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NeuroView

How COVID-19 has transformed my science

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The COVID-19 pandemic has caused a seismic shift in my career, including its scientific focus, research approach, and efforts to communicate with non-scientists. In this NeuroView, I recount pivotal moments that have transformed the way I do science.

Introduction

Prior to the pandemic, my laboratory was studying innate and adaptive immune responses to a variety of viruses. My long-standing interest has been to understand how virus infections lead to various disease consequences. We studied how herpes simplex viruses (HSVs) cause disease and how the immune system can be engaged to prevent and treat these viruses. We developed a vaccine strategy called Prime and Pull (Shin and Iwasaki, 2012) to promote local tissue-resident memory that can prevent and treat genital HSV infection. HSV and Zika virus studies have taught us a lot about immune responses in neural tissues and how to leverage such insights to overcome the blood-brain barrier. We also apply our insights on immune trafficking for cancer therapy. By manipulating the lymphatic vasculature of the meninges, immune priming and effector mechanisms can be mobilized against glioblastoma within the brain (Song et al., 2020). In addition to the neurotropic viruses, we study respiratory tract viral infections caused by influenza viruses and rhinoviruses and address how environmental factors such as temperature and humidity impact host response to these viruses. We were in the midst of all these activities when the COVID-19 pandemic hit.

The beginning: January 2020

We began hearing about the novel coronavirus that originated in Wuhan, China at the end of 2019 to early 2020. Most people in the United States were complacent, thinking that a virus infecting people halfway around the world is unlikely to

impact us in the USA. However, the virus was already silently spreading around the globe. I attended the symposium on January 30, 2020 put together by my Yale virologist colleagues called “2019 Novel Coronavirus (2019-nCoV): Virologists’ Perspective.” The discussion covered background on coronaviruses, clinical symptoms, spreading, and possible protective measures. There, I happened to sit next to Professor Albert Ko, an experienced epidemiologist/infectious disease doctor with whom I collaborated during the Zika pandemic in 2015–2016. During the coffee break, Albert and I decided we should get together to talk more about what we can do to study this novel coronavirus. That coronavirus was later named SARS-CoV-2, and the disease caused by it COVID-19, by the WHO on February 11.

A fateful meeting of the IMPACT team

On March 2, 2020, Albert called together a fateful meeting of people who, unbeknownst to us, would begin a journey together to diagnose, analyze, and treat COVID-19 (Figure 1A). Present were: Dr. Albert Ko, with deep experience in multiple epidemics and pandemics; Dr. Saad B. Omer, the director of Yale Global Health Institute with expertise in pandemics, vaccination, and policy; Dr. Nathan Grubaugh, an assistant professor of epidemiology who is a molecular epidemiologist and viral genomics whiz; Dr. Ellen Foxman, an assistant professor of Laboratory Medicine who is an expert on respiratory innate antiviral immunity; and Dr. Marie Landry, the head of virology at

the department of Laboratory Medicine and a world authority on viruses and diagnoses. I joined as an immunologist who specializes in antiviral immunity. This meeting was to decide whether we put forces together to create a human investigation protocol to study COVID patients in real time and to help Dr. Landry with diagnostic testing. Of course, we decided to do both! Later on, we gave our team the name IMPACT, which stands for Implementing Medical and Public health Action against Coronavirus (Connecticut, CT).

My decision to engage in science communication

In the midst of the chaos and panic of the pandemic, in addition to my own science, I felt the need and duty to communicate science to the public. Science is supported in large part by taxpayers. Scientists owe the public to educate and inform to save people’s lives. I began using Twitter more frequently to communicate with the public about the virus, precautionary measures, the immune system, and vaccines. I teamed up with Bio-Render, a graphics software company, to produce a video on “COVID-19 Immunology 101 for Non-immunologists” to explain what the immune system is and how it works to prevent infections. More recently, I also made a video in Japanese explaining the effectiveness and safety of mRNA vaccines. In addition to TV appearances and videos, I have also contributed to science communication through more traditional media. Early in the pandemic, I wrote an op-ed with Dr. Ruslan Medzhitov (who is also my husband) explaining to lay people that our immune system will



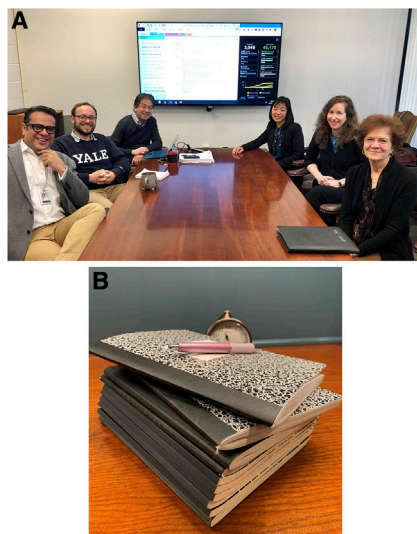


Figure 1. The Yale IMPACT team and documentation

(A) The first meeting of the Yale IMPACT Team, March 2, 2020. Clockwise from left: Saad Omer, YIGH; Nathan Grubaugh, YSP; Albert Ko, YSP; Akiko Iwasaki, YSM, Immunobiology; Ellen Foxman, YSM, Lab Med; Marie Landry, YSM, Lab Med. (B) Meeting notebooks filled since the start of the COVID-19 pandemic.

work to protect us against COVID through vaccines (<https://www.nytimes.com/2020/07/31/opinion/coronavirus-antibodies-immunity.html>). I also co-authored with my graduate student, Alice Lu-Culligan, an op-ed dispelling misinformation about vaccines and infertility (<https://www.nytimes.com/2021/01/26/opinion/covid-vaccine-rumors.html>).

My goal was and continues to be to use my expertise, knowledge, and teaching skills to provide scientifically accurate information and to calm the panic around COVID-19 immunity and vaccines. I take multiple interviews a day from reporters and contribute my opinion on everything related to COVID.

Asking for volunteers and getting everyone to help

Recall that in March of 2020, there was paucity of testing, and reagents and PCR machines were scarce. On March 19, the day of the Yale lockdown, I asked for a couple of volunteers from the lab to help with PCR testing efforts for IMPACT to test and inform our healthcare workers for infection with SARS-CoV-2. I was hoping for 2 or 3 to say yes. Instead, I had the entire lab volunteering to do this! By contacting our own network of scientists, we were

able to secure extra qPCR machines, reagents, gloves, tubes, and pipettes to start testing healthcare workers on a daily basis. People in my lab worked around the clock in shifts as part of a well-oiled viral diagnosis machine involving the Grubaugh lab (where RNA is extracted from nasopharyngeal swabs and saliva), runners transporting the RNA to our lab, setting up RT-PCR assays and analyzing data, returning the data back to the central data repository, and alerting the positive tests back to the individual. This went on every day for months, with people finishing their run well past midnight. I have never felt so proud to be a part of such an amazing lab of selfless and dedicated individuals.

Benefiting from team science

One of the biggest investments I made during the pandemic was to connect and work with a number of amazing colleagues on various aspects of COVID-19 immunity. I spent countless hours meeting, coordinating, and organizing with a network of people who each brought different skills and contributions to the table. I recorded every meeting by taking notes (Figure 1B). I learned not only their expertise and goals, but their background and motivation. This team building was not without challenges. I spent a lot of time trying to resolve personal conflicts and misunderstandings. There were unfortunate power dynamics and some people got hurt. I spent hours meeting with various Deans to discuss personnel issues and possible resolutions. At one point my own mental health was deteriorating. I had to choose between collaborating with difficult individuals versus my mental health, and I chose the latter. In the end, we all found what works and what doesn't and found a solution to working together or not. Everyone is a key piece of the large and intricate machine. I will apply a team science approach to everything from now on!

Setting our scientific goals

After our first IMPACT meeting, we expanded the team to include physician scientists who would ultimately become the people taking care of the sickest patients in the ICU in our hospital. The leaders of that team were Drs. Shelli Farhadian and Charles Dela Cruz. On March 22, Albert convened a meeting with Shelli,

Charles, and I, and we spent all day Sunday in the Laboratory of Epidemiology and Public Health conference room, socially distanced, discussing and highlighting our scientific goals. We each listed what we wanted to achieve through studying patient samples and discussed areas of collaboration with each other. As a bonus, we even got some epidemiology lessons from Albert! I learned the importance of setting goals at the beginning of a project and following through.

Shifting from basic science to translational research

Before the pandemic, much of our work was based on animal models and cell lines. This all changed dramatically in March of 2020. We were suddenly at the forefront of carrying out blood processing, cell isolation, and analysis of immune responses as they happened in real time in our patients. I quickly learned about the different blood tubes and how many are needed for our analyses. Every little detail of aliquoting, barcoding, archiving, and retrieving samples became so important. I never appreciated what a difference a great clinical coordinator makes in such an effort—IMPACT was fortunate to have Allison Nelson in this role. Another major new avenue for me was to correlate various clinical symptoms and conditions with the biological data for each patient. I learned about various databases and servers that are used to record, annotate, and distribute clinical data. What preexisting conditions do patients have, what medications are they on, what are their clinical lab results, are those results consistent with our research results, what do they mean, how do we interpret them? Here, I encountered an incredible data scientist, Dr. Wade Schulz (Director of CORE Center for Computational Health at Yale School of Medicine). He developed what I think of as a “magic wand” that can analyze electronic data associated with any disease or symptoms of interest and the patient phenotype across the medical network while preserving the privacy of the patients. I have a new level of appreciation for data science and how powerful and instrumental it is to translational research.

Discoveries enabled by IMPACT

The Yale IMPACT team made significant advances in characterizing the viral

spread and the immune responses to SARS-CoV-2, resulting in dozens of published and preprint papers. To highlight some of these, we found that severe COVID patients have misfiring of the immune system, where Th1, Th2, Th17, and their associated immune effector responses were all elevated (Lucas et al., 2020). Ironically, we found elevated levels of type I IFNs, the very cytokines that are supposed to control viral replication, in severe and lethal cases. We found top biomarkers of mortality to be IL-18 and IFN- α . We also found that there are sex differences in immune responses that we observed from COVID-19 patients (Takahashi et al., 2020). These results suggest that biological sex should be considered an important factor in infectious disease and immunology. More recently, we collaborated with Dr. Aaron Ring and his team, who developed a crucial new technology called rapid extracellular antigen profiling (REAP) that allows detection of autoantibodies to thousands of self-antigens. Using REAP, we discovered that COVID patients develop diverse and functional autoantibodies against immune factors and tissue antigens (Wang et al., 2021). A key partner in all of these studies is Dr. Saad B. Omer and his team, who bring biostatistical and epidemiological insights that are crucial to our analyses and interpretations. His global health and policy expertise also shaped tremendously the way we are approaching science together. Over the entire course of study, there were over 130 people involved in the IMPACT effort, including clinicians, nurses, study coordinators, researchers, students, and volunteers. Beyond immunology, IMPACT is continuously making important discoveries about viral spread (Fauver et al., 2020) and developed an easy and reliable saliva detection method (Wyllie et al., 2020), which is now used by a number of sites around the world. Importantly, numerous young investigators are continuing to publish studies as first and corresponding authors.

The power of social media and our launch of long COVID research

In addition to providing content on Twitter, I also receive innumerable key insights in near real-time as they appear on social media. They include the latest

preprints from scientists, published work being explained in tweetorial threads, and debates about everything from longevity of immune response, to the airborne nature of the virus, to effectiveness of masks. One of the pivotal moments came when I stumbled on a tweet by the patient group-led survey by Survivor Corps, showing that 40% of COVID long haulers are feeling better after vaccine, while 15% are feeling worse. This was accompanied by a tweet by my colleague Dr. Daniel Griffin, who has become a podcast star communicator on COVID-19. Similar improvement and worsening after vaccination were reported by a video explainer by Long Covid SOS. These posts lit a light bulb inside my head. I thought if vaccines are making some people feel better, this can be explained by generating robust immunity that gets rid of persistent virus or viral ghost. Alternatively, vaccines, by inducing strong cytokine responses, might temporarily hinder autoreactive lymphocytes, shutting down their pathologic activities, akin to how recombinant IFN- β is used to treat multiple sclerosis patients. The former would be a cure, while the latter would be a temporary relief.

Around the time I was thinking and tweeting these ideas, I was invited to serve on a Zoom panel with Dr. Harlan Krumholz, the director of Center for Outcomes Research and Evaluation at Yale. I told the audience about this idea of vaccines and long COVID and how my dream would be to figure out this disease and help find a cure. Harlan said on the panel that he wanted to do whatever he can to help support this effort and make this a reality. I thought he was just being nice, but he was serious! After numerous Zoom meetings, Harlan did make it happen! He galvanized multiple groups, including Survivor Corps and the founder Diana Berrent (who also became a key partner in this effort), and wrote an IRB application to recruit long COVID patients to collect specimens before and after the vaccine so we can study how their immune responses to the vaccine are affecting various symptoms (improvement or worsening). I learned the importance of involving patients as key and equal partners in our collective effort to understand disease.

If it were December 2019 all over again, what would I do differently and what would I do the same?

I would not change much of what I did, as everything was a learning opportunity. One thing I might change would be to put my own mental health above other priorities from the beginning. The toughest part of the pandemic is not about working 24/7, but dealing with numerous personal conflicts, which is utterly draining. My mistake was not realizing how much of this stress was impacting my own health.

Looking toward the future

One pivotal event that ignited my desire to work on long COVID was an interview with Ed Yong. When he asked me about how long hauler disease might happen from an acute viral infection in May of 2020, I thought about it, and came up with a couple of hypotheses. Long-lasting symptoms may be a result of lingering virus infection, remnants of the virus that persist (I called it viral ghost), or autoimmune reaction (<https://www.theatlantic.com/health/archive/2020/06/covid-19-coronavirus-longterm-symptoms-months/612679/>). In another article by Ed, Dr. David Putrino, the director of Rehabilitation Innovation at Icahn School of Medicine at Mount Sinai, was being interviewed. David provides therapy to those suffering from long COVID, and I decided to reach out to him to collaborate to find out what is causing this disease. He immediately responded with a yes! Now, David and I are collaborating daily to figure out the pathobiology of long COVID. With David's team, my lab is dedicated to understanding the pathobiology of long COVID and other post-infection syndromes that result in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). This is a huge unmet medical need and frankly an area that has been dismissed by many physicians and scientists. Just because something is complicated and difficult, we cannot ignore the patients and dismiss their suffering. I believe ME/CFS is an immunological disorder. Even after we contain the pandemic with vaccines, there will be tens of millions of people suffering from long-term debilitating symptoms. I would like to contribute to the understanding of this enigmatic disease. Actually, I suspect that there are likely multiple diseases that are currently

considered under the umbrella of post-acute COVID-19 syndrome—one driven by persistent viral infection, another driven by purely autoimmunity, and yet another that is a combination. There may also be disease caused by tissue damage that is unrepaired or due to reactivation of existing viruses (Proal and VanElzakker, 2021). My dream would be to find biomarkers for these various disease types and to recommend an appropriate treatment for each based on the underlying disease mechanisms. Promising candidates can then be tested in randomized clinical trials to assess efficacy.

Moving forward, I plan on communicating science to the public whenever I can, explaining complex immunology in an accessible way. If I can save one person's life by convincing them to get the vaccine, that would be more than I can hope for. Finally, tackling science, medicine, and public health's greatest challenges requires diverse perspectives and strong team efforts. The pandemic has amplified disparities among the most vulnerable and marginalized. My advocacy for women and under-represented minorities in science will continue. Until the day we reach parity, we are falling short of our collective scientific capacity. We need to double down on these efforts to restore damage sustained from the

pandemic and make the future of science brighter for the next generation.

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DECLARATION OF INTERESTS

A.I. served as a consultant for Spring Discovery, Boehringer Ingelheim, and Adaptive Biotechnologies and is a member of the scientific advisory board of 4BIO Capital. A.I. is a co-founder of RI-GImmune. A.I. holds a patent entitled "Interferon Production Using Short RNA Duplexes," United States Patent Number 10947543.

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