SciMedCentral

Annals of Vaccines and Immunization

Review Article

Strategic Approaches to Multivalent Vaccine Development against Dengue Virus Infection

Shamshul Ansari[1] and Andrew W. Taylor-Robinson[2]*

[1]*Department of Microbiology, Chitwan Medical College Teaching Hospital, Nepal*
[2]*School of Medical & Applied Sciences, Central Queensland University, Australia*

***Corresponding author**
Andrew Taylor-Robinson, School of Medical & Applied Sciences, Central Queensland University, Rockhampton, QLD 4702, Australia, Tel: 617-492-32008; Email: a.taylor-robinson@cqu.edu.au

Submitted: 20 August 2014

Accepted: 05 October 2014

Published: 08 October 2014

Keywords
- Dengue
- Virus
- Immunity
- Vaccine
- Serotype
- Antibody

Abstract

The mosquito-transmitted viral infectious disease dengue is a major public health problem in tropical and sub-tropical countries, where it causes dengue fever, dengue haemorrhagic fever and dengue shock syndrome. Almost 400 million people are infected by dengue each year, causing around 20,000 deaths. There are no vaccines or therapeutic regimens currently available for the prevention and treatment of disease. A number of vaccines are under development and several have entered clinical trials while others are still in the pre-clinical phase. Most dengue vaccines in animal models have been found to provide a degree of protective immunity by eliciting neutralizing antibodies against all tested serotypes of the dengue virus, and this forms a foundation for future vaccine design. It is probable that a refined, second generation multivalent vaccine will be required to target each of the five now recognized dengue serotypes.

INTRODUCTION

Dengue is an acute febrile illness caused by dengue virus (DENV), a small, enveloped, positive sense, single-stranded RNA virus belonging to the family *Flaviviridae* and genus *Flavivirus* [1]. Based on neutralization assays, there are five distinct serotypes, DEN-1 to DEN-5, the last of which was discovered only very recently [2]. DENV is transmitted from human to human by mosquitoes of the species *Aedes aegypti* and, less frequently, *Aedes albopictus* [1]. During the 19thcentury dengue was considered a sporadic disease, causing epidemics at long intervals. However, dramatic changes in this pattern have occurred and currently dengue ranks as the most important arthropod-borne viral disease worldwide. The nature of infection varies from a mild self-limiting febrile illness to severe forms like haemorrhagic fever with warning signs (abdominal pain, persistent vomiting, fluid accumulation, mucosal bleeding, lethargy, increasing haematocrit (with decreasing platelets), and life-threatening shock syndrome (with profound plasma leakage, severe bleeding, or organ failure) [3]. In recent decades, the global prevalence of dengue has increased markedly, partly due to differences in serotype genetic diversity, geographical origin and distribution.The disease is now considered endemic in more than 100 countries in Africa, the Americas, the eastern Mediterranean, South East Asia and the Western Pacific, such that more than 2.5 billion people are under threat of infection. Worldwide, recent estimates suggest that 390 million people are infected by dengue annually, of which 96 million present with clinical or subclinical severity [4]. Of those persons, 500,000 require hospitalization with life-threatening complications, resulting in up to 20,000 deaths [1].

Typically, serotype-specific protection occurs in which infection with one dengue serotype confers long-term protection against re-infection by the same serotype. However, in cases of re-infection by a heterologous dengue serotype with the presence noted of cross-reactive antibodies [5] and/or cross-reactive T cells [6,7], the potential risk of antibody-dependent enhancement of disease is increased. The greatest risk factor for dengue haemorrhagic fever is secondary infection. Therefore, the challenge of vaccine development against DENV is to achieve pan-serotype immunity without triggering associated pathology. This has focused on tetravalent formulations that can simultaneously provide protection to all four well-characterized DENV serotypes. At present, there are several candidate tetravalent DENV vaccines at various stages of preclinical and clinical testing [8]. Evaluation of DEN-5 is in its infancy but this serotype will no doubt be incorporated into future vaccine formulations.

CURRENT DENGUE VACCINATION STRATEGIES

The first dengue candidate vaccine was evaluated in 1929 [9,10]. Since then, dengue vaccines have been continually under development. In an attempt to produce an effective vaccine,

several technologies are now being implemented usinglive-attenuated virus, purified inactivated virus, recombinant subunits, virus-like particles and plasmid or viral vectors. All of these approaches are at different stages of development and each has its advantages and disadvantages [11]. Currently, CYD tetravalent dengue vaccine (TDV) developed by Sanofi Pasteur and a live-attenuated TDV developed by the Walter Reed Army Institute of Research (WRAIR) in collaboration with GlaxoSmithKline Vaccines (GSK) have been found in clinical trial studies to be acceptable for human use [12,13].

There are several types of TDV which have undergone recent pre-clinicalor clinical evaluation:

Live-attenuated tetravalent dengue vaccine

Development of a first live-attenuated dengue vaccine by serial passage of virus in a non-human host was started at the University of Hawaii and then transferred to Mahidol University in Bangkok, Thailand, for further evaluation and testing [14,15]. This candidate vaccine was used for phase I and II clinical trials in Thai adults and children but neutralizing antibody (NAb) was not found in those volunteers who did not seroconvert to all four then known dengue serotypes. Furthermore, unacceptable reactogenicity was experienced by some volunteers and consequently further clinical testing ceased [16-18]. WRAIR and GSK developed a TDV candidate representing each of the four DENV serotypes attenuated by serial passage in primary dog kidney cells [19,20]. This vaccine was identified as safe, well-tolerated and immunogenic in a phase II trial conducted in adult subjects in the US [21]. The re-derived form of this vaccine was evaluated in a phase II clinical trial and approved as clinically acceptable in healthy adults [12].

In a similar tetravalent live-attenuated DENV vaccine strategy, a TDV consists of a molecularly characterized attenuated DEN-2 strain (TDV-2) and three chimeric viruses containing the pre-membrane (prM) and envelope (E) genes of DEN-1, -3 and -4 expressed in the context of the TDV-2 genome. In a pre-clinical trial, efficient NAb responses to all four DENV serotypes were primed and induced after administration subcutaneously or intradermally of two full doses of this vaccine. Cynomolgus macaques challenged with DEN-2 were protected, showed no detectable viraemia and exhibited sterilizing immunity (no increase of neutralizing titre post challenge) [22].

Robust, long-lasting, broad humoral and cellular immune responses were elicited by a live-attenuated vaccine but are associated with a higher rate of adverse events that cannot be used in some at-risk groups, such as immune compromised individuals. Although inactivated vaccines have reduced potential for reactogenicity they tend to develop a diminished ability to induce broad and durable immune responses [23]. Conventional tetravalent DENV vaccines based on live-attenuated viruses have shown low efficacy during clinical trials, to which viral interference and incomplete monotypic, heterotypic and multitypic immune protection have been suggested as possible contributory factors [24,25,38].

Recombinant tetravalent dengue vaccine

A recombinant, live-attenuated TDV (CYD-TDV; Sanofi-Pasteur, Lyon, France) is in the late stages of clinical development. It has been evaluated in clinical trials in Thailand and Philippines and showed promising results [24, 26]. It contains four recombinant viruses (CYD-1 to -4), each of which expresses the dengue prM and E proteins of one of four dengue serotypes together with the non-structural and capsid proteins of the attenuated yellow fever (YF) vaccine virus YF-17D [27,28]. A phase IIb study conducted in the Ratchaburi province of Thailand investigated the efficacy of the vaccine against virologically confirmed symptomatic dengue [24], while another clinical trial was conducted in Latin America to determine the immunogenicity and safety of this vaccine in children and adolescents aged 9-16 years in preparation for a large phase III study [29]. Findings from previousphase II studies were confirmed in this trial. Vaccination with a three-dose CYD-TDV regimen showed that this was well-tolerated and elicited NAb responses against all four dengue virus serotypes in both flavivirus (FV) seropositive and FV seronegative participants. A higher immune response to vaccination was observed in FV seropositive individuals in comparison to their FV seronegative counterparts. This finding suggests that pre-existing FV seropositivity may increase the vaccine-induced antibody response to CYD-TDV [29].

Most recently, the promise of this vaccine was substantiated by publication of a phase III study undertaken in five countries in the Asia-Pacific region [13]. The primary objective was to estimate protective efficacy against symptomatic, virologically confirmed dengue after the completion of three doses of CYD-TDV given six months apart from birth. The incidence of dengue during the 25-month active surveillance period was 1.8 % among vaccinated children and 4.1% in those in the control group, translating into an overall, serotype-specific protective efficacy of 56.5%. Moreover, vaccine efficacy against dengue haemorrhagic fever was impressive; 80% after one or two injections and 88.5% after a third [13]. Hence, the principal benefit of this vaccine would be seen in protecting against severe disease, thereby reducing hospital admissions and hence health-care costs, and potentially preventing deaths.

DNA-based dengue vaccines

The concept of using DNA to immunize people was first advanced in the early 1990s when it gained immediate widespread recognition due to its apparent simplicity and elegance [30-32]. As five antigenically related serotypes of DENV commonly co-circulate, an effective vaccine must cover all serotypes. Safety, balance between immunogenicity and attenuation, and 'interference' among DENV serotypes represent hurdles to be overcome for live-attenuated dengue vaccine candidates [25,33-38]. A DNA-based vaccine is an alternative strategy that both circumvents the concern of these issues and provides many direct benefits [40]. Unlike a live-attenuated dengue vaccine which requires at least six months' gap for an effective boosting dose from the last immunization [41,42], an advantage of a DNA vaccine is its ability to boost much sooner. There are several DNA based dengue vaccines:

Chimeric tetravalent dengue DNA vaccine: Chimeric vaccines are created by cloning segments of DNA from one virus into another virus to generate a 'chimera'. The advantage of chimeric tetravalent dengue DNA vaccine strategy is that the DNA

shuffling and screening technology produces single DNA vaccine candidates that express antigens containing immunogenic epitopes from four (and potentially five) dengue serotypes. The DNA chimeric vaccine constructs encoding antigens comprised of prM and E epitopes of each of the four tested DENV serotypes in a single construct was developed by utilizing this DNA shuffling technique [43,44]. A regimen of three doses of this vaccine was administered to rhesus macaques on days 0, 28 and 84. Variable NAb responses were detected four weeks after the third dose with individual shuffled DNA clones, only one clone inducing NAb to multiple DENV serotypes [44]. Higher NAb titres were induced to all four tested DENV serotypes by a formulation containing all three shuffled DNA clones. A disappointing observation of only partial protection against DEN-1 and no protection against DEN-2 was made upon challenge at week 32 with wild-type DEN-1 or DEN-2. The immune response induced by these constructs may be improved by incorporating immune stimulatory sequences or adjuvants [44]. DNA remains the only platform that does not induce anti-vector immunity, thereby making it suitable for vaccine regimens that include both priming and boost immunizations. Furthermore, since manufacturing of plasmid DNA relies primarily on bacterial hosts for production, it is considerably faster and easier than for most other vaccine platforms. Moreover, DNA is relatively stable at room temperature, making the requirement to maintain the vaccine cold-chain less critical compared to other vaccine platforms. In addition, the manufacture of DNA is extremely safe especially compared to killed pathogenic vaccine platforms.

Syncon tetravalent dengue DNA vaccine: DENV contains a 10.7 Kb RNA genome that encodes three structural proteins (coat, C; prM and E), and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5). E protein, which induces NAbs, is divided into three domains (EDI, EDII and EDIII) based on structural characterization by X-ray crystallography [45, 46].

In SynCon tetravalent dengue DNA vaccine strategy, tetravalent immunity was elicited by a synthetic consensus (SynCon) human codon-optimized DNA vaccine. The consensus DIII domains of E protein from all four tested serotypes were cloned and expressed as a single open reading frame in a mammalian expression vector, pDV-U-DIII (dengue-vaccine universal). A significant level of anti-DIII antibody that neutralizes each dengue serotype was elicited in BALB/c mice by this construct, thereby preventing cell death induced by dengue infection [47].

Tetravalent DNA vaccine with adjuvant: In this strategy, prM and E proteins of DEN-1, -2 and -3 were each expressed in plasmids and minor changes were introduced in the sequences just upstream of the initiating methionine codon in order to remove certain redundant sequences [48,49]. A DEN-4 vaccine construct was similarly prepared and the tetravalent dengue DNA vaccine (TVDV) was produced by mixing the four plasmids in equal ratio. Vaxfectin, a cationic lipid-based adjuvant, was combined with TVDV to produce an adjuvanted vaccine containing both DNA and lipid at a final concentration of 1 mg/mL (TVDVVax). Intramuscular injection of this vaccine in New Zealand white rabbits elicited a strong NAb response to all serotypes. Subsequently, a phase 1 clinical trial of this vaccine was initiated in early 2012, the results of which are awaited [50].

Electroporation-enhanced tetravalent DNA vaccine: The method of introducing macromolecules such as nucleic acids into cells, either *in vivo* or *in vitro*, by application of brief electric pulses to increase the transient and reversible permeability of the cell membrane is known as electroporation. Utilization of this technique has escalated from an experimental protocol to its current use in several clinical trials to deliver nucleic acids as well as drugs to a variety of target tissues [51]. When injected by intramuscular electroporation as a tetravalent cocktail into ICR mice, the recombinant dengue prM and E DNA vaccine candidates generated respectable Nab titres against all serotypes of DENV [52]. The dengue-specific NAb induced by this TVDV candidate was detectable a minimum of three months following the last immunization. A prior study demonstrated that NAb induced by DNA vaccine encoding prM and E can endureuntil 30 weeks [53]. This persistence of immunological memory may be explained by observations that DNA vaccines are capable of inducing both memory Band helper T cells [54,55]. Further research is warranted in non-human primates and thereafter in clinical trials in order to determine whether this vaccine is effective in a sequential boosting regimen. The rationale is that administration before a rainy season would enhance recall memory cells and NAb responses in a manner similar to the strategy deployed for seasonal influenza vaccines [56-59].

Sub-unit tetravalent dengue vaccine

The most potent NAbs against DENV bind to EDIII and have been shown in some cases to be effective as passive prophylaxis in rodents [60-62]. Hence, rather than full-length E protein, EDIII can be used as a promising region for a subunit vaccine candidate. Several reports have indicated that EDIII can be produced in various expression systems, including *Escherichia coli*, *Pichia pastoris* yeast and insect cells, and induces specific immune responses against DENV in mice or non-human primates [63-67].

In order to develop a sub-unit TDV, the tandem EDIII of two serotypes of DENV was first constructed. These were connected by a (Gly4Ser)3 flexible linker to create bivalent antigens. Tandem EDIIIs of two serotypes (type 1-2 and type 3-4) of DENV connected by a Gly-Ser linker were expressed in *E. coli* to produce bivalent recombinants. The TDV candidate MixBiEDIII was then formed by mixing these two bivalent recombinant EDIIIs. Specific immunoglobulin (Ig)G and NAbs against all four tested serotypes of DENV were induced successfully byimmunization of BALB/c mice with MixBiEDIII in Freund'scomplete adjuvant. Furthermore, significant protection against tetravalent DENV challenge was achieved recently in similar suckling mice immunized with MixBiEDIII [68].

Nanoparticle-adsorbed tetravalent dengue vaccine

Generation of polymeric nanoparticles with adsorbed or entrapped antigens represents a novel method for controlling the release of immunogens and to optimise the immune response via selective targeting of antigen-presenting cells (APC) [69]. Biodegradable nanoparticles made by coating bovine serum albumin (BSA) with proteins represent a promising method for *in vivo* delivery of protein-based vaccines directly to the immune system. Biodegradable nanoparticles are currently used as drug carriers or as adjuvants for vaccines [70]. For adsorption

of inactivated viral particles to the surface of nanoparticles, a suspension of tetravalent DENV antigens (equivalent of 1.2 x 10^4 plaque forming unitsper serotype) was incubated with nanoparticles. Six week-old Swiss Webster mice were immunized subcutaneously on days 0, 7 and 14. Anti-dengue IgG to all serotypes was elicited but no neutralizing activity was found [71].

Since nanoparticles are phagocytosed by dendritic cells (DC) and other APC, the adjuvant effect of BSA nanoparticles may be explained by their rapid internalization by skin-resident APC, such as DC. A similar mechanism was described for whole inactivated influenza virus, for which it was demonstrated that the viral RNA present in inactivated virus particles could trigger Toll-like receptor 7 to augment the adaptive humoral response [72].

Vector-based vaccines

Recombinant poxviruses and adenoviruses expressing foreign proteins have been demonstrated to induce strong humoral and cellular responses in humans against various pathogens. Several live virus vectors such as adenovirus, alphavirus and vaccinia virus are designed for direct administration to the host and have been engineered to express DENV E protein for evaluation as dengue vaccine candidates [73,74].

It has been demonstrated recently that a non-propagating Venezuelan equine encephalitis virus replicon expression vector (VRP) expressing the ectodomain of DENV E protein (E85) overcomes maternal interference in a BALB/c mouse model [75]. NAb and T cell responses to each serotype may be induced by a single immunization with a tetravalent VRP vaccine at a level equivalent to the monovalent vaccine components, suggesting that this vaccine modality can overcome serotype interference. Although the neonatal immune response was found to be lower in magnitude than responses in adult mice, neonatal immunization was durable and could be boosted later in life to increase further NAb and Tcell responses. Hence, since VRP vaccines expressing DENV antigens are immunogenic and protective in neonates, they are promising candidates for safe and effective vaccination in early life [75].

Another encouraging vaccine platform is the use of replication-defective recombinant adenovirus (Ad) vectors. In a wide variety of cell types, these vectors have the ability to express antigens at high levels making them ideal for inducing potent immune responses. Ad vectors have been studied as a delivery vehicle for a wide variety of infectious agents, including dengue virus [76], tick-borne encephalitis virus [77], human immunodeficiency virus [78], Ebola virus [79-81] and Marburg virus [82,83]. However, the major limitation to the traditional Ad vector vaccine approaches is the volume of antigenic information that can be carried by a single vector. Specifically, in the Ad-based dengue vaccine, only a fraction of the E gene sequence of a single DENV serotype was expressed [76]. ATDV based on a novel complex adenovirus platform that is capable of expressing multiple antigens *de novo* has also been developed [84]. This dengue vaccine was constructed as a pair of vectors that each expresses prM and E genes of two different DENV serotypes. Upon vaccination of C57BL/6 mice, natural infection was mimicked and both NAb and cellular immune responses against multiple serotypes of DENV were induced [84]. As several epitopes of the E protein are known to play a significant role in the induction of both NAbs and T cell-mediated immunity, both prM and E were selected as antigens [85,86], while expression of the flavivirus prM protein is necessary for correct processing and expression of E [87-89]. The vast majority of the global human population becomes rapidly immune to adenovirus, particularly subtype-5, that most common used for vector-based gene therapy and vaccine design [90]. Thus, a common criticism of Ad vector use in humans is the likelihood of pre-existing immunity. The presence of circulating Ad NAbs has the potential to limit the efficacy of an Ad-based vector vaccine. However, a recent clinical trial found no correlation between pre-existing Ad-NAb titres and potency of an Ad-based influenza vaccine in humans [91].

Challenges in the development of tetravalent dengue vaccines

Despite numerous studies to date on DENV, no effective vaccine is currently available [92,93]. In order to provide long-term broad protection against all serotypes, dengue vaccine design has targeted a multivalent strategy (Table 1). However, a number of major scientific challenges have slowed down development. The lack of an entirely appropriate animal model, coupled with insufficient understanding of correlates of successful human immunity and immune pathology following infection, are significant obstacles to the development of an effective vaccine [94,95]. In addition, within each of the DENV serotypes there are multiple genotypes, reflecting a high degree of mutation due to evolutionary selective pressure. Specific genotypes may exhibit differences in viral fitness and be associated with more severe clinical phenotypes. It remains unclear how important identifying genotypic variation is to dengue vaccine development [24]. Furthermore, infection by one of the DENV serotypes has been shown to confer lasting protection against homotypic reinfection but only transient protection against a secondary heterotypic infection. Secondary heterotypic infection is associated with an increased risk of severe disease which is referred to as immune enhancement of disease [12]. A paucity of knowledge of the contribution of NAbs to protection versus other immune mechanisms such as cytotoxic T cell responses, a lack of appreciation of the most suitable target epitopes for vaccines, an unrecognized role of non-structural proteins in dengue immunity, viral interference of multivalent combinations, and concern about reactogenicity in flavivirus-exposed individuals are examples of further challenges associated with the development of safe and effective dengue vaccines [95].

FUTURE PERSPECTIVES

Most of the TDVs developed so far have shown qualified success, generating NAb responses but not necessarily reducing viraemia. Importantly, although research is ongoing, to date these candidates have not provided sufficient indicationof delivering broad protection against all tested serotypes (Table 1) [16]. Many TDVs are based on live virus vectors that can potentially elicit an adverse effect in immune suppressed patients, while the newly discovered dengue serotype, DEN-5, is also found to be associated with infection [2]. In this context, there is a pressing need to identify novel pentavalent vaccine candidates which

Table 1: Characteristics of various tetravalent dengue vaccines under trial.

Vaccine type	Animal model/ human	Route of vaccination	Important observation	Reference
Live-attenuated	Cynomolgus macaques	Subcutaneous/intradermal	Neutralizing antibody response to DEN-2 showed no significant increase in titre in all vaccinated groups	Ambuel et al. 2014 [22]
Recombinant	Human (children & adolescents)	Subcutaneous	Vaccination elicited neutralizing antibody response against all serotypes and was well tolerated in children/adolescents	Dayan et al. 2013 [29]
Chimeric DNA	Rhesus macaques	Intramuscular	Reduction in viraemia for DEN-1 but not DEN-2, i.e. partial protection against DEN-1 but no protection against DEN-2	Raviprakash et al. 2006 [44]
DNA Syncon	BALB/c mice	Intramuscular electroporation	Significant level of neutralizing antibodies to all serotypes	Ramanathan et al. 2009 [47]
DNA with adjuvant	New Zealand white rabbits	Intramuscular	All animals elicited strong neutralizing antibody response to all serotypes	Raviprakash et al. 2012 [50]
Electroporation- enhanced DNA	ICR mice	Intramuscular electroporation	A good neutralizing antibody response was induced in all animals	Prompetchara et al. 2014 [52]
Sub-unit	BALB/c mice	Subcutaneous	Neutralizing antibodies were induced against all serotypes	Zhao et al. 2014 [68]
Nanoparticle- adsorbed	Swiss Webster mice	Subcutaneous	Anti-dengue IgG to all serotypes was elicited but no neutralizing activity	Silvaet al. 2012 [71]
Alphavirus-based	BALB/c mice	Intraperitoneal	Elicited protective immunity by neutralizing antibodies against all serotypes in neonatal mice	Khalil et al. 2014 [75]
Adenovirus- based	C57Bl/6 mice	Intraperitoneal	Neutralizing antibody against all serotypes was elicited	Holman et al. 2007 [84]

may engender effective protection against all acknowledged serotypes.

CONCLUSION

Although several TDV candidates are undergoing pre-clinical testing and a number of others are currently in clinical trials, an effective DENV vaccine has yet to become commercially available. Several of the tetravalent vaccine candidates have not fulfilled their early promise in animal models by eliciting immunity against each of the four dengue serotypes measured in human participants. Therefore, development of a second generation of new or refined vaccine candidates is most likely required to provide protection against all serotypes, including the recently recognized fifth serotype.

ACKNOWLEDGEMENTS

The authors' research is supported by Central Queensland University and the Australian Government's Collaborative Research Networks Program.

REFERENCES

1. Gubler DJ. Dengue and dengue hemorrhagic fever. Clin. Microbiol. Rev. 1998; 11: 480-496.
2. Normile D. Tropical medicine. Surprising new dengue virus throws a spanner in disease control efforts. Science. 2013; 342: 415.
3. Malavige GN, Fernando S, Fernando DJ, Seneviratne SL. Dengue viral infections. Postgrad Med J. 2004; 80: 588-601.
4. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL. The global distribution and burden of dengue. Nature. 2013; 496: 504-507.
5. Halstead SB, Mahalingam S, Marovich MA, Ubol S, Mosser DM. Intrinsic antibody-dependent enhancement of microbial infection in macrophages: disease regulation by immune complexes. Lancet Infect Dis. 2010; 10: 712-722.
6. Rothman AL. Dengue: defining protective versus pathologic immunity. J Clin Invest. 2004; 113: 946-951.
7. Rothman AL. T lymphocyte responses to heterologous secondary dengue virus infections. Ann N Y Acad Sci. 2009; 1171 Suppl 1: E36-41.
8. Whitehead SS, Blaney JE, Durbin AP, Murphy BR. Prospects for a dengue virus vaccine. Nat Rev Microbiol. 2007; 5: 518-528.
9. Blanc G, Caminopetros J. Recherches experimentalessur la dengue. Ann. Inst. Pasteur Paris. 1930; 44: 367-436.
10. Simmons J, St John J, Reynolds F. Experimental studies of dengue. Philippine J. Sci. 1931; 44: 1-252.
11. Wilder-Smith A, Macary P. Dengue: challenges for policy makers and vaccine developers. Curr Infect Dis Rep. 2014; 16: 404.
12. Guy B, Barrere B, Malinowski C, Saville M, Teyssou R, Lang J. From research to phase III: preclinical, industrial and clinical development of the Sanofi Pasteur tetravalent dengue vaccine. Vaccine. 2011; 29: 7229-7241.
13. Capeding MR, Tran NH, Hadinegoro SR, Ismail HI, Chotpitayasunondh T, Chua MN, et al. Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial.Lancet. 2014.
14. Bhamarapravati N, Sutee Y. Live attenuated tetravalent dengue vaccine. Vaccine. 2000; 18 Suppl 2: 44-47.

15. Halstead SB, Marchette NJ. Biologic properties of dengue viruses following serial passage in primary dog kidney cells: studies at the University of Hawaii. Am J Trop Med Hyg. 2003; 69: 5-11.

16. Sabchareon A, Lang J, Chanthavanich P, Yoksan S, Forrat R, Attanath P. Safety and immunogenicity of tetravalent live-attenuated dengue vaccines in Thai adult volunteers: role of serotype concentration, ratio, and multiple doses. Am J Trop Med Hyg. 2002; 66: 264-272.

17. Sabchareon A, Lang J, Chanthavanich P, Yoksan S, Forrat R, Attanat. Safety and immunogenicity of a three dose regimen of two tetravalent live-attenuated dengue vaccines in five- to twelve-year-old Thai children. Pediatr Infect Dis J. 2004; 23: 99-109.

18. Sanchez V, Gimenez S, Tomlinson B, Chan PK, Thomas GN, Forrat R. Innate and adaptive cellular immunity in flavivirus-naïve human recipients of a live-attenuated dengue serotype 3 vaccine produced in Vero cells (VDV3). Vaccine. 2006; 24: 4914-4926.

19. Innis BL, Eckels KH. Progress in development of a live-attenuated, tetravalent dengue virus vaccine by the United States Army Medical Research and Materiel Command. Am J Trop Med Hyg. 2003; 69: 1-4.

20. Edelman R, Wasserman SS, Bodison SA, Putnak RJ, Eckels KH, Tang D. Phase I trial of 16 formulations of a tetravalent live-attenuated dengue vaccine. Am J Trop Med Hyg. 2003; 69: 48-60.

21. Sun W, Cunningham D, Wasserman SS, Perry J, Putnak JR, Eckels KH. Phase 2 clinical trial of three formulations of tetravalent live-attenuated dengue vaccine in flavivirus-naïve adults. Hum Vaccin. 2009; 5: 33-40.

22. Ambuel Y, Young G, Brewoo JN, Paykel J, Weisgrau KL, Rakasz EG, et al. A rapid immunization strategy with a live attenuated tetravalent dengue vaccine elicits protective neutralizing antibody responses in non-human primates. Front. Immunol. 2014; 5: 263.

23. Schmitz J, Roehrig J, Barrett A, Hombach J. Next generation dengue vaccines: a review of candidates in preclinical development. Vaccine. 2011; 29: 7276-7284.

24. Sabchareon A, Wallace D, Sirivichayakul C, Limkittikul K, Chanthavanich P, Suvannadabba S. Protective efficacy of the recombinant, live-attenuated, CYD tetravalent dengue vaccine in Thai schoolchildren: a randomised, controlled phase 2b trial. Lancet. 2012; 380: 1559-1567.

25. Swaminathan S, Khanna N, Herring B, Mahalingam S. Dengue vaccine efficacy trial: does interference cause failure? Lancet Infect Dis. 2013; 13: 191-192.

26. Capeding RZ, Luna IA, Bomasang E, Lupisan S, Lang J, Forrat R. Live-attenuated, tetravalent dengue vaccine in children, adolescents and adults in a dengue endemic country: randomized controlled phase I trial in the Philippines. Vaccine. 2011; 29: 3863-3872.

27. Guirakhoo F, Weltzin R, Chambers TJ, Zhang ZX, Soike K, Ratterree M. Recombinant chimeric yellow fever-dengue type 2 virus is immunogenic and protective in nonhuman primates. J Virol. 2000; 74: 5477-5485.

28. Guirakhoo F, Arroyo J, Pugachev KV, Miller C, Zhang ZX, Weltzin R. Construction, safety, and immunogenicity in nonhuman primates of a chimeric yellow fever-dengue virus tetravalent vaccine. J Virol. 2001; 75: 7290-7304.

29. Dayan GH, Garbes P, Noriega F, Izoton de Sadovsky AD, Rodrigues PM, Giuberti C. Immunogenicity and safety of a recombinant tetravalent dengue vaccine in children and adolescents ages 9-16 years in Brazil. Am J Trop Med Hyg. 2013; 89: 1058-1065.

30. Tang DC, DeVit M, Johnston SA. Genetic immunization is a simple method for eliciting an immune response. Nature. 1992; 356: 152-154.

31. Ulmer JB, Donnelly JJ, Parker SE, Rhodes GH, Felgner PL, Dwarki VJ. Heterologous protection against influenza by injection of DNA encoding a viral protein. Science. 1993; 259: 1745-1749.

32. Wang B, Ugen KE, Srikantan V, Agadjanyan MG, Dang K, Refaeli Y. Gene inoculation generates immune responses against human immunodeficiency virus type 1. Proc Natl Acad Sci U S A. 1993; 90: 4156-4160.

33. Guy B, Barban V, Mantel N, Aguirre M, Gulia S, Pontvianne J. Evaluation of interferences between dengue vaccine serotypes in a monkey model. Am J Trop Med Hyg. 2009; 80: 302-311.

34. Kitchener S, Nissen M, Nasveld P, Forrat R, Yoksan S, Lang J. Immunogenicity and safety of two live-attenuated tetravalent dengue vaccine formulations in healthy Australian adults. Vaccine. 2006; 24: 1238-1241.

35. Durbin AP, Kirkpatrick BD, Pierce KK, Elwood D, Larsson CJ, Lindow JC. A single dose of any of four different live attenuated tetravalent dengue vaccines is safe and immunogenic in flavivirus-naive adults: a randomized, double-blind clinical trial. J Infect Dis. 2013; 207: 957-965.

36. Anderson KB, Gibbons RV, Edelman R, Eckels KH, Putnak RJ, Innis BL. Interference and facilitation between dengue serotypes in a tetravalent live dengue virus vaccine candidate. J Infect Dis. 2011; 204: 442-450.

37. Sun W, Edelman R, Kanesa-Thasan N, Eckels KH, Putnak JR, King AD. Vaccination of human volunteers with monovalent and tetravalent live-attenuated dengue vaccine candidates. Am J Trop Med Hyg. 2003; 69: 24-31.

38. Halstead SB. Identifying protective dengue vaccines: guide to mastering an empirical process. Vaccine. 2013; 31: 4501-4507.

39. Kutzler MA, Weiner DB. DNA vaccines: ready for prime time? Nat Rev Genet. 2008; 9: 776-788.

40. Danko JR, Beckett CG, Porter KR. Development of dengue DNA vaccines. Vaccine. 2011; 29: 7261-7266.

41. Thomas SJ, Eckels KH, Carletti I, De La Barrera R, Dessy F, Fernandez S. A phase II, randomized, safety and immunogenicity study of a re-derived, live-attenuated dengue virus vaccine in healthy adults. Am J Trop Med Hyg. 2013; 88: 73-88.

42. Simmons M, Burgess T, Lynch J, Putnak R. Protection against dengue virus by non-replicating and live attenuated vaccines used together in a prime boost vaccination strategy. Virology. 2010; 396: 280-288.

43. Apt D, Raviprakash K, Brinkman A, Semyonov A, Yang S, Skinner C. Tetravalent neutralizing antibody response against four dengue serotypes by a single chimeric dengue envelope antigen. Vaccine. 2006; 24: 335-344.

44. Raviprakash K, Apt D, Brinkman A, Skinner C, Yang S, Dawes G. A chimeric tetravalent dengue DNA vaccine elicits neutralizing antibody to all four virus serotypes in rhesus macaques. Virology. 2006; 353: 166-173.

45. Kuhn RJ, Zhang W, Rossmann MG, Pletnev SV, Corver J, Lenches E. Structure of dengue virus: implications for flavivirus organization, maturation, and fusion. Cell. 2002; 108: 717-725.

46. Modis Y, Ogata S, Clements D, Harrison SC. Structure of the dengue virus envelope protein after membrane fusion. Nature. 2004; 427: 313-319.

47. Ramanathan MP, Kuo YC, Selling BH, Li Q, Sardesai NY, Kim JJ. Development of a novel DNA SynCon tetravalent dengue vaccine that elicits immune responses against four serotypes. Vaccine. 2009; 27: 6444-6453.

48. Raviprakash K, Porter KR, Kochel TJ, Ewing D, Simmons M, Phillips I. Dengue virus type 1 DNA vaccine induces protective immune responses in rhesus macaques. J Gen Virol. 2000; 81: 1659-1667.

49. Blair PJ, Kochel TJ, Raviprakash K, Guevara C, Salazar M, Wu SJ. Evaluation of immunity and protective efficacy of a dengue-3 pre-membrane and envelope DNA vaccine in Aotus nancymae monkeys. Vaccine. 2006; 24: 1427-1432.

50. Raviprakash K, Luke T, Doukas L, Danko J, Porter K, Burgess T, et al. A dengue DNA vaccine formulated with Vaxfectin® is well tolerated, and elicits strong neutralizing antibody responses to all four dengue serotypes in New Zealand white rabbits. Hum. Vaccin. Immunother. 2012; 8: 1764-1768.

51. Draghia-Akli R, Khan A. Electroporation of plasmid-based vaccines and therapeutics.In: Gene and Cell Therapy: Therapeutic Mechanisms and Strategies. 3rd ed. Smyth Templeton N, editor.Boca Raton: CRC Press; 2008. pp. 363-371.

52. Prompetchara E, Ketloy C, Keelapang P, Sittisombut N, Ruxrungtham K. Induction of neutralizing antibody response against four dengue viruses in mice by intramuscular electroporation of tetravalent DNA vaccines. PLoS One. 2014; 9: e92643.

53. Konishi E, Kosugi S, Imoto J. Dengue tetravalent DNA vaccine inducing neutralizing antibody and anamnestic responses to four serotypes in mice. Vaccine. 2006; 24: 2200-2207.

54. Mattapallil JJ, Douek DC, Buckler-White A, Montefiori D, Letvin NL, Nabel GJ. Vaccination preserves CD4 memory T cells during acute simian immunodeficiency virus challenge. J Exp Med. 2006; 203: 1533-1541.

55. Pasetti MF, Ramirez K, Resendiz-Albor A, Ulmer J, Barry EM, Levine MM. Sindbis virus-based measles DNA vaccines protect cotton rats against respiratory measles: relevance of antibodies, mucosal and systemic antibody-secreting cells, memory B cells, and Th1-type cytokines as correlates of immunity. J Virol. 2009; 83: 2789-2794.

56. Eick-Cost AA, Tastad KJ, Guerrero AC, Johns MC, Lee SE, Macintosh VH, et al. Effectiveness of seasonal influenza vaccines against influenza-associated illnesses among US military personnel in 2010-11: acase-control approach. PLoS One. 2012; 7.

57. Johns MC, Eick AA, Blazes DL, Lee SE, Perdue CL, Lipnick R. Seasonal influenza vaccine and protection against pandemic (H1N1) 2009-associated illness among US military personnel. PLoS One. 2010; 5: e10722.

58. Vesikari T, Pellegrini M, Karvonen A, Groth N, Borkowski A, O'Hagan DT . Enhanced immunogenicity of seasonal influenza vaccines in young children using MF59 adjuvant. Pediatr Infect Dis J. 2009; 28: 563-571.

59. Cowling BJ, Ng S, Ma ES, Cheng CK, Wai W, Fang VJ, et al. Protective efficacy of seasonal influenza vaccination against seasonal and pandemic influenza virus infection during 2009 in Hong Kong. Clin. Infect. Dis. 2010; 51: 1370-1379.

60. Gromowski GD, Barrett ND, Barrett AD. Characterization of dengue virus complex-specific neutralizing epitopes on envelope protein domain III of dengue 2 virus. J Virol. 2008; 82: 8828-8837.

61. Shrestha B, Brien JD, Sukupolvi-Petty S, Austin SK, Edeling MA, Kim T. The development of therapeutic antibodies that neutralize homologous and heterologous genotypes of dengue virus type 1. PLoS Pathog. 2010; 6: e1000823.

62. Sukupolvi-Petty S, Austin SK, Purtha WE, Oliphant T, Nybakken GE, Schlesinger JJ, et al. Type- and subcomplex-specific neutralizing antibodies against domain III of dengue virus type 2 envelope protein recognize adjacent epitopes. J Virol. 2007; 81: 12816-12826.

63. Chen HW, Liu SJ, Li YS, Liu HH, Tsai JP, Chiang CY. A consensus envelope protein domain III can induce neutralizing antibody responses against serotype 2 of dengue virus in non-human primates. Arch Virol. 2013; 158: 1523-1531.

64. Clements DE, Coller BA, Lieberman MM, Ogata S, Wang G, Harada KE. Development of a recombinant tetravalent dengue virus vaccine: immunogenicity and efficacy studies in mice and monkeys. Vaccine. 2010; 28: 2705-2715.

65. Marcos E, Gil L, Lazo L, Izquierdo A, Brown E, Suzarte E. Purified and highly aggregated chimeric protein DIIIC-2 induces a functional immune response in mice against dengue 2 virus. Arch Virol. 2013; 158: 225-230.

66. Nguyen NL, Kim JM, Park JA, Park SM, Jang YS, Yang MS, et al. Expression and purification of an immunogenic dengue virus epitope using a synthetic consensus sequence of envelope domain III and Saccharomyces cerevisiae. Protein Expr Purif. 2013; 88: 235-242.

67. Yang J, Zhang J, Chen W, Hu Z, Zhu J, Fang X. Eliciting cross-neutralizing antibodies in mice challenged with a dengue virus envelope domain III expressed in Escherichia coli. Can J Microbiol. 2012; 58: 369-380.

68. Zhao H, Jiang T, Zhou X-Z, Deng Y-Q, Li X-F, Chen SP, et al. Induction of neutralizing antibodies against four serotypes of dengue viruses by MixBiEDIII, a tetravalent dengue vaccine. PLoS One. 2014.

69. Klippstein R, Pozo D. Nanotechnology-based manipulation of dendritic cells for enhanced immunotherapy strategies. Nanomedicine. 2010; 6: 523-529.

70. Rice-Ficht AC, Arenas-Gamboa AM, Kahl-McDonagh MM, Ficht TA. Polymeric particles in vaccine delivery. Curr Opin Microbiol. 2010; 13: 106-112.

71. Silva EF, Orsi M, Andrade AL, Domingues RZ, Silva BM, de Araújo HR. A tetravalent dengue nanoparticle stimulates antibody production in mice. J Nanobiotechnology. 2012; 10: 13.

72. Geeraedts F, Goutagny N, Hornung V, Severa M, de Haan A, Pool J. Superior immunogenicity of inactivated whole virus H5N1 influenza vaccine is primarily controlled by Toll-like receptor signalling. PLoS Pathog. 2008; 4: e1000138.

73. Halstead S, Thomas S. Dengue vaccines. In: Therapeutic Advances in Vaccines.Plotkin S, Orenstein W, Offit P,editors. Beijing: Elsevier; 2013. pp. 1042-51.

74. Wan SW, Lin CF, Wang S, Chen YH, Yeh TM, Liu HS. Current progress in dengue vaccines. J Biomed Sci. 2013; 20: 37.

75. Khalil SM, Tonkin DR, Mattocks MD, Snead AT, Johnston RE, White LJ. A tetravalent alphavirus-vector based dengue vaccine provides effective immunity in an early life mouse model. Vaccine. 2014; 32: 4068-4074.

76. Jaiswal S, Khanna N, Swaminathan S. Replication-defective adenoviral vaccine vector for the induction of immune responses to dengue virus type 2. J Virol. 2003; 77: 12907-12913.

77. Timofeev AV, Ozherelkov SV, Pronin AV, Deeva AV, Karganova GG, Elbert LB. Immunological basis for protection in a murine model of tick-borne encephalitis by a recombinant adenovirus carrying the gene encoding the NS1 non-structural protein. J Gen Virol. 1998; 79: 689-695.

78. Barouch DH, Nabel GJ. Adenovirus vector-based vaccines for human immunodeficiency virus type 1. Hum Gene Ther. 2005; 16: 149-156.

79. Sullivan NJ, Geisbert TW, Geisbert JB, Xu L, Yang ZY, Roederer M. Accelerated vaccination for Ebola virus haemorrhagic fever in non-human primates. Nature. 2003; 424: 681-684.

80. Sullivan NJ, Sanchez A, Rollin PE, Yang ZY, Nabel GJ. Development of a

preventive vaccine for Ebola virus infection in primates. Nature. 2000; 408: 605-609.

81. Wang D, Raja NU, Trubey CM, Juompan LY, Luo M, Worarattanadharm J. Development of a cAdVax-based bivalent ebola virus vaccine that induces immune responses against both the Sudan and Zaire species of Ebola virus. J Virol. 2006; 80: 2738-2746.

82. Wang D, Hevey M, Juompan LY, Trubey CM, Raja NU, Deitz SB. Complex adenovirus-vectored vaccine protects guinea pigs from three strains of Marburg virus challenges. Virology. 2006; 353: 324-332.

83. Wang D, Schmaljohn AL, Raja NU, Trubey CM, Juompan LY, Luo M. De novo syntheses of Marburg virus antigens from adenovirus vectors induce potent humoral and cellular immune responses. Vaccine. 2006; 24: 2975-2986.

84. Holman DH, Wang D, Raviprakash K, Raja NU, Luo M, Zhang J. Two complex, adenovirus-based vaccines that together induce immune responses to all four dengue virus serotypes. Clin Vaccine Immunol. 2007; 14: 182-189.

85. Crill WD, Roehrig JT. Monoclonal antibodies that bind to domain III of dengue virus E glycoprotein are the most efficient blockers of virus adsorption to Vero cells. J Virol. 2001; 75: 7769-7773.

86. Livingston PG, Kurane I, Lai CJ, Bray M, Ennis FA. Recognition of envelope protein by dengue virus serotype-specific human CD4+ CD8- cytotoxic T-cell clones. J Virol. 1994; 68: 3283-3288.

87. Allison SL, Stadler K, Mandl CW, Kunz C, Heinz FX. Synthesis and secretion of recombinant tick-borne encephalitis virus protein E in soluble and particulate form. J Virol. 1995; 69: 5816-5820.

88. Konishi E, Mason PW. Proper maturation of the Japanese encephalitis virus envelope glycoprotein requires cosynthesis with the premembrane protein. J Virol. 1993; 67: 1672-1675.

89. Ocazionez Jimenez R, Lopes da Fonseca BA. Recombinant plasmid expressing a truncated dengue-2 virus E protein without co-expression of prM protein induces partial protection in mice. Vaccine. 2000; 19: 648-654.

90. Nwanegbo E, Vardas E, Gao W, Whittle H, Sun H, Rowe D. Prevalence of neutralizing antibodies to adenoviral serotypes 5 and 35 in the adult populations of The Gambia, South Africa, and the United States. Clin Diagn Lab Immunol. 2004; 11: 351-357.

91. Van Kampen KR, Shi Z, Gao P, Zhang J, Foster KW, Chen DT. Safety and immunogenicity of adenovirus-vectored nasal and epicutaneous influenza vaccines in humans. Vaccine. 2005; 23: 1029-1036.

92. Martina BE, Koraka P, Osterhaus AD. Dengue virus pathogenesis: an integrated view. Clin Microbiol Rev. 2009; 22: 564-581.

93. Jupatanakul N, Sim S, Dimopoulos G. Aedes aegypti ML and Niemann-Pick type C family members are agonists of dengue virus infection. Dev Comp Immunol. 2014; 43: 1-9.

94. Sanyal S, Taylor-Robinson AW. Host-virus interactions in dengue infection indicate targets for detection and therapeutic interventions. Immun. Dis. 2013; 1, a7 1-4.

95. Wilder-Smith A, Ooi EE, Vasudevan SG, Gubler DJ. Update on dengue: epidemiology, virus evolution, antiviral drugs, and vaccine development. Curr Infect Dis Rep. 2010; 12: 157-164.

Cite this article

Ansari S, Taylor-Robinson AW (2014) Strategic Approaches to Multivalent Vaccine Development against Dengue Virus Infection. Ann Vaccines Immunization 1(2): 1005.