Review

The First Approved COVID-19 Vaccines: The Road to Cancer Vaccines

Leonor Saldanha [1] and Nuno Vale [1,2,3,*]

1 OncoPharma Research Group, Center for Health Technology and Services Research (CINTESIS), Rua Dr. Plácido da Costa, 4200-450 Porto, Portugal; leonorpessanha@gmail.com
2 Department of Community Medicine, Health Information and Decision (MEDCIDS), Faculty of Medicine, University of Porto, Alameda Prof. Hernâni Monteiro, 4200-319 Porto, Portugal
3 CINTESIS, Faculty of Medicine, University of Porto, Al. Prof. Hernâni Monteiro, 4200-319 Porto, Portugal
* Correspondence: nunovale@med.up.pt; Tel.: +351-220426537

Abstract: In the past decade, mRNA vaccines have been highly discussed as a promising therapy for cancer. With the pandemic of COVID-19, some researchers redirected their studies to the development of a new vaccine for COVID-19 due to the urgent need. With the pandemic's deceleration due to the vaccines' success, the research and development of mRNA vaccines have turned to cancer again. Considering the new evidence and results generated by the vaccination of millions of people with mRNA vaccines, this article intends to provide a perspective on how the results from COVID-19 vaccination could now provide new insights for the development of an mRNA cancer vaccine. Many lessons were learned, and new evidence is available to re-focus and enhance the potential of the mRNA technology to cancer. Pfizer-BioNTech and Moderna's mRNA technologies, and their significant advancements, allowed mRNA to overcome many of the challenges and blockers related to this platform in the past, now providing a new breadth of hope on using the mRNA technology to treat many diseases, namely cancer. This study also reports a better understanding of how it was possible to boost an accelerated development process of COVID-19 vaccines from a regulatory point of view. It is also relevant to consider other synergies and factors that contributed to gathering all the conditions ensuring the development of these vaccines in such a short period. Suppose the same efforts from all stakeholders could be applied to the development of new cancer vaccines, aligned now with the new scientific evidence generated from the current mRNA vaccines for COVID-19. In that case, mRNA cancer vaccines are near, and a new era for cancer treatment is about to begin.

Keywords: COVID-19; SARS-CoV-2; vaccines; mRNA; cancer

1. Introduction

The pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been assigned as a serious threat to public health which also led to a social and economic crisis in the world. It was the cause of millions of deaths and also caused many constraints in the world's style of living. The development of a safe and effective vaccine was urgent to the ensure the global health and to bring back the sense of normality to everyone.

It is important to understand that vaccines hold a global health success history as they assumed control over many infectious diseases and therefore millions of deaths are avoided per year. Vaccination has eradicated smallpox, reduced global child mortality rates, and prevented countless birth defects and lifelong disabilities such as polio and rubella. A lot of diseases can be prevented by vaccines [1]. Along with clean water, sanitation, and antibiotics, vaccines are one of the greatest public health achievements. This is why vaccine hesitancy is now one of the ten threats to global health according to the World Health Organization (WHO) [2].

However, the development of the vaccines has always faced some challenges related with the pathogens and diseases themselves and the population (since it is hard to reach

some individuals, infants, pregnant women, immunocompromised persons, or older adults). Additionally, challenging circumstances are also related to emerging infections, epidemics, and pandemics as these are linked to a raise in pressure and concerns. Therefore, new strategies have been developed to overcome these challenges: new antigens, new antigen presentation (eg., DNA, mRNA), new delivery strategies (e.g., live vectors), and new adjuvants [3,4].

In terms of development timelines, the history of vaccines is interesting as it is undeniable how over the years it has been possible to shorten the time of the development. For varicella, it took 25–30 years to develop a vaccine [5]. For Ebola, it took 5 years [6] and for COVID-19 it took 1 year [7,8]. It is worth to question how it was possible to accelerate this process and why for other diseases, such as cancer, for which there are no adequate treatment options available, similar efforts could not be done in the same way. The answer to this question is implicit in the word Pandemic. Governments, social media, and the world population was looking at a vaccine to prevent SARS-CoV-2. Competition within the pharmaceutical industry together with their investors boosted this development, along with pro-active actions from the side of the agency regulators such as the EMA and FDA who provided strategies on how to accelerate the process through rolling reviews and expedited programs for COVID-19 to allow a progressive and urgent support to the Marketing Authorization Holders (MAH) [8–10]. Furthermore, some aspects related to the vaccine itself were already established from previous outbreaks of SARS-CoV in 2003 and Middle East respiratory syndrome (MERS) in 2012. Both coronavirus and SARS-CoV-2 belong to the family Coronaviridae. Various studies concluded that SARS-CoV-2 is 80% genetically identical to SARS-CoV. Therefore, the selection of spike protein as the antigen target was well supported by previous studies and lessons from these two coronaviruses [11,12]. In addition, the prefusion stabilization strategy was also previously developed and established for the respiratory syncytial virus (RSV) MERs vaccines [13,14]. It is also important to highlight that the vaccines from BioNTech/Pfizer and Moderna were both nucleoside-modified mRNA vaccines. This kind of platform has been studied in vaccine development for other infectious diseases such as RSV, influenza, and dengue. The incorporation of modified nucleosides into mRNA reduces the immunogenicity and improves the stability and translational capacity of mRNA, making this technology feasible as a vaccine delivery platform [15–17]. Additionally, it is important to consider that the first approved vaccines reflect the new strategies that have been developed to overcome some challenges of older vaccines and were already being developed to treat other diseases. This means that the technology was already being established and it just needed to follow another direction. This is the case of the mRNA vaccines from Pfizer/BioNTech and Moderna [8,9,18].

To better understand the strategy behind cancer and mRNA COVID-19 vaccines, it is important to highlight basic concepts of immunology. This study will allow the readers to understand how vaccines being developed for cancer were successfully applied into COVID-19 and how this success may now impact the continuation of the development of cancer vaccines (Figure 1).
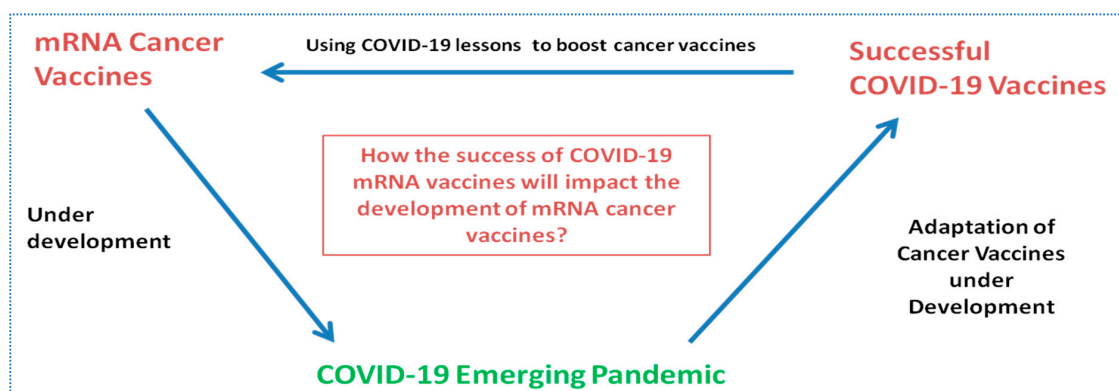
Figure 1. Influence and relationship in the development of mRNA cancer vaccines and mRNA vaccines.

2. Search Strategy

2.1. Data Collection Process for COVID-19 Vaccines

Since many studies have been published since the start of the pandemic, it was needed to provide the details on how this data collection was conducted. It is important to highlight and recognize that due to multiple publishing of studies related to COVID-19, selecting the relevant articles can be a challenge and a limitation if not done properly.

Therefore, exhaustive research was conducted in the main scientific databases, namely Web of Science and Pubmed, where the most prominent articles were analyzed. Three main criteria were considered for the article's selection: number of citations, impact factor of the journal, and article year. Considering the amount of uncertainty in the earlier published studies for COVID-19, articles from 2019 were discarded and only articles from 2021 and 2022 were considered. In case the evidence was acceptable, articles from 2020 were considered. The EMA, FDA, and CDC websites were also considered.

This literature selection allowed the generation of different sets of data to produce the results presented and analyzed in this work.

For the research conducted at Web of Science and Pubmed, the combination of the terms "COVID-19 vaccine" on the title with "development" and "technolog *" on the fields were used. On Pubmed, the combination of the terms "COVID-19" + "vaccine" + "strategy" + technology" filtered under systematic review was also used.

To make sure the most accurate scientific evidence was prioritized, only articles from journals under Q1 were considered and some Q2 were considered acceptable.

A medicine search was conducted at the EMA website applying the filter "COVID-19" for the 'medicine type' category in order to find the European Public Assessment Reports (EPARs) for all the centrally authorized vaccines. This search reflected the status of the EMA repository on the 02.02.2022. The results were reviewed individually to collect the information within the European Public Assessment Reports (EPARs) for each vaccine.

The EPARs were analyzed to consult the details of the clinical studies conducted during phases I and III of their clinical development and the respective regulatory achievements. The full list of indications and the dosage for each vaccine were taken from the EPARs for the EU products. For US products, the FDA and CDC websites were consulted to collect this kind of information.

2.2. Data Collection Process for mRNA Cancer Vaccines

To collect data related with mRNA cancer vaccines, the Web of Sciences and Pubmed were also used together with ClinicalTrials.gov. In Clinical Trials.gov, research was conducted using the three following terminologies and results were gathered afterwards: "mRNA cancer vaccine", "mRNA oncology vaccine", and "mRNA tumor vaccine". Articles and data from any date in time were considered in this case. The intention for this is to be able to understand what was being developed for mRNA vaccines prior to the COVID-19 pandemic, how the pandemic was able to influence new mRNA studies, and what were the most researched technology platforms on mRNA vaccines for cancer prior and after the pandemic.

For the research conducted at Web of Science and Pubmed, the combination of the terms "mRNA vaccine" on the title with "cancer", was used. On Pubmed, the combination of the terms "mRNA" + "vaccine" + "cancer" was used.

To make sure the most accurate scientific evidence was prioritized, only articles from journals under Q1 were considered and some Q2 could be considered acceptable.

2.3. Data Collection for Immunology Concepts

To collect data for basic immunology concepts, both Web of Sciences and Pubmed were used.

In the Web of Sciences, the term "Immunology" was applied and filtered by "Highly cited papers". This allowed a good level of confidence to the researchers considering that

these were all highly cited articles, and among these only those from journals under Q1 were considered and some Q2 were also considered acceptable.

For the Pubmed research, the term "Immune system cells" was searched following the same rational and only journals under Q1 were considered and some Q2 were considered acceptable. The British Society for Immunology website was consulted to complement immunology concepts.

3. Data Analysis and Study Limitations

Study limitations can be associated with selection of the best studies considering the impact factor. Publications evolved rapidly since the pandemic and selectivity of the studies had to be rigorous. Regarding mRNA cancer vaccines under development, we have access only to information that is publicly available. The published results do not reflect the truth in the universe of mRNA cancer vaccines under development since pharmaceutical companies might be developing their vaccines and might be in a research phase or in a pre-clinical phase and therefore nothing is yet available to the public. Additionally, ongoing studies in any of the phases (I, II, II) could have been abandoned or not published due to poor results.

4. Results

4.1. Immunology Concepts

Before analyzing the results, it is important to briefly address some basic concepts of immunology. The development of vaccines against a new pathogen or a tumor highly demands an understanding on how the immune system enhances protection [4].

The immune system should protect us from infection through various lines of defense [19]. It is linked into a complex and interactive network of lymphoid organs, cells, humoral factors, and cytokines [20]. These complex interactions must be balanced since any perturbance may cause disease. When underactivity of the immune system occurs, it may result in severe infections and tumours of immunodeficiency, while when overactivity occurs, it may result in allergic and autoimmune disease [20].

The immune system has been divided into two main subsystems: the innate system and the adaptive system [20,21]. Both the innate and adaptive immunity include humoral components (e.g., antibodies, complement proteins, and antimicrobial peptides) and cell-mediated components (that involve the activation of phagocytes and the release of various cytokines) [21].

The term innate immunity includes physical (i.e., skin, saliva), chemical, and microbiological barriers and provides immediate defense [20]. It is considered to be non-specific in terms of response as it based on a large family of pattern recognition receptors. In other words, it can be said that the responses are the same for all potential pathogens, despite the differences they may have [21].

The adaptive immune response is specific as it depends on distributed receptors for certain specific antigens. This means that cells are able to distinguish between and respond differently to a variety of antigens. The adaptive immune system focuses on the lymphocytes' role to fight these pathogens [21].

Therefore, it can be said that the antigen-specific reactions through T lymphocytes and B lymphocytes triggers the adaptive system responses [20].

It is important to highlight that the innate response is rapid, but it may damage the normal tissues due to the lack of specificity. On the other hand, the adaptive response is precise, but can take days or weeks to develop. However, any defect in either innate or adaptive system can lead to immunopathological disorders such as autoimmune diseases [22]. From this perspective, adaptive immunity could also damage healthy tissues if it is directed to an undesirable target such as self-protein, as it occurs in autoimmune diseases [23]. It is consistent across many studies that the adaptive response has memory, which means that further exposure leads to a more determined and faster response [20].

Despite the solid acknowledgment of these basic immunology concepts across many studies, some recent results have provided insights about the innate immune memory, which can be associated with macrophages or NK cells, and this requires a continuous research in the field of immunology [21,24]. Figure 2 illustrates the components involved in the adaptive and innate immune systems and how they interact.
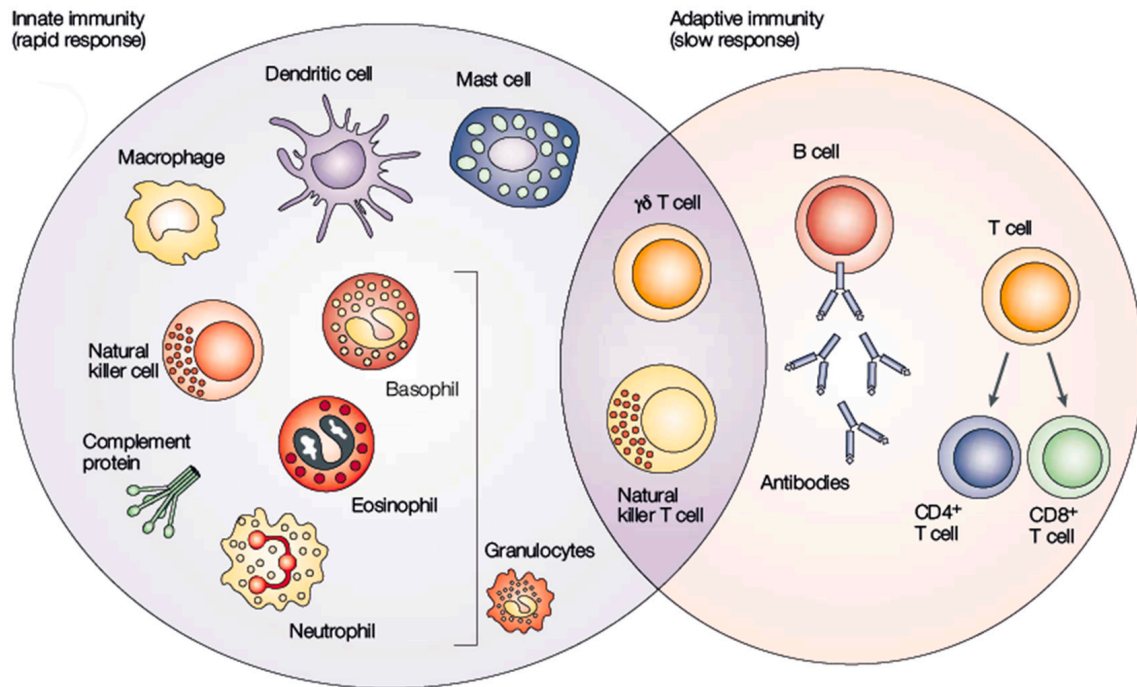
Figure 2. Interaction between innate and adaptive immune systems. Adapted from [25].

Cells from innate immunity are generated by myeloid lineage cells and mature into monocytes, macrophages, erythrocytes, platelets, and granulocytes, providing the first line of defense. Cells from the adaptive immune system come from lymphoid progenitor cells and provide natural killer (NK) cells, B-cells, and T-cells that are responsible for the second line of defense against pathogens and other abnormalities [26].

Magrophages and denditric cells (DC) from the innate immune system can recognize external antigens through pattern recognition receptors and trigger naive CD8+ and CD4+ T-cells, respectively, from the adaptive immune system [27]. The triggering of CD4 or CD8 depends on whether the epitope (part of antigen) is presented by MHC-I or MHC-II. MHC-I can be found in any human cells, and the recognition and presentation of epitope is restricted by MHC-I trigger CD8 T-cells. MHC-II molecules are only presented in neutrophils, macrophages, and DC (the so-called antigen-presenting cells) presented epitopes to CD4 T-cells [28]. Additionally, professional antigen-presenting cells (APC) interact with T-cells using positive and negative feedback systems by producing cytokines. These cytokines, and other mediators such as hormones, and other antigens will stimulate the innate immune system to produce either IL-12 or IL-4 in the local microenvironment around a newly activated T cell. This so called native Th0 lymphocytes may be differentiated into T helper type 1 (Th1) cells when they are activated in a microenvironment rich in IL-12 or can be inhibited from developing into Th1 cells in case the microenvironment is rich in IL-4, IL-10, or other substances such as corticosteroids and catecholamines. In fact, the same naïve Th0 cells, if exposed to IL-4, will differentiate into T helper type 2 (Th2) cells. However, exposure of naive Th0 cells to IL-12 inhibits polarization to Th2 cells. It is important to understand that when both IL-4 and IL-12 are present upon activation of naive T-cell, the effects of the IL-4 will dominate, and a type 2 response will ensue.

Th1 stimulates type 1 immunity, which is characterized by intense phagocytic activity and Th2 cells stimulate type 2 immunity, which is characterized by high antibody titers. Type 1 and type 2 immunity do not have the exact same meaning to cell-mediated and humoral immunity, since Th1 cells can also be responsible for enhancing moderate levels of antibody production and Th2 cells actively suppress phagocytosis.

In the majority of infections, type 1 immunity is considered to be protective, and type 2 responses will assist with the resolution of cell-mediated inflammation [29].

A non-randomized open-label phase I/II trial in healthy adults, 18–55 years of age in study from 2020, involving the mRNA vaccine for COVID-19 (BNT162b1) demonstrated that the vaccine induces CD4+ and CD8+ T cell responses in most of the participants, with Th1 polarization of the helper response [30]. There are much more interactions and cascades that trigger interaction between both systems and the purpose of this short summary is to highlight that there are many molecular and cellular mechanisms that connect both innate and adaptive immunity. [27]

Therefore, the most important concept to be retained in this section is that the immune system is very complex and that the innate and the adaptive systems cooperate with each other to ennhance protection [21].

Other concepts that are important to retain in this chapter are the innate immune responses against mRNA vaccines and similar and different immune responses between infectious diseases and cancer.

4.1.1. Innate Immune Responses against mRNA Vaccines

The innate immune system represents the first line of immune response against mRNA vaccination. During the vaccination, the mRNA is recognized by various pattern recognition receptors (PRRs) which are responsible for producing IFNs and proinflammatory cytokines [31].

The mRNA binding PRRs can be classified into cytosolic PRRs and endosomal PRRs. In the cytosol, the PRRs include the nucleotide oligomerization domain-like receptors (NLRs) and the RIG-I-like receptors (RLRs), while inside the endosomes, the PRRs are represented by the toll-like receptors (TLRs). Once they recognize mRNA, a cascade of interactions and signaling pathways is initiated, leading to the production of the IFNs and pro-inflammatory cytokines as explained above [32].

Therefore, mRNA not only encodes an antigen, but it also has intrinsic immune-stimulating activity that is responsible to contribute to vaccine efficacy and support the intended therapy. It can be considered a self-adjuvant effect. mRNA vaccination can bring this additional innate immune stimulation. However, this additional immunogenicity should be carefully controlled and balanced to ensure the safety of the therapy, as it may result in side effects of having flu-like symptoms or risk of autoimmune diseases [32].

To sum up, the optimal innate immune response and inflammatory cytokine release are crucial to enable T- and B-cell immune responses. However, in case there are excessive innate immune responses, they might lead to cytokine storms and damage of the tissue. This is why the induced immune response by mRNA should be controlled but at the same time should retain antibody production [31].

At the moment, the approved mRNAs vaccines by the EMA and FDA are effective at preventing SARS-CoV-2 infection and have fortunately overcome previous limitations related with this platform and were able to reflect the potential of this technology.

4.1.2. Differences and Similarities across Immune Responses between Infectious Diseases and Cancer

As already described, the immune system is able to provide protection against tumors and pathogens. For many years, it was established a close relationship between the immune system and its capability on fighting infectious diseases. This has not happened in the cancer field and only more recently immune system has been explored and studied in cancer, leading immediately to the recent successes of immunotherapy.

Today, it is unquestionable that the control of the immune system is a key approach in treating and preventing both infectious diseases and cancer [33].

Regarding the similarities between cancer and infectious diseases in terms of immunology, it is important to acknowledge that generalizations should be carefully done due to diversity of both infectious agents and cancers. However, it is a fact that there are similar immunological mechanisms across both pathologies, and the study of the link between these two therapeutic areas should be continued [33].

Tumor cells have to develop mechanisms to be able to evade the immune system and infectious agents also have to overcome the body barriers and immune mechanisms.

Both diseases may share the fact of having reduced expression of class I MHC molecules, being then able to escape from our proctective cytotoxic T-cells. Both tumor cells and infections will prevent access to immune mechanisms [34].

Therefore, it is known that innate and adaptive immunity are activated by both infections and tumors. Regarding this similarity and also the fact that the way immune cells infiltrate infected tissues share the same way to infiltrate neoplastic tissues, it is important to understand that their function in the first setting is quite different in both diseases. This is because infected tissues are represented by an acute inflammatory environment that develop the generation of protective immunity. These acute infections are usually associated with evident inflammation. On another hand, tumors are represented by chronic inflammation that suppresses antitumor immune responses and promotes tumor growth, escaping from the immune system. Therefore, neoplastic lesions will induce initially a low inflammatory landscape or immune reaction, which means that only after tissue destruction based on tumor expansion, inflammation and tissue repair will become evident [35]. In fact, it is well known that the chronic inflammation associated with certain persistent infections, for instance, those caused by H. pylori or human papilloma virus (HPV), are believed to be an important cause of the gastric and cervical cancers associated with these agents. They not only cause cancer but inflammation caused by these infectious also contribute to the morbidity and mortality of cancer [33].

This means that a wide understanding of how the immune system successfully responds to pathogens may lead to the design and implementation of strategies to replicate common responses to tumors. Therefore, it is very important to have present some concepts immunology in cancer and infectious diseases as knowledge and advancements in both fields may influence each other in achieving successful treatments for both diseases. It is known, for instance, that studies of infection led to cancer immunotherapies (checkpoint immunotherapies, CAR-T, vaccines, therapeutic targeting of PRRs) and that success of cancer immunotherapy may also be applied to infectious disease and are already being exploited [33].

4.2. Vaccine Techonologies for SARS-CoV-2 Candidates

Many factors contributed to the immediate success of implementing new technologies on COVID-19 vaccines leading to their fast development. The main regulatory agencies implemented rapid scientific advice and rolling review methods that allowed the development to progress in a fast pace [36,37].

The first approved vaccines for COVID-19 can be seen in Figure 3 and information about their indications and dosage are compiled in Table 1.

Table 1. Principal data for four vaccines to COVID-19 about indications and dosage.

MAH	Name	Strategy	Active Component	Formulation	Dosage	How It Works
Pfizer BioNTech	BNT162b2	mRNA vaccines. The mRNA provides instructions the body uses to build a harmless piece of a protein from the virus that causes COVID-19. This protein causes an immune response that helps protect the body from getting sick with COVID-19 in the future [38,39].	Nucleoside modified mRNA (Single-stranded, 5'-capped messenger RNA produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2) Prefusion stabilized spike protein [40]	Individuals 12 years of age and older Lipids (help the mRNA to enter the cells) - 2[(polyethylene glycol (PEG))-2000]-N,N-ditetradecylacetamide-1,2-distearoyl-sn-glycero-3-phosphocholine - Cholesterol (plant derived) - (4hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)) Salts (keep the vaccine molecules stable while the vaccine is manufactured, frozed, shipped, and stored) - Dibasic sodium phosphate dihydrate; - Monobasic potassium phosphate - Potassium chloride (common food salt) - Sodium chloride (basic table salt) - Sucrose (basic table sugar) [38]	Individuals 12 years of age and older 2 shots, 21 days apart [38] One dose (0.3 mL) contains 30 micrograms of tozinameran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles) [40]	Comirnaty and Spikevax work by preparing the body to defend itself against COVID-19. It contains a molecule called mRNA which has instructions for making the spike protein. This is a protein on the surface of the SARS-CoV-2 virus which the virus needs to enter the body's cells. When a person is given the vaccine, some of their cells will read the mRNA instructions and temporarily produce the spike protein. The person's immune system will then recognise this protein as foreign and produce antibodies and activate T-cells (white blood cells) to attack it. If, later on, the person comes into contact with SARS-CoV-2 virus, their immune system will recognise it and be ready to defend the body against it. The mRNA from the vaccine does not stay in the body but is broken down shortly after vaccination [40,41].
Moderna	RNA-1273		CX-024414 Nucleoside modified mRNA (single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2) Prefusion stabilized spike protein [41]	Individuals 12 years of age and older Lipids (help the mRNA to enter the cells) - PEG2000-DMG: 1,2-dimyristoyl-rac-glycerol, methoxypolyethylene glycol - 1,2-distearoyl-sn-glycero-3-phosphocholine - BotaniChol® (non-animal origin cholesterol) - SM-102: heptadecane-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino) octanoate Salts (keep the vaccine molecules stable while the vaccine is manufactured, frozed, shipped, and stored) - Sodium acetate - Sucrose (basic table sugar) - Tromethamine - Tromethamine hydrochloride - Acetic acid (the main ingredient in white household vinegar) [39]	Individuals 12 years of age and older One dose (0.5 mL) contains 100 micrograms of messenger RNA (mRNA) (embedded in SM-102 lipid nanoparticles) Spikevax is administered as a course of 2 (two) 100 microgram doses (0.5 mL each). It is recommended to administer the second dose 28 days after the first dose [41]	

Table 1. *Cont.*

MAH	Name	Strategy	Active Component	Formulation	Dosage	How It Works
AstraZeneca	AZD1222	Vaxzevria is made up of another virus (of the adenovirus family) that has been modified to contain the gene for making a protein from SARS-CoV-2. Vaxzevria does not contain the virus itself and cannot cause COVID-19 [42].	ChAdOx1-SARS-CoV-2 Prefusion stabilized spike protein [42]	L-Histidine L-Histidine hydrochloride monohydrate Magnesium chloride hexahydrate Polysorbate 80 (E 433) Ethanol Sucrose Sodium chloride Disodium edetate (dihydrate) Water for injections [43]	Individuals 18 years of age and older One dose (0.5 mL) contains: Chimpanzee Adenovirus encoding the SARS-CoV-2 Spike glycoprotein (ChAdOx1-S), not less than 2.5×10^8 infectious units (Inf.U) * Produced in genetically modified human embryonic kidney (HEK) 293 cells and by recombinant DNA technology. This product contains genetically modified organisms (GMOs). Individuals 18 years of age and older The Vaxzevria vaccination course consists of two separate doses of 0.5 mL each. The second dose should be administered between 4 and 12 weeks (28 to 84 days) after the first dose [43]	Vaxzevria works by preparing the body to defend itself against COVID-19. It is made up of another virus (adenovirus) that has been modified to contain the gene for making the SARS-CoV-2 spike protein. This is a protein on the surface of the SARS-CoV-2 virus which the virus needs to enter the body's cells. Once it has been given, the vaccine delivers the SARS-CoV-2 gene into cells in the body. The cells will use the gene to produce the spike protein. The person's immune system will then recognise this protein as foreign and produce antibodies and activate T-cells (white blood cells) to attack it. If, later on, the person comes into contact with SARS-CoV-2 virus, their immune system will recognise it and be ready to defend the body against it. The adenovirus in the vaccine cannot reproduce and does not cause disease [42].
Janssen Pharmaceuticals Companies of Johnson & Johnson	JNJ-78436735	COVID-19 Vaccine Janssen is made up of another virus (of the adenovirus family) that has been modified to contain the gene for making a protein found on SARS-CoV-2 [44]. This harmless version of a virus unrelated to the COVID-19 virus provides instructions the body uses to build a harmless piece of a protein from the virus that causes COVID-19. This protein causes an immune response that helps protect the body from getting sick with COVID-19 in the future [45].	Adenovirus type 26 encoding the SARS-CoV-2 spike glycoprotein (Ad26.COV2-S) Prefusion stabilized spike protein [44]	Sugars, salts, acid, and acid stabilizer: - Polysorbate-80 - 2-hydroxypropyl-β-cyclodextrin - Trisodium citrate dihydrate - Sodium chloride (basic table salt) - Citric acid monohydrate (closely related to lemon juice) - Ethanol (a type of alcohol) All the compenents work together to help keep the vaccine molecules stable while the vaccine is manufactured, shipped, and stored until it is ready to be given to a vaccine recipient [45]	Individuals 18 years of age and older 1 shot requiring a booster dose Everyone ages 18 years and older should get a booster dose of either Pfizer-BioNTech or Moderna (mRNA COVID-19 vaccines) at least 2 months after receiving the Johnson & Johnson's Janssen (J&J/Janssen) vaccine in most situations [45]. One dose (0.5 mL) contains: Adenovirus type 26 encoding the SARS-CoV-2 spike glycoprotein * (Ad26.COV2-S), not less than 8.92 log10 infectious units (Inf.U). [46]	COVID-19 Vaccine Janssen works by preparing the body to defend itself against COVID-19. It is made up of another virus (an adenovirus) that has been modified to contain the gene for making the SARS-CoV-2 spike protein. This is a protein on the SARS-CoV-2 virus which it needs to enter the body's cells. The adenovirus passes the SARS-CoV-2 gene into the vaccinated person's cells. The cells can then use the gene to produce the spike protein. The person's immune system will recognise the spike protein as foreign and produce antibodies and activate T-cells (white blood cells) to target it. Later, if the person comes into contact with SARS-CoV-2 virus, the person's immune system will recognise the spike protein on the virus and be ready to defend the body against it. The adenovirus in the vaccine cannot reproduce and does not cause the disease [44]

* Produced in the PER.C6 TetR Cell Line and by recombinant DNA technology. The product contains genetically modified organisms (GMOs) [46].
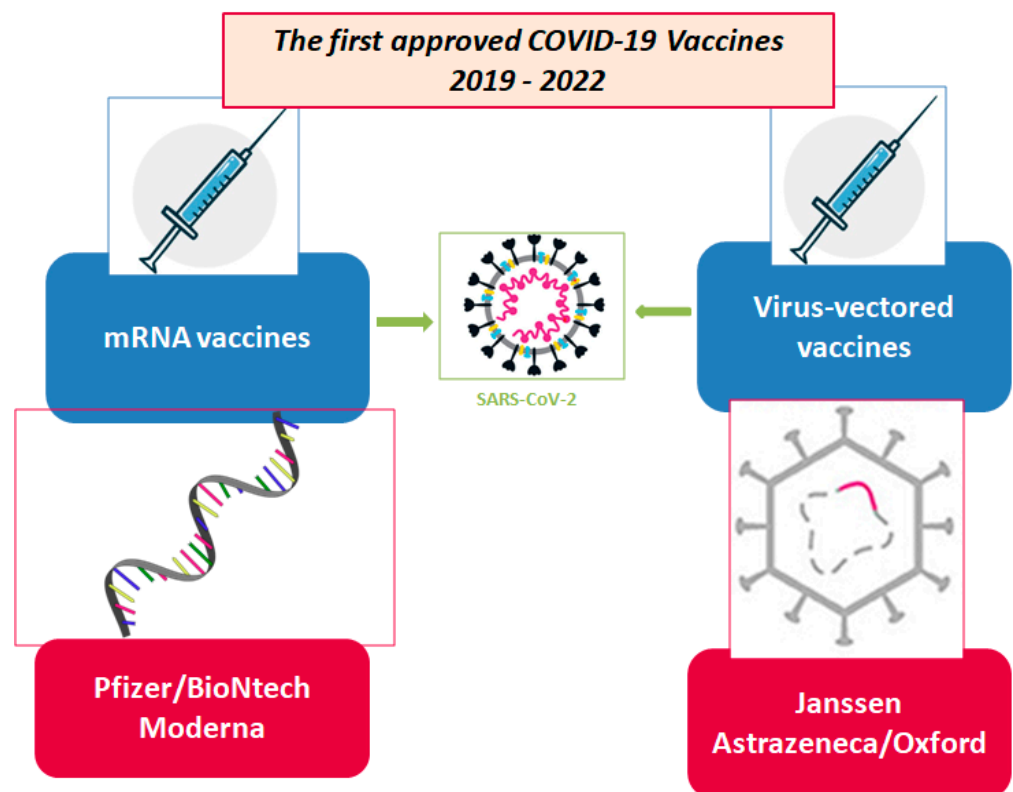
Figure 3. Technologies for SARS-CoV-2 first generation of vaccine candidates. Adapted from [4].

4.3. mRNA Platform for Vaccines—Advantages and Disadvantages

One of the most important challenges related with the mRNA technology has been associated with the delivery system, the instability, and the excessive immunogenicity [47].

However, because of its potential, the scientists continued their research and development and during the past decades, especially more recently, progresses were made in the safety, efficacy, and production of mRNA vaccines [47,48].

The hope reflected in the mRNA technology for vaccines is related to the several advantages it represents. mRNA is precise as it will only express a specific antigen and induce a directed immune response, unlike attenuated or inactivated vaccines. Furthermore, it promotes both humoral and cellular immune response and induces the innate immune system. mRNA is more effective when comparing to DNA-based vaccines since it does not need to enter the nucleous of the cells and it has no chance of performing any random genome integration. Additionally, mRNA is quickly degraded by cellular processes, with no traces found after 2–3 days. In fact, this is also one of its disadvantages, due to the fact of mRNA being related with a lot of instability.

Another positive point is related with its manufacturing. A change in the encoded antigen does not affect the mRNA backbone physical–chemical characteristics, and since production is based on an in vitro cell-free transcription reaction, safety concerns that are found in other technologies are minimized since the presence of cell-derived impurities and viral contaminants are not common [49].

The first approved mRNA vaccines in the world are the vaccines against SARS-CoV-2 [48]. The approval of these vaccines in the EMA came through the conditional approval procedure. The Pfizer's Vaccine Comminarty was granted conditional approval on 21 December 2020 [40] and Spikevax (previously Moderna COVID-19 Vaccine) for COVID-19 was granted conditional approval on 2021 [41].

The legal basis of conditional marketing authorization procedure is defined under the Article 14-a of Regulation (EC) No 726/200 and the provisions for granting a conditional

marketing authorisation are further elaborated in Regulation (EC) No 507/2006. This procedure establishes that, under very specific and duly authorized conditions, for certain medicines addressing unmet medical needs and that are the interest of public health, the grant of conditional approval can be based on less comprehensive clinical, pharmaceutical, or non-clinical data than normally required, where the benefit of immediate availability of the medicine outweighs the risk inherent in the fact that additional data are still required. These authorisations are valid for one year and can be renewed annually. The marketing authorisation holder must fulfil specific obligations within defined timelines and the authorization can be converted into a standard marketing authorisation once all obligations (such as completing ongoing or new studies or collecting additional data) are fulfilled and the complete data confirms that the benefits outweigh the risks. The EMA can take any regulatory action, such as suspending or revoking the marketing authorisation, in case the benefits no longer outweigh the risks [50].

Now, since the approval of these mRNA vaccines and its administration in millions of people, more information about safety and efficacy has become available, and those technology platforms have been validated [51,52].

Overall, there are two major types of mRNA technology for vaccines: non-replicating mRNA and virally derived, self-amplifying RNA. The first encodes the antigen of interest and contains 5′ and 3′ untranslated regions (UTRs), while the self-amplifying RNAs encode not only the antigen but also the viral replication machinery that enables intracellular RNA amplification and abundant protein expression [53].

In terms of delivery platforms, it is important to understand that mRNA has to cross the cell membrane to reach the cytosol. This is a very challenging step due to mRNA characteristics such as having a large size (300–5000 kDA) and being prone to degradability. Therefore, it was needed to overcome this limitation [49]. The solution is to deliver mRNA using the right strategy. A proper delivery system will enable mRNA vaccines to achieve full therapeutic mRNA [48]. There are many ways to deliver mRNA: naked mRNA with direct injection; conjugation with lipid-based carriers, polymers, or peptides; via transfection of dendritic cells (DC); through viral vectors; and many other platforms [48,49].

4.4. mRNA Cancer Vaccines

When developing cancer vaccines, it is also very important to consider a proper adjuvant. This will boost and promote inflammation at the delivery site, facilitating immune cell recruitment and activation. Other important points that should be considered are related to the choice of the targeting antigen, the timing of vaccination, manipulation of the tumor environment, and the combination with other treatments that might cause additive or even synergistic anti-tumor effects [51].

Due to mRNA characteristics already described above and the fact that the molecule is also negatively charged, naked RNA is prone to nuclease degradation and has difficulty in crossing the cell membrane [48].

Table 2 reflects the results from the data collection research at Clinical Trials. Gov, aiming to find all clinical trials related to mRNA vaccines for cancer.

Table 2. ClinicalTrials.gov Search Results from 30 April 2022 for all mRNA-based cancer vaccines.

Title	Status	Study Results	Conditions	Interventions	Characteristics	Dates—Study Start	Locations	Trial Identifier
Trial of Vaccine Therapy With mRNA—Transfected Dendritic Cells in Patients with Advanced Malignant Melanoma	Completed	No Results Available	• Malignant Melanoma	• Biological: Dendritic Cells (DC) malignant melanoma • Procedure: IL-2	Phase: • Phase 1 • Phase 2	March 2002		NCT01278940
Carcinoembryonic Antigen-loaded Dendritic Cells in Advanced Colorectal Cancer Patients	Completed	No Results Available	• Colorectal Cancer • Liver Metastases	• Biological: CEA-loaded dendritic cell vaccine	Phase: • Phase 1 • Phase 2	December 2003	• Radboud University Nijmegen Medical Center, dept. of Medical Oncology, Nijmegen, Netherlands	NCT00228189
Peptide-pulsed vs. RNA-transfected Dendritic Cell Vaccines in Melanoma Patients	Completed	No Results Available	• Melanoma Stage III or IV	• Biological: autologous dendritic cell vaccine	Phase: • Phase 1 • Phase 2	April 2004	• Radboud University Nijmegen Medical Center, Nijmegen, PO Box 9101, Netherlands	NCT00243529
Peptide-specific Vaccination in HLA-A*02 Positive Patients with Biochemical Recurrence After Radical Prostatectomy	Unknown status	No Results Available	• Recurrent Prostate Cancer	• Biological: Peptide vaccine • Drug: Montanide ISA-51 • Drug: Granulocyte macrophage colony stimulating factor (GM- CSF) • Drug: Imiquimod • Drug: mRNA • Drug: Protamin • Procedure: local hyperthermia	Phase: • Phase 1 • Phase 2	April 2004		NCT02452307
Intradermal Vaccination with Stabilized Tumor mRNA—a Clinical Phase I/II Trial in Melanoma Patients	Completed	No Results Available	• Malignant Melanoma	• Biological: GRNVAC1	Phase: • Phase 1 • Phase 2	July 2004	• Department of Dermatology, University of Tübingen, Tübingen, Germany	NCT00204607
Dendritic Cell Vaccination for Patients with Acute Myeloid Leukemia in Remission	Completed	No Results Available	• Acute Myeloid Leukemia (AML)	• Biological: injection of antigen-loaded cultured dendritic cells	Phase: Phase 1	March 2005	• Antwerp University Hospital/Center for Cellular Therapy and Regenerative Medicine, Edegem, Belgium	NCT00834002
Vaccine Therapy in Treating Patients with Newly Diagnosed Glioblastoma Multiforme	Active, not recruiting	No Results Available	• Malignant Neoplasms of Brain	• Biological: tetanus toxoid • Biological: therapeutic autologous dendritic cells • Biological: therapeutic autologous lymphocytes	Phase: Phase 1	January 2006	• Duke University Medical Center, Durham, North Carolina, United States	NCT00639639
Vaccination With Tumor mRNA in Metastatic Melanoma—Fixed Combination Versus Individual Selection of Targeted Antigens	Completed	No Results Available	• Malignant Melanoma	• Biological: mRNA coding for melanoma associated antigens • Drug: GM-CSF	Phase: • Phase 1 • Phase 2	April 2007	• Department of Dermatology, University of Tuebingen, Tuebingen, Germany	NCT00204516
Basiliximab in Treating Patients With Newly Diagnosed Glioblastoma Multiforme Undergoing Targeted Immunotherapy and Temozolomide-Caused Lymphopenia	Completed	No Results Available	• Malignant Neoplasms Brain	• Biological: RNA-loaded dendritic cell vaccine • Drug: basiliximab	Phase: Phase 1	April 2007	• Duke University Medical Center, Durham, North Carolina, United States	NCT00626483

Table 2. *Cont.*

Title	Status	Study Results	Conditions	Interventions	Characteristics	Dates—Study Start	Locations	Trial Identifier
A Study of Active Immunotherapy with GRNVAC1 in Patients With Acute Myelogenous Leukemia (AML)	Completed	No Results Available	• Acute Myelogenous Leukemia	• Biological: Autologous Dendritic Cells	Phase: Phase 2	July 2007	• Emory University School of Medicine, Atlanta, Georgia, United States • Loyola University Medical Center, Maywood, Illinois, United States • Washington University School of Medicine, Siteman Cancer Center, Saint Louis, Missouri, United States • University of Nebraska Medical Center, Omaha, Nebraska, United States • Ohio State University, Columbus, Ohio, United States • UT Southwestern Medical Center, Dallas, Texas, United States	NCT00510133
Feasibility Study of Acute Myelogenous Leukemia mRNA Plus Lysate Loaded Dendritic Cell Vaccines	Terminated	No Results Available	• Leukemia	• Biological: mRNA-4157 • Biological: Pembrolizumab	Phase: Phase 1	July 2007	• UT MD Anderson Cancer Center, Houston, Texas, United States	NCT00514189
Human Telomerase Reverse Transcriptase Messenger RNA (hTERT mRNA) Transfected Dendritic Cell Vaccines	Withdrawn	No Results Available	• Metastatic Prostate Cancer	• Biological: hTERT mRNA DC	Phase: • Phase 1 • Phase 2	January 2008		NCT01153113
Trial for Vaccine Therapy with Dendritic Cells in Patients With Metastatic Malignant Melanoma	Terminated	No Results Available	• Metastatic Malignant Melanoma	• Biological: Dendritic cells—transfected with hTERT-, survivin- and tumor cell derived mRNA + ex vivo T cell expansion and reinfusion • Drug: Temozolomide	Phase: • Phase 1 • Phase 2	August 2009	• The Norwegian Radium Hospital, Department of Clinical Cancer Research, Oslo, Montebello, Norway	NCT00961844
A Study on the Safety and Immunogenicity of Combined Intradermal and Intravenous Administration of an Autologous mRNA Electroporated Dendritic Cell Vaccine in Patients with Previously Treated Unresectable Stage III or IV Melanoma	Completed	No Results Available	• Melanoma	• Biological: TriMix-DC	Phase: Phase 1	December 2009	• UZ Brussel, Laken, Brussels, Belgium	NCT01066390
Trial of Bi-shRNA-furin and GMCSF Augmented Autologous Tumor Cell Vaccine for Advanced Cancer	Completed	No Results Available	• Ewings Sarcoma • Non Small Cell Lung Cancer • Liver Cancer	• Biological: Vigil™	Phase: Phase 1	December 2009	• Florida Cancer Specialists, West Palm Beach, Florida, United States • Dartmouth-Hitchcock Medical Center/Norris Cotton Cancer Center, Lebanon, New Hampshire, United States • Mary Crowley Cancer Research Centers, Dallas, Texas, United States • Cancer Care Northwest, Spokane, Washington, United States	NCT01061840
Safe Study of Dendritic Cell (DC) Based Therapy Targeting Tumor Stem Cells in Glioblastoma	Completed	No Results Available	• Glioblastoma • Brain Tumor	• Biological: Dendritic cell vaccine with mRNA from tumor stem cells	Phase: • Phase 1 • Phase 2	January 2009		NCT00846456
Messenger Ribonucleic Acid (mRNA) Transfected Dendritic Cell Vaccination in High Risk Uveal Melanoma Patients	Terminated	No Results Available	• Uveal Melanoma	• Biological: autologous dendritic cells electroporated with mRNA	Phase: • Phase 1 • Phase 2	June 2009	• Radboud University Nijmegen Medical Centre, Nijmegen, Gelderland, Netherlands • The Rotterdam Eye Hospital, Rotterdam, Zuid-Holland, Netherlands	NCT00929019

Table 2. *Cont.*

Title	Status	Study Results	Conditions	Interventions	Characteristics	Dates—Study Start	Locations	Trial Identifier
Toll-like Receptor (TLR) Ligand Matured Dendritic Cell Vaccination in Melanoma Patients	Completed	No Results Available	• Melanoma	Biological: autologous dendritic cell vaccination	Phase: • Phase 1 • Phase 2	June 2009	• Radboud University Nijmegen Medical Centre, Nijmegen, Gelderland, Netherlands	NCT00940004
Trial of an RNActive®-Derived Cancer Vaccine in Stage IIIB/IV Non-Small Cell Lung Cancer (NSCLC)	Completed	No Results Available	• Non-Small Cell Lung Cancer	Biological: CV9201	Phase: • Phase 1 • Phase 2	May 2009	• RWTH Aachen, Aachen, Germany • Medizinische Klinik III, Universitätsklinikum Bonn, Bonn, Germany • Medizinische Klinik V, Klinikum Darmstadt, Darmstadt, Germany • Medizinische Klinik I, Universitätsklinikum Dresden, Dresden, Germany • Nordwest Krankenhaus, Frankfurt, Germany • Krankenhaus Großhansdorf, Großhansdorf, Germany • Universitätsklinikum Hamburg Eppendorf, Medizinische Klinik II, Hamburg, Germany • Thoraxklinik am Universitätsklinikum Heidelberg, Heidelberg, Germany • Universitätsklinikum des Saarlandes, Homburg, Germany • III. Medizinische Klinik und Poliklinik, Universitätsmedizin Mainz, Mainz, Germany • and 4 more	NCT00923312
Transfected Dendritic Cell Based Therapy for Patients with Breast Cancer or Malignant Melanoma	Completed	No Results Available	• Breast Cancer • Malignant Melanoma	• Biological: DC vaccine	Phase: Phase 1	September 2009	• Department of Oncology, Herlev University Hospital, Herlev, Denmark	NCT00978913
Vaccine Therapy in Treating Patients Undergoing Surgery for Recurrent Glioblastoma Multiforme	Completed	No Results Available	• Recurrent Central Nervous System Neoplasm	• Biological: BTSC mRNA-loadedDCs	Phase: Phase 1	September 2009	• Duke University Medical Center, Durham, North Carolina, United States	NCT00890032
Single-step Antigen Loading and TLR Activation of Dendritic Cells in Melanoma Patients	Completed	No Results Available	• Melanoma	• Biological: autologous dendritic cell vaccine	Phase: • Phase 1 • Phase 2	April 2010	• Radboud University Nijmegen Medical Centre, Nijmegen, Gelderland, Netherlands	NCT01530698
Efficacy of Dendritic Cell Therapy for Myeloid Leukemia and Myeloma	Unknown status	No Results Available	• Acute Myeloid Leukemia • Chronic Myeloid Leukemia • Multiple Myeloma	• Biological: dendritic cell vaccination (active specific immunotherapy)	Phase: Phase 2	January 2010	• University Hospital Antwerp, Edegem, Antwerp, Belgium	NCT00965224
Safety of Active Immunotherapy in Subjects with Ovarian Cancer	Unknown status	No Results Available	• Ovarian Epithelial Cancer	• Biological: Procure	Phase: Phase 1	September 2010	• Hospital Landeskrankenhaus Innsbruck, Innsbruck, Austria • Hospital Korneuburg, Korneuburg, Austria • Hospital Barmherzigen Schwestern, Linz, Austria • Semelweis University, Budapest, Hungary • National Oncology Institute, Budapest, Hungary	NCT01456065
Vaccine Therapy in Curative Resected Prostate Cancer Patients	Active, not recruiting	No Results Available	• Prostate Cancer	• Biological: Dendritic cell vaccine	Phase: • Phase 1 • Phase 2	September 2010	• The Norwegian Radium Hospital, Department of Clinical Cancer Research, Oslo, Norway	NCT01197625

Table 2. *Cont.*

Title	Status	Study Results	Conditions	Interventions	Characteristics	Dates—Study Start	Locations	Trial Identifier
Trial of Vaccine Therapy in Recurrent Platinum Sensitive Ovarian Cancer Patients	Terminated	No Results Available	• Recurrent Epithelial Ovarian Cancer	• Biological: DC-006 vaccine	Phase: • Phase 1 • Phase 2	April 2011	• Oslo University Hospital- Norwegian Radium Hospital, Oslo, Norway	NCT01334047
Dendritic Cell Vaccination for Patients with Solid Tumors	Unknown status	No Results Available	• Glioblastoma • Renal Cell Carcinoma • Sarcomas • Breast Cancers • Malignant Mesothelioma • Colorectal Tumors	• Biological: autologous dendritic cell vaccination	Phase: • Phase 1 • Phase 2	February 2011	• Antwerp University Hospital, Center for Cellular Therapy and Regenerative Medicine, Edegem, Antwerp, Belgium	NCT01291420
Platin-based Chemotherapeutics to Enhance Dendritic Cell Vaccine Efficacy in Melanoma Patients	Completed	No Results Available	• Melanoma	• Biological: DC vaccination • Biological: DC vaccination with cisplatinum	Phase: Phase 2	February 2011	• Radboud University Nijmegen Medical Centre, Nijmegen, Gelderland, Netherlands	NCT02285413
Trial of Vaccine Therapy With mRNA-Transfected Dendritic Cells in Patients with Androgen Resistant Metastatic Prostate Cancer	Completed	No Results Available	• Prostate Cancer	• Biological: Dendritic Cells (DC) prostate	Phase: • Phase 1 • Phase 2	No information available	• Oslo university Hospital, Oslo, Norway	NCT01278914
Immune Responses to Autologous Langerhans-type Dendritic Cells Electroporated with mRNA Encoding a Tumor-associated Antigen in Patients With Malignancy: A Single- arm Phase I Trial in Melanoma	Active, not recruiting	No Results Available	• Melanoma	Biological: Langerhanstype dendritic cells (a.k.a. Langerhans cells or LCs)	Phase: Phase 1	October 2011	• Memorial Sloan Kettering Cancer Center, New York, New York, United States	NCT01456104
Dendritic Cell Vaccination and Docetaxel for Patients with Prostate Cancer	Completed	No Results Available	• Prostatic Neoplasms	• Biological: mRNA transfected dendritic cell Drug: Docetaxel	Phase: Phase 2	October 2011	• Center for Cancer Immune Therapy, Dept. of Haematology/Oncology, Copenhagen, Herlev, Denmark • Department of Oncology, Herlev Hospital, Herlev, Denmark	NCT01446731
Efficacy Study of Dendritic Cell Vaccination in Patients with Acute Myeloid Leukemia in Remission	Recruiting	No Results Available	• Acute Myeloid Leukemia	• Biological: DC vaccine	Phase: Phase 2	October 2012	• ZNA Stuivenberg, Antwerp, Belgium • Antwerp University Hospital, Antwerp, Belgium • University Hospital Brussels, Brussels, Belgium • Cliniques Universitaires Saint-Luc, Brussel, Belgium • Ghent University Hospital, Ghent, Belgium • Centre Hospitalier Universitaire de Liège, Liège, Belgium • AZ Delta, Roeselare, Belgium • CHU Mont Godinne, Yvoir, Belgium	NCT01686334
DC Vaccination for Postremission Therapy in AML	Completed	No Results Available	• Acute Myeloid Leukemia	• Biological: DC vaccination forpostremission therapy in AML	Phase: • Phase 1 • Phase 2	November 2013	• Hospital of the University of Munich, LMU; Department od Medicine III, Munich, Germany	NCT01734304
DC Vaccine Combined with CIK Cells in Patients With Esophagus Cancer	Unknown status	No Results Available	• Esophagus Cancer	• Biological: adenovirus- transfected autologous DC vaccine plus CIK cells	Phase: • Phase 1 • Phase 2	August 2014	• Affiliated Hospital to Academy of Military Medical Sciences, Beijing, China	NCT02693236

Table 2. *Cont.*

Title	Status	Study Results	Conditions	Interventions	Characteristics	Dates—Study Start	Locations	Trial Identifier
CT7, MAGE-A3, and WT1 mRNA-electroporated Autologous Langerhans-type Dendritic Cells as Consolidation for Multiple Myeloma Patients Undergoing Autologous Stem Cell Transplantation	Active, not recruiting	No Results Available	• Multiple Myeloma	• Biological: CT7, MAGE-A3, and WT1 mRNA-electroporated Langerhans cells (LCs) • Other: Standard of care	Phase: Phase 1	January 2014	• Memorial Sloan Kettering Cancer Center, New York, New York, United States	NCT01995708
An Open Label Randomised Trial of RNActive® Cancer Vaccine in High Risk and Intermediate Risk Patients with Prostate Cancer	Terminated	No Results Available	• Prostate Carcinoma	• Biological: CV9104 • Device: needle free injectiondevice (Tropis®)	Phase: Phase 2	June 2014	• Nationales Zentrum für Tumorerkrankungen, Medizinische Onkologie, Heidelberg, Baden-Württemberg, Germany • Klinik für Urologie, Universitätsklinikum Tübingen, Tübingen, Baden-Württemberg, Germany • Klinikum rechts der Isar, Urologische Klinik und Poliklinik der Technischen Universität München, München, Bayern, Germany	NCT02140138
Adjuvant Dendritic Cell-immunotherapy Plus Temozolomide in Glioblastoma Patients	Recruiting	No Results Available	• Glioblastoma Multiforme of Brain	• Biological: Dendritic cell vaccine plus temozolomide chemotherapy	Phase: • Phase 1 • Phase 2	December 2015	• Antwerp University Hospital, Edegem, Antwerp, Belgium	NCT02649582
Natural Dendritic Cells for Immunotherapy of Chemo-naive Metastatic Castration-resistant Prostate Cancer Patients	Completed	No Results Available	• Prostatic Neoplasms • Immunotherapy • Dendritic Cells • Vaccines	• Biological: mDC vaccination • Biological: pDC vaccination • Biological: mDC and pDC vaccination	Phase:Phase 2	September 2015	• Radboud University Nijmegen Medical Centre, Nijmegen, Gelderland, Netherlands	NCT02692976
Cellular Immunotherapy for Patients with High Risk Myelodysplastic Syndromes and Acute Myeloid Leukemia	Active, not recruiting	No Results Available	• Myelodysplastic Syndromes • Acute Myeloid Leukemia	• Biological: Autologous dendritic cells electroporated with WT1 mRNA	Phase: • Phase 1 • Phase 2	August 2016	• Hematology and Transfusion Medicine Center, Campinas, São Paulo, Brazil	NCT03083054
Vaccine Therapy for the Treatment of Newly Diagnosed Glioblastoma Multiforme	Recruiting	No Results Available	• Glioblastoma Multiforme • Glioblastoma • Malignant Glioma • Astrocytoma, Grade IV • GBM	• Biological: pp65-shLAMP DC with GM-CSF • Biological: unpulsed PBMC and saline • Drug: Td • Drug: Saline • Biological: pp65-flLAMP DC with GM-CSF	Phase: Phase 2	August 2016	• University of Florida, Gainesville, Florida, United States • Orlando Health, Orlando, Florida, United States • Duke University Medical Center, Durham, North Carolina, United States	NCT02465268
Safety and Efficacy of DC-CIK in Patients with Advanced Non-Small-Cell Lung Cancer With Bone Metastases	Unknown status	No Results Available	• Non-Small-Cell Lung Cancer with Bone Metastases	• Biological: genetically modified dendritic cells + cytokine- induced killer	Phase: • Phase 1 • Phase 2	February 2016	• Affiliated Hospital to Academy of Military Medical Sciences, Beijing, Beijing, China	NCT02688686
MiHA-loaded PD-L-silenced DC Vaccination After Allogeneic SCT	Completed	No Results Available	• Hematological Malignancies	• Biological: MiHA-loaded PD-L-silenced DC Vaccination	Phase: • Phase 1 • Phase 2	January 2016	• Trialoffice Haematology-Oncology, Nijmegen, Gelderland, Netherlands	NCT02528682

Table 2. *Cont.*

Title	Status	Study Results	Conditions	Interventions	Characteristics	Dates—Study Start	Locations	Trial Identifier
Nivolumab With DC Vaccines for Recurrent Brain Tumors	Completed	Has Results	• Malignant Glioma • Astrocytoma • Glioblastoma	• Drug: nivolumab • Biological: DC	Phase: Phase 1	January 2016	• Duke University Medical Center, Durham, North Carolina, United States	NCT02529072
Personalized Cellular Vaccine for Brain Metastases (PERCELLVAC3)	Unknown status	No Results Available	• Brain Cancer • Neoplasm Metastases	• Biological: Personalized cellularvaccine	Phase: Phase 1	June 2016	• Guangdong 999 Brain Hospital, Guangzhou, Guangdong, China	NCT02808416
Personalized Cellular Vaccine for Recurrent Glioblastoma (PERCELLVAC2)	Unknown status	No Results Available	• Glioblastoma	• Biological: Personalized cellular vaccine	Phase: Phase 1	June 2016	• Guangdong 999 Brain Hospital, Guangzhou, Guangdong, China	NCT02808364
Personalized Cellular Vaccine for Glioblastoma (PERCELLVAC)	Unknown status	No Results Available	• Glioblastoma	• Biological: Personalized cellular vaccine	Phase: Phase 1	March 2016	• Guangdong 999 Brain Hospital, Guangzhou, Guangdong, China	NCT02709616
Autologous Dendritic Cell Vaccination in Mesothelioma	Recruiting	No Results Available	• Malignant Pleural Mesothelioma	• Biological: dendritic cell vaccination plus chemotherapy	Phase: • Phase 1 • Phase 2	August 2017	• Antwerp University Hospital, Edegem, Antwerp, Belgium • AZ Middelares, Ghent, Belgium • AZ Nikolaas, Sint-Niklaas, Belgium	NCT02649829
Safety, Tolerability, and Immunogenicity of mRNA-4157 Alone in Participants With Resected Solid Tumors and in Combination with Pembrolizumab in Participants With Unresectable Solid Tumors	Recruiting	No Results Available	• Solid Tumors	• Biological: mRNA-4157 • Biological: Pembrolizumab	Phase: Phase 1	August 2017	• University of Arizona, Tucson, Arizona, United States • Florida Cancer Specialists, Sarasota, Florida, United States • H Lee Moffitt Cancer Center and Research Institute, Tampa, Florida, United States • Massachusetts General Hospital, Boston, Massachusetts, United States • John Theurer Cancer Center, Hackensack, New Jersey, United States • NYU Langone, New York, New York, United States • Duke Cancer Institute, Durham, North Carolina, United States • The Cleveland Clinic Foundation, Cleveland, Ohio, United States • Providence Portland Medical Center, Portland, Oregon, United States • Sarah Cannon Research Institute, Tennessee Oncology, Nashville, Tennessee, United States	NCT03313778
Phase 1/2 Study of Combination Immunotherapy and mRNA Vaccine in Subjects With NSCLC	Completed	No Results Available	• Metastatic Non-small Cell Lung Cancer • NSCLC	• Drug: Durvalumab • Drug: Tremelimumab • Biological: BI 1361849	Phase: • Phase 1 • Phase 2	December 2017	• Research Facility, Gilbert, Arizona, United States • Research Facility, Tampa, Florida, United States • Research Facility, Detroit, Michigan, United States • Research Facility, New York, New York, United States • Research Facility, Milwaukee, Wisconsin, United States	NCT03164772

Table 2. *Cont.*

Title	Status	Study Results	Conditions	Interventions	Characteristics	Dates—Study Start	Locations	Trial Identifier
Dendritic Cell Immunotherapy Against Cancer Stem Cells in Glioblastoma Patients Receiving Standard Therapy	Recruiting	No Results Available	• Glioblastoma	• Biological: Dendritic cell immunization • Drug: Adjuvant temozolomide	Phase: • Phase 2 • Phase 3	April 2018	• Oslo University Hospital, Oslo, Norway	NCT03548571
Clinical Study of Personalized mRNA Vaccine Encoding Neoantigen in Patients with Advanced Digestive System Neoplasms	Unknown status	No Results Available	• Advanced Esophageal Squamous Carcinoma • Gastric Adeno-carcinoma • Pancreatic Adenocarci-noma • Colorectal Adenocarci-noma	Biological: Personalized mRNA Tumor Vaccine	Phase: Not Applicable	May 2018	• Changhai Hospital, Shanghai, Shanghai, China	NCT03468244
Messenger RNA (mRNA)-Based, Personalized Cancer Vaccine Against Neoantigens Expressed by the Autologous Cancer	Terminated	Has Results	• Melanoma • Colon Cancer • Gastrointestinal Cancer • Genitourinary Cancer • Hepatocellular Cancer	Biological: National Cancer Institute (NCI)-4650, a messenger ribonucleic acid (mRNA)-based, Personalized Cancer Vaccine	Phase: • Phase 1 • Phase 2	May 2018	• National Institutes of Health Clinical Center, Bethesda, Maryland, United States	NCT03480152
PRO-MERIT (Prostate Cancer Messenger RNA Immunotherapy)	Recruiting	No Results Available	• Prostate Cancer	• Biological: W_pro1 • Drug: Cemiplimab	Phase: • Phase 1 • Phase 2	December 2019	• The University of Arizona Cancer Center, Tucson, Arizona, United States • University of California San Francisco, San Francisco, California, United States • University of Miami Hospital & Clinics/Sylvester Comprehensive Cancer Center, Miami, Florida, United States • University of Pittsburgh Cancer Inst., Pittsburgh, Pennsylvania, United States • Urology San Antonio P.A., San Antonio, Texas, United States • University of Virginia Cancer Center, Charlottesville, Virginia, United States • Virginia Cancer Specialists, Fairfax, Virginia, United States • Universitätsklinikum Bonn, Bonn, Germany • Klinikum der Johann Wolfgang Goethe-Universität, Frankfurt, Germany • Nationales Centrum für Tumorerkrankungen, Heidelberg, Germany • and 15 more	NCT04382898

Table 2. *Cont.*

Title	Status	Study Results	Conditions	Interventions	Characteristics	Dates—Study Start	Locations	Trial Identifier
An Efficacy Study of Adjuvant Treatment with the Personalized Cancer Vaccine mRNA-4157 and Pembrolizumab in Participants With High- Risk Melanoma (KEYNOTE-942)	Active, not recruiting	No Results Available	• Melanoma	• Biological: mRNA-4157 • Biological: Pembrolizumab	Phase: Phase 2	July 2019	• University of Arizona, Tucson, Arizona, United States • California Pacific Medical Center Research Institute -CPMCRI, San Francisco, California, United States • Angeles Clinic and Research Institute, Santa Monica, California, United States • University of Colorado Cancer Center, Aurora, Colorado, United States • Smilow Cancer Center at Yale New Haven Hospital, New Haven, Connecticut, United States • Lombardi Cancer Center, Washington, District of Columbia, United States • Orlando Health UF Health Cancer Center, Orlando, Florida, United States • UPMC Hillman Cancer Center, Chicago, Illinois, United States • Massachusetts General Hospital, Boston, Massachusetts, United States • Dana Farber Cancer Institute, Boston, Massachusetts, United States • and 12 more	NCT03897881
A Study of mRNA-5671/V941 as Monotherapy and in Combination With Pembrolizumab (V941-001)	Active, not recruiting	No Results Available	• Neoplasms • Carcinoma, Non-Small-Cell Lung • Pancreatic Neoplasms • Colorectal Neoplasms	Biological: V941 • Biological: Pembrolizumab	Phase: Phase 1	June 2019	• Banner MD Anderson Cancer Center (Site 1008), Gilbert, Arizona, United States • City of Hope (Site 1002), Duarte, California, United States • University of California at San Francisco (Site 1006), San Francisco, California, United States • Smilow Cancer Hospital at Yale New Haven (Site 1005), New Haven, Connecticut, United States • Dana-Farber Cancer Institute (Boston) (Site 1007), Boston, Massachusetts, United States • Comprehensive Cancer Centers of Nevada (Site 1012), Las Vegas, Nevada, United States • Tennessee Oncology Nashville Drug Development Unit (Site 7000), Nashville, Tennessee, United States • START San Antonio (Site 1004), San Antonio, Texas, United States • Baylor Scott & White Medical Center—Temple (Site 1009), Temple, Texas, United States • Northwest Medical Specialties, PLLC (Site 1001), Tacoma, Washington, United States • and 16 more	NCT03948763
Clinical Study of Personalized mRNA Vaccine Encoding Neoantigen in Patients with Advanced Esophageal Cancer and Non-small Cell Lung Cancer	Not yet recruiting	No Results Available	• Esophageal Cancer • Non-Small Cell Lung Cancer	Biological: Personalized mRNA Tumor Vaccine	Phase: Not Applicable	May 2019		NCT03908671

Table 2. *Cont.*

Title	Status	Study Results	Conditions	Interventions	Characteristics	Dates—Study Start	Locations	Trial Identifier
Ovarian Cancer Treatment with a Liposome Formulated mRNA Vaccine in Combination With (Neo-)Adjuvant Chemotherapy	Recruiting	No Results Available	• Ovarian Cancer	• Drug: W_ova1 Vaccine	Phase: Phase 1	November 2019	• UMCG, Groningen, Netherlands	NCT04163094
Immunotherapy Targeted Against Cytomegalovirus in Patients with Newly-Diagnosed WHO Grade IV Unmethylated Glioma	Suspended	No Results Available	• Glioblastoma	• Biological: Human CMV pp65-LAMP mRNA-pulsed autologous DCs containing GM CSF • Drug: Temozolomide • Biological: Tetanus-Diphtheria Toxoid (Td) • Biological: GM-CSF • Biological: 111-Indium-labeling of Cells for in vivo Trafficking Studies	Phase: Phase 2	September 2019	• Duke University Medical Center, Durham, North Carolina, United States	NCT03927222
A Study of RNA-lipid Particle (RNA-LP) Vaccines for Newly Diagnosed Pediatric High- Grade Gliomas (pHGG) and Adult Glioblastoma (GBM)	Recruiting	No Results Available	• Adult Glioblastoma	• Biological: Autologous total tumor mRNA and pp65 full length (fl) lysosomal associated membrane protein (LAMP) mRNA loaded DOTAP liposome vaccine administered intravenously (RNA loaded lipidparticles, RNA-LPs)	Phase: Phase 1	October 2021	• UF Health, Gainesville, Florida, United States	NCT04573140
Adjuvant Dendritic Cell Immunotherapy for Pediatric Patients with High-grade Glioma or Diffuse Intrinsic Pontine Glioma	Recruiting	No Results Available	• High Grade Glioma • Diffuse Intrinsic Pontine Glioma	• Biological: Dendritic cell vaccination + temozolomidebased chemoradiation • Biological: Dendritic cell vaccination +- conventional next-line treatment	Phase: • Phase 1 • Phase 2	September 2021	• Unitversity Hospital Antwerp, Edegem, Belgium	NCT04911621
Safety and Efficacy of Personalized Neoantigen Vaccine in Advanced Gastric Cancer, Esophageal Cancer and Liver Cancer	Recruiting	No Results Available	• Gastric Cancer • Esophageal Cancer • Liver Cancer	• Biological: neoantigen tumor vaccine with or without PD-1/L1	Phase: Not Applicable	February 2022	• PLA General Hospital, Beijing, Beijing, China	NCT05192460
A Study of Neoantigen mRNA Personalised Cancer in Patients with Advanced Solid Tumors	Not yet recruiting	No Results Available	• Solid Tumor	• Drug: Neoantigen mRNA Personalised Cancer SW1115C3	Phase: Phase 1	March 2022		NCT05198752
Monocyte Antigen Carrier Cells for Newly Diagnosed GBM	Not yet recruiting	No Results Available	• Glioblastoma • Glioma, Malignant	• Biological: MT-201-GBM monocyte vaccine	Phase: Phase 1	March 2022	• The Preston Robert Tisch Brain Tumor Center at Duke University Medical Center, Durham, North Carolina, United States	NCT04741984
Safety and Efficacy of Personalized Neoantigen Vaccine in Advanced Gastric Cancer	Not yet recruiting	No Results Available	• Gastric Cancer	• Biological: neoantigen tumor vaccine with or without PD-1/L1	Phase: Not Applicable	March 2022	• Department of GI Oncology, Peking University Cancer Hospital, Beijing, China	NCT05227378
Novel RNA-nanoparticle Vaccine for the Treatment of Early Melanoma Recurrence Following Adjuvant Anti-PD-1 Antibody Therapy	Not yet recruiting	No Results Available	• Melanoma	• Biological: Autologous total tumor mRNA loaded DOTAP liposome vaccine	Phase: Phase 1	May 2022		NCT05264974

According to the gathered data (Table 2), it was possible to verify that the most used strategy to load mRNA in cancer vaccines was through dendritic Cells (DC).

Dendritic cells (DCs) are considered the "professional" antigen-presenting cells of the immune system. They are capable of stimulating novel or enhancing existing anti-tumor immune responses. To achieve this result, DCs need to present antigenic peptides and provide co-stimulatory signals, similar to those provided by CD80/CD86 and CD70 or cytokines such as IL-12p70 [54]. DCs can be loaded with RNAs by endocytosis. This process can be improved by electroporation. External loading of DCs will enable and facilitate efficient targeting of antigen presenting cells.

According to Table 2, in the most recent clinical trials, it is possible to verify that other strategies have started to become being developed and implemented such as monocytes loaded with mRNA, neoantigens, liposomes (nanoparticles), and also neo-adjuvants.

These new technologies will help naked RNA to be injected through a carrier. These carriers will improve RNA stability and uptake. Lipid nanoparticles (LNPs) are now one of the most promising delivery systems. They are easy to produce and they are safe [51].

From Table 2, it is also possible to conclude that these recently new technological platforms have been studied more recently after the COVID-19 pandemic. This conclusion is supported by the nine clinical trials from November 2019 to May 2022. By filtering in the table the word "dendritic", 25 results appear from March 2002 to September 2021. Therefore, it is possible to conclude that clinical trials with mRNA vaccines for cancer have been developed prior to the pandemic focusing more on dendritic cells vaccines and more recently other delivery systems are being developed. This trend on lipid nanoparticles might be based on the validated platforms from Pfizer and Moderna's mRNA vaccine since both used lipids to help the mRNA enter the cells as reflected in Table 1.

5. Conclusions and Future Directions

There is huge hope for mRNA technology vaccines in cancer due to success of these vaccines in COVID-19. Platforms have been validated and safety and efficacy data are available. It is therefore needed to engage with the new data available to continue the development and the improvement of mRNA cancer vaccines.

From the regulators, investors, and government side, it is also very important that all these stakeholders recognise that if the same efforts could be applied to the development of mRNA vaccines in oncology, then we could say that improvements in the development of successful mRNA cancer vaccines could be expected and a new era for cancer treatment is possibly about to begin.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

References

1. Greenwood, B. The contribution of vaccination to global health: Past, present and future. *Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci.* **2014**, *369*, 20130433. [CrossRef] [PubMed]
2. WHO. *Ten Threats to Global Health in 2019*; WHO: Geneva, Switzerland, 2019.
3. Dong, Y.; Dai, T.; Wei, Y.; Zhang, L.; Zheng, M.; Zhou, F. A systematic review of SARS-CoV-2 vaccine candidates. *Signal Transduct. Target. Ther.* **2020**, *5*, 237. [CrossRef] [PubMed]
4. Dai, L.; Gao, G.F. Viral targets for vaccines against COVID-19. *Nat. Rev. Immunol.* **2020**, *21*, 73–82. [CrossRef] [PubMed]
5. CDC. Varicella. In *Epidemiology and Prevention of Vaccine-Preventable Diseases*; CDC: Atlanta, GA, USA, 2021.
6. Wolf, J.; Bruno, S.; Eichberg, M.; Jannat, R.; Rudo, S.; VanRheenen, S.; Coller, B.A. Applying lessons from the Ebola vaccine experience for SARS-CoV-2 and other epidemic pathogens. *Npj Vaccines* **2020**, *5*, 51. [CrossRef]
7. Bok, K.; Sitar, S.; Graham, B.S.; Mascola, J.R. Accelerated COVID-19 vaccine development: Milestones, lessons, and prospects. *Immunity* **2021**, *54*, 1636–1651. [CrossRef]
8. Ball, P. The lightning-fast quest for COVID vaccines—And what it means for other diseases. *Nature* **2020**, *589*, 16–18. [CrossRef]
9. Dolgin, E. How COVID unlocked the power of RNA vaccines. *Nature* **2021**, *589*, 189–191. [CrossRef]
10. Lythgoe, M.P.; Middleton, P. Comparison of COVID-19 Vaccine Approvals at the US Food and Drug Administration, European Medicines Agency, and Health Canada. *JAMA Netw. Open* **2021**, *4*, e2114531. [CrossRef]
11. Saadi, F.; Pal, D.; Sarma, J.D. Spike Glycoprotein Is Central to Coronavirus Pathogenesis-Parallel Between m-CoV and SARS-CoV-2. *Ann. Neurosci.* **2021**, *28*, 201–218. [CrossRef]
12. Badgujar, K.C.; Badgujar, V.C.; Badgujar, S.B. Vaccine development against coronavirus (2003 to present): An overview, recent advances, current scenario, opportunities and challenges. *Diabetes Metab. Syndr. Clin. Res. Rev.* **2020**, *14*, 1361–1376. [CrossRef] [PubMed]
13. Su, S.; Du, L.; Jiang, S. Learning from the past: Development of safe and effective COVID-19 vaccines. *Nat. Rev. Genet.* **2020**, *19*, 211–219. [CrossRef] [PubMed]
14. Riley, T.P.; Chou, H.T.; Hu, R.; Bzymek, K.P.; Correia, A.R.; Partin, A.C.; Li, D.; Gong, D.; Wang, Z.; Yu, X.; et al. Enhancing the Prefusion Conformational Stability of SARS-CoV-2 Spike Protein Through Structure-Guided Design. *Front. Immunol.* **2021**, *12*, 660198. [CrossRef] [PubMed]
15. Khandker, S.S.; Godman, B.; Jawad, I.; Meghla, B.A.; Tisha, T.A.; Khondoker, M.U.; Haq, A.; Charan, J.; Talukder, A.A.; Azmuda, N.; et al. A Systematic Review on COVID-19 Vaccine Strategies, Their Effectiveness, and Issues. *Vaccines* **2021**, *9*, 1387. [CrossRef] [PubMed]
16. Fang, E.; Liu, X.; Li, M.; Zhang, Z.; Song, L.; Zhu, B.; Wu, X.; Liu, J.; Zhao, D.; Li, Y. Advances in COVID-19 mRNA vaccine development. *Signal Transduct. Target. Ther.* **2022**, *7*, 94. [CrossRef] [PubMed]
17. Granados-Riveron, J.T.; Aquino-Jarquin, G. Engineering of the current nucleoside-modified mRNA-LNP vaccines against SARS-CoV-2. *Biomed. Pharmacother.* **2021**, *142*, 111953. [CrossRef]
18. DDolgin, E. Unlocking the potential of vaccines built on messenger RNA. *Nature* **2019**, *574*, S10–S12. [CrossRef]
19. British Society for Immunology, What Is Immunology? Available online: https://www.immunology.org/public-information/what-is-immunology (accessed on 5 February 2022).
20. PParkin, J.; Cohen, B. An overview of the immune system. *Lancet* **2001**, *357*, 1777–1789. [CrossRef]
21. Eftimie, R.; Gillard, J.J.; Cantrell, D.A. Mathematical Models for Immunology: Current State of the Art and Future Research Directions. *Bull. Math. Biol.* **2016**, *78*, 2091–2134. [CrossRef]
22. Marshall, J.S.; Warrington, R.; Watson, W.; Kim, H.L. An introduction to immunology and immunopathology. *Allergy, Asthma Clin. Immunol.* **2018**, *14*, 49. [CrossRef]
23. Zhang, Y.; Yang, W.; Li, W.; Zhao, Y. NLRP3 Inflammasome: Checkpoint Connecting Innate and Adaptive Immunity in Autoimmune Diseases. *Front. Immunol.* **2021**, *12*, 732933. [CrossRef]
24. Sherwood, E.R.; Burelbach, K.R.; McBride, M.A.; Stothers, C.L.; Owen, A.M.; Hernandez, A.; Patil, N.K.; Williams, D.L.; Bohannon, J.K. Innate Immune Memory and the Host Response to Infection. *J. Immunol.* **2022**, *208*, 785–792. [CrossRef] [PubMed]
25. Dranoff, G. Cytokines in cancer pathogenesis and cancer therapy. *Nat. Cancer* **2004**, *4*, 11–22. [CrossRef] [PubMed]
26. Haseeb, M.; Anwar, M.A.; Choi, S. Molecular Interactions Between Innate and Adaptive Immune Cells in Chronic Lymphocytic Leukemia and Their Therapeutic Implications. *Front. Immunol.* **2018**, *9*, 2720. [CrossRef] [PubMed]
27. Nishimura, T.; Kitamura, H.; Iwakabe, K.; Yahata, T.; Ohta, A.; Sato, M.; Takeda, K.; Okumura, K.; Van Kaer, L.; Kawano, T.; et al. The interface between innate and acquired immunity: Glycolipid antigen presentation by CD1d-expressing dendritic cells to NKT cells induces the differentiation of antigen-specific cytotoxic T lymphocytes. *Int. Immunol.* **2000**, *12*, 987–994. [CrossRef]
28. Wieczorek, M.; Abualrous, E.T.; Sticht, J.; Álvaro-Benito, M.; Stolzenberg, S.; Noé, F.; Freund, C. Major Histocompatibility Complex (MHC) Class I and MHC Class II Proteins: Conformational Plasticity in Antigen Presentation. *Front. Immunol.* **2017**, *8*, 292. [CrossRef]

29. Spellberg, B.; Edwards, J.E., Jr. Type 1/Type 2 Immunity in Infectious Diseases. *Clin. Infect. Dis.* **2001**, *32*, 76–102. [CrossRef]
30. Sahin, U.; Muik, A.; Derhovanessian, E.; Vogler, I.; Kranz, L.M.; Vormehr, M.; Baum, A.; Pascal, K.; Quandt, J.; Maurus, D.; et al. COVID-19 vaccine BNT162b1 elicits human antibody and TH1 T-cell responses. *Nature* **2020**, *586*, 594–599. [CrossRef]
31. Lee, S.; Ryu, J.-H. Influenza Viruses: Innate Immunity and mRNA Vaccines. *Front. Immunol.* **2021**, *12*, 710647. [CrossRef]
32. Minnaert, A.-K.; Vanluchene, H.; Verbeke, R.; Lentacker, I.; De Smedt, S.C.; Raemdonck, K.; Sanders, N.N.; Remaut, K. Strategies for controlling the innate immune activity of conventional and self-amplifying mRNA therapeutics: Getting the message across. *Adv. Drug Deliv. Rev.* **2021**, *176*, 113900. [CrossRef]
33. Vance, R.E.; Eichberg, M.J.; Portnoy, D.A.; Raulet, D.H. Listening to each other: Infectious disease and cancer immunology. *Sci. Immunol.* **2017**, *2*, eaai9339. [CrossRef]
34. Benharroch, D.; Osyntsov, L. Infectious Diseases Are Analogous With Cancer. Hypothesis And Implications. *J. Cancer* **2012**, *3*, 117–121. [CrossRef] [PubMed]
35. Trinchieri, G. Cancer Immunity: Lessons From Infectious Diseases. *J. Infect. Dis.* **2015**, *212*, S67–S73. [CrossRef] [PubMed]
36. EMA. COVID-19 Vaccines: Development, Evaluation, Approval and Monitoring. 2020. Available online: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/vaccines-covid-19/covid-19-vaccines-development-evaluation-approval-monitoring (accessed on 3 February 2022).
37. Marinus, R.; Mofid, S.; Mpandzou, M.; Kühler, T.C. Rolling Reviews During COVID-19: The European Union Experience in a Global Context. *Clin. Ther.* **2022**, *44*, 352–363. [CrossRef] [PubMed]
38. CDC. Pfizer-BioNTech COVID-19 Vaccine. Available online: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines/Pfizer-BioNTech.html (accessed on 2 February 2022).
39. CDC. Moderna COVID-19 Vaccine. Available online: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines/Moderna.html (accessed on 2 February 2022).
40. EMA. EPAR Comirnaty. Available online: https://www.ema.europa.eu/en/medicines/human/EPAR/comirnaty (accessed on 3 February 2022).
41. EMA. EPAR Spikevax. Available online: https://www.ema.europa.eu/en/medicines/human/EPAR/spikevax (accessed on 3 February 2022).
42. EMA. EPAR Vaxzevria. Available online: https://www.ema.europa.eu/en/medicines/human/EPAR/vaxzevria-previously-covid-19-vaccine-astrazeneca (accessed on 3 February 2022).
43. AstraZeneca, A.B. Summary of Product Characteristics, Vaxzevria. 2021. Available online: https://www.ema.europa.eu/en/documents/product-information/vaxzevria-previously-covid-19-vaccine-astrazeneca-epar-product-information_en.pdf (accessed on 3 February 2022).
44. EMA. EPAR COVID-19 Vaccine Janssen. Available online: https://www.ema.europa.eu/en/medicines/human/EPAR/covid-19-vaccine-janssen (accessed on 4 February 2022).
45. CDC. Johnson & Johnson's Janssen COVID-19 Vaccine. Available online: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines/janssen.html (accessed on 4 February 2022).
46. Janssen-Cilag International, N.V. Summary of Product Characteristics. Available online: https://www.ema.europa.eu/en/documents/product-information/covid-19-vaccine-janssen-epar-product-information_en.pdf (accessed on 3 February 2022).
47. Wang, Y.; Zhang, Z.; Luo, J.; Han, X.; Wei, Y.; Wei, X. mRNA vaccine: A potential therapeutic strategy. *Mol. Cancer* **2021**, *20*, 33. [CrossRef]
48. Chakraborty, C.; Sharma, A.R.; Bhattacharya, M.; Lee, S.-S. From COVID-19 to Cancer mRNA Vaccines: Moving From Bench to Clinic in the Vaccine Landscape. *Front. Immunol.* **2021**, *12*, 679344. [CrossRef]
49. Rosa, S.S.; Prazeres, D.M.F.; Azevedo, A.M.; Marques, M.P.C. mRNA vaccines manufacturing: Challenges and bottlenecks. *Vaccine* **2021**, *39*, 2190–2200. [CrossRef]
50. Conditional Marketing Authorisation, EMA. Available online: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorisation (accessed on 7 May 2022).
51. Heine, A.; Juranek, S.; Brossart, P. Clinical and immunological effects of mRNA vaccines in malignant diseases. *Mol. Cancer* **2021**, *20*, 52. [CrossRef]
52. Chaudhary, N.; Weissman, D.; Whitehead, K.A. mRNA vaccines for infectious diseases: Principles, delivery and clinical translation. *Nat. Rev. Drug Discov.* **2021**, *20*, 817–838. [CrossRef]
53. Pardi, N.; Hogan, M.J.; Porter, F.W.; Weissman, D. mRNA vaccines—A new era in vaccinology. *Nat. Rev. Drug Discov.* **2018**, *17*, 261–279. [CrossRef]
54. Benteyn, D.; Heirman, C.; Bonehill, A.; Thielemans, K.; Breckpot, K. mRNA-based dendritic cell vaccines. *Expert Rev. Vaccines* **2015**, *14*, 161–176. [CrossRef]