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A vaccine candidate for Zika with potential for reduced risk of antibody-dependent enhancement (ADE)

Zika virus (ZIKV) is a mosquito-borne flavivirus that has rapidly extended its geographic range. Its association with abnormal fetal brain development, sexual transmission, and lack of a preventive vaccine have constituted a global health concern. Designing a safe and effective vaccine requires significant caution due to the overlapping geographical distribution of ZIKV with dengue virus (DENV) and other flaviviruses, potentially resulting in more severe disease in vaccine recipients who become flavivirus infected. Such an effect can be caused by Antibody-Dependent Enhancement (ADE), a phenomenon involved in pathogenesis of DENV infection, and a risk associated with ZIKV vaccines using ZIKV structural envelope proteins as immunogens.

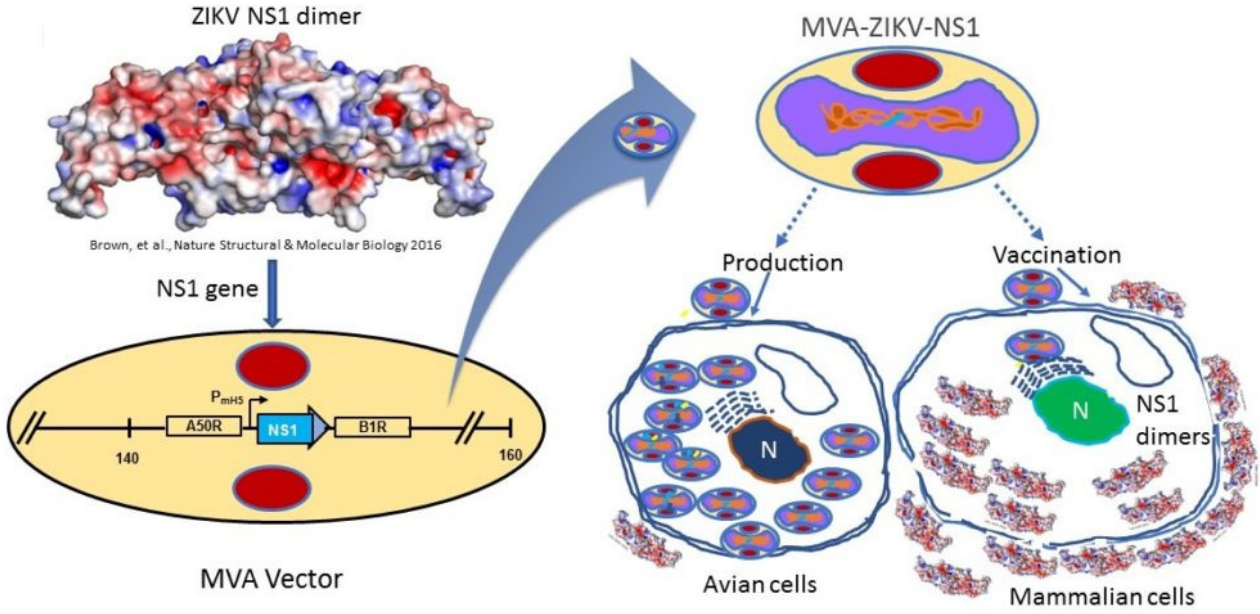

Fig. 1. ZIKV NS1 gene (Suriname 2015 isolate) was inserted into the MVA restructured and modified deletion III. This insertion site has been identified to support high expression and insert stability. PmH5, modified H5 promoter. Numbers are coordinates in the MVA genome. MVA vaccines are replication competent in avian cells used for vaccine production, yet replication deficient in mammalian cells, making them putatively safe for humans, including immunocompromised or pregnant individuals.

Here, we describe the development of a Modified Vaccinia Ankara (MVA) vaccine expressing the ZIKV non-structural protein NS1, thus averting the potential risk of ADE associated with structural protein-based ZIKV vaccines. A single intramuscular immunization of immunocompetent adult mice with the MVA-ZIKV-NS1 vaccine candidate provided robust humoral and cellular responses and afforded 100% protection against a lethal intracerebral dose of ZIKV (strain MR766).

ADE of viral infection has been documented *in vitro* and *in vivo* as a potential risk with ZIKV envelope protein (E)-directed vaccines. This is especially relevant for cross-reactive antibodies between DENV and ZIKV, because DENV seroprevalence can be up to 90% in newly affected

ZIKV areas and ZIKV and DENV are genetically and antigenically similar (56% AA identity) and cross reactivities between them are documented extensively. Until larger-scale Phase III clinical studies with ZIKV E immunogens are performed to evaluate the threat of ADE in DENV-endemic areas (e.g., enhancement of DENV infections by ZIKV immunity or vice versa), ADE will remain a concern for use of these vaccines in the populations most in need of ZIKV immunization. While the E protein is considered as a desired antigenic target for eliciting protective neutralizing antibodies against ZIKV, NS1 has been shown to induce protective non-neutralizing antibodies that target and kill virus-infected cells. The NS1 protein plays an important role in immune evasion (in both human and mosquito hosts) by modulating the host cellular machinery to help propagate flaviviruses in the host. Therefore, NS1 protein and anti-NS1 antibodies have been proposed as flaviviral vaccines and therapeutic candidates, respectively. Unlike potential enhancement of infection between DENV and ZIKV by anti-E antibodies, anti-NS1 antibodies should not pose a risk of ADE to vaccinated individuals since NS1 proteins are not packaged with the virus or found on the surface of virions. Therefore, we expect that our NS1-based vaccine could not only protect individuals against symptomatic ZIKV disease, without any risk of ADE, but could also reduce infection rates in the mosquito vector, thus interrupting ZIKV transmission in areas of high endemicity with lower vaccine coverage.

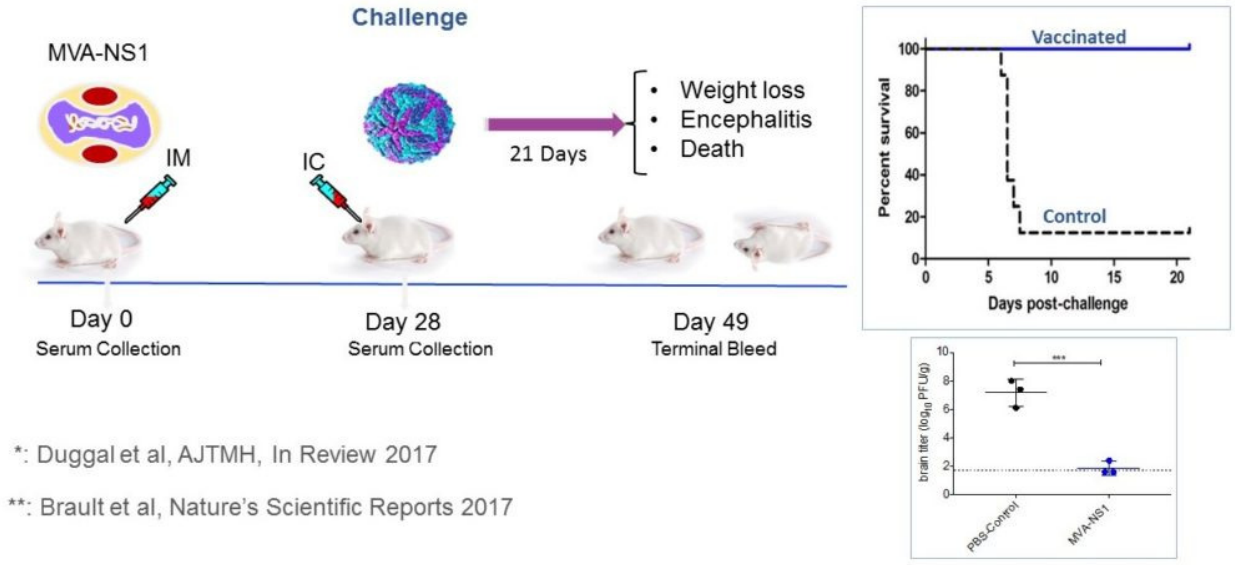

Fig. 2. Immunization of CD-1/ICR mice with a single dose of MVA-ZIKV-NS1 vaccine followed by intracerebral challenge with neuroadapted ZIKV strain MR766 (Left Panel). All vaccinated mice (N=23) survived the challenge while 90% of controls (n=10) died (Right Top Panel). On Day 5, brains of three mice from each group were titrated on Vero cells by plaque assay to determine levels of ZIKV. Individual points are shown for each mouse. The limit of detection (LOD) was 1.7log10 PFU/gram. The brain titers at Day 5 post infection (previously determined as the peak virus titer) in vaccinated mice was 200,000-fold lower than those of control animals indicating a rapid clearance of the infectious virus in brains of vaccinated and challenged mice.

The NS1 was cloned into a recombinant MVA vector which has previously induced robust and durable protective immunity in preclinical and clinical HIV vaccine trials and preclinical Ebola studies. Immunocompetent mice were immunized with a single dose of the NS1 vaccine, and immunogenicity and protective efficacy were assessed in a newly developed lethal intracranial (IC) challenge model (Fig. 2). Vaccinated mice developed robust anti-NS1, a Th1-biased immune response, significant killing of the ZIKV infected cells, complement fixing activity, and strong CD8+ T cell responses (secreting IL2 and IFN-gamma cytokines) (Data not shown) and were fully protected after the IC challenge witout any significant symptoms or weight loss. In contrast, most sham-immunized animals lost weight and were euthanized (~70-100%) according to the Institutional Animal Care and Use Committee (IACUC) proptocol. At 5 days post infection, the mean brain titer in control mice was 7.2 $\log_{10}$ PFU/g tissue, whereas no detectable viral load was observed in two of three MVA-NS1 immunized mice (Fig. 2). The mean viral load in the brains of vaccinated mice was 200,000-fold lower than that observed in the PBS immunized mice ($p>0.001$). The vaccine is currently being tested in non-human primates for efficacy.

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Publication

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