Advances in Research on Dengue Virus 3' UTRΔ30 Vaccines: Postprint

Authors: Xu Jiayue, Li Ziqian, Zhang Ge

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Abstract

Diseases such as dengue fever caused by dengue virus impose substantial economic, healthcare, and social burdens globally each year, posing a serious threat to human life and health. Among the various dengue virus vaccines currently under investigation, the 3' UTRΔ30 series of live attenuated vaccines, produced using reverse genetics technology, have demonstrated good protective efficacy in clinical trials and are advancing rapidly in development, owing to their favorable immunogenicity, high potency, and low cost. The 3' UTRΔ30 tetravalent vaccine, which elicits balanced immune protection against all four dengue virus serotypes, is currently in Phase III clinical trials, exhibiting strong efficacy and minimal adverse reactions; it is anticipated to be approved for market launch upon completion of the follow-up period, representing one of the most promising dengue attenuated inactivated vaccines available today. To provide a more comprehensive understanding of the 3'UTRΔ30 series vaccines, this review primarily introduces their origin, preparation methods, and clinical research progress.

Full Text

Research Progress on Dengue Virus 3' UTRΔ30 Series Vaccines

Xu Jiayue, Li Ziqian, Zhang Ge*
School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, China

Abstract

Dengue fever and related diseases caused by dengue virus impose considerable economic, medical, and social burdens worldwide each year, posing a serious threat to human health. Among the various dengue virus vaccines under investigation, the 3' UTRΔ30 series of live attenuated vaccines produced by reverse

genetics have demonstrated promising protective effects in clinical trials due to their good immunogenicity, high titer, and low cost, with rapid research advancement. The 3' UTRΔ30 tetravalent vaccine, which can elicit balanced immune protection against all four serotypes of dengue virus, is currently in Phase III clinical trials. It shows strong efficacy and few adverse reactions, and is expected to be marketed after the completion of the follow-up period, making it one of the most promising dengue attenuated vaccines today. To provide a deeper understanding of the 3' UTRΔ30 series vaccines, this review focuses primarily on their origin, preparation methods, and clinical research.

Keywords: dengue virus; 3' UTRΔ30 vaccine; preparation methods; clinical research

Dengue virus (DENV) belongs to the Flaviviridae family and is a single-stranded positive-sense RNA virus approximately 11 kb in length. The complete genome contains a 5' UTR with an m7-GpppA-m2 cap structure (Cap-1 structure) and a relatively conserved sequence in the 3' UTR without a polyA tail [1]. DENV is the pathogen causing dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS). Due to population mobility and greenhouse effects, its infection and transmission have shown a significant increasing trend, particularly in tropical and subtropical regions where frequent dengue outbreaks pose a serious threat to human life and health. It is estimated that over 390 million people are infected with DENV annually worldwide, with 96 million symptomatic cases [3]. In recent years, the dengue epidemic situation in China has also become increasingly severe, with outbreaks in South China being the most serious. For example, in 2014 alone, nearly 40,000 confirmed cases were reported in Guangzhou alone. In summary, DENV causes enormous economic losses and imposes substantial social and medical burdens globally.

Despite the severity of dengue fever, there are still no effective preventive methods or specific treatments apart from controlling mosquito vectors, making vaccine development the most effective approach to combat this disease. Based on antigenic differences, DENV can be divided into four serotypes: DENV-1, DENV-2, DENV-3, and DENV-4. Primary infection with any serotype can produce neutralizing antibodies that confer long-lasting immunity against the same serotype. However, primary infection also generates low-concentration, low-affinity cross-reactive non-neutralizing antibodies. If a subsequent infection involves a different serotype, these cross-reactive antibodies form antigen-antibody complexes that enter and infect macrophages via Fc receptors, causing massive viral proliferation and leading to severe complications such as DHF and DSS. This phenomenon is known as antibody-dependent enhancement (ADE) [4]. Therefore, an effective dengue vaccine must be tetravalent, capable of eliciting robust and balanced immune responses against all four DENV serotypes to avoid the ADE effect.

Current vaccine types under investigation include live attenuated vaccines (LAV), recombinant viral vaccines, purified inactivated vaccines (PLV), virus-like particles (VLPs), subunit and recombinant protein vaccines, and DNA

vaccines. Among these, the 3' UTRΔ30 series of live attenuated vaccines can induce immune responses similar to wild-type virus, exhibiting excellent immunogenicity and protective effects with low cost and high titer, and are advancing rapidly in current research. Its tetravalent formulation, TV003, is a novel live attenuated vaccine with good antibody response levels that requires only a single dose for application. It is currently undergoing Phase III clinical trials and is considered a highly promising tetravalent dengue vaccine candidate [5]. This review summarizes the 3' UTRΔ30 series vaccines from multiple perspectives, including principles, preparation, improvements, and clinical trial results.

Development and Preparation of 3' UTRΔ30 Vaccines

1.1 DENV Gene Structure

The dengue virus genome consists of a single open reading frame (ORF) encoding three structural proteins—core protein (C), membrane protein (M), and envelope protein (E)—and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5) [Figure 1: see original paper]. The mature virion' s outer lipid envelope is embedded with two transmembrane proteins, M and E, with the E protein involved in viral entry and fusion and serving as the primary target for antibody responses in the host. Additionally, the viral genome RNA contains non-coding regions (UTRs) at both the 5' and 3' ends, with the 3' UTR playing a particularly important role in viral translation and replication [6]. Deletions in this sequence may alter the secondary structure of genomic RNA and its interaction with structural proteins, thereby affecting dengue virus proliferation and infection processes and leading to attenuation.

Previous studies on attenuation mechanisms provided theoretical basis for obtaining DENV attenuated strains through site-directed mutagenesis. In 1997, Kinney identified five amino acid differences between the attenuated strain DENV-2 PDK53 and wild-type virus, establishing a link between DENV attenuation and genetic variation. Butrapet found that two to three amino acid changes in DENV-2 PDK53 could cause significant phenotypic changes. Later, Puri et al. discovered that mutation sites increased with passage number, indicating that DENV virulence is controlled by multiple sites [7]. Therefore, considering the structural and functional characteristics of the DENV 3' UTR, partial deletion mutations in the 3' UTR represent a logical approach for obtaining attenuated vaccine strains.

1.2 Reverse Genetics Technology

Novel DENV attenuated vaccine development based on reverse genetics technology, which involves deliberate DNA recombination or site-directed mutagenesis at the molecular level, is becoming a research hotspot. In 1991, Lai et al. first constructed a full-length cDNA clone of DENV4, making artificial directional attenuation of DENV possible. Whitehead et al. further optimized this to ob-

tain a simple and stable DENV4 reverse genetics system [8]. Later, Blaney et al. constructed reverse genetics systems for DENV1, DENV2, and DENV3 using an optimized pBR322 vector, completing the vaccine research platform. This provided an important technical foundation for the construction, preparation, and improvement of 3' UTRΔ30 vaccines.

Preparation and Improvement of 3' UTRΔ30 Vaccines

In 1996, Men et al. at the National Institute of Allergy and Infectious Diseases (NIH NIAID) deleted 30 nucleotides from positions 172–143 in the 3' UTR of the DENV-4 814669 strain to obtain the attenuated strain rDENV4Δ30 [Figure 2: see original paper]. This attenuation did not alter viral replication characteristics, and monkey studies showed not only attenuated features but also antibody levels equivalent to the parental strain [9]. In Phase I and II clinical trials, rDENV4Δ30 exhibited low reactogenicity and low viremia [10-11]. To further improve the attenuation stability of rDENV4Δ30 and reduce adverse reactions such as hepatotoxicity, Julie H. et al. introduced mutations at codons 200 and 201 in the NS5 coding region to obtain rDENV4Δ30-200,201, which achieved 100% seroconversion in Phase I trials with no detectable viremia or alanine aminotransferase elevation in any recipients. Peter F. et al. introduced a site-directed mutation at nucleotide 4995 in the NS3 coding region to obtain rDENV4Δ30-4995, which achieved 95% seroconversion in 20 healthy volunteers with no detectable viremia or alanine aminotransferase elevation.

Applying the same principle to DENV-1 by deleting the homologous region yielded the attenuated strain rDENV1Δ30 [Figure 2: see original paper], which demonstrated good safety and immunogenicity in preclinical and Phase I clinical trials with adverse reactions similar to rDENV4Δ30 [15-16]. For DENV-2 and DENV-3, the same strategy failed to reduce virulence. Researchers therefore used the attenuated rDENV4Δ30 as a backbone and replaced the PrM and E protein coding genes of rDENV4Δ30 with those from wild-type DENV-2 and DENV-3 to create intertypic chimeric vaccine strains rDENV2/4Δ30 [Figure 3: see original paper] and rDENV3/4Δ30, both of which showed effective attenuation and induced serotype-specific antiviral responses in animal studies [17-18]. In Phase I trials of rDENV2/4Δ30, no recipients developed dengue fever symptoms, though some showed transient viremia and alanine aminotransferase elevation [19]. Additionally, deleting 31 more nucleotides upstream of the 55 bp region on the basis of the existing 30-nucleotide deletion in the 3' UTR yielded rDENV3Δ30/31. Replacing the entire 3' UTR region of rDENV3 with that of rDENV4Δ30 produced the chimeric attenuated strain rDENV3-3' D4Δ30. Phase I clinical trial results showed both vaccines exhibited good safety after administration, with seroconversion rates of 95% and 80%, respectively; some recipients experienced rash and headache as adverse reactions [20].

Based on these eight attenuated live vaccine strains, NIAID designed five formulation schemes, each using different DENV1-DENV4 attenuated strains with slight variations in dose ratios, resulting in the 3' UTRΔ30 tetravalent

vaccines TV001-TV005 [21]. TV003 and TV005 have identical components, differing only in the dose of rDENV2/4Δ30. The specific formulation ratios of rDENV1Δ30:rDENV2/4Δ30:rDENV3Δ30/31:rDENV4Δ30 (PFU) are 10^3:10^3:10^3:10^3 and 10^3:10^4:10^3:10^3, respectively [22].

Clinical Trials of 3' UTRΔ30 Tetravalent Vaccines

The development of TV001-TV005 marked the initial formation of the 3' UTRΔ30 tetravalent dengue vaccine. To evaluate the safety and immunogenicity of single-dose TV001-TV004, NIAID conducted Phase I clinical trials in 112 healthy volunteers. Volunteers were divided into four groups of 28, each receiving one of the four vaccines. The experimental group received a 0.5 ml subcutaneous injection of 10^3 PFU vaccine on day 0, while the control group received the same volume of placebo (vaccine diluent). Serum antibody levels against all four dengue virus serotypes were measured on days 0, 28, 42, and 180. Analysis of seroconversion rates against the four serotypes revealed that a single dose of these vaccines achieved 75%-95% seroconversion against three serotypes. TV003 showed the best results, achieving 85%-100% seroconversion against all serotypes except DENV-2, for which the rate was only 50% [21].

TV005 differs from TV003 by having an increased content of rDENV2/4Δ30. To evaluate and compare the safety and immunogenicity of TV005, NIAID administered TV003 and TV005 subcutaneously to 168 healthy volunteers in two doses (6 months apart), with a placebo control group. Clinical evaluations and relevant indicator examinations were performed on days 21, 28, 42, 180 and days 3, 8, 10, 12, 14, 16, 21, 28, 56, 90, 180 after each vaccination. Results showed that by day 90 post-vaccination, the TV005 regimen achieved 97% seroconversion against DENV-2, significantly higher than the TV003 group. TV005 produced balanced cellular and humoral immune responses similar to TV003. Additionally, both this trial and another study specifically examining a second dose of TV003 one year later showed that booster vaccination did not significantly enhance immune titers, indicating that a single immunization achieves adequate protective effects [22-23].

To further evaluate the protective efficacy of TV003, Kirkpatrick et al. conducted a randomized, double-blind, placebo-controlled study in 48 healthy volunteers. Six months after receiving a single dose of TV003, subjects were challenged with rDENV2Δ30 virus. Primary endpoints included protection against viral infection and occurrence of rDEN2VΔ30 viremia, as well as observation of adverse reactions such as rash and neutropenia. Results showed that none of the 21 subjects in the vaccine group developed viremia, rash, or neutropenia, while 16 cases of rash and 4 cases of neutropenia were observed among 20 volunteers in the placebo group, demonstrating that TV003 provides complete and robust immune protection against dengue virus infection [24].

Previous clinical research progress on TV003 provided a solid theoretical and practical foundation for Phase II trials in Thailand and Phase III trials in Brazil.

Since the duration of immune response after a single TV003 dose remains unclear, Phase II and III studies need to verify the efficacy of a single-dose regimen [23]. Additionally, to comprehensively evaluate Phase III results, the vaccine protocol includes a 5-year follow-up period to ensure good efficacy without significant side effects. Currently, TV003 has been approved for production in Brazil, Vietnam, and India, with Merck (USA) and GSK (UK) showing strong interest in this candidate vaccine, seeking to conduct more in-depth research and even planning to combine it with their own proprietary vaccine candidates.

Comparison with Licensed Dengue Vaccine CYD-TDV

CYD-TDV is a dengue vaccine developed by Sanofi Pasteur over 20 years and represents the first licensed dengue vaccine. Like the 3' UTRΔ30 tetravalent vaccine TV003, CYD-TDV is a chimeric live attenuated vaccine, but differs in that it uses the yellow fever virus YF-17D as a vector into which the PrM and E genes of DENV are inserted [27-28]. Prior to licensure, CYD-TDV demonstrated good immune protection in Phase III trials across more than 10 countries, but several defects emerged during clinical trials and follow-up that TV003 can better address .

TABLE:3 Comparison between TV003 and CYD-TDV

Characteristic	CYD-TDV	TV003
NS proteins	Lacks all DENV non-structural proteins	Contains all DENV NS proteins
Immunization schedule	Requires 3 doses at months 0, 6, and 12 [29]	Single dose
Protective efficacy	Fails to provide balanced protection against four DENV serotypes [30-31]; short durability	Balanced immune protection; long-lasting efficacy
Population differences	Significant population differences observed	No significant population differences observed to date

Characteristic	CYD-TDV	TV003
	Protection rate significantly higher in those >9 years than <9 years [32-33] Overall protection efficiency lower in DENV-naïve or seronegative individuals	

NS proteins often contain CD8+ epitopes, so CYD-TDV, lacking NS proteins, typically fails to induce CD8+ T cell-mediated serotype-specific immune responses. In contrast, TV003, which retains complete NS proteins, preserves CD8+ T cell-mediated immunity, resulting in more significant effects in reducing severe DF disease. Regarding immunization frequency, CYD-TDV' s failure to provide balanced protection against all four DENV serotypes, particularly low levels against DENV-2, necessitates three doses within one year to overcome this issue. For TV003, however, a single immunization induces sufficient immune efficacy, and booster doses do not significantly enhance immune titers.

Furthermore, clinical trials have shown that TV003 rarely produces vaccine-related adverse reactions such as viremia and neutropenia. In summary, TV003 demonstrates significant advantages in antibody response levels and can induce CD8+ T cell immune responses against DENV, making it the most promising dengue vaccine candidate today.

Summary and Outlook

Since its emergence more than two decades ago, the 3' UTRΔ30 dengue vaccine has undergone continuous improvement and clinical trial analysis, culminating in the tetravalent formulation TV003 with good safety, strong protective efficacy, and low adverse reactions, representing significant progress in humanity' s fight against dengue fever. However, it must be acknowledged that since Phase III clinical trials are not yet complete, and previous clinical studies involved relatively small subject numbers and short evaluation periods, the reliability of these conclusions requires further investigation [34]. Key remaining questions include the unclear duration of immune response after single immunization and the uniformity of protection against all four DENV serotypes under natural infection conditions. A recent study addressing these issues compared daily gene expression patterns and subsequent neutralizing antibody titers between vaccinated volunteers and naturally infected patients, identifying time periods of strong transcriptional responses and potential early markers of dengue virus infection, bringing answers to these questions closer [35]. Future work should

focus on expanding clinical trial coverage, comprehensively analyzing follow-up results, closely coordinating with viral molecular epidemiology surveillance, and dynamically monitoring vaccine-related indicators in subjects to enable more effective population application of TV003.

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