# Dendritic Cells: A Missing Puzzle Piece in Our Understanding of the Immune Response in COVID-19 Patients

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## INTRODUCTION

Currently, nearly 35 million COVID-19 cases have been confirmed worldwide, with more than a million deaths associated with the disease (1). The virus that causes COVID-19 is known as SARS-CoV-2 and shares 79% nucleotide homology with SARS-CoV-1, the virus responsible for the SARS pandemic of 2003. 80% of COVID-19 cases are mild, 15% are moderate and 5% are severe. In total, 1-2% of cases result in death. Severe COVID-19 is characterized by a cytokine storm which consists of significantly elevated amounts of proinflammatory cytokines. These cytokines have roles in recruiting inflammatory cells to the lungs which cause pulmonary damage and even escalation to acute respiratory distress syndrome (ARDS). The depletion of T cells (T cell lymphopenias) also occurs, and the extent of depletion correlates with disease severity.

Dendritic cells (DCs) are antigen-presenting cells that link the innate and adaptive arms of the immune system. They have pivotal roles in priming and controlling inflammatory responses, produce anti-viral signaling molecules and are the most potent stimulators of T cells. They are of interest to vaccine developers, owing to their ability to trigger the development of memory B and T cells.

## HYPOTHESIS

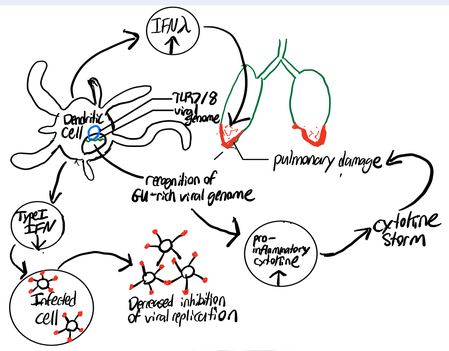
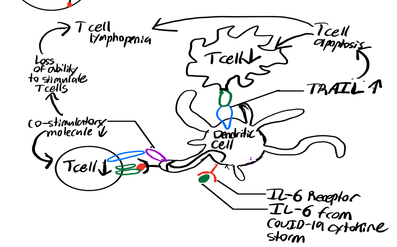
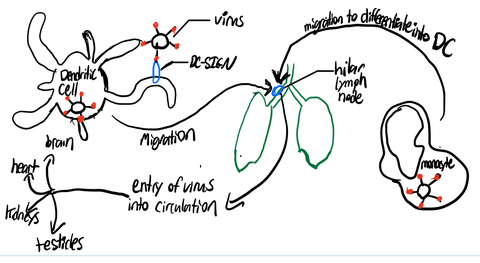
***Dendritic Cells are a critical immune cell type that regulates immune responses to COVID-19.***

## METHODS

In light of the roles between DC functions and clinical manifestations of COVID-19, I spent the rest of the summer searching Pubmed for all available literature that mentions both COVID-19 and DCs. I also considered all of the literature that mentions SARS and DCs to speculatively fill in the current gaps in understanding of how DCs behave in patients with COVID-19. I collated and discussed our findings in a review that is in the process of being submitted for publication.

When labs reopened, I spent a few weeks conducting experiments for our COVID-19 vaccine project. Our vaccine platform utilizes Ebola virus-pseudotyped lentivirus particles which express SARS-CoV-2 Spike (S) protein. The pathogen antigen (SARS-CoV-2 S protein) is directed to DCs and macrophages for phagocytosis and antigen presentation using Ebola virus glycoprotein (EBOV-GP). Our vaccine concept is illustrated in Figure 1.

## Table 1. Key Findings From Literature Review (Fisk et al, Manuscript in preparation for submission. References cited in the manuscript)

| In COVID-19 | Contribution or Behaviour of DCs | Illustration of Speculated DC Activity *in vivo* | Recommendations for Future Work |
|---|---|---|---|
| **Innate Immunity** | • DCs may act as cell sources of many cytokines and chemokines that are elevated in patients during cytokine storms, including IL-6, IL-10, TNFα and IP-10.<br>• Decreased type I IFN production is associated with higher viral loads and severer disease in COVID-19 patients. moDCs infected with SARS-CoV-2 have suppressed type I IFN production due to STAT1 inhibition. Interestingly, older individuals produce less type I IFN in response to infection, which may explain disproportionately adverse outcomes in this population.<br>• Interferon-λ (IFN-λ) production by lung-resident DCs contributes to impaired tissue repair and increased susceptibility to bacterial superinfection.<br>• A GU-rich region of the SARS-CoV-1 genome bound TLR7 and TLR8 (expressed by some DC subsets) and was sufficient to trigger hyperinflammatory responses and death in mice. The SARS-CoV-2 possesses more of these GU-rich regions and may play a role in disease escalation. |  | • Infect plasmacytoid DCs (the greatest producers of type I IFN) with SARS-CoV-2 to reveal whether the virus directly suppresses type I IFN production by this important subset.<br>• TLR7 and TLR8 antagonists should be evaluated in vitro to see whether they can reduce the production of inflammatory cytokines.<br>• Early administration of an IFN-λ antagonist might prevent lung injury in patients that are more likely to progress to severe disease. |
| **Adaptive Immunity** | • SARS-CoV-1-infected moDCs up-regulate TRAIL, a protein which triggers apoptosis of T cells. If SARS-CoV-2 behaves similarly, this may help explain the correlation that has been observed between TRAIL expression and disease severity in COVID-19 patients.<br>• The supernatant of a SARS-CoV-1-infected cell line abolishes the ability of moDCs to stimulate naïve T cells by down-regulating costimulatory molecules that are essential for T cell stimulation. This ability is mostly restored when IL-6, an inflammatory cytokine elevated in COVID-19 patients, is neutralized using antibodies.<br>• The ability of DCs to migrate to lymph nodes to activate T cell proliferation is diminished with age and may explain the greater lymphopenias in older patients who have severe disease. |  | • Co-culture DCs with supernatant from infected cell lines to identify any suppression of DC stimulation of T cells.<br>• Blocking IL-6 might ameliorate disease by both taming the inflammatory response and improving T cell activation, promoting recovery from the infection. |
| **Viral Dissemination** | • SARS-CoV-1-infected monocytes travel to the hilar lymph nodes (LNs) in macaques and produces virus after differentiating into moDCs that might become bloodborne.<br>• DCs infected with SARS-CoV-1 migrate to LNs 2 days post-infection and the virus disseminates systemically shortly afterward.<br>• DC-SIGN is a receptor expressed by some DCs that was found to bind SARS-CoV-1 S protein. Similar to HIV, SARS-CoV-2 may disseminate to the LNs by remaining attached to DC-SIGN during migration<br>• Autopsies have revealed SARS-CoV-2 dissemination to the kidneys, testicles, heart and brain. Could DCs directly contribute to SARS-CoV-2 dissemination? |  | • In vivo models of COVID-19 which monitor DC migration and virus dissemination. If DCs disseminate virus, this may be a target for future therapies. |

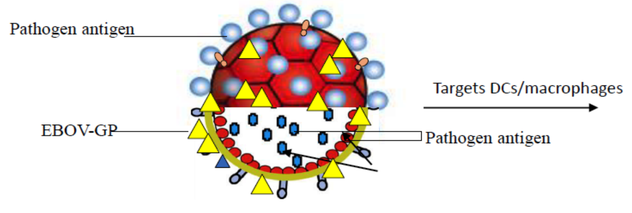



**Figure 1. Concept of DC-Targeted COVID-19 Vaccine**

- Effects of anti-S protein antibodies and T cell immunity generated by our vaccine will be evaluated by injecting mice with a cancer cell line (4T1) that expresses S protein. Antibodies resulting from vaccination should target S protein-expressing cancer cells and trigger destruction of cancer cells or prevent growth
- I genetically modified the cancer cell lines as described in Figure 2.

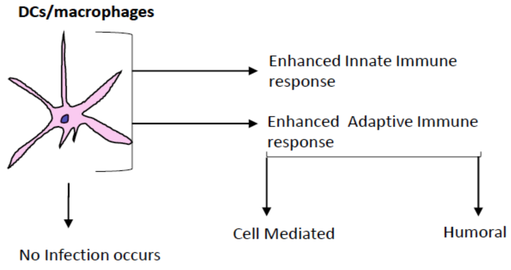
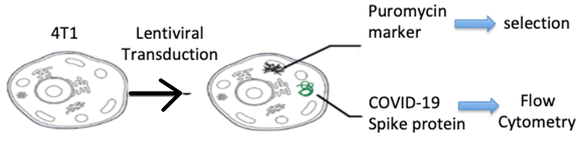



**Figure 2. Preparation of S protein-expressing 4T1 cell line.**




**References (for the COVID-19 vacine**

(1) Lammam, C., & Macintyre, H. (2018, May 1). What happens when you offer "basic income" for not working? People stop working. Financial Post. https://financialpost.com/opinion/what-happens-when-you-offer-basic-income-for-not-working-people-stop-working#:~:text=Second%2C%20because%20additional%20income%20earned

(2) Olukitibi TA, Ao Z, Mahmoudi M, Kobinger GA, Yao X. Dendritic Cells/Macrophages-Targeting Feature of Ebola Glycoprotein and its Potential as Immunological Facilitator for Antiviral Vaccine Approach. Microorganisms. 2019;7(10):402. Published 2019 Sep 29. doi:10.3390/microorganisms7100402

## CONCLUSION

The data so far suggest that DCs may be implicated in the inflammatory damage caused by COVID-19 and dysfunctional antiviral and adaptive immune responses seen in patients with severe disease. Their critical roles in achieving memory to various pathogens lead us to believe that they are a noteworthy candidate for vaccine development.

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