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Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	A description of all covariates tested
☒	☐	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	FlowJo (10.5.3), MiSeq 3.1, BaseSpace, CytExpert (2.3.1.22), BD FACS Chorus (1.3.3), BD FACS Diva (8), SoftMax Pro (7.1)
Data analysis	usearch (v11), ublast (v11), R (3.4.2), ggplot2 (3.1.0), igraph (1.2.4.1), GraphPad Prism (v8), msa (1.60.0), tcR (2.3.2), vegan (2.5.5), SoftMax Pro (7.1), FlowJo (v10)

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

Plasmid and cloning insert sequences are available on GenBank (GA1 backbone, GenBank accession number MW079271; GA1 product, GenBank accession number MW079272; synthetic amplicon insert, GenBank accession number MW079275; GA2 product, example plasmid sequence provided as GenBank accession number MW079273; PMD-4681, GenBank accession number MW079274. Sequencing data are available in the Short Read Archive (SRA) under project identifier PRJNA649279.
Figures 2, 3, 4, and 5 have associated raw sequence data.
All raw data not deposited in data repositories (ELISAs, flow cytometry, in vitro neutralization assays, etc.) can be made available on reasonable request for non-commercial use.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Figure 3b: No power analysis was performed to predetermine an appropriate sample size for this experiment. Figure 4d: No power analysis was performed to predetermine an appropriate sample size for this experiment. Figure 5b: No power analysis was performed to predetermine an appropriate sample size for this experiment. Figure 5d, Supplementary Figure S39: No power analysis was performed to predetermine an appropriate sample size for this experiment. Supplementary Figures S13, S23, S30, S31: No power analysis was performed to predetermine an appropriate sample size for this experiment.
Data exclusions	No data were excluded.
Replication	Figure 2. (a) Each data point represents a single measurement at a single test article dilution, in a single experiment. (b) Each plot summarizes a single FACS experiment with one yeast scFv library. (c) Each data point represents a single measurement at a single test article dilution, in a single experiment. (e) Each data point represents a single measurement at a single test article dilution, in a single experiment. (f) Each test article was run in duplicate using different aliquots of cells and virus, in a single experiment, with the same result observed for each replicate. Figure 3. (a) Each data point represents a single test article measured against a single Dengue serotype. (c) Each data point represents a single test article measured against a single Dengue serotype, in a single experiment. (d) Each data point represents a single measurement at a single test article dilution, in a single experiment. Figure 4. (b) Each data point represents a single measurement at a single test article dilution, in a single experiment. (c) Each data point represents a single measurement at a single test article dilution, in a single experiment. (d) Measurements were performed in duplicate, with similar results. (e) This experiment was performed once. Figure 5. (b) Each data point represents a single measurement at a single test article dilution, in a single experiment. Each measurement was performed in triplicate. (c) This experiment was performed once. (d) This experiment was performed once.
Randomization	Figure 4(e): Mice were randomized into treatment groups by animal identifier after inoculation with Hib bacteria. Figure 5(b) and 5(c): Mice were randomized by body weight on Day 5 after PBMC engraftment.
Blinding	For all in vitro and in vivo work, test articles were assigned unique identifiers. Investigators were blinded to the identities of all test articles for all work performed external to GigaGen (live coronavirus neutralization, Zika virus pseudotype neutralization, ADE assays, Hib and pneumococcus in vitro studies, all in vivo work).

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☐	☒ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☐	☒ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used	Anti-myc primary (A21281; Thermo Fisher Scientific, Waltham, MA, USA) AF488 secondary antibody (A11039; Thermo Fisher Scientific, Waltham, MA, USA) polyclonal HRP goat anti-rabbit IgG (E28002 Novodiax, Hayward, CA, USA) anti-SARS CoV-2 (CR3022; Absolute Antibody, San Diego, CA, USA) anti-SARS CoV-2 (SAD-S35; Acro Biosystems, Newark, DE, USA)

plasma-derived IVIG (Gamunex; Grifols, S.A., Sant Cugat, Spain)
rabbit anti-human IgG HRP conjugate (Southern Biotech 6140-05, Birmingham, AL, USA)
anti-Zika (UWI-mAb1; IgG1 isotype cloned from de-identified donor by University of the West Indies, found to be cross-reactive to Zika and Dengue 1-4)
anti-Zika/Dengue sera (UWIS; de-identified sample screened positive for Zika and Dengue 1-4 by University of the West Indies);
Thymoglobulin (Sanofi Genzyme; Cambridge, MA, USA)
mouse anti-human IgG HRP (109-035-088; Jackson ImmunoResearch, West Grove, PA, USA)
anti-CD45 BV650 (clone HI30; BioLegend 304043, San Diego, CA, USA)
anti-CD45 PE (clone HI30; BioLegend 304008, San Diego, CA, USA)
anti-CD3 (clone UCHT1; BioLegend 300439, San Diego, CA, USA)
CD8 (clone BW135/80; Miltenyi 130-113-157, Bergisch Gladbach, Germany)
anti-CD20 (clone 2H7; BioLegend 302340, San Diego, CA)
anti-CD56 (clone 5.1H11; BioLegend 362509, San Diego, CA, USA)
anti-CD16 (clone 3G8; BioLegend 302017, San Diego, CA, USA)
lot 89SF serum (National Institute for Biological Standards and Control; Hertfordshire, UK)

Validation

Anti-myc primary (A21281; Thermo Fisher Scientific, Waltham, MA, USA) -- validated by vendor using flow cytometry.
AF488 secondary antibody (A11039; Thermo Fisher Scientific, Waltham, MA, USA) -- validated by vendor using flow cytometry and Western blot.
polyclonal HRP goat anti-rabbit IgG (E28002 Novodiax, Hayward, CA, USA) -- validated by vendor using ELISA
plasma-derived IVIG (Gamunex; Grifols, S.A., Sant Cugat, Spain) -- GMP product approved by FDA
Thymoglobulin (Sanofi Genzyme; Cambridge, MA, USA) -- GMP product approved by FDA
rabbit anti-human IgG HRP conjugate (Southern Biotech 6140-05, Birmingham, AL, USA) -- validated by vendor using Western blots and ELISA
mouse anti-human IgG HRP (109-035-088; Jackson ImmunoResearch, West Grove, PA, USA) -- validated by vendor using Western blots and ELISA
anti-CD45 BV650 (clone HI30; BioLegend 304043, San Diego, CA, USA) -- validated by vendor using flow cytometry.
anti-CD45 PE (clone HI30; BioLegend 304008, San Diego, CA, USA) -- validated by vendor using flow cytometry.
anti-CD3 (clone UCHT1; BioLegend 300439, San Diego, CA, USA) -- validated by vendor using flow cytometry.
CD8 (clone BW135/80; Miltenyi 130-113-157, Bergisch Gladbach, Germany) -- validated by vendor using flow cytometry.
anti-CD20 (clone 2H7; BioLegend 302340, San Diego, CA) -- validated by vendor using flow cytometry.
anti-CD56 (clone 5.1H11; BioLegend 362509, San Diego, CA, USA) -- validated by vendor using flow cytometry.
anti-CD16 (clone 3G8; BioLegend 302017, San Diego, CA, USA) -- validated by vendor using flow cytometry.
Certificates of analysis were obtained from commercial vendors for all commercial antibodies used in the study.

In addition to the vendor validations for the antibodies listed above, the study investigators validated each antibody with positive control reference samples with known reactivities using appropriate methods (ELISA or flow cytometry). The antibodies all generally performed as expected.

Recombinant hyperimmune globulin test articles were subjected to endotoxin quantification, ELISA, SDS-PAGE, and SEC HPLC prior to any in vitro or in vivo work. All commercially- and academically-sourced drug test article antibodies (anti-Zika serum, anti-SARS CoV-2 serum, anti-SARS CoV-2 monoclonal antibodies) were assessed by ELISA, flow cytometry, and/or other functional assay in parallel with other negative and positive controls, and generally performed as expected.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)

Flp-In™-CHO were from Thermo Fisher Scientific (Waltham, MA, USA).
CHO line CHOZN® GS-/- was obtained from MilliporeSigma (St. Louis, MO, USA).
EBY100 yeast strain was from ATCC (MYA-4941; Manassas, VA, USA).
HEK 293T cells were from ATCC (CRL-11268; Manassas, VA, USA).
BHK/DC-SIGN cells were from ATCC (CRL-325; Manassas, VA, USA).
K562 cells were from ATCC (CCL-243; Manassas, VA, USA).
Vero E6 cells were from ATCC (CRL-1586; Manassas, VA, USA).
HL60 cells were from ATCC (CCL-240; Manassas, VA, USA).

Authentication

Certificates of analysis were obtained from vendors for all cell lines used in the study.

CHO cells were sequence verified using shotgun whole genome sequencing or targeted sequencing (Illumina). Other than the CHO cells, the identities of the cell lines were not authenticated independently by the study investigators.

All cellular assays were validated with positive and negative control test articles. All cell lines performed as expected in their respective assays or applications.

Mycoplasma contamination

Flp-In™-CHO and CHOZN GS tested negative for mycoplasma.

The study investigators did not assess any other cell lines used in this study for mycoplasma.

Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used in this study.

Animals and other organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Laboratory animals	Humanized mice were engineered by Trianni (San Francisco, CA, USA). Trianni mice were bred and obtained from Charles River Laboratories (Wilmington, MA, USA). All mice were male and 12-15 weeks old at the start of the immunization process. Antibody Solutions (Santa Clara, CA, USA) performed all Trianni Mouse immunizations. Local ethical regulations were followed for mouse immunizations by the Antibody Solutions IACUC. The mice were ear marked for identification by the breeder and housed in individually ventilated cages (Innovive, San Diego, CA, USA) and racks with HEPA filtered air at a density of up to 5 mice per cage. The animal room was lighted entirely with artificial fluorescent lighting, with a controlled 12 h light/dark cycle (7 am to 7 pm light). The normal temperature and relative humidity ranges in the animal rooms were 20-22.2°C and 30-70%, respectively. The animal rooms were set to have up to 10 air exchanges per hour. Sunnyvale municipal tap water and rodent chow (Teklad Global, Indianapolis, IN, USA) were provided ad libitum. NOD scid gamma (NSG) mice (genotype: NOD.Cg-Prkdcscid Il2rgtm1Wjl/SzJ) were from Jackson Labs. All mice were female, age 6-8 weeks. The mice were ear notched for identification and housed in individually ventilated polysulfonate cages with HEPA filtered air at a density of up to 5 mice per cage. The animal room was lighted entirely with artificial fluorescent lighting, with a controlled 12 h light/dark cycle (6 am to 6 pm light). The normal temperature and relative humidity ranges in the animal rooms were 22-26°C and 30-70%, respectively. The animal rooms were set to have up to 15 air exchanges per hour. Filtered tap water, acidified to a pH of 2.5 to 3.0, and standard rodent chow was provided ad libitum. rhATG study: Balb/cJ mice were from Taconic, Denmark. All mice were female, age 6-8 weeks. The temperature and humidity were registered daily in the animal facilities. The temperature was 22°C +/- 2°C and can be regulated by heating and cooling. The humidity was 55 +/- 10%. The air changes per hour were approximately 8-12 times (70-73 times per hours inside cages), and light/dark period was in 12-hours interval of 6 am - 6 pm / 6 pm – 6 am. The mice had free access to domestic quality drinking water and food (Teklad Global diet 2916C-Envigo) and occasionally peanuts and sunflower seeds (Køge Korn A/S). The mice were housed in IVC cages , 6-8 mice per cage, with bedding from Tapvei. Further, the animals were offered Enviro-Dri nesting material and cardboard houses (Bio-Serv).
Wild animals	No wild animals were used in this study.
Field-collected samples	No field collected samples were used in this study.
Ethics oversight	For Trianni Mouse immunizations, the Antibody Solutions IACUC was responsible for study oversight. For the GVH model for rhATG, the Jackson Labs IACUC was responsible for study oversight. For the Hib challenge model, the SSI IACUC was responsible for study oversight.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Human research participants

Policy information about studies involving human research participants

Population characteristics	rCIG: Donors were recruited from a single hospital in New Orleans among patients randomly presenting with symptoms of COVID-19. 22% of the donors were Male, 78% of the donors were Female. 10% of the donors were Black, and 90% of the donors were white. The average age of the donors was 50. The youngest donor was 24 and the oldest donor was 71. No genetic information was collected for the donors. Inclusion criteria: - Any gender - Aged 18-71 years - Prior infection with COVID-19 determined by clinical symptoms (2 or more of the following: fever, sore throat, coughing, or shortness of breath) or positive test result - Note: diseases other than autoimmune and viral infections specifically stated in the Exclusion criteria are irrelevant; any prior medical history is irrelevant Exclusion criteria: - <18 years - >70 years - No history of COVID-19 infection - Female currently pregnant - Known autoimmune disease - Known infection with HIV, HBV, HCV [Note: we would eventually need these samples to be screened for these to confirm] - Other pre-existing conditions are not an exclusion criteria rPIG: Healthy male or female donors aged 19-64, recruited at a single blood center from a database of frequent blood donors. Three donors (Donor 1, 57-year-old Caucasian male; Donor 2, 44-year-old Caucasian male; Donor 3, 35-year-old Caucasian/ Asian male) were immunized with Pneumovax23 vaccine (Merck, Kenilworth, NJ, USA).

No genetic information was collected for the donors.

rHIG: Healthy male or female donors under the age of 40, recruited at a single blood center from a database of frequent blood donors.
Two donors (Donor 1, a 26-year-old Caucasian female, and Donor 2, a 21-year-old Asian male) were immunized with PedvaxHIB vaccine (Merck, Kenilworth, NJ). USA)
No genetic information was collected for the donors.

Recruitment

rCIG: Sample size of n=50 may have been large enough to reflect the characteristics of the population presenting with COVID-19 at one hospital in New Orleans. However, self-selection bias or other biases that may have been present may have impacted the nature of the study subjects, thereby impacting the antibody repertoires captured. As a result, the study investigators made no attempts to generalize the repertoire data to any broader population.

rPIG: Sample size was only n=3, representative of no particular population. Self-selection bias or other biases that may have been present may have impacted the nature of the study subjects, thereby impacting the antibody repertoires captured. As a result, the study investigators made no attempts to generalize the repertoire data to any broader population.

rHIG: Sample size was only n=2, representative of no particular population. Self-selection bias or other biases that may have been present may have impacted the nature of the study subjects, thereby impacting the antibody repertoires captured. As a result, the study investigators made no attempts to generalize the repertoire data to any broader population.

Ethics oversight

rCIG: Institutional Review Board (IRB) protocol #PRO00026464 (Advarra, Columbia, MD, USA) to Access Biologicals.
rPIG: IRB protocol #7000-SOP-045 (Alpha IRB, San Clemente, CA, USA) to AllCells.
rHIG: IRB protocol #PRO00028063 (Medical College of Wisconsin/Froedtert Hospital IRB) to GigaGen.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Flow Cytometry

Plots

Confirm that:

☒ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☒ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☒ All plots are contour plots with outliers or pseudocolor plots.

☒ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation

Yeast scFv sorting (SARS CoV-2, only): Surface displayed scFv sequences express C-terminal myc tag to identify scFv expression. Yeast are stained with an anti-myc primary (A21281; Thermo Fisher Scientific, Waltham, MA, USA) and AF488 secondary antibody (A11039; Thermo Fisher Scientific, Waltham, MA, USA). Binding to antigen was identified by staining with 1200nM biotinylated antigen and stained with Streptavidin-APC.
CD45 flow cytometry: (in vitro) PBMCs were isolated, incubated overnight with ATG in RPMI. Cells were stained for immune markers.
CD45 flow cytometry (in vivo): Whole blood was taken retro-orbitally, stained with CD3-FITC, CD45-PE, 7AAd and CD8-AF647, RBC were lysed with ammonium chloride solution and CountBright beads were added.

Instrument

Yeast scFv sorting: FACSMelody (BD)
CD45 flow cytometry (in vitro): Cytoflex (Beckman Coulter)
CD45 flow cytometry (in vivo): FACSCanto (BD)

Software

Yeast scFv sorting: BD FACSChorus™ software
CD45 flow cytometry (in vitro): CytExpert
CD45 flow cytometry (in vivo): BDFACSDiva™ software

Cell population abundance

Yeast scFv sorting: 5000 gated cmyc+antigen+ events were collected.
CD45 flow cytometry (in vitro): Sample was collected for 150 seconds/sample to control cell population abundance.
CD45 flow cytometry (in vivo): Sample was collected according 20,000 CD45+ cells and cell abundance normalized to absolute number of cells using CellBright bead counts.
Refer to online methods and supplementary figures for further detail.

Gating strategy

Yeast scFv sorting: cmyc+ Antigen+ cells were sorted for enrichment of antigen-specific scFv.

Gating strategy	CD45 flow cytometry (in vitro): All analysis was done on gated PBMCs, singlets, and CD45+ cells for all cultures. Effector cells were: subsequently gated as CD3+CD8+ ; Helper cells were subsequently gated as CD3+CD8-; B cells were subsequently gated as CD20+ and NK cells were subsequently gated as CD16+CD56+. CD45 flow cytometry (in vivo): All analyses were done on gated PBMC singlets, live cells and CD45+ cells.

☒ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.