Application of Dendritic Cell Vaccines in COVID-19

By

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Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I/We have acknowledged all main sources of help.

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Approval

The project titled "[Dendritic Cell Vaccines: a ray of hope to fight COVID-19 pandemic]" submitted by Md. Shohan Khan (18146030) of Spring, 2022 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy on March 10,2022.

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Ethics Statement

No human or animal tests were involved in this study.

Abstract

Immunotherapy may hold promise as a treatment for coronavirus disease, the greatest epidemic this generation has seen, a disease that has wreaked havoc on the world's health and economic systems. We believe that using DC vaccine therapy as a treatment method for COVID-19 could be beneficial. Due to their immune-compromised status, cancer patients are among the most vulnerable people. In this review, the various approaches and conventional technologies employed to develop vaccines against COVID-19 will be compared with dendritic cell vaccines to show how dendritic cell vaccines can be a ray of hope for the world to be a healthy place again and also how it can boost up the overall vaccination process.

Keywords: Dendritic cell; vaccines; COVID-19; immune-response; cytokines

Dedication

I want to dedicate this study wholeheartedly to my respected supervisor Professor Dr. Hasina Yasmin for her guidance and continuous support.

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List of Acronyms

VLP	Virus-like Particles
ID	Infectious Disease
APC	Antigen Presenting Cells
PRR	Pattern Recognition Receptors
CTL	Cytotoxic T Lymphocyte

Chapter 1

Introduction

1.1 Viral infections and immunity

Humans can be infected by virus which can lead to different symptoms, and in vast majority of cases, the sickness disappears with or without tissue damage. Some of the viruses have effective immunization. Major damage of the tissue can occur in the patients who are infected by different virus and infections can be severe. We don't have effective vaccines against all of the viruses because of having different traits which allows them to decrease its efficiency of the host's innate and adaptive immunity (Rouse & Sehrawat, 2010).

Almost all viral infections cause inflammatory cell types to be recruited and activated, which then produce a variety of substances which cause tissue damage or malfunction. Damaging of tissue is mediated by both innate and adaptive immunological signalling processes. Scientists have been working hard to better understand various infections and how the immune system reacts to them (Rouse & Sehrawat, 2010).

Medical students from the 1980s frequently recount being discouraged from pursuing a career in infectious diseases (ID). They said that ID was an ancient specialization that would soon become extinct, claiming that once antibiotics had taken care of diseases, there would be no need for ID specialists. The advent of the human immunodeficiency virus broke this positivistic and illuminist view of scientific progress as an unstoppable trajectory creating a wide range of solutions to our problems (Barré-Sinoussi et al., 1983; R. C. Gallo et al., 1983; Levy et al., 1984), Even if remnants of positivistic medical aspirations still believed that vaccines will quickly end the HIV pandemic. We are still waiting for an HIV vaccine, but thanks to scientific advancements, a number of antiretroviral compounds have been developed, allowing HIV infection to be managed as a chronic illness (Oy et al., 2009). This result prompted a huge

number of reports from public health specialists stating that developed-country health-care systems could be drastically altered: acute, emergency medicine should be drastically decreased in favour of chronic illnesses and rehabilitation (Beaglehole et al., 2007; Nugent, 2008). Then, in the winter of 2019, SARS-CoV-2 emerged, swept the globe by storm, and once again demonstrated that microorganisms, particularly viruses, and the deadly diseases they cause are far from being eradicated (Chu et al., 2016). Infectious pathogens, such as viruses, infect hosts. The immune system confronts infections, fights them, and, if all goes well, defeats them to restore health (Clerici, 2021). Viruses and the immune system are constantly fighting with one other. Viruses use a variety of processes and mutations to avoid immune detection and/or develop mechanisms that allow them to build more successful, more widespread infections. Molecules of immune systems like- proteins, and cells are continually improving their ability to recognize infections, reducing their ability to infiltrate cells and proliferate within the host (Barré-Sinoussi et al., 1983; Sironi et al., 2015).

1.2 COVID-19

On the first day of the year 2020, COVID-19, an infectious illness with the potential to become a global pandemic, was identified in the Chinese city of Wuhan. COVID-19, despite its unique transmission and pathogenicity, shares different flu-like conditions with zoonotic diseases such as other SARS variations and MERS. Because of these similarities, COVID-19 patients have been treated with clinical approaches that have been proved to be successful against SARS. The disease is marked by a high fatality rate, a lack of medical countermeasures, and a wide reservoir distribution (Kim et al., 2020). The devastating economic repercussions of this epidemic are immeasurable, with many countries straining their health-care resources and job losses across a variety of industries. COVID-19 is a highly contagious and virulent virus (Poland, 2020; Shereen et al., 2020). COVID-19 individuals experience cough, fever, and dyspnoea as symptoms. Severe types of the virus are linked to severe acute respiratory distress, pneumonia and mortality (Wu et al., 2020). It's difficult to estimate the number of

asymptomatic COVID19 affected people. Cough, fever, rhinitis, exhaustion, and other symptoms of the disease usually appear within a few days for those who are experiencing symptoms. About 75% of COVID-19 individuals have symptoms that can be diagnosed with computed tomography. Blood gas deviations, reduced oxygen saturation, interlobular involvement, and alveolar exudates are frequent signs of viral pneumonia in individuals in the second or third week of symptomatic infection. Lympopenia is usually associated with elevated levels of proinflammatory cytokines and inflammatory markers (Velavan & Meyer, 2020). Individual transmission of SARS-CoV-2 is extremely increased (X. Cao, 2020). It is increasingly growing, and despite the availability of many therapeutic alternatives, there are currently no viable medications to address this. The mainstay of therapy is oxygen therapy and symptom management, with mechanical ventilators utilized for patients with pulmonary failure (X. Cao, 2020). H5N1 influenza A virus, SARS-CoV, H1N1 2009, and the Middle East respiratory syndrome coronavirus have all transmitted from birds or animals to humans in the previous two decades (Wu et al., 2020). Two of the most prevalent respiratory disorders are acute respiratory distress syndrome (ARDS) and acute lung damage. As per the John Hopkins University Coronavirus Resource Center in Baltimore, Maryland, USA, 250,925,501 persons were affected and roughly 5,069,182 died. We're in the midst of a virus outbreak. It has to come to an end. I'll be talking about the possibility of DC immunization as a way to add another soldier to the fight against the virus (*COVID Live Update: 250,925,501 Cases and 5,069,182 Deaths from the Coronavirus - Worldometer*, 2021).

1.3 Dendritic Cells

Dendritic cells are antigen-presenting cells that can activate naive T cells and help them mature into effector cells. They have the ability to initiate, coordinate, and govern adaptive immune responses (Banchereau et al., 2000). They were first discovered in the spleen of mice and are known for their peculiar shape and ability to activate naive lymphocytes (Steinman & Idoyaga, 2010). Though their ability to capture, process, and deliver antigens is regarded as their most important feature, their phenotypic variation is remarkable, and their actions can have quite

varied outcomes. In homeostatic settings, they are also implicated in the induction and maintenance of immunological tolerance. Their phenotypic and functional variability reflects their tremendous flexibility and ability to adjust the acquired immune response in response to their environment, but it also makes correct classification difficult and subject to repeated revisions and improvements (Mastelic-Gavillet et al., 2019).

1.4 Vaccination

Dendritic cells are the most powerful antigen-presenting cells (APC) in the body, and they control both innate and adaptive immune responses (Banchereau & Steinman, 1998). DC patrol the tissue microenvironment in their immature stage and become activated in the presence of external pathogens. In response to external threat signals, pattern recognition receptors such as Toll-like receptors are activated (P. M. Gallo & Gallucci, 2013). DCs migrate to the draining lymph node, where they provide T lymphocytes with processed epitopes. DC activate the TCR, produce particular cytokines, and promote immunological responses toward TH1 or TH2 depending on the cytokine environment during T cell activation. DC have been employed as vaccination platforms to produce anti-tumor cytotoxic T lymphocyte (CTL) CD8+ immunological responses due to their ability to cross-present antigens (Bonasio & von Andrian, 2006).

1.5 Aim

In this study, a concise overview of DC vaccine therapy in order to properly understand the interactions which can occur in between the body's immunity and diseases like- cancer, infectious diseases will be provided. It can open the way for the further development of properly designed treatment methods in particular for the immune-compromised cancer patients and patients who are being infected by SARS-CoV-2 virus.

1.6 Objectives

Firstly, a brief knowledge on Dendritic cell vaccines and the pathophysiology of COVID-19 will be provided. Furthermore, the alternative treatment procedures to treat the disease in the clinics will be discussed. Finally, the various approaches and conventional technologies employed to develop vaccines against COVID-19 will be compared with dendritic cell vaccines to show how dendritic cell vaccines can be a ray of hope for the world to be a healthy place again and also how it can boost up the overall vaccination process.

Chapter 2

Methodology

This review was based on recent and important research papers and articles from journals with high impact factors. A thorough search of peer-reviewed publications, clinical trial papers, and articles was conducted. Basic and supplementary material was gathered from several books to supplement the review study. ResearchGate, Science Direct, PubMed, Elsevier, and others were utilized to gather data for this paper, with notable publications such as Nature, ACS, IDI(Infectious Disease Institute), Molecular Cell, Journal of Global Infectious Disease, Journal of Medicine, Science, and others. To generate an optimal quality review on the potentialities of Dendritic Cell vaccines in the context of COVID-19, a thorough scan of journals was conducted, followed by a filtering down to the most recent and relevant ones.

Chapter 3

COVID-19

3.1 Pathogenesis

SARS-pathophysiology CoV-2's has yet to be fully understood. Patients with COVID-19 had higher plasma levels of interleukins, interferon, fibroblast growth factor, granulocyte colony-stimulating factor etc. and vascular endothelial growth factor in comparison to healthy people (Huang et al., 2020).

3.2 Sign and symptoms:

The symptoms of coronavirus disease 2019 might show anywhere from 2 to 14 days after exposure. Some of the most prevalent signs and symptoms are listed below-

Common Symptoms	Different Symptoms
• Fever • Cough	• Shortness of breath • Muscle aches
• Tiredness	• Chills • Sore throat • Runny nose • Headache • Chest pain • Nausea • Vomiting • Diarrhea

	• Rash

3.3 Current treatment options

1. **Convalescent plasma therapy**

Patients with viral illnesses such as severe acute respiratory syndrome, Middle East respiratory syndrome, or influenza are routinely treated with convalescent plasma therapy (Qu et al., 2020). Some proof suggest that convalescent plasma treatment can help COVID-19 patients recover more quickly. In most cases, patients get 3 days of improved laboratory and clinical outcomes and 1 week for virus eradication (Qu et al., 2020). When convalescent plasma becomes available, it may be a feasible choice for treating very ill COVID-19 patients, based on these promising early results.

2. **Interferon**

Type I interferons are antiviral signaling molecules that stimulate key intracellular pathways, preventing virus internalization, replication, and transmission while enhancing immune cell activation. Interferon treatment, while effective, can cause influenza-like symptoms and mood swings, making it unsuitable for individuals with severe autoimmune diseases (Song et al., 2020).

3. **Tocilizumab**

Because COVID-19 patients often have high levels of IL-6 in their blood, inhibitors of IL-6 signaling have been proposed as potential therapy to reduce systemic inflammation.

Tocilizumab is a recombinant humanised monoclonal antibody that targets the IL-6 receptor and has been demonstrated to be useful in the treatment of CRS (W. Cao et al., 2020). Tocilizumab has been shown in certain studies to reduce SARS-CoV-2-related inflammation but its safety and therapeutic efficacy have yet to be determined.

4. **Antiviral therapy**

Antiviral treatments are received by most of the patients which includes-ribavirin, favipiravir, remdesivir, lopinavir-ritonavir, chloroquine and hydroxychloroquine. These antiviral medicines may be useful in the treatment of this condition. However, it is not suggested to use three or more antiviral drugs in a patient, and their usage has to be discontinued if they have unacceptable side effects (Qu et al., 2020).

5. **Remdesivir**

Remdesivir is a prodrug that reduces SARS-CoV-2 viral replication in vitro by reducing viral RNA polymerase activity. Remdesivir's nucleoside analogue activity can cause premature viral RNA chain termination. Like a consequence, it's considered one of the most effective COVID19 broad-spectrum antiviral treatments(**Warren et al, 2016**).

6. **Chloroquine and hydroxychloroquine**

For more than 70 years, chloroquine has been used as an antimalarial and autoimmune diseases can be treated, but there is proof that it can also be used as an antiviral treatment in some conditions. SARS-CoV-2 infectivity is more robustly inhibited by hydroxychloroquine, a safer chloroquine derivative. In one trial, a combination of hydroxychloroquine and azithromycin was found to be effective in reducing viral load and improving treatment results in COVID-19 patients. When evaluating the application of these drugs, it is critical to analyze the risk of each individual patient.

Chapter 4

Conventional SARS COV-2 Vaccines

Vaccination is the most common intervention technique for preventing coronavirus infection and transmission. A vaccination, on the other hand, can take ten to fifteen years to develop. Thanks to the rapid identification and publication of the SARS-CoV-2 gene sequence, the first vaccine candidate was ready for clinical testing in just a few months.

4.1 Inactivated coronavirus vaccine

The virus's nucleic acids can be destroyed while the antigens are preserved. Animal models were employed to explore the immunological features and efficacy of inactivated CoV vaccine during the original SARS virus outbreak. An inactivated SARS-CoV vaccine was assessed in rhesus monkeys and found to produce humoral and mucosal protection, indicating that it might be employed in clinical trials (J. Zhou et al., 2005).

Antibodies produced against SARS-CoV-2 were found to neutralize 10 distinct strains, suggesting their broad utility against the virus. 26 Incomplete inactivation, on the other hand, could constitute a public health risk by triggering undesired immune or inflammatory responses (Amanat & Krammer, 2020).

4.2 Live-attenuated coronavirus vaccine

Live coronavirus vaccines are made from coronaviruses whose pathogenicity has been reduced in the lab. This approach allows the virus to spread throughout the host while posing little or no risk to the host. Its suitability for the elderly, who are more susceptible to serious illnesses, is also a subject of concern (Amanat & Krammer, 2020). Live-attenuated viral vaccinations,

on the other hand, are unlikely to be the best option due to concerns about safety, especially among the elderly(Yadav et al., 2020).

4.3 Recombinant COVID-19 vaccines

1. **Nucleic acid-based coronavirus vaccine**

The ability to develop DNA and RNA-based vaccines quickly and with few side effects is their main advantage. DNA vaccines have shown a great potential for inducing immune responses against CoVs in animal models. On the other hand, clinical data on the efficacy of DNA vaccines in humans is lacking. On 35 rhesus monkeys, a series of prototype DNA vaccines encoding multiple SARS-CoV-2 S proteins were evaluated. Different humoral and cellular immune responses were seen in the vaccinated macaques. The animals showed a significant reduction in viral replication in the upper and lower respiratory tracts after
being infected with SARS-CoV-2. Findings demonstrated the importance of a DNA vaccination in the context of COVID (Smith et al., 2020).

These vaccines can be manufactured in a short period of time because of its less time-consuming standardization technique. BNT162b1 is a lipid nano particle-based vaccine made from nucleoside-modified mRNA that encodes a trimerized SARS-CoV2 spike glycoprotein receptor-binding domain (Jingxin Li et al., 2021).

2. **Protein-based coronavirus vaccine**

Because of the S protein's role in host cell receptor binding and membrane fusion, a SARSCoV-2 vaccination based on it could successfully stimulate antibody production and viral neutralization. As a result, the S protein appears to be a suitable vaccination target. Tazehkand and Hajipour (2020) combined an envelope and nucleocapsid protein with multi epitopes acquired from the S protein and RNA-dependent RNA polymerase to generate a fusion vaccine. Despite the fact that the vaccine's structural stability, physicochemical qualities, and

immunological properties were all verified during a preliminary screening, the authors predicted that more tests with laboratory animals would be required(Chauhan et al., 2018).

Chapter 5

Dendritic cells

DCs are immune system regulators that have a reputation for initiating adaptive immunity. DCs were previously classified based on cell shape, expression of certain markers, and functional characteristics such the ability to move to T cell regions of secondary lymphoid organs and activate T lymphocytes. Such properties, on the other hand, are not qualitative, and they vary often in the presence of inflammation or infection (Schraml & Reis e Sousa, 2015).

5.1 Mechanism of action of Dendritic cell vaccines

DCs mature in lymph nodes, spleens, and Peyer's patches before migrating to secondary lymphoid organs where they interact with T and B cells. cDCs are transported from nonlymphoid tissues to lymph node T cell-rich locations via afferent lymph. pDCs are expected to use CCR7 and CD62-L to access secondary lymphoid tissue T cell regions via lymph node high endothelial venules and the splenic marginal zone (Penna et al., 2002).

During DC maturation, costimulatory and MHC molecules must be overexpressed in order to form stable and long-lasting connections with T cells, which is needed for the growth of T-cell and differentiation into memory and effector T cells. Memory and naive B cells can be activated by DCs, mainly via activating CD4+ T cells and it increases B-cell proliferation and production of antibody. By generating XCL1 and XCL2, NK cells and CD8+ T cells can recruit and induce particular responses in XCR1 expressing DCs (Fox et al., 2015). Finally, DCs expressing invariant CD1 molecules and presenting glycolipid molecules activate NKT cells. As a result, by activating numerous arms of the immune system, DCs play a critical role in both the innate and adaptive immune systems (Cools et al., 2007). Immature DCs acquire self-antigens as part of immune surveillance (Frleta et al., 2012).

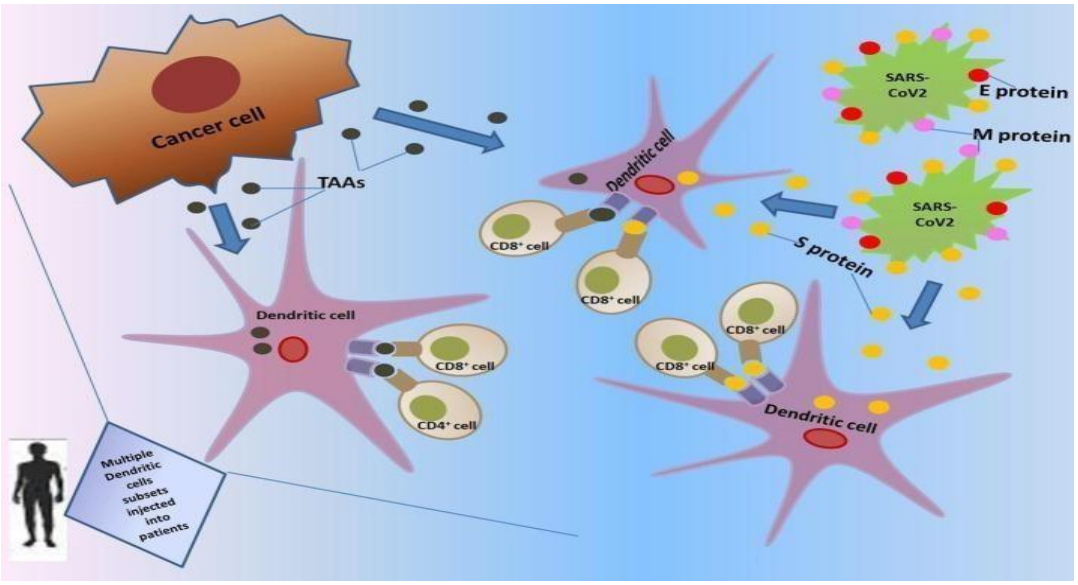

Figure 1: In cancer patients, a DC vaccination treatment strategy against COVID-19

5.2 Strategies of Dendritic cell vaccination approaches

The use of CD40 and CLR ligation to target DCs in vivo is a recent approach. Antagonist CD40 antibodies were applied to mimic DC activation and it is needed for the generation of proinflammatory cytokines and the development of T cell activation. In animal models, CD40 antibody was given after chemotherapy and was demonstrated to have a synergistic impact in stimulating CD8+ T cell responses, leading to tumor eradication (Beatty et al., 2013). Anti-CD40 may alter the TME via activating monocytes, which is interesting. Different DC subsets have been identified to express different CLRs, which are implicated in the identification and capture of a variety of glycosylated antigens, making CLRs an especially intriguing target. Antigens targeting CLRs resulted in effective induction of T cell responses in animals. In animal models, antigen targeting with Clec9a showed good result (Jessica Li et al., 2015). Humanized mice models of Clec9a-mediated antigen targeting have shown antigen-specific T cell responses, indicating that this technique could be used in the clinic. The relationship between clinical responses is unclear, and more research is needed to examine the effectiveness (Fossum et al., 2015).

Tumor antigens delivered via systemic RNA lipoplex injection could be employed in new ways to target in vivo DCs. The RNA is protected from degradation by the lipoplexes, while the RNA activates pDCs and causes type I IFN to be produced. The safety of IV injection of the RNA-LPX vaccine is currently being assessed in melanoma patients in a phase I dosage escalation trial (Kranz et al., 2016).

Finally, DC vaccines are being explored in immunological prevention due to their safety profile. Immune prevention is a method of preventing cancer recurrence. Microsatellite instability in patients with colorectal cancer is increasingly being researched. In high-risk recurrence situations, a long-term goal is to immunize patients prophylactically (Sabado et al., 2017).

Chapter 6

Promising roll of DCs in the infection of SARS-CoV-2 infection

We postulated that mobilizing DCs with the purpose of generating both antibody-mediated and cell-mediated immune responses could be crucial for the SARS-CoV-2 vaccine, given their relevance in the host cell's battle against infection by an invading pathogen. The advantages of using DCs can be applied in a variety of ways in general. Patients who recovered from SARS during convalescence have shown T-cell responses, and memory T-cell responses have been observed up to 6 years after infection. They released several effector cytokines that effectively reduced viral titers in the lungs of SARS-CoV-infected animals (Zhao et al., 2010). DCs can efficiently encourage CD4+ T cells to develop into IFN-secreting Th1 CD4+ T cells. CD4+ T cells also assist B cells in secreting antibodies and altering antibody isotypes. It was discovered that DC-delivered peptides stimulate a particular immune response hundred to one thousand times more effectively than non-specifically delivered peptides. The function of CD8+ T cells is then generated by stimulations from mature DC. Furthermore, both CD4+ and CD8+ responses can be induced by mature DCs (Steinman & Banchereau, 2007). Furthermore, DC as a carrier has the potential to significantly increase vaccine safety. Some studies found that immunizing monkeys with an adenoviral-based SARS vaccine resulted in antibodies and T cell-mediated responses, which could lead to adverse immune responses and inflammation (Weingartl et al., 2004). This is one of the reasons why vaccinations based on viral vectors have failed. They give B cells antigen-antibody complexes, which cause them to proliferate, mature, and switch immunoglobulin classes. B lymphocytes create neutralizing antibodies that neutralize viruses, protecting the host cells from infection (H. Zhou et al., 2019).

Pulsing APCs to generate a specific response is done with peptides that have a stronger capability for binding to HLA in vitro. The term "immunological" refers to the process of

identifying antigens through the engagement of immune components. Theoretically, we could use this to mobilize DCs for CoVs therapy, which would be a relatively safe option(Han et al., 2021).

6.1 DC in other disease

Increased knowledge of DCs and the ability to generate large numbers of DCs ex vivo have led to the introduction of DC vaccinations in cancer patients as a novel cancer therapy approach in the last decade. For patients with advanced tumors who have failed to react to standard cancer treatments, cancer immunotherapy with DCs offers the best hope. In some cancers, DC's have showed great result which can also prevent the autoimmune diseases. During 1998, the researchers reported therapeutic responses. Clinical reactions, whether full or partial, were uncommon (Bonab, 2015). Sipuleucel-T, a DC vaccine, was licensed by the USFDA in 2010 for the treatment of individuals with asymptomatic or slightly symptomatic metastatic hormone-refractory prostate cancer. So yet, the USFDA has only approved this DC vaccine for the treatment of cancer. Sipuleucel-T can help patients survive for many months longer. This vaccine is made up of autologous DCs generated from monocytes that have been pulsed with the tumor antigen PAP (Kantoff et al., 2010). Due to innovations in DC vaccine preparation processes or combinational therapy, the efficacy of DC immunizations has increased in recent years (Hobo et al., 2013).

2 of 5 patients with ovarian cancer who were vaccinated with DCs pulsed with hypochlorous acid-oxidized tumor lysate reported two years or more of progression-free life after DC vaccination. After two years, 16 patients having neck squamous cell carcinoma who were vaccinated with DCs loaded with the tumor peptide p53 had an 88 percent disease-free survival rate. Patients with invasive hepatocellular carcinoma who received a tumor lysate-pulsed DCs vaccination in combination with ex vivo-activated T cells following curative surgery had longer recurrence-free survival and overall survival. In nine of thirteen people with metastatic melanoma, vaccination with autologous MART-1pulsed DCs paired with adoptive transplant of TCR transgenic T cells resulted in tumor regression. Patients with stage III/IV squamous

cell carcinoma of the head and neck who received intranodally administered apoptotic tumor cell-loaded DCs were disease-free for more than five years (Bonab, 2015).

6.2 Beneficial aspects of DC vaccines for COV therapy

The COVID-19 causal agent, SARS COV-2, belongs to the Corona viridae family of viruses, which are named for their surface crown-shaped glycoproteins. Spike protein, envelope protein, membrane protein, and nucleocapsid protein are the four structural proteins found in a virion particle. The alpha and beta coronaviruses are the only members of the family that can only replicate in mammals, but the gamma and delta coronaviruses can replicate in both, although primarily in birds (Saadeldin et al., 2021). Some beta corona strains multiply in humans and causes the common cold. SARS-genomic CoV-2's material is a single-stranded, positive-sense RNA that encodes a number of open reading frames, including those for the S-protein. The virus's attachment to the angiotensin-converting enzyme-2 receptor on the host cell's surface and subsequent endosome engulfment is controlled by the S protein. The replicase enzyme, as well as other accessory and structural proteins, are also encoded, albeit not all accessory proteins' activities are well understood.

S1 and S2 are the two functional subunits that make up S. S1 affects virus-ACE2 receptor binding, whereas S2 causes virus-cell membrane fusion. This could explain why the SARS-CoV2 virus causes such severe immunopathology following infection (Saadeldin et al., 2021). Immature DCs modify their profile of expressed molecules, including chemokine receptors, during the transit phase and become incapable of collecting new antigens. They are in charge of inducing the adaptive immune system's initial antiviral response as well as the robust infection of the targeted T cells, resulting in systemic viral dispersion in the host (Geijtenbeek et al., 2000).

6.3 Ongoing Clinical Trials DC vaccines

In this section, some of the most recent DC vaccine clinical studies are listed, along with their indications. Clinical trials for a DC vaccine against COVID-19 are now underway. This is a phase 2 randomized, double-blind clinical trial to prevent COVID-19 infection using an antiSARS-CoV-2 COVID-19 vaccine made on site with a vaccine-enabling kit from PT AIVITA

Biomedika Indonesia. The vaccine is made up of autologous dendritic cells and lymphocytes (DCL) that have been treated with a small amount of SARS-CoV-2 spike protein and has been shown to be safe in a phase 1 study in Indonesia. Efficacy is determined in this phase 2 study by comparing pre- and post-vaccination data for increased S-protein-specific T-cell response. To ensure patient safety, laboratory findings, observation, and regular patient reporting are all used.

Table-1: List of recent ongoing clinical trials using DC-based vaccine.

NCT Number	**Indication**
NCT05007496	COVID-19
NCT00703105	Ovarian cancer
NCT01204684	Glioma
NCT02503150	Metastatic colorectal cancer
NCT02301611	Malignant melanoma
NCT02496520	Advanced solid tumours
NCT03300843	Pancreatic Cancer

Three clinical trials for COVID-19 therapy are currently listed in China. Lentivirus minigenes were used to express SARS-CoV-2 antigens in APCs, a pathogen specific aAPC vaccine was developed and fully tested for safety. The LV-SMENP-DC vaccine was created by injecting a lentivirus vector into dendritic cells that contained the COVID-19 minigene SMENP and

immune-modulatory genes. The antigens were designed to activate cytotoxic T lymphocytes (Lythgoe & Middleton, 2020).

A phase 3 trial is now assessing a DC vaccine loaded with autologous tumor lysate in patients with newly diagnosed glioblastoma after surgery as a supplement to standard of care, which includes radiation and chemotherapy. Patients are administered temozolomide + DCVax-L or temozolomide and placebo. DCVax-L is administered intradermally six times the first year and twice the following year. After a recurrence, all patients are eligible for DCVax-L. According to the initial published results, the median OS after surgery was 23.1 months, compared to 1517 months in earlier studies employing only SOC. Only 2.1 percent of those who received the vaccination reported a grade 3 or 4 adverse event. Because of its superior safety profile, this DC vaccine has the potential to be utilized for a number of indications and in a variety of combinations (Liau et al., 2018).

Chapter-7

Conclusion and future prospects

The application of the DC based immunotherapy is increasing day by day because of its promising mechanism of action. If we evaluate the data's obtained from the clinical and preclinical studies, we can see that DC vaccines are already playing a vital role in cancer immunotherapy. The world has been dealing with the COVID-19 epidemic since 2019. Patients with cancer are more sensitive to infection and its negative consequences due to its severely compromised health and inadequate immunity. As DC's are being investigated more and more hopefully it will be able to overcome the challenges caused from different parameters. Based on our current scientific understanding of the virus, cancer, and the Dendritic cell, one question that could be addressed is whether it is possible to target both cancer and the COVID-19 virus with a single weapon. Future researches and studies will answer this question. But we have got promising results so far. Combinatorial techniques and the development of new clinic technology should continue to improve DC vaccine effectiveness. Further researches will create more scopes for DC vaccines to treat COVID-19. After the successful clinical trials, when it will come to the market it will be added as another soldier which will combat COVID-19 with more efficacy and one day this world will be free of COVID-19 cases.

Reference

Amanat, F., & Krammer, F. (2020). SARS-CoV-2 Vaccines: Status Report. *Immunity*, *52*(4), 583. https://doi.org/10.1016/J.IMMUNI.2020.03.007

Banchereau, J., Briere, F., Caux, C., Davoust, J., Lebecque, S., Liu, Y. J., Pulendran, B., & Palucka, K. (2000). Immunobiology of dendritic cells. *Annual Review of Immunology*, *18*, 767–811. https://doi.org/10.1146/ANNUREV.IMMUNOL.18.1.767

Banchereau, J., & Steinman, R. M. (1998). Dendritic cells and the control of immunity. *Nature 1998 392:6673*, *392*(6673), 245–252. https://doi.org/10.1038/32588

Barré-Sinoussi, F., Chermann, J. C., Rey, F., Nugeyre, M. T., Chamaret, S., Gruest, J., Dauguet, C., Axler-Blin, C., Vézinet-Brun, F., Rouzioux, C., Rozenbaum, W., & Montagnier, L. (1983). Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). *Science (New York, N.Y.)*, *220*(4599), 868–871. https://doi.org/10.1126/SCIENCE.6189183

Beaglehole, R., Ebrahim, S., Reddy, S., Voûte, J., & Leeder, S. (2007). Prevention of chronic diseases: a call to action. *Lancet*, *370*(9605), 2152–2157. https://doi.org/10.1016/S0140-6736(07)61700-0/ONLINE/FOCUS/MENTAL_HEALTH/COLLECTION

Beatty, G. L., Torigian, D. A., Gabriela Chiorean, E., Saboury, B., Brothers, A., Alavi, A., Troxel, A. B., Sun, W., Teitelbaum, U. R., Vonderheide, R. H., & O'Dwyer, P. J. (2013). A phase I study of an agonist CD40 monoclonal antibody (CP-870,893) in combination with gemcitabine in patients with advanced pancreatic ductal adenocarcinoma. *Clinical Cancer Research : An Official Journal of the American Association for Cancer Research*, *19*(22), 6286–6295. https://doi.org/10.1158/1078-0432.CCR-13-1320

Bonab, F. S. (2015). Dendritic Cell Vaccine and its Application in Cancer Therapy. *International Journal of Vaccines & Vaccination*, *Volume 1*(Issue 1). https://doi.org/10.15406/IJVV.2015.01.00002

Bonasio, R., & von Andrian, U. H. (2006). Generation, migration and function of circulating dendritic cells. *Current Opinion in Immunology*, *18*(4), 503–511. https://doi.org/10.1016/J.COI.2006.05.011

Cao, W., Liu, X., Bai, T., Fan, H., Hong, K., Song, H., Han, Y., Lin, L., Ruan, L., & Li, T. (2020). High-Dose Intravenous Immunoglobulin as a Therapeutic Option for Deteriorating Patients With Coronavirus Disease 2019. *Open Forum Infectious Diseases*, *7*(3), 1–6. https://doi.org/10.1093/OFID/OFAA102

Cao, X. (2020). COVID-19: immunopathology and its implications for therapy. *Nature Reviews Immunology 2020 20:5*, *20*(5), 269–270. https://doi.org/10.1038/s41577-020-0308-3

Chauhan, N., Khatri, V., Banerjee, P., & Kalyanasundaram, R. (2018). Evaluating the Vaccine Potential of a Tetravalent Fusion Protein (rBmHAXT) Vaccine Antigen Against Lymphatic Filariasis in a Mouse Model. *Frontiers in Immunology*, *9*, 1520. https://doi.org/10.3389/FIMMU.2018.01520/BIBTEX

Cheong, C., Choi, J. H., Vitale, L., He, L. Z., Trumpfheller, C., Bozzacco, L., Do, Y., Nchinda, G., Park, S. H., Dandamudi, D. B., Shrestha, E., Pack, M., Lee, H. W., Keler, T., Steinman, R. M., & Park, C. G. (2010). Improved cellular and humoral immune responses in vivo following targeting of HIV Gag to dendritic cells within human anti-human DEC205 monoclonal antibody. *Blood*, *116*(19), 3828–3838. https://doi.org/10.1182/BLOOD-2010-06-288068

Chu, H., Zhou, J., Wong, B. H. Y., Li, C., Chan, J. F. W., Cheng, Z. S., Yang, D., Wang, D., Lee, A. C. Y., Li, C., Yeung, M. L., Cai, J. P., Chan, I. H. Y., Ho, W. K., To, K. K. W.,

Zheng, B. J., Yao, Y., Qin, C., & Yuen, K. Y. (2016). Middle East Respiratory Syndrome Coronavirus Efficiently Infects Human Primary T Lymphocytes and Activates the Extrinsic and Intrinsic Apoptosis Pathways. *The Journal of Infectious Diseases*, *213*(6), 904. https://doi.org/10.1093/INFDIS/JIV380

Clerici, M. (2021). Understanding the Struggle Between Viruses and the Immune System: A Quintessential Grand Challenge. *Frontiers in Virology*, *0*, 3. https://doi.org/10.3389/FVIRO.2021.671745

Colino, J., Shen, Y., & Snapper, C. M. (2002). Dendritic cells pulsed with intact Streptococcus pneumoniae elicit both protein- and polysaccharide-specific immunoglobulin isotype responses in vivo through distinct mechanisms. *The Journal of Experimental Medicine*, *195*(1), 1–13. https://doi.org/10.1084/JEM.20011432

Cools, N., Ponsaerts, P., Van Tendeloo, V. F. I., & Berneman, Z. N. (2007). Balancing between immunity and tolerance: an interplay between dendritic cells, regulatory T cells, and effector T cells. *Journal of Leukocyte Biology*, *82*(6), 1365–1374. https://doi.org/10.1189/JLB.0307166

COVID Live Update: 250,925,501 Cases and 5,069,182 Deaths from the Coronavirus - Worldometer. (2021, November 8). https://www.worldometers.info/coronavirus/

Diurno, F., Numis, F. G., Porta, G., Cirillo, F., Maddaluno, S., Ragozzino, A., Negri, P. D. E., Gennaro, C. D. I., Pagano, A., Allegorico, E., Bressy, L., Bosso, G., Ferrara, A., Serra, C., Montisci, A., D'Amico, M., Lo Morello, S. S., Costanzo, G. D. I., Tucci, A. G., … Facchini, G. (2020). Eculizumab treatment in patients with COVID-19: Preliminary results from real life ASL Napoli 2 Nord experience. *European Review for Medical and Pharmacological Sciences*, *24*(7), 4040–4047. https://doi.org/10.26355/EURREV_202004_20875

Fossum, E., Grødeland, G., Terhorst, D., Tveita, A. A., Vikse, E., Mjaaland, S., Henri, S., Malissen, B., & Bogen, B. (2015). Vaccine molecules targeting Xcr1 on cross-presenting DCs induce protective CD8+ T-cell responses against influenza virus. *European Journal of Immunology*, *45*(2), 624–635. https://doi.org/10.1002/EJI.201445080

Fox, J. C., Nakayama, T., Tyler, R. C., Sander, T. L., Yoshie, O., & Volkman, B. F. (2015). Structural and agonist properties of XCL2, the other member of the C-chemokine subfamily. *Cytokine*, *71*(2), 302–311. https://doi.org/10.1016/J.CYTO.2014.11.010

Frleta, D., Ochoa, C. E., Kramer, H. B., Khan, S. A., Stacey, A. R., Borrow, P., Kessler, B. M., Haynes, B. F., & Bhardwaj, N. (2012). HIV-1 infection-induced apoptotic microparticles inhibit human DCs via CD44. *The Journal of Clinical Investigation*, *122*(12), 4685–4697. https://doi.org/10.1172/JCI64439

Gallo, P. M., & Gallucci, S. (2013). The Dendritic Cell Response to Classic, Emerging, and Homeostatic Danger Signals. Implications for Autoimmunity. *Frontiers in Immunology*, *4*(JUN). https://doi.org/10.3389/FIMMU.2013.00138

Gallo, R. C., Sarin, P. S., Gelmann, E. P., Robert-Guroff, M., Richardson, E., Kalyanaraman, V. S., Mann, D., Sidhu, G. D., Stahl, R. E., Zolla-Pazner, S., Leibowitch, J., & Popovic, M. (1983). Isolation of human T-cell leukemia virus in acquired immune deficiency syndrome (AIDS). *Science (New York, N.Y.)*, *220*(4599), 865–867. https://doi.org/10.1126/SCIENCE.6601823

Geijtenbeek, T. B. H., Kwon, D. S., Torensma, R., Van Vliet, S. J., Van Duijnhoven, G. C. F., Middel, J., Cornelissen, I. L. M. H. A., Nottet, H. S. L. M., KewalRamani, V. N., Littman, D. R., Figdor, C. G., & Van Kooyk, Y. (2000). DC-SIGN, a Dendritic Cell–Specific HIV1-Binding Protein that Enhances trans-Infection of T Cells. *Cell*, *100*(5), 587–597. https://doi.org/10.1016/S0092-8674(00)80694-7

Han, J., Sun, J., Zhang, G., & Chen, H. (2021). DCs-based therapies: potential strategies in severe SARS-CoV-2 infection. *International Journal of Medical Sciences*, *18*(2), 406. https://doi.org/10.7150/IJMS.47706

Hobo, W., Novobrantseva, T. I., Fredrix, H., Wong, J., Milstein, S., Epstein-Barash, H., Liu, J., Schaap, N., Van Der Voort, R., & Dolstra, H. (2013). Improving dendritic cell vaccine immunogenicity by silencing PD-1 ligands using siRNA-lipid nanoparticles combined with antigen mRNA electroporation. *Cancer Immunology, Immunotherapy : CII*, *62*(2), 285–297. https://doi.org/10.1007/S00262-012-1334-1

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., Cheng, Z., Yu, T., Xia, J., Wei, Y., Wu, W., Xie, X., Yin, W., Li, H., Liu, M., … Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*, *395*(10223), 497–506. https://doi.org/10.1016/S0140-6736(20)30183-5/ATTACHMENT/D5332CA1-83D8-4C4C-BC57-00A390BF0396/MMC1.PDF

Kantoff, P. W., Higano, C. S., Shore, N. D., Berger, E. R., Small, E. J., Penson, D. F., Redfern, C. H., Ferrari, A. C., Dreicer, R., Sims, R. B., Xu, Y., Frohlich, M. W., & Schellhammer, P. F. (2010). Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *The New England Journal of Medicine*, *363*(5), 411–422. https://doi.org/10.1056/NEJMOA1001294

Kim, E., Erdos, G., Huang, S., Kenniston, T. W., Balmert, S. C., Carey, C. D., Raj, V. S., Epperly, M. W., Klimstra, W. B., Haagmans, B. L., Korkmaz, E., Falo, L. D., & Gambotto, A. (2020a). Microneedle array delivered recombinant coronavirus vaccines: Immunogenicity and rapid translational development. *EBioMedicine*, *55*. https://doi.org/10.1016/J.EBIOM.2020.102743

Kim, E., Erdos, G., Huang, S., Kenniston, T. W., Balmert, S. C., Carey, C. D., Raj, V. S., Epperly, M. W., Klimstra, W. B., Haagmans, B. L., Korkmaz, E., Falo, L. D., &

Gambotto, A. (2020b). Microneedle array delivered recombinant coronavirus vaccines: Immunogenicity and rapid translational development. *EBioMedicine*, *55*. https://doi.org/10.1016/J.EBIOM.2020.102743

Kranz, L. M., Diken, M., Haas, H., Kreiter, S., Loquai, C., Reuter, K. C., Meng, M., Fritz, D., Vascotto, F., Hefesha, H., Grunwitz, C., Vormehr, M., Hüsemann, Y., Selmi, A., Kuhn, A. N., Buck, J., Derhovanessian, E., Rae, R., Attig, S., … Sahin, U. (2016). Systemic RNA delivery to dendritic cells exploits antiviral defence for cancer immunotherapy. *Nature*, *534*(7607), 396–401. https://doi.org/10.1038/NATURE18300

Levy, J. A., Hoffman, A. D., Kramer, S. M., Landis, J. A., Shimabukuro, J. M., & Oshiro, L. S. (1984). Isolation of lymphocytopathic retroviruses from San Francisco patients with AIDS. *Science (New York, N.Y.)*, *225*(4664), 840–842. https://doi.org/10.1126/SCIENCE.6206563

Li, Jessica, Ahmet, F., Sullivan, L. C., Brooks, A. G., Kent, S. J., De Rose, R., Salazar, A. M., Reis e Sousa, C., Shortman, K., Lahoud, M. H., Heath, W. R., & Caminschi, I. (2015). Antibodies targeting Clec9A promote strong humoral immunity without adjuvant in mice and non-human primates. *European Journal of Immunology*, *45*(3), 854–864. https://doi.org/10.1002/EJI.201445127

Li, Jingxin, Hui, A., Zhang, X., Yang, Y., Tang, R., Ye, H., Ji, R., Lin, M., Zhu, Z., Türeci, Ö., Lagkadinou, E., Jia, S., Pan, H., Peng, F., Ma, Z., Wu, Z., Guo, X., Shi, Y., Muik, A., … Zhu, F. (2021). Safety and immunogenicity of the SARS-CoV-2 BNT162b1 mRNA vaccine in younger and older Chinese adults: a randomized, placebo-controlled, double-blind phase 1 study. *Nature Medicine 2021 27:6*, *27*(6), 1062–1070. https://doi.org/10.1038/s41591-021-01330-9

Liau, L. M., Ashkan, K., Tran, D. D., Campian, J. L., Trusheim, J. E., Cobbs, C. S., Heth, J. A., Salacz, M., Taylor, S., D'Andre, S. D., Iwamoto, F. M., Dropcho, E. J., Moshel, Y.

A., Walter, K. A., Pillainayagam, C. P., Aiken, R., Chaudhary, R., Goldlust, S. A., Bota, D. A., … Bosch, M. L. (2018). First results on survival from a large Phase 3 clinical trial of an autologous dendritic cell vaccine in newly diagnosed glioblastoma. *Journal of Translational Medicine*, *16*(1), 1. https://doi.org/10.1186/S12967-018-1507-6

Lythgoe, M. P., & Middleton, P. (2020). Ongoing Clinical Trials for the Management of the COVID-19 Pandemic. *Trends in Pharmacological Sciences*, *41*(6), 363. https://doi.org/10.1016/J.TIPS.2020.03.006

Mastelic-Gavillet, B., Balint, K., Boudousquie, C., Gannon, P. O., & Kandalaft, L. E. (2019a). Personalized dendritic cell vaccines-recent breakthroughs and encouraging clinical results. *Frontiers in Immunology*, *10*(APR), 766. https://doi.org/10.3389/FIMMU.2019.00766/BIBTEX

Mastelic-Gavillet, B., Balint, K., Boudousquie, C., Gannon, P. O., & Kandalaft, L. E. (2019b). Personalized Dendritic Cell Vaccines—Recent Breakthroughs and Encouraging Clinical Results. *Frontiers in Immunology*, *10*(APR), 766. https://doi.org/10.3389/FIMMU.2019.00766

Mohsen, M. O., Zha, L., Cabral-Miranda, G., & Bachmann, M. F. (2017). Major findings and recent advances in virus-like particle (VLP)-based vaccines. *Seminars in Immunology*, *34*, 123–132. https://doi.org/10.1016/J.SMIM.2017.08.014

Monteil, V., Kwon, H., Prado, P., Hagelkrüys, A., Wimmer, R. A., Stahl, M., Leopoldi, A., Garreta, E., Hurtado del Pozo, C., Prosper, F., Romero, J. P., Wirnsberger, G., Zhang, H., Slutsky, A. S., Conder, R., Montserrat, N., Mirazimi, A., & Penninger, J. M. (2020). Inhibition of SARS-CoV-2 Infections in Engineered Human Tissues Using Clinical-Grade Soluble Human ACE2. *Cell*, *181*(4), 905-913.e7. https://doi.org/10.1016/J.CELL.2020.04.004

Nazario, B. (2021). *Coronavirus & COVID-19 Overview: Symptoms, Risks, Prevention, Treatment & More*. https://www.webmd.com/lung/coronavirus

Neupane, K., Ahmed, Z., Pervez, H., Ashraf, R., & Majeed, A. (2020). Potential Treatment Options for COVID-19: A Comprehensive Review of Global Pharmacological Development Efforts. *Cureus*, *12*(6). https://doi.org/10.7759/CUREUS.8845

Nugent, R. (2008). Chronic diseases in developing countries: health and economic burdens. *Annals of the New York Academy of Sciences*, *1136*, 70–79. https://doi.org/10.1196/ANNALS.1425.027

Oy, R., Ulick, M. G., Ohn, J., Ellors, W. M., Oseph, J., Ron, J. E., Harles, C., Onzalez, G., Eborah M C, D., Ahon, M., Ichman, O. D. R., Alentine, R. T. V, Eslie, L., Onas, J., Nne, A., Eibohm, M., Mini, M. A. E., Effrey, J., & Hodakewitz, A. C. (2009). Treatment with Indinavir, Zidovudine, and Lamivudine in Adults with Human Immunodeficiency Virus Infection and Prior Antiretroviral Therapy. *Http://Dx.Doi.Org/10.1056/NEJM199709113371102*, *337*(11), 734–739. https://doi.org/10.1056/NEJM199709113371102

Penna, G., Vulcano, M., Sozzani, S., & Adorini, L. (2002). Differential migration behavior and chemokine production by myeloid and plasmacytoid dendritic cells. *Human Immunology*, *63*(12), 1164–1171. https://doi.org/10.1016/S0198-8859(02)00755-3

Poland, G. A. (2020). Another coronavirus, another epidemic, another warning. *Vaccine*, *38*(10), v. https://doi.org/10.1016/J.VACCINE.2020.02.039

Qu, L., Li, J., & Ren, H. (2020). COVID-19: the epidemiology and treatment. *Https://Doi.Org/10.12968/Hmed.2020.0580*, *81*(10). https://doi.org/10.12968/HMED.2020.0580

Roberts, E. W., Broz, M. L., Binnewies, M., Headley, M. B., Nelson, A. E., Wolf, D. M., Kaisho, T., Bogunovic, D., Bhardwaj, N., & Krummel, M. F. (2016). Critical Role for

CD103(+)/CD141(+) Dendritic Cells Bearing CCR7 for Tumor Antigen Trafficking and Priming of T Cell Immunity in Melanoma. *Cancer Cell*, *30*(2), 324–336. https://doi.org/10.1016/J.CCELL.2016.06.003

Rothan, H. A., & Byrareddy, S. N. (2020). The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *Journal of Autoimmunity*, *109*, 102433. https://doi.org/10.1016/J.JAUT.2020.102433

Rouse, B. T., & Sehrawat, S. (2010). Immunity and immunopathology to viruses: what decides the outcome? *Nature Reviews Immunology 2010 10:7*, *10*(7), 514–526. https://doi.org/10.1038/nri2802

Saadeldin, M. K., Abdel-Aziz, A. K., & Abdellatif, A. (2021). Dendritic cell vaccine immunotherapy; the beginning of the end of cancer and COVID-19. A hypothesis. *Medical Hypotheses*, *146*, 110365. https://doi.org/10.1016/J.MEHY.2020.110365

Sabado, R. L., Balan, S., & Bhardwaj, N. (2017). Dendritic cell-based immunotherapy. *Cell Research*, *27*(1), 74. https://doi.org/10.1038/CR.2016.157

Sæterdal, I., Bjørheim, J., Lislerud, K., Gjertsen, M. K., Bukholm, I. K., Olsen, O. C., Nesland, J. M., Eriksen, J. A., Møller, M., Lindblom, A., & Gaudernack, G. (2001). Frameshiftmutation-derived peptides as tumor-specific antigens in inherited and spontaneous colorectal cancer. *Proceedings of the National Academy of Sciences of the United States of America*, *98*(23), 13255–13260. https://doi.org/10.1073/PNAS.231326898

Schraml, B. U., & Reis e Sousa, C. (2015). Defining dendritic cells. *Current Opinion in Immunology*, *32*, 13–20. https://doi.org/10.1016/J.COI.2014.11.001

Shereen, M. A., Khan, S., Kazmi, A., Bashir, N., & Siddique, R. (2020). COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. *Journal of Advanced Research*, *24*, 91. https://doi.org/10.1016/J.JARE.2020.03.005

Sironi, M., Cagliani, R., Forni, D., & Clerici, M. (2015). Evolutionary insights into host–pathogen interactions from mammalian sequence data. *Nature Reviews Genetics 2015 16:4*, *16*(4), 224–236. https://doi.org/10.1038/nrg3905

Smith, T. R. F., Patel, A., Ramos, S., Elwood, D., Zhu, X., Yan, J., Gary, E. N., Walker, S. N., Schultheis, K., Purwar, M., Xu, Z., Walters, J., Bhojnagarwala, P., Yang, M., Chokkalingam, N., Pezzoli, P., Parzych, E., Reuschel, E. L., Doan, A., … Broderick, K. E. (2020). Immunogenicity of a DNA vaccine candidate for COVID-19. *Nature Communications*, *11*(1). https://doi.org/10.1038/S41467-020-16505-0

Song, Y., Zhang, M., Yin, L., Wang, K., Zhou, Y., Zhou, M., & Lu, Y. (2020). COVID-19 treatment: close to a cure? A rapid review of pharmacotherapies for the novel coronavirus (SARS-CoV-2). *International Journal of Antimicrobial Agents*, *56*(2), 106080. https://doi.org/10.1016/J.IJANTIMICAG.2020.106080

Spruth, M., Kistner, O., Savidis-Dacho, H., Hitter, E., Crowe, B., Gerencer, M., Brühl, P., Grillberger, L., Reiter, M., Tauer, C., Mundt, W., & Barrett, P. N. (2006). A doubleinactivated whole virus candidate SARS coronavirus vaccine stimulates neutralising and

protective antibody responses. *Vaccine*, *24*(5), 652. https://doi.org/10.1016/J.VACCINE.2005.08.055

Steinman, R. M., & Banchereau, J. (2007). Taking dendritic cells into medicine. *Nature*, *449*(7161), 419–426. https://doi.org/10.1038/NATURE06175

Steinman, R. M., & Idoyaga, J. (2010). Features of the dendritic cell lineage. *Immunological Reviews*, *234*(1), 5–17. https://doi.org/10.1111/J.0105-2896.2009.00888.X

Velavan, T. P., & Meyer, C. G. (2020). The COVID-19 epidemic. *Tropical Medicine & International Health*, *25*(3), 278–280. https://doi.org/10.1111/TMI.13383

Weingartl, H., Czub, M., Czub, S., Neufeld, J., Marszal, P., Gren, J., Smith, G., Jones, S., Proulx, R., Deschambault, Y., Grudeski, E., Andonov, A., He, R., Li, Y., Copps, J., Grolla, A., Dick, D., Berry, J., Ganske, S., … Cao, J. (2004). Immunization with modified vaccinia virus Ankara-based recombinant vaccine against severe acute respiratory syndrome is associated with enhanced hepatitis in ferrets. *Journal of Virology*, *78*(22), 12672–12676. https://doi.org/10.1128/JVI.78.22.12672-12676.2004

Winograd, R., Byrne, K. T., Evans, R. A., Odorizzi, P. M., Meyer, A. R. L., Bajor, D. L., Clendenin, C., Stanger, B. Z., Furth, E. E., Wherry, E. J., & Vonderheide, R. H. (2015). Induction of T-cell Immunity Overcomes Complete Resistance to PD-1 and CTLA-4 Blockade and Improves Survival in Pancreatic Carcinoma. *Cancer Immunology Research*, *3*(4), 399–411. https://doi.org/10.1158/2326-6066.CIR-14-0215

Woo, E. Y. (2001). Regulatory CD4(+)CD25(+) T cells in tumors from patients with earlystage non-small cell lung cancer and late-stage ovarian cancer - PubMed. *Cancer Research*. https://pubmed.ncbi.nlm.nih.gov/11406550/

Wu, C., Liu, Y., Yang, Y., Zhang, P., Zhong, W., Wang, Y., Wang, Q., Xu, Y., Li, M., Li, X., Zheng, M., Chen, L., & Li, H. (2020). Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. *Acta Pharmaceutica Sinica B*, *10*(5), 766–788. https://doi.org/10.1016/J.APSB.2020.02.008

Yadav, T., Srivastava, N., Mishra, G., Dhama, K., Kumar, S., Puri, B., & Saxena, S. K. (2020). Recombinant vaccines for COVID-19. *Human Vaccines & Immunotherapeutics*, *16*(12), 2905. https://doi.org/10.1080/21645515.2020.1820808

Yang, Z. Y., Kong, W. P., Huang, Y., Roberts, A., Murphy, B. R., Subbarao, K., & Nabel, G. J. (2004). A DNA vaccine induces SARS coronavirus neutralization and protective immunity in mice. *Nature*, *428*(6982), 561–564. https://doi.org/10.1038/NATURE02463

Zhao, J., Zhao, J., & Perlman, S. (2010). T Cell Responses Are Required for Protection from

Clinical Disease and for Virus Clearance in Severe Acute Respiratory Syndrome Coronavirus-Infected Mice. *Journal of Virology*, *84*(18), 9318. https://doi.org/10.1128/JVI.01049-10

Zhou, H., Chen, Y., Zhang, S., Niu, P., Qin, K., Jia, W., Huang, B., Zhang, S., Lan, J., Zhang, L., Tan, W., & Wang, X. (2019). Structural definition of a neutralization epitope on the N-terminal domain of MERS-CoV spike glycoprotein. *Nature Communications*, *10*(1). https://doi.org/10.1038/S41467-019-10897-4

Zhou, J., Wang, W., Zhong, Q., Hou, W., Yang, Z., Xiao, S. Y., Zhu, R., Tang, Z., Wang, Y., Xian, Q., Tang, H., & Wen, L. (2005). Immunogenicity, safety, and protective efficacy of an inactivated SARS-associated coronavirus vaccine in rhesus monkeys. *Vaccine*, *23*(24), 3202–3209. https://doi.org/10.1016/J.VACCINE.2004.11.075

Zhu, F. C., Li, Y. H., Guan, X. H., Hou, L. H., Wang, W. J., Li, J. X., Wu, S. P., Wang, B. Sen, Wang, Z., Wang, L., Jia, S. Y., Jiang, H. D., Wang, L., Jiang, T., Hu, Y., Gou, J. B., Xu, S. B., Xu, J. J., Wang, X. W., … Chen, W. (2020). Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a doseescalation, open-label, non-randomised, first-in-human trial. *Lancet (London, England)*, *395*(10240), 1845–1854. https://doi.org/10.1016/S0140-6736(20)31208-3