YALE RESEARCH TACKLE COVID
Across Yale Cancer Center this spring, most research labs shut down to protect their personnel from COVID-19. To protect patients, clinical trial enrollment also took a two-month pause. But several of our researchers with relevant expertise have continued to conduct critical research on SARS-CoV-2, the deadly new coronavirus that causes COVID-19.

Since the pandemic hit, these Yale Cancer Center scientists have worked overtime to investigate topics like abnormal blood clotting, antibodies to the virus, and the mechanism of SARS-CoV-2 replication and pathogenesis, as well as the unique reactions of patients with cancer to COVID-19. What they are learning has already changed the way doctors care for patients with coronavirus.
“I am so proud of what our research scientists and research staff have done,” said Charles S. Fuchs, MD, MPH, Director of Yale Cancer Center and Physician-in-Chief of Smilow Cancer Hospital. “We were well suited to do this work,” he said. “It’s just inspiring.” The pivot to COVID-19 projects has been incredibly fast, he added.

For example, on the evening of Sunday, March 22, the National Cancer Institute (NCI) emailed Dr. Fuchs offering YCC researchers the chance to compete for additional funds. The catch: the application would be due that Friday, a stunningly fast deadline for a process that normally takes months.

A rapid grant competition was designed and announced Monday morning. By that Wednesday, Dr. Fuchs and Daniel DiMaio, MD, PhD, Waldemar Von Zedtwitz Professor of Genetics and Professor of Molecular Biophysics and Biochemistry and of Therapeutic Radiology and Deputy Director of Yale Cancer Center, had received thirty applications from YCC researchers. A quickly-assembled review panel spent Thursday reading and narrowing them down.

“By Friday morning we had a rank list,” Dr. DiMaio said. They nominated a study of antibodies to the coronavirus headed jointly by Aaron Ring, MD, PhD, Assistant Professor of Immunobiology, and Eric Meffre, PhD, Associate Professor of Immunobiology and of Medicine (Immunology). “Dr. Fuchs and I wrote a cover letter and sent the application to the NCI with about two minutes to spare on Friday afternoon.”

The project won YCC one of the coveted $250,000 federal grants. “Everybody was very compliant and supportive, we all played well together, and it was a great outcome,” Dr. DiMaio said.

Early in the pandemic, physicians noticed that many COVID-19 patients develop coagulopathy, or abnormal blood clotting, a sometimes lethal complication. In a recent Grand Rounds presentation, hematologist Alfred Lee, MD, PhD, Assistant Professor of Laboratory Medicine and of Immunobiology, is working to understand that interaction. His lab dove into SARS-CoV-2 research early, synthesizing the virus’s infamous spike protein—the one that allows it to enter human cells—shortly after its genetic sequence went public in January.

Thanks to University support, Dr. Wilen was able to rapidly equip Yale’s Level 3 Biosafety lab to study the respiratory virus, stocking the facility with high-end imaging and drug-screening equipment and research basics like freezers and centrifuges.

Then began weeks of what Dr. Wilen calls “non-glamorous, but essential” work to determine how to wrangle the coronavirus in captivity. How best to grow it and to count up its numbers? What kinds of host cells did it multiply in? Finally came a key experiment: detecting which of eight airway cell types the virus likes best, and whether it tends to infect different cell types over time.

Many questions about CAC remain and Dr. Lee’s team is continuing to investigate, these data led YNHHS’s critical care leaders to add aspirin, an antiplatelet medication, to COVID-19 ICU patients’ anticoagulation regimen, in addition to clinical trials of other drugs that may help to lessen the severity of the disease.

Exactly how infection with the novel coronavirus might lead to endothelial cell damage remains unclear, but it might directly invade them, as it does airway cells. Virologist Craig Wilen, MD, PhD, Assistant Professor of Laboratory Medicine and of Immunobiology, is working to understand that interaction. His lab dove into SARS-CoV-2 research early, synthesizing the virus's infamous spike protein—the one that allows it to enter human cells—shortly after its genetic sequence went public in January.

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Dr. Wilen’s team set up a system that simulates lung cells’ interface between liquid and air, growing human bronchial cells on a filter. They added virus to the air side of the paper, allowing it to infect the cells. A few days later, they used a novel technique called single-cell RNA sequencing to measure the virus’s presence in each different cell. The lab of David van Dijk, PhD, Assistant Professor of Computer Science and Medicine (Cardiovascular Medicine), performed the computational analysis.

Drs. Wilen and van Dijk found that the virus first infects ciliated cells, which include long tail-like projections that move in unison to beat mucus and debris up and out of the lungs. The virus might be enabling its own persistence in the lungs by disrupting the way these protective cells function.
Dr. Wilen’s lab has also performed a genome-wide genetic screen to detect which host genes are essential for infection. Armed with these data, they’re exploring which drugs might target those gene products and potentially help control the infection. “It feels like the most powerful Excel spreadsheet I’ve ever had in my life,” Dr. Wilen exclaimed.

As of the end of May, YCC’s clinical trials are once more becoming available to new cancer patients. Those who are already enrolled will resume more active participation after a two-month period of remote treatment and monitoring.

But some patients with cancer at Yale—those hospitalized with COVID-19—have been able to supply researchers with invaluable information during the pandemic. That’s thanks to the IMPACT biorepository, which stores samples of bodily fluids, such as blood and nasal swabs, from COVID-19 patients as well as from healthcare workers. These samples offer scientists like Akiko Iwasaki, PhD, the opportunity to map out the body’s changing immune response during a bout with the coronavirus.

Dr. Iwasaki, who is the Waldemar Von Zedtwitz Professor of Immunobiology and a Professor of Molecular, Cellular and Developmental Biology, is studying immune cells and immune proteins, including antibodies and cytokines. The goal is to understand how patient characteristics like age, sex, or chronic conditions like diabetes affect the immune response to SARS-CoV-2 infection over time.

“These questions are acutely urgent so we can treat patients appropriately depending on what kind of demographic they come from,” said Dr. Iwasaki. “We’re learning in real time how patients are reacting to this virus.”

She is also collaborating with other Yale researchers on a host of other studies on the immune response to SARS-CoV-2, such as developing antibody tests, understanding how the body generates protective antibodies, and characterizing immune cell receptors.

Among the people contributing samples to the IMPACT biorepository is a small but growing number of patients with cancer who have been diagnosed with COVID-19. Michael Chiorazzi, MD, PhD, and Roy S. Herbst, MD, PhD, are particularly interested in what their immune reactions may reveal about the virus.

They hope to answer two questions. First, what are the differences in course of illness and clinical outcomes with COVID-19 for the patients with and without cancer? Second, among patients with cancer, how do the therapies they are prescribed impact their immune responses and outcomes?

Patients with cancer may be in a unique position to help scientists unravel how the virus kills some of its sufferers. Because many are taking medications that suppress the immune system, they might be particularly susceptible to an immune overreaction called a “cytokine storm.” This phenomenon can also be a side effect of some cancer immunotherapy drugs. Yet immunotherapies can also result in enhanced immunity, raising the tantalizing possibility that they could be helpful in COVID-19.

“[Does] being on immunotherapy make you more likely to clear the virus and never develop symptoms? Or does it make you more likely, if you do develop symptoms, to have a worse course in the hospital?” Dr. Chiorazzi asked. Either scenario is plausible, he noted.

“Hopefully, we can better design a treatment for cancer patients based on what we find,” said Dr. Iwasaki, who is studying their immune responses in collaboration with Drs. Chiorazzi and Herbst. “It’s actually a really important cohort of patients to look into. Just imagine if one of these drug treatments used for cancer are actually beneficial in COVID-19.”

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