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Review Article

Current status of therapeutic and vaccine approaches against Zika virus

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ABSTRACT

Zika virus (ZIKV) is a global threat because it is spreading at an alarming rate because of its wider range of transmission routes. The neuroteratogenic nature of ZIKV infection is posing serious threats to unborn lives therefore, it is necessary to develop an ideal ZIKV prophylactic or therapeutic agent urgently. Researchers are having tough time finding a treatment for ZIKV in part because of serious consequences of vaccines and drugs to unborn lives and pregnant women. However, *in vitro* and *in vivo* evaluation of therapeutic efficacy of DNA vaccine, recombinant subunit vaccine, and ZIKV purified inactivated vaccine offers hope for human protection. Large number of food and drug administration (FDA) approved drugs as wells as compounds with anti-ZIKV activity offer valuable opportunity to control the massive bio-burden of this catastrophic epidemic. Some evidences suggest that immunotherapeutics might prove to be winning strategy in pregnant females. Here, we review the recent advances and current knowledge regarding therapeutic interventions against ZIKV infection. This article will provide baseline data and roadmap to prosecute further research for the development of novel therapeutic strategy to curb the explosive rise in ZIKV.

1. Introduction

ZIKV is single-stranded RNA mosquito borne virus of *Flavivirus* genus [1,2]. Prior to 2007, ZIKV caused only sporadic infections with negligible clinical manifestation but the recent spread of virus to >60 countries has drawn the attention of entire globe towards this life-threatening agent [3,4]. The virus is likely to spread more because it can be transmitted vertically, sexually as well as through mosquito bites, breast-milk, and blood transfusions [5–8]. The World Health Organization (WHO) declared ZIKV a Global Emergency of Public Health Concern because of massive rise in teratogenic outcomes and neurological complications such as Guillain Barre Syndrome and microcephaly [9,10]. No specific treatment options are available now but success is not far off because researchers are making serious efforts to develop anti-virals and vaccines. Vaccine Research Center (VRC), National Institute of Allergy and Infectious Disease (NIAID) is trying to develop anti-ZIKV vaccine based on vaccine platforms that have been used successfully for other *flavivirus*. Several vaccine approaches showed efficacy against ZIKV in tissue culture and animal models. Single vaccine will be effective against all strains of ZIKV because of low strain diversity among ZIKV strains [11–16]. Molecular targets of anti-viral drugs and vaccines have also been identified. Putative ZIKV candidate targets include small-inducible cytokine B10, interferon stimulated genes (OAS1, ISG15, ISG20, MX1), FURIN, PPIB, TLR3, RIG-I, HLA class I/II histocompatibility antigens, cytokines/interferons, transporters, EIF2AK2, EIF2AK2, IL6, CXCL10, IFIH1, LTA, MAVS, TLR3, TNF, IFITM3, MX1, AXL, EIF1AK2, and TMEM173 [17,18]. Decades of experience with other *flavivirus* provide mechanistic insights into the biology of ZIKV infection however, an efficient treatment method to mitigate the sudden emergence of ZIKV as an evolving epidemic has yet to be explored. Here, we extensively review ZIKV related therapeutic interventions that have been studied so far (Table 1).

2. Vaccine development

Global bioburden of many *flavivirus* infections have been reduced with the development of successful vaccination programs. Currently, a number of vaccine candidates are under clinical trials because the explosive rise in ZIKV has made the development of effective and safe vaccine a public health priority.

The scarce information regarding ZIKV biology or immunity, antibody dependent enhancement of disease, co-circulating *flavivirus*, and the need to protect pregnant women are some of the major challenges that stand on the way of vaccine development against ZIKV. Single dose of live-virus vaccine may provide protection but these candidate vaccines are not appropriate for use in pregnancy. During pregnancy, recombinant subunit, inactivated, and other non-replicating vaccines are more safe and effective but multiple doses are required for protection. Therefore, the standard practice for durable control of ZIKV infections

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Table 1
Summary of ZIKV related therapeutic interventions.

Therapeutic intervention		Efficacy	Ref.
Vaccines	ZIKV Inactivated purified vaccine	Single shot conferred protection in mice and rhesus monkey.	[14,15]
	Plasmid DNA vaccine	Single shot conferred protection in mice and rhesus monkey.	[14,15]
	Recombinant subunit vaccine	Subunit recombinant E protein vaccine elicited high titer neutralizing antibody in C57BL/6 mice.	[14,15,19]
	Vectored	Single shot of rhesus adenovirus serotype 52 vector (RhAd52) protected monkeys and pups from ZIKV.	[14,15]
Anti-viral drugs	Pyrimidine synthesis inhibitors	Brequinar and CID91632869 showed potent anti-ZIKV activity *in vitro*.	[20]
	Adenosine analog	NITD008 exhibited anti-ZIKV activity *in vitro*.	[20]
	GTP synthesis inhibitors	Ribavirin and mycophenolic acid showed no anti-ZIKV activity.	[20]
	Endocytosis blocking agent	Chloroquine and monansin showed potent anti-ZIKV activity *in vitro*.	[20]
	Uridine analog	6-Azauridine prominent anti-ZIKV activity *in vitro*.	[20]
	vATPase inhibitor	Saliphe showed potent anti-ZIKV agents *in vitro*.	[20]
	Nucleotide analog	Sofosbuvir inhibited ZIKV replication *in vitro*.	[21]
	NIH Clinical Collection library	Lovastatin, 5-Fluorouracil, palonosetron, kitasamycin, 6-Azauridine	[22]
	Library of FDA-approved drugs	Daptomycin, mycophenolate mofetil, sertraline ivermectin, MPA, pyrimethamine, cyclosporine A, azathioprine, obatoclax, gemcitabine, azithromycin, and mefloquine inhibit Zika virus infection *in vitro*	[23]
Immune-based therapy	Monoclonal antibodies	Potent neutralizing activity against ZIKV strains observed in mice model.	[24–26]
	T-cell therapy	Adoptive transfer of ZIKV-immune $CD8^+$ T cells decreased viral burden.	[27]
	Interferon therapy	Interferon-α (IFN-α), IFN-β and IFN-γ are the potent inhibitor of ZIKV growth.	[28]

is the establishment of immunogenicity in pediatric populations before person makes any sexual contact [29–32]. A study has recently reported the significant level of overlap between known antigenic sites on ZIKV polyproteins with other *flavivirus* proteins [12]. Researchers must also take into account preexisting immunity to other *flaviviruses* because the immune response to other *flavivirus* infections or vaccines can either promote or obstruct immunity of ZIKV vaccine [33].

Multiple vaccine platforms that are being employed to combat ZIKV have been proved efficacious for other viruses. Sanofi Pasteur's successful launch of licensed vaccines against Japanese Encephalitis, Dengue, and Yellow Fever Virus encourages optimism for ZIKV vaccine [11,34]. Several studies demonstrate the efficacy of different approaches such as subunit protein vaccines, whole inactivated virus vaccines, viral-vectored vaccines, and DNA vaccines in animal models. The robust protection observed in animals suggests a path forward for ZIKV vaccine development in humans [32,35,36]. An integrative multi-omics platform has identified 32 potential vaccine epitope candidates comprising of T-cell epitopes, B-cell epitopes, and MHC binders [37].

Recently developed ZIKV purified inactivated vaccine (ZPIV) and DNA vaccine expressing series of deletion mutants as well as ZIKV pre-membrane and envelope (prM-Env) exhibited complete protection in mice. An excellent efficacy was measured by Env-specific antibody titers and absence of viraemia. Single immunization with ZPIV and DNA vaccine resulted in varying degrees of protection against ZIKV-BR

Table 2
Pipeline of ZIKV vaccine candidates.

Advanced Candidates already in clinical development	Candidates ready to enter clinical development in early 2017	Candidates in late preclinical development, expected to enter phase I later in mid/late 2017	Candidates in preclinical development
• Inovio DNA vaccine Phase I completed (June 2015, US & Canada) Ongoing phase 2 in Puerto Rico since September 2016	• NIAID/Butantan pentavalent live-attenuated vaccine (ZIKV + DENV) phase III currently ongoing in Brazil for DENV. Phase 1 planned in early 2017 for ZIKV.	• (BARDA/Takeda) inactivated, adjuvanted, whole Zika virus vaccine phase I scheduled in 2017	• (Sanofi) live attenuated recombinant vaccine • (EVI/Inst. Pasteur) recombinant measles vector • (GEOVAX) Modified Vaccinia Virus Ankara--Virus-Like Particle (MVA-VLP) • (Valvena) purified inactivated vaccine • (Butantan) inactivated vaccine • (FioCruz) VLPs • (FioCruz/Evandro Chagas Institute/University of Texas) live attenuated vaccine (FioCruz) Chimeric ZIKV/YF vaccine
• (NIAID(VRC)) DNA-based vaccine Ongoing phase I Phase II scheduled in early 2017 at 30 sites in the Caribbean, Central and South America	• (BARDA/Moderna) mRNA vaccine candidate Two Phase I clinical trials have been planned for 2017.	• (NIAID/GSK) self-amplifying mRNA vaccine Scheduled to phase I in mid/late 2017	
• (NIAID/BARDA/WRAIR/Sanofi Pasteur/+Fiocruz, ZPIV Ongoing phase I Phase II scheduled in early 2018	• (Bharat) inactivated vaccine Asked permission for phase I trial.	• (ProteinSciences/UMN Pharma Japan) recombinant E protein Announced phase I in 2017	
		• (NIAID) VSV-vectored Expected to enter phase I in late 2017	
		• (WRAIR/Harvard): plasmid DNA vaccine • (WRAIR/Harvard) recombinant rhesus adenovirus serotype 52 vector vaccine (FioCruz) inactivated vaccine	

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