How scientists launched a study within days to probe COVID-19's unpredictability

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On a Friday afternoon in mid-March 2020, as the emergency department at Massachusetts General Hospital began admitting its first coronavirus patients, attending emergency physician and researcher Michael Filbin recognized an urgent need to quickly learn about the emerging pathogen. With a surge of COVID-19 patients expected in the hospital in the

coming weeks, Filbin decided to assemble a team of researchers to answer a key question that made the illness so hard to treat: why is the disease mild for some, yet deadly for others? To generate enough data to answer that question, the researchers would need to enroll COVID-19 patients in a study during the coming surge, which meant they'd need to plan and launch the study in record time.

The hospital's emergency preparedness team had just informed Filbin that clinical research studies, including his investigations into the life-threatening condition known as sepsis, would be paused so that medical teams could focus on the anticipated rise in COVID-19 cases. Filbin realized that the existing workflows he and his collaborators at Mass General and the Broad Institute of MIT and Harvard had been using for the past two years to study the immune response to sepsis were ideally suited to study COVID-19 and how the body responds to the infection.

The team expanded their sepsis research pipeline to prepare for the COVID-19 surge and worked quickly with the hospital administration to launch the study. Two weeks after first discussing the idea, the team enrolled the first patients in the COVID-19 Acute Cohort Study. "That turnaround is absolutely unheard of in the research world," said Filbin, who is also an associate member at the Broad.

During six weeks of grueling, around-the-clock work, Filbin and his collaborators at Mass General collected and processed more than 800 blood samples from 384 people, 306 of whom tested positive for the coronavirus. Many of the patients enrolled had severe disease, and some eventually died, whereas others recovered more quickly. Scientists at the Broad and Mass General are now collaborating to analyze those samples to learn more about the virus's unpredictable effects on the body. By studying antibodies, genomic activity in single immune cells, and protein signatures in the blood samples, the researchers hope to find risk factors for severe disease that could inform treatment decisions or help

prioritize patients for clinical trials. The findings could also help pinpoint cellular pathways that could be targeted by new therapeutics.

The Mass General and Broad researchers were able to quickly launch this ongoing study thanks to their existing, long-standing collaboration, a lot of quick thinking and actions from both physicians-scientists in the clinic and Mass General administrators and leaders, and the participation of patients and their families.

"We launched this study with the incredible support of hospital leadership," said Marcia Goldberg, an infectious disease physician at Mass General and an associate member of the Broad who is co-leading the study. "And of course, we're extremely grateful for the patients whose contributions have made this all possible."

Preparing for a surge

On that mid-March afternoon, Filbin exchanged a flurry of emails and text messages with his collaborators Goldberg and Nir Hacohen, an institute member at the Broad and director of the MGH Center for Cancer Immunotherapy and Broad's Cell Circuits Program, to get them on board. The next afternoon, Goldberg and Filbin met with Libby Hohmann, physician director of the Partners Human Research Committees, to brainstorm how they could enroll COVID-19 patients in a new study. The team spent the weekend amending their sepsis protocols to be applied to COVID-19 and, after the hospital's bimonthly institutional review board meeting that Monday, they secured approval for the study.

Research associates at Mass General who worked countless hours to process blood samples for the COVID Acute Cohort Study (from left to right: Anna Gonye, Irena Gushterova, and Tom Lasalle) Credit: Alexandra-Chloé Villani

The study leaders worked 16-hour-long days over the next two weeks to build teams for enrolling patients and processing blood samples. "Our research pipeline seemed perfect to transition to COVID, but the challenge was access to patients in an environment of lockdown and restricted access to the clinical space in preparation for the coming surge," said Filbin. In addition, they needed to set up enhanced biosafety containment conditions for sample processing.

He reassigned all nine of the emergency department's research

coordinators to the COVID-19 study, to collect an extra tube of blood from patients arriving at the emergency department with breathing difficulties and suspected COVID-19 infection. Access to sick patients was only possible through strong support from emergency department administration and nursing staff, and MGH COVID-19 Hospital Incident Command System and Infection Control Unit leadership. However, the frontline nurses and research staff were the key to success. "We owe a great deal of credit to the frontline nurses and our own research coordinators who risked exposure to COVID-19 every day to obtain these precious blood samples," said Filbin.

Filbin and Goldberg secured support from Kathy Hall, a nurse practitioner in the hospital's clinical trials group, to obtain additional blood samples from enrolled patients periodically during their time at the hospital, including while in the ICU. Collecting multiple samples from the same patients over time is a critical part of the study that will hopefully allow scientists to track important changes in the immune response to the virus. "Kathy put together an amazing team. She really did a phenomenal job," said Goldberg. "It was a tremendous help to our study."

Processing samples, night and day

Around this time, Hacohen got an email from Alexandra-Chloé Villani, a principal investigator at the MGH Center for Immunology & Inflammatory Diseases and an associate member and director of the Single Cell Genomics Research Program at the Broad. Hacohen and Villani had collaborated closely on Human Immune Cell Atlas projects. She shared that her lab was also planning a study to analyze immune cells from coronavirus patients, so the two joined forces to build a team to process the study's blood samples and prepare them for analysis.

They assembled and trained a team of 17 scientists from their two labs,

as well as two from Goldberg's group, to process the blood samples as they were collected. Because the samples needed to be processed for the study within just a few hours of being drawn from patients, and many samples were quickly arriving at the lab, the scientists had to work nearly around the clock everyday for six weeks to pull out the immune cells and proteins from the samples for later analysis. The team included research associates, graduate students, postdoctoral fellows, and physician-scientists who assisted with the study before they were called in to treat patients during the surge's peak.

"It was nice to see our research families coming together, but it was also necessary to build a large team because the long days were grueling," said Villani. "We needed extra hands to work seven days a week, from 7:00 AM to 2:00 AM, because by the time the evening's last batch of blood came in around 10:00 PM, you needed a few hours more to process it."

The team processed samples using protocols designed by Villani and Moshe Sade-Feldman, a staff scientist at the Broad and Mass General. Sade-Feldman directs the hospital's Translational Cancer Immunology lab, which was repurposed to process samples for the study. "Our biggest advantage is that we're located at the main campus at the hospital itself, so it's a five-minute journey from the emergency department to our lab, and we were well equipped to adapt to the new protocols," said Sade-Feldman. "This study was only feasible because of the amazing teamwork we had with Mike, Marcia, and their clinical research coordinators, and because we worked so quickly to set things up."

To protect the researchers and prevent the spread of virus, the clinical research coordinators brought blood samples from the clinic up to the lab, where they left them for a contactless handoff to the processing scientists, who also wore thorough protective gear. "I can tell you, when you wear the full gear with the mask, face shield, gown, booties, and

sleeves up to your elbow on an eight- to 10-hour shift, it's something, all right," said Villani. "I'm impressed by the commitment of the team, who've been spectacular to say the least."

The study was initially designed to enroll 100 patients, but soon expanded to include nearly 400.

Searching for clues to COVID's severity

With the collection phase complete and all samples processed, the research team is now studying immune cells and proteins in the blood to learn how the pathogen causes disease and how the body responds to it, and how that changes over time.

"We're now asking the question, what causes the switch in the body to truly severe disease and when," said Hacohen.

Hacohen and members in his lab at the Broad are studying how the immune system responds to the virus, using an assay developed by Mateo Gentilli, a postdoctoral researcher in Hacohen's lab. The assay measures "neutralizing antibodies" in the blood that increase after infection. The team wants to learn if these antibodies are involved in controlling the infection or leading to severe symptoms, and if they are, how. "We want to know how the body is able to either protect itself or not," said Hacohen.

In another set of analyses, the team is collaborating with Galit Alter at the Ragon Institute of MGH, MIT, and Harvard, who studies the role of antibodies in the body. Antibodies perform other functions besides neutralizing infection, such as activating immune cells to fight the virus. The researchers want to know if antibody function differs in people with different COVID-19 symptoms and severity.

The team is also looking for proteins that could lead to insights into why some patients get severely ill or die, potentially identifying host pathways that could be targeted by therapeutics. Those proteins could also be biomarkers that predict how sick a patient will get. "We want to find proteins that reflect clinically what's happening in the patient before the clinical symptoms get severe," said Hacohen. "That will help physicians know what to do, but also give us clues about what's causing those symptoms."

To do this, the team is collaborating with two companies, Olink Proteomics and SomaLogic (with support from Novartis). Through these collaborations, the researchers are analyzing hundreds of proteins in blood plasma that could signal how the virus is affecting tissues throughout the body. Because blood passes through every tissue via the circulation, it can pick up clues along the way about the health of tissues. "A blood sample gives you a reflection of what's happening in any tissue," said Hacohen.

Another set of analyses is led by Villani and Hacohen. At the Broad, the scientists are performing single-cell RNA sequencing on several blood cell types, to examine the exact cell types and activation states that are associated with good or poor outcomes. The findings could point to specific cellular pathways, genes, or molecules that are linked to severe disease and could potentially be targeted by drugs.

In a separate but related study, Villani and Orit Rozenblatt-Rosen, senior director of single-cell genomics for the Broad's Klarman Cell Observatory, are performing single-cell analysis at the Broad of tissues from patients who passed away from COVID-19 at Mass General and other Boston-area hospitals. Some patients in this autopsy study were first enrolled in the acute cohort blood study before unfortunately succumbing to the disease; an analysis of blood and tissue samples from the same deceased patients can provide insight on the biological events

that ultimately lead to severe disease and death.

The cutting-edge single-cell technologies used by the scientists are a powerful platform to explore the cellular basis of disease. "Studying hundreds of thousands of individual immune cells isolated from COVID-19 patients throughout the course of their disease along with immune cells isolated from infected tissues may give us insights into both local and systemic immune response," said Villani. "Together, these results may allow us to identify markers of disease severity that could be used in the clinic to improve patient care management and identify potential novel therapeutic targets."

Foundation for future work

In September, the researchers released their first set of proteomics data from the collaboration with Olink, including measurements of more than 1,400 proteins in the plasma of all patients that participated in this study. They also recently released their first set of single-cell genomics data online in the COVID-19 Cell Atlas to be used by the global research community in other studies. The researchers will continue releasing additional data in the weeks to come, soon after it's generated.

The researchers say insights from this ongoing work could pave the way for more studies that test specific hypotheses, such as whether targeting a certain cellular pathway or molecule might reduce disease severity, and when during the infection would be the best time to intervene.

"It's critical that any drug or therapy be tested with appropriate controlled trials before it becomes standard practice," said Goldberg, who added that it is equally important to understand the underlying biology of both the disease and any drugs used to treat it. "It would be a huge mistake to try and short-change any of those efforts in the long run." Results of the acute cohort study may also help classify patients

appropriately for clinical trials, by identifying patients most likely to benefit from a particular intervention.

The researchers acknowledge that their study is possible only because of the amazing multidisciplinary teamwork across institutions and departments, and participation of patients and their families. Villani is grateful for the team's commitment to working non-stop, seven days a week since March. "It is truly inspiring to see everyone coming together selflessly to try to find solutions to better care for patients infected with SARS-CoV-2. We know so little about this disease and patients are so vulnerable," she said. "We hope that our translational effort will result in important insights that could lead to new therapeutic avenues."

Provided by Broad Institute of MIT and Harvard

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