Review article
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Using the vaccinia virus MVA strain for developing recombinant vector vaccines against current arboviral infections

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Abstract

Epidemic vector-borne viral infections pose a serious threat to public health worldwide. There is currently no specific preventive treatment for most of them. One of the promising solutions for combating viral fevers is development of vector vaccines, including MVA-based vaccines, which have virtually no adverse side effects. The safety of the MVA strain and absent reactogenicity of recombinant MVA vaccines have been supported by many clinical trials.

The article focuses on test results for similar preventive products against viral fevers: Crimean-Congo hemorrhagic fever, Rift Valley fever, yellow fever, Chikungunya and Zika fevers.

Their immunogenicity was evaluated on immunocompetent and immunocompromised white mice; their protective efficacy was assessed on immunocompromised white mice deficient in IFN-α/β receptors, that are used for experimental modeling of the infection. Nearly all the new recombinant vaccines expressing immunodominant antigens demonstrated 100% protective efficacy. It has been found that although the vaccine expressing Zika virus structural proteins induced antibodies against specific viral glycoproteins, it can be associated with high risks when used for prevention of Zika fever in individuals who had dengue fever in the past, due to the phenomenon known as antibody-dependent enhancement of infection, which can occur in diseases caused by antigenically related flaviruses. For this reason, the vaccine expressing non-structural protein 1 (NS1) was developed for vaccination against Zika fever.

The yellow fever vaccine developed on the MVA platform had immunogenicity similar to that of the commercial 17D vaccine, outperforming the latter in safety.

Keywords: *vaccinia virus, MVA strain, priming, boosting, Crimean-Congo hemorrhagic fever, Rift Valley fever, yellow fever, Chikungunya fever, Zika fever*

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Научный обзор
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Применение штамма MVA вируса вакцины для создания рекомбинантных векторных вакцин против актуальных арбовирусных инфекций

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Аннотация

Эпидемические трансмиссивные вирусные инфекции представляют собой серьёзную угрозу для здравоохранения многих стран. Для большинства из них отсутствуют средства специфической профилактики.

В настоящее время одним из перспективных направлений борьбы с вирусными лихорадками является создание векторных вакцин, в том числе на основе штамма MVA, которые практически не вызывают побочных реакций. Безопасность штамма MVA и отсутствие реактогенности рекомбинантных вакцин, разработанных на его основе, показана в многочисленных клинических испытаниях.
В статье рассматриваются результаты испытаний подобных профилактических препаратов против вирусных лихорадок: Крымской-Конго геморрагической лихорадки, лихорадки долины Рифт, жёлтой лихорадки, лихорадок Чикунгунья и Зика.
Их иммуногенность оценивалась на иммунокомпетентных и иммунодефицитных белых мышах, а протективная эффективность — на иммунодефицитных белых мышах, дефектных по α-, β-рецепторам интерферона, на которых моделируют эту инфекцию. Почти все разработанные рекомбинантные вакцины, экспрессирующие иммунодоминантные антигены, обеспечивали 100% защитную эффективность. Показано, что, хотя вакцина, экспрессирующая структурные белки вируса Зика, индуцировала антитела против специфических вирусных гликопротеинов, её применение может вызывать опасность для профилактики лихорадки Зика у лиц, переболевших лихорадкой денге, в связи с наличием феномена антителозависимого усиления инфекции при заболеваниях, вызванных антигенно-родственными флавивирусами. По этой причине для иммунизации против лихорадки Зика разработана вакцина, экспрессирующая неструктурный белок NS-1.
Сконструированная на основе штамма MVA вакцина против жёлтой лихорадки обладала такой же иммуногенностью, что и коммерческая вакцина 17D, однако по уровню безопасности превосходила её.

Ключевые слова: *вирус вакцины, штамм MVA, праймирование, бустирование, Крымская-Конго геморрагическая лихорадка, лихорадка долины Рифт, жёлтая лихорадка, лихорадка Чикунгунья, лихорадка Зика*

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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Introduction

The modified vaccinia virus, MVA strain, is licensed as a smallpox vaccine in Europe and Canada, and currently undergoing clinical development in the United States. The strain was derived from the parental Ankara strain, vaccinia virus, by over 575 serial passages on chicken embryo fibroblast cells. During the passaging, the strain genome went through multiple mutations and acquired large deletions as compared to the DNA of the original strain, thus becoming highly attenuated and unable to replicate in mammalian cells [1]. By their safety, the MVA vaccines are classified as third generation smallpox vaccines [2]. After the mandatory vaccination against smallpox stopped, the herd immunity against smallpox is low to non-existent; therefore, it cannot interfere with vector vaccines based on the vaccinia virus [3, 4]. Prior to the abrogation of the mandatory smallpox vaccination, MVA was used as a priming vaccine in 120,000 people in Germany in 1970 [5]. MVA did not have systemic side effects; sometimes it could produce a mild injection-site reaction. Its safety was evaluated in clinical trials with participation of healthy volunteers aged 18–30 years [6], volunteers with cardiovascular diseases [7], in the 56–80-year-old age group [8], in 18–40-year-old patients with atopic dermatitis [9], tuberculosis patients [10], and HIV-infected patients [11]. It formed the basis for development of MVA-based vector vaccines against different viral infections.

Crimean-Congo hemorrhagic fever

The Crimean hemorrhagic fever transmitted by *Hyalomma* ticks was originally described in 1945 when the viral etiology of the infection was identified [12]. However, in 1969, it was found that the virus causing this disease was identical to the virus isolated in Congo in 1956 [13], and the international name of the pathogen of Crimean-Congo hemorrhagic fever (CCHF) was adopted.

CCHF is endemic in Africa, Asia, and Europe. Besides, imported cases of CCHF to non-endemic countries have been reported. For example, in 2012, in the United Kingdom, the fatal case of the hospitalized patient who had recently returned from Afghanistan was reported [14]. The first-generation vaccine was developed in Bulgaria; it is a chloroform-inactivated suckling mouse brain derived vaccine, which has been successfully used in this country since 1974. It induces cellular and humoral immune responses when administered in multiple doses [15]; it has not been approved for use in other endemic regions. The recently developed DNA vaccine expressing CCHF viral glycoprotein induced specific neutralizing antibodies in approximately 50% of the vaccinated mice [16]. The vaccine expressing CCHF viral glycoprotein in transgenic tobacco leaves induced IgG and IgA in mice [17].

The protective activity of the above vaccines was assessed only in 2010, when it was found that adult A129 mice deficient in STAT-1 or IFN-α/β receptors

were susceptible to CCHF and could be used as experimental model for this infection [18].

In 2014, the first reports were released with the information about the development and testing of a recombinant MVA vaccine expressing the full-length CCHF glycoprotein precursor — MVA-GP [14]. The vaccine was injected into immunocompetent 129 Sv/Ev mice and immunocompromised A129 mice; then, 14 days later, the mice were infected with a lethal dose of the virulent virus (**Table**).

The immunization induced a humoral immune response mainly mediated by IgG antibodies and a CCHF glycoprotein-specific cellular response. No disease symptoms were observed in the immunized mice. The immunocompromised mice were fully protected against infection with the lethal dose of the native virus [14].

The importance of cellular and humoral immune responses for protection from potential further infection with a virulent virus is supported by the studies involving passive transfer of immune serum and T lymphocytes to non-immunized A129 mice [19].

In addition to the tested vaccine expressing viral glycoprotein [14], another recombinant MVA strain was constructed, integrating the viral nucleoprotein (NP) gene. The authors believed that NP, as a dominant antigen highly conserved among strains of genus *Nairovirus* of the *Bunyaviridae* family , would be a good alternative to glycoprotein [20]. Besides, vaccines expressing nucleoprotein demonstrated protective effect against two other representatives of this family: the hantavirus (genus *Hantavirus*) and the Rift Valley fever virus (genus *Phlebovirus*) [21].

The immunogenicity of the MVA-NP3010 vaccine candidate was assessed on A129 and 129 Sv/Ev mice, which were vaccinated twice. 14 days later, they were infected with a lethal dose of the native virus. The assessment of the immunogenicity of this vaccine candidate showed that all the animals produced NP-specific antibodies and an NP-specific T-cellular response. However, despite the induced immune response, all the mice died on the 4^{th}-5^{th} day after the infection with the lethal dose of the native virus [20].

Thus, currently, the MVA-GP construct is the only one that is effective against CCHF, thus being a potential candidate for vaccines.

Rift Valley fever

The Rift Valley fever virus is transmitted through mosquito bites and causes periodic outbreak of the disease among livestock and humans in many African countries. After the outbreaks on the continent, the disease spread into the Arabian Peninsula. There is a highly effective, live vaccine Clone 13, which is used in many countries of Africa, though it is intended only for livestock and has not been approved for human use [22].

In 1967, an inactivated live vaccine for immunization of people was developed in the United States. It is a formalin-inactivated preparation of a pantropic virus (Entebbe strain). The vaccine was used for immunization of more than 4,000 people. A significant level of neutralizing antibodies was observed in 80–85% of the vaccinated people 14 days after the immunization. The fully-immunized and re-vaccinated patients had neutralizing antibodies to the Rift Valley virus for several years [23].

MVA-based vaccine candidates and DNA vaccines (PCMV) expressing viral glycoproteins (GnGc) or nucleoprotein (N) were developed for human protection [24]. The tests to assess the level and protective efficacy of the induced immune response were performed on immunocompetent BALB/c mice; they showed that the mice immunized with MVA-GnGc demonstrated a moderate humoral and $CD8^+$ T-cellular response specific to the viral glycoprotein, and only this group of mice was fully protected against infection with a lethal dose of the virulent virus. The immunization with the DNA vaccine, also expressing viral glycoproteins, resulted in generation of antibody titers comparable with those induced by MVA-GnGc immunization; however, the mice had symptoms of the disease and some of them died. None of the vaccines expressing nucleoprotein provided full protection of animals against the subsequent infection with the lethal dose of virulent virus, even in the MVA-GnGc + MVA-N combination. The immunization of immunocompromised 129Sv/EvI-FNAR$^{-/-}$ mice with the MVA-GnGc vaccine did not protect them against death after they had been infected with a lethal dose of the virus, thus implying the importance of naturally acquired immunity for protection against Rift Valley fever [24].

Yellow fever

Yellow fever is a severe mosquito-borne disease, which is endemic in tropical areas of Africa and South America. According to the World Health Organization (WHO), yellow fever is estimated to cause 200,000 cases and 30,000 deaths per year [25]. A live vaccine based on the attenuated 17D strain was developed in 1937. The vaccine is widely used at present. The total number of immunized people runs to 400 million. The vaccine used to be reputed as one of the safest and immunogenic. In the meantime, a few post-vaccination cases with symptoms suggestive of neurotropic and viscerotropic diseases were reported, most of them among patients aged over 60 years and women of childbearing age. Serious side effects, including deaths, were reported in Iceland, Brazil, USA, Australia, and Thailand [26]. All the above triggered the urgency of development of a new and safer vaccine.

The dominant role played by envelope proteins in inducing a protective immune response prompted development of vector vaccines based on two replication-deficient MVA and Dvv strains of the vaccinia virus with the deleted uracil-DNA-glycosylase gen.

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REVIEWS

Assessment results of the immune response induced by MVA-based vaccines in immunocompetent and immunocompromised mice

Disease	Expressing proteins	Induced immune response				Protect's' efficacy on immunocompromised mice	References
		humoral		T-cellular			
		on immuno-competensed mice	on immuno-compromised mice	on immuno-competensed mice	on immuno-compromised mice		
Crimean-Congo haem-orrhagic fever	Glycoprotein GP	+	+	+	+	100%	14
	Nucleoprotein NP	+	+	+	+	Death on days 4–5	20
Rift Valley fever	Glycoprotein Gn/Gc	+	+	+	No date	Partial. On immuno-competensed — complete	24
Yellow fever	Precursors of membrane and envelope proeins (prMR)	+	No date	+	No date	Complete	27
Chikungunya fever	C, E3, E2, 6K, E1	+	No date	+	No date	Complete	30
	E3, E2	+	+	+	+	Complete	29
	6K, E1	No date	+	No date	No date	Partial	31
	E3, E2	No date	+	No date	No date	No date	
	E3, E2, 6K, E1	No date	+	No date	No date	No date	
Zika fever	Premembrane (prM) and envelope (E)	+	+	+	No date	Complete	35
	Nonstructure protein-1 (NS-1)	+	No date	+	No date	On immuno-competensed — complete	34

It also belongs to third-generation smallpox vaccines expressing precursors membrane and envelope (prMR) proteins, i.e. proteins identical to those expressed by the 17D strain. Both vector vaccines were assessed against the commercial live 17D vaccine by immunogenicity and safety after a single intramuscular immunization of BALB/c mice. The level of the induced immune response was assessed after the intracerebral infection of immunized animals with a virulent strain of the yellow fever virus at a dose of more than 1,000 LD_{50} for white mice [27].

The results of the studies showed that the level of the humoral and cellular immune responses for both vaccine candidates was similar to the level demonstrated by the 17D vaccine. The cellular immune response was mediated by functionally active $CD8^+$ and $CD4^+$ T cells secreting interferon-gamma (IFN-γ). Both variants fully protected mice against lethal infection with the virulent virus. As opposed to the conventional 17D vaccine, the safety of the MVA and Dvv-based vaccine candidates was very high, as demonstrated when BALB/c mice were injected intracerebrally with very high doses ranging from 1×10^5 to 1×10^7. All the mice survived, contrary to the mice in the control group where the mice were infected with doses ranging from 1×10^1 to 1×10^3 CPD_{50} of 17D strain, provided that the 1×10^3 CPD_{50} dose was lethal for 100% of mice. The pre-existing vaccination of mice with the vaccinia virus did not affect the results of the immunization against yellow fever [27].

Thus, recombinant vaccines based on both strains of the vaccinia virus, which expressed precursor membrane and envelope proteins, induced humoral and cellular immune responses protecting against the infection with a lethal dose of the yellow fever virus. They were safer than the commercial 17D vaccine [27].

Chikungunya fever

The Chikungunya virus transmitted by *Aedes* mosquitoes belongs to the *Togaviridae* family. The infection was first described in Tanzania in 1952, and the virus was isolated in 1953. In 2005, a major outbreak of this infection broke out on La Réunion Island; then the disease spread into different regions of Africa and Southeast Asia, to the islands of the Indian Ocean, to India, Southern Europe (Italy, France), the Caribbean and continental America. A total of 6 million cases were reported [28, 29].

There is currently no vaccine against Chikungunya fever. Live attenuated vaccines are known to be most immunogenic, though involving a tangible risk of reversion to the original virulent strain. Therefore, MVA-vectored vaccines are seen as the best potential candidates for development of vaccines against this infection.

A recombinant MVA strain containing structural genes of the C-E3-E2-6K-E1 virus was constructed for a vaccine candidate [30]. To assess the level of the immune response, immunized C57Bl/6 mice were infected with one and two lethal doses of the virulent virus 7 weeks after the last immunization.

The C-E3-E2-6K-E1 vaccine induced an immune response and provided full protection of animals against infection with a lethal dose even after a single immunization; no symptoms of the disease were observed in the animals. The immune response was represented by a strong polyfunctional $CD8^+$ T-cellular response directed mainly against E1 and E2 proteins and was characterized by immune $CD8^+$ T-cellular memory. The immunization produced high titers of neutralizing IgG antibodies against the Chikungunya virus, which tended to increase after booster immunization. The specific immune response against the Chikungunya virus coupled with polyfunctional $CD8^+$ T-cellular response and T-cellular memory against the vaccinia virus. The obtained results prompted the authors to offer the product as a candidate vaccine for preventive vaccination of people [30].

Approximately at the same time, another group of researchers [29] was assessing the immunogenicity of the construct based on recombinant MVA strain expressing E3 and E2 proteins of the Chikungunya virus. The efficacy of the vaccine was tested and assessed on immunocompetent BALB/c mice and immunocompromised A129 mice after single and two-dose immunization. Two weeks after the last vaccination, the animals were infected with a lethal dose of the virulent virus. The BALB/c mice that had two-dose vaccination were fully protected. Relying on the obtained results, the authors offer the new recombinant MVA construct as a potential vaccine candidate against Chikungunya fever [29].

To measure the proportion of specific structural proteins of the Chikungunya virus, which are instrumental for protective activity of vector vaccines, scientists created recombinant MVA strains expressing specific structural proteins of the Chikungunya virus: MVA-6KE1, MVA-E3E2, and MVA-E3E26KE1 (the latter produced virus-like particles). The efficacy of these products was assessed on immunocompromised AG129 mice, which were infected with a lethal dose of virulent Chikungunya virus 6 weeks after the immunization [31]. The recombinant MVA-E3E26KE1 variant induced higher levels of antibodies compared to the other two variants and it protected, similar to the MVA-E3E2 product, 100% of mice against the subsequent infection with the virulent virus, even after single immunization. Recombinant MVA-6KE1 protected only 75% of mice. Taking into account the prior data on E1E2 protein expression, the authors concluded that the E2 protein and its B domain, in particular, were most significant for full protection of the immunized mice against lethal infection with the virulent virus [31, 32].

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There are currently several vaccine candidates against Chikungunya fever. In 2015, scientists conducted tests evaluating the following candidate products: the attenuated virus with a large deletion in the replicase gene; the vaccine based on the DNA replicon with the deleted capsid protein, and the recombinant MVA vaccine with inserted C-E3-E2-6K-E genes, which was used for immunization of *Macaca fascicularis* with different doses. The best results were demonstrated when the vaccine was used to create a booster effect [33].

Zika fever

The virus that causes Zika fever was first isolated in Uganda in 1947 [34]. For many years, it had been known as an etiological agent of sporadic febrile illnesses in Africa. However, in 2007, there was a major outbreak of Zika fever in Micronesia; then another outbreak was reported in French Polynesia in 2013. After the virus was reported in Brazil at the end of 2014, the pandemic infection rapidly spread to regions of South and Central America and the Caribbean. Its primary transmitters, along with the dengue and Chikungunya viruses, are *Aedes aegypti* and *Aedes albopictus* mosquitoes. Currently, cases of Zika fever have been reported in South and Central America, Africa, Southeast Asia, and southern islands of the Pacific Ocean, presenting a potential threat of a new pandemic [34]. Besides, several imported cases of the disease were reported in non-endemic countries in 2015-2016 [35].

In most cases, Zika fever develops an asymptomatic form or as an acute febrile illness (without fatal outcomes). In some cases, patients have Guillain Barré syndrome, which may also develop in patients with dengue, West Nile, and Chikungunya fever. Microcephaly was reported among babies born from infected women. Infants can be infected with the Zika virus through breastfeeding or blood transfusions [35].

There is currently no vaccine against Zika fever. As the disease can spread rapidly, there is an urgent need to create a safe and efficient preventive vaccine, which can be also used for immunization of pregnant women. The safety of the MVA strain has been confirmed by multiple trials involving human volunteers and pregnant macaques [36]; it was used for constructing a candidate vaccine against Zika fever (MVA-ZIKV); the vaccine expresses pre-membrane (prM) and structural (E) (prM-E) proteins of the Zika virus [35]. Expressed prM-E proteins produced virus-like particles in infected cells.

The immunization of immunocompetent BALB/c mice induced neutralizing antibodies against different strains of the Zika virus and polyfunctional virus-specific $CD8^+$ T-cellular response.

To assess protective efficacy of the MVA-ZIKV construct, immunocompromised IFNAR-1 (deficient in IFN-α/β receptors) mice were immunized one or two times; then, four weeks after the immunization, they were infected with a lethal dose of the virulent virus [35]. The subsequent boosting significantly increased titers of virus-neutralizing antibodies and significantly decreased viremia levels. During 15-day monitoring period, all the mice remained alive. Based on the obtained results, the above construct is offered by its authors for production of a new, safe, highly immunogenic, and relatively inexpensive vaccine against Zika fever [35].

In the meantime, in flaviviral infections, the phenomenon of antibody-dependent enhancement (ADE) of infection plays a significant role in the response of the human immune system to the pathogen. ADE is a phenomenon, in which virus-specific antibodies enhance the entry of the virus into phagocytic cells by interacting with the FcR receptor and/or complement receptors on the surface of phagocytic cells. Among the infection processes caused by flaviviruses, the ADE phenomenon has been most thoroughly studied for dengue and yellow fever [37, 38]. The primary infection caused by one of the 4 dengue viruses (D1, D2, D3, D4) is generally asymptomatic in humans and results in life-long immunity to the virus serotype causing it. If it comes across another virus serotype, the FcR-ADE phenomenon comes into play and the disease can develop into a severe hemorrhagic fever with the probability of fatal outcomes reaching 15%. Zika and dengue fevers are common in the same areas, as they have common transmitters. Since Zika and dengue viruses are antigenically related (belonging to the *Flaviviridae* family, genus *Flavivirus*), antibodies to the dengue virus can enhance the infection caused by the Zika virus, and vice versa, antibodies against glycoproteins of the Zika virus can affect the development of dengue fever [39].

Therefore, another group of scientists offered an MVA vaccine expressing non-structural protein 1 (NS1) of the Zika virus, which exists in a native form in infected cells [34]. The NS1 protein was chosen due to the protective immune response generated against it, similarly to other flaviviruses, as demonstrated in the tests on the mouse model [38]. The immunogenicity and protective efficacy of the MVA-ZIKV-NS-1 construct were assessed on the new model - immunocompetent CD-1/ICR mice, which were immunized one or two times. Even after the single-dose immunization, the humoral response against the NS1 protein, the level of which increased after the boosting, provided full protection of mice from death after the subsequent intracerebral infection with a lethal dose of the virulent virus in the absence of disease symptoms. 10 days after the immunization, the mice demonstrated a virus-specific $CD8^+$ T-cellular response. The virus was not detected in the brains of the immune mice 21 days after the infection. The pre-existing immunity to the MVA vector did not have any effect on the immunization results. Proceeding from these results, the authors believe that seropositive individuals, who live in areas where the

dengue virus or other flaviviruses are endemic, will not have ADE after they are immunized with the ZIKV-NS-1 vaccine [34].

The results of the studies assessing the immunogenicity of MVA vaccines against pathogens of arboviral infections are presented in the Table. The data demonstrate that recombinant MVA-based vaccines are characterized by high immunogenicity. When genes of envelope glycoproteins were inserted, the induced immune response protected immunocompromised mice against infection with a lethal dose of the virulent virus. The insertion of other genes resulted only in partial protection of the animals.

Besides, it has been found that the MVA-based vaccine against yellow fever is safer compared to the conventional attenuated 17D vaccine. The new constructs have been tested only on laboratory animals so far. In the near future, the candidate vaccines will be tested and evaluated in clinical trials.

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