REPORT

CORONAVIRUS

Development of an inactivated vaccine candidate for SARS-CoV-2

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The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in an unprecedented public health crisis. Because of the novelty of the virus, there are currently no SARS-CoV-2–specific treatments or vaccines available. Therefore, rapid development of effective vaccines against SARS-CoV-2 are urgently needed. Here, we developed a pilot-scale production of PiCoVacc, a purified inactivated SARS-CoV-2 virus vaccine candidate, which induced SARS-CoV-2–specific neutralizing antibodies in mice, rats, and nonhuman primates. These antibodies neutralized 10 representative SARS-CoV-2 strains, suggesting a possible broader neutralizing ability against other strains. Three immunizations using two different doses, 3 or 6 micrograms per dose, provided partial or complete protection in macaques against SARS-CoV-2 challenge, respectively, without observable antibody-dependent enhancement of infection. These data support the clinical development and testing of PiCoVacc for use in humans.

The World Health Organization declared the outbreak of coronavirus disease 2019 (COVID-19) to be a Public Health Emergency of International Concern on 30 January 2020 and classified it as a pandemic on 11 March 2020. It is reported that ~80% of COVID-19 patients have mild to moderate symptoms, whereas ~20% develop serious manifestations such as severe pneumonia, acute respiratory distress syndrome, sepsis, and even death (*1*). The number of COVID-19 cases has increased at a staggering rate globally. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative virus of the ongoing pandemic, belongs to the genus *Betacoronavirus* (β-CoV) of the family Coronaviridae (*2*). SARS-CoV-2, along with the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle Eastern respiratory syndrome-related coronavirus (MERS-CoV), constitute the three most life-threatening species of the coronaviruses that affect humans. SARS-CoV-2 harbors a linear, single-stranded, positive-sense RNA genome encoding four structural proteins, spike (S), envelope (E), membrane (M), and nucleocapsid (N). Of these, S is a major protective antigen that elicits highly potent neutralizing antibodies (NAbs), 16 nonstructural proteins (nsp1 to nsp16), and several accessory proteins (*3*). No specific antiviral drugs or vaccines against the newly emerged SARS-CoV-2 are currently available. Therefore, urgency in the development of vaccines is of vital importance to curb the pandemic and to prevent new viral outbreaks.

Multiple SARS-CoV-2 vaccine types, such as DNA- and RNA-based formulations, recombinant subunits containing viral epitopes, adenovirus-based vectors, and purified inactivated virus, are under development (*4*–*6*). Purified inactivated viruses have been traditionally used for vaccine development, and such vaccines have been found to be safe and effective for the prevention of diseases caused by viruses such as influenza virus and poliovirus (*7*, *8*). To develop preclinical in vitro neutralization and challenge models for a candidate SARS-CoV-2 vaccine, we isolated SARS-CoV-2 strains from bronchoalveolar lavage fluid samples of 11 hospitalized patients (including five patients in intensive care), of which five are from China, three from Italy, one from Switzerland, one from the United Kingdom, and one from Spain (table S1). These patients were infected with SARS-CoV-2 during the most recent outbreak. The 11 samples contained SARS-CoV-2 strains that are widely scattered on the phylogenic tree constructed from all available sequences, representing to some extent circulating SARS-CoV-2 populations (Fig. 1A and fig. S1). We chose strain CN2 to develop a purified inactivated SARS-CoV-2 virus vaccine, PiCoVacc, and another 10 strains, CN1, CN3 to CN5, and OS1 to OS6, as preclinical challenge strains. The CN1 and OS1 strains are closely related to 2019-nCoV-BetaCoV Wuhan/WIV04/2019 and EPI_ISL_412973, respectively, which have been reported to cause severe clinical symptoms, including respiratory failure requiring mechanical ventilation (*9*, *10*).

To obtain a viral stock adapted for efficient growth in Vero cells for PiCoVacc production, the CN2 strain was first plaque purified and passaged once in Vero cells to generate the P1 stock. After this, another four passages were performed to generate the P2 to P5 stocks. Growth kinetics analysis of the P5 stock in Vero cells showed that this stock replicated efficiently and reached a peak titer of 6 to 7 $\log_{10}$ median tissue culture infectious dose ($TCID_{50}$)/ml by 3 or 4 days post-infection (dpi) at multiplicities of infection of 0.0001 to 0.01 and temperatures between 33° and 37°C (Fig. 1B). To evaluate the genetic stability of PiCoVacc, five more passages were performed to obtain the P10 stock, and its whole genome, together with those of the P1, P3, and P5 stocks, was sequenced. Compared with P1, only two amino acid substitutions, Ala→Asp at E residue 32 (E-A32D) and Thr→Ile at nsp10 residue 49 (nsp10-T49I), occurred in the P5 and P10 stocks (table S2), suggesting that the PiCoVacc CN2 strain has excellent genetic stability without the S mutations that might potentially alter the NAb epitopes. To produce pilot-scale PiCoVacc for animal studies, the virus was propagated in a 50-liter culture of Vero cells using the Cell Factory system and inactivated using β-propiolactone (Fig. 1C). The virus was purified using depth filtration and two optimized steps of chromatography, yielding a highly pure preparation of PiCoVacc (Fig. 1D). Additionally, cryo–electron microscopy analysis showed intact, oval-shaped particles with diameters of 90 to 150 nm, which were embellished with crown-like spikes, representing a prefusion state of the virus (Fig. 1E).

To assess the immunogenicity of PiCoVacc, groups of BALB/c mice (n = 10) were injected at days 0 and 7 with various doses of PiCoVacc mixed with alum adjuvant (0, 1.5, 3, or 6 μg per dose, with 0 μg in physiological saline as the sham group). No inflammation or other adverse effects were observed. Spike-specific, receptor binding domain (RBD)–specific, and N-specific antibody responses were evaluated by enzyme-linked immunosorbent assays (ELISAs) at weeks 1 to 6 after the initial immunization (fig. S2).

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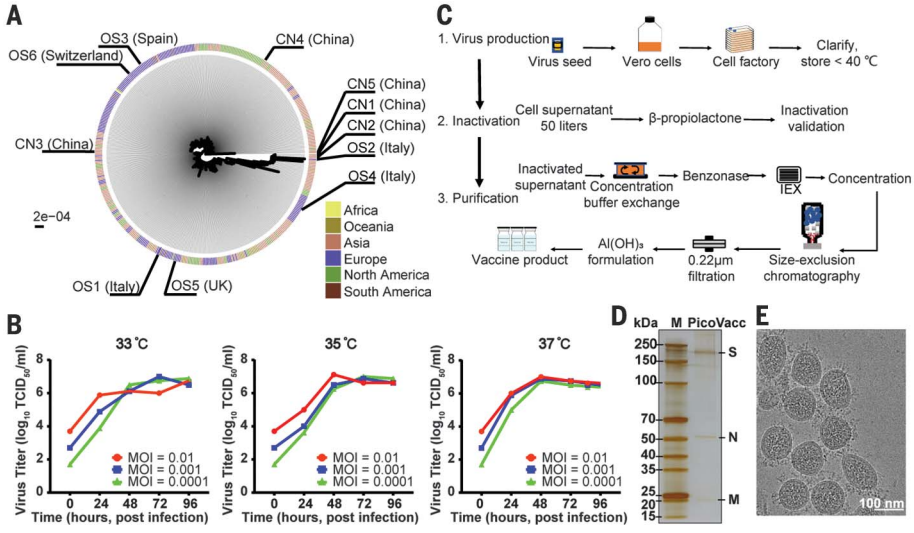

Fig. 1. Characterization of the SARS-CoV-2 vaccine candidate PiCoVacc. (**A**) SARS-CoV-2 maximum likelihood phylogenetic tree. The SARS-CoV-2 isolates used in this study are depicted with black lines and labeled. Viral strains were isolated in infected patients who traveled from the continents indicated. (**B**) Growth kinetics of PiCoVacc (CN2) P5 stock in Vero cells. (**C**) Flowchart of PiCoVacc preparation. (**D**) Protein composition and purity evaluation of PiCoVacc by NuPAGE 4 to 12% Bis-Tris gel. (**E**) Representative electron micrograph of PiCoVacc. White scale bar 100 nm.

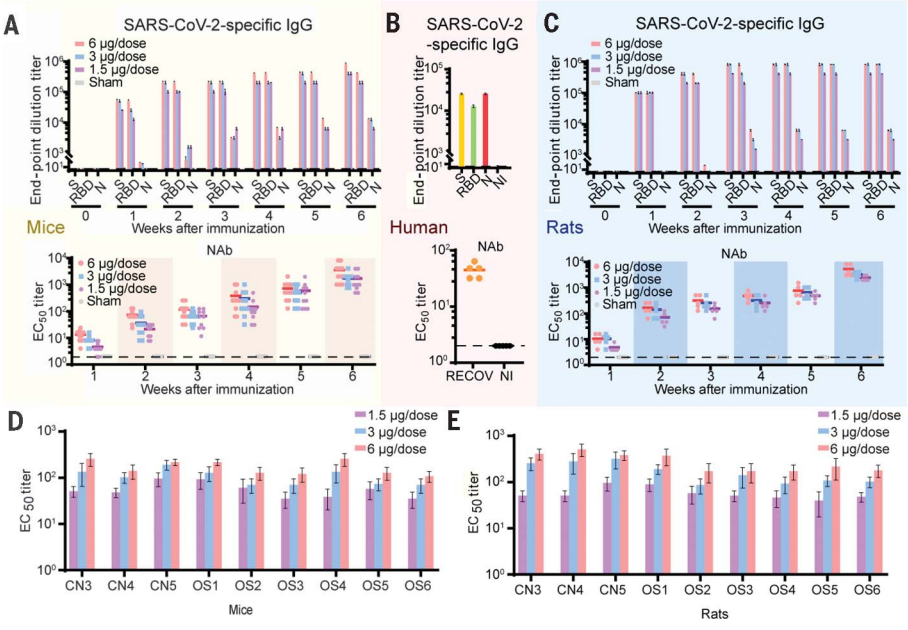

Fig. 2. PiCoVacc immunization elicits an NAb response against 10 representative SARS-CoV-2 isolates. BALB/c mice and Wistar rats were immunized with various doses of PiCoVacc or control (adjuvant only) (n = 10). Sera from recovered COVID19 patients (RECOV) and noninfected (NI) individuals were used as positive and negative controls, respectively. The antibody responses were analyzed in mice (**A**), humans (**B**), and rats (**C**). Top: SARS-CoV-2–specific IgG responses as measured by ELISA. Bottom: NAb titer as determined by microneutralization assay. The spectrum of neutralizing activities elicited by PiCoVacc was investigated in mice (**D**) and rats (**E**). Neutralization assays against the other nine isolated SARS-CoV-2 strains were performed using mouse and rat sera collected 3 weeks after vaccination. Data points represent mean ± SEM of individual animals and humans from five to 10 independent experiments. Error bars indicate SEM. Dotted lines indicate the limit of detection. Horizontal lines indicate the geometric mean titer of median effective concentration (EC_{50}) for each group.

SARS-CoV-2 S-specific and RBD-specific immunoglobulin G (IgG) developed quickly in the sera of vaccinated mice and peaked at a titer of 819,200 (>200 μg/ml) and 409,600 (>100 μg/ml), respectively, at week 6 (Fig. 2A). RBD-specific IgG accounted for half of the S-induced antibody responses, suggesting that RBD is the dominant immunogen; this closely matches the serological profile of the blood of recovered COVID-19 patients (Fig. 2, A and B) (*11*). Unexpectedly, the amount of N-specific IgG induced was ~30-fold lower than that of antibodies targeting S or RBD in immunized mice (Fig. 2A). Previous studies have shown that the N-specific IgG is abundant in the sera of COVID-19 patients and serves as one of the clinical diagnostic markers (*11*). PiCoVacc could elicit ~10-fold higher S-specific antibody titers in mice compared with serum from the recovered COVID-19 patients (Fig. 2, A and B). Although this observation is currently not indicative of PiCoVacc's ability to produce similar results in humans, it highlights its potential to induce a strong and potent immune response. Our findings, coupled with the fact that the antibodies targeting N of SARS-CoV-2 do not provide protective immunity against the infection (*12*), suggest that PiCoVacc might be capable of eliciting more effective antibody responses (Fig. 2, A and B).

Next, we measured SARS-CoV-2–specific NAbs over time using microneutralization (MN50) assays. Similar to S-specific IgG responses, the NAb titer against the CN1 strain emerged at week 1 (titer of 12 for the high-dose immunization), surged after the week 2 booster, and reached a titer up to 1500 for the low and medium doses and 3000 for the high dose at week 7 (Fig. 2A). By contrast, the sham group did not develop detectable SARS-CoV-2–specific antibody responses (Fig. 2, A and B). In addition, immunogenic evaluations of PiCoVacc in Wistar rats with the same immunization strategy yielded similar results: The maximum neutralizing titers reached 2048 to 4096 at week 7 (Fig. 2C). To investigate the spectrum of neutralizing activities elicited by PiCoVacc, we conducted neutralization assays against the other nine isolated SARS-CoV-2 strains using mouse and rat serum collected 3 weeks after vaccination. Neutralizing titers against these strains demonstrated that PiCoVacc is capable of eliciting antibodies that may exhibit potent neutralization activities against the SARS-Cov-2 strains circulating worldwide (Fig. 2, D and E).

We next evaluated the immunogenicity and protective efficacy of PiCoVacc in rhesus macaques (*Macaca mulatta*), a nonhuman primate species that shows a COVID-19–like disease caused by SARS-CoV-2 infection (*13*). Macaques were immunized three times intramuscularly with medium doses (3 μg per dose) or high doses (6 μg per dose) of PiCoVacc at days 0, 7, and 14 (n = 4). S-specific IgG and NAb were induced at week 2 and rose to ~12,800 and ~50,

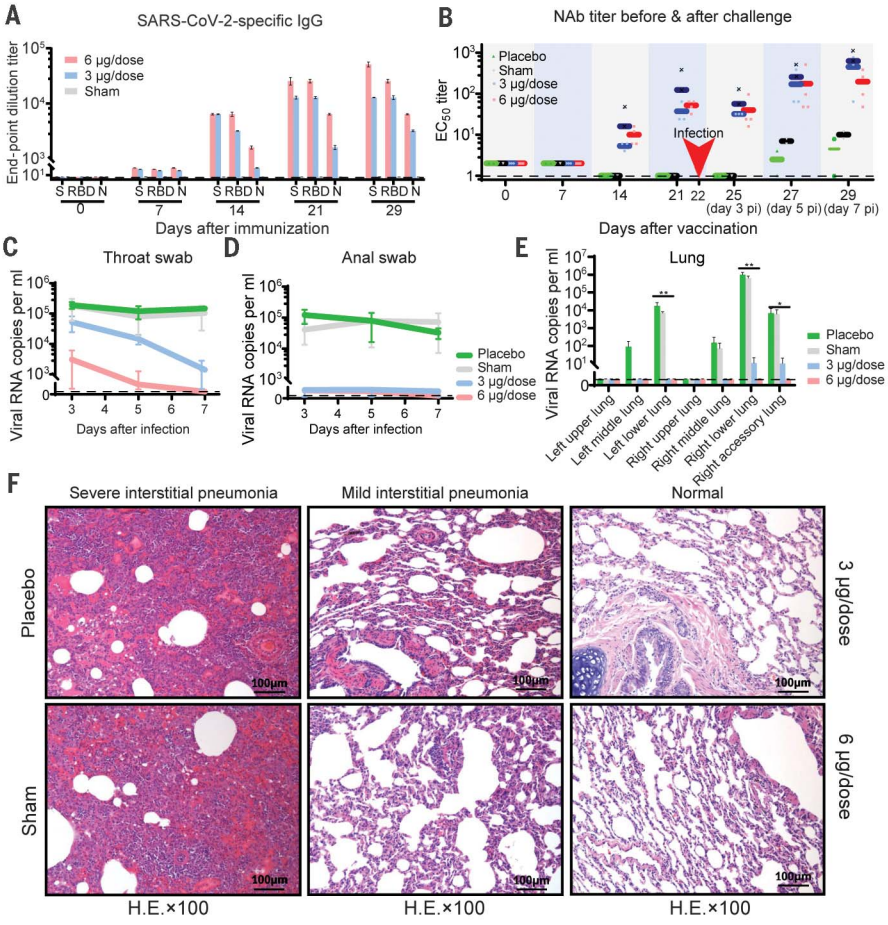

Fig. 3. Immunogenicity and protective efficacy of PiCoVacc in nonhuman primates. Macaques were immunized three times intramuscularly with various doses of PiCoVacc or adjuvant only (sham) or placebo (n = 4). SARS-CoV-2–specific IgG response (**A**) and NAb titer (**B**) were measured. Data points represent mean ± SEM of individual macaques from four independent experiments. Error bars indicate SEM. Dotted lines indicate the limit of detection. Horizontal lines indicate the geometric mean titer of EC_{50} for each group. (**C** to **F**) The protective efficacy of PiCoVacc against SARS-CoV-2 challenge at week 3 after immunization was evaluated in macaques. Viral loads of throat (C) and anal (D) swab specimens collected from the inoculated macaques at 3, 5, and 7 dpi were monitored. Viral loads in various lobes of lung tissue from all the inoculated macaques at 7 dpi were measured (E). RNA was extracted and viral load was determined by quantitative reverse transcription polymerase chain reaction. All data are presented as means ± SEM from four independent experiments. Error bars indicate SEM. Asterisks indicate significance: $^{*}P < 0.05$ and $^{**}P < 0.01$. (F) Histopathological examinations in lungs from all the inoculated macaques at 7 dpi. Lung tissue was collected and stained with hematoxylin and eosin.

respectively, at week 3 (before virus challenge) in both vaccinated groups; their titers were similar to those of sera from the recovered COVID-19 patients (Fig. 3, A and B). Unexpectedly, NAb titers (61) in the medium-dose group were ~20% greater than those (50) observed in the high-dose group at week 3, possibly because of individual differences in the ability of one animal in the medium-dose group in eliciting an ~10-fold higher titer compared with the other three animals (Fig. 3B). Excluding this exception, the NAb titer in the medium-dose group decreased to 34, ~40% lower than that in the high-dose group. Subsequently, we conducted a challenge study by a direct inoculation of 10^6 $TCID_{50}$ of SARS-CoV-2 CN1 into the animals' lungs intratracheally at day 22 (1 week after the third immunization) in vaccinated and control macaques to verify the protective efficacy. As expected, all control macaques [those receiving adjuvant (sham group) and those receiving physiological saline (placebo group)] showed excessive copies (10^4 to 10^6/ml) of viral genomic RNA in the pharynx, crissum, and lung by 3 to 7 dpi, along with severe interstitial pneumonia (Fig. 3, C to F). By contrast, all vaccinated macaques were largely protected against SARS-CoV-2 infection, with very mild and focal histopathological changes in a few lobes of lung, probably caused by a direct inoculation of 10^6 $TCID_{50}$ of virus into the lung through the intratracheal route that needed a longer time (>1 week) to recover completely (Fig. 3F). Viral loads decreased significantly in all vaccinated macaques but increased slightly in control animals at 3 to 7 dpi (Fig. 3, C to E). All four macaques that received the high dose had no detectable viral loads in pharynx, crissum, or lung at 7 dpi. In the medium-dose group, we indeed partially detected the viral blip from pharyngeal (3/4), anal (2/4), and pulmonary (1/4) specimens at 7 dpi, whereas viral loads presented an ~95% reduction compared with the sham groups (Fig. 3, C to E). The NAb titer in vaccinated groups decreased by ~30% by 3 dpi to neutralize viruses, then rapidly increased from 5 to 7 dpi to maintain neutralization efficacy. Compared with the high-dose group (titer of ~145), the higher NAb titers observed in the medium-dose group at 7 dpi (titer of ~400 for four macaques) might have resulted from relatively low levels of viral replication, suggesting that a longer time was required for complete viral clearance. No antibody-dependent enhancement (ADE) of infection was observed for the vaccinated macaques despite the observation that a relatively low NAb titer existed within the medium-dose group before infection, offering partial protection. The possibility of manifestation of ADE after antibody titers wane could not be ruled out in this study. Further studies involving observation of challenged animals at longer periods of time after vaccination are warranted to address this.

Previous reports on the development of SARS and MERS vaccine candidates raised concerns about pulmonary immunopathology, either directly caused by a type 2 helper T-cell (Th2) response or as a result of ADE (*4*, *14*, *15*). Although T cell responses elicited by many vaccines have been demonstrated to be crucial for acute viral clearance, protection from subsequent coronavirus infections is largely mediated by humoral immunity (*16*, *17*). The "cytokine storm" induced by excessive T cell responses has actually been shown to accentuate the pathogenesis of COVID-19 (*18*, *19*). Therefore, T cell responses elicited by any SARS-CoV-2 vaccine(s) would have to be well controlled to avoid immunopathology. In this context, we systematically evaluated the safety of PiCoVacc in macaques by recording a number of clinical observations and biological indices. Two groups of macaques (n = 10) were immunized

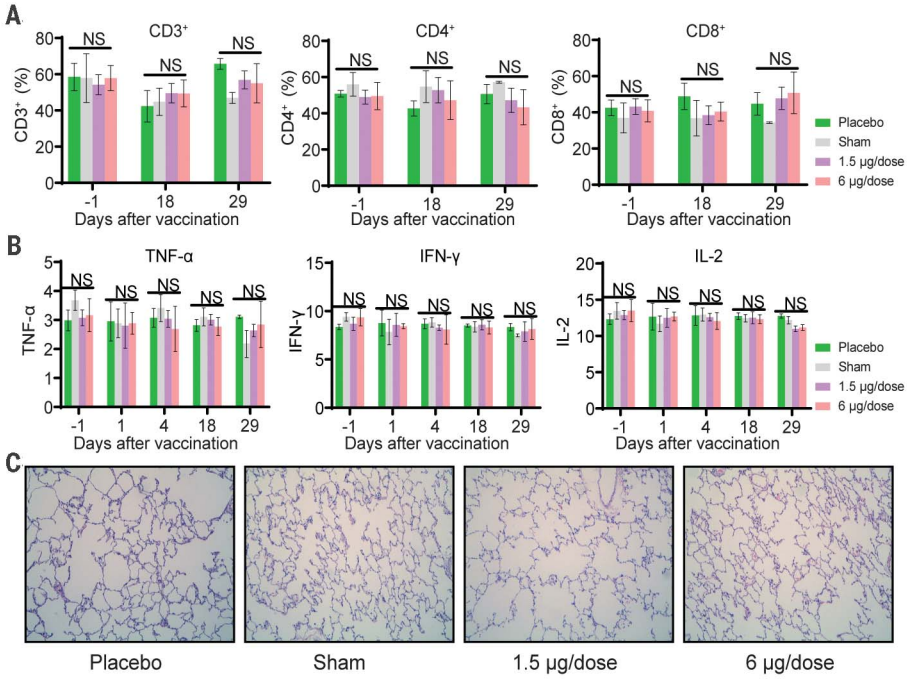

Fig. 4. Safety evaluation of PiCoVacc in nonhuman primates. Macaques were immunized three times at days 0, 7, and 14 intramuscularly with low-dose (1.5 μg per dose) or high-dose (6 μg per dose) PiCoVacc or adjuvant only (sham) or placebo. (**A** and **B**) Hematological analysis in all four groups of macaques (n = 4). (A) Percentage of lymphocytes, including $CD3^+$, $CD4^+$, and $CD8^+$, were monitored at days −1 (1 day before vaccination), 18 (3 days after the second vaccination), and 29 (7 days after the third vaccination). (B) Key cytokines containing TNF-α, IFN-γ, and IL-2 were examined at days −1, 1 (the day of the first vaccination), and 4, 18, and 29 after vaccination. Data points show mean ± SD from four independent experiments. Error bars indicate SD. (**C**) Histopathological evaluations in lungs from four groups of macaques at day 29. Lung tissue was collected and stained with hematoxylin and eosin.

by intramuscular injection with low (1.5 μg) or high (6 μg) doses, and another two groups of macaques (n = 10) were immunized with adjuvant (sham) and physiological saline (placebo) three times at the 0, 7, and 14 dpi time points. Neither fever nor weight loss was observed in any macaque after immunization with PiCoVacc, and the appetite and mental state of all animals remained normal (fig. S3). Hematological and biochemical analysis, including biochemical blood test, lymphocyte subset percentage ($CD3^+$, $CD4^+$, and $CD8^+$), and key cytokines [tumor necrosis factor (TNF)-α, interferon (IFN)-γ, and interleukin (IL)-2, IL-4, IL-5, and IL-6], showed no notable changes in the vaccinated groups compared with the sham and placebo groups (Fig. 4, A and B, and figs. S4 and S5). In addition, histopathological evaluations of various organs, including lung, heart, spleen, liver, kidney, and brain, from the four groups at day 29 demonstrated that PiCoVacc did not cause any notable pathology in macaques (Fig. 4C and fig. S6).

The serious COVID-19 pandemic and the precipitously increasing numbers of deaths worldwide necessitate the urgent development of a SARS-CoV-2 vaccine, and this requires a new pandemic paradigm. Safety and efficacy are essential for vaccine development at both preclinical studies and clinical trials. Although it is still too early to define the best animal model for studying SARS-CoV-2 infections, rhesus macaques, which mimic COVID-19–like symptoms after SARS-CoV-2 infection, appear to be promising candidates. We provide evidence for the safety of PiCoVacc in macaques, and did not observe infection enhancement or immunopathological exacerbation in our studies. Our data also demonstrate complete protection against SARS-CoV-2 challenge with a 6-μg dose of PiCoVacc in macaques. Collectively, these results suggest a path forward for the clinical development of SARS-CoV-2 vaccines for use in humans. Phase I, II, and III clinical trials with PiCoVacc, as well as other SARS-CoV-2 vaccine candidates, are expected to begin later this year.

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SUPPLEMENTARY MATERIALS

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Materials and Methods
Figs. S1 to S6
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Development of an inactivated vaccine candidate for SARS-CoV-2

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Vaccine candidate tested in monkeys

Global spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to an urgent race to develop a vaccine. Gao *et al.* report preclinical results of an early vaccine candidate called PiCoVacc, which protected rhesus macaque monkeys against SARS-CoV-2 infection when analyzed in short-term studies. The researchers obtained multiple SARS-CoV-2 strains from 11 hospitalized patients across the world and then chemically inactivated the harmful properties of the virus. Animals were immunized with one of two vaccine doses and then inoculated with SARS-CoV-2. Those that received the lowest dose showed signs of controlling the infection, and those receiving the highest dose appeared more protected and did not have detectable viral loads in the pharynx or lungs at 7 days after infection. The next steps will be testing for safety and efficacy in humans.

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