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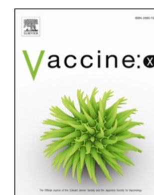

HTLV-1 vaccination Landscape: Current developments and challenges

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A B S T R A C T

Human T-lymphotropic virus type 1 (HTLV-1) is a retrovirus that is distinguished for its correlation to myelopathy/tropical spastic paraparesis (HAM/TSP) and adult T-cell leukemia/lymphoma (ATLL). As well, HTLV-1 has been documented to have links with other inflammatory diseases, such as uveitis and dermatitis. According to the World Health Organization (WHO), the global distribution of HTLV-1 infection is estimated to extend between 5 and 10 million individuals. Recent efforts in HTLV-1 vaccine development primarily involve selecting viral components, such as antigens, from structural and non-structural proteins. These components are chosen to trigger a vigorous immune response from cytotoxic T lymphocytes (CTLs), helper T lymphocytes (HTLs), and B cells. Investigation into developing a vaccine against HTLV-1 is ongoing, and current surveys have explored several approaches, including viral vector vaccines, DNA vaccines, protein and peptide vaccines, dendritic cell-based vaccines, mRNA vaccines, and other platforms. Despite these investigations have shown promising results, challenges like the necessity for long-term protective immunity, addressing viral diversity, and managing potential side effects remain. It is critical to keep track of the progress made in HTLV-1 vaccination research to comprehend the development status and its possible impacts. The evolving nature of vaccine development underscores the importance of staying informed about advancements as we strive to combat HTLV-1-associated diseases through effective vaccination strategies. In this review, our goal is to provide an overview of the current status of HTLV-1 vaccination efforts, emphasizing the progress, challenges, and potential future directions in this vital area of research.

Introduction

The recognition of Human T-lymphotropic virus type 1 (HTLV-1) over 40 years ago marked a substantial breakthrough as it became the first retrovirus with oncogenic properties to be discovered [1]. It is estimated that around 5 to 10 million people across the world are affected by HTLV-1. Incidence rates diverge widely and are endemic in several regions of the world, such as the southwestern region of Japan, sub-Saharan Africa, South America, the Caribbean area, and focal points in the Middle East and Australo-Melanesia. This differential distribution is likely due to a founder effect in certain groups, leading to a continued high virus transmission rate [2,3]. HTLV-1 spreads through direct contact with bodily fluids, including breast milk, blood, and semen [4]. Risk factors for infection with HTLV-1 comprise sexual activities without using protection, injecting drugs, and undergoing transplants involving tissue, blood, and blood products [5]. Individuals who are infected are at risk for developing a rare and aggressive peripheral T-cell neoplasm known as adult T-cell leukemia/lymphoma (ATLL), along with a severe and progressive neurological disorder named myelopathy/tropical spastic paraparesis (HAM/TSP) [6]. People detected with HTLV-1 infection should be informed that their infection is lifelong and refrain from donating blood or other tissues. Multiple methods are available for forecasting the advancement of diseases associated with this virus, such as assessing the HTLV-1 proviral load, conducting flow cytometric analysis, and analyzing the clonality of HTLV-1 infected cells [4,7,8]. A challenging aspect of managing HTLV-1 infection is its long incubation

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period [9].

Ongoing research in pursuing a vaccine for HTLV-1 involves investigating diverse methods. Recent studies have delved into different approaches, including viral vector vaccines, DNA vaccines, protein and peptide vaccines, dendritic cell-based vaccines, mRNA vaccines, and various other platforms (Fig. 1). These studies have utilized different HTLV-1 proteins like Tax, Glycoprotein (GP), polymerase (Pol), HTLV-1 bZIP factor (HBZ), Gag, and Rex to develop the vaccines [10]. The ideal vaccine should generate stable neutralizing antibodies (Abs) and induce cellular immunity. Achieving this goal may pose challenges to achieving a single vaccine because immunization protocols for inducing cellular-mediated immunity are different [11]. Altogether, more research on the efficacy and safety of HTLV-1 vaccines is needed.

In this review, we aim to present the current state of HTLV-1 vaccination endeavors, emphasizing advancements, obstacles, and potential future avenues in this crucial realm of research.

HTLV-1 vaccine development

An overview of HTLV-1 vaccination

Research for an HTLV-1 vaccine commenced immediately after the identification of HTLV-1 almost four decades ago. While there are presently no potential HTLV-1 vaccines undergoing clinical trials, it remains feasible to develop an effective vaccine in the future (Fig. 1). [9,12]. HTLV-1 envelope (Env) glycoproteins, gp46, and gp21, are antigens that are genetically highly conserved, and it is shown that the HTLV-1 genome has few sequence variations. gp46 have functions related to syncytia induction, cell–cell transmission, and antibody production. These glycoproteins can trigger both humoral and cellular immune responses, leading to the production of neutralizing antibodies in individuals who are infected. Therefore, gp46 and gp21 immunogens may be suitable candidates for developing preventing vaccines against HTLV-1 [9,12].

HTLV-1 vaccine platforms

Viral vector vaccine

Viral vector vaccine employs a genetically modified virus with impaired replicative or pathogenicity genes to transport specific genes encoding crucial pathogen antigens into target cells. Following infection by the viral vector, target cells express antigens, which can induce immune responses and protect the body from disease [13]. A variety of viral vectors have been used to express HTLV-1 genes, including adenovirus (AdV), cytomegalovirus (CMV), vaccinia virus (VV), variola virus (VARV), and baculovirus (BV) (Table 1) [13]. One of the earliest documented investigations into an HTLV-1 vaccine dates back to 1987, employing the recombinant vaccinia virus (rVV). The HTLV-1 envelope glycoprotein was substituted for the vaccinia hemagglutinin gene within this vector [14]. The hemagglutinin gene is unnecessary for virus replication and is a valuable candidate for gene insertion. Two kinds of recombinant vaccinia virus with the env gene were designed. In one rVV (WR-envl7), the env gene was inserted into a region that encodes signal peptide sequences of hemagglutinin protein. Another one (WR-proenvl) was inserted downstream of a vaccinia 7.5 K promoter region. Next, the construct of the promoter-env element was introduced into the hemagglutinin gene. Introducing both vaccine candidates into rabbits stimulated the production of anti-env antibodies, resulting in a protective effect against HTLV-1 infection. It was anticipated that the env proteins produced by rVV would be highly immunogenic, and a single vaccine produced a high titer of antibodies that persisted for 49 weeks. These findings suggest a possible HTLV-I vaccine development strategy [14]. Subsequently, to examine the antibody responses to various forms of HTLV-1 envelope protein, three recombinant vaccinia viruses (rVV E1, rVV E2, and rVV E3) were employed to express HTLV-1 envelope proteins [15]. RVV E1 expressed the native HTLV-1 envelope proteins gp46 and gp21, while the envelope precursor, gp160, with the deleted proteolytic cleavage site, was expressed by rVV E2, and rVV E3 expressed gp46. One benefit of employing rVV constructs is the production of native proteins, in this case, native HTLV-1 envelope proteins. These vaccines were inoculated to three different strains of mice: BALB/c, A/J, and C57BL/6. BALB/c mice responded weakly to all three rVV vaccine platforms. C57BL/6 mice generated neutralizing antibodies after administering each of the three rVV vaccines. In A/J mice, neutralizing antibodies were induced only in response to the rVV E1 vaccine. It has been demonstrated that the mouse strain employed resulted in a wide range of antibody responses to the rVV envelope constructions. Also, immune responses are contingent on the variations of the envelope protein expressed by the vaccinia vector. Generally, RVV E2 immunization resulted in the widest range of antibody production. The covalent bond between gp46 and gp21 may lead to T cells helping produce antibodies directed against gp21 [15]. Also, attenuated smallpox virus vectors (NYVAC derived from the vaccinia virus and ALVAC derived from the canarypox virus) were investigated to express the entire HTLV-1 envelope DNA sequence (DNA sequence obtained from an HTLV-1 infected patient in West Africa). These recombinant vectors were inoculated into live New Zealand white rabbits [16]. The vaccination regimens contained injection of the poxvirus recombinant vaccines alone and in combination with recombinant gp63 HTLV-I envelope precursor protein boost. According to findings, immunizing rabbits against an HTLV-1 challenge exposure with ALVAC alone was adequate to produce a protective immune response. The prime/boost method did not provide protection, so the ALVAC was used to prime immune responses and the gp63 subunit as a booster. This suggests that using the gp63 subunit neutralized the protective effects of the ALVAC. The cause of this outcome is unknown. Maybe the recombinant gp63 is different from the env protein generated by the NYVAC and ALVAC-infected cells, or the immunosuppressive area present in the transmembrane segment of the recombinant gp63 impaired the anti-HTLV-I immune response. The NYVAC vaccine candidate also induced a protective response in rabbits exposed to HTLV-1 shortly following vaccination. It has been shown that NYVAC and ALVAC initial protection against HTLV-1 was observed up to 5 months after the last immunization. Five months after immunization, immunized animals exposed to HTLV-1 were subsequently infected. The trial showed that these recombinant poxvirus vectors are promising candidates to inhibit HTLV-1 infection [16]. An investigation was conducted on cynomolgus monkeys involving the evaluation of a modified vaccinia virus that expressed the gp46 protein of the HTLV-1 Env [17]. This modified virus was created using the pSFB5 plasmid, incorporating the type A inclusion body promoter from cowpox viruses and five copies of the synthetic promoter found in the vaccinia virus. This synthetic construct facilitates the expression of the envelope protein gp46 derived from HTLV-1. The monkeys were immunized with the WR-SFB5-env vaccine. The vaccine was found to induce neutralizing antibodies that remained effective for up to 136 weeks after immunization. After 136 weeks, the immunized monkeys were challenged with HTLV-1, but no HTLV-1 antigen or provirus was observed in the spleen, lymph nodes, and peripheral blood mononuclear cells (PBMCs) of immunized monkeys. Also, this vaccine elicited HTLV-1-specific cytotoxic T lymphocytes (CTL). The findings demonstrated that rVV-expressing gp46 protein induces long-term protective responses against HTLV-1, including neutralizing antibodies and specific CTL in cynomolgus monkeys. Therefore, rVV expressing the HTLV-1 env gene is a viable strategy for creating a vaccine against HTLV-1 [17]. Another research examined a combination vaccine therapy involving two attenuated vaccinia virus-derivative NYVAC express HTLV-1 envelope gene or both gag and envelope genes in combination with the DNA-based vaccine encoding HTLV-1 Env as prime/boost in squirrel monkeys [18]. In this study, one group of squirrel monkeys was primed with NYVAC and boosted with naked DNA encoding HTLV-1 Env, while the other group was primed with naked DNA encoding HTLV-1 Env and boosted with NYVAC vaccine. It was shown that more efficient humoral

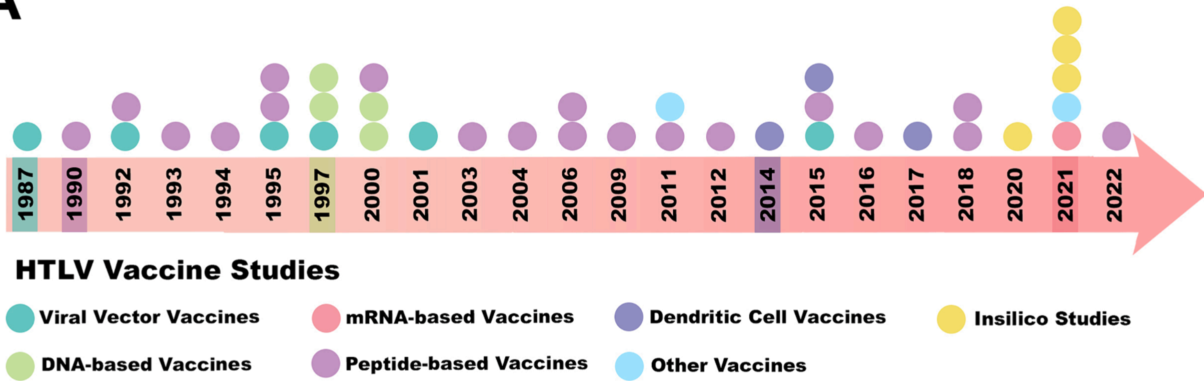

Fig. 1. HTLV-1 vaccine platforms. This figure shows timeline of various HTLV-1 platforms from 1987. There are several platforms that have been investigated such as viral vector vaccines, DNA vaccines, protein and peptide vaccines, vaccines based on dendritic cells, mRNA vaccines and some other platforms. Until now, there is no approved vaccine for HTLV-1.

Table 1
HTLV-1 Viral vector and DNA vaccines. The table delineates details pertaining to HTLV-1 viral vector and DNA vaccines, encompassing information on the route of administration, the year and country of study, authorship, key findings or results, and the type of study conducted.

Target antigens	Route of administration	Year/country/Author	Finding result	Type of study	References
HTLV-1 gp gene inserted in the rVV hemagglutinin gene	ID	1987 /Japan/ Shida,H	Inoculation to rabbit induced protective anti- Env antibody responses	in vivo	[14]
rVV E1, rVV E2, and rVV E3, express three different HTLV-I Env proteins. rVV E1 expressed the native HTLV-I gp46 and gp21, rVV E2 expressed the Env precursor with the proteolytic cleavage site deleted. rVV E3 expressed gp46	Intraperitoneal	1992/ Canada and United States /Ford, C. M	Inoculated to Balb/c, A/J, and C57BL/6 mice. Balb/c mice responded poorly to all three rVV vaccine platforms. C57BL/6 mice produced neutralizing antibodies to all three rVV vaccine. in A/J mice neutralizing antibodies induced only in response to rVV E1 vaccine.	in vivo	[15]
HTLV-1 Env DNA sequence was expressed in an attenuated smallpox virus vector	IM	1995/ United States / Franchini, G	Inoculated into New Zealand white rabbits and elicited initial protection against HTLV-1, but unable to induced neutralizing antibody responses	in vivo	[16]
rVV expressing HTLV-1 gp46 was made using the pSFB5 plasmid	ID	1997/Japan/Ibuki, K	Inoculated to cynomolgus monkeys and induced neutralizing antibody	in vivo	[17]
attenuated VV derivative NYVAC to express HTLV-1 Env genes or both gag and Env genes, followed by boosting with naked DNA encoding HTLV-1 Env	IM	2001/France/ Kazanji, M	Inoculate to squirrel monkeys. one group was primed with NYVAC and boosted with naked DNA, while the other group was primed with naked DNA and boosted with NYVAC vaccine. More efficient humoral and cellular immune responses generated in the naked DNA prime/NYVAC boost group	in vivo	[18]
rVV expressing HTLV-1 Hbz or Tax	skin scarification	2015/Japan/ Sugata, K	Induced HTLV-1-specific T cell responses with anti-lymphoma effect in rhesus monkeys and mice	in vivo	[19]

Abbreviations; recombinant vaccinia virus (rVV), Envelope (Env), Glycoprotein (gp).

and cellular immune responses were generated in the naked DNA prime/ NYVAC containing the env and gag genes boost group. In conclusion, using this protocol protected squirrel monkeys against HTLV-1 infection. Also, Rats have undergone testing using a blend of a recombinant virus and naked DNA that expresses the HTLV-1 Env gene. Cytotoxic T lymphocytes targeted against HTLV-1 were isolated from rats initially vaccinated with recombinant adenovirus five and later received a boost using naked DNA expressing the HTLV-1 Env gene [18].

Another study developed rVVs expressing either Tax or HBZ protein to investigate the immunogenic capacity of these proteins. rhesus monkeys and mice C57BL/6 immunized with this vaccine, and it was shown that rVV expressing HBZ could induce HBZ-specific CD4+ T cells and $CD8^{+}$ T cell responses. It has been demonstrated that in comparison to Tax protein, the immunogenicity of HBZ protein is low. The low production of HBZ protein in vivo may contribute to its limited CTL response. Hence, immunizing with a vector that provides the appropriate quantity of HBZ protein elicits CTL responses. Considering that this vaccine induces anti-HBZ specific CTL responses, HBZ protein can be proposed as an HTLV-1 peptide-based vaccine candidate epitope. Furthermore, HBZ expression is prolonged in adult T-cell lymphoma (ATL), and CTLs targeting HBZ exhibit an anti-lymphoma impact, suggesting the potential use of HBZ as a target in immunotherapeutic approaches to manage ATL or eliminate developing in those with HTLV-1 infection [19].

A recent study was carried out to assess the immune response capacity of a produced recombinant Modified Virus Vaccinia Ankara (MVA-HBZ) and DNA plasmid expressing a multi-epitope protein of HBZ, aimed at serving as a potential therapeutic vaccine against HTLV-1 [20]. In this analysis, mice underwent immunization using a prime-boost heterologous protocol. Subsequently, their splenocytes, specifically T $CD4^{+}$ and T $CD8^{+}$ cells, were analyzed using flow cytometry to determine their immunophenotype. The humoral response was also assessed via ELISA, utilizing HBZ protein expressed in a prokaryotic vector as the antigen. The immunogenic reaction observed in this preclinical test demonstrated the elicitation of multifunctional dual-positive responses for IFN-γ and TNF-α, as well as for TNF-α and IL-2, in both T $CD4^{+}$ and T $CD8^{+}$ lymphocytes. Additionally, it led to the activation of CTLs and the cytotoxic response. As acknowledged in their paper, one drawback of the current research is the utilization of peptides forecasted through computational methods for human MHC-I alleles in a BALB/c model, potentially leading to less-than-optimal reactions [20].

DNA vaccines

DNA-based vaccines contain an expression plasmid encoding an immunogen, delivered to a specific tissue inside the body to induce an immune response against the immunogen. DNA-based vaccines result in the production of adequately folded glycosylated native protein antigens. These vaccines often cause a broad spectrum of immunological responses, such as neutralizing antibodies and cytotoxic T-cell responses [21,22]. One research examined direct DNA inoculation with a plasmid encoding the HTLV-1 envelope and boosting with recombinant gp62 protein of baculovirus in BALB/c mice (Table 2). two DNA constructs (CMVenvLTR and CMVenv plasmids) expressing the complete HTLVI env gene were used. It has been shown that DNA inoculation was not adequate for inducing humoral responses, but protein-boosting improves antibody responses in mice primed with DNA expressing HTLV-1 envelope proteins [23]. These antibodies were specific to HTLV-1 env and had neutralizing effects. There was no difference in the immunization between the two plasmids, and only a greater antibody titer was observed for the CMVenvLTR immunization. The antibody isotypes in immunized mice were identified; IgG2a was mainly induced following priming with CMVenvLTR and protein boosts, and IgGl following priming with CMVenv and protein boosts [23]. In conclusion, inoculating DNA constructs that encode the HTLV-I env gene could generate memory B cells that stimulate humoral and cellular immune responses to env protein-boosting [23].

A group of researchers incorporated the HTLV-1 Env gene into a genetic construct that includes the adenovirus five major late promoters (Ad5-MLP) [24]. Two vaccination schedules targeting HTLV-1 were experimented with WKY and Fischer F-344 rats. WKY rats were initially exposed to either Ad5-HTLV-1-env or naked DNA plasmids carrying the HTLV-1 Env gene. Subsequently, they received a supplementary dose containing Ad5 encoding the HTLV-1 gp46 gene or baculovirus-derived recombinant gp46. Cellular immune responses were triggered in all immunized groups, but no antibody response was observed. In Fischer F-344 rats, which were primed and improved with recombinant vaccinia virus expressing the HTLV-1 Env gene, it was demonstrated that immunization led to the production of non-neutralizing antibodies targeting HTLV-1 gp21 and gp46 [24].

Consequently, neither immunization approach achieved complete

Table 2
HTLV-1 DNA vaccines. The table outlines details pertaining to HTLV-1 viral vector and DNA vaccines, encompassing information on the route of administration, the year and country of study, authorship, key findings or results, and the type of study conducted.

Target antigens	Route of administration	Year/country/Author	Finding result	Type of study	References
plasmid encoding entire HTLV-1 envelope	IM (vector)/IP (protein)	1997/France/Grange, M. P	boosting with recombinant gp62 protein of baculovirus, it was observed that protein boosting increases antibody responses in mice primed with DNA expressing HTLV-1 envelope proteins	in vivo	[23]
HTLV-1 Env gene into an expression cassette containing the adenovirus 5 major late promoter (Ad5-MLP)	IM/intradermally	1997/France/kanzaji, M	Two vaccination schedules were experimented in WKY and Fischer F-344 rats. WKY rats primed with Ad5-HTLV-I-env or naked DNA plasmids expressing HTLV-1 Env gene and boosted with Ad5 encoding HTLV-1 gp46 gene or with baculovirus-derived recombinant gp46. In all immunized groups cellular immune responses was induced, but antibody response was not found. Fischer F-344 rats primed and boosted with rVV expressing HTLV-1 Env gene resulted in inducing non-neutralizing antibodies against the HTLV-1 gp21 and gp46.	In vivo and in vitro	[24]
DNA vaccine expressing the Tax gene	The Helios Gene Gun system	2000/Japan/Ohashi, T	induced HTLV-1-specific cytotoxic T cells in rats with lymphoma. It was also produced effective anti-tumor immunity	–	[25]
plasmid containing DNA encoding the complete HTLV-1 envelope gene under the control of the CMV promoter and DNA encoding the complete HTLV-1 envelope gene under the control of the human Desmin muscle specific promoter	IM	2000/France/Armand, M. A	inoculation into mice, the Des promoter elicited a higher humoral response and better neutralization properties than CMV promoter	in vivo	[26]

Abbreviations; recombinant vaccinia virus (rVV), Envelope (Env), Glycoprotein (gp).

protection against HTLV-1, and the substantial level of protection against HTLV-I was mediated by cellular immune responses [24]. A DNA vaccine containing the Tax gene was examined to determine if it may trigger specific CTL activity against Tax. This DNA vaccine was observed to trigger HTLV-1-specific cytotoxic T cells in lymphoma-afflicted rats. Furthermore, the DNA vaccine expressing the Tax gene demonstrated successful generation of anti-tumor immunity in these rats, indicating its potential to impede the growth of tumor cells. These findings, which highlight the need for safe and efficient vaccine design, significantly affected the prevention and management of ATL [25].

Additionally, a contrast was drawn between the use of a plasmid carrying DNA encoding the entire HTLV-1 envelope gene, controlled by the CMV promoter with (CMVenvLTR) or without (CMVenv) the tax/rex genes, and another plasmid harboring DNA encoding the complete HTLV-1 envelope gene, regulated by the human Desmin muscle-specific promoter (DesEnv). After introducing these vectors into mice, DesEnv prompted a more robust humoral response and demonstrated superior neutralization properties than CMV plasmids. Consequently, research indicates that selecting an appropriate DNA vector significantly influences the strength of immune responses [26].

Protein and peptide vaccines

Protein vaccines consist of isolated components from a virus that triggers the immune system. While these protein fragments are innocuous on their own, when administered as a vaccine, they are identified by the immune system. This recognition trains the immune system to identify the entire virus, protecting against infection by that virus. Protein-based vaccines are frequently employed in research on retrovirus vaccines. Notably, these vaccines played a pivotal role in the initial clinical trial for HIV, marking the first instance of testing an HIV vaccine on human subjects [27,28]. In investigations related to the development of an HTLV-1 vaccine, a research study involved extracting soluble HTLV-1 proteins from the MT2 cell line and vaccinated pig-tailed macaques (Macaca nemestrina) with these soluble HTLV-1 proteins. (Table 3). Then, these monkeys were challenged using a cell line producing simian T-cell lymphotropic virus type 1 (STLV-1). The results of laboratory investigations showed that a robust serological response was created, and the antibodies generated by control and vaccinated groups exhibited ADCC activity against HTLV-1 and STLV-1-infected target cells. Also, no reverse transcriptase activity was observed in vaccinated macaques compared to control macaques. Therefore, this vaccine protects against STLV-1 infection [29].

Peptide vaccines include synthetic peptides that are immunogenic and able to elicit the production of antibodies and CTL responses. Peptide vaccine candidates are combined with different adjuvants to increase immune responses. These vaccines have also demonstrated efficacy in trials for developing a vaccine against HTLV-1 [9,30]. In an initial investigation, a synthetic peptide originating from the external envelope region of HTLV-1 (specifically amino acids 242–257) was used. The vaccine was inoculated to rabbits and induced antibody responses against gp46. Nevertheless, these antibodies proved ineffective in preventing the cell fusion induced by HTLV-1 but could identify gp46 epitopes on the surface of infected cells. The vaccine also failed to induce proliferative T-cell lymphocyte responses in immunized rabbits and was not protected against reinfection with HTLV-1[31].

Subsequently, several Env peptides were examined as vaccine candidates in a rabbit model. Rabbits produced neutralizing antibody responses when exposed to a synthetic gp46 peptide encompassing amino acids 190 to 199 and 180 to 204. Antibodies capable of impeding the formation of syncytia and the transmission of HTLV-1 could identify these epitopes. When these vaccinated rabbits were re-infected with HTLV-1, no detectable provirus was observed in the PBMCs of immunized rabbits over the long term. These findings imply that immunizing animals with synthetic peptides might induce anti-gp46 neutralizing antibody responses, which may provide in vivo protection against HTLV-I infection. These findings imply that immunizing animals with synthetic peptides might induce anti-gp46 neutralizing antibody responses, which may provide in vivo protection against HTLV-1 infection [32]. Examining how N-linked glycosylation impacts the immunogenicity and structure of HTLV-1 peptides, a peptide was constructed using amino acids 233 to 253 of gp46. Specifically, N-acetyl glucosamine was introduced at residue Asn244 to investigate the role of N-linked glycosylation, a viral mechanism employed to diminish neutralizing antibody responses. This analysis studied peptides 233–253 and glycosylated peptides 233–253. Both peptides were chimeric with T cell epitope. After inoculation to rabbits, both chimeric peptides were immunogenic and induced antibodies that could be bound to gp46 and the whole virus within three weeks after vaccination. The blood serum from individuals

Table 3
HTLV-1 protein/peptide vaccines. This table presents data on HTLV-1 protein/peptide vaccines, focusing on essential attributes. Information includes details on the route of administration, the year, country, and author of the study, findings or results derived from the investigation, and the type of study conducted.

Target antigens	Route of administration	Year/country/ Author	Finding result	Type of study	References
soluble HTLV-1 proteins isolated from the MT2 cell line	–	1990/ Columbus/ Dezzutti, C.S	Inoculated to pig-tailed macaques. the immunized macaques re-infected with STLV-1 and was successful in protecting against STLV-1	in vivo	[29]
synthetic peptide derived from the HTLV-1 external envelope region (Env5, amino acids 242–257)	SC	1992/USA/ Lairmore, M.D	Inoculated into rabbits and induced antibody responses against gp46, however, these antibodies failed to inhibit HTLV-1-mediated cell fusion. The vaccine also failed to induce T cell responses	in vivo	[31]
Entire HTLV-1envelope genes express in baculovirus non-fusion vector system and	intraperitoneal	1993/USA/ Arp.J	BALB/c, C57BL/6, CFW/D mice were immunized with the envelope protein inclusion bodies in the presence or absence of an adjuvant. HTLV-I envelope neutralizing antibody induced in the presence of adjuvant. Also, combined immunization by rVV E1 and rVV E3 were done and neutralizing antibodies increased following priming by rVV E3 vaccine	in vivo	[15,46]
synthetic gp46 peptide containing amino acids 190 to 199 and 180 to 204	IM	1994/Japan/ Tanaka.Y	Inoculated to rabbit and induced antibodies that could inhibit syncytia and transmission of HTLV-1. no detectable provirus in immunized rabbits PBMCs	in vivo	[32]
amino acids 233 to 253 of gp46 was used and a peptide was engineered to contain N-acetyl glucosamine at residue Asn244 and were chimeric with T cell epitope	–	1995/ Columbus/ Conrad,S,F	Inoculate to rabbits, both glycosylated and non-glycosylated chimeric peptides were immunogenic and induced antibodies. hence, glycosylation of HTLV-1 gp46 does not affect its structure, stability and immunogenicity	in vivo	[33]
One peptide was related to amino acid 181–203 and the other was related to amino acid 181–210 of gp46, both of which were synthesized with a branched polylysine oligomer	IM/SC	1995/Japan/ Babe,E	Inoculated to New Zealand White rabbits and it was showed that synthetic peptide 181–210 elicited higher levels of neutralizing antibodies than the other peptide, which was due to the presence of the T-cell epitope at amino acids 194–210	in vivo	[34]
amino acid sequence of 175–218 of the gp46 peptide attached to the T-cell epitope of the measles virus fusion protein (MVF) (amino acids 288–302) by using a four-residue turn (GPSL)	IM	2000/ USA/ Frangione-Beebe, M	Inoculated to mice and rabbits and elicited high antibody titers which were able to inhibit HTLV-1 cell fusion. In addition, the chimeric peptide was encapsulated in poly(D,L-lactide-co-glycolide) microspheres. encapsulated peptide induced a humoral response similar to free peptide, but encapsulated peptide did not require adjuvants. But free peptide vaccine failed to induce cellular immune responses	in vivo	[35]
Tax-derived multivalent peptide consisted of three HLA-A(*)0201 restricted CTL epitopes attached to double arginine residues	SC	2003/USA/ Sundaram, R	Inoculated to HLA-A(*)0201 transgenic mice. induced cellular immune responses. Also, this multivalent peptide can also be used in immunotherapy.	in vivo	[37]
peptide derived from amino acid 347–374 of gp21 and T-cell epitope derived either from tetanus toxin (amino acids 947–967) or measles virus fusion protein (amino acids 288–302)	SC	2004/USA/ Sundaram, R	Inoculated to New Zealand white rabbits and mice. This vaccine induced antibodies. this anti-gp21 antibodies could disrupt cell–cell fusion	in vivo	[36,38]
three HLA-A-0201-restricted CTL epitopes derived from Tax protein (Tri-Tax) and B-cell env epitope (aa 175–218)	IM	2006/France/ kanzaji, M	Inoculated to male squirrel monkeys. Induced high titre of antibodies and IFN-gamma-producing cells. It was shown this vaccine could induce partial protection in infectious animals	In vivo	[47]
HLA-DR-restricted CD4 + T-cell epitopes of HTLV-1 Tax peptide (191–205, 305–319)	–	2006/Florida/ Kobayashi	Tax 191–205 was restricted by the HLA-DR1 and DR9 alleles, responses to Tax 305–3190 was restricted by either DR15 or DQ. Both epitopes can use for immunotherapy	In vitro	[48]
HTLV-1/hepatitis B virus core (HBc) chimeric particle incorporating the HLA-A-0201-restricted HTLV-1 Tax-epitope	intradermally	2009/ Japan/ Kozako, T	Inoculated to HLA-A*0201-transgenic mice. This vaccine induced HTLV-1-specific CTLs and interferon gamma responses. Also, exposure of mice DCs to this particle increased DCs co-stimulatory markers. It was showed that this chimeric particle induced cellular immunity responses and can use for immunotherapy	In vivo	[39]
oligomannose-coated liposomes (OMLs) encapsulating the HLA-A*0201-restricted HTLV-1 Tax-epitope (OML/Tax)	IM	2011/ Japan/ Kozako, T	Inoculated to HLA-A*0201-transgenic mice. OML/Tax induced HTLV-1-specific CTLs and interferon gamma responses. Also, exposure of mice DCs to OML/Tax increase DCs co-stimulatory markers. It was showed that OML/Tax induced specific cellular immunity responses	in vivo	[40]
HLA-DR-bound peptide from the IL-9 receptor alpha of HTLV-1-transformed T cells	–	2012/ Florida/ Kobayashi	specific CD4 helper T cells which were restricted by HLA-DR15 or HLA-DR53 molecules induced in vitro and could recognize and lyse HTLV-1+, IL-9Rα + T cell lymphoma cell. Therefore, this peptide can be	In vitro	[41]

(continued on next page)

Table 3 (*continued*)

Target antigens	Route of administration	Year/country/ Author	Finding result	Type of study	References
			used for immunotherapy against IL-9Rα positive ATLL		
twelve peptides of encompassing whole Tax protein (contain 40–42 amino acids)	SC	2015/Japan/ Fujisawa	Inoculated to hu-NOG mouse model. induced specific CTL responses and IL12 secretion, also suppress leukemia and after HTLV-1 infection the outgrowth of human lymphocytes was retarded	in vivo	[49]
recombinant proteins of gp46 (Env23 (162–209) and Env13 (125–209)) coating by chitosan (CHT) and trimethylchitosan (TMC) nanoparticles	nasal/SC	2016/Iran/ Amirnasr, M	Inoculated to BALB/c mice. Both nanoparticles had good adjuvant potential and higher IgG level induced compared to antigen solution. IgG2a levels and IgG2a/IgG1 ratio was higher in nasal administration compared to subcutaneous and Env23 antigen induced higher cellular immune responses compared to Env13. Hence, Env 23 is a better candidate for HTLV-1 vaccination	in vivo	[42]
chimeric peptide containing immunodominant epitopes of Tax, gp21, gp46, and Gag also was mixed with monophosphoryl lipid A (MPLA) or ISCOMATRIX (IMX) adjuvants	nasal/SC	2018/Iran/ Kabiri, M	Inoculated to BALB/c male mice. induced IgA, IgG1and IgG2a antibody titer and promoted cellular and mucosal responses	in vivo	[43]
six MHC-I restricted peptides were isolated from HTLV-1 infected cells	intradermal near the base of the tail and subcutaneous on the flank	2018/USA/ Mulherkar,R	Inoculated to HLA-A2 transgenic mice. Induced specific CTL for each of these peptides. Therefore, all these peptides can be used for therapeutic vaccine platforms	in vivo and in vitro	[44]
recombinant Fc-fusion protein which is containing DNA sequences of Tax 11–19 and gp46, gp21 epitopes fused to the mouse-Fcγ2a, or His-tag (Tax-Env: mFcγ2a and Tax-Env:His)	intraperitoneal	2022/Iran/ shafifar, M	Inoculated to BALB/c mice. both vaccines induced protection and reduced viral load, however Tax-Env: mFcγ2a vaccine induced more TH1 responses and Tax-Env:His shifted to more TH2 responses	in vivo	[45]

infected with HTLV-1 demonstrated the ability to identify glycosylated and non-glycosylated formations. These data show that glycosylation of HTLV-1 gp46 may not influence its structure, stability, and immunogenicity [33]. In separate research conducted in Japan, two peptide vaccines were investigated; one peptide was related to amino acid 181–203, and the other was related to amino acid 181–210 of gp46, and both of them were synthesized with a branched polylysine oligomer. New Zealand White rabbits were immunized, and it was shown that the synthetic peptide 181–210 elicited higher levels of neutralizing antibodies than the other peptide due to the presence of the T-cell epitope at amino acids 194–210. In addition, T cells of most patients with HTLV-1 infection increased when exposed to peptides containing amino acids 194–210. Therefore, peptides 181–210 might end up as one contender for a human HTLV-1 vaccine based on peptides [34].

Subsequently, a group of researchers attached the amino acid sequence of 175–218 of the gp46 peptide to the T-cell epitope of the measles virus fusion protein (MVF) (amino acids 288–302) by using a four-residue turn (GPSL) to increase the immunogenicity of the peptide vaccine [35]. It was shown that this chimeric peptide induced robust antibody responses in both mice and rabbits, effectively hindering the cell fusion of HTLV-1. Furthermore, this chimeric peptide was enclosed within microspheres made of poly (D, L-lactide-co-glycolide) to prevent the need for further booster immunization. The findings showed that introducing the encapsulated peptide generated a humoral response comparable to the free peptide, yet the encapsulated version achieved this without the need for adjuvants. However, antibody responses in both mice and rabbits prevent the production of syncytium. Still, rabbits were not protected against cell-mediated viral reinfection, indicating that the vaccine failed to induce the necessary cellular immune responses. To prevent cell-associated viral infection, it is notable that HTLV-1 vaccine development needs to include the capacity to stimulate cell-mediated immune responses. [35]. Another vaccine research used a Tax-derived multivalent peptide coupled with double arginine residues. These arginine residues serve as cleavage sites for proteasomes, facilitating the generation of MHC class I ligands. This multivalent peptide consisted of three HLA-A (*)0201 restricted CTL epitopes and immunization of HLA-A (*)0201 transgenic mice with this vaccine-induced cellular immune responses. These data also showed that this multivalent peptide can be used in immunotherapy approaches. According to findings, it was proved that using single CTL epitopes would not be as advantageous as activating multi-specific CTLs against one or more antigens. These peptides are promising candidates for creating vaccines using multivalent subunit peptides [36,37].

In a different investigation, scientists employed a peptide originating from amino acids 347–374 of gp21, along with a T-cell epitope sourced from either tetanus toxin (amino acids 947–967) or the fusion protein of the measles virus (amino acids 288–302). The immunogenicity of these peptides was assessed using either mice or rabbits. In immunized animals, antibody responses were induced, and the findings showed that neutralizing anti-gp21 antibodies could inhibit cell–cell fusion. It was highlighted that the gp21 protein can be a significant protein for creating vaccine candidates [36–38]. It was found that inoculation of HTLV-1/hepatitis B virus core (HBc) chimeric particle inserting the HLA-A-0201-restricted HTLV-1 Tax-epitope to HLA-A*0201-transgenic mice could induce HTLV-1-specific CTLs and IFN-γ responses [39]. Also, the exposure of mice DCs to this chimeric particle increased the co-stimulatory markers of DCs. It was shown that this chimeric particle induced cellular immunity responses without adjuvants and can be used for therapeutic vaccine platforms [39].

Additionally, the investigation involved the examination of OML/Tax, which represents oligo mannose-coated liposomes encapsulating the HLA-A-0201-restricted HTLV-1 Tax epitope. This vaccine was inoculated to HLA-A*0201-transgenic mice, and it was shown that OML/Tax could induce HTLV-1-specific CTLs, IFN-γ responses, and DC stimulation, similar to the previous study. OML/Tax may be used as a prophylactic vaccine [40]. A research investigation focused on extracting HLA-DR-bound peptides originating from the IL-9 receptor alpha found in T cells transformed by HTLV-1. Antigen-specific CD4 helper T cells were restricted by HLA-DR15 or HLA-DR53 molecules induced in vitro. It was demonstrated that T cells can identify and destroy T cell lymphoma cells that are positive for HTLV-1 and express IL-9Rα. This peptide holds promise for immunotherapy targeting ATLL with IL-9Rα positivity [41].

Another study developed Recombinant proteins of gp46 containing Env23 (162–209) and Env13 (125–209) and coating antigens with chitosan (CHT) and trimethyl chitosan (TMC) nanoparticles which function as an adjuvant. BALB/c mice were immunized with these antigens in nasal and subcutaneous administration [42]. It was shown that after

subcutaneous administration of nanoparticles and higher Env proteins, IgG1 and IgG total levels were induced compared to antigen solution. Furthermore, nasal administration for env23 resulted in elevated IgG2a levels and a higher IgG2a/IgG1 ratio than subcutaneous administration. Both nanoparticles demonstrated immune-adjuvant solid capabilities. Moreover, the Env23 antigen elicited more significant cellular immune responses than Env13. Therefore, Env23 is a more favorable candidate for HTLV-1 vaccination [42]. A chimeric peptide containing essential immunodominant segments derived from Tax, gp21, gp46, and Gag was utilized, combined with either monophosphoryl lipid A (MPLA) or ISCOMATRIX (IMX) adjuvants to boost the effectiveness of the vaccine. The outcomes exhibited that when the mixture of the chimeric peptide was administered intranasally, either with or without MPLA and IMX adjuvants, a strong Th1 response and mucosal response were produced. Whereas subcutaneous administration of this vaccine elicited cell-mediated responses, as seen by increased IgG2a and IFN-γ levels and decreased TGF-β1 levels. Hence, developing an efficient multi-epitope vaccine requires careful preparation, production, and inoculation [43]. Furthermore, six MHC-I-restricted peptides were isolated from HTLV-1-infected cells in another study. These peptides are derived from viral proteins, including Tax, Gag, and envelope glycoproteins. The inoculation of these peptides in HLA-A2 transgenic mice induced HTLV-1-specific CTL responses for each of these peptides in vivo and in vitro. Results showed that both in vivo and in vitro generated HTLV-1-specific CTLs had cytotoxic and immunogenic responses. Hence, the data indicated that therapeutic vaccine platforms against HTLV-1 can leverage all of these candidate peptides. [44]. Finally, a recent study used recombinant Fc-fusion protein, which contained DNA sequences of Tax 11–19 and gp46, gp21 epitopes fused to the mouse-Fcγ2a, or His-tag named Tax-Env: mFcγ2a and Tax-Env: His respectively. It was shown that both vaccines induced protection and reduced viral load; however, the Tax-Env: mFcγ2a vaccine induced TH1 responses with elevated IFN-γ and IL-12 production, which had a negative relationship with proviral load, whereas Tax-Env: His vaccine shifted T cell responses to TH2 responses with increasing of IL-4. Consequently, it may be essential to induce both T helper responses, particularly Th1, to provide a suitable response against HTLV-1. Hence, Tax-Env: mFcγ2a may be more effective [45].

Dendritic cell-based vaccines

The majority of discussed HTLV-1 vaccines have primarily focused on preventive measures. Nevertheless, therapeutic applications of vaccines can be explored, mainly through dendritic cell-based vaccines. Only one dendritic cell (DC) vaccine has received FDA approval, primarily for treating prostate cancer. Dendritic cells are crucial as antigen-presenting cells, present antigens to T lymphocytes, and induce humoral and cellular responses. Different types of DCs, such as conventional DCs, plasmacytoid DCs, and monocyte-derived DCs, have been identified. Various approaches to DC-based vaccine development include in-vitro generation of DCs by culturing patient-derived peripheral blood mononuclear cells (PBMC), loading targeted antigens onto them, and creating engineered antigen-loaded DCs [50–52].

Epitope vaccine based on DCs. In 2014, the Tax 11-19 epitope was utilized under various conditions, with or without adjuvants and/or dendritic cells (DCs). This examination was undertaken to assess the immune responses of $CD8^+$ T cells. In this study, a hybrid mouse strain (HLA-A2/DTR) carrying HLA-A2.1 and CD11c-DTR genes was used, and the results showed that the Tax epitope could naturally induce a $CD8^+$ T cell response, but after DC depletion, this was unsuccessful [53]. A determination was made on the impact of DC depletion on the serum cytokines, and it showed that IL-6, the Th17 cytokine, IL-12, and the Th1 cytokine were increased. It confirmed that DC presence is crucial for preserving tolerance while T-cell priming occurs. It was also observed that using adjuvant (Freund's adjuvant) promoted Tax 11-19 epitope-specific response. Following adjuvant administration, whether DCs are present or not, the TGF-β level decreased. Subsequently, the Tax-specific CD8 T cell response was enhanced. In addition, IL-17A cytokine was elicited following the administration of an adjuvant in the presence of DCs. Therefore, the Tax 11-19 epitope might be a potential candidate for an HTLV-1 vaccine based on dendritic cells [53].

In 2015, an investigation was conducted to observe the efficacy of a vaccine centered around dendritic cells. Autologous dendritic cells and the Tax peptide associated with CTL epitope were used. In some individuals infected with HTLV-1 and most ATLL (Adult T-cell Leukemia/ Lymphoma) patients, CTL responses are often compromised, which leads to increased viral load. The study showed that Tax-specific CTL responses peaked 16 to 20 weeks after vaccination in ATLL patients [54]. Three ATLL patients were treated with this vaccine, resulting in relative improvement in two patients within the first eight weeks, with one eventually achieving complete recovery and not requiring any more chemotherapy. The third patient, whose tumor cells did not show Tax expression, remained stable for the first eight weeks. The disease progressed gradually, and additional therapy was not required for 14 months. In addition, in the PBMC samples taken from these three patients, Proliferative responses of Tax-specific CTLs and a producing response of CTL were seen, and the proviral load in the peripheral blood in all three patients stayed primarily below 100 copies per 1000 PBMCs for at least a year following immunization. These results confirm the safety and effectiveness of the tax peptide DC vaccine for immunotherapy, even though more clinical trials involving a larger patient population are required to validate this vaccination therapy's anti-tumor efficacy [54].

Peptide-Pulsed DCs for virus reduction. In 2017, a Tax-specific CTL epitope (180–188) was employed in conjunction with bone marrow–derived dendritic cells (BMDCs) of orally HTLV-1-infected and BMDCs of uninfected rats. This vaccine was inoculated to rats orally infected four weeks prior with or without HTLV-1 [55]. Orally, HTLV-1-infected rats had a defective Tax-specific response and a high proviral load. It was shown that peptide-pulsed BMDC vaccination induced Tax-specific $CD8^+$ T cells and reduced proviral load because of Tax-specific CTL responses in Orally HTLV-1-infected rats. Furthermore, the findings demonstrated that the ability of BMDCs generated from infected and uninfected rats to stimulate Tax-specific $CD8^+$ T cells is similar. Considering that half of the vaccinated rats showed robust proliferation and IFN-γ production of Tax-specific CTLs, it suggests that to maximize Tax-specific $CD8^+$ T cell responses, the BMDC vaccination method needs to be improved. Results suggest that therapy with peptide-pulsed DC contributes to inducing specific HTLV-1 CTLs. Also, this vaccine can have prophylactic effects in limiting the development of ATLL (Table 4**)** [55].

mRNA vaccines

Developing mRNA vaccines against viral infections has become a promising preventive strategy. The remarkable success of mRNA vaccines, exemplified by their effectiveness in countering COVID-19, has sparked renewed interest and accelerated research in this innovative field [65]. mRNA vaccines introduce a piece of mRNA related to a viral protein to target cells. Cells that express this viral protein are targeted, prompting recognition by the immune system. This recognition, in turn, leads to immune responses, with a particular emphasis on generating antibody responses. Immunization with mRNA vaccines has advantages over traditional vaccines, including non-integration of mRNA into the genome and cell-free production, allowing for rapid, scalable, and cost-effective production. In 2021, An epitope platform with 15 epitopes and 104 residues that could be extended to 400 amino acids by spacers was proposed **(**Table 4**)**. This epitope can be appropriate for mRNA and nanoparticle vaccine platforms [56,66,67]. A new study in 2024 developed a codon HTLV-1 envelope (Env) mRNA that was delivered in a lipid nanoparticle (LNP). This vaccine was inoculated in New Zealand

Table 4
Other vaccine studies. This table delineates information on Dendritic cell-based vaccines and mRNA vaccines targeting HTLV-1. It includes data on the route of administration, the year, country, and authorship of the study, key findings or results, and the type of study conducted.

Target antigens	Route of administration	Year/country/ Author	Finding result	Type of study	Reference s
Dendritic cell-based vaccines					
The Tax (11–19) epitope was used in the absence or presence of adjuvants and/or dendritic cells (DCs)	ID/SC	2014/ USA/ Sagar, D	a hybrid mouse strain (HLA-A2/DTR) carrying HLA-A2.1 and CD11c-DTR genes used and the CD8 T cell immune responses were assessed. Tax epitope induced a specific-CTL response, but after DC depletion, this was unsuccessful	in vivo	[53]
Autologous dendritic cells, along with the Tax peptide associated with CTL epitope	SC	2015/Japan/ Suehiro, Y	Induced Tax-specific CTL responses in ATL patients. relative improvement in two patients with one eventually achieving complete recovery. the third patient remained stable and disease progressed slowly	Human	[54]
HTLV-1 Tax-specific CTL epitope-pulsed dendritic cell	SC	2017/Japan/ Ando, S	reduced viral load and induced Tax-specific CTLs	in vivo	[55]
mRNA vaccine					
15 epitopes with 104 residues that could be extended by spacers up to 400 amino acids	–	2021/Germany/ Lucchese	This platform can reduce some disadvantages of conventional vaccines	in vitro	[56]
a codon optimized HTLV-1 Env mRNA delivered in a lipid nanoparticle (LNP)	IV	2024/USA/ Joshua J Tu	Inoculated New Zealand rabbits. After challenging vaccinated rabbits with HTLV-1, proviral load decreased and CD4+/IFN-γ + and CD8+/IFN-γ + T-cells increased. Also, neutralizing anti-Env elicited	in vivo	[57]
Other vaccines					
recombinant soluble gp46 fused with the human IgG Fc region (sRgp46-Fc)	–	2011/Scotland/ Kuo, C. W	Immunized mice using this vaccine. The recombinant gp46 glycoprotein showed high immunogenicity and induced high-titer antibody responses. These antibodies could recognize HTLV-1 infected cells and inhibit HTLV-1 fusion to host cells	–	[58]
Mitomycin C-treated HLA-A2-negative HTLV-1-infected T-cell lines or cultured PBMC	–	2021/Japan/ Ishizawa, M	cultured autologous PBMC from ATL patients could induce Tax- specific CTL responses	in vitro	[59]
In silico study					
prediction of 14 epitopes of envelope gp62(outer membrane protein of HTLV-1)	–	2020/ Bangladesh/Alam	HLA-epitope binding prediction, and B-cell epitope prediction were done and it has showed that ALQTGITLV and VPSSSTPL epitopes interact with three MHC alleles and had nearly 70 % Protection	in silico	[60]
cytotoxic T lymphocytes and helper T lymphocyte epitopes of HTLV-1 TAX, HBZ, gp62 proteins, and NY-ESO-1 protein	–	2020/Iran/ Farahi, E	excellent structure and being both antigenic and allergy-free. This vaccine candidate might effectively improve cellular and humoral immunity	in silico	[61]
eight-epitopes including B and T cells epitopes constructed of Gag, Env, Pol, Hbz, and Tax proteins	–	2021/Iran/ Jahantigh, HR	It has showed that humoral and cellular immune responses elicited and predicted epitopes interacted strongly to immune receptors	in silico	[62]
Predicted HTLV-1 Tax protein consist of CTL and B cell epitopes and contains 109 amino acids	–	2021/ Bangladesh/ Thosif Raza, M. T	It has showed highly antigenic and immunogenic properties	in silico	[63]
Predicted vaccine containing 382 amino acids from p12I, gp62 and TAX-1 protein by selecting cytotoxic T lymphocytes, helper T lymphocytes and B cell epitopes	–	2021/Pakistan /Tariq, M. H	It has showed higher levels of cell-mediated immunity and highly antigenic properties	in silico	[64]

rabbits and after vaccination, rabbits were challenged by injecting irradiated HTLV-1-producing cells [57]. In response to the HTLV-1 challenge, half of the rabbits had moderate protection, and the other half had total protection. Fifteen weeks later, these rabbits were rechallenged. It was shown that proviral load was decreased in vaccinated rabbits, and following the second challenge, CD4+/IFN-γ+ and $CD8^{+}$/IFN-γ^{+} T-cells were increased. Env mRNA-LNP vaccine stimulated neutralizing anti-Env antibody, associated with reducing the proviral load. Hence, in preclinical research, the mRNA-LNP vaccine elicited protective immune responses against HTLV-1. Encapsulated mRNA vaccination has several advantages over traditional vaccinations, such as increased efficacy and safety due to introducing a non-infectious agent and stability and translation regulation. Since this mRNA-LNP vaccine is effective and has few significant side effects, mRNA vaccines are now the standard platform for developing new vaccines [57].

Other vaccines

Some studies on HTLV-1 vaccines are not categorized within the described specified platforms. In a particular investigation to assess the immunological properties of envelope-based vaccine candidates, a recombinant soluble surface glycoprotein (gp46, SU) was fused with the human IgG Fc region (sRgp46-Fc) [58]. This fusion vaccine was utilized as an immunogen to vaccinate mice. The recombinant gp46 glycoprotein showed high immunogenicity and induced high titer of antibodies. These antibodies could recognize HTLV-1-infected cells and inhibit HTLV-1 fusion to host cells. Also, several of these antibodies had neutralizing activity, enhanced the cytotoxic responses of neutrophils against HTLV-1-infected cells, and will probably going to be necessary in limiting the spread of HTLV-1. Thus, the recombinant form of gp46 could be a candidate for vaccine development [58].

In 2021, another investigation was employed to develop Tax-specific cytotoxic T lymphocytes without HLA restriction. This approach involved using HTLV-1-infected cells from patients as a personalized vaccine [59]. A co-culture system was utilized to evaluate the ability of HTLV-1-infected T-cells to stimulate specific CTL through antigen-presenting cells. The findings revealed that mitomycin C-treated HLA-A2 T-cell lines infected with HTLV-1, or cultured peripheral blood mononuclear cells (PBMC) from ATL patients, were able to induce Tax antigen cross-presentation when co-cultured with HLA-A2-positive antigen-presenting cells. This led to the activation of Tax-specific HLA-A2-restricted CTLs. Antigen-presenting cells co-cultured with HTLV-1-infected cells also promoted IL-12 generation and CD86 expression. In addition, after co-culture with autologous lymphocytes derived from the PBMC of a chronic ATL patient, dendritic cells derived from the PBMC of

the same patient exhibited elevated levels of CD86 and IL-12 (Table 4). results suggested that cultured PBMCs from ATL patients can be used in vaccine production to induce Tax-specific CTL responses [59].

In silico vaccine study

The advanced use of bioinformatics in immunology, through the examination of HTLV-1 immunogenic regions, has paved the way for the development of new vaccination approaches. One research approach targeted the GP62 envelope glycoprotein, which has several epitopes. Analyses of GP62 binding to MHC class I and MHC class II demonstrated 14 epitopes with good HLA binding capacity. Out of all the anticipated peptides, the ALQTGITLV and VPSSSTPL epitopes interact with three MHC alleles and provide 70 % protection. Also, B cell epitope prediction showed that 19 epitopes had antigenic potential, which makes them viable contenders to design an epitope-based HTLV-1 vaccine [60]. Sequences of HTLV-1 TAX, HBZ, gp62 proteins, and New York esophageal squamous cell carcinoma 1 (NY-ESO-1) protein, as immune response inducer, were analyzed to determine the cytotoxic T lymphocytes and helper T lymphocyte epitopes [61].

Additionally, RS09 adjuvant, as a TLR4 agonist, was employed to ensure the stimulation of an immunological response. Subsequently, a three-dimensional model of the protein vaccine was created, demonstrating excellent structure and being both antigenic and allergy-free. This vaccine candidate appears to enhance humoral and cellular immunity efficiently; nevertheless, in vitro and in vivo immunological tests should be used to confirm the vaccination's potency [61]. Amino acid sequences of structural and regulatory proteins of HTLV-1, including Gag, Env, Pol, HBZ, and Tax, were evaluated for predicting B cell, CTL, and helper T lymphocyte epitopes. Also, a protein vaccine candidate was developed with eight epitopes, including epitopes found on both T and B cells. Then, the interaction between the epitope and immune receptors was validated in in-silico research. Findings showed that both intended peptide and protein vaccines may trigger humoral and cellular immunity [62]. In one study, the B-cell and T-cell epitopes of HTLV-1 TAX have been predicted for potential use as vaccine candidates. It was predicted that the most antigenic and immunogenic epitopes were determined to be two B cell epitopes, which ranged from amino acids 324–349 and 252–268, and T cell epitopes, which ranged from amino acids 11–19, 163–171, and 233–241. According to this study, a multi-epitope vaccination may boost the immune response against HTLV-1 and enable the creation of vaccines against HTLV-1[63]. Also, a vaccine comprising 382 amino acids from p12I, gp62, and TAX-1 proteins was designed (Table 4). This was achieved by choosing cytotoxic T lymphocytes, helper T lymphocytes, and B cell epitopes. Predicted epitopes and adjuvants might be immunogenic against HTLV-1 and can be utilized to design epitope-based vaccines [64].

Challenges in HTLV-1 vaccine development

Despite extensive research, there is no HTLV-1 candidate vaccine in experimental trials, and challenges remain in HTLV-1 vaccine advancement. The complex life cycle of HTLV-1 poses difficulties due to the virus's ability to infect and persist in $CD4^+$ T cells. The cell-to-cell transmission of HTLV-1 complicates vaccine development, as it facilitates immune evasion. Adequate protection may require the induction of both neutralizing antibody and cellular responses. Another challenge is the need for more structural research tools, particularly in understanding the HTLV-1 Env structure, especially the gp46 subunit compared to gp21. Understanding the configuration of the HTLV-1 gp46 subunit can contribute significantly to creating a successful HTLV-1 vaccine [68–70].

While various vaccine approaches against HTLV-1 have revealed hopeful responses in preclinical experiments, the limited number of human clinical trials hinders a comprehensive understanding of their safety and efficacy. Further clinical trials are necessary to assess the viability of these approaches in humans [71].

Conclusion

In conclusion, the quest for effective HTLV-1 vaccines is a critical imperative in public health. Challenges persist while substantial progress has been made in exploring various vaccine platforms, including viral vectors and protein-based vaccines. Notably, the need for robust and sustained immune responses underscores the importance of continuous research and innovation in vaccine design. The limitations, such as weak immune responses, call for a concerted effort to explore novel strategies. Incorporating adjuvants and administering booster doses are potential solutions to bolster vaccine efficacy. However, the complexity of HTLV-1 demands a comprehensive and multidisciplinary approach to ensure successful vaccine development. The urgency of this research is underscored by the significant health implications of HTLV-1, impacting millions worldwide. As we navigate the evolving landscape of vaccine development, collaboration across scientific, medical, and public health domains becomes paramount. The global experience with vaccine research, exemplified by recent successes, highlights the potential for collective efforts to address neglected viruses like HTLV-1. The need for numerous research endeavors in HTLV-1 vaccine design is a scientific necessity and a moral imperative for global health. It is a call to action for sustained dedication, innovation, and international collaboration to develop effective vaccines that can mitigate the impact of HTLV-1 and contribute to the overall improvement of public health worldwide.

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