Mini Review

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Development of DNA-Based Vaccine Towards the Predominant Dengue Virus Serotypes in Saudi Arabia

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Abstract

Dengue is the most pivotal arboviral infection worldwide that is transmitted by (Aedes aegypti and Aedes albopictus) mosquitoes. Dengue fever (DF) is considered a global health concern that is epidemic and endemic in tropical and subtropical regions with an estimate of 100 million apparent infections reported annually including 10000 death incidences. The virus infection is estimated to be prevalent in approximately 128 countries with around 4 billion people at risk. The average number of reported cases has noticeably undergone a persistent increase from nearly a thousand cases reported annually worldwide during the 1950s, to over 3 million cases till 2013.The high prevalence of dengue in tropical and subtropical areas is supported by increased urbanization level, by diverse climate changes manifesting as the rise in humidity, precipitation, temperature, due to failure of vector control programs in metropolitans. Dengue virus is a positive-sense single-stranded RNA. There are four common serotypes of dengue virus that are distinct genetically; DENV-1, DENV-2, DENV-3 and DENV-4. Infection with one serotype generally confers lifelong immunity against that serotype, yet life-threatening circumstances might develop in case of re-infection with different serotypes. Saudi Arabia is a highly endemic area with dengue where the occurrence of infection is restricted to the Western and Southern provinces. No effective antiviral treatment is yet present for dengue, but different approaches have been employed to develop a safe, efficacious cost-effective vaccine against dengue serotypes. The only licensed vaccine (Dengvaxia) was developed by Sanofi-Pasteur (France) company could accomplish clinical trial phase III, had been licensed in 2015 to be used in specific countries this vaccine had recently found to cause pathological issues. The aim of this mini-review is to suggest a new approach, to construct a universal tetravalent DNA-based vaccine that is able to induce strong neutralizing antibody responses and cell-mediated immunity against the highly conserved Epitopes of the Dengue viral proteins to be efficiently used against all dengue serotypes as prophylactic and therapeutic vaccine.

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A dengue virus (DENV) belongs to the genus flavivirus, within the family Flaviviridae. The flavivirus genus is comprised of over 70 serologically related enveloped viruses with more than half of these being the causative agents for a number of human diseases [1,2]. Most Flaviviruses are arthropod-borne pathogenic to humans and animals [3]. The virion has a spherical shape with icosahedral symmetry which is surrounded by a lipopolysaccharide envelope. The viral genome is a single-stranded RNA that has a positive polarity and consists of about 11kb. The genome has one open reading frame (ORF) restricted by 5′ and 3′ both of which contain untranslated regions. Viral genome encodes for structural proteins {capsid protein (C), pre-membrane protein (prM), envelop protein (E)} and non-structural proteins (NS1, NS2a, NS2b, NS3, NS4a, NS4b, NS5) [3-5]. Dengue is transmitted primarily by Aedes mosquitoes' bite, which comprises over 31 subspecies capable of acquiring transmitting the virus, yet Aedes aegypti and Aedes albopictus are

the main transmitters [6]. Infection with dengue might possibly occur through using of contaminated blood products [7], or via organ transplantation [8].

The infection is initiated via biting an infected person by a female mosquito. Following biting, the acquired virus propagates in the midgut of the mosquito and travels through the bloodstream to the salivary glands through which the virus exits and the vector body infects new individuals during subsequent bite [9]. Clinical dengue infection is characterized by non-specific symptoms including fever, nausea, severe headache, swollen glands, rash, and myalgia. Severe dengue occurs mainly in secondary exposure to heterologous serotype leading to serious and fatal consequences known as dengue hemorrhagic fever and dengue shock syndrome [10,11]. Severe dengue mortality has pertained to severe hemorrhage, plasma drainage [12], fluid accumulation, respiratory dysfunction, or organ damage as reported by World health organization [13]. Dengue is endemic in over 100 tropical and subtropical geographical areas including Southeast Asia, Africa, Central and South America, Eastern Mediterranean regions and Western Pacific [14,15]. The global distribution of dengue is expanding, and the occurrence has increased 30 times in five decades [16].

It is estimated that among 25 billion people dwelling in endemic regions, there were 50 million reported cases and 25000 deaths [14]. Recently, dengue incidence underwent substantial increase and the most significant outbreaks occurred in China and Southeast Asia in 2014 [17,18]. Dengue distribution is demonstrated in Japan, Croatia, Southeast of France, Spain, Madeira Island and USA (Florida) [16]. Nevertheless, the actual global burden of dengue is thought to be four times higher than the estimated incidence [9,13,19]. The highest dengue incidence and mortality occurred in southeast Asia, where severe dengue is one of the leading causes of hospital admission and death among children [20]. Saudi Arabia has the biggest endemic of Dengue Fever (DF) in the Middle East. The occurrence of DF in Saudi Arabia dates back to the 1990s when the first case of DF was reported in Jeddah, November 1993 [21]. The patient visited a clinic with fever signs of hemorrhage. After a couple of weeks, the patient developed hepato-renal failure and died. The death was supposed to be due to viral hepatitis infection. Later, investigation announced that the patient was dengue-infected which the first dengue reported case. Accordingly, the surveillance system was launched in 1994 and reported 300 cases in Jeddah during 1994 [21], followed by minor epidemics comprising 15 cases Fakeeh et al. [21]. The largest outbreaks occurred during 2004 and 2015 which involved Jeddah, and other cities in Western province, Makkah, Al-Madinah, and Southern cities such as Jizan, and Najran. In 2015, the western province in Saudi Arabia was declared to be endemic to DF [22]. Until now, no antiviral treatment is available, which mandates vaccines development. It is essential to develop vaccines as they play a significant role in underpinning society's immunities and decreases disease epidemicity. Dengue vaccine researches have started fifty years ago, but until today, many challenges impede the construction of ideal vaccines. The only licensed vaccine (Dengvaxia®) has limited approval of use due to safety issues [11]. Thus, manufacturing a vaccine that meets ideal properties regarding safety, cross-reactivity, immunogenicity, genetic stability, protection longevity, cost-effectiveness, storage, and transportation suitability is required [11].

Several studies focused on the development of DNA vaccines because it is believed to be safer, stable, simple to construct on manufacturing scale, cost-effective and safe in handling compared to conventional vaccines [23,24]. Therefore, in the present review, we will focus on in silico construction of a tetravalent DNA -based vaccine encoding Envelope protein domain III of the DENV (DVE-PIII) from the four DV serovars and its cloning into Nano plasmid vector capable to have large antigen-coding inserts with unique features for high efficient expression and efficient stimulation of immune response in vitro and in an animal model.

Construction of DNA Vaccines

Tetravalent DNA vaccine will be constructed encoding domains III of the E protein from the four DV serovars by using bioinformatics tools and multiple sequence alignment for selecting the most consensus Epitope region.The 3rd generation Nano plasmid vector from Nature Technology Corporation, Lincoln, Nebraska, USA, can be used in cloning instead of using conventional plasmids. The Nano plasmid™ is antibiotic-free and expression levels and duration are very profound and has unexpected beneficial effects. This mammalian expression Nano plasmid™ vector is selected for cloning the DVE-PIII from each serotype with suggested name as NTC8685-DVE-PIII (Figure 1). The Nano plasmid vector capacity can have a gene insert up to 3762 bp.Plasmid based DNA vaccines are emerging as a promising alternative to traditional vaccines due to several advantages, including faster production of DNA plasmids using E. coli.However, further increases in transgene expression are needed to meet efficacy requirements for various non-viral gene therapy and DNA vaccination applications. While existing minicircle DNA technology has been shown to offer improved levels and durations of transgene expression by removal of the bacterial region from the plasmid, low yields production may be a barrier to the widespread use of minicircle DNA for vaccination. The FDA and European Union (EU) has issued guidelines that include vector design considerations for plasmid DNA vectors intended for human use [25,26]. Vectors, in particular, those that encode cryptic ORF that can be expressed in the target organism, should be minimized to eliminate extra nonfunctional sequences. This is particularly important within the transcribed UTRs to prevent the production of vector encoded cryptic peptides in the target organism [27]. This is especially critical that may induce inappropriate adaptive immune responses [28,29]. The presence of the human T-cell leukemia virus type I R region (HTLV-I R) 5' UTR downstream of the CMV promoter enhances the efficiency of mRNA translation and further increases the DVE-PIII expression in mice and non-human primates [27,30,]. HTLV-I R encoding DNA vaccines proved an excellent safety profile in multiple human clinical trials [31].

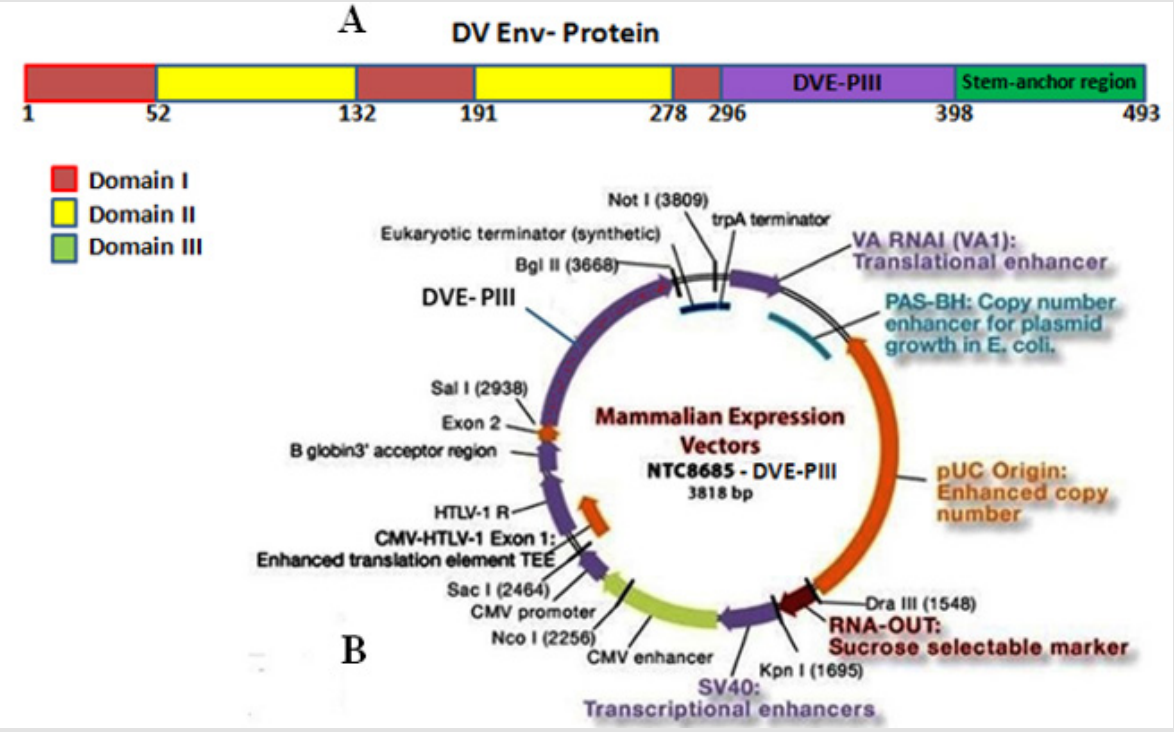

Figure 1: In silico strategy for construction of the selected safe mammalian expression vector containing

A. The Dengue virus Envelope protein domain III (DVE-PIII)

B. The nanoplasmid, NTC8685-DVE-PIII, with some unique features such as markerless (sucrose selection), enhanced transcription (SV40/CMV), enhanced translation (CMV/HTLV-1-R), enhanced translation (VA1),enhanced plasmid production (PAS-BH) NTC8685 nanoplasmid vector developed by Nature Technology Corporation, Lincoln, Nebraska, USA.

DVE-PIII Design Considerations

Transgene design becomes easy to be tailored for accurate gene expression for the potential production of DNA vaccines. Commercial gene synthesis has become fast and cheap, allowing for the design, synthesis and antigens synthesis for the production of DNA vaccines in a very short time. In the current approach, the conserved sequence of DVE-PIII genes of the four serotypes via multiple sequence alignments is either be amplified by PCR or synthetically constructed rather than using multiple plasmids. Engineering a single broadly cross-neutralizing antigen may be used to accomplish this possibility via bioinformatics. The DVE-PIII transgene may be an exact copy of the original antigen or little bit modified with degenerate sequences to improve efficacy or safety. Improving adaptive immune responses can be enhanced by promoting antigen processing MHC class I /or class II presentation [32,33]. This can be achieved by the addition of a targeting peptide that directs antigens to various intracellular destinations. An optimized signal sequence may be used dramatically to improve the transgene expression which has been accomplished using an optimized tissue plasminogen activator (TPA) signal peptide [34,35] or IgE gene leader [32]. An optimized heterologous secretion tag is often included in DNA vaccine vectors; the transgene is cloned downstream and in-frame with the signal peptide [36]. Alternatively, the signal peptide may be included when designing the synthetic gene. Many trials should be done to determine if the DNA vaccine targeting is compatible with either N-terminal TPA signal peptide (secretion targeting), N-terminal and C-terminal LAMP1 (endosomal targeting) or N-terminal destabilizing Ubiquitin A76 (proteosome targeting).Because, in some DNA vaccines, proteosomal targeting using an N-terminal ubiquitin tag (terminal ubiquitin G76 residue altered to A76 to destabilize the fusion protein) is used to promote MHC class I antigen presentation [37], while endosomal targeting by transgene insertion within the LAMP protein is used to promote MHC class II antigen presentation [38].

Immunology of DNA Vaccine

Recent research studies have been focused on strategies to improve the immunogenicity of DNA vaccines. As known, DNA vaccines activate intracellular DNA-sensing pathways to induce adaptive immunity [39,40]. DNA vaccination activates innate immunity through adjuvant effect which is mediated by activation of the cytoplasmic double-stranded DNA sensing stimulator of interferon genes/TANK-binding kinase 1 (STING/TBK1) dependent innate immune signaling pathway [41]. This is the 1ry pathway required to induce antigen-specific B cells and CD4+ T-cells in response to DNA vaccination. However, various studies have investigated the role of the immunostimulatory sequence motif CpG DNA sensing Toll-like receptor 9 (TLR9) signaling in provoking CD8+ T cell responses [42-44]. Hyde et al. [45] reported that cationic

liposomal delivery of plasmid DNA vaccine can activate a CpG dependent inflammation response in the lung, therefore, the TLR9 may enhance the adaptive immunity in response to DNA vaccines in a specific tissue.The combination of cationic liposomal DNA vaccine with a newly developed digitally controlled hollow microneedle injection system (DC-hMN-iSystem) may stimulate antigen-specific CD4+, CD8+T-cell response [46]. Mostly, the animal model used frequently in order to test the efficacy of dengue vaccines during dengue vaccine development is based on intracerebral inoculation of mice with a mouse-brain-adapted dengue virus. However, this model does not represent a natural disease as encephalitis is not commonly associated with dengue infections. Due to the lack of a good animal model to test dengue vaccines and to the fact that humans and mosquitoes represent the only two natural hosts for DENV, it is unrealistic to hope that a single mouse model will address all the features of dengue pathogenesis and may account for some unexpected results, such as the lack of protection of 20% of the immunized mice [47].

Conclusion

In conclusion, the current approach using the presumptive NTC8685-DVE-PIII DNA vaccine may induce strong humoral and cellular immune responses. Despite not well addressed in murine models, increased antigen expression correlates with improved immunogenicity in humans and large animals as reported by (Kutzler and Weiner, 2008) [32]. According to the current review, the next generation vector developed by Nature Technology, USA could improve antigen expression, and may provoke a human immune response. Application of this improved expression vector in vaccine production should be cautious to ensure efficacy, safety and cost-effective manufacture.

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Conflict of Interest

No conflict of interest.

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