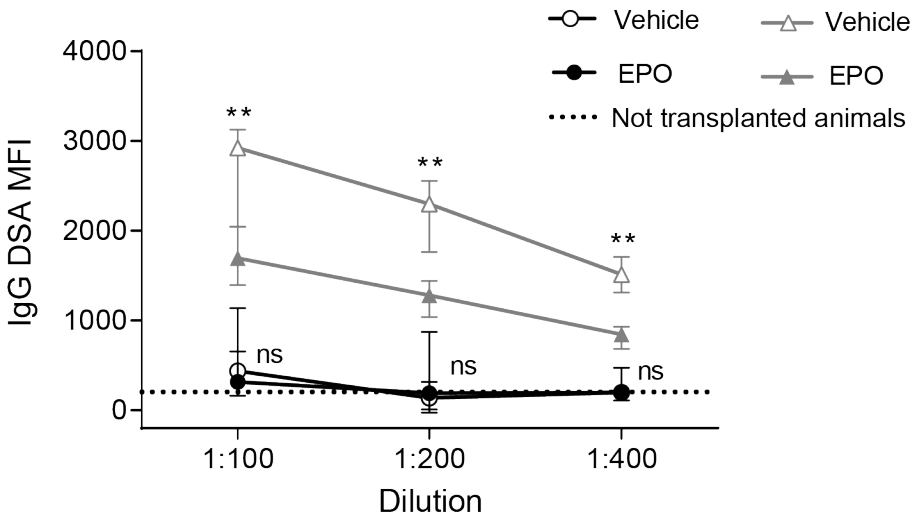
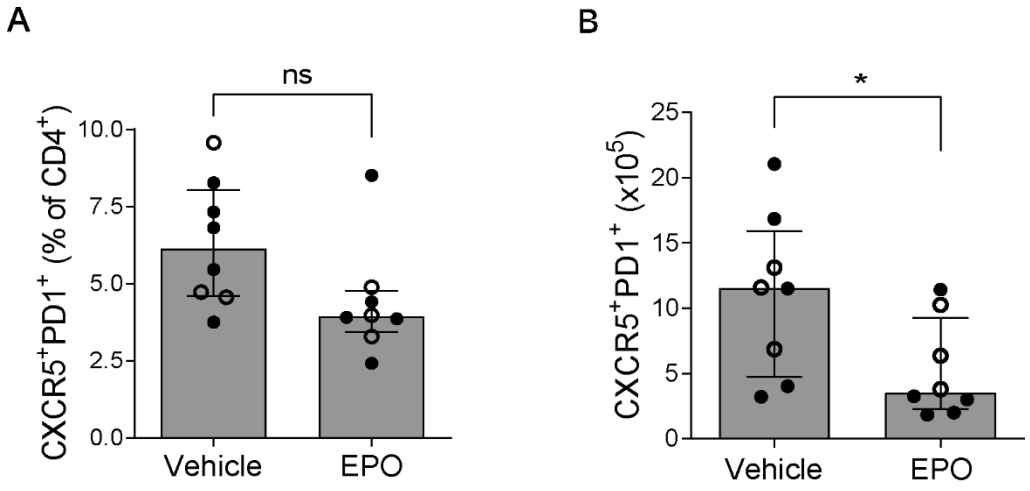
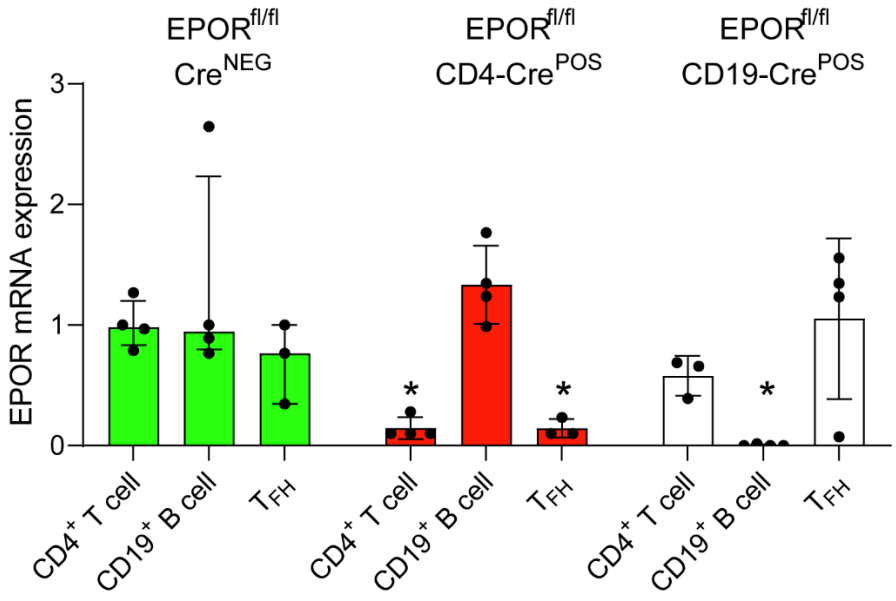
SUPPLEMENTAL MATERIAL TABLE OF CONTENTS



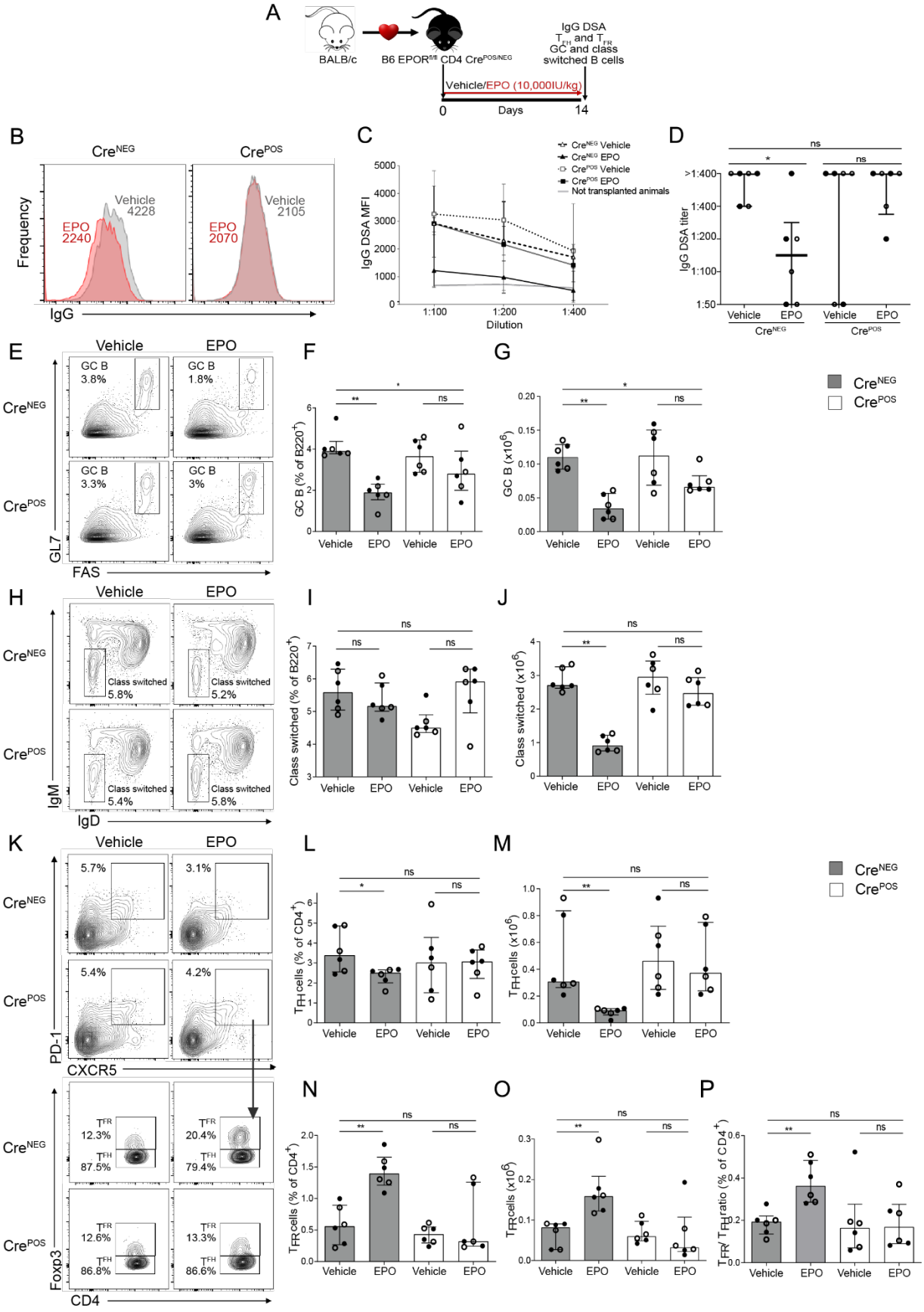
Supplemental Figure 1. **MFI levels of anti-donor and third-party antibodies in EPO- and vehicle treated B6 recipients of an allogenic transplantation from BALB/c mice.** Grey and black lines represent the MFI for donor-specific or anti-third-party (*H-2*^{k}) serum IgG, respectively, in transplanted B6 recipients of BALB/c hearts measured. The quantification was done using thymocytes as target sells (see methods for further details). Not transplanted B6 animals were used as controls. Syngeneic B6 target cells were used as further negative controls for serum from transplanted animals and did not display any antibody binding (not shown). Data represent means ± IQR. ***P* < 0.01; ns: not significant between EPO and vehicle. Data were analyzed using a Two-way ANOVA test.



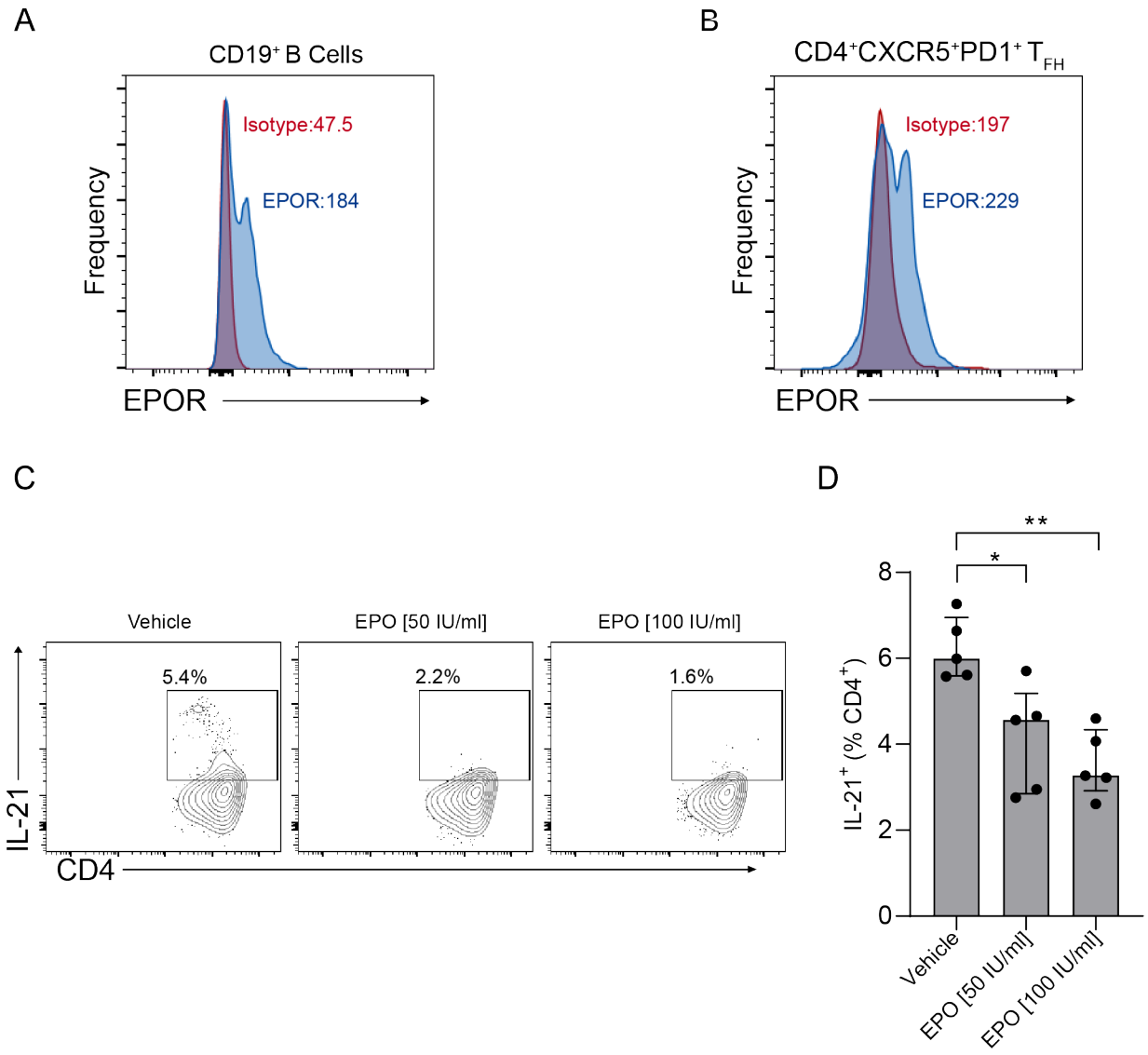
Supplemental Figure 2. EPO reduces $CD4^+CXCR5^+PD1^+$ T cells after heart transplantation in mice. Quantified percentages (**A**) and total numbers (**B**) of $CD4^+PD1^+CXCR5^+$ T cells in B6 recipients of an allogeneic heterotopic transplantation from BALB/c animals at 2 weeks post-transplant. Data represent means ± IQR. Empty circles represent male animals, full circles females. *$P < 0.05$; ns: not significant between EPO and vehicle. Data were analyzed using non-parametric unpaired Mann-Whitney test.



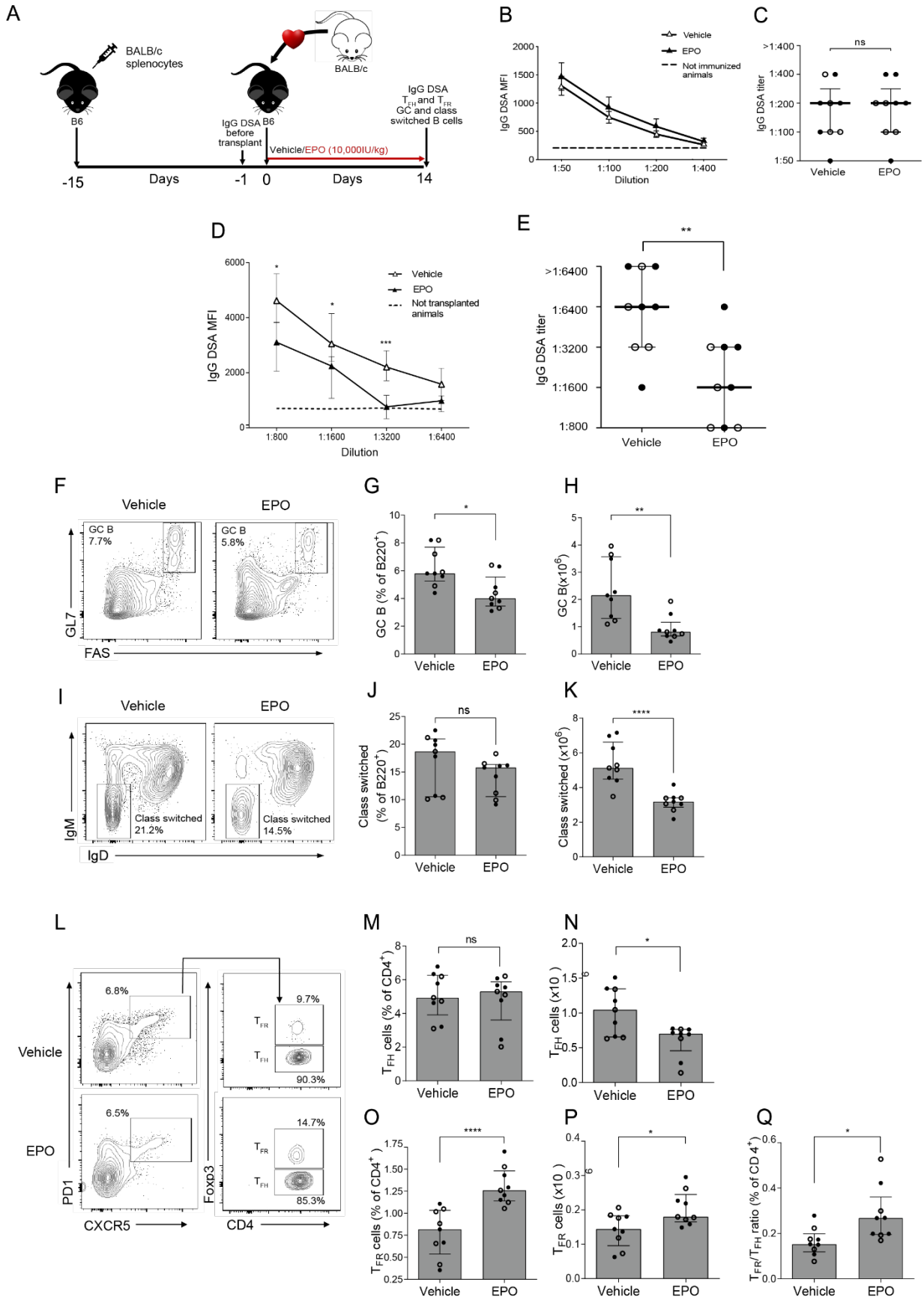
Supplemental Figure 3. EPOR expression in murine T and B cells. Quantification of EPOR mRNA expression in EPOR$^{fl/fl}$ Cre^{NEG} control (green), EPOR$^{fl/fl}$ CD4-Cre^{POS} (red), and EPOR$^{fl/fl}$ CD19-Cre^{POS} (white) mice. For each type of mouse, EPOR mRNA expression was measured in isolated total CD4$^+$ T cells, CD19$^+$ B cells, and CD4$^+$CXCR5$^+$PD1$^+$ T$_{FH}$ cells. Data represent means ± IQR. *P < 0.05. Data were analyzed using non-parametric unpaired Mann-Whitney test.


A
BALB/c
B6 EPOR^f/f CD4 Cre^POS/NEG
IgG DSA
T_FH and T_FR
GC and class
switched B cells
Vehicle/EPO (10,000IU/kg)
0
Days
14
B
Cre^NEG
Cre^POS
Frequency
Vehicle
4228
EPO
2240
Vehicle
2105
EPO
2070
IgG
C
Cre^NEG Vehicle
Cre^NEG EPO
Cre^POS Vehicle
Cre^POS EPO
Not transplanted animals
IgG DSA MFI
Dilution
1:100
1:200
1:400
D
IgG DSA titer
>1:400
1:400
1:200
1:100
1:50
Vehicle
EPO
Cre^NEG
Cre^POS
ns
E
Vehicle
EPO
Cre^NEG
Cre^POS
GC B
3.8%
1.8%
3.3%
3%
GL7
FAS
F
GC B (% of B220+)
G
GC B (x10^6)
H
Class switched
5.8%
5.2%
5.4%
5.8%
IgM
IgD
I
Class switched (% of B220+)
J
Class switched (x10^6)
K
5.7%
3.1%
5.4%
4.2%
PD-1
CXCR5
T^FR
12.3%
T^FH
87.5%
T^FR
20.4%
T^FH
79.4%
T^FR
12.6%
T^FH
86.8%
T^FR
13.3%
T^FH
86.6%
Foxp3
CD4
L
T_FH cells (% of CD4+)
M
T_FH cells (x10^6)
N
T_FR cells (% of CD4+)
O
T_FR cells (x10^6)
P
T_FR/ T_FH ratio (% of CD4+)

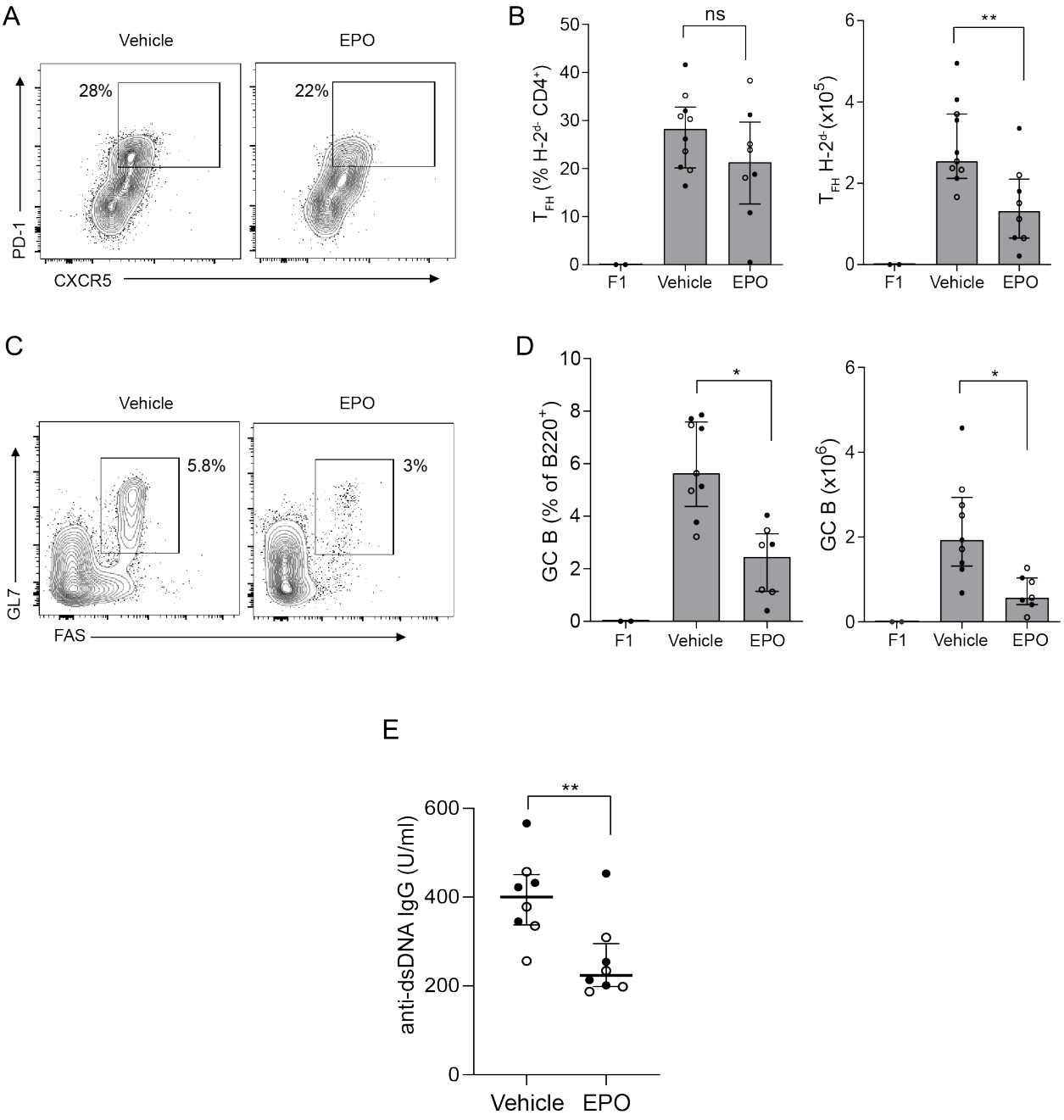
Supplemental Figure 4. EPO does not inhibit formation of alloantibodies in mice lacking EPOR on T cells undergoing heart transplant. (**A**) B6 $EPOR^{fl/fl}$ CD4-Cre^{POS} and CD4-Cre^{NEG} recipients of an allogeneic heterotopic transplantation from BALB/c mice were treated with EPO (10,000 IU/kg, i.p.) or vehicle control from the day of transplant up to day 14 post-transplant, when the animals were euthanized to measure T_{FH}, T_{FR}, GC, and class switched B cells and DSA. (**B-D**) Representative histograms of DSA IgG (**B**), MFI levels (**C**), and titers (**D**) in EPO- and vehicle treated mice. (**E-J**) Representative plots depicting percentages of $B220^{+}Fas^{+}GL7^{+}$ GC (**E**) and $B220^{+}IgM^{-}IgD^{-}$ class-switched (**H**) B cells in the same mice. Quantified percentages (**F, I**) and absolute numbers (**G, J**) of GC and class switched B cells. Representative plots depicting percentages of $CD4^{+}PD1^{+}CXCR5^{+}Foxp3^{-}$ T_{FH} and $CD4^{+}PD1^{+}CXCR5^{+}Foxp3^{+}$ T_{FR} in mice treated with EPO or vehicle control (**K**). Quantified percentages (**L, N**) and absolute numbers (**M, O**) of T_{FH} and T_{FR}, and T_{FH}/T_{FR} ratios (**P**). Data represent median ± IQR. Empty circles represent male animals, full circles females. $*P < 0.05$; $**P < 0.01$; ns: not significant. Data were analyzed using non-parametric unpaired Mann-Whitney test.



Supplemental Figure 5. Human B and T_{FH} cells express EPOR and EPO inhibits *in vitro* human T_{FH} induction. Representative plots of EPOR expression in human $CD19^+$ B cells (**A**) and $CD4^+CXCR5^+PD1^+$ T_{FH} cells (**B**). Representative plots (**C**) and data quantification (**D**) of human $CD4^+IL\text{-}21^+$ T_{FH} induced from naïve $CD4^+$ T cells, cultured under T_{FH} cell-inducing conditions for 5 days in the presence or absence of EPO. Each dot represents the mean of three different culture wells from different healthy donors. Data represent means ± IQR. *P < 0.05; **P < 0.01. Data were analyzed using non-parametric unpaired Mann-Whitney test.


A
BALB/c splenocytes
B6
BALB/c
IgG DSA B6 before transplant
Vehicle/EPO (10,000IU/kg)
IgG DSA T_FH and T_FR GC and class switched B cells
-15
Days
-1
0
Days
14
B
Vehicle
EPO
Not immunized animals
IgG DSA MFI
Dilution
C
ns
IgG DSA titer
Vehicle
EPO
D
Vehicle
EPO
Not transplanted animals
IgG DSA MFI
Dilution
E
**
IgG DSA titer
Vehicle
EPO
F
Vehicle
EPO
GC B 7.7%
GC B 5.8%
GL7
FAS
G
GC B (% of B220+)
Vehicle
EPO
H
GC B(x10^6)
Vehicle
EPO
I
Vehicle
EPO
Class switched 21.2%
Class switched 14.5%
IgM
IgD
J
ns
Class switched (% of B220+)
Vehicle
EPO
K
****
Class switched (x10^6)
Vehicle
EPO
L
Vehicle
EPO
6.8%
9.7%
90.3%
6.5%
14.7%
85.3%
PD1
CXCR5
Foxp3
CD4
M
ns
T_FH cells (% of CD4+)
Vehicle
EPO
N
*
T_FH cells (x10^6)
Vehicle
EPO
O
****
T_FR cells (% of CD4+)
Vehicle
EPO
P
*
T_FR cells (x10^6)
Vehicle
EPO
Q
*
T_FR/T_FH ratio (% of CD4+)
Vehicle
EPO

Supplemental Figure 6. EPO prevents DSA increase in pre-sensitized heart transplant recipient mice. (**A**) B6 mice received allogeneic immunization with BALB/c splenocytes (20 x 10^6, i.p.), and after 14 days we measured DSA and allocated them to EPO (10,000 IU/kg, i.p.) or vehicle control treatment based on similar DSA MFI levels (**B**), and titers (**C**). On day 15, B6 mice received an allogeneic heterotopic transplantation from BALB/c mice and were treated with EPO or vehicle control from the day of transplant up to day 14 post-transplant, when the animals were euthanized. Representative plots of DSA MFI levels (**D**), and titers (**E**) in EPO- and vehicle treated mice. (**F-K**) Representative plots depicting percentages of $B220^+Fas^+GL7^+$ GC (**F**) and $B220^+IgM^-IgD^-$ class-switched (**I**) B cells in the same mice. Quantified percentages (**G, J**) and absolute numbers (**H, K**) of GC and class switched B cells. (**L-Q**) Representative plots (**L**), percentages and absolute numbers of T_{FH} (**M, N**) and T_{FR} (**O, P**) and T_{FR}/T_{FH} ratio in the same mice (**Q**). Data represent median ± IQR. **P* < 0.05; ***P* < 0.01; *****P* < 0.0001; ns: not significant. Data were analyzed using non-parametric unpaired Mann-Whitney test.



Supplemental Figure 7. EPO prevents immunological changes in the B6 into B6 x BALB/c parent to F1 model. CD8-depleted B6 spleen cells were injected into B6xBALB/c (bxd) F1 recipients that were treated with EPO (10,000 IU/kg/day, i.p.) or vehicle control until euthanasia on day 14. Representative plots (**A**, **C**) and data quantification (**B**, **D**) for T_{FH} and GC B cells in EPO or vehicle-treated animals. Anti-dsDNA IgG in the two treatment groups (**E**). Empty circles represent male animals, full circles represent females. Data represent median ± IQR. *P < 0.05; **P < 0.01; ns: not significant between EPO and vehicle. Data were analyzed using non-parametric unpaired Mann-Whitney test.