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Challenger Treats Zika Virus

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Abstract

Purpose of review Arthropod-borne viruses (arboviruses) are zoonotic, and the common vectors are ticks and hematophagous mosquitoes. Currently, dengue, chikungunya, yellow fever, West Nile, and Japanese encephalitis virus infections have been causing worldwide concerns. In 2015, a large outbreak was documented with another mosquito-borne flavivirus, the Zika virus (ZIKV), and ravaging South and Central Americas and the Caribbean. ZIKV was declaring a public health emergency, because of the clinical evidence neurological complications.
Recent findings The flavivirus infection is difficult to differentiate only with clinical manifestation. It has been reported 2366 cases of microcephaly or congenital defects associated with ZIKV in Brazil, and the mechanism or processes that lead to these neurological complications are still under investigation. No antivirals are available to treat ZIKV infection, leading to no option to prevent the fetal infection during pregnancy which could avoid the congenital Zika syndrome. In this review, we will describe the drugs that are being tested in vitro and in animal models against ZIKV.
Summary We reviewed several publications that test the compounds for the treatment of ZIKV disease. We conclude that some of these compounds testing in vitro and in vivo have shown a therapeutic possibilities to consider and to be test in pregnancy and in individuals with high risk of infection.

Introduction

Zika virus (ZIKV) is a flavivirus transmitted by *Aedes* spp. mosquitoes, isolated in 1947 the Zika Forest in Uganda [1]. ZIKV is an enveloped, RNA virus of the Flaviviridae family [2]; the genome is 11 kbp long with three structural proteins—capsid (C), the precursor of membrane (prM)/membrane (M), and

envelope (E)—and seven nonstructural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS5) [3]. In 2007, the epidemic in Yap Island, Micronesia, infected 73% of the population and only 19% of infected subjects described symptoms compatible to a clinical disease [4]. Zika virus can be transmitted by urine, sex, saliva, and breast feeding [5–7]. Only 20% of the cases ZIKV infections present symptoms, which are generally similar to dengue. Patients may present pruritic maculopapular rash, fever, arthritis, arthralgia, and edema of the extremities [4, 8]. The major concern is the linkage with congenital microcephaly and Guillain-Barré Syndrome (GBS) [9–11]. Increased cases of GBS were documented in the French Polynesia outbreak in 2013 [9]. In 2015, Brazil was in high alert with the ZIKV epidemic, as at least 0.5–1.5 million people were infected by the virus and the cases of GBS and neonatal microcephaly dramatically increased [12, 13]. The Brazilian epidemic was probably a consequence of high *Aedes* spp. mosquitoes infestation and the viral introduction in a vastly naïve population [14].

It is important to establish good animal models to test vaccine and drug candidates. Vaccines are in phase I and II clinical trials, whereas ZIKV-specific neutralizing antibody therapies have shown promise in the mouse and non-human primates model [15]. There are currently no FDA-approved drugs available for the prevention or treatment of ZIKV infection or its complications.

Li et al. demonstrated that chloroquine could inhibit ZIKV infection in vitro, by blocking virus internalization, however, has not antiviral effect when administrated 24-h post-infection in mouse models. More studies with chloroquine could be done, since it is a FDA approved, commonly used antimalarial drug that can be used in pregnancy [15].

Xu et al. identified Emricasan and Niclosamide as an antiviral activity, protecting cell death and with neuroprotective ability, capable of suppressing ZIKV replication and cell death in multiple neural cell types [16]. Barrows et al. described that mycophenolic acid, bertezomib, and damptomycin reduce ZIKV infection in multiple cell types. These drugs are FDA approved with positive safety profiles, many already used in pregnant women [17••]. Bullard-Feibelman et al. have demonstrated that Sofosbuvir inhibited ZIKV infection in vitro. This finding is encouraging, since sofosbuvir had activity against several ZIKV strains [18••]. 25-hydroxycholesterol (25HC) inhibits infection by ZIKV and other flaviviruses. Treatment with pre- or post-ZIKV infection significantly reduces the morbidity and mortality in mice and considerably reduces fever and viremia in monkeys [19].

Review

The ZIKV infection is describe to cause several neuropathology and congenital syndrome associated with this flavivirus. However, no vaccines or any therapeutic interventions are currently available for clinical use. Here we will describe the compounds testing in vitro and in vivo for block viral entry, neuroprotective activity, and protect against cell death.

Vaccines are in early trials for effective ZIKV prevention, in Clinicaltrials.gov has four recruiting studies and six active, not recruiting for ZIKV vaccine [20]. There are no available treatments for any member of the Flavivirus genus.

Some drugs were tested in different models and with other pathogens.

Bortezomib

It is a drug approved by FDA to treat multiple myeloma [17••, 21] and is an antineoplastic proteasome inhibitor by ubiquitin proteasome pathway [22].

In vitro, inhibit replication of dengue virus type 1–4 and yellow fever virus (YF17D strain) in primary monocytes with low-nanomolar concentrations [21]. Anti-dengue efficacy of bortezomib was demonstrated in C57BL/6 mice

infected with DENV2 treated with a single dose of bortezomib where observed reduction of viral burden, degree of thrombocytopenia, plasma leakage, and the levels of TNF-α [21].

Bortezomib is capable to reduce the infection of ZIKV MEX_I_7 and ZIKV DAK_4152 in HuH-7 cells and human neuronal stem cell (hNSCs) with moderate toxicity [17••].

Bromocriptine

Bromocriptine is an agonist of dopamine receptors 2 and 3 which used to treat galactorrhea [23] and Parkinson's disease [24–26] and is safe in pregnancy [27]. In 2016, was a reported that demonstrated an antiviral activity against all dengue virus serotypes, with low cytotoxic by interfering in the RNA synthesis [26]. Bromocriptine inhibited ZIKV protease activity in docking model, interacting with several active site residues of ZIKV-NS2B-NS3 [28]. In vitro assays with Vero cells infect with Puerto Rico strain; this drug inhibits the ZIKV NS2B-NS3 protease [28].

Chloroquine

Chloroquine (also known as chloroquine phosphate) is an antimalarial medicine [29] and has been used as secondary drug in the rheumatic arthritis and systematic lupus erythematosus [30]. Chloroquine can be prescribed to adults and children of all ages and also be safely taken by pregnant women and nursing mothers [29].

Clinical trial realized in 2013 showed anti-inflammatory action by chloroquine in individuals which had dengue [30] and in vitro demonstrated antiviral act against HIV and severe acute respiratory syndrome [31].

Li et al. (2017) demonstrated that chloroquine can prevent in acute infection of animal model, ZIKV-induced mortality but not after 24-h post-infection [15].

Cyclosporine A

It is a cyclophilin inhibitor with immunosuppression action, and it has been used in patients after organ transplants [32, 33]. Inhibitor activity against dengue, yellow fever, and West Nile virus was reported in vitro assay by blocked the replication with nontoxic concentration [33].

Screen analysis shows a potential inhibition of ZIKV in HuH-7 cell and hNSC; however, this drug changes the cell morphology and cause death due to the high toxicity [17••].

Daptomycin

Daptomycin, also known LY 146032, is a cyclic lipopeptide antibiotic against selected gram-positive bacteria and has been used since 1986 [34].

Anti-flaviviral effect had never been reported until Barrows et al. (2017) when was observed reduction of ZIKV_MEX_I-7 infection rate in Huh-7 cell, HELA cell, and primary human amnion epithelial cells (hAECs) [17••].

Duramycin

tetracyclic peptide specifically binds phosphatidylethanolamine (PE) lantibiotic agent [35]. However, duramycin was reported to lyse red cells at high concentrations [36]. The phospholipid PE is present at the surface of

enveloped viruses and is a ligand for a T cell immunoglobulin and mucin (TIM1) domain protein family that regulates innate and adaptative immune functions and cell survival [37]. This drug is capable to block ZIKV infection of primary placental cytotrophoblasts and amniotic epithelial cells, blocking the interaction of ZIKV and TIM1, a cofactor [38••]. In other study, it showed an efficiently bound to dengue virus type 2 and a virus-like particle West Nile virus and Ebola virus [36].

Emricasan

Emricasan is an inhibitor of activated pan-caspases and was identified as the most potent anti-cell-death compound, with no significant adverse events in humans [39]. Xu et al. (2016). tested emricasan in the Uganda and Cambodian strain and showed neuroprotective activity of human neural progenitor cells (hNPCs), but did not suppress ZIKV replication [16].

Ivermectin

It is used for human treatment of onchocerciasis, but is effective for several worm infections [40]. In the acute phase of infection (14 h in vitro assay), ivermectin is capable to inhibited yellow fever virus infection [41], however, only in a particular phase of the flaviviral replication cycle [42]. Barrow et al. (2016) demonstrated ability of inhibit ZIKV infection in HELA cells, JEG3 cells, and hNPCs, however, caused a reduction in the amount cell, probably because the cytotoxicity [17••].

Mefloquine

Mefloquine is used to suppress the malaria infection [43]. This drug belongs to B pregnancy category by FDA and has been shown to cross the placenta allowing the opportunity to treat not only the mother but also the fetus. Antiviral activity against the strain ZIKV MEX_I_7 was tested in different cell lines as neuronal and embryonic; however, the cells that presented the most inhibitory effect were HELA and hAECs [17].

Mycophenolic acid

Mycophenolic acid, an antibiotic, has been used since 1969 [44]. Currently, this drug is approved by FDA and is used as an immunosuppressive agent [45, 46]. In vitro assay demonstrated high anti-dengue activity by decreasing the infectious particle. The mechanism action is the depletion of the intracellular pool of guanosine nucleotides resulting in inhibition of RNA synthesis [45–47]; the effect observed in yellow fever and West Nile virus too [46]. This inhibitory effect is also present in the midgut of mosquitoes infected with DENV2 where this drug blocked infection in the vector [48].

Screens realized by Barrows et al. (2016) and Raush et al. (2017) demonstrated the efficacy of MPA to prevent replication and proliferation of ZIKV [17••, 49].

Nanchangmycin

It is a polyether and natural product of *Streptomyces nanchangensis* [50]. This drug shows insecticidal and anti-bacterial activity [50, 51] and potently reduced infection of African, Asian, and American ZIKV strain in human osteosarcoma

lineage, human microvascular endothelial cells, human trophoblast cell line Jeg-3, human primary uterine microvascular endothelial cells, and human umbilical vein endothelial cells [49]. Nanchangmycin has antiviral effect against dengue, chikungunya and West Nile virus too. The pathway used by the drug is blocking the clathrin via where mediated the endocytosis process of all viruses [49].

Niclosamide

Niclosamide is an FDA-approved drug used for years to treat worm infections, is the most promising compound identified to use in pregnant patients [16, 52, 53], and has low toxicity in mammals [53]. Jurgeit et al. (2012) describe that this drug has ability to neutralize endolyssomal pH and interferes with membrane fusion [54]. It is known to inhibit several virus in vitro assays including the Japanese encephalitis and severe acute respiratory syndrome [54–56].

Niclosamide inhibits Puerto Rico ZIKV strain infection in hNSC, and astrocytes probably at the viral RNA replication step [16].

Novobiocin

Novobiocin is an aminocoumarin antibiotic that exerts its antibacterial effects [57] but was reported antiviral activity by halting the Epstein Barr virus replication and virion production [58].

In silico analysis indicated that the binding between novobiocin and ZIKV NS2B-NS3 was highly stable, suggesting a cross-protection against different ZIKV subtypes/strains. This statement was proved by functional fluorescence-based protease inhibition assay [59].

Sertraline

Sertraline is an antidepressant drug that acts in the serotonin reuptake inhibitor [60]. Drug screen against Ebola virus shows inhibition in the viral fusion blocked the viral entry [61]. This inhibitor effect was test against ZIKV with screen technique too. In vitro, this drug reduced the ZIKV infection in HuH-7 cells, hNSCs, and human amnion epithelial cell with some cytotoxicity. This drug can cross the placenta like mefloquine drug [17••].

Suramin

Suramin, also known as Germanin or Bayer-205, is an antiparasitic drug market-authorized drug for the treatment of trypanosome [53, 62]. In vitro, efficiently inhibited CHIKV, Ebola virus [62] and exhibited antiviral properties in Vero Cells infected with ZIKV strain MRS_OPY_Martinique_PaRi_2015 [63]. Suramin is inhibiting viral adsorption, entry, replication, and release but not neutralizing the Zika virus [51, 63].

Sofosbuvir

Sofosbuvir is an FDA-approved drug for hepatitis C virus [64, 65]. It is orally bioavailable and is administered via ingestion. Using a multiple human tumor cell lines and isolated human fetal-derived neuronal stem cells, it was demonstrated that sofosbuvir inhibits replication of ZIKV infection in several ZIKV strains [18••]. Other study suggests that sofosbuvir has activity against ZIKV, but they only looked at ZIKVNS1 [65]; no results were demonstrated in

Table 1. Animal models and/or in vitro test drugs for ZIKV infection

Reference	Drugs	Action
Adams et al. (1999) Choy et al. (2015) Barrows et al. (2016)	Bortezomib	It is antineoplastic proteasome inhibitor [22]. In vitro, inhibit dengue virus (DENV) 1–4 infection and yellow fever stain (YF17D) in monocytes by inhibition of the proteasome [21]. Animal model shows that t is capable to reduce viral load and the pro-inflammatory response [21]. Antiviral activity against ZIKV MEX_I_7 and ZIKV DAK_41525 with moderate toxicity was demonstrated in vitro model using HuH-7 cells and human neuronal stem cell (hNSCs) [17••].
Thorner et al. (1974) Calne et al. (1974) Perachon et al. (1999) Zhang et al. (1999) Kato et al. (2016) Chan et al. (2017)	Bromocriptine	It is an agonist of dopamine receptors 2 and 3 which is used to treat galactorrhea [23] and Parkinson's disease [24, 25, 66]. It is potent antiviral against DENV by inhibiting the replication and also shows low cytotoxicity [26]. In vitro, the antiviral activity was observed in Vero cells infected with ZIKV PRVABC59 by inhibited ZIKV NS2B/NS3 protease [28].
Savarino et al. (2003) Borges et al. (2013) CDC (2018) Li et al. (2017)	Chloroquine	Also known as chloroquine phosphate. It is an antimalarial medicine [29] and has been used to treat rheumatic arthritis and systematic lupus erythematosus [30]. It is safe to use in pregnant, children, and adults [29]. Anti-inflammatory action was observed in patients with acute dengue [30], and antiviral activity was reported against HIV and severe acute respiratory syndrome [31]. Chloroquine can prevent ZIKV acute infection in animal model when administered before 24-h post-infection [15].
Liebert et al. (1983) Qing et al. (2009) Barrows et al. (2016)	Cyclosporine A	It is a cyclophilin inhibitor with immunosuppression action [32]. Inhibited the West Nile virus (WNV), DENV, and yellow fever virus (YF) in culture cells by blocking RNA synthesis [33]. In vitro, reduced the ZIKV MEX_I_7 infection in HuH-7 cell and hNSCs but strongly decrease the cell number due to toxicity [17••].
Eliopoulos et al. (1986) Barrows et al. (2016)	Daptomycin	It is a lipopeptide antibiotic [34]. It shows antiviral activity in Huh-7 cell, HELA cell, and HAECs infect with ZIKV_MEX_I-7 [17••].
Chen et al. (1987) Iwamato et al. (2007) Freeman et al. (2010) Richard et al. (2015) Tabata et al. (2016)	Duramycin	It is an antibiotic [67] which has peptide that binds specific in phosphatidylethanolamine present at the surface of envelope viruses [37, 38••]. Efficiently inhibits the entry of WNV, DENV-2, and Ebola viruses in the Vero cells by binding in the phosphatidylethanolamine protein [36].

Table 1. (Continued)

Reference	Drugs	Action
		This fact also blocks the ZIKV infection in all primary placenta cells, from mid and late gestation, and chorionic villous leading to a reduction in infection rates in these cells [38••].
Hoglen et al. (2004) Xu et al. (2016)	Emricasan	It is an inhibitor of activated caspases [39]. In vitro, does not suppress totally ZIKV replication in hNPCs but shows neuroprotective activity because inhibit ZIKV-induced caspase-3 activity in this cells [16].
WHO (1995) Mukhopadhyay et al. (2005) Mastrangelo et al. (2012) Lundberg et al. (2013) Varghese et al. (2015) Barrows et al. (2016)	Ivermectin	It is an antiparasitic drug [68]. Antiviral activity has been seen in Venezuelan equine encephalitis virus [69], chikungunya virus (CHIKV) [70], YF [42], WNV, DENV, and tick-borne encephalitis virus. The inhibition mechanism is unwinding the helicase activity [41]. In vitro, strong reduction ZIKV MEX_I_7 infection in JEG3 cells, HELA cells, hNSCs, and hAECs but shows high cytotoxicity in these cells [17••].
Rieckmann et al. (1974) Barrows et al. (2016)	Mefloquine	It is anti-parasitic drug use to treat malaria [43]. It can be use during pregnancy and shows the ability to cross the placenta [17••]. In vitro, inhibits ZIKV MEX_I_7 infection in cervical, placental cells type, hAECs, and hNSCs possibly by disrupting lysosomal pH. hNSc shows a decrease in the cellular amount due to the toxicity [17••].
Franklin et al. (1969) Diamond et al. (2002) Ng et al. (2007) Takhampunya et al. (2006) Kang et al. (2014) Barrows et al. (2016)	Mycophenolic acid (MPA)	It is an antibiotic [44] inhibitor of inosine monophosphate dehydrogenase [17••, 46]. In vitro, it was demonstrated that has high-antiviral activities against DENV-2 in different cell lineages [45–47]. Antiviral effect was observed in the mosquitoes infect with DENV; analysis in the midgut of them shows a decrease in the viral load [48]. Strongly inhibit ZIKV MEX_I_7 infection in cervical, placental, hAECs, and human fetal brain-derived neural stem cell (hNSCs) [17••].
Sun et al. (2002) Abrams et al. (2017) Rausch et al. (2017)	Nanchangmycin	It is a polyether and natural product of *Streptomyces nanchangensis*, shows insecticidal and anti-bacterial activity [50, 51]. In vitro, has active against West Nile, dengue, CHIKV and Inhibit ZIKV infection by blocking the pathway clathrin–mediated endocytosis [49]
Pereira et al. (1970) WHO (1995) Jurgeit et al. (2012) Fang et al. (2013) Wu et al. (2004)	Niclosamide	It is anthelmintic drug. The WHO recommends that niclosamide can be used during pregnancy because it has not been shown to be mutagenic, teratogenic or embryotoxic [52, 68].

Table 1. (Continued)

Reference	Drugs	Action
Xu et al. (2016)		Niclosamide is an entry inhibitor for a number of pH-dependent respiratory viruses, including influenza virus and human rhinoviruses [54], Japonese encephalitis [56] and Severe acute respiratory syndrome [55] by a mode of action distinct from that of endosomal pH neutralizing agents [54, 56]. Suppress the ZIKV particle in hNPCs by interfering in the viral RNA replication step [16].
Kirby et al. (1956) Molander et al. (1964) Wu et al. (2014) Yuan et al. (2017)	Novobiocin	It is an antibiotic that shows antibacterial effects mainly against *Staphylococcus* spp. [57, 71]. The inhibitory antiviral activity was described in Epstein-Barr virus [58] and others DNA viruses by acting in the viral replication step [59]. In vitro shows antiviral activity against ZIKV_PRVABC59 strain by inhibited ZIKV NS2-NS3 protease activity in HuH-7 and Vero Cells. In mouse model reduced the viral load in blood and the major of tissues, including testis and kidney, during both early and late stages of infection. It was also observed limited penetration into central nervous system in vivo assay [59].
Koe et al. (1983) Johansen et al. (2015) Barrows et al. (2016)	Sertraline	It is selective setoronin re-uptake inhibitor (antidepressant) [60]. In vitro and In vivo essay demonstrated antiviral activity against Ebola by affecting viral fusion [61]. In vitro, reduced the ZIKV infection in HuH-7 cells, hNSCs and human amnion epithelial cell with some cytotoxicity. This drug can cross the placenta allowing the opportunity to treat the mother and the fetus [17••].
WHO (1995) Henß et al. (2016) Abrams et al. (2017) Tan et al. (2017)	Suramin	It is an antiparasitic drug [68]. In vitro, efficiently inhibited CHIKV, Ebola virus [62] and exhibited significant antiviral properties against ZIKV strain MRS_OPY_Martinique_PaRi_2015 in Vero Cells infected [63]. Interacts with multiple ZIKV targets, inhibiting viral entry, replication and release [51, 63].
Onorati et al. (2016) FDA (2017) Bullard-Feibelman et al. 2017	Sofosbuvir	Is approved by FDA to use in hepatitis C virus treatment in both children ages 12–17 years and adult. It is a new generation drug that has direct-acting antiviral drugs [64]. Inhibited replication of multiple ZIKV strains in vitro [18••] and protect neuronal lineage of ZIKV infection and death [65].

replication level. The infectivity and lethality of ZIKV infection were significantly inhibited in vivo mouse models. In vitro results demonstrated inhibition of replication in multiple cell lineages [18••].

Conclusions

The Zika virus infection outbreak occurred in Brazil and was linked to a 20-fold increase in cases of microcephaly in the year of 2015. In endemic regions, it is difficult to differentiate the flavivirus infection only with clinical manifestations. Establishing differential diagnosis of suspected case of Zika virus infection and understanding the pathology of the infection will be essential to improve the efficacy of the development of the drugs or vaccine. The drugs to treat acute viral infections are limited, and the anti-flaviviral drugs are in early phases of development. Here, we describe the several compounds that were tested in vivo and in vitro model to establish a next step for treating Zika infection (Table 1). More studies need to be done to understand the pathogenesis, interaction of the virus with the target cells, and immune response of the Zika virus. It is important to highlight since we do not have no vaccine or antiviral therapy available; some interventions are necessary in endemic areas: controlling *Aedes* mosquitoes, personal protection as repellent, and people who live in or have traveled to an area with active Zika virus transmission should prevent sexual transmission.

Compliance with Ethical Standards

Conflict of Interest
Karina Inacio Carvalho, Caroline Mitiká Watanabe, and Esper George Kallas declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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