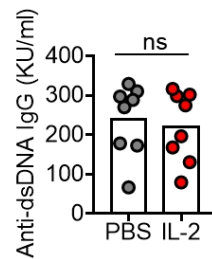
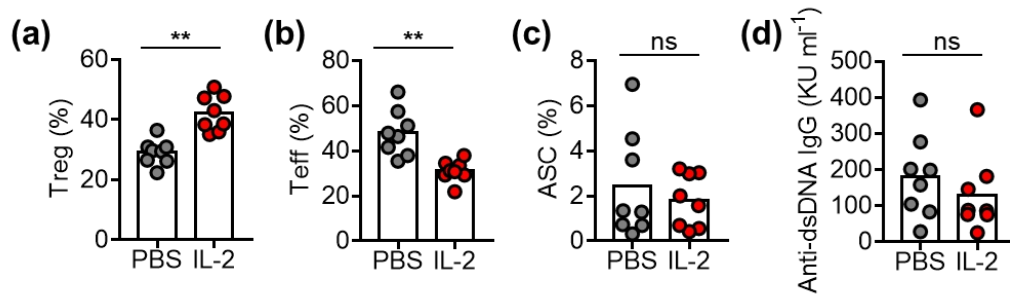


## Sustained low-dose IL-2 therapy alleviates pathogenic humoral immunity *via* elevating the Tfr/Tfh ratio in lupus

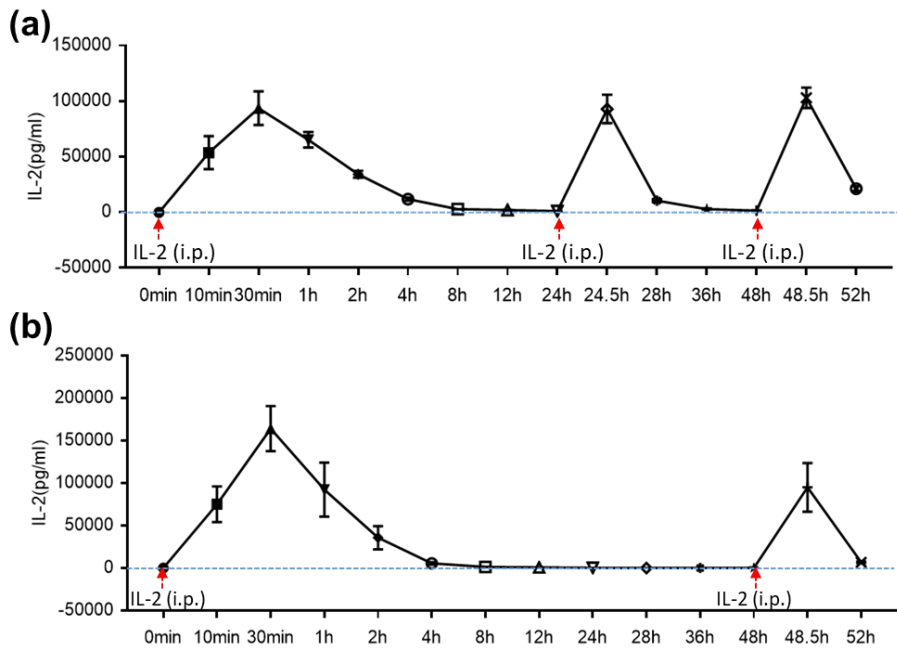
### Supplementary information



**Supplementary figure 1.** Anti-dsDNA IgG was remained unaltered in NZB/W mice with short treatment of IL-2. ELISA measurement of anti-dsDNA IgG titer in the serum of NZB/W F1 mice with short treatment regimen of low-dose IL-2 therapy or PBS for 7 days. Data are shown for individual (dots,  $n = 8$ ) and mean (bars) values. Data are representative of three independent experiments and analysed by the Student's unpaired  $t$ -test. ns:  $P > 0.05$ .



**Supplementary figure 2.** Medium treatment regimen of low-dose IL-2 therapy increased Treg cell, reduced Teffs, but not ASC and anti-dsDNA titers in female NZB/W F1 mice. The frequencies of **(a)** Treg cells, **(b)** Teff cells and **(c)** ASC in spleens of NZB/W F1 mice with 14 days of PBS or IL-2 treatment. **(d)** ELISA measurement of anti-dsDNA IgG titer in the serum of NZB/W F1 mice with 14 days of PBS or IL-2 treatment. Data are shown for individual (dots,  $n = 8$ ) and mean (bars) values. Data are representative of three independent experiments. and analysed by the Student's unpaired  $t$ -test or the Mann-Whitney  $U$ -test. \*\*:  $P < 0.01$ .



**Supplementary figure 3.** Pharmacokinetics of recombinant human interleukin-2 following intraperitoneal administration. **(a, b)**, Kinetics of serum IL-2 in female NZB/W F1 mice with daily (0, 24 and 48 hours) **(a)** or every two days of IL-2 injection (0 and 48 hours) **(b)**. F1 mice (20 weeks of age,  $n = 4$ ) were intraperitoneally injected with  $3 \times 10^4$  IU IL-2, and ELISA measurement of serum IL-2 at indicated time point (0, 10, 30 minutes, 1, 2, 4, 8, 12, 24, 24.5, 28, 36, 48, 48.5 and 52 hours). Data are representative of three independent experiments.

**Supplementary table 1.** Reanalysis of previous clinical trial data (NCT02084238, He *et al.* *Nat Med* 2016) - Baseline characteristics of patients with SLE receiving low-dose rhIL-2 (n = 23)

<b>Characteristic</b>	<b>Value</b>
Age, year, median (range)	35 (18-60)
Female/Male	22/1
Duration of SLE, year, median (range)	5 (0.5-15)
Prednisone dose, mg per day, median (range)	45 (0-50)
Use of concomitant agents (no. of patients)	
Hydroxychloroquine	20
Cyclophosphamide	4
Azathioprine	1
Cyclosporine	0
Methotrexate	0
Mycophenolate mofetil	8
Leflunomide	1
Thalidomide	0

**Supplementary table 2.** Reanalysis of previous clinical trial data (NCT02084238, He *et al.* *Nat Med* 2016) - Clinical characteristics of patients before and after low-dose IL-2 therapy (n = 23)

<b>Characteristics</b>	<b>Baseline</b>	<b>week 12</b>	<b>P value</b>
SELENA-SLEDAI, median (range)	10 (8-23)	4 (0-12)	<0.001
Rash, n (%)	15 (65.2)	3 (13.04)	<0.001
Alopecia, n (%)	9 (39.1)	0 (0)	0.002
Arthritis, n (%)	8 (34.8)	1 (4.3)	0.022
Leukopenia, n (%)	7 (30.4)	1 (4.34)	0.047
C3, g L <sup>-1</sup> , median (range)	0.495 (0.274-1.46)	0.799 (0.548-1.13)	<0.001
C4, g L <sup>-1</sup> , median (range)	0.084 (0.016-0.54)	0.16 (0.089-0.32)	<0.001
Anti-dsDNA, IU mL <sup>-1</sup> , median (range)	442.3 (71-3987.5)	230.5 (10-2413.2)	0.003

**Supplementary table 3.** Demographic and clinical characteristics of SLE patients (n = 16)

<b>Characteristics</b>	<b>Value</b>
Age, year, median (range)	37.5(24-61)
Female/Male	16/0
WBC, $\times 10^9 \text{ L}^{-1}$ , median (range)	5 (2.85-9.92)
Positive ANA, n (%)	7 (44)
Anti-dsDNA, IU $\text{mL}^{-1}$ , median (range)	33.25 (21.9-181.9)
Positive anti-Sm antibodies, n (%)	7 (44)