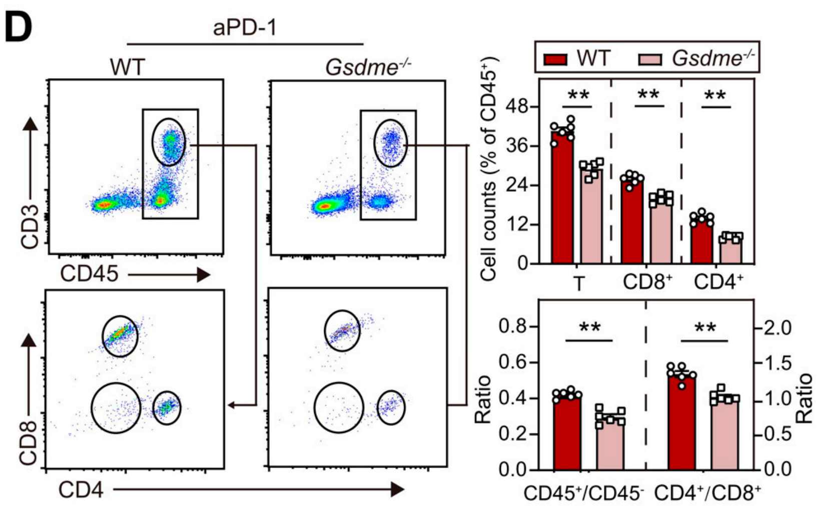
Primers for mouse *18S* Forward	This study	CTACCACATCCAAGGAAGC
Primers for mouse *18S* Reverse	This study	TTTTCGTCACTACCTCCCCG
Primers for mouse *Col1a1* Forward	This study	TTCTCCTGGCAAAGACGGAC
Primers for mouse *Col1a1* Reverse	This study	CTCAAGGTCACGGTCACGAA
Primers for mouse *Col3a1* Forward	This study	GAGGAATGGGTGGCTATCCG
Primers for mouse *Col3a1* Reverse	This study	TCGTCCAGGTCTTCCTGACT
Primers for mouse *Axl* Forward	This study	TTCAACTGTGCTACGTCCCC
Primers for mouse *Axl* Reverse	This study	GGGTCCCTCTAGGTAAGCCA
Primers for mouse *Nos2* Forward	This study	AACAGGGAGAAAGCGCAAAAC
Primers for mouse *Nos2* Reverse	This study	TCCACTGCCCCAGTTTTTGA
Primers for mouse *H2-DMa* Forward	This study	AGGGGGTATATGGAGCACTCT
Primers for mouse *H2-DMa* Reverse	This study	CGCAGCAGGTCTCTCGTTTT
Primers for mouse *GzmB* Forward	This study	GAAGCCAGGAGATGTGTGCT
Primers for mouse *GzmB* Reverse	This study	GCACGTTTGGTCTTTGGGTC
Primers for mouse *Prf1* Forward	This study	TCTTGGTGGGACTTCAGCTT
Primers for mouse *Prf1* Reverse	This study	TGCTTGCATTCTGACCGAGT
Primers for mouse *IFN-γ* Forward	This study	CGGCACAGTCATTGAAAGCC
Primers for mouse *IFN-γ* Reverse	This study	TGCATCCTTTTTCGCCTTGC
Primers for mouse *IL-2* Forward	This study	GCCCCAAGGGCTCAAAAATG
Primers for mouse *IL-2* Reverse	This study	GCGCTTACTTTGTGCTGTCC
Primers for mouse *IL-17A* Forward	This study	GCTGACCCCTAAGAAACCCC
Primers for mouse *IL-17A* Reverse	This study	GAAGCAGTTTGGGACCCCTT
Primers for mouse *IL-6* Forward	This study	ATGAAGTTCCTCTCTGCAAGAGAC
Primers for mouse *IL-6* Reverse	This study	CACTAGGTTTGCCGAGTAGATCTC

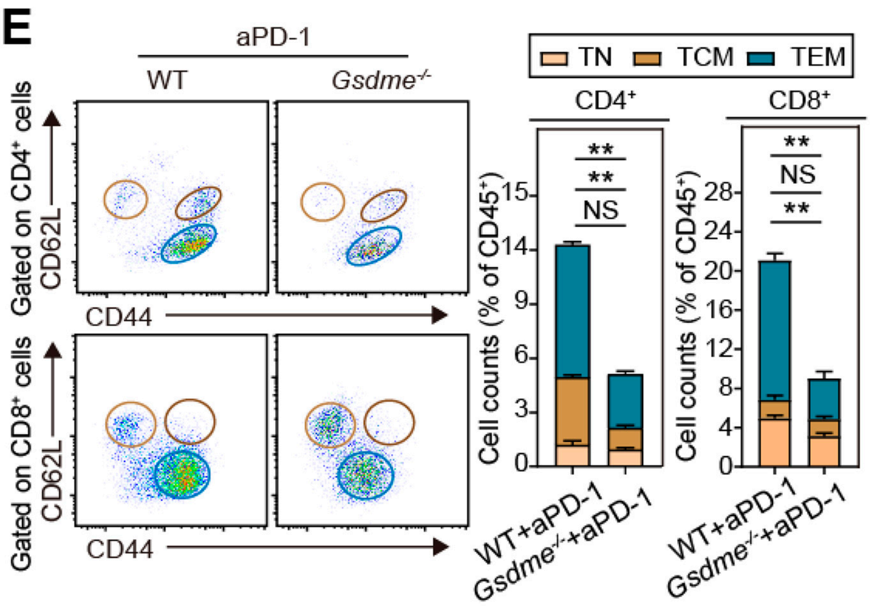
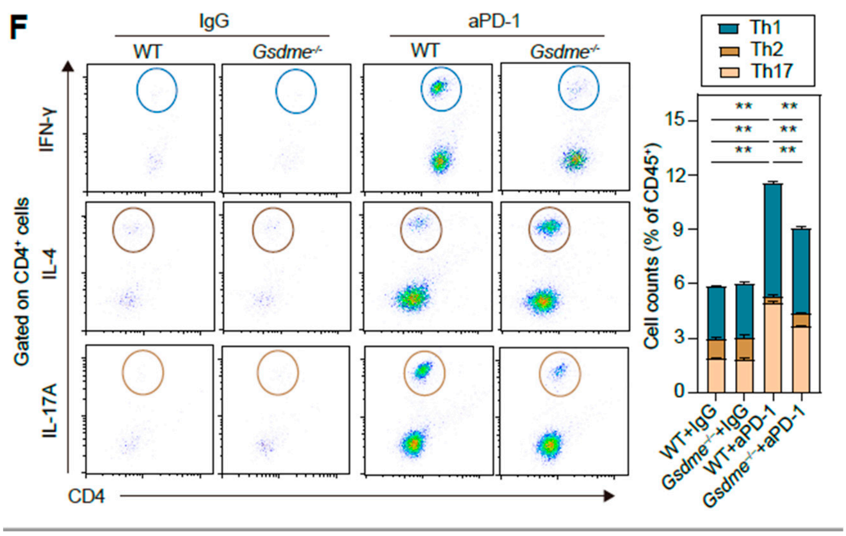
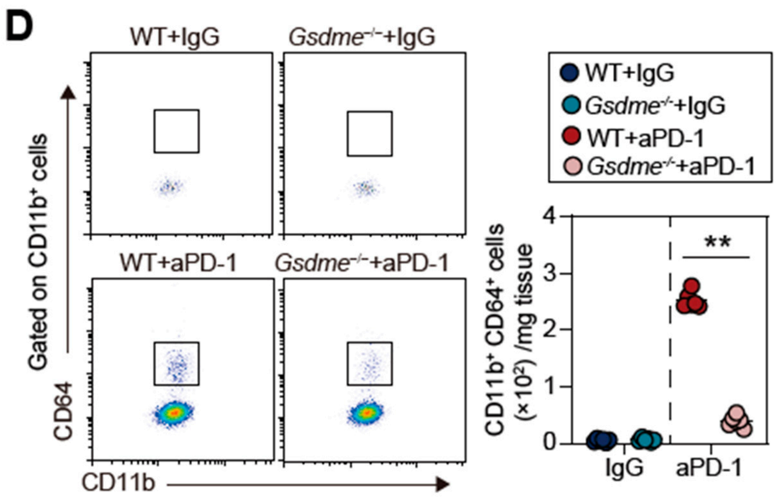
Primers for mouse *IL-18* Forward	This study	GTAAGAGGACTGGCTGTGACCC
Primers for mouse *IL-18* Reverse	This study	CTTTTGGCAAGCAAGAAAGTGT
Primers for mouse *IL-1β* Forward	This study	TGCCACCTTTTGACAGTGATG
Primers for mouse *IL-1β* Reverse	This study	AAGGTCCACGGGAAAGACAC
Primers for mouse *Elane* Forward	This study	CTTCATCCGAGGAGGCTGTG
Primers for mouse *Elane* Reverse	This study	GAGGTCTCTGGTAGAGGGGG
Primers for mouse *Padi4* Forward	This study	CCTACAGGTGAAAGCAGCCA
Primers for mouse *Padi4* Reverse	This study	TCAAAGTCCATTCCGGAGGC
Primers for mouse *IL-4* Forward	This study	CCATATCCACGGATGCGACA
Primers for mouse *IL-4* Reverse	This study	AAGCCCGAAAGAGTCTCTGC
Primers for mouse *IL-10* Forward	This study	GCTCCAAGACCAAGGTGTCT
Primers for mouse *IL-10* Reverse	This study	CGGAGAGAGGTACAAACGAGG
Primers for mouse *Ccr5* Forward	This study	GCAGTTTCGGAGCAGTGTTG
Primers for mouse *Ccr5* Reverse	This study	ACATGTGCACAGAAATCCCAG
Primers for mouse *Il22* Forward	This study	TGCGATCTCTGATGGCTGTC
Primers for mouse *Il22* Reverse	This study	CCTCGGAACAGTTTCTCCCC
Primers for mouse *Tnfa* Forward	This study	AGGCACTCCCCCAAAAGATG
Primers for mouse *Tnfa* Reverse	This study	CCACTTGGTGGTTTGTGAGTG
Primers for mouse *Ccl5* Forward	This study	TGCTCCAATCTTGCAGTCGT
Primers for mouse *Ccl5* Reverse	This study	GCAAGCAATGACAGGGAAGC
Primers for mouse *Gapdh* Forward	This study	CCCATCACCATCTTCCAGGAG
Primers for mouse *Gapdh* Reverse	This study	TTCACCACCTTCTTCTTGATGTCAT
Software and Algorithms		

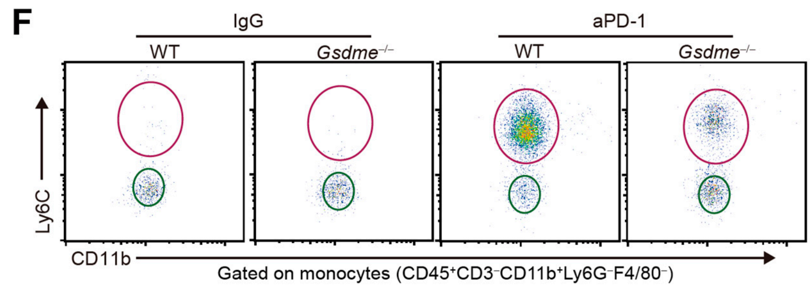
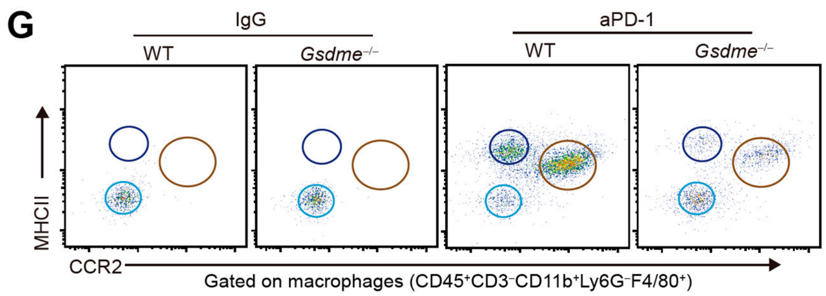
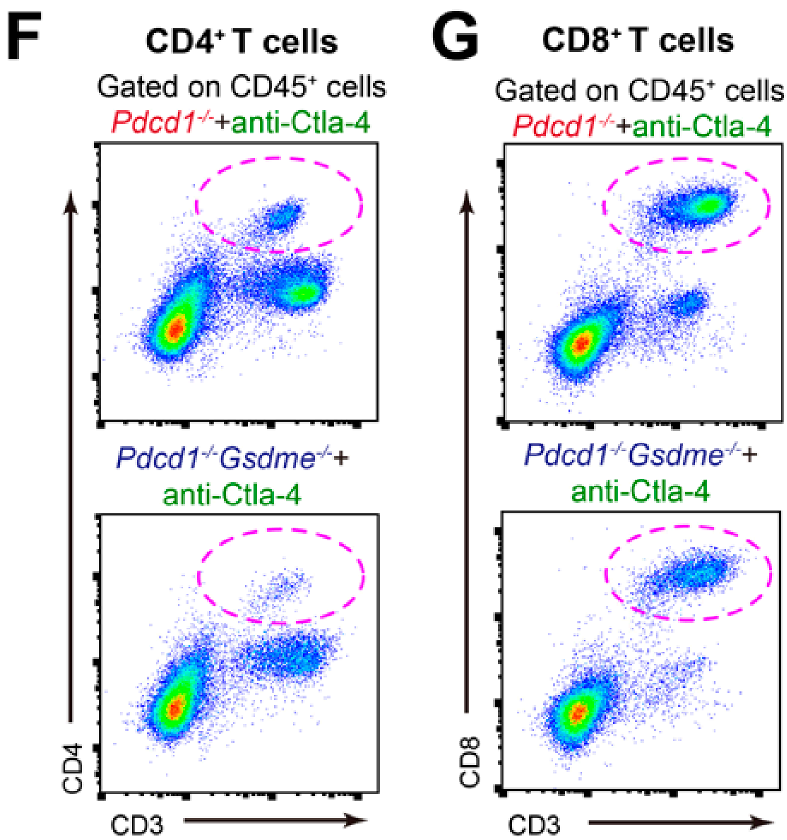
GraphPad Prism version 8	GraphPad software	https://www.graphpad.com/, RRID:SCR_002798
FlowJo v.10	FlowJo, LLC	https://www.flowjo.com/solutions/flowjo, RRID:SCR_008520
Image J	National Institutes of Health	https://imagej.nih.gov/ij/, RRID:SCR_003070
Vevo 2100 v3.1.1	VisualSonics	https://www.visualsonics.com/product/imaging-systems/vevo-2100

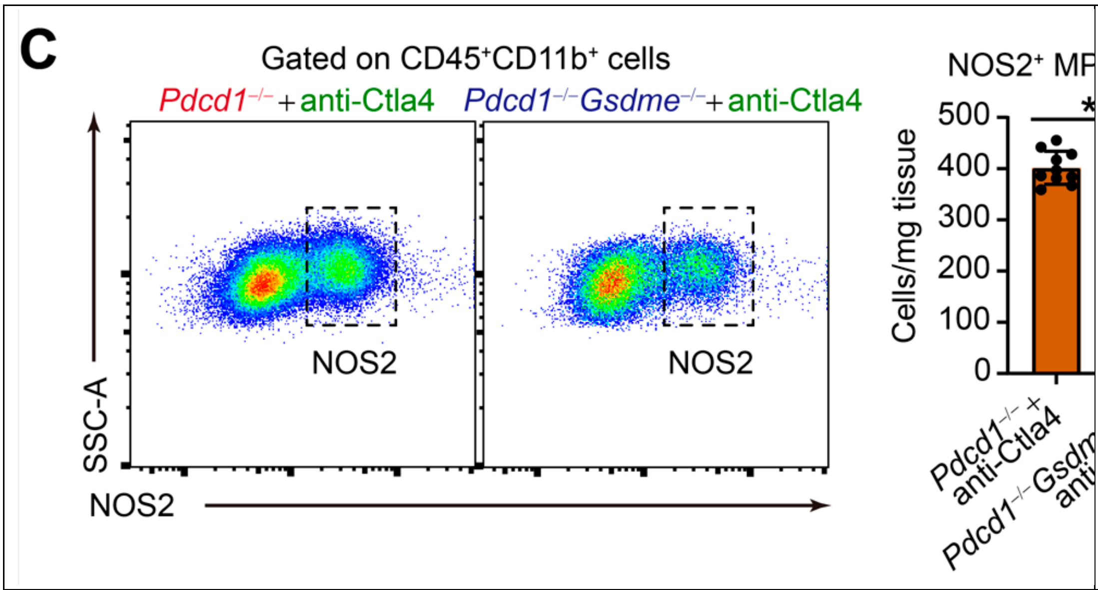
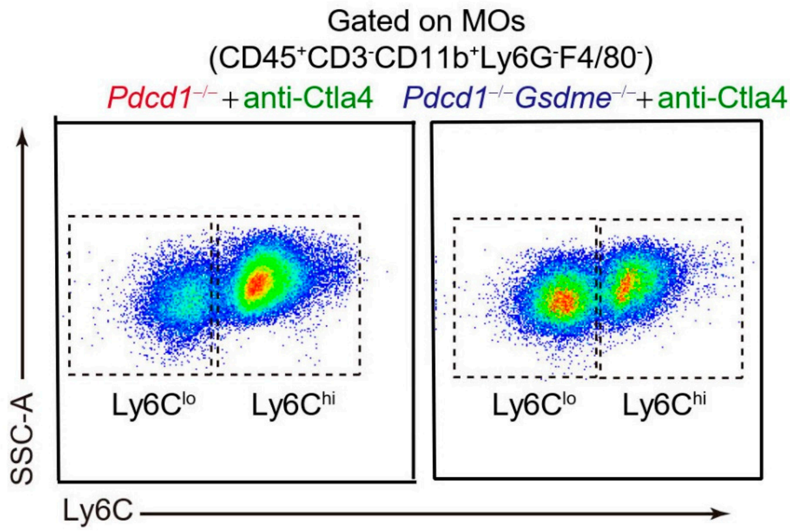
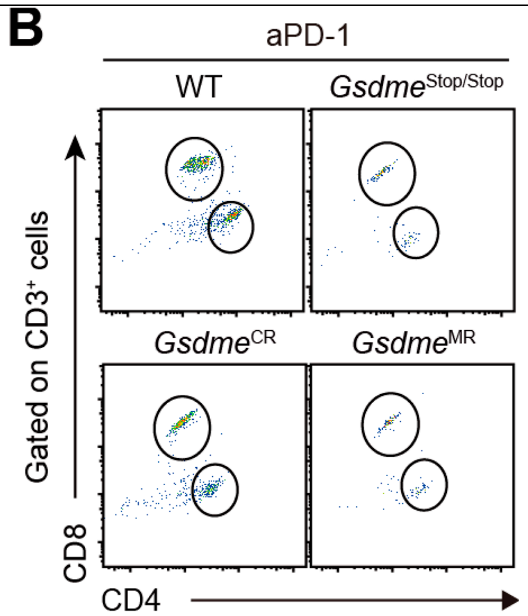
4

Supplemental Table 4. Gating strategy for flow cytometry

Flow cytometry plot in Figures	Gating strategies
	(Figure 1D) Gated on single cells
	(Figure 1G) Gated on single cells
	(Figure 3D) Gated on single cells

	(Figure 3E up) Gated on CD45⁺CD3⁺CD4⁺ cells (Figure 3 E below) Gated on CD45⁺CD3⁺CD8⁺ cells
	(Figure 3F) Gated on CD45⁺ CD4⁺ cells
	(Figure 4D) Gated on CD45⁺CD11b⁺ cells

	(Figure 4F) Gated on $CD45^{+}CD3^{-}$ $CD11b^{+}Ly6G^{-}$ $F4/80^{-}$ cells
	(Figure 4G) Gated on $CD45^{+}CD3^{-}$ $CD11b^{+}Ly6G^{-}$ $F4/80^{+}$ cells
	(Figure 5F and G) Gated on $CD45^{+}$ cells

	(Figure 6C) Gated on CD45⁺CD11b⁺ cells
	(Figure 6D) Gated on CD45⁺Cd3⁻ CD11b⁺Ly6G⁻ F4/80⁻ cells
	(Figure 8B) Gated on CD45⁺CD3⁺ cells

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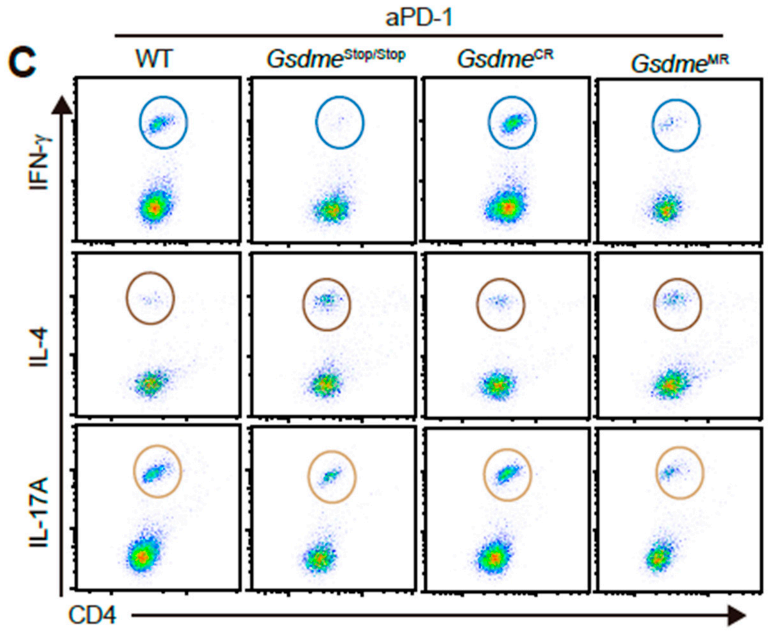
<td>
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<td>(Figure 8C)
Gated on
$CD45^+CD4^+$
cells</td>
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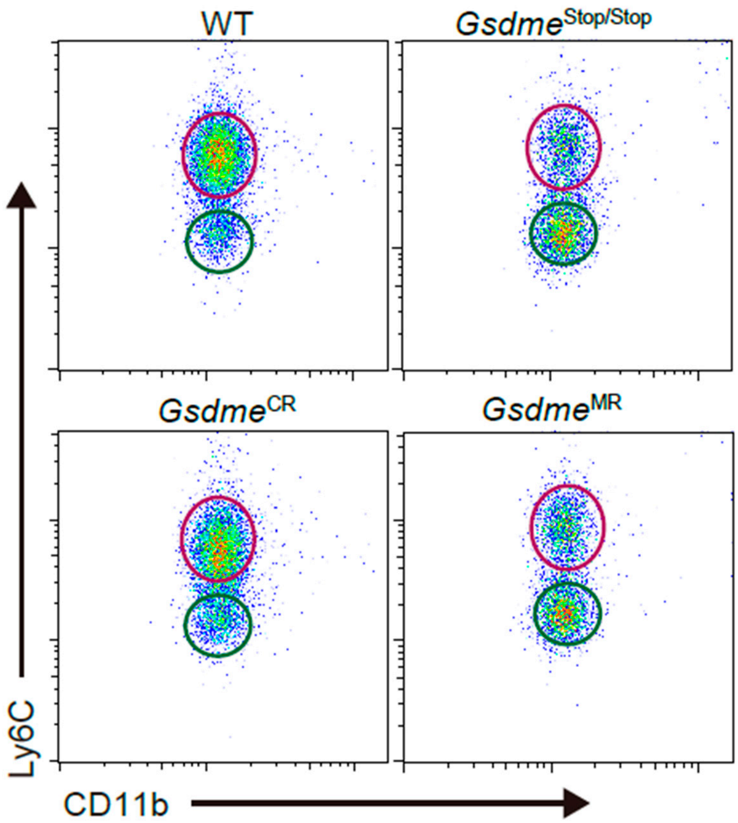
<td>
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<td>(Figure 8F)
Gated on
$CD45^+CD3^-$
$CD11b^+Ly6G^-$
$F4/80^-$ cells</td>
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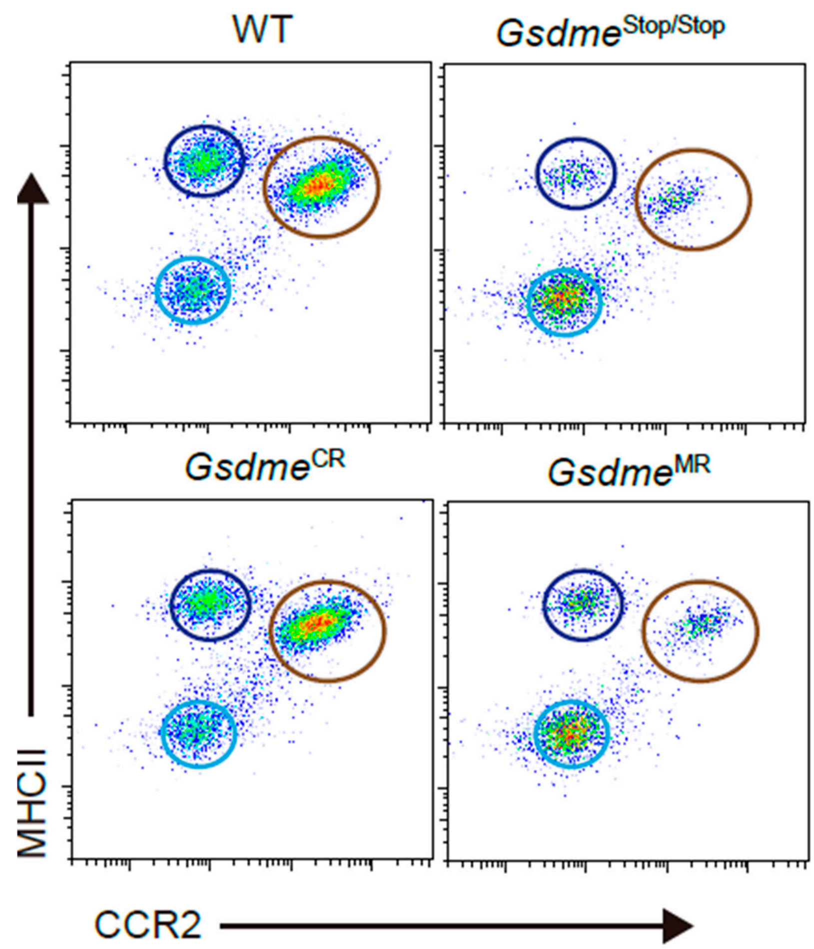
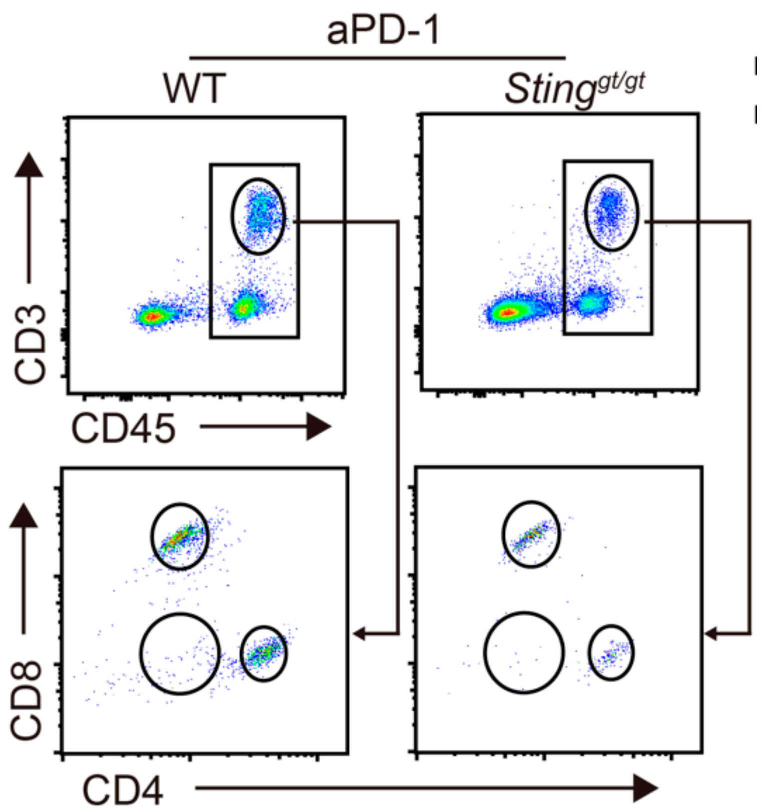
	(Figure 8G) Gated on CD45⁺CD3⁻ CD11b⁺Ly6G⁻ F4/80⁺ cells
M 	(Figure 9M) Gated on single cells

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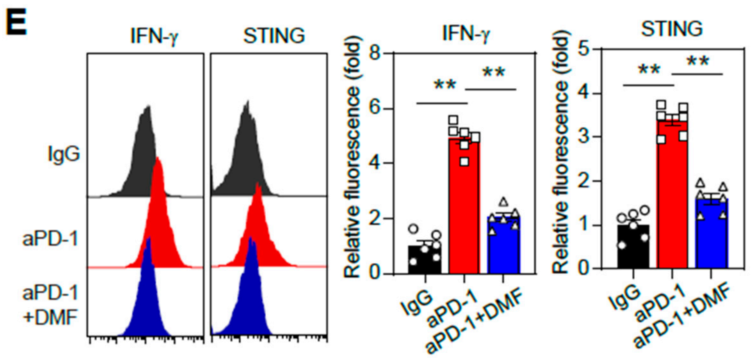
<td>
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<td>(Figure 9E) Gated on single cells</td>
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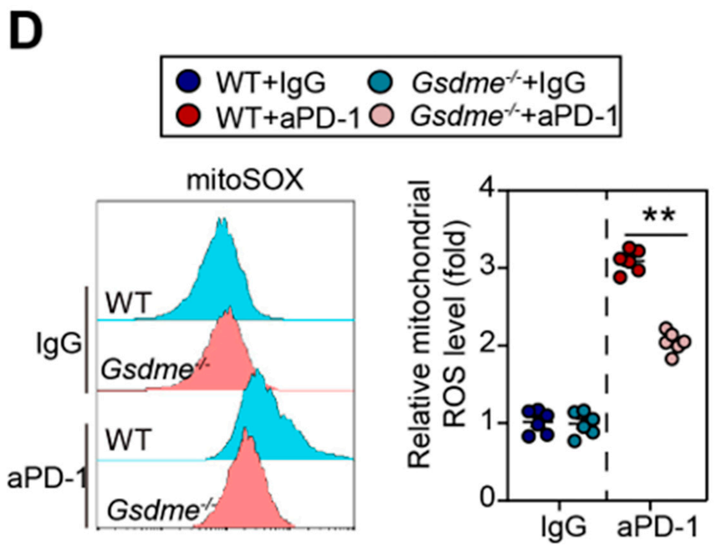
<td>
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<td>(Supplemental Figure 4D) Gated on single cells</td>
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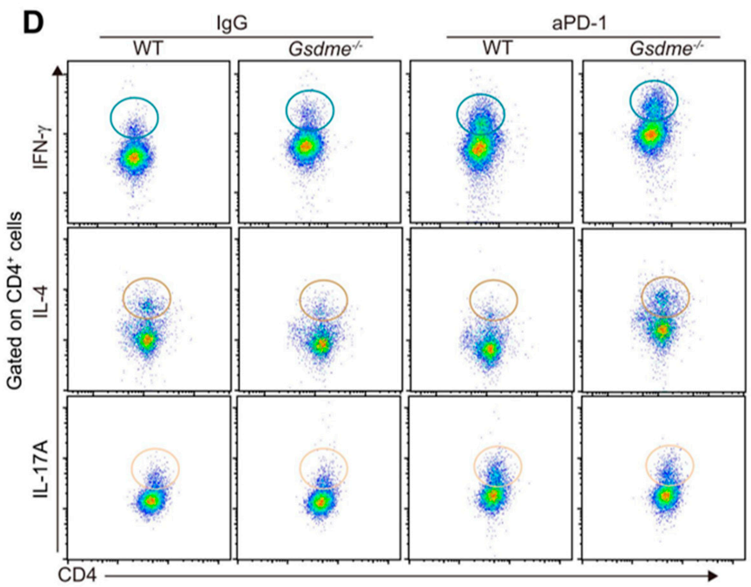
<td>
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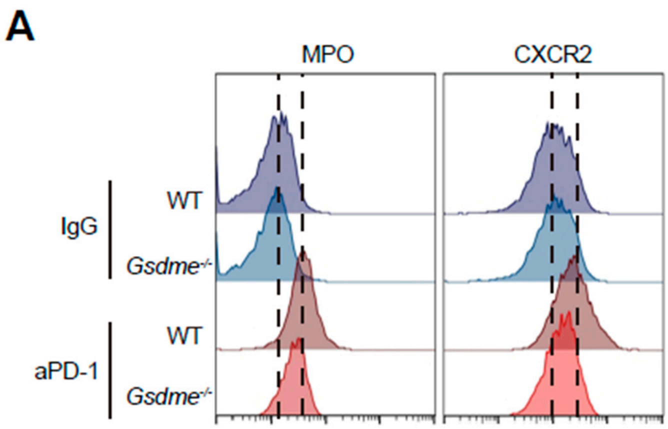
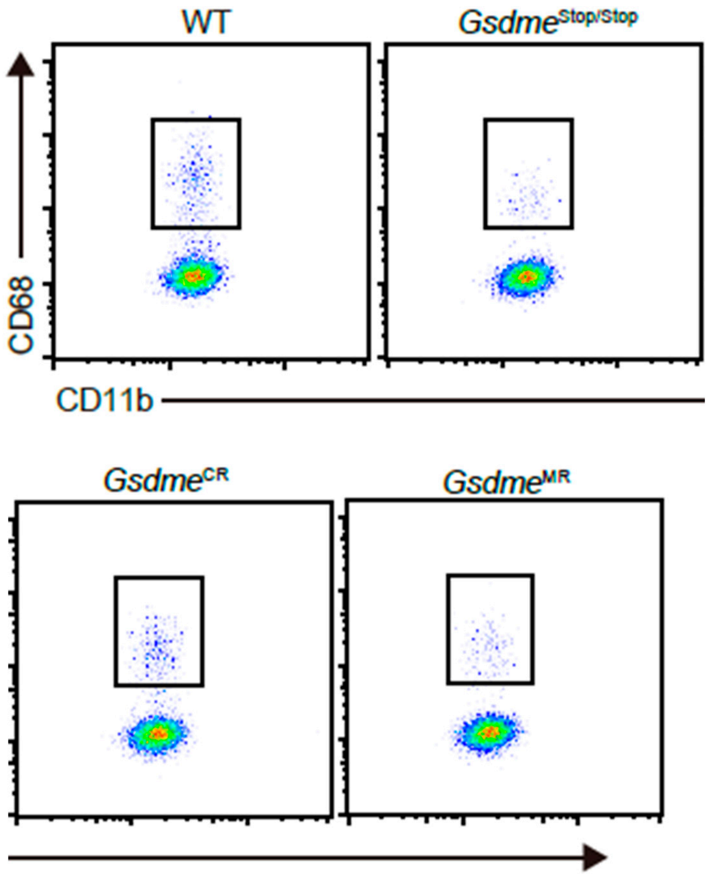
 	(Supplemental Figure 7 A) Gated on single cells
 	(Supplemental Figure 13B) Gated on $CD45^+CD11b^+$ cells