

## Recent Efforts in the Development of Therapies against Zika Virus

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Recent outbreaks of Zika infection in Latin America and Florida and its associated complications have attracted a lot of attention and are currently a significant public health concern. Zika is a virus (ZIKV) that is spread primarily by the bite of an infected *Aedes* species mosquito (*Aedes aegypti* and *Aedes albopictus*) [1]. The Zika virus can also be sexually transmitted [2]. The symptoms of Zika virus disease range from fever, rash, joint and muscle pain to microcephaly and other birth defects. Zika virus is a member of flavivirus family. Similarly to other flaviviruses, ZIKV genome includes structural genes that encode capsid, pre-membrane protein (prM), and envelope protein (E). The structure of ZIKV is similar to other members of flavivirus family, especially to all four serotypes of Dengue virus (DENV). Currently there are no licensed treatments available for Zika virus disease [3]. It has been recently projected that around 1.65 million childbearing women and approximately 93.4 million people in total could become infected before the end of the first wave of the epidemic [4]. Therefore, a considerable effort is underway to come up with effective prevention and treatment options against Zika infection. Currently, there exists a number of promising prevention therapies and potential treatment options including small molecules (some of which have previously been approved by FDA to treat other diseases), vaccine candidates, and neutralizing purified antibodies. Below are an overview of such current experimental antiviral therapies and the discussion of their potential advantages and disadvantages.

### Vaccines against Zika

Vaccination is one of the most effective forms of protection against the viral infections. It was recently shown that a single immunization with a plasmid DNA vaccine expressing ZIKV prM and E genes or a purified inactivated virus vaccine provide complete protection in susceptible mice and rhesus monkeys against challenge with a strain of ZIKV involved in the outbreak in northeast Brazil. Furthermore, an adoptive transfer of purified IgG from vaccinated mice and rhesus monkeys was shown to confer passive protection in both respective animals [5,6]. These results are promising, since they suggest that ZIKV vaccine would be able to protect the host against infections caused by a related DENV. Consistent with this notion, monoclonal antibodies derived from DENV patients have been shown to cross-inhibit DENV and ZIKV in cellular assays [7].

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Although it was previously observed that a primary DENV infection protects from reinfection with the same serotype and thus might be used for protection from ZIKV infection, it unfortunately leads to the enhancement of infection with a different DENV serotype. This phenomenon is thought to occur by the “antibody-dependent enhancement” mechanism, where antibody-bound DENV binds to Fc receptors on the surface of monocytes and infects those host cells. Therefore, the potential concern of ZIKV vaccine is an increase in the severity of subsequent infections with DENV. In fact, several studies have shown that monoclonal ZIKV antibodies activate the pathogenicity of DENV in cellular assays, and vice versa [8,9].

### Zika–Neutralizing Monoclonal Antibodies

Neutralizing Monoclonal Antibodies (NmAbs) function by neutralizing any biological effects of a pathogen. Several recent studies have identified NmAbs that effectively inhibit pathogenicity of ZIKV in cellular and animal studies. The authors of these studies have also determined epitopes on ZIKV surface bound by these neutralizing antibodies. Three epitopes were localized within ZIKV E protein amino acids 301–404, which comprise E protein domains DI and DIII important for virus maturation [10]. Another recent study identified a fourth ZIKV-NmAb, shown to bind to E protein region known as a “fusion loop”, a protein region important for fusion of viral membrane

with that of endosomes. The fusion loop is highly conserved between ZIKV and all DENV serotypes, and the identified antibody inhibits ZIKV *in vitro* and *in vivo* experiments [11]. A fifth identified ZIKV–NmAb was identified and shown to bind to yet another loop of E protein, called a “glycan loop”. The glycan loop is thought to be important for the binding of ZIKV to host cellular receptors, and additionally, this broadly neutralizing monoclonal antibody (BNmAb) was shown to inhibit the pathogenicity of ZIKV and all DENV serotypes in cellular assays [12].

## Repurposing Approved Drugs as Zika Therapies

Vaccines and monoclonal antibodies are often criticized for being expensive, requiring cold chain storage, and as a result their usage in developing countries had been limited. On the other hand, current interest in repurposing of small molecule drugs already approved by U.S. Food and Drug Administration (FDA) as treatment options of new indications have shown a rapidly growing degree of global interest. Plus there is an urgent need to find drugs to treat already-infected individuals [13]. Due to the rapid spread of Zika and its devastating effects on the human health, a number of research groups have focused their efforts on the repurposing of FDA-approved drugs as new treatments of Zika infection. Such drugs may already have well-established safety and pharmacokinetic profiles in humans and animals, and thus, could be rapidly repurposed as Zika drugs. In the past several years, there have been numerous successful efforts of

drug repurposing against biological threat agents, including Zika [14-16].

In one of the studies aimed on identifying next treatments for ZIKV infection through drug repurposing, several anti-microbial small molecule drugs were shown to effectively inhibit the infectivity of ZIKV in cellular assays, such as anti-bacterial drug Daptomycin and the anti-malarial drug, Mefloquine [14]. Moreover, two concurrent studies have demonstrated that structurally-unrelated small molecule drugs previously approved as anti-helminthic, act as host-oriented anti-ZIKV countermeasures by targeting host caspases [15,16]. Pro-apoptotic host caspases have recently been shown to be induced by ZIKV in infected host neuronal cells [17,18]. Xu et al. showed that anti-helminthic Niclosamide inhibited ZIKV replication by inhibiting host caspase-3 [16]. Leonardi et al. showed that anti-helminthic Bithionol inhibited ZIKV infectivity by inhibiting host caspases-3, -6, -7, -9, and -1 [15]. Since many viruses and other pathogenic agents cause host cell death by inducing host caspases, caspase inhibitors can be used as broad-spectrum therapies. In fact, the study by Leonardi et al. demonstrated that Bithionol effectively protected host cells from other bacterial toxins and ricin [15].

It is thrilling to observe and contribute to the combined global effort to combat various epidemics, including Ebola and Zika. As a scientist, I have full confidence that the newly elected US government will dedicate more funding for scientific research on infectious diseases, especially vector-borne diseases like Zika.

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