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Development of replication-competent viral vectors for HIV vaccine delivery

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Abstract

Purpose of review—Briefly describe some of the replication-competent (RC) vectors being investigated for development of candidate HIV vaccines focusing primarily on technologies that have advanced to testing in macaques or have entered clinical trials.

Recent findings—RC viral vectors have advanced to the stage where decisions can be made regarding future development of HIV vaccines. The viruses being used as RC vector platforms vary considerably, and their unique attributes make it possible to test multiple vaccine design concepts and also mimic various aspects of an HIV infection. RC viral vectors encoding SIV or HIV proteins can be used to safely immunize macaques, and in some cases, there is evidence of significant vaccine efficacy in challenge protection studies. Several live HIV vaccine vectors are in clinical trials to evaluate immunogenicity, safety, the effect of mucosal delivery, and potential effects of pre-existing immunity.

Summary—A variety of DNA and RNA viruses are being used to develop RC viral vectors for HIV vaccine delivery. Multiple viral vector platforms have proven to be safe and immunogenic with evidence of efficacy in macaques. Some of the more advanced HIV vaccine prototypes based on vesicular stomatitis virus, vaccinia virus, measles virus, and Sendai virus are in clinical trials.

Keywords

Replication-competent viral vectors; HIV vaccine; SIV challenge model

INTRODUCTION

Although HIV was linked to AIDS more than 25 years ago [1, 2], development of an effective vaccine remains a major challenge [3]. Importantly, findings from the RV144 clinical trial showed that the incidence of HIV transmission could be reduced with an HIV

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Conflicts of interest CLP and CRK are named as inventors on patent applications submitted by the International AIDS Vaccine Initiative related to canine distemper virus and vesicular stomatitis virus vector technology. LJP and Oregon Health and Science University (OHSU) have a significant financial interest in TomegaVax, Inc., a company with a commercial interest in CMV vector technology. The potential individual and institutional conflicts of interest have been reviewed and managed by OHSU.

vaccine regimen based on a nonreplicating canarypox vector encoding Gag, Pro, and Env immunogens, plus an Envelope subunit protein [4], but the results also pointed to the need to increase the frequency of vaccine-induced immunity and durability of immune protection [5].

The fact that live-attenuated viral vaccines (LAVVs) have been remarkably effective in both human and animal healthcare [6, 7] suggests that delivery of an HIV vaccine with a live vector might be one approach to improving efficacy. Licensed LAVVs induce durable, multi-component immunity that prevents illness and controls the spread of highly infectious pathogens [8], making a compelling case for investigating some form of live HIV vaccine. Furthermore, the success of licensed LAVVs are mirrored by results in the rhesus macaque model where live-attenuated viruses like SIVmac239 *nef* are the most effective experimental vaccine for preventing AIDS [9]. Unfortunately, applying the LAVV strategy to HIV is impractical at this time, because there are safety risks associated with lentivirus genome recombination, genetic reversion to a more virulent phenotype, and host chromosome modification caused by provirus integration [10-14]. Thus, RC viral vectors presently are a more practical alternative for delivering HIV immunogens in the context of a viral infection.

To elicit protective immunity, RC vectors probably will need to incorporate features of LAVVs as well as live attenuated SIVmac239. Perhaps the most important feature will be sufficient replicative capacity to produce a mild infection, which will stimulate pathogen recognition and cell death pathways, provide prolonged antigen exposure, and engage the adaptive arm of the immune system [15-17]. A vaccine vector also may need to induce potent immunity that strengthens defenses at the mucosal barrier and in submucosal tissues, which are at the front lines of HIV transmission by sexual contact [18]. Some RC viral vectors are well suited to achieve this since they naturally infect mucosal surfaces and initiate replication in submucosal tissues. Viral vectors that preferentially replicate in lymphoid tissues have similar potential advantages [19].

Although there are many probable benefits to developing HIV vaccines based on replicating viruses, advancing RC vectors to clinical trial is challenging and dependent on strategic selection of a virus genetic background, ability to readily engineer stable recombinant viruses, and availability of relevant animal models. Common hurdles include attaining adequate immunogen expression, engineering genetically stable vectors, reaching reasonable yields of vaccine from qualified cell substrates, development of downstream processes needed to make a vaccine with acceptable purity, stability, and potency, and perhaps most challenging, achieving the correct balance of replicative capacity and attenuation that ensures both immunogenicity and safety [20, 21]. *In vivo* models also are vital to demonstrate vaccine immunogenicity and to assess safety risks [21], and importantly, they must be tractable to allow iterative study while developing and improving the vaccine concept. Taken together, it is clear that sustained commitment will be necessary to fully test and advance RC vectors for use as HIV vaccines.

Below we provide a relatively brief description of RC vectors in development focusing primarily on those being tested in macaques or in clinical trials, and we refer readers to other

informative reviews [21-30] on the topic. The Table also includes references to some additional vector technologies not described in the text.

DNA VIRUS VECTORS

Adenovirus, vaccinia virus, and herpes viruses including cytomegalovirus each have distinct advantages for the construction of a HIV vaccine.

Adenovirus (Ad)

RC Ad technology has both advantages and disadvantages when compared to the widely used nonreplicating vectors [74, 75]. Foreign insert capacity in the RC vector is more limited because essential genes in the E1 region must be retained. Deletion in the E3 region generates capacity for inserts, and also attenuates replication *in vivo*. An important advantage of RC Ad vectors is their natural ability to infect mucosal surfaces and subsequently replicate [25]. Moreover, there is clinical experience with LAVVs based on the adenovirus type 4 (Ad4) and Ad7, which are delivered orally to immunize U.S. Military personnel for prevention of respiratory and enteric illness [76].

Several different replicating Ad technologies are emerging. Recent clinical experience with an Ad4 vector encoding influenza virus polypeptides [31] should facilitate advancement of a mucosally delivered HIV vaccine candidate. Moreover, an Ad4-HIV Env vaccine was shown to be immunogenic in rabbits [77], and it is anticipated that a vaccine composed of Ad4-Gag and Ad4-Env will enter a phase 1 clinical trial in 2013 (M. Gurwith, personal communication). Replicating Ad5 [32, 33] and Ad26 [34] also are being advanced as mucosal delivery vectors. RC Ad5-SIV vectors expressing Gag, Env, and Rev were immunogenic in macaques after administration by several different mucosal routes [33], and when used in combination with an SIV Env gp120 boost, some control over SIVmac251 infection was observed. For Ad26, clinical development will be necessary to further evaluate immunogenicity since replication of this Ad serotype is restricted in simian cells. Finally, because nonreplicating chimp Ads have shown promise in human trials [78, 79], new simian viruses are being identified [35] and developed as RC vectors (D. Barouch, personal communication).

Cytomegalovirus (CMV)

Cytomegaloviruses are members of the herpesvirus family, and as such persist indefinitely in their host following primary infection [80]. CMV persistence and resulting continuous, low-level immune stimulation maintains an expanded pool of effector-differentiated T cells, which control infection and prevents CMV disease [81]. Thus, vectors based on rhesus CMV (RhCMV) were ideally suited to test the hypothesis that persistent antigen exposure could confer immune control over SIV infection.

A multivalent RhCMV-SIV vaccine covering nearly the complete SIVmac239 proteome was studied extensively in the SIVmac239 challenge-protection model [36, 37]. As designed, the RhCMV-SIV vectors established persistent infections and maintained expanded pools of T cells responsive to a sizable breadth of SIV epitopes. Additionally, it should be emphasized that preexisting CMV infection and immunity did not compromise

vector immunogenicity as all animals were RhCMV-seropositive before vaccination. The SIV-specific immunity induced in two independent studies protected 50% of the macaques from progressive SIVmac239 infection. Protected animals were infected, but viral control was early, stringent and durable with SIVmac239 genome copies in the blood reduced to undetectable levels, regardless of whether challenge was conducted rectally [36] or vaginally (LJP, in preparation).

The notable efficacy of RhCMV-SIV vector warrants clinical development of a prototype CMV-based HIV vaccine. This will be challenging, as a new vector based on human CMV (HCMV) must be developed due to tight host-restriction. Although HCMV and RhCMV are biologically highly homologous and the majority of viral proteins are related, their very large complex genomes express unique polypeptides and microRNAs [82-84], and thus developing an exact HCMV analog of the RhCMV vector is not straightforward. Furthermore, HCMV infection during pregnancy is linked to birth defects [85], and the virus also causes serious complications in some immunosuppressed patients undergoing organ transplants [81]; thus, use of an attenuated HCMV strain for clinical development is essential to minimize risk. Using RhCMV as a model, and focusing on genes that are conserved between HCMV and the rhesus virus, gene knockouts have been identified that highly attenuate RhCMV replication *in vivo* but still allow the virus to establish a persistent infection with full immunogenicity (LJP, unpublished).

In considering clinical development, it also is important to note that HCMV infection is relatively widespread by an early age [81]. As mentioned above, studies with RhCMV indicate that superinfection is possible thus pre-existing immunity will not be a significant hurdle for use of an hCMV-HIV vaccine.

Rhadinovirus

Rhesus rhadinovirus (RRV), another member of the herpes virus family, also has been used to develop a vector that can establish a persistent infection. Like CMV, RRV encoding SIV immunogens could infect sero-positive animals. Notably, in vaccinated macaques, peak and chronic virus loads were reduced more than 10-fold following a stringent intravenous SIVmac239 challenge [39].

Poxviruses

Poxviruses that abortively infect human cells have been studied extensively as vaccine vectors particularly host-restricted strains of vaccinia virus (MVA and NYVAC) and avipoxviruses (fowlpox and canarypox) [86]. Interest remains high in development of the nonreplicating vectors because they can be used safely in humans, are immunogenic, and notably, a canarypox vector was used in the RV-144 clinical trial [4].

The RC poxvirus vector in the most advanced clinical trials is based on the Tiantan vaccinia virus (TV) strain, which is derived from the smallpox vaccine once used in China [87]. In a Phase 1 study, the TV-HIV vaccine delivered by scarification caused skin reactions typical of smallpox vaccination and induced HIV-specific T cell responses in vaccinia virus-naïve study participants [28, 41]. TV-HIV is presently advancing to a Phase II study (National

Center for AIDS/STD Control and Prevention, China CDC; ClinicalTrials.gov NCT01705223) where it will be used as a boost for a DNA prime administered by electroporation. Notably, significant protection from mucosal SIVmac239 challenge was observed recently in Chinese rhesus macaques vaccinated with a regimen including TV-SIV prime administered mucosally and intramuscular Ad5-SIV boost [88].

Additional TV vectors also are being investigated [44], which have alterations in virus-encoded immune modulatory functions.

New RC vaccinia virus vectors have been generated by systematically adding genes back to the host-restricted NYVAC strain [89] restoring varying degrees of replicative capacity in human cells [42, 43]. RC NYVAC-KC vectors have been tested safely in macaques and were found to be more potent inducers of cellular and humoral immunity when compared to vectors based on nonreplicating NYVAC (G. Pantaleo, personal communication); consequently, a NYVAC-KC vector is being considered for advancement to a Phase I trial.

RNA VIRUS VECTORS

RNA viruses are attractive vector platforms as a number of LAVVs are already used to vaccinate people and animals. Recent progress has made developing RNA virus vectors for mucosal delivery, targeting vaccine delivery to specific tissues, and producing virus particles that incorporate Envelope.

Negative-strand RNA viruses

Technology needed to engineer vectors from this class of viruses emerged more slowly than for most others because naked genomic RNA cannot initiate an infectious cycle following transfection [90, 91]. Development of a virus rescue system made it possible to investigate multiple different negative-strand viruses as HIV vaccine vectors.

Vesicular stomatitis virus (VSV)—VSV was one of the earliest RNA viruses investigated as a live HIV vaccine vector [30]. Administration by several different routes, including intranasal, was safe and the resulting immunity controlled SHIV 89.6P infection following challenge [61]. In this study, it was notable that 2nd and 3rd vaccine administrations were performed with vectors in which the VSV glycoprotein (G) was exchanged for G of a different serotype to minimize effects of anti-vector immunity [60, 61].

Following the positive preclinical results, Profectus Biosciences, Inc. and the NIAID developed a modified highly attenuated prototype VSV-HIVgag vaccine [62, 63]. Recent Phase I trial results indicated that the vector induced T cells specific for Gag after intramuscular injection without causing serious adverse reactions [92]. In a follow up study (clinicaltrials.gov NCT01578889), the VSV-HIVgag vector will be used as a boost following DNA prime administered by electroporation. An expanded repertoire of HIV genes is being considered for use in the next generation of vaccines and a candidate expressing the env gene from the clade C transmitted/founder strain 1086.C [93] has completed manufacture (John Eldridge, personal communication).

Evidence of efficacy has been observed in multiple macaque studies conducted with other VSV-based SIV and HIV vaccines [71, 94-97]. Adverse reactions have not been reported even though these vectors were not engineered specifically to attenuate replication as was done for the vaccine tested in humans. Findings from these studies also showed that RC VSV-based vaccines are potent additions to heterologous prime-boost regimens and that they are immunogenic when administered mucosally.

VSV also is used to develop chimeric vaccines in which VSV G is replaced by a functional heterologous cell surface receptor binding glycoprotein such as Env [65]. Promising results have been produced during preclinical evaluation of chimeric vaccines for Ebola virus and Marburg [98, 99], and chimeric VSV vectors [64] with SIV or HIV Env functioning as the attachment protein are being tested in macaques currently (CLP and CRK). These chimeras are of particular interest since their design imparts multiple features similar to an infectious HIV particle: CD4/co-receptor dependent infection; expression of functional trimeric Env; and, incorporation of Env spikes into progeny VSV particles. The ability to incorporate functional Env into the vector particles makes this a potentially important immunogen display technology, and we are actively studying the characteristics of the incorporated Envelope trimer in our laboratory (CLP and CRK).

Rabies virus (RV)—Live vectors based on RV [56, 57], a rhabdovirus related to VSV, have been developed using a G serotype exchange strategy similar to those described above [60, 61]. In macaques, vaccination with RV vectors evoked T and B cell responses [56, 57] and reduced SIVmac251 viremia [56] or provided protection from acute illness caused by SHIV89.6 [57].

Sendai virus (SeV)—RC SeV vectors are being developed to determine if intranasal vaccination enhances mucosal immunity as this virus naturally infects the respiratory tract of rodents [100]. Encouragingly, priming macaques with DNA-SIV followed by an intranasal SeV-SIV vector boost resulted in strong suppression of SIVmac239 replication following IV challenge [58, 59].

A clinical trial has commenced with a prototype SeV-HIVgag vector (International AIDS Vaccine Initiative and DNAVEC, Japan; [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01705990) Identifier: NCT01705990). The trial is designed to evaluate immunogenicity following intranasal vaccination, assess SeV and Ad35 in a heterologous prime-boost regimen, and monitor the potential effects of pre-existing cross-reacting human parainfluenza virus type 1 antibodies [101]. Interestingly, preclinical studies indicate that the intranasal vaccination route may reduce the negative effects of pre-existing cross-reactive immunity on SeV vector administration [102].

Measles virus (MeV) and canine distemper virus (CDV)—MeV and CDV are related morbilliviruses, which are controlled by wide spread use of LAVVs. They are important vaccine platforms because they are naturally lymphotropic [103, 104] making them applicable to producing vectors that target lymphoid tissues mimicking a prominent feature of attenuated SIVmac239 [19]. It also is worth noting that cells infected with morbilliviruses may persist for some time following cessation of symptoms [105], which may help to evoke lasting immune responses.

When administered parentally like the live measles-mumps-rubella vaccine, MeV-HIV vectors are immunogenic in macaques, and as expected, cause no serious adverse reactions [49, 50]. These favorable results spurred advancement of MeV-HIV vaccine vector candidates into a Phase 1 clinical trial, which has been concluded (Institut Pasteur, [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01320176) NCT01320176).

Pre-existing immunity generated by widespread measles vaccination is a perceived limitation to use of MeV vectors. The modest serum antibody titers induced by measles vaccination are significantly lower than produced following a natural infection [106, 107] nevertheless they may reduce the potency of a MeV vector. Strategies to minimize potential effects of pre-existing antibodies might include vaccine administration mucosally [102, 108, 109], using higher doses, or introducing vector modifications such as replacing MeV glycoproteins with those from CDV [110] or a more distantly related virus [111] such as HIV [51].

CDV also is being developed as a vector to take advantage of morbillivirus lymphoid tissue targeting while lessening potential effects of pre-existing anti-MeV antibodies [47]. CDV neutralizing antibodies are reported to be quite low in humans [110], and a serum survey is in progress to analyze this further (CLP and CRK). In considering a potential path to clinical development for a CDV vector, it is relevant to note that no human diseases are associated with CDV infection [112] and attenuated canine vaccines can be used as the genetic background for vector development. Testing of a CDV-SIV vaccine developed from a veterinary vaccine is underway in macaques, and preliminary results indicate that intranasal vaccination caused no observable adverse reactions and immune responses were induced against SIV Gag and Env (CLP and CRK).

Positive-strand RNA viruses

Poliovirus was one of the earliest positive-strand RNA viruses to be investigated as an autonomously replicating HIV vaccine vector [38, 68]. Limited insert capacity and genetic stability associated with this class of viral vectors has focused most vaccine development effort on single-cycle replicons [26, 113]. Some recent progress made developing novel replicating vectors is provided below.

Yellow Fever (YF) virus—Live attenuated YF virus strain 17D (YF 17D) has been widely used to control disease in endemic areas [114], thus it is an attractive background for RC vector development. Chimeric YF virus vectors in which the natural attachment proteins are replaced with those from Dengue virus, West Nile virus, or Japanese encephalitis virus [21] are immunogenic and in some cases approved for use [115, 116].

Introducing foreign glycoprotein genes into YF virus chimeras has been very successful because these proteins are essential for vector replication. It has been much more challenging to find a way to introduce and maintain a foreign coding sequence for which there is no selective advantage. Recently, progress has been made stabilizing foreign sequence inserts encoding SIV immunogens, and the resulting YFV-SIV vectors have been tested in macaques [72, 73]. The results show that these YFV-SIV vectors primed T cell responses that were boosted effectively with a heterologous Ad5-SIV vaccine.

Venezuelan equine encephalitis virus (VEEV)—VEEV is an alphavirus that also has been used to construct chimeric viruses. To more closely mimic an HIV or SIV particle, novel RC VEEVSHIV or VEEV-SIV chimeras were generated in which Env was introduced in place of the VEEV glycoproteins and a modified SIV Gag replaced much of the natural capsid and nucleocapsid functions. Consequently, VEEV-SHIV or -SIV chimeric particles contain functional Env on their surface and viral genomic RNA is packaged inside mature Gag particles [117]. Preliminary studies indicate that the RC VEEV-SIV chimera can be administered to macaques with no obvious clinical reactions, and importantly, anti-Env antibodies capable of neutralizing tier-1 SIV pseudoviruses were induced (R. Johnston, K. Young, V. Traina-Dorge, J. Whitley, C. LaBranche, D. Montefiori, and C. Jurgens, personal communication).

Semliki Forrest virus (SFV)—Finally, a unique vector has been developed based on a Semliki Forrest virus (SFV) RNA replicon [70] that propagates in membrane vesicles. RC SFV replicons encoding SIV Gag or Env have been used as a boost for macaques primed with RC VSV-SIV. Vaccinated animals effectively suppressed chronic infection by SIVsmE660 [71].

CONCLUSIONS

A varied menu of RC viral vectors is now available and data is accumulating to demonstrate safety as well as immunogenicity, and in some cases, efficacy in challenge-protection studies. The availability of these prototype vaccines makes it possible to evaluate new vaccination regimes and determine the benefits of using RC vectors with distinctive properties. As more comprehensive *in vivo* studies are conducted, greater insight into how these vectors modulate the immune response will guide vector design improvements. We anticipate that some RC vectors will emerge as strong candidates for clinical development because they enhance immunity at the mucosal barrier, induce a greater magnitude and/or breadth of durable T cell responses, or elicit protective antibodies against Env.

The RC vectors are effective priming or boosting agents and we can expect continued exploration of such regimes preclinically and clinically. RC vectors also provide one possible option for testing a modified RV-144 regimen in which ALVAC-HIV component might be substituted with a live vector, perhaps one that is capable of expressing an immunogen that closely resembles a native Env spike.

Having RC vectors available provides important new options for HIV vaccine development. While immune correlates of protection remain unclear for any HIV vaccine, new information flowing from continued analysis of the RV-144 trial or the more recent DNA prime/Ad5 boost HVTN 505 phase IIb study ([clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00865566) NCT00865566) should provide further insight into immune response patterns that must be evoked. During final preparation of this review, the HVTN 505 phase IIb trial ([clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00865566) NCT00865566) was halted for futility [118]. Analysis of the immune responses induced by vaccination as well as the incidence of HIV infection in vaccine and placebo groups is ongoing, but it was notable that a non-statistically significant trend toward more HIV infections in the vaccine group was observed reminiscent of the HVTN 502 (Step Study) trial. However, it seems

clear from the results of HVTN 505, as well as the other AIDS vaccine efficacy trials conducted to date [3], that vaccine design will need to achieve a significant improvement in the magnitude and quality of immune responses. Live vectors might provide an effective mechanism to achieve the desired response. Designing vaccines that overcome the HIV genetic diversity also is necessary and RC vectors may be part of the solution if they can significantly increase the magnitude or breadth of responses against T cell immunogens composed of conserved elements or mosaic polypeptides [119-121]. An HIV vaccine also will need to induce antibodies with specificity for the trimeric Env spike, but expressing immunogens that mimic the structure of a functional trimer has been a long-term technical hurdle [122], and accordingly, we as well as others are investigating RC vectors designed to express authentic Env spikes on virus particles. In conclusion, we can anticipate an exciting period over the next few years as RC vectors advance through both preclinical and clinical testing with the goal of developing a safe and effective HIV vaccine.

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KEY POINTS

- Replication-competent viral vectors have been developed for HIV vaccine delivery based on multiple viruses with diverse biological properties.
- Many have been tested safely in the rhesus macaque model and the nature of the immune response they induce is being characterized. Importantly, some vectors have evoked immunity that protects macaques from challenge with pathogenic SIV or SHIV.
- Some replicating viral vectors have been entered into clinical trials and more are anticipated to advance in the next 5 years.
- Replication competent vectors have the potential to solve some of the hurdles that an HIV vaccine must overcome including the generation of long-lasting and broadly effective immune responses.

Table

Listing of RC viral vectors in various stages of development. Some vectors not described in the text have been included here. NHP: nonhuman primate studies.

Replication-competent Vector	Stage of Development	References
<i>DNA viruses</i>		
Human adenovirus type 4	Preclinical / clinical development	[31]
Human adenovirus type 5	NHP	[32, 33]
Human adenovirus type 26	Preclinical development	[34]
Simian adenovirus	Preclinical development	[35]
Rhesus cytomegalovirus	NHP	[36, 37]
Human cytomegalovirus	Preclinical / clinical development	LJP
Herpes simplex virus	NHP	[38]
Rhesus rhadinovirus	NHP	[39]
Varicella zoster virus	NHP	[40]
Vaccinia virus – Tiantan	Clinical trial, ClinicalTrials.gov NCT01705223	[28, 41]
Vaccinia virus – NYVAC-KC	NHP	[42, 43]
Vaccinia virus – modified Tiantan	Preclinical development	[44]
Vaccinia virus – Guang9	Preclinical development	[45]
Vaccinia virus – LC16m8	Preclinical development	[46]
<i>RNA virus – negative strand</i>		
Canine distemper virus	NHP	[47]
Influenza virus	NHP	[48]
Measles virus	Clinical trial, ClinicalTrials.gov NCT01320176	[49, 50]
Measles virus chimeras	Preclinical development	[51]
Mumps virus	Preclinical development	[52]
Newcastle disease virus	Preclinical development	[53-55]
Rabies virus	NHP	[56, 57]
Sendai virus	Clinical Trial, ClinicalTrials.gov NCT01705990	[58, 59]
Vesicular stomatitis virus	Clinical trial; ClinicalTrials.gov NCT01578889	[60-63]
Vesicular stomatitis virus chimeras	NHP	[64, 65]
<i>RNA virus – Positive strand</i>		
Coxsackie virus	Preclinical development	[66]
Poliovirus	NHP	[67, 68]
Rubella virus	Preclinical development	[69]
Semiliki Forrest virus chimeras	NHP	[70, 71]
Venezuelan equine encephalitis virus chimeras	NHP	[64]

Replication-competent Vector	Stage of Development	References
Yellow Fever virus	NHP	[72, 73]