Viral Vectored Vaccines

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Viral Vectored Vaccines are vaccines that use a viral vector as a carrier to deliver a protein (or antigen) from a pathogen (namely viruses and bacteria) in order to elicit an immune response against this pathogen. The DNA or RNA sequence for this protein antigen is inserted into the genome of the virus vector. The resultant recombinant virus expresses the necessary components of the viral vector so that functional virus particles can be made to express the foreign protein antigen. Viral vectored vaccines are classified by the virus vector they use and whether they can reproduce inside cells to produce new virus particles (i.e., are replication competent) or whether they can only enter cells but do not produce new virus particles (i.e., are replication incompetent or single-cycle replication). Different viral vector backbones can serve different needs for developing preventive and therapeutic vaccines depending on the context and diseases they aim to prevent or treat, respectively.

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1. Introduction

Current Food and Drug Administration (FDA)-approved vaccines include live attenuated, inactivated, and subunit vaccines for a variety of human diseases [1]. In general, a live attenuated vaccine is made by attenuating the virulent nature of a pathogen while keeping a certain level of its replication competency. Current examples of live attenuated vaccines include smallpox, MMR combined vaccine (measles, mumps, rubella), chickenpox, and yellow fever. Inactivated vaccines are replication-deficient or killed viruses or bacteria that are administered in order to create immunological memory to a particular vaccine antigen (immunogen), or even a toxin, from the pathogen. Current examples of inactivated vaccines include hepatitis A, annual (seasonable) influenza vaccine, polio vaccine, and rabies vaccine. Another commonly used vaccine design approach is subunit vaccines, which contain certain antigens from the pathogen that can stimulate a protective immune response against the pathogen when administered as a vaccine. For a complete list of FDA-approved vaccines, please follow this web-link: https://www.fda.gov/vaccines-blood-biologics/vaccines/vaccines-licensed-use-united-states.

Despite recent advances in vaccinology, there are still many infectious diseases such as AIDS, malaria, and hepatitis C that still do not have FDA-approved vaccines despite decades of intense investigation. The lack of a vaccine for these and other intractable diseases can be explained by many different factors that include but are not necessarily limited to the unique properties of the individual pathogen, lack of relevant animal models or economic incentives to produce and test a vaccine, and/or insurmountable regulatory and/or ethical issues associated with vaccine-associated clinical trials, especially in pediatric and immunocompromised human populations [2]. However, another more simplistic reason may include the inability of traditional vaccine design methods to produce a functionally protective vaccine. Therefore, it is important to consider new technologies for vaccine design and development.

2. General Concepts and Approaches to the Development of Viral Vectors

There are four common approaches to the development of viral vaccine vectors, which include methods to produce replication-competent (RC) viral vectors, replication-defective (RD) viral vectors, single-cycle (SC) viral vectors, and multi-segmented (MS) viral vectors. The general strategies for their development will be discussed in this section, with more specific examples of the different viral vectored vaccines being detailed in separate sections thereafter.

An attractive aspect of viral vectors for use in vaccine development is their ability to replicate (reproduce) in the proper host cells. An RC viral vector is one that is capable of infecting cells, replicating (duplicating) its genetic information, and creating new viral progeny that can then infect new cells. A major advantage with this type of viral vector is its ability to amplify the vaccine antigen (immunogen) that is built into the genome of the viral vector. By replicating, the viral vector is able to amplify not only its genome but also the immunogenic gene of interest. Studies performed on four serotypes of RC

adenovirus (RC-Ad) demonstrated that each of these viral vectors could produce 10^3 to 10^5 infectious particles per cell [3][4]. This creates a large amount of the vaccine immunogen to drive an effective adaptive immune response [3]. However, there are drawbacks associated with these RC-Ad vectors due to their potential to cause unintended side effects, especially in immunosuppressed or immunocompromised individuals [5]. In order to alleviate some of these concerns, RC viral vectors, including RC-Ad [6], have been attenuated through deletion of certain viral genes, such as the viral intrinsic immunomodulating genes encoded in the wild-type virus genome [7][8][9]. Through these strategies, RC viral vectors have shown improved safety profiles, but the potential for these virus vectors to cause undesirable side effects still needs to be carefully monitored.

On the other hand, RD viral vectors have been used for a variety of vaccine applications due to their excellent safety profiles. Because these RD viral vectors are unable to replicate, they do not produce infectious viruses. Typically, to make the viral vector replication-defective, one or more genes required for viral genome replication, synthesis, and/or assembly are deleted. The virus is then propagated in the complementing cell line that expresses the missing viral gene product(s) in trans [10]. Even though their replication is restricted, RD viral vectors are still able to express the desired immunogen in order to induce innate and adaptive immune responses that are generally localized to the site of RD viral vector administration [10]. The heterologous (immunogenic) gene(s) expressed by the RD viral vectors are presented through the major histocompatibility complex MHC class I and class II pathways. This effectively stimulates the adaptive arm of the immune response. In addition, RD viral vectors are thought to activate innate immune sensor pathways, such as toll-like receptors, thereby acting as their own adjuvants [10]. The strengths and specifics of the immune response elicited by RD viral vectors depend on the vector used, which will be detailed in later sections. Upon comparing the vaccine potency of candidate viral vectors for the Ebola virus (EBOV), RD-Ad vaccines and RC vesicular stomatitis virus (RC-VSV) vaccines both elicited strong immune responses despite RD-Ad being unable to replicate, which supports the promise of these RD vectors [10]. After considering phase I trial data with a remarkable rate of protection (almost 100%) in ring vaccination trials [11], VSV-ZEBOV was selected to continue in development and became the only available viral vector-based vaccine on the market [12], which is now known as ERVEBO® (rVSVΔG-ZEBOV-GP) vaccine, produced by Merck & Co. [13]. However, the success of RD viral vectors is not unanimous and some RD viral vectors, such as modified vaccinia virus Ankara (MVA), have been found to induce limited immune responses in clinical trials [14]. In summary, while RD viral vectors represent a safer alternative to RC viral vectors, further development is needed for certain RD viral vectors in order to ensure that they can induce sufficient protective immune responses.

Another viral vector platform consists of the single-cycle virus (SC) vectors that are able to replicate and amplify the inserted heterologous gene but do not express the viral late genes needed for making functional progeny virions due to their targeted deletion from the virus genome. Instead, virus particles are produced by transfecting cells that express these viral late genes in trans. When given as a vaccine, these virus particles can infect their target cells but are not able to produce virus particles and instead transcribe only viral RNA [3]. Therefore, this SC viral vector has a better biosafety profile as it does not continuously produce infectious virus with the potential to cause adverse side effects or diseases in certain vulnerable populations [15]. In studies of a green fluorescent protein (GFP)-encoding SC-Ad vector in macaques, SC-Ad6 induced high levels of anti-GFP antibodies and T cell responses [15]. Overall, SC viral vaccine vectors are generally good approaches for vaccine development as they have fewer safety risks than RC viral vectors and can amplify the heterologous gene (immunogen) through a single cycle of virus replication, which is lacking by the RD viral vectors.

A new generation of viral vaccine vectors includes those viruses with a multi-segmented (MS) RNA genome. The genome of these MS viral vectors contains multiple genomic strands that encode for more than one viral gene product and therefore can also accommodate multiple vaccine antigen(s). Along with expanding the repertoire of protein antigens (immunogens) that can elicit effective immune responses, a major advantage of the MS viral vaccine vectors is the attenuating features that allow for an increased safety profile. These unique characteristics have recently been demonstrated by the tri-segmented reverse genetics systems of arenaviruses, such as the lymphocytic choriomeningitis virus (LCMV) [16][17] and Pichinde virus (PICV) [18].

3. Application of Viral Vectored Vaccines for Zoonotic Infection of a High-Consequence Pathogen, SARS-CoV-2, the Causative Agent of COVID-19

Viral vectored vaccine development is crucial to respond to rapidly emerging zoonotic pathogens in order to produce to a diverse pool of vaccine candidates for immediate testing, especially considering that vaccine candidates have a 33% success rate of progressing from phase I of clinical trials to approval [19]. The urgency of vaccine development to curb the transmission of SARS-CoV-2, the causative agent of COVID-19, has produced a number of viral vaccine candidates that

are currently in clinical testing. The most prominent examples are several adenovirus-based SARS-CoV-2 vaccine candidates. The RD chimpanzee adenoviral vaccine AZD1222 (formerly known as ChAdOx1 nCov) from Oxford University entered phase III clinical trials in August 2020 (Table 1) [20][21].

Table 4. Viral vectored vaccines currently in development for SARS-CoV-2 *.

Vaccine Name	Vaccine Vector	Company and Country	Preliminary Results
AZD1222 (ChAdOx1 nCoV-19)	Adenovirus	Oxford University, UK	• **Phase I/II clinical trials showed that vaccine did not induce severe side effects and induced humoral and cell-mediated responses;** • **Vaccine was found to induce humoral, CD8, and Th1-predominant CD4 responses in mice and rhesus macaques, and both a prime and prime-boost schedule protected rhesus macaques from development of pneumonia;** • **Entered phase III clinical trials in August 2020;** • **Trials were paused in September 2020 due to unexplained serious illness. Trials have resumed in the UK but not in the USA**
Ad5-nCoV	Adenovirus	CanSino Biologics, China	• **Phase I/II clinical trials showed that vaccine induced antibody and cell-mediated responses with a single dose and did not induce severe side effects;** • **Entered phase III clinical trials in August 2020;** • **Approved by the Chinese government for its use in its military**
Ad26.COV2.S	Adenovirus	Johnson and Johnson, USA	• **Induced antibody and T cell responses in rhesus macaques with a single dose and lower viral titers were found in animals with higher antibody titers;** • **Entered phase III clinical trials in August 2020;** • **Trials were paused in October 2020 due to unexplained serious illness**
Gam-COVID-Vac	Adenovirus	Gamaleya Research Institute of Epidemiology and Microbiology, Russia	• **Approved for use in the general public by the Russian government before the release of clinical trial data and before phase III clinical trials had begun;** • **Entered phase III clinical trials in August 2020;**
GRAd-COV2	Adenovirus	ReiTherra, Italy	• **Entered phase I clinical trials in August 2020.**
VXA-CoV2-1	Adenovirus	Vaxart, USA	• **Entered phase I clinical trials in September 2020;**
TMV-083	Measles	Institut Pasteur, France	• **Entered phase I clinical trials in August 2020**
V591 and V590	Measles	Merck, USA	• **Entered phase I clinical trials in August and September 2020**
MVA-SARS-2-S	Vaccinia Ankara	Universitätsklinikum Hamburg-Eppendorf, Germany	• **Entered phase I clinical trials in September 2020**

* COVID19 vaccine data compiled with the aid of the BioRender COVID19 Vaccine and Drug Tracker: https://biorender.com/covid-vaccine-tracker.

The same adenoviral backbone was previously used by the same group to produce a vaccine against Middle East respiratory syndrome coronavirus (MERS-CoV), which causes Middle East respiratory syndrome, by encoding the MERS-CoV spike (S) protein. Because this vaccine protected against six strains of MERS-CoV in rhesus macaques [22], this vaccine design is thought to have the potential for developing a vaccine for SARS-CoV-2. AZ1222 induced humoral and T cell-mediated immune responses in phase I/II clinical trials and did not induce any severe side effects [20]. AZD1222 also induced a humoral, CD8, and Th1-dominant CD4 response in mice and rhesus macaques. Notably, both a prime and a prime-boost dosing schedule prevented the development of pneumonia in rhesus macaques. However, unvaccinated and vaccinated macaques that were challenged with SARS-CoV-2 had no difference in the amount of nasal viral shedding [21]. It should be noted that the phase III clinical trial of the AZD1222 was paused in September 2020 after a participant in the UK trial developed a severe and unexplained illness [23]. The trials have since resumed in the UK but not yet in the US for undisclosed reasons.

Several additional RD adenoviral vectored SARS-CoV2 vaccines have also started clinical trials. Currently in phase I/II clinical trials, the Ad5-nCoV vaccine from CanSino Biologics induced robust humoral and T cell responses with a single dose of vaccination and showed only rare instances of moderate to severe side effects that were present mostly in the groups receiving a higher dose [24]. Following the release of these data, the Chinese government approved this vaccine for use in its military members. The Ad26.COV2.S vaccine candidate from Johnson and Johnson also resulted in robust antibody and T cell responses in rhesus macaques with a single dose of immunization, and upon viral challenge, lower viral titers were observed in animals with higher antibody titers [25]. The phase III trial of the Ad.26.COV2.S vaccine was also paused in October 2020 due to an unexplained serious illness [26]. The Gam-COVID-Vac adenoviral candidate from the Gamaleya Research Institute of Epidemiology and Microbiology was the first SARS-CoV-2 vaccine to gain approval from the Russian government for use in the general public before phase III clinical trials had begun [27][28]. Finally, the MVA gorilla adenovirus-vectored candidate from ReiThera began phase I clinical trials in Italy in August 2020 [29] and the VXA-CoV2-1 adenovirus type 5 vaccine candidate from Vaxart began phase I clinical trials in September 2020 [30].

Several vaccines based on other viral backbones have also started clinical trials. The TMV-083 live attenuated measles candidate from the Institut Pasteur expresses a modified SARS-CoV-2 surface glycoprotein (spike) and entered phase I clinical trials in August 2020 [31]. Additionally, the V591 and V590 live attenuated measles candidates from Merck also entered phase I clinical trials in August and September 2020, respectively [32][33]. Finally, the MVA-SARS-2-S Vaccinia Ankara vectored candidate from the Universitätsklinikum Hamburg-Eppendorf entered phase I clinical trials in Germany in September 2020 [34]. In addition to these viral vectored COVID-19 vaccine candidates that are in various stages of clinical trials, many other COVID-19 vaccine candidates, including non-viral vaccines, are also currently in preclinical development and clinical testing and have been reviewed elsewhere [35][36].

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