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designed, executed, and interpreted the NMR experiments; and A.M., P.S., and R.T. designed and interpreted experiments and wrote the paper. We thank F. Gualdrini, C. Esnault, and P. Costello for characterizing gene regulation in reconstituted TKO MEFs, sharing their unpublished data, and generating reconstituted TKO MEF cells; the Crick Genomics and Flow Cytometry technology platforms for technical support; and A. Behrens, V. Calleja, A. Chakraborty, M. Diefenbacher, C. Duellberg, R. Nicolas, P. Riou, M. Skehel, and our group members for advice and discussions.

SUPPLEMENTARY MATERIALS

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VACCINES

Rapid development of a DNA vaccine for Zika virus

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Zika virus (ZIKV) was identified as a cause of congenital disease during the explosive outbreak in the Americas and Caribbean that began in 2015. Because of the ongoing fetal risk from endemic disease and travel-related exposures, a vaccine to prevent viremia in women of childbearing age and their partners is imperative. We found that vaccination with DNA expressing the premembrane and envelope proteins of ZIKV was immunogenic in mice and nonhuman primates, and protection against viremia after ZIKV challenge correlated with serum neutralizing activity. These data not only indicate that DNA vaccination could be a successful approach to protect against ZIKV infection, but also suggest a protective threshold of vaccine-induced neutralizing activity that prevents viremia after acute infection.

The emergence of Zika virus (ZIKV) in the Americas and Caribbean follows a series of global threats to public health from mosquito-borne viral diseases over the past three decades. Because of the profound impact on individuals and society from a disabling congenital disease caused by ZIKV infection in pregnant women, the World Health Organization declared ZIKV a global health emergency in February 2016. Although it is likely that the incidence of ZIKV infection will decline considerably within 1 to 2 years (1), it is also likely that ZIKV will become endemic in tropical and subtropical regions, with sporadic outbreaks and potential for spread into new geographical areas, as observed with other emerging arboviruses such as West Nile (WNV) and chikungunya. Therefore, unless immunity is established before childbearing age, pregnant women will continue to be at risk for an infection that could harm their fetus. Further, because men can harbor ZIKV in semen for several months after a clinically unapparent

infection and can sexually transmit virus to a pregnant partner (2), even women in nonendemic regions will have some ongoing risk if exposed to men who have traveled to endemic regions. These characteristic features of transmission and disease suggest that there will be an ongoing need for a ZIKV vaccine to maintain a high level of immunity in the general population and in travelers to endemic regions to reduce the frequency of fetal infection.

To rapidly address the critical need for a preventive vaccine to curtail the ongoing ZIKV outbreak in the Americas, we chose a gene-based vaccine delivery approach that leverages our prior experience with a DNA-based WNV vaccine (3). Advantages of DNA vaccines include the ability to rapidly produce multiple candidate antigen designs, the ability to rapidly produce material that conforms to safety manufacturing practices, an established safety profile in humans, and a relatively straightforward regulatory pathway into clinical evaluation.

Antigen design was guided by prior knowledge about humoral immunity to flaviviruses. Vaccine-

elicited neutralizing antibodies (NAbs) are associated with protection from flavivirus-mediated disease (4). Because the most potent monoclonal flavivirus NAbs map to conformational epitopes in domain III (DIII) of the envelope (E) protein (5), or to more complex quaternary epitopes that bridge between antiparallel E dimers or between dimer rafts arrayed on the virus surface (6, 7), our goal was to identify constructs that produced particles that faithfully captured the antigenic complexity of infectious virions. Expression of the structural proteins premembrane (prM) and E are sufficient for the production and release of virus-like subviral particles (SVPs) with antigenic and functional properties similar to those of infectious virions (8, 9).

To identify promising vaccine candidates, prM-E constructs were synthesized and screened for expression and efficiency of particle release from transfected cells. prM-E sequences were inserted into a cytomegalovirus immediate early promoter-containing vector (VRC8400) that has been evaluated clinically in several previous studies (3, 10, 11). These constructs are distinct from one reported in recent studies by Larocca *et al.* (12) and Abbink *et al.* (13) that was based on a Brazilian isolate (strain

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BeH815744) and did not express the first 93 amino acids of prM, encoding only the short M peptide that is the product of furin cleavage of prM during natural infection. Because prM plays a critical role in the folding of the E protein and the release of particles from cells (14, 15), it is not known how the antigenicity of that product compares to the prM-E product described here. The prM-E sequence in the constructs used in this study was selected from a French Polynesian isolate (strain H/PF/2013) that is identical or highly related to strains circulating in the Americas. Neutralization studies using contemporary sera against temporally and geographically diverse strains indicate that ZIKV exists as a single serotype, suggesting that a single vaccine antigen will provide protection against all ZIKV strains (16). To improve expression, the ZIKV prM signal sequence was exchanged with the analogous region of Japanese encephalitis virus (JEV), as previously reported (17), to create vector VRC5283 (Fig. 1A). VRC5283 was further modified to create a second prM-E construct, VRC5288, in which the final 98 amino acids of E, comprising the stem and transmembrane regions (ST-TM), were exchanged with corresponding JEV sequences. This substitution has been previously shown to improve SVP secretion (18). Both vectors exhibited expression by mammalian cells (Fig. 1B, right panel), with more efficient SVP release into supernatants by VRC5288 (Fig. 1B, right panel, and Fig. 1C) (19). Electron microscopic analysis of negative-stained purified VRC5288 SVP preparations revealed roughly spherical particles that are consistent with the appearance of other flavivirus SVPs (Fig. 1D) (8, 20).

Next, we assessed the immunogenicity of each DNA candidate in BALB/c and C57BL/6 mice. Mice were immunized intramuscularly once with 50 μ g of DNA in the quadriceps, using electroporation, as previously described (21). Serum was evaluated for binding to ZIKV SVPs by enzyme-linked immunosorbent assay (ELISA) (fig. S1A) and neutralizing activity by using ZIKV reporter virus particles (RVPs) (fig. S1, B to D) (16). Vaccination with either VRC5283 or VRC5288 elicited ZIKV-specific NAb after a single immunization, with reciprocal EC_{50} (half-maximal inhibition of virus infection) serum dilution titers up to 10^5 in C57BL/6 mice (fig. S1D). NAb titers were similar in mice vaccinated with 2, 10, or 50 μ g of DNA (fig. S2) and were of similar magnitude to titers induced by a previously described WNV DNA vaccine (fig. S3) (3).

Immunogenicity in rhesus macaques was evaluated after delivering vaccine intramuscularly by a needle-free injection device (PharmaJet) (Fig. 2 and figs. S4 and S5). Six animals per group received two 1-mg (VRC5283) or 4-mg (VRC5283 and VRC5288) doses of vaccine at 0 and 4 weeks, and one group received a single 1-mg dose of VRC5288 at week 0. After a single dose of DNA, binding and neutralizing antibodies were detectable by week 2 and peaked at week 3. All ZIKV vaccine groups had significantly higher NAb responses than macaques that received VRC8400 control vector when comparing the area under the curve (AUC) using a Kruskal-Wallis test ($P =$

0.022; Fig. 2D). Macaques that received a single 1-mg dose of VRC5288 had significantly lower NAb titers than macaques that received two doses of either vaccine at either dose level ($P = 0.022$). There were no significant differences, when comparing the AUC, in NAb titers between animals that received two doses of VRC5283 and animals that received two doses of VRC5288. Sera collected at week 6 were also evaluated for NAb activity by the conventional focus-reduction neutralization test (FRNT) (22, 23) and a microneutralization (MN) assay (12, 13, 24). The results of both the FRNT and MN assays strongly correlated with EC_{50} RVP values (fig. S6 and table S1), although the RVP assay was more sensitive than the MN assay, as demonstrated by the detection of neutralizing activity in macaques that received only a single 1-mg dose of VRC5288 (average week 6 reciprocal EC_{50} serum NAb titers of 322 versus <10 for RVP and MN assays, respectively). Further comparison of these assays showed that MN values above the limit of detection corresponded more closely to EC_{90} RVP values (1.3-fold average difference between RVP EC_{90} and MN EC_{50} versus 9.6-fold average difference between RVP EC_{50} and MN EC_{50} NAb titers for all animals at week 6). These data indicate that both VRC5283 and VRC5288 elicit substantial ZIKV-specific NAb in macaques.

Eight weeks after the first immunization, all animals were challenged subcutaneously with 10^3 focus-forming units (FFU) of the Puerto Rican ZIKV strain PRVABC59 (GenBank identifier, KU501215.1), and blood was collected daily for quantitative polymerase chain reaction (qPCR)

analysis of ZIKV genome copies in plasma (13, 19). Control animals showed a peak virus load (VL) at day 3 or 4 of between 10^4 and 10^6 genome copies/ml. Animals that received two 4-mg or 1-mg doses of VRC5283 or two 4-mg doses of VRC5288 were largely protected from viremia, with 17 of 18 animals having no detectable viremia (Fig. 3A). One animal that received two 4-mg doses of VRC5288 had a low-level positive PCR in one of two assays performed on day 3 and another positive blip at day 7. All six animals that received a single 1-mg dose of VRC5288 were viremic, with a peak VL at day 3 of between 10^2 and 10^5 genome copies/ml. This VL was significantly reduced relative to that of animals that received two doses of VRC8400 control vector (comparing AUC by a Wilcoxon exact test; two-sided $P = 0.041$). The cutoff for low values has been established at <100 genome copies/ml, so it cannot be ruled out that low-level viremia may have occurred in other animals.

Of the animals that received two doses of vaccine, 17 of 18 (94%) had no detectable viremia after challenge. The animal with blips above background levels at days 3 and 7, which received two 4-mg-doses of VRC5288, had a prechallenge reciprocal EC_{50} NAb titer of 1218, which was among the lowest titers of all those measured in the two-dose vaccine groups (Fig. 4A). A probability analysis indicated that one could anticipate 70% protection from viremia if a reciprocal EC_{50} serum NAb titer of 1000 is achieved in the RVP assay (Fig. 4B). This corresponds roughly to a reciprocal EC_{50} MN titer of ~ 100 (fig. S6), which is similar to the NAb titer that has been shown to prevent

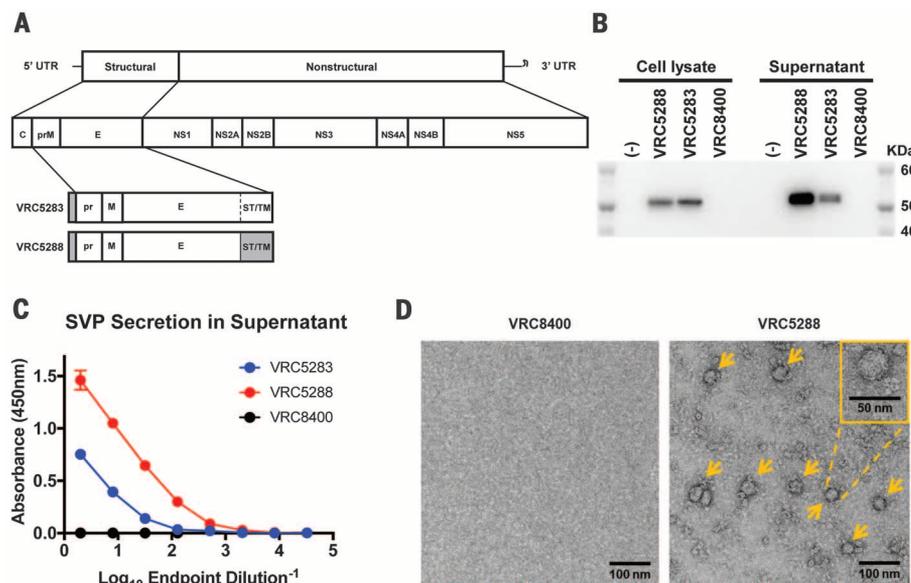


Fig. 1. ZIKV DNA vaccine design and characterization. (A) Schematic representation of the ZIKV genome and ZIKV DNA vaccine constructs VRC5283 and VRC5288. UTR, untranslated region; C, capsid; NS, nonstructural. (B) Expression and secretion of ZIKV E was analyzed by Western blot of transfected 293 T cell lysates and SVP precipitate pelleted from culture supernatants through a 20% sucrose cushion, demonstrating that VRC5288 secretes more particles than VRC5283. (C) Particle-capture ELISA quantifying the secretion of ZIKV SVPs from transfected cells. (D) ZIKV SVPs were purified from the culture supernatant of VRC5288-transfected 293F cells and subjected to negative staining and electron microscopy. SVPs are labeled with arrowheads. The VRC8400 empty backbone plasmid vector was used as a control.

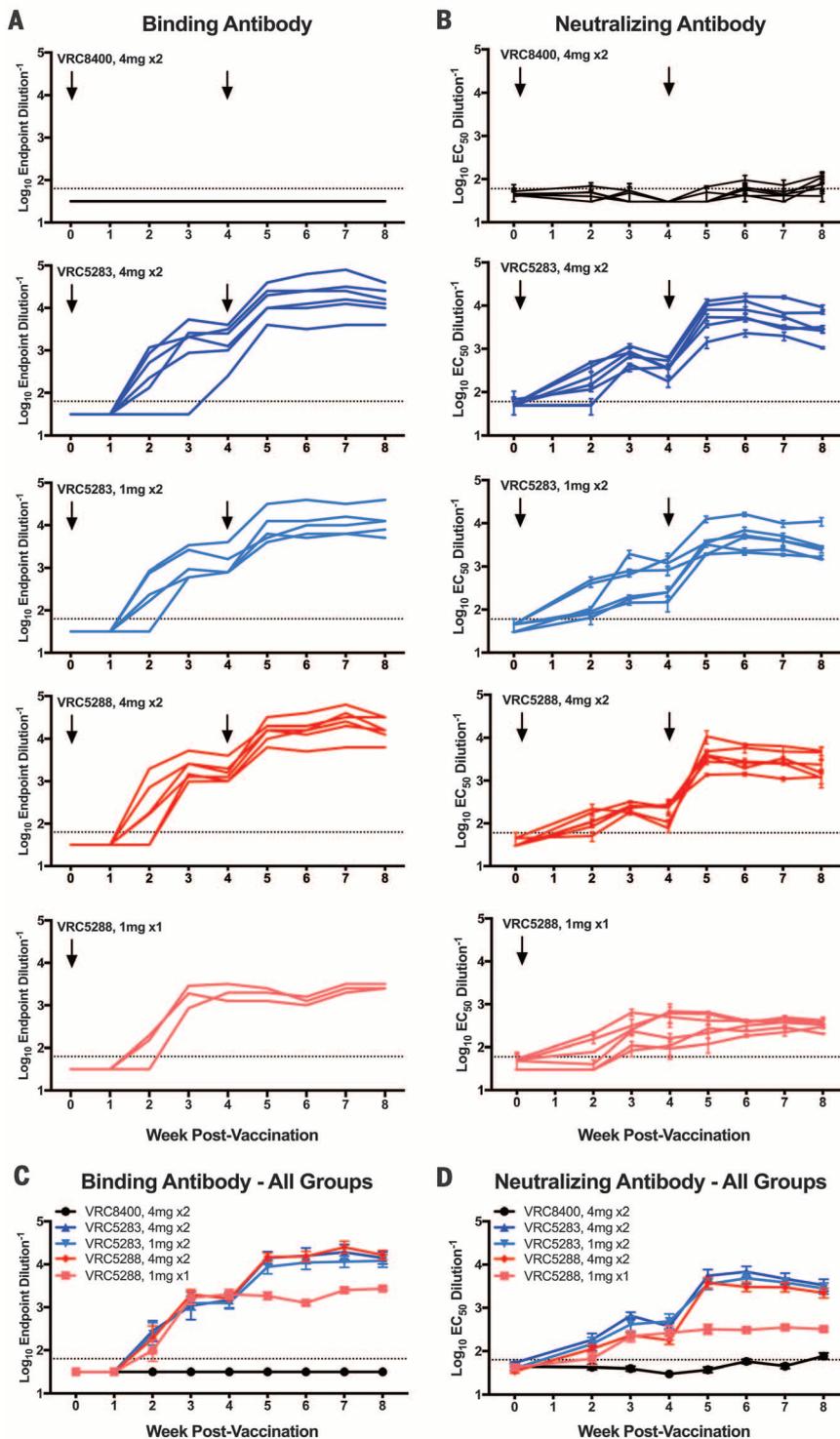


Fig. 2. ZIKV DNA vaccines elicit robust binding and neutralizing antibodies in nonhuman primates. Rhesus macaques ($n = 6$ per group) were either mock-immunized with VRC8400 empty backbone plasmid or vaccinated with VRC5283 or VRC5288 plasmids intramuscularly; doses and number of vaccinations are indicated. **(A)** Macaque sera were assayed weekly by ELISA for ZIKV binding antibodies. Each line represents the average titer of an individual animal from one or two technical duplicates, and the dashed line indicates the limit of detection (reciprocal titer of 64). Any measurement below the limit of detection was assigned a value of half the limit of detection for graphing and statistical purposes. **(B)** The NAb response elicited by vaccination was analyzed using ZIKV RVPs. The dilution of sera required for half-maximal inhibition of virus infection (EC_{50}) was estimated by nonlinear regression analysis. Lines connect average EC_{50} values from two to five independent experiments, each performed with technical duplicates, for the individual monkeys in each group at each time point. The dotted line denotes the limit of confidence for the RVP assay (reciprocal titer of 60). Measurements below the limit of detection were assigned a value of 30. The average **(C)** binding antibody and **(D)** NAb responses for each vaccine group are shown. Throughout, error bars denote SEM.

viremia in nonhuman primates passively treated with immune serum (13).

Animals receiving a single 1-mg dose of VRC5288 had prechallenge reciprocal EC_{50} NAb titers measured by the RVP assay of between 203 and 417. The two animals with the highest NAb activity were the ones with delayed onset of viremia at day 3. MN titers at the 6-week time point, as noted above, were undetectable in the group receiving

a single 1-mg dose, and these animals uniformly had breakthrough infection (table S1). Therefore, the larger dynamic range of the RVP assay will allow a more precise definition of the protective threshold needed to prevent viremia in a particular model or against a particular challenge inoculum (figs. S5 and S7).

One concern that is routinely raised about vaccination against flaviviruses is the possibility of

enhanced disease if there is incomplete or waning immunity, as observed in a subset of secondary dengue virus infections (25). In this study, the group that received a single 1-mg dose of VRC5288 had low, subprotective NAb levels that resulted in breakthrough infections. In those animals, there were reduced levels of viremia relative to unvaccinated controls and no visible signs of illness or enhancement of replication. Retrospectively, we also determined that one animal in the mock-immunized control group and one in the single 1-mg-dose VRC5288 group with detectable levels of ZIKV antibody binding, but no neutralizing activity at week 0, had preexisting WNV-specific NAb (fig. S8). The levels of virus replication in these animals were near the group average, and there was no evidence of disease enhancement in the setting of prior flavivirus exposure.

Vaccine development for ZIKV must be specific and guided by an expanded understanding of ZIKV virology, pathogenesis, immunity, and transmission. It must also be strategic, matching technical and manufacturing feasibility with the target populations that will benefit most. In addition, to achieve both rapid deployment and long-term protection, it should be staged. This means that a rapid response to the global health emergency may require a different vaccine approach than the longer-term goal of achieving durable immunity in the general population as ZIKV becomes a sporadic, endemic infection. Both VRC5288 and VRC5283 will be evaluated in human trials. A phase 1 clinical trial (ClinicalTrials.gov identifier, NCT02840487) of VRC5288 has already been launched to test a variety of regimens and doses for safety and immunogenicity. These trials constitute the initial efforts to define the level of

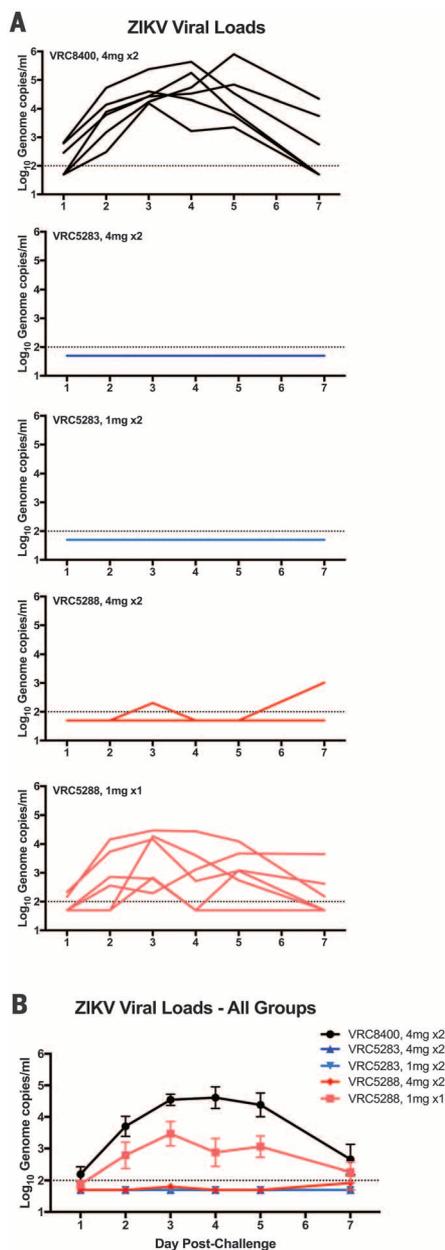


Fig. 3. ZIKV DNA vaccines reduce viremia in ZIKV-challenged rhesus macaques. Eight weeks after the first vaccination, macaques were challenged with 10^3 FFU of ZIKV strain PRVABC59. **(A)** qPCR of the capsid gene was used to determine the number of genome copies per milliliter on days 1 to 5 and 7 after challenge. Each line represents an individual animal. **(B)** Mean viral load after challenge in each group. Error bars represent SEM. The dashed line indicates the limit of detection (100 copies/ml). Any value below the limit of detection was assigned a value half the limit of detection for graphing and AUC calculation.

vaccine-induced NAbs required for the prevention of ZIKV viremia. Establishing a functional serological correlate of sterilizing immunity is key for leveraging the information gained from efficacy

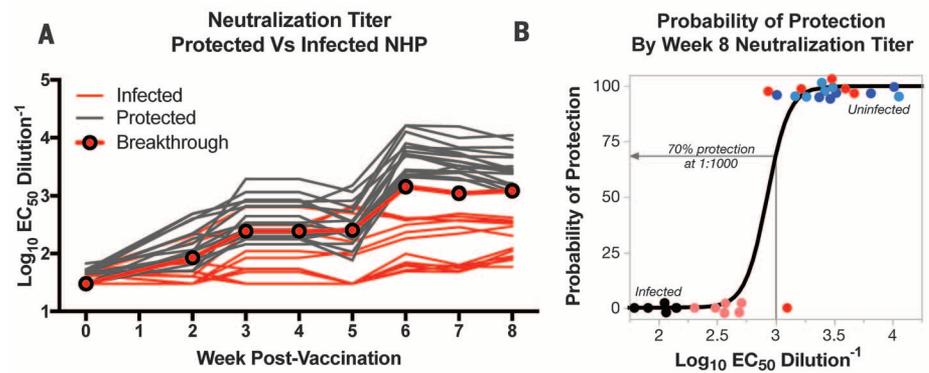


Fig. 4. Protection from ZIKV challenge correlates with NAb titers present at challenge. Animals that had detectable viremia after challenge were analyzed with respect to prechallenge NAb activity. **(A)** The reciprocal EC_{50} NAb titer of each animal is individually plotted to reflect whether infection occurred. Lines represent individual animals. Protected (no detectable viremia) and infected (viremia detectable on 2 successive days) animals are represented by gray and red lines, respectively. The sole animal that received two 4-mg doses of VRC5288 and was found to have a low level of viremia on days 3 and 7 after challenge is denoted as “breakthrough” (circles with black outlines). **(B)** The probability of protection (logit) based on the reciprocal EC_{50} NAb titer is shown and indicates that prevention of viremia would be expected in ~70% of animals with NAb titers >1000 . The colors of the circles indicate vaccination group (black, VRC8400, 4 mg \times 2; blue, VRC5283, 4 mg \times 2; light blue, VRC5283, 1 mg \times 2; red, VRC5288, 4 mg \times 2; pink, VRC5288, 1 mg \times 1).

trials of various candidate vaccines. The phase 1 clinical trials of VRC5288 and VRC5283 are being designed in parallel with efforts by other groups to evaluate a purified, protein-based, whole-inactivated ZIKV vaccine and live-attenuated vaccine approaches. These studies and others to evaluate alternative antigen designs, delivery approaches, and combination vaccine regimens will inform the next steps of vaccine development and provide options for achieving both the short-term goal of protecting women of childbearing age in the present ZIKV outbreak and the long-term goal of vaccinating the general population of, and travelers to, endemic regions.

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Rapid development of a DNA vaccine for Zika virus

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Editor's Summary

A DNA vaccine candidate for Zika

The ongoing Zika epidemic in the Americas and the Caribbean urgently needs a protective vaccine. Two DNA vaccines composed of the genes that encode the structural premembrane and envelope proteins of Zika virus have been tested in monkeys. Dowd *et al.* show that two doses of vaccine given intramuscularly completely protected 17 of 18 animals against Zika virus challenge. A single low dose of vaccine was not protective but did reduce viral loads. Protection correlated with serum antibody neutralizing activity. Phase I clinical trials testing these vaccines are already ongoing.

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