MINISTRY OF ECONOMY
BRAZILIAN NATIONAL INSTITUTE OF INDUSTRIAL PROPERTY

OBSERVATORY OF TECHNOLOGIES RELATED TO COVID-19

Landscape of patent applications related to vaccines based on viral vectors for prevention of COVID-19

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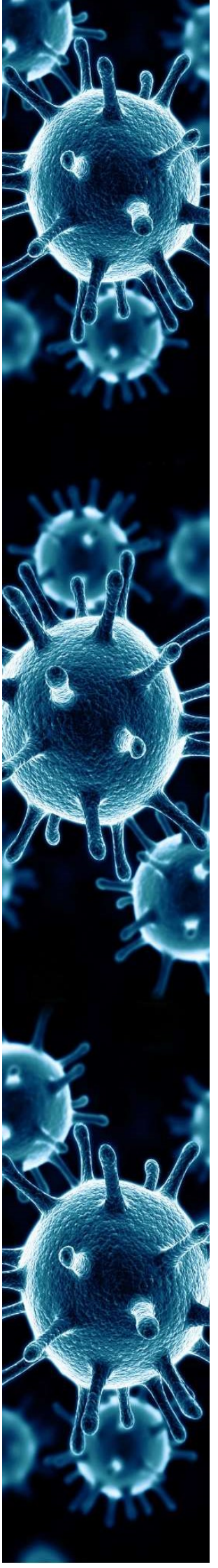

EXECUTIVE SUMMARY

The aim of this study is to present the qualitative evaluation of a selection of patent documents related to technologies that use viral vectors to develop vaccines. The scope of the study encompasses the vaccines under development against the SARS-COV-2 virus, which causes COVID-19, that are currently under clinical trials worldwide. Similarities and differences as to clinical trial phases, institutions engaged in the development and production of the vaccines, and details on the vectors used are presented.

The methodology to survey the documents can be described according to the following steps: a) identification of the vaccines against COVID-19 based on viral vectors under phase 2, 3, or 4-clinical trials; b) survey on the patent documents using the combination of the International Patent Classification (IPC) and/or Cooperative Patent Classification (CPC) codes, keywords, and information on the applicants as a search strategy (considering developers/producers, synonyms, and corresponding codes in the *Derwent Innovation* database); and c) evaluation of the relevance of the patent documents by reading the titles and abstracts, aiming at identifying documents related to technologies described for the vaccines produced by these institutions.

It is worth mentioning that this study should not be used as an analysis of freedom of operation. The study is a photograph of a limited period, i.e., applications published until June 18, 2021.

Additionally, considering this is a very recent technology, several patent applications related to the vaccines may still be confidential. Therefore, the search strategy created in this study intends to identify technologies close to those mentioned for the viral vector vaccine candidates under development by the institutions in charge. Moreover, it is worth remembering that the vaccine production process itself is complex and may engage additional technologies, whose patents may not have been recovered using the strategy employed in this study. We emphasize that patent applications filed by means of the Patent Cooperation Treaty (PCT) agreement have a 30-month period to enter into national phase in each one of the countries of interest that are parties in the agreement. Additionally, some strategies used by the companies, which may involve the names of the applicants, in addition to mergers and acquisitions, should be considered in this type of approach.

1. *VIRAL VECTOR VACCINES*

The viral vectors are composed of non-pathogenic or attenuated viruses, which carry in their genome genetic information that makes them capable of producing antigens of other pathogens when inoculated into vaccinated individuals. For creating a viral vector, a strain of virus is genetically modified not to cause disease, eliminating genes that are essential for its replication and/or pathogenicity. Additionally, the genetic material of interest, which encodes the immunogen of the vaccine, leading to its expression when the viral vector infects the cells of the vaccinated individual, is inserted into this modified virus. By mimicking a viral infection, the vector is expected to be capable of stimulating a strong immune response, both humoral and cellular.

In general, the viral vector vaccine development technologies are divided into two groups: the replicating and non-replicating viral vectors. The replicating viral vectors, as evidenced by the name itself, have as their main feature maintaining their capability of replicating in the host cells, creating new viral particles after infection. The replicating vectors used are non-pathogenic in human beings, such as the vesicular stomatitis virus (VSV), or carry genetic modifications that attenuate their virulence, e.g., the adenoviruses, the measles virus, or the poxvirus. [1]

One of the advantages related to the use of this type of vector is that, when it replicates inside the cell, it amplifies not only its own genome but also the gene that encodes the antigen of interest attached to it. Thus, it provides a high production of the vaccine antigen to stimulate the adaptive immune response, which enables achieving immune protection by using a lower dose of the vaccine. Moreover, the natural infection provided by the model and the very viral vector used trigger a complete immune response (innate and adaptive) and the induction of co-stimulatory molecules with adjuvant effect. However, there are some issues regarding the safety profile of replicating viral vectors, which might present unwanted side effects, especially in immunosuppressed or immunocompromised individuals. [2], [3]

The non-replicating viral vectors, as defined by the name itself, have no replication capability and, when inoculated into the host, do not produce new viral particles. These vectors are developed upon the deletion of one or more genes related to virus replication, synthesis, or assembly. Its *in vitro* production is made through cell lineages that express, in a complementary manner, the genetic material absent in the virus and necessary for its replication.

The non-replicating viral vectors express the antigen of interest and induce an adaptive immune response by the route of antigen presentation through surface molecules related to the major histocompatibility complex (MHC), as well as by the route of the innate immune response, which act as adjuvants. These vaccines tend to be safe and cause a strong immune response, however, pre-existing immunity may affect the efficacy of the vaccine. Figure 1, presented below, is illustrative of replicating and non-replicating viral vectors. [2], [3]

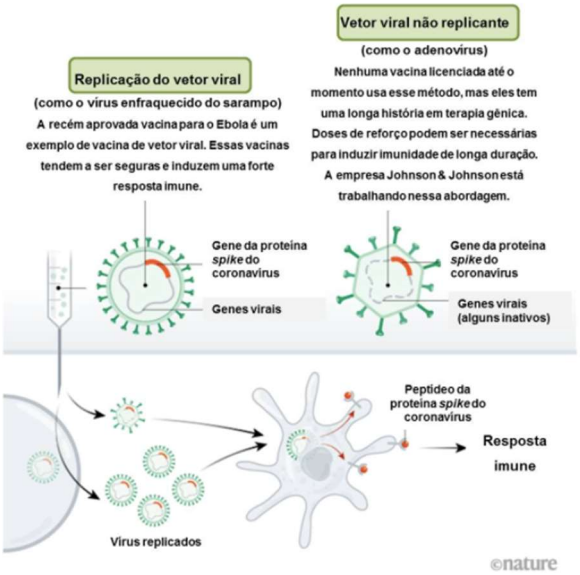

Figure 1 – adapted and translated from Callaway, E. (2020)[1]

The urgency to develop vaccines to restrain the transmission of SARS-COV-2, the causative agent of COVID-19, produced some vaccines and a series of vaccine candidates that are currently under clinical trials. The World Health Organization – WHO provides the landscape of vaccines against COVID-19 under development, compiling detailed information regarding the vaccine platform, vaccination schedule, route of administration, developer, and clinical trial phase.[2] The candidate vaccines under development using the viral vector technology that are in a more advanced development phase and will be the target of this study are listed in Table 1.

Table 1. Vaccines for protection against COVID-19 based on viral vector technology in more advanced clinical trial phases (Phases 2 to 4).

1 Original figure in English https://www.nature.com/articles/d41586-020-01221-y

Figure translated to Portuguese: https://profissaobiotec.com.br/5-tecnologias-desenvolvimento-vacina-covid19/ https://profissaobiotec.com.br/5-tecnologias-desenvolvimento-vacina-covid19/

2 https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

Description of the vaccine platform	Candidate vaccine	Number of doses	Interval between doses	Route of administration	Developers	Clinical trial phase
Non-replicating viral vector	ChAdOx1-S – (AZD1222) (Covishield)	1-2	Day 0 + 28	Intramuscular	AstraZeneca; University of Oxford	Phase 4
Non-replicating viral vector	Ad26.COV2.S	1-2	Day 0 or Day 0 + 56	Intramuscular	Janssen Pharmaceutical	Phase 4
Non-replicating viral vector	Gam-COVID-VacAdeno-based (rAd26-S+rAd5-S) Sputnik	2	Day 0 + 21	Intramuscular	Gamaleya National Research Center for Epidemiology and Microbiology; Ministry of Health of the Russian Federation	Phase 3
Non-replicating viral vector	Recombinant novel coronavirus vaccine (Ad 5)	1	Day 0	Intramuscular	CanSino Biological Inc./Beijing Institute of Biotechnology	Phase 4
Non-replicating viral vector	GRAd-COV2 (Replication defective Simian Adenovirus (GRAd) encoding S)	1	Day 0	Intramuscular	ReiThera; Leukocare; Univercells	Phase 2/3
Replicating viral vector	DelNS1-2019-nCoV-RBD-OPT1 (Intranasal flu-based-RBD)	2	Day 0 + 28	Intranasal	University of Hong Kong; Xiamen University; Beijing Wantai Biologica Pharmacy	Phase 2

Source: Created by the researchers based on data from the World Health Organization.[3]

2. PURPOSE

On January 30, 2020, the WHO declared that the new coronavirus outbreak is a Public Health Emergency of International Concern (PHEIC) – the Organization's highest alert level.[4] This study aims at presenting the technologies involved in developing the vaccines based on viral vectors under clinical trials for immunization against the SARS-COV-2 virus, which causes COVID-19.

Based on the description of the technologies, we sought to link these vaccines to the patent applications that could be closely related to the latest developments by the engaged institutions, although the actual vaccine patents have probably not been published yet, given the 18-month confidentiality period.

3. METHODOLOGY

The strategy employed in this study was created based on the list of vaccines whose development was already in advanced clinical trial phases, as explained on the World Health Organization's website. The six vaccines presented in Table 1 were selected.

The survey of patents and/or patent applications was conducted on the Derwent Innovations Index base by using the name(s) of the institution(s) that developed them. The efforts were concentrated on the analysis of the patent documents filed by the institution indicated as "originator" by the Integrity/Clarivate database and on those referred to as developers by the World Health Organization in 'COVID-19 vaccine tracker and landscape'.[5]

In cases in which the number of applications from the research institution was very large, patents were selected through patent classification codes (the International Patent Classification (IPC) and the Cooperative Patent Classification (CPC)) and keywords according to the technology described by the developers for the vaccines analyzed. After that, the applications were evaluated as to their relevance to this study by reading the titles, abstracts, and claims.

The documents found during search and deemed most relevant will be referred to throughout the text for each vaccine, one representative per patent family. In case of a Brazilian equivalent document in the family, such document will be preferably referred to.

Information on the bibliographic data of the applications was collected from the Derwent Innovation™ database, which provided INPI with its information for dissemination. The platform initiative was to collaborate with INPI in actions that directly or indirectly contribute to the search for solutions for treating the COVID-19 pandemic.

The work results are also available in spreadsheets in Excel format for better user analysis. The accompanying spreadsheets are composed of the list of patent applications addressing the technologies related to each viral vector vaccine candidate.

4. RESULTS AND DISCUSSION

As the technological developments fostered as a result of the coronavirus pandemic are quite recent and patent

3 https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

4 https://www.paho.org/pt/news/30-1-2020-who-declares-public-health-emergency-novel-coronavirus

5 https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

applications have an 18-month confidentiality period, we understand that, in their majority, the patent applications related to SARS-COV-2 are not yet public. Nevertheless, considering that the vaccines under development against COVID-19 described in this study are based on pre-existing viral vector platforms, this study aims at identifying the patents of these platforms that enabled the institutions in charge to achieve the products that are currently in the clinical trial phase. Many of them have already been approved by the regulatory agencies and are used in several countries, including Brazil.

4.1 UNIVERSITY OF OXFORD/ASTRAZENECA (ChAdOx1-S / AZD1222 / Covishield / Vaxzevria)

The ChAdOx1-S vaccine, also referred to as AZD1222, Covishield, or Vaxzevria, was developed by the University of Oxford in a partnership with AstraZeneca. Such vaccine was based on a chimpanzee adenovirus serotype Y25 (ChAd), which was modified by recombinant DNA technology using an *Escherichia coli* bacteriophage λ to replace the sequences from the E4 region, orf4, orf6, and orf6/7, for those of the HAdV-5 human adenovirus, originating the non-replicating ChAdY25-E viral vector, renamed as ChAdOx1. [4] Because it uses, as a platform, a virus to which human beings are not naturally exposed, the ChAdOx1 viral vector reduces the possibility of the immunity against the vector to reduce the performance of the vaccine.

The ChAdOx1 vector had already been used in candidate vaccines for several infectious diseases (malaria, human immunodeficiency virus (HIV), tuberculosis, influenza, hepatitis C, respiratory syncytial virus (RSV), and Ebola), including a potential vaccine against the MERS (Middle East Respiratory Syndrome) coronavirus, ChAdOx1-MERS-CoV-S, in an early clinical trial phase. (clinicaltrials.gov/ct2/show/NCT03399578) [5] There are also some patents from these developers that describe the use of the viral vector technology for cancer, some autoimmune, or neurological disease gene therapy.

In the vaccine against COVID-19, the ChAdOx1 viral vector was modified to express the Spike (S) glycoprotein of the SARS-CoV-2 virus complete sequence, modified to optimize codons, connected to a tissue plasminogen activator (tPA) leader sequence. [6] ChAdOx1 was deemed to be safe and immunogenic, capable of generating a cellular and humoral immune response against the SARS-COV-2 virus, and a booster dose to increase the titles of neutralizing antibodies is necessary, presenting an efficacy of 70% in the phase-III clinical trials. Multicentric phase-III and IV clinical trials are currently in progress.

Still at the end of 2020, the vaccine was approved for emergency use in the United Kingdom, and soon after was approved by the European Medicines Agency **(**EMA). In Brazil, the emergency use of the AZD1222 vaccine by the Brazilian Health Surveillance Agency – ANVISA was approved in January 2021, requested by Fundação Oswaldo Cruz – Fiocruz,[6] an institution that established an agreement with the vaccine developers for production and transfer of technology of this vaccine. The vaccine approved for use is applied through intramuscular injection in two doses.

In March 2021, questions regarding the safety of the vaccine were raised due to some individuals that presented thrombosis, leading to the discontinuation of its use in some European countries.[7] The World Health Organization (WHO) issued a statement affirming that safety data related to the vaccine would be reviewed together with the regulatory agencies, but also affirmed that it recommended that vaccinations continued for considering that the benefits outweighed the risks.[8]

The Derwent database was searched using a strategy that combined CPC and IPC related to this vaccine technology (A61K39 or C12N15 or A61K48) associated with terms that identified the Universities and pharmaceutical company involved, Oxford and Isis Innovation. Thereafter, a selection was made by identifying the term 'ChadOx' in the text fields (title, abstract, claims), and 87 documents were identified (DWPI/INPADOC families), which were then analyzed by reading titles, abstracts, and claims, generating a total of 15 documents deemed relevant and related to the development of the vaccine.

Among the patent applications filed by the University of Oxford, documents directly related to the ChAOx1-S vector and that mentioned this nomenclature were identified. There is also the description of other vectors based on adenoviruses, and these were selected given their relation with the description of technologies deemed close to the vaccine developed by the University of Oxford with pharmaceutical company AstraZeneca.

One of the latest patent applications, WO2018215766, is related to a vaccine for protection against the Middle East respiratory syndrome Coronavirus, MERS-CoV. This application describes the adenovirus-based vector ChAdOx 1 in which the spike (S) of the coronavirus is present as a fusion protein with the tissue plasminogen activator (tPA) sequence in the order N-terminal – tPA – spike protein – C-terminal.

The technology dates back to older patent applications from 2008 and 2009, such as WO2008122811 and WO2009044165, which are related to a molecular adjuvant, a component of the TLR signaling pathway, a co-stimulatory molecule, and an NKG2D ligand, IL-7 or IL-15.For the former, the equivalent application filed in Brazil is PI0810163.For the latter, no equivalent application filed in Brazil was found.

Patent document BR112013030222 describes the use of the capsid protein of the chimpanzee adenovirus AdY25 to encapsulate a nucleic acid molecule containing an exogenous nucleotide sequence of interest. This cassette then becomes linked to expression control sequences that direct translation, transcript, and/or expression in the host cells and an adenovirus packaging signal sequence.

There are also other applications describing two different vectors being used in the first and second doses of the vaccine in the same patient. The purpose of using a prime-

6 https://www.gov.br/anvisa/pt-br/assuntos/paf/coronavirus

7 https://www.euronews.com/2021/04/20/how-have-different-european-countries-reacted-to-the-astrazeneca-vaccine-doubts

8 "WHO statement on AstraZeneca COVID-19 vaccine safety signals". World Health Organization (WHO). 17 March 2021.

boost of the vaccine with a different vector is to induce a better immune response to the pathogen of interest, preventing the patient's immune response to the vector itself. Most of the time, the prime-boost vector is the modified vaccine Ankara (vaccine, poxvirus), or MVA. On this technology, we highlight patent applications BR200014138 (WO2001021201), WO2015082922, WO2015052543, and WO2019219851.

Other patent applications were deemed to be relevant, as they contain the term "prime-boost". Namely: WO2011128704, WO2014053861, WO2004110485, WO2011098837, WO2008122817, WO2001012829, WO2003047617.

4.2 JANSSEN PHARMACEUTICAL COMPANIES (Ad.26.COV2.S, recombinant/JNJ- 78436735)

The Ad26.COV2.S vaccine was developed by the company Janssen Vaccines, formerly Crucell (a company acquired by Johnson & Johnson), and Janssen Pharmaceuticals, both subsidiaries of the company Johnson & Johnson. The vaccine was produced based on non-replicating viral vector Ad26, created from human adenovirus serotype 26 (Ad26), a virus considered to have a low prevalence in the population and that causes low neutralizing antibody titles capable of blocking its use as a viral vector for clinical application. For creating the vector, Ad26 was modified through deletion in the E1 and E3 genes to turn it incapable of replicating, in addition to other genetic alterations in order to optimize heterologous gene expression and production of the vector. Another alteration is the deletion of the Ad26 E4-orf6 sequence, which is replaced by the corresponding Ad5 sequence.

The Ad26 viral vector has been used in candidate vaccines against several diseases, such as those caused by Ebola (Ad26.ZEBOV), HIV (Ad26.ENVA.01, Ad26.Mos.HIV, Ad26.Mos4.HIV), respiratory syncytial virus or RSV (Ad26.RSV.FA2 and Ad26.RSV.preF) viruses, and the protozoan that causes malaria (Ad26.CS.01). [8] The vaccine regime against Ebola, consisting of two viral vector-based vaccines: Zabdeno (Ad26.ZEBOV) and Mvabea (MVA-BN-Filo), was granted market authorization of the European Commission in July 2020.[9]

In the vaccine against COVID-19 Ad26.COV2-S, viral vector Ad26 is modified to express the Spike (S) protein of the SARS-CoV-2 virus in a stabilized way.

The Spike protein of the coronavirus changes its conformation during infection, and when it modifies its three-dimensional structure, it changes the exposure of its antigenic sites. The protein expressed by the viral vector in the Ad26.COV2-S vaccine is modified to stabilize it so that the conformation of the protein is not changed from its pre-fusion form to its post-fusion form. Thus, the wild type sequence of the protein is modified with stabilizing mutations in two residuals for proline (K986 and V987), as well as mutations at the cleavage site by furin (from RRAR to SRAG). [9], [10]

The Ad26.COV2-S vaccine, currently under phase-IV clinical trials, proved to be 85% effective in the prevention of severe COVID-19 cases in all multicentric clinical trial regions. [10] The vaccine was approved for use in several countries with intramuscular injection of a single dose. In February 2021, the Food and Drug Administration – FDA, a US Agency, granted authorization for emergency use of the vaccine, and EMA, a European Agency, authorized its use in March. In Brazil, the emergency use of the vaccine, requested by Janssen-Cilag, was approved by ANVISA in March 2021.[11] In April 2021, FDA and the Center for Disease Control and Prevention – CDC recommended that the application of the vaccine was paused, due to the occurrence of cerebral venous sinus thrombosis (CVST) in individuals that have received the vaccine.[12]

Considering that the Ad26.COV2-S vaccine was developed by the company Janssen (formerly Crucell), a search for such institutions was carried out in the Derwent database. After selection using selected IPCs and CPCs (A61K39, C12N15, or A61K48), a filter for the keyword "adenovirus" was applied in the text fields (title, abstract, claims) and 388 DWPI patent families were identified, which were then analyzed by reading titles, abstracts, and claims, generating a total of 85 documents deemed close to the description of the technology of this vaccine.

The most relevant documents found, possibly related to the vaccine against COVID-19 that has been developed by Janssen, will be listed below. Document WO2007104792 describes the replication-defective viral vector Ad26, with a deletion in E1 and E3 and the replacement of E4-orf6 region for Ad5 E4-orf6.

In this document, the rAd26 adenoviral vector expressing viral antigens is used as an immunogen for HIV. It is also worth highlighting the preceding documents, WO2000070071 and EP1816204, which describe the replication-defective recombinant adenovirus serotype 26.

Furthermore, specifically related to the rAd26 vector, we found documents BR112012019023 and BR112012019023, which are related to methods for its production, and document BR112016005761, on formulations containing rAd26 to preserve adenoviruses in vaccines.

There are also other documents describing the technology more generally, and related to the creation of adenoviral vectors (BR200308783, WO1999055132, BR112018075969, WO2016166088, BR112014022323, WO2004001032, BR112018072865, BR112019015671), as well as those related to the production and/or purification of the vectors, including the use of complementary cells PER.C6 (US9228205, US7527961, PI0409895, US6974695, BR112019015671, US20080199433, EP1108787, WO2001005945, PI0015846, WO2004104190, BR200414670, WO2005080556, WO2006108707,

9 European Commission. Vaccine against Ebola: Commission grants new market authorisations. July 1 2020. https://ec.europa.eu/commission/presscorner/detail/en/ip_20_1248

10 https://www.nih.gov/news-events/news-releases/janssen-investigational-covid-19-vaccine-interim-analysis-phase-3-clinical-data-released

11 https://www.gov.br/anvisa/pt-br/assuntos/paf/coronavirus

12 https://www.fda.gov/news-events/press-announcements/joint-cdc-and-fda-statement-johnson-johnson-covid-19-vaccine

BR112012008507, BR112012008516, WO2000032754, WO2002040665, US7344883).

Several immunizing agents using the Ad26 adenoviral vector, alone or in combination with other viral vectors, were developed against different pathogens, such as HIV (BR112017005917, US10973907, US10525123, BR112018011122, WO2018045267, WO2015128421, BR112019026126, WO2020064621, WO2019055888, WO2019018724, WO2009065800); filovirus/Ebola (BR112013014712, BR112017004202, BR112017003891, WO2016187613, WO2018011768, WO2018011198, WO2018185732); RSV (BR112018070323, BR112014023196, BR112020004143, WO2018210871, BR112014023195, WO2020229579, WO2020229577); HPV (US10555996, US10071151, BR112017009177, US20200164057, US10287323, BR112018003019, WO2018011196, BR112018072372); zika (BR112020007884, BR112021000274); HBV (US11020476, BR112020012273, BR112020011976); influenza (BR112020014343); malaria (BR112013004582, WO2017125463), and tuberculosis (WO2012038367, PI0518933).

4.3 GAMALEYA RESEARCH INSTITUTE (Gam-Covid-Vac / Gam-Covid-Vac adeno-Based (rAd26-S+rAd5-S) / Sputnik V)

The Sputnik V vaccine was developed by the Gamaleya National Research Center for Epidemiology and Microbiology of the Ministry of Health of the Russian Federation. The vaccine was produced based on two non–replicating viral vectors, one vector created from the human adenovirus serotype 26 – Ad26 and the other vector created from the widely disseminated human adenovirus serotype 5 – Ad5.Both rAd26 and rAd5 viral vectors are modified to carry the complete gene to the glycoprotein (spike) and referred to as rAd26-S and rAd5-S. [11]

The strategy adopted in the development of Sputnik V is the heterologous prime-boost type of vaccination, in which the individual is immunized twice, with a different type of immunizing agent at each time. As mentioned above, the use of a type of adenovirus at the initial sensitization dose (prime) and a different type at the booster dose (boost) aims at reducing the negative effect related to the immune response caused by the components of the vector itself, which could mitigate the response induced by the vaccine antigen. This strategy had already been developed before in the Gamaleya National Research Center for Epidemiology and Microbiology for the vaccine against Ebola, registered with the Ministry of Health of Russia,[13] containing VSV and Ad5 vectors, both expressing the envelope glycoprotein of the Ebola virus. [12] The vaccines containing rAd26-S and rAd5-S vectors are administered through the intramuscular route with an interval of 21 days between them.

The Sputnik V vaccine is currently under phase-III clinical trials in several countries and was considered to be safe and capable of inducing humoral and cellular immune response in the individuals who have received the immunizing agent. The provisional analysis of phase-III data revealed that the vaccine had a 91.6% efficacy against COVID-19. [13]The authorization for emergency use of the vaccine was registered in Russia still in August 2020.

In Brazil, the request for emergency use of the Sputnik V vaccine was filed by pharmaceutical company União Química and is currently under analysis by ANVISA. [14] The patent application for the vaccine with EMA, a European Agency, was initiated in March 2021 and also is under analysis.[15] More recently, in May 2021, the Sputnik Light vaccine was approved for emergency use by the Ministry of Health of Russia. It is a single-dose version of the vaccine, which is composed of the primary component (recombinant human adenovirus serotype 26 (rAd26-S)) of the Sputnik V vaccine.[16, 17]

Considering that the Sputnik vaccine was developed by the Gamaleya National Research Center for Epidemiology and Microbiology and by the Ministry of Health of Russia, the search for such institutions was carried out in the Derwent database. After selection using selected IPCs and CPCs (A61K39, C12N15, or A61K48), 70 DWPI patent families were identified, which were then analyzed by reading titles, abstracts, and claims, generating a total of 11 documents deemed relevant for development of this vaccine.

The most relevant documents found, possibly related to the vaccine against COVID-19 that has been developed by the Gamaleya National Research Center for Epidemiology and Microbiology, are documents WO2021002776, WO2021076009, and WO2021076010.

They are specifically related to immunogens against SARS-COV-2, claiming the viral vectors and immunogens, consisting of the human adenovirus Ad5-based viral vectors, in which E1 and E3 regions were deleted, and human adenovirus Ad26, in which E1 and E3 regions were deleted and ORF6-Ad26 region was replaced by ORF6-Ad5, as well as simian adenovirus serotype 25 (simAd25), in which E1 and E3 regions were deleted, and such vectors contained different sequences encompassing the S protein of the SARS-COV-2 virus.

There are also four documents specifically related to immunogens against SARS-COV-2: documents RU2743963 and RU2743962, which claim the lyophilized and liquid forms of the immunogens, and documents RU2744442 and RU2744444, which claim the use of the immunogens for individuals over 60 years old and with chronic diseases, as well as for booster vaccination.

Among the other documents selected, there are also the ones describing technologies that are close to those described for the vaccine but applied to other pathogens. There is document RU2709659, which addresses immunogens consisting of viral vectors produced from

13 https://gamaleya.org/en/research/ebola/

14 https://www.gov.br/anvisa/pt-br/assuntos/paf/coronavirus

15 https://www.ema.europa.eu/en/news/ema-starts-rolling-review-sputnik-v-covid-19-vaccine / https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/covid-19-vaccines

16 https://www.bioworld.com/articles/506893

17 https://sputnikvaccine.com/prt/about-vaccine/

recombinant Ad5 and Ad26 containing different sequences encompassing the S protein of the MERS-CoV virus. In addition to this, we found documents WO2016130047, which addresses immunogens created from the replicating-defective recombinant viral vector Ad5 expressing Ebola virus antigens, and WO2016159823, which addresses two different immunogens, one produced from the attenuated vesicular stomatitis virus (VSV) and the other from the replicating-defective recombinant Ad5, both encoding the glycoprotein (GP) of the Ebola virus. Document RU2016118518 presents an immunogen against chlamydia applied as prime-boost with the viral vector Ad5 expressing the antigen as the initial sensitization dose and a later booster with the antigen recombinant protein.

4.4 CANSINO BIOLOGICAL / BEIJING INSTITUTE OF BIOTECHNOLOGY (Ad5-nCoV / Recombinant Novel Coronavirus Vaccine (Adenovirus type 5 Vector) / Convidecia / Convidicea)

The Ad5-nCoV vaccine was developed by the company CanSino Biologics, together with the Beijing Institute of Biotechnology/ Academy of Military Medical Sciences. The vaccine was produced based on the non-replicating viral vector Ad5, created from human adenovirus C serotype 5 (HAdV-5), which causes the common cold.

In the manufacturing of the vaccine, the Ad5 viral vector, with deletions in E1 and E3 regions, and insertion of the optimized Spike (S) glycoprotein sequence of the SARS-CoV-2 virus linked to the tissue plasminogen activator (tPA) signal peptide, a heterologous sequence commonly used to increase the expression levels of recombinant proteins in host cells, was used. [14]

The adenoviral vector Ad5 had already been used previously in the development of other vaccine by CanSino Biologics, Ad5-EBOV, which uses the replicating-defective adenovirus type 5 vector, expressing the Ebola virus glycoprotein, and was authorized in China, still in 2017, to foster protection against the Ebola virus.[18]

The vaccine, which is currently under phase-IV clinical trials, was considered to be safe and induced significant immune response in the individuals vaccinated with a single dose of the immunizing agent. [15] The provisional analysis of the phase-III trials revealed that the vaccine had a 65.7% efficacy in prevention of moderate cases and 90.98% in prevention of severe cases.[19] In June 2020, the vaccine was approved in China for military use and subsequently authorized for general use in February 2021.[20] In Brazil, the request for emergency use of the vaccine was filed in May 2021 by company Belcher Farmacêutica, representative of the Chinese laboratory CanSino Biologics in Brazil and is currently under analysis by ANVISA. [21]

Considering that the Ad5-nCoV vaccine was developed by the company CanSino Biologics together with the Beijing Institute of Biotechnology of the Academy of Military Medical Sciences (China), the search for patent documents filed by such institutions was carried out in the Derwent database. After selection using selected IPCs and CPCs (A61K39, C12N15, or A61K48), a filter for the keyword "adenovirus" was applied in the text fields (title, abstract, claims) and 77 DWPI patent families were identified, whose documents were then analyzed by reading titles, abstracts, and claims, generating a total of 17 documents considered relevant for development of this vaccine.

The most relevant document found, possibly related to the vaccine against COVID-19 that has been developed by company CanSino Biologics, is document CN111218459, which specifically addresses immunogens for SARS-COV-2. The document presents an immunogen for vaccine production, created from a replication-defective recombinant Ad5 vector, with deletions in E1 and E3 regions, into which the optimized S protein sequence of the novel coronavirus was inserted.

The viral vector Ad5 was created using the company Microbix Biosystem's Admax system. Document CN112094814, which was also deemed relevant, presents a method for culture of host cells used for adenovirus replication, especially the recombinant adenovirus that expresses a structural protein of the SARS-COV-2 virus.

Among the other documents selected, some describe a technology close to those described for the vaccine but applied to other pathogens, such as documents EP3342865 and WO2018103601, which describe the immunogen against the Ebola virus created from the optimized envelope glycoprotein (GP) of the Ebola virus, inserted into a replication-defective adenovirus vector. In this document, the Ad5 viral vector was also created using the Admax system. Documents WO2019214110 and CN108018298, in their turn, use the same system to produce, respectively, immunogens against *Mycobacterium tuberculosis* and the Marburg virus. There also documents CN103045630, CN103045545, CN103014063, CN103014044, CN102964433, CN101967186, and CN101967185, which are related to immunogens for viral encephalitis or the rabies virus produced with replication-defective recombinant Ad5 viral vector, using other adenoviral vector (Ad5) production systems, such as AdEasy.

It is also worth highlighting document WO2019042307, which describes a cell strain (HEK293.CS) for reduction in replication-competent adenovirus (RCA) production during large-scale recombinant Ad5 culture for vaccine production.

Considered less relevant for development of the Ad5-nCoV vaccine are documents CN109295096, which addresses a new adenoviral vector (Ad5) system encompassing two plasmids (pKAd5f11p-EF1aP and pKAd5f11pES-PmeI) for preparation of recombinant vaccines, and document CN103160538, which describes a method for preparation of adenoviruses using calcium chloride and disodium phosphate to protect adenovirus particles from the

18 https://www.nature.com/articles/d42473-018-00219-5. ADVERTISEMENT FEATURE A best shot at global public health response

19 https://www.bloomberg.com/news/articles/2021-02-08/pakistan-says-cansino-s-covid-vaccine-shows-65-7-efficacy

20 https://www.reuters.com/article/us-health-coronavirus-china-vaccine-idUSKBN2AP1MW

21 https://www.gov.br/anvisa/pt-br/assuntos/paf/coronavirus

immune system and the antibodies. Finally, document CN111217917 addresses a fusion protein encompassing the receptor-binding domain (RBD) of the SARS-COV-2 virus, a linker, and CTB or CRM197, which may be used in adenoviral vector vaccines.

4.5 REITHERA (Grad-Cov2 (Replication Defective Simian Adenovirus (Grad) Encoding S)

GRAd-COV2 is a candidate vaccine developed by the company ReiThera based on a newly isolated gorilla adenovirus species C, from which the replication-defective adenoviral vector referred to as GRAd32 was then created. Simian-derived adenoviruses are known for not infecting or causing diseases in human beings and, therefore, having low or no seroprevalence in the human population.

The GRAd-COV2 viral vector was created upon deletion of E1 and E3 regions in order to make the virus replication-defective and increase its cloning capacity. Additionally, the E4 region was also deleted and replaced by the E4-orf6 region of the human Ad5 in order to optimize viral production, originating the GRAd32c vector.

In the GRAd-COV2 (GRAd32c-S-2P) candidate vaccine, a modified version of the Spike (S) protein of the SARS-COV-2 virus, stabilized and in its pre-fusion (S-2P) form, was inserted into the viral vector by replacing proline in two residuals (K986P and V987P), plus an influenza hemagglutinin (HA) tag in the C-terminal. [16] The developed formulation establishes intramuscular injection in a single dose.

The GRAd-COV-2 vaccine is currently under phase-II/III clinical trials to assess its efficacy, safety, and immunogenicity in adults, both on the single-dose and the two-dose regime.[22]

This candidate vaccine has been developed by the company ReiThera, formerly Okairos, which was acquired by the pharmaceutical company GlaxoSmithKline. Considering such information, the names of the three companies were searched for in the Derwent database. After selection using selected IPCs and CPCs (A61K39, C12N15, or A61K48), a filter for the keyword “adenovirus” was applied in the text fields (title, abstract, claims) and 115 DWPI patent families were identified, whose documents were then analyzed by reading titles, abstracts, and claims. No documents indicating ReiThera as the applicant were retrieved. No documents related to gorilla-derived viral vectors or referring to the SARS-COV-2 virus were found either.

There is a high probability that, in case there is a patent application for this vaccine filed by ReiThera, it is still in the confidentiality period (18 months after filing).Nevertheless, 43 documents related to the chimpanzee-derived simian adenoviral vector technology developed by the companies GlaxoSmithKline and/or Okairos were identified. Documents owned by these companies describing the use of these adenoviral vectors in immunization against several pathogens, their production processes, and immunogenic formulations based on such adenoviral vectors were also verified.

Among such documents, it is possible to highlight documents PI1008018, BR112018001683, BR112017026523, BR112019003462, BR112019010906, BR112017026639, and BR112020024285, which address chimpanzee-derived, replication-defective adenoviral vectors (ChAd3, ChAd155, Chad157, among others), presenting deletion in E1 and E3 regions and also in the E4 region, the latter replaced by the E4-orf6 region of the Ad5 virus.

4.6 BEIJING WANTAI BIOLOGICAL PHARMACY/XIAMEN UNIVERSITY/UNIVERSITY OF HONG KONG (DelNs1-2019-Ncov-Rbd-Opt1 (Intranasalflu-Based-RBD))

DelNS1-2019-nCoV-RBD-OPT1 is a candidate vaccine developed by the University of Hong Kong and Xiamen University, as well as by the company Beijing Wantai Biological Pharmacy. The vaccine is based on a replicating viral vector and uses the live attenuated influenza virus (LAIV)-based platform, containing a deletion in the non-structural protein 1 (NS1), a central element for viral virulence and immune antagonists. Also referred to as DelNS1-SARS-CoV-2-RBD, in this candidate vaccine, the viral vector is modified to express the Spike (S) protein of the receptor binding domain (RBD) of the SARS-CoV-2 virus.In addition to using a replicating viral vector, another differential aspect of this vaccine is its administration through the intranasal route. This live attenuated influenza virus-based viral vector model was used by the University of Hong Kong for creation of an immunogen against the MERS-CoV virus, the causative agent of the Middle East respiratory syndrome (MERS), DelNS1-MERS-RBD LAIV, which proved itself to be an effective vaccine in an animal model.[23] The DelNS1-MERS-RBD LAIV vaccine encompasses an attenuated H1N1 A influenza virus (California(CA)/04/09) that is adapted to the cold and replicating-competent, expressing the S protein receptor binding domain (RBD) of the MERS-CoV virus, as well as presenting deletion at the positions 56-529 in the NS1 protein region, a mutation in the nucleoprotein (NP) at the position D101N, and a mutation in the NS-region nuclear export protein (NEP) at positions L79V and E95G. [24]

The candidate vaccine DelNS1-2019-nCoV-RBD-OPT1 is currently under phase-II clinical trials to assess the immunogenicity and safety, as well as the effect of pre-existing immunity to H1N1 influenza virus in the immunogenicity of the vaccine.[25]

In order to search for the documents related to the DelNS1-2019-nCoV-RBD-OPT1 vaccine, it was considered that it was developed by the University of Hong Kong, Xiamen University, and also by the company Beijing Wantai Biological Pharmacy. The Integrity/Clarivate database has only information on the MERS-RBD-DelNS1 vaccine, in which the organization Emerging Viral Vaccine appears as the developer, and it was also included in the scope of the search. Therefore, such institutions were searched for in the Derwent

22 Study of GRAd-COV2 for the Prevention of COVID-19 in Adults – ClinicalTrials.gov / https://clinicaltrials.gov/ct2/show/NCT04791423

23 https://www.hku.hk/press/press-releases/detail/20788.html

24 Integrity/Clarivate – DelNS1-MERS-RBD

25 ChiCTR2000039715 http://www.chictr.org.cn/showprojen.aspx?proj=63754

database. After selection using selected IPCs and CPCs (A61K39, C12N15, or A61K48), a filter for the keywords "influenza" or "live-attenuated" was applied in the text fields (title, abstract, claims) and 38 DWPI patent families were identified, which were then analyzed by reading titles, abstracts, and claims, generating a total of 4 documents considered relevant for development of this vaccine.

The most relevant document found, possibly related to the vaccine against COVID-19 that has been developed by the company Beijing Wantai Biological Pharmacy, was WO2017184626. The document describes an attenuated virus for production of vaccines that consists of the influenza virus H1N1 encompassing a deletion of nucleotides 57 to 528 in NS1 protein (DelNS1) and also has other mutations that enable its replication in MDCK cells into embryonated eggs in the absence of the virulence factor and adaptation to the cold (NP position G346A (D101N) and NEP position T261G (L79V) and A310G (E95G)). The document claims the viral vector, in which the S protein receptor binding domain (RBD) of the MERS-CoV virus is inserted, for use as a vaccine against MERS, and it is expected to be administered through the intranasal route.

Other relevant documents found were WO2016192670 and WO2016074644, which address attenuated influenza viruses, including H1N1, with a deletion in the NS1 protein (DelNS1) and replacement of bases in the matrix protein sequence of the virus for use in immunization, and document WO2020097923, which describes an attenuated influenza virus B (LAIV B) encompassing a deletion in the region that encodes the NS1 protein and other mutations, such as PA (T210C), NA (T1424C), NP (C182T), and M (A281G), in which the immunogenic composition is claimed, and it is expected to be administered through the intranasal route.

FINAL CONSIDERATIONS

This study presents a photograph of the viral vector-based COVID-19 vaccine developing companies' know-how to date and, therefore, it is limited to the publication date of the documents until June 18, 2021.

The study reflects the patent documents related to the viral vector-based vaccines technology filed by the institutions (universities, pharmaceutical companies) involved in their development. This study was based only on vaccines that already are in the most advanced phases of the immunogen clinical trials. The products (actual vaccines) that are currently available on the market need to be approved by each country or region's regulatory institutions (ANVISA in Brazil; EMA in Europe; FDA in the United States, and so on). That was done, and some of these vaccines have already been approved and are being applied in the population.

Reading titles and abstracts brings to light a selection of patent documents that is not an exhaustive list but reflects the analysis and categorization of data based on the search strategy developed by the team.

The production of vaccines and biological products is a complex process. Thus, it is very likely that other documents are relevant to carry out the production process from beginning to end and were not contemplated in this analysis. These applications may address, e.g., important adjuvants, excipients, types of conservation of products, production of primary and secondary cell and virus seed lots (working lots). Hence, it is important to emphasize that the mentioned and attached documents do not represent, to any extent, an exhaustive list regarding the patents related to the production of vaccines and, therefore, it is not an analysis of freedom to operate (FTO).

It is worth noting that the Oxford/Astrazeneca vaccine was the object of technological order (ETEC) agreements [26] between the vaccine developers and Bio-Manguinhos, the technical unit of the Oswaldo Cruz Foundation – Fiocruz, so that the vaccine is produced in Brazil. However, it is not possible to directly connect the patents that were the object of licensing in this agreement and the patents described in this study, mainly because they are very recent and still confidential.

It is worth mentioning that, in the sample assessed by INPI, the applications mentioned in Vax Pal, a website dedicated to COVID-19-related vaccines and produced by Medicines Patent Pool, [27] were included.

The search strategy established and the method followed in this study may be applied from time to time for an update of these data over time.

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26 On the documents: . https://portal.fiocruz.br/vacina-covid19-contratos-e-documentos. To learn more about the purchase of innovative solutions by the Brazilian government, see details on https://www.youtube.com/watch?v=ba3rNNr02wM.

27 https://medicinespatentpool.org/what-we-do/disease-areas/vaxpal/

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