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Perspective

The Vaccine Protects against Zika Virus Pregnancy Transmission and Testicular Damage

Anne Conel*

Department of Paediatric Immunology and Infectious Diseases, Children's Health Ireland at Crumlin, Dublin, Ireland

DESCRIPTION

Infection with the Zika virus during pregnancy can result in congenital abnormalities or foetal death. The persistence of the Zika virus in the male reproductive system raises the possibility of sexual transmission. We show that live-attenuated Zika virus vaccine candidates with deletions in the 3′ untranslated region of the Zika virus genome (ZIKV-3′UTR-LAV) prevent viral transmission during pregnancy, testis damage, and nonhuman primate infection. Pregnant mice challenged with Zika virus at embryonic day 6 and evaluated at embryonic day 13 have significantly lower levels of viral RNA in maternal, placental, and foetal tissues after a single dose vaccination. Male mice vaccinated against Zika virus were protected from testis infection, injury, and oligospermia. A single rhesus macaque immunisation elicited a rapid and robust antibody response, conferring complete protection upon challenge. Furthermore, the safety profile of the ZIKV-3′UTR-LAV vaccine candidates is favourable. These findings suggest that further research into ZIKV-3′UTR-LAV for humans is necessary.

Zika virus (ZIKV) is a member of the Flavivirus genus in the Flaviviridae family and is closely related to dengue, yellow fever, Japanese encephalitis, West Nile, and tick-borne encephalitis viruses. Flaviviruses have a positive-sense RNA genome that is single-stranded and consists of a 5′ Untranslated Region (UTR), a single Open Reading Frame (ORF), and a 3′UTR. The single ORF encodes three structural proteins (C-prM/M-E) and seven nonstructural proteins (NS1-NS2A-NS2B-NS3-NS4A-NS4B-NS5). ZIKV is primarily transmitted by peridomestic Aedes mosquitos, but it can also be acquired via sexual, vertical, and blood transfusion routes. Although only about 20% of infected people develop clinical signs or symptoms, ZIKV infection has been linked to the development of Guillain-Barré syndrome in some adults. Microcephaly, craniofacial disproportion, spasticity, seizures, ocular abnormalities, cerebral calcification, and miscarriage are the most devastating manifestations of ZIKV infection in foetuses and infants of women infected while pregnant. Longitudinal human studies in Brazil revealed that 42% of live infants born to ZIKV-positive women had grossly abnormal clinical or brain imaging findings. Furthermore, ZIKV infection can persist in the male reproductive tract for up to 69 and 188 days after the onset of symptoms, respectively; infected males can transmit virus to sexual partners during this period of persistent infection. ZIKV persistence in the testis has been linked to seminiferous tubule damage, testicular atrophy, oligospermia, and lower fertility rates in mice. A number of promising ZIKV vaccine platforms, including inactivated, subunit (prM-E proteins expressed from DNA, RNA, or viral vectors), and live-attenuated vaccines, have been developed, with several of them entering phase I-II clinical trials.

The prM-E RNA vaccine and live-attenuated vaccine (lacking NS1 glycosylations) have recently been shown to protect against vertical transmission in a mouse pregnancy model. Furthermore, a DNA vaccine expressing prM-E proteins was recently shown to protect mice against ZIKV-induced testicular damage.

They show that live-attenuated ZIKV vaccine candidates with deletions in the 3′UTR of the ZIKV genome (ZIKV-3′UTR-LAV) prevent viral transmission during pregnancy, testis damage, and Nonhuman Primate Infection (NHPs). We also show that the vaccine candidates have a favourable safety profile. Our findings suggest that ZIKV-3′UTR-LAV warrants further research for human use.

Correspondence to: Anne Conel, Department of Paediatric Immunology and Infectious Diseases, Children's Health Ireland at Crumlin, Dublin, Ireland, E-mail: anne.conel@ucd.ie

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