Myles McLean

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IMPACT OF COVID-19 ON MY RESEARCH

With regard to all the viruses that attack humans, coronaviruses are large. They belong to a family of viruses that use RNA to replicate, but they really stand out for their extraordinarily giant genomes that encode almost 30 different proteins (1). As a comparison, their genomes are more than three times as large as HIV and hepatitis C (2). In addition, coronaviruses are among the few RNA viruses that have a genomic proofreading mechanism that prevents it from accumulating mutations that may weaken it (3).

SARS-Cov-2, the coronavirus responsible for the globally widespread COVID-19 disease, possesses an array of adaptations to help it breach human cells — the first step in causing the disease (4). It infects the throat and lungs by rupturing the protective membrane of host cells using its spike proteins. The protein's receptor-binding domain then binds to a receptor called ACE2, which is perched on the surface of the host cell. Enzymes such as TMPRSS2, on the exterior of human cells break the spike protein; this in turn exposes fusion peptides that fuse the viral membrane with that of the host cell. At that point, the virus's RNA has entered the human cell, where it will hijack the host's machinery to start making its own viral proteins (4).

Much interest revolves around the viral replicating proteins of SARS-Cov-2. These proteins that commandeer the machinery of human cells to sustain viral replication are thought to be important for causing the infection (1). For Myles McLean, a third-year doctoral student in the Physiology department at McGill University, the smaller SARS-CoV-2 accessory proteins that are not required for viral replication are equally as important. "A lot of these proteins are hypothesized to interfere with the immune system in various ways," he says now.

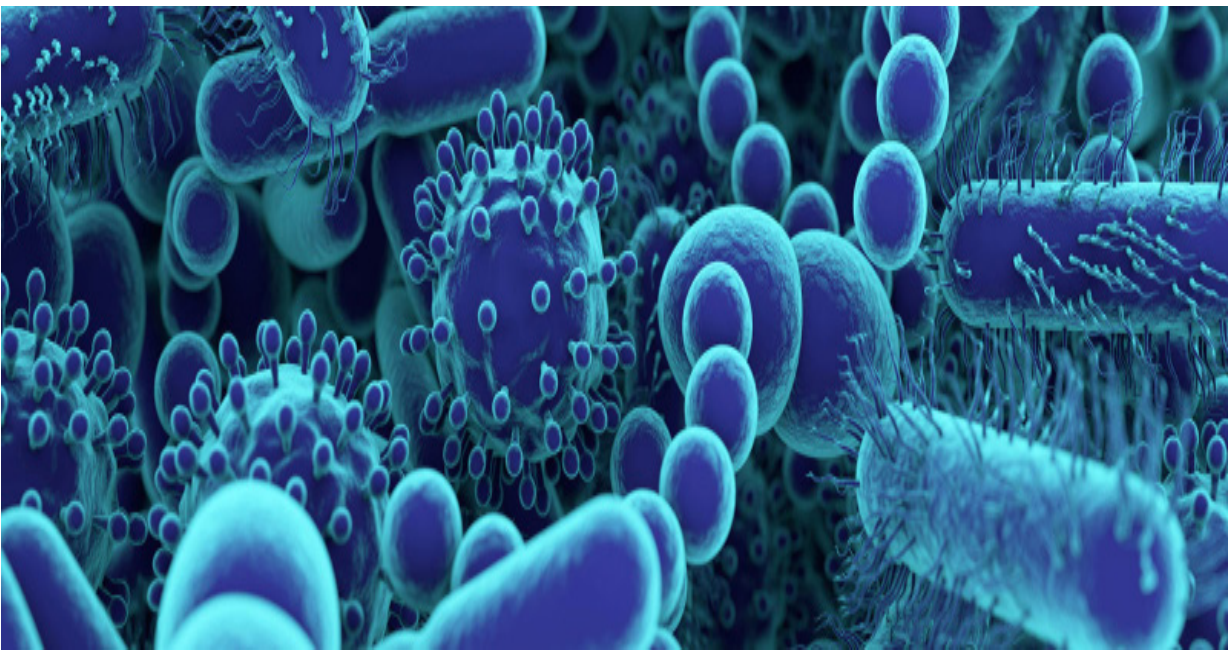
When the COVID-19 outbreak was first declared a pandemic by the World Health Organization (WHO) on March 11, 2020 (5), Myles, like other McGill graduate students, reluctantly went home. But a short two months later, he returned to the lab to tackle a new project on coronaviruses. With his viral expertise, it seemed like the perfect fit — his research interests are centered around innate immune proteins that, via various mechanisms, interfere with viral replication and life cycle.

Montreal-native Myles McLean completed his undergraduate degree at McGill University with a major in Physiology. Interested in pursuing research, he started his master's degree in Physiology at the Lady Davis Institute in Montreal's Jewish General hospital before fast-tracking to a PhD. "What made me pursue grad school was a combination of an interest in research/not fully knowing what to do as a career yet," Myles says. "I did enjoy my master's but didn't feel like I had enough time to complete it, that's why I decided to fast-track."

Co-supervised by Mark Blostein and Chen Liang, associate professors in the departments of Physiology and Microbiology & Immunology respectively, Myles began working on a collaborative project on Gas6, a vitamin K dependent protein involved in the blood coagulation pathway (6), and its potential role in Zika virus infection. The Zika virus, transmitted by the bite of infected mosquitos, became the first major infectious disease connected to human birth defects to be identified in more than half a century (7). During the 2015-2016 Zika virus epidemic, outbreaks of the virus were recorded in Africa, the Americas, Asia and the Pacific (7). It, too, spurred such global alarm that the WHO declared it a Public Health Emergency of International Concern (8). Myles's hypothesis was that Gas6, which usually binds to phospholipids on apoptotic cells, may also bind to a phospholipid on an envelope of the virus and link it to a family of kinase receptors. He anticipated that the cascade of events initiated by the protein would ultimately facilitate the Zika virus to infect cells.

However, after working on the project for two and a half years, the data did not suggest that Gas6 had a substantial effect on the outcome of the virus. "We did have a mouse colony for Gas6 knockout mice. We had some data, but the phenotype wasn't strong enough. There were definitely things that were there, but I guess the main part was whether the mice expressed Gas6 or not didn't affect their outcomes of the virus. They both survived the same number of days; it didn't really matter whether it was there or not." After abandoning the Gas6 project, Myles helped his lab mates with their research on the underlying molecular mechanisms of host restriction factors, which are anti-viral proteins that constitute a first line of defense in preventing viral replication and propagation (9), in HIV infection. Six months later, McGill University began ramping down all research activities due to the COVID-19 pandemic.

Fortunately for Myles, he was granted a new project to discover the functions of SARS-CoV-2 accessory proteins. Coronavirus accessory proteins are highly variable in number, location and size; although not required for virus replication, they are associated with pathogenicity in the host (10). However, the molecular functions of many accessory proteins continue to be unknown due to the scarcity of commonalities with accessory proteins of other coronaviruses (11). To explore these new proteins, Myles screened all the different proteins in various cell lines and is currently working on generating mouse models for each of these proteins to observe how they



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function individually in vivo. When asked about hiccups along the way, Myles admitted that a new technique he is using for generating adeno- or adeno-associated viral vectors to express the proteins to infect mice with was a little tough and has taken a lot of time to perfect. But he says that his challenges are not unique to him. "Most grad students spend a lot of time trouble-shooting, you try a new system that you haven't done before, try a bunch of different things and hope that it eventually works. I had plenty of support from my two supervisors and lab members. Right now, pretty much the rest of the lab is also working on COVID and there's only one other person who's working on HIV."

Although Myles's project is not in the hopes of developing new drugs or vaccines for SARS-Cov-2, understanding the mechanisms by which the accessory proteins function is just as crucial and will pave the way for future advances. "We think it's important to see how these viruses' function because they are quite complicated, as far as viruses go. And this is the third major outbreak of a highly pathogenic coronavirus in the last 20 years. So, this might be something we'll have to deal with more and more in the future. Understanding how these proteins work and how they suppress our immune system is kind of important."

In addition to Myles, other investigators are also cur rently uncovering accessory proteins in the novel coronavirus. For instance, Nevan Krogan's research group at the Quantitative Biosciences Institute in University of California San Francisco recently predicted nine accessory protein open reading frames, which are sequences in DNA that have the ability to be converted to protein (12). Moreover, Michel and colleagues in Strasbourg, France, used a computational tool to further delineate sequence properties of SARS-CoV-2 accessory genes (10). Research from dedicated scientists just like Myles continue to help piece together how the new coronavirus behaves and reveal the complex biology that is powering the COVID-19 pandemic.

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