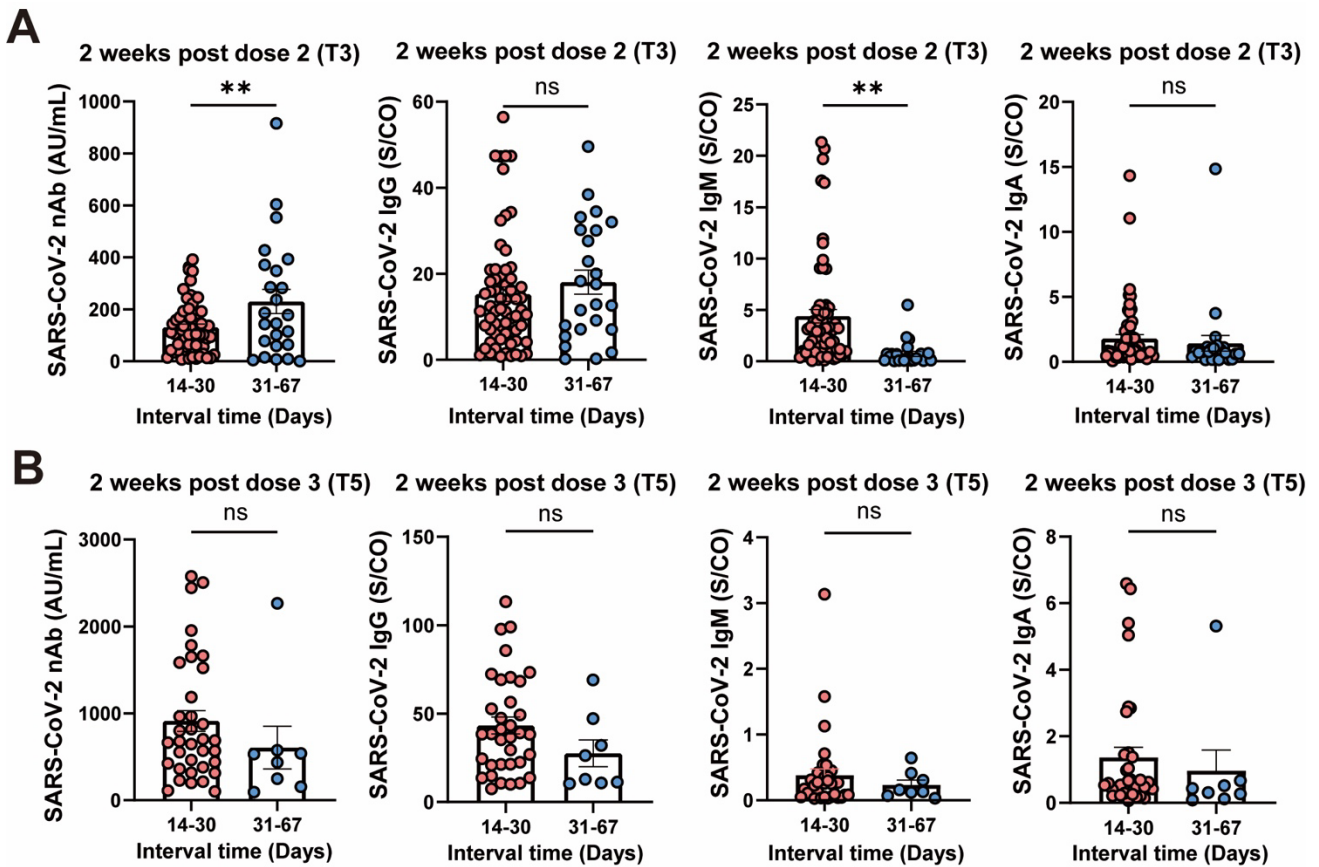


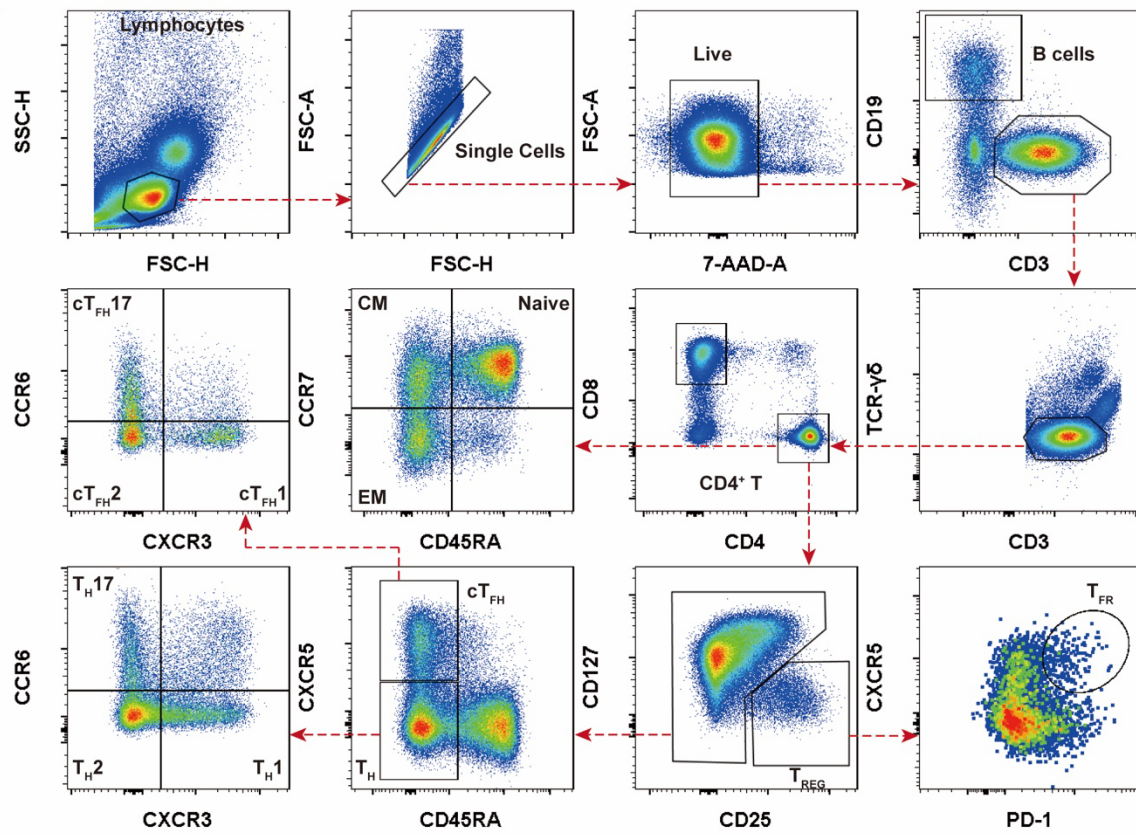
## Supplementary Figure



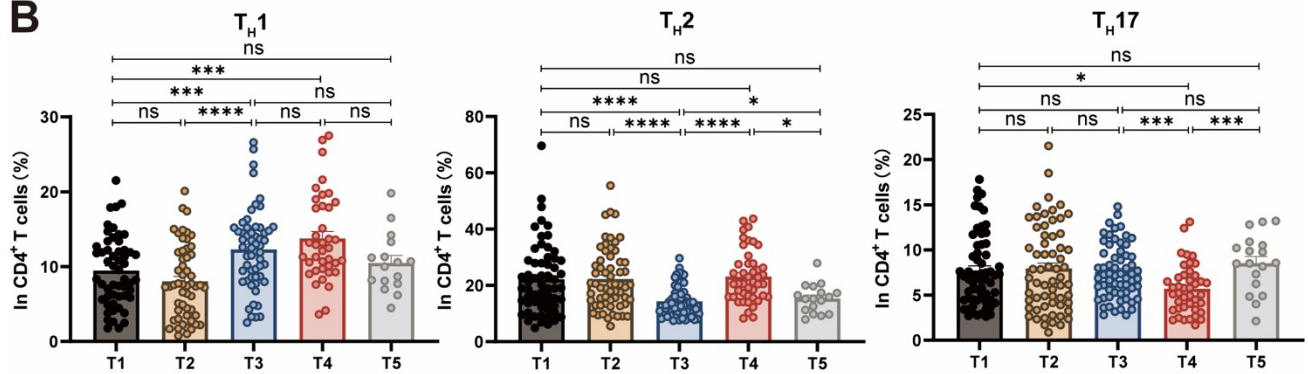
**Supplementary figure S1: Vaccination interval and the levels of SARS-CoV-2-specific antibodies induced by CoronaVac vaccine**

Effect of different time intervals between the primary and second dose on the levels of SARS-CoV-2 IgM, IgG, IgA and nAb at 2 weeks after the 2<sup>nd</sup> dose of vaccine (T3) (A) and 2 weeks after the 3<sup>rd</sup> dose of vaccine (T5) (B). Each dot represents an individual subject. Bars represent the mean values with SEM. Statistics were calculated using Mann-Whitney U test (A, B). \* $P < 0.05$ ; \*\* $P < 0.01$ ; ns, not significant.

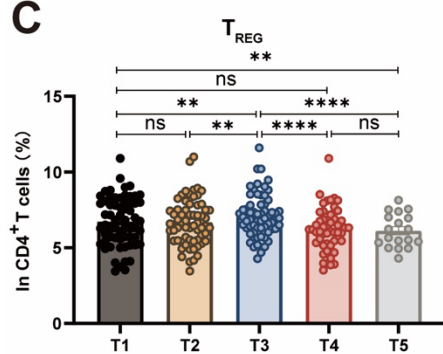
**A**



**B**



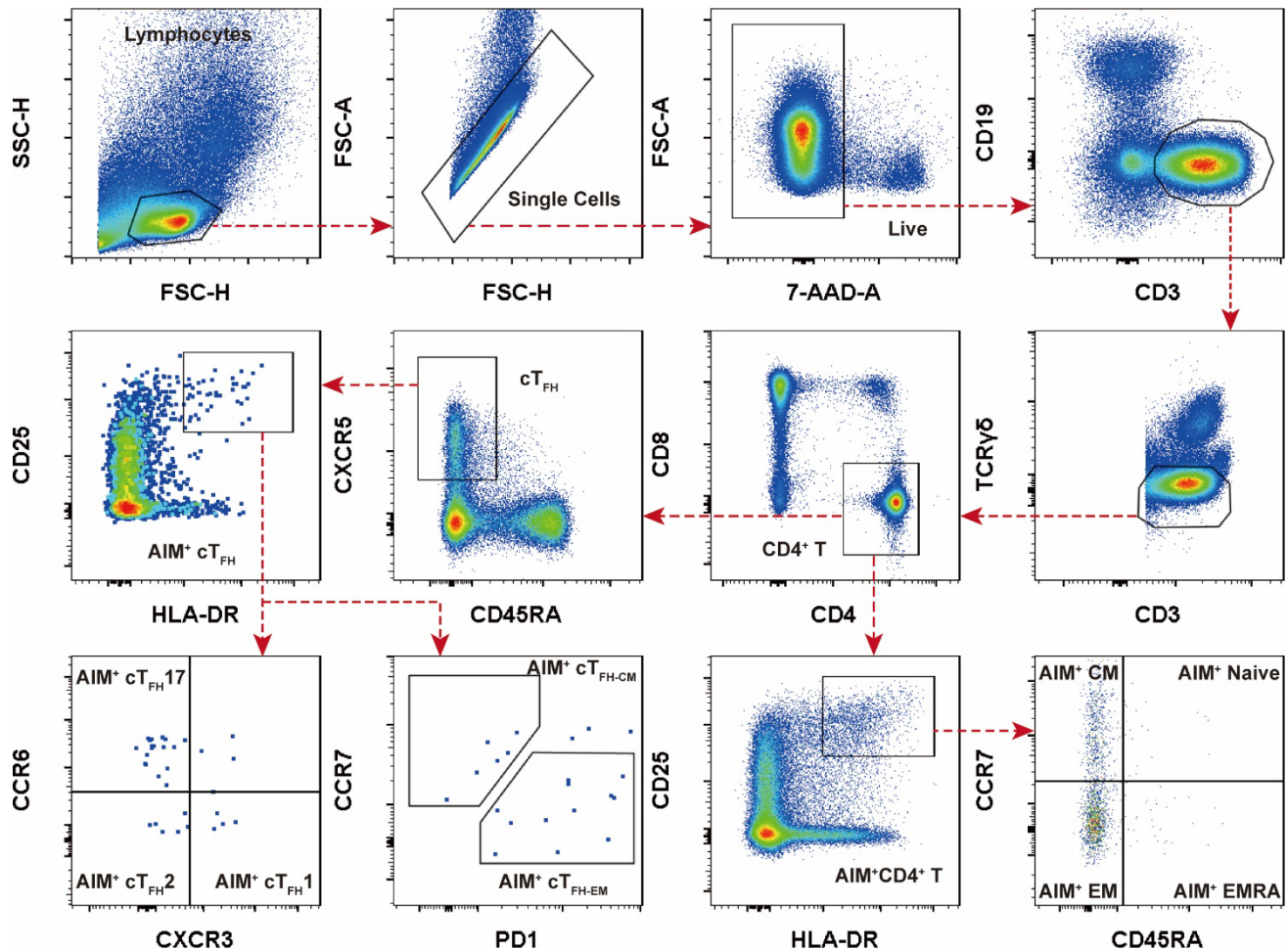
**C**



**Supplementary figure S2: Polyclonal circulating CD4<sup>+</sup> T cells.**

(A) Representative plots illustrate the gating strategy of polyclonal CD4<sup>+</sup> T cells. Lymphocytes were firstly gated, and doublets were excluded by FSC-H and FSC-A signals. Live cells were

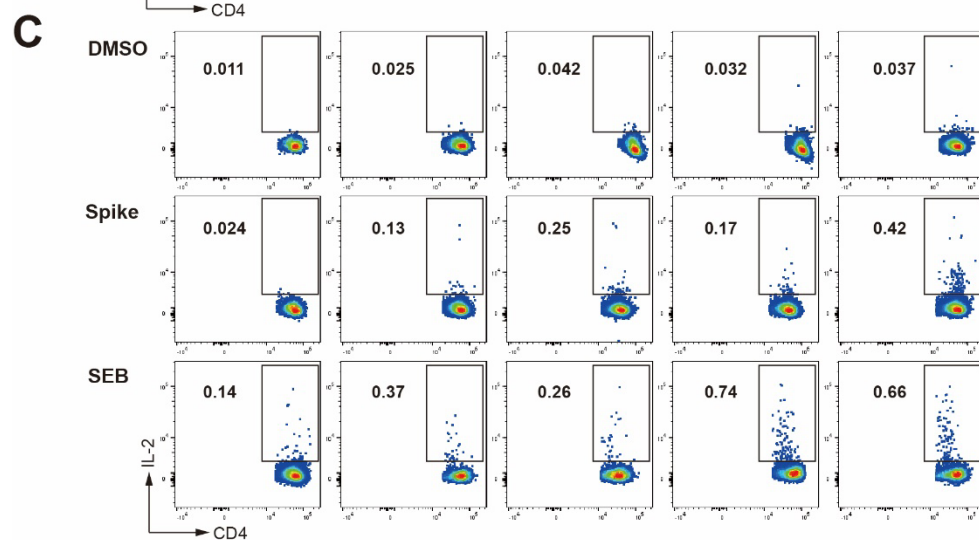
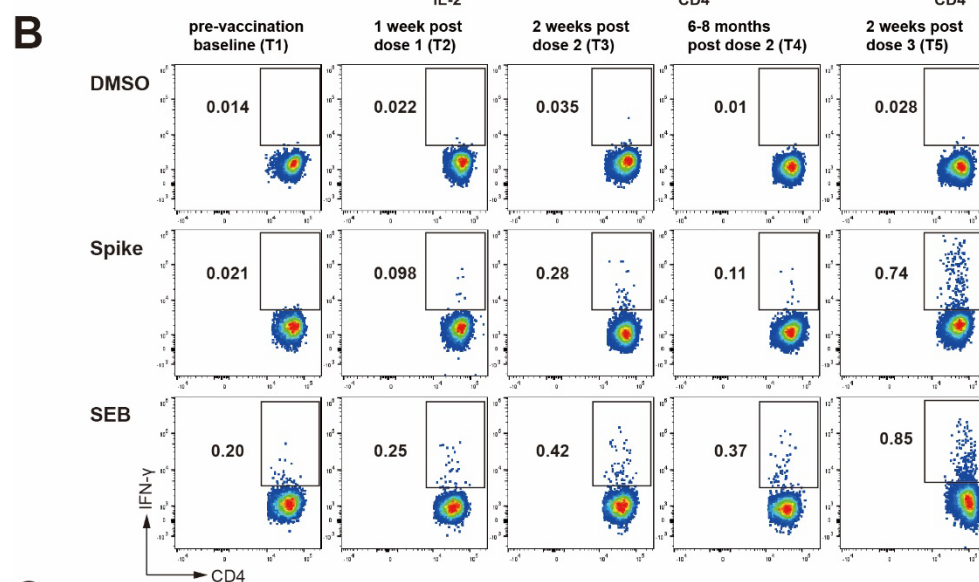
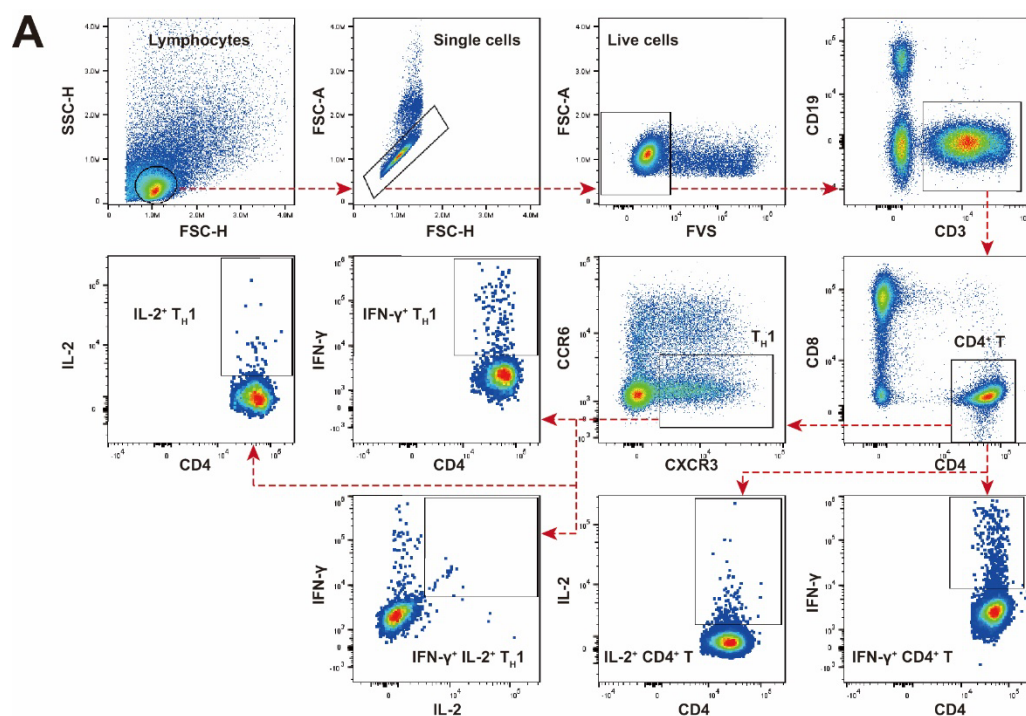
identified by 7-AAD. CD4<sup>+</sup> T cells were gated on CD3<sup>+</sup>CD19<sup>-</sup>TCR $\gamma\delta$ <sup>-</sup> cells. In particular, EM (CD45RA<sup>-</sup>CCR7<sup>-</sup>), CM (CD45RA<sup>-</sup>CCR7<sup>+</sup>) and naïve cells (CD45RA<sup>+</sup>CCR7<sup>+</sup>) are defined accordingly. T<sub>REG</sub> (CD25<sup>+</sup>CD127<sup>low</sup>) and T<sub>FR</sub> (CD25<sup>+</sup>CD127<sup>low</sup>CXCR5<sup>+</sup>PD-1<sup>+</sup>) cells are gated accordingly. CD25 negative cells can be divided into cT<sub>FH</sub> (CD45RA<sup>-</sup>CXCR5<sup>+</sup>) cells and T<sub>H</sub> (CD45RA<sup>-</sup>CXCR5<sup>-</sup>) cells. Based on the expression of CXCR3 and CCR6, cT<sub>FH</sub> cells were further divided into cT<sub>FH</sub>1 (CXCR3<sup>+</sup>CCR6<sup>-</sup>), cT<sub>FH</sub>2 (CXCR3<sup>-</sup>CCR6<sup>-</sup>) and cT<sub>FH</sub>17 (CXCR3<sup>-</sup>CCR6<sup>+</sup>) cells, while T<sub>H</sub> cells were divided into T<sub>H</sub>1 (CXCR3<sup>+</sup>CCR6<sup>-</sup>), T<sub>H</sub>2 (CXCR3<sup>-</sup>CCR6<sup>-</sup>), and T<sub>H</sub>17 (CXCR3<sup>-</sup>CCR6<sup>+</sup>) cells. Longitudinal dynamics of polyclonal T<sub>H</sub>1, T<sub>H</sub>2, T<sub>H</sub>17 (B) and T<sub>REG</sub> (C) cells during three doses of vaccines at five timepoints. Each dot represents an individual subject. Bars represent the mean values with SEM. Statistics were calculated using Wilcoxon matched-pairs signed rank for comparison between timepoints (B, C). \*,  $P < 0.05$ ; \*\*,  $P < 0.01$ ; \*\*\*,  $P < 0.001$ ; \*\*\*\*,  $P < 0.0001$ ; ns, not significant.



### Supplementary figure S3: Gating-strategy for spike-specific CD4<sup>+</sup> T and cT<sub>FH</sub> cells.

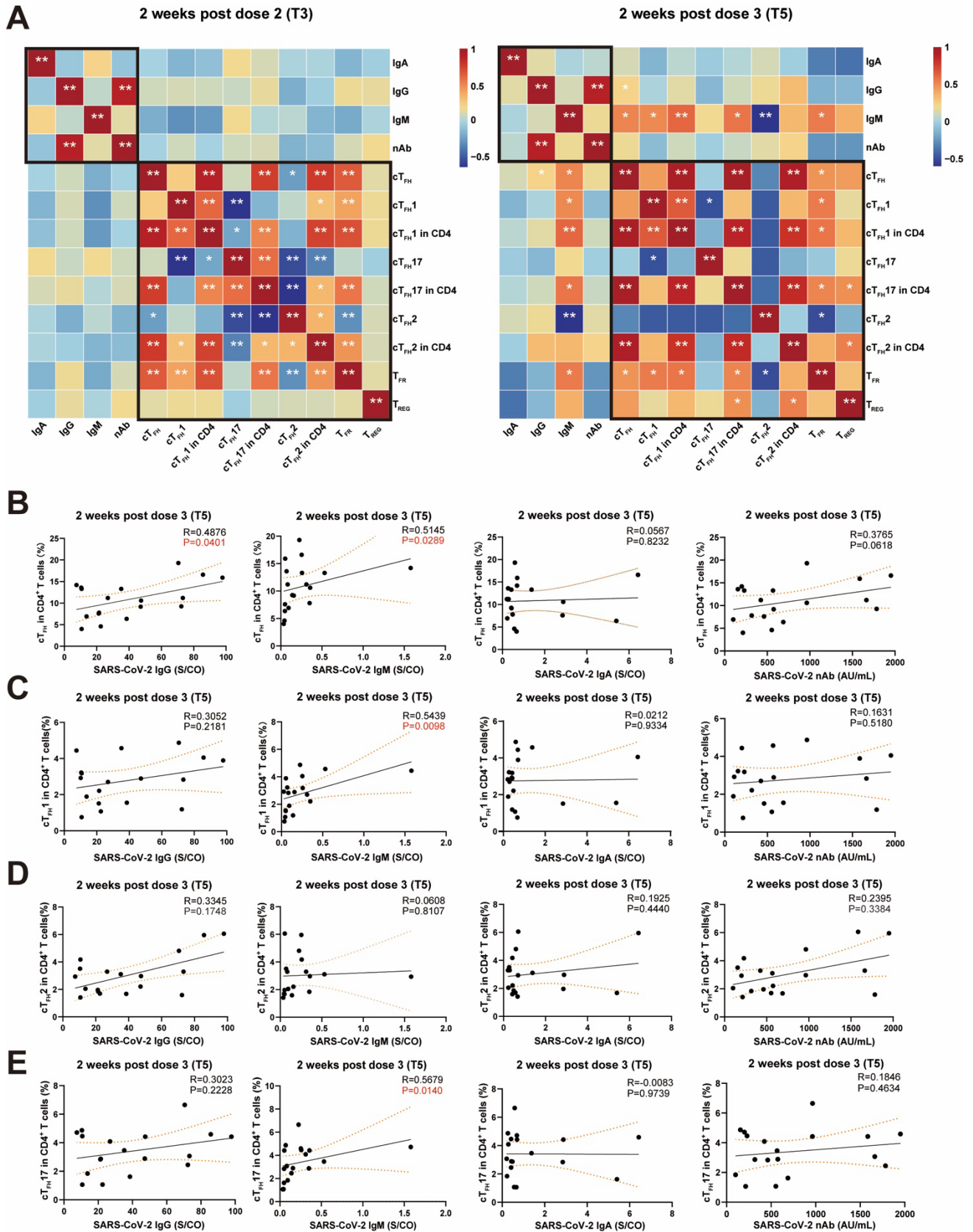
PBMCs were stimulated with SARS-CoV-2 spike protein (S1+S2, 2 ug/mL, SinoBiological) for 24h. Representative plots illustrate the gating strategy. CD4<sup>+</sup> T cells were driven from CD3<sup>+</sup>CD19<sup>-</sup>TCRγδ<sup>-</sup> gating. Spike-specific CD4<sup>+</sup> T cells and spike-specific cT<sub>FH</sub> cells were defined as HLA-DR<sup>+</sup>CD25<sup>+</sup>CD4<sup>+</sup> and CXCR5<sup>+</sup> HLA-DR<sup>+</sup>CD25<sup>+</sup>CD4<sup>+</sup>, respectively. Spike-specific CD4<sup>+</sup> T cells were further divided into memory and naïve cells. Spike-specific cT<sub>FH</sub> cells were further divided into cT<sub>FH</sub>1, cT<sub>FH</sub>2 and cT<sub>FH</sub>17 cells according to the expression of surface molecules CXCR3 and CCR6, and divided into AIM<sup>+</sup> cT<sub>FH</sub>-CM and cT<sub>FH</sub>-EM cells by CCR7 and PD1.





**Supplementary figure S4: Gating-strategy and representative plots for spike-specific CD4<sup>+</sup> T cells using ICS assay.**

(A) Representative plots illustrate the gating strategy of spike-specific CD4<sup>+</sup> T cells. CD4<sup>+</sup> T cells were gating from live CD3<sup>+</sup>CD19<sup>-</sup> lymphocytes. T<sub>H</sub>1 cells were defined as CXCR3<sup>+</sup>CCR6<sup>-</sup> CD4<sup>+</sup> T cells. IFN- $\gamma$ <sup>+</sup> CD4<sup>+</sup> T cells, IL-2<sup>+</sup> CD4<sup>+</sup> T cells, IFN- $\gamma$ <sup>+</sup> T<sub>H</sub>1, IL-2<sup>+</sup> T<sub>H</sub>1 and IFN- $\gamma$ <sup>+</sup> IL-2<sup>+</sup> T<sub>H</sub>1 were further gated based on the cytokine production. Representative FACS plots of IFN- $\gamma$ <sup>+</sup> CD4<sup>+</sup> T cells (B) and IL-2<sup>+</sup> CD4<sup>+</sup> T cells (C) were shown at five time points (T1-T5). DMSO and SEB were used as negative and positive controls, respectively.



**Supplementary figure S5: Correlations between polyclonal  $CD4^+$  T cells and antibody responses following CoronaVac vaccination.**

(A) Correlation heatmaps of the polyclonal CD4<sup>+</sup> T cell subsets and SARS-CoV-2 specific antibodies at two weeks post dose 2 (T3) and dose 3 (T5). Correlation analysis between the frequency of polyclonal cT<sub>FH</sub> cells (B), cT<sub>FH</sub>1 cells (C), cT<sub>FH</sub>2 cells (D), cT<sub>FH</sub>17 cells (E) and SARS-CoV-2-specific IgG, IgM, IgA and nAb titers at two weeks post dose 3 (T5). Each dot represents an individual subject. The non-parametric Spearman's rank correlation was used (A, B, C, D, E). \* $P < 0.05$ ; \*\* $P < 0.01$  (A).  $P$  and  $R$  values were indicated (B, C, D, E).



**Supplementary table 1 Antibodies and other key resources**

REAGENT or RESOURCE	SOURCE	IDENTIFIER
<b>Antibodies</b>		
Brilliant Violet 570 Anti-Human CD8a (Clone: RPA-T8)	BioLegend	Cat# 301038
Alexa Fluor 488 Anti-Human CD45RA (Clone: HI100)	BioLegend	Cat# 304114
Alexa Fluor 532 Hu CD3 (Clone: UCHT1)	eBioscience	Cat# 58-0038-42
PE Anti-Human CD25 (Clone: M-A251)	BioLegend	Cat# 356104
PE-Cy7 Anti-Human CCR7 (CD197) (Clone: 3D12)	BD	Cat# 557648
APC Anti-Human CD185 (CXCR5) (Clone: J252D4)	Biosciences	Cat# 356908
APC-R700 Anti-Human CD127 (Clone: HIL-7R-M21)	BioLegend	Cat# 356908
APC/Fire 750 Anti-Human HLA-DR (Clone: L243)	BD	Cat# 565185
Brilliant Violet 421 Anti-Human CD183 (CXCR3) (Clone: G025H7)	Biosciences	Cat# 307658
Super Bright 436 Anti-Human CD19 (Clone: HIB19)	BioLegend	Cat# 307658
BV480 Anti-Human Gma Dta TCR (Clone: B1)	BioLegend	Cat# 353716
Brilliant Violet 605 Anti-Human CD196 (CCR6) (Clone: G034E3)	eBioscience	Cat# 62-0199-42
Brilliant Violet 650 Anti-Human CD279 (PD-1) (Clone: EH12.2H7)	BD	Cat# 566076
BV750 Anti-Human CD4 (Clone: SK3)	Biosciences	Cat# 566355
PE-Cy7 Anti-Human IFN- $\gamma$	BioLegend	Cat# 502528
APC-R700 Anti-Human IL-2	BD	Cat# 565136
	Biosciences	
<b>Chemicals, Peptides, and Recombinant Proteins</b>		
7AAD Staining Solution	eBioscience	Cat# 00-6993-50
FACS Lysing Solution	BD	Cat# 349202
Human Fc Block	Pharmingen	Cat#130-059-901
Ficoll-Paque <sup>TM</sup> PLUS Media	Miltenyi	Cat#17144002
Cytofix/Cytoperm	GE Healthcare Life Sciences	Cat#51-2090KZ
BD Perm/Wash	BD	Cat#51-2091KZ
FBS	Pharmingen	Cat#10100147
SARS-CoV-2 spike Peptide Pool	Gibco	Cat#PP003
	SinoBiological	

SEB	Toxin Technology	Cat#BT-202
Purified anti-human CD3 Antibody	BioLegend	Cat#317326
Purified anti-human CD28 Antibody	BioLegend	Cat# 302933
Purified anti-human CD49d Antibody	BioLegend	Cat# 304339
<b>Critical Commercial Assays</b>		
Anti-SARS-CoV-2 IgG MCLIA kit	Autobio Diagnostics	Cat# CMU0302
Anti-SARS-CoV-2 IgM MCLIA kit	Autobio Diagnostics	Cat# CMU0402
Anti-SARS-CoV-2 IgA MCLIA kit	InnoDx Biotechnology Beckman	Cat# CT0725
SARS-CoV-2 neutralization antibody CLIA microparticles	Autobio Diagnostics	Cat# CMU0702