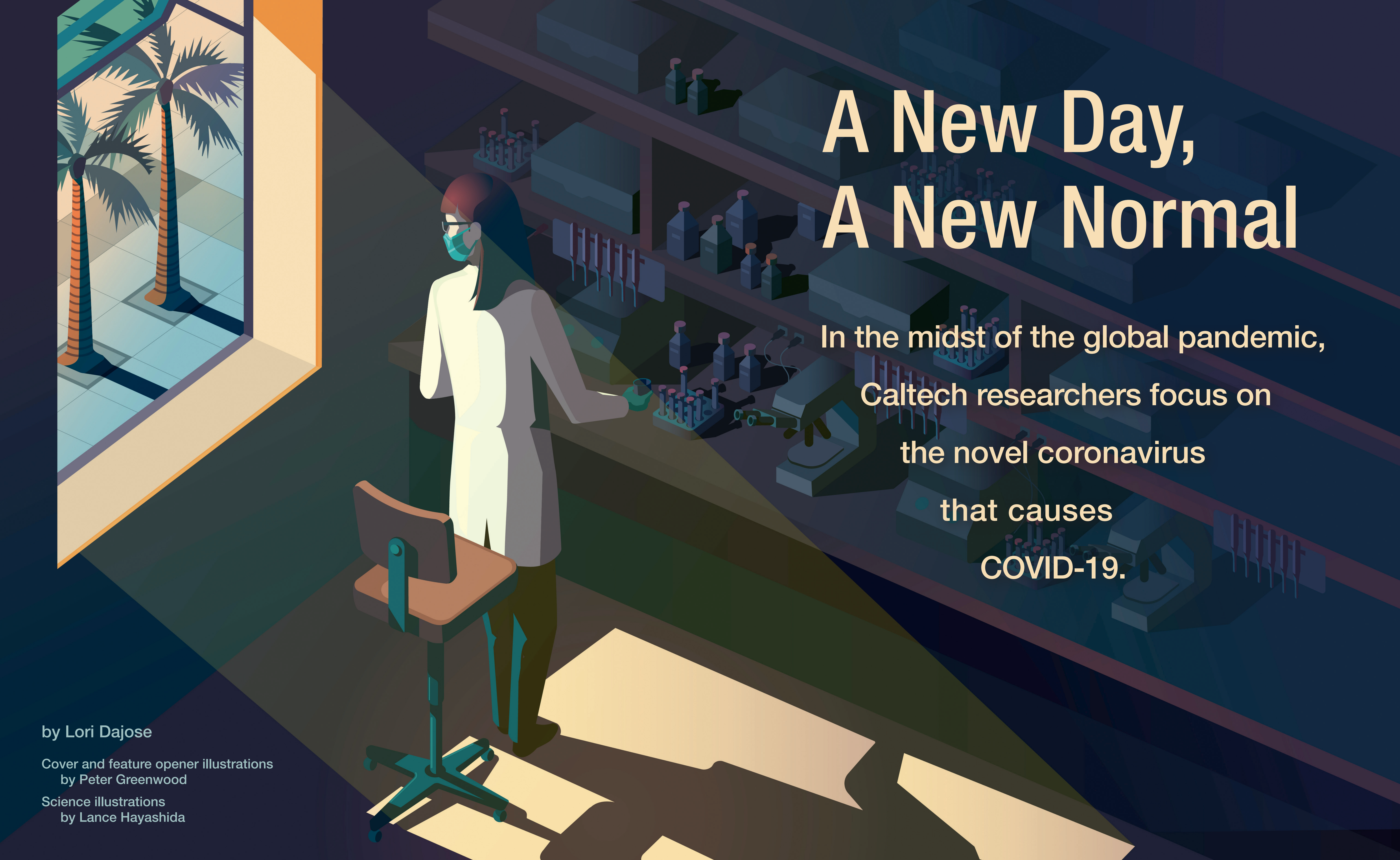

A New Day, A New Normal

In the midst of the global pandemic, Caltech researchers focus on the novel coronavirus that causes COVID-19.

by Lori Dajose

Cover and feature opener illustrations by Peter Greenwood

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Rain fell steadily on campus the day the labs began to shut down.

A March 16 email from Caltech's president and provost had informed the community that, to limit the spread of COVID-19 and support the efforts of public-health authorities, all nonessential research needed to be deferred or transitioned to remote operations.

The atmosphere in the laboratories turned eerie, without the perpetual whir of motors and pumps. The atomic physicists carefully turned off their cryocoolers, slowly, to ensure that evaporating gas did not create too much pressure; the chemists shut down their X-ray photoelectron spectroscopy machines and electron-beam evaporators, sealing off volatile chemicals and glove boxes.

In less than a week, research operations at Caltech had been turned upside down.

But almost as suddenly as their original work was paused, some groups pivoted to a new focus: the novel coronavirus causing the COVID-19 pandemic, SARS-CoV-2.

Studying Antibodies from Recovered Patients

Pamela Björkman's laboratory was one of a few allowed to remain open for essential research. Social-distancing protocols made the labs strangely quiet, a few lights on in some of the windows at night providing the only clues to the activity within.

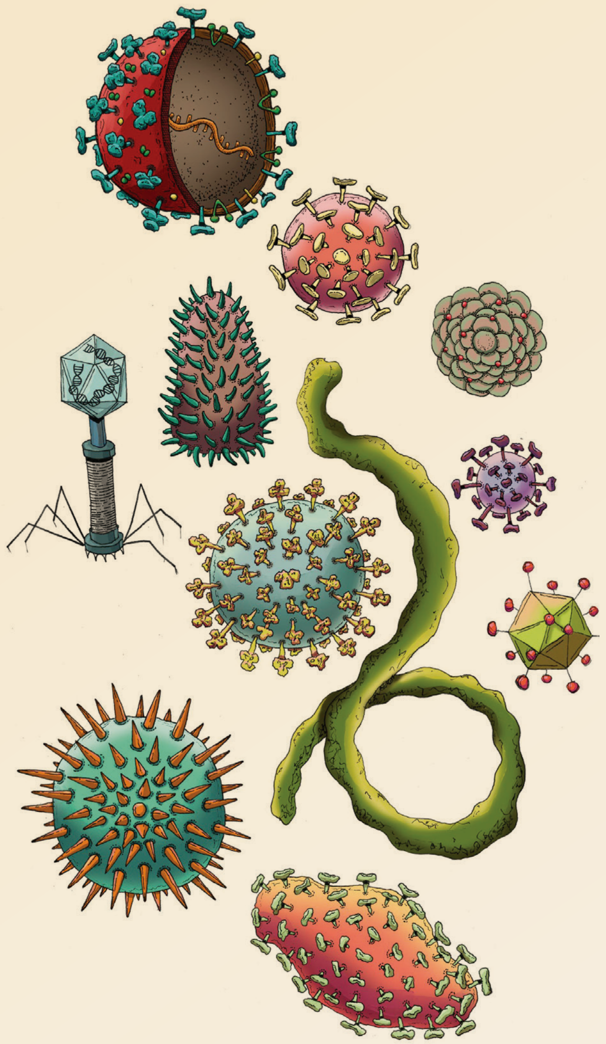
For Björkman, Caltech's David Baltimore Professor of Biology and Bioengineering, whose laboratory studies HIV, the focus was not entirely new; her research group had received funding from the NIH to begin a project on SARS-CoV-2 in February. But as her lab's research ramped up, Björkman faced another coronavirus-related matter: her daughter, who had been teaching in Malaysia as a Fulbright fellow when the pandemic began to take hold internationally, had been told she must return to the United States. But Malaysia was shutting down internal travel, and it was not clear how to get to an international airport.

"The situation was chaotic, with things changing on an almost hourly basis. In the end, our daughter was unable to return to the rural village where she had been teaching to retrieve her possessions, but she was able to get a flight back to the U.S. Fortunately, she tested negative for COVID-19; she was one of the lucky few who were able to be tested in mid-March," says Björkman. "This experience made the urgency of the global pandemic more personal for me."

The work in Björkman's lab has centered on the potential of antibodies to help individuals fight coronavirus infections. "I am very grateful that the researchers in my lab, especially [postdoctoral scholar] Christopher Barnes, who led the efforts, put in long hours and a lot of brainpower to learn how the body uses immune defenses to combat the virus. We hope that this knowledge will pave the way to create an effective vaccine, which is needed not only against SARS-CoV-2 but also against new coronaviruses that are likely to emerge from animal hosts in the future. From our research into immune responses to other viruses, we have ideas for how to create a universal coronavirus vaccine, which we are in the process of developing and evaluating."

Whenever the body is confronted by a pathogen of any sort, including the novel coronavirus, one of its responses is to develop antibodies, proteins that are specialized to recognize and neutralize new pathogens. Then, if the pathogen invades the body again, antibodies produced by memory immune cells can quickly recognize and destroy it before it can take hold. This explains how vaccines protect against specific infections and is why some diseases can infect a person only one time.

What is a Virus?
Viruses occupy a gray area between the living and nonliving realms. Scientists have identified more than 200 virus species with the potential to infect humans.



Postdoctoral scholar Christopher Barnes at work in the lab before the pandemic began. He has since pivoted his research from HIV to the virus that causes COVID-19.

For years, Björkman's laboratory has studied the HIV virus and antibodies to the myriad strains of the virus. Both SARS-CoV-2 and HIV are enveloped viruses, meaning that each individual virus has a fatty membrane around it. On this membrane are so-called spike proteins, which a virus uses like claws to grab onto a host cell. Coronaviruses have particularly large spikes that give the spherical virus an appearance similar to a crown, hence the name for this class of viruses, "corona" being the Latin word for crown.

The most effective antibodies are usually ones that block this spike protein. In a recent study published in the journal *Cell,* Barnes and a team of collaborators used antibodies isolated from people who had recovered from COVID-19. They studied the various forms that these antibodies can take and exactly how they interact with SARS-CoV-2.

In the same way that a defensive soccer player can use many strategies to block another player's shot, there are many ways for an antibody to try to block a virus. Some, however, are more effective than others. Barnes created an atomic-level model of a particularly potent antibody clinging to a SARS-CoV-2 spike using the same techniques he uses to study HIV antibodies. This antibody was found to be highly effective in its ability to neutralize the virus, or render it unable to infect. Barnes found that this antibody grabs onto a specific region of the spike protein called the receptor-binding domain, or RBD, which is particularly important for the protein to make a connection with a host cell.

"Our work suggests that if bioengineers can design antibodies that target the RBD, that could be an effective way to treat people with COVID. Or, a vaccine could be designed that induces a person's body to produce antibodies that home in on that region," Barnes says. Before the pandemic, Barnes and his wife, Caltech postdoctoral scholar Naima Sharaf, who have two young children, had been busy negotiating academic job offers. It was a challenge to then also shift their research to this urgent situation. Barnes says they make a great team; Sharaf is a co-author on the new paper.

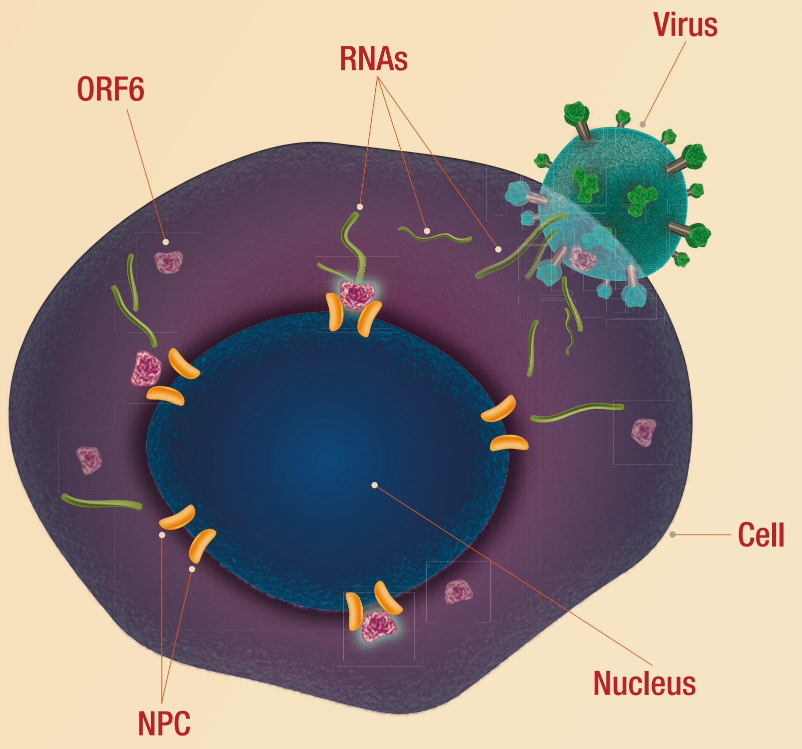


Illustration of a coronavirus infecting a cell, blocking its nuclear pore complex (yellow) with its ORF6 proteins (pink).

A Protein's Unexpected Role in Infection

Unlike the Björkman laboratory, the research group of André Hoelz (Caltech chemistry professor, Howard Hughes Medical Institute Faculty Scholar, and Heritage Medical Research Institute Investigator) had not previously focused on viruses. Hoelz studies the microscopic machinery in the cells of eukaryotes (the so-called higher life-forms), focusing specifically on the nuclear pore complex (NPC), the massive protein machine that controls access to the DNA-containing heart of the cell. The NPC is targeted by SARS-CoV-2 when the virus infects a cell.

To understand what the NPC does and the role it plays in a coronavirus infection, it helps to know some basics about how a cell is structured.

In eukaryotes, a cell's genetic material is held inside a ball-shaped organelle called the nucleus, which holds the information the cell needs to perform its functions and controls the actions of other parts of the cell.

In a normally functioning cell, the nucleus makes copies of the instructions held in its genetic material in the form of short strands of RNA, which are then sent out via pores in the nuclear membrane into the main chamber of the cell, known as the cytoplasm. The pores are not just holes but instead are composed of a collection of proteins collectively known as the NPC.

After a strand of RNA passes through the NPC into the cytoplasm, the RNA provides the instructions to manufacture a given protein needed by the cell. Many viruses will try to block or destroy the NPC, preventing the cell from exporting its RNA strands and thus allowing the virus to have nearly unfettered access to the cell's machinery to manufacture its own proteins.

As SARS-CoV-2 began to take an international toll, Hoelz and his team started to suspect the virus was attacking the NPC in cells. They planned to pivot their research to investigate this. Then, Hoelz was contacted by a team at UC San Francisco that had found hints that a particular viral protein called ORF6 may be responsible for blocking a cell's NPC. The ORF6 protein is known to be used by the coronaviruses that cause other diseases (such as SARS, MERS, and the common cold) to prevent cells from signaling to their neighbors that they have been infected. Because Hoelz is an expert on the NPC, the UCSF team enlisted his help to examine how the NPC and ORF6 interact.

"We could show that ORF6 does indeed target the NPC and associated mRNA export machinery, and we are currently working toward elucidating the detailed chemical basis of this activity," Hoelz says.

Hoelz notes that the nature of his research has changed with the advent of the virus and social distancing. "For more than two decades, I haven't been away from the lab for longer than a few weeks at a time. While video calls do allow us to communicate and carry on with our work, I greatly miss the direct face-to-face interactions that have been a key element of our daily lives as scientists."

Wearable Sensors to Catch Infections Early

One of the most telltale symptoms of a COVID-19 infection is a fever: an elevated core body temperature. A fever may even begin to set in before other symptoms, such as a cough. Monitoring a person's temperature, therefore, could provide an early warning that an infection may be present.

In the laboratory of Chiara Daraio, professor of mechanical engineering and applied physics, researchers have been developing polymeric materials, thin and flexible like Saran Wrap, that can measure temperature changes very precisely. When COVID-19 took hold, Daraio and her team focused on ways they could design those materials into a wearable device to continuously monitor a person's core temperature.

Wearable technology is not usually suitable for monitoring fever, because the surface of the skin does not reflect the body's core temperature. But Daraio's team realized that their polymer materials could be stacked in thin layers, and by measuring the variation in temperature between the layers in what is known as a dual heat flux calorimeter, they could extrapolate the core temperature.

Daraio then partnered with Azita Emami, Andrew and Peggy Cherng Professor of Electrical Engineering and Medical Engineering and Heritage Medical Research Institute Investigator, for help in building the device. "Our group is focused on materials, but we needed help with the miniaturization of electronics. Azita is the go-to person at Caltech," Daraio says.

"Wearable sensors have generally been seen as gizmos and not taken seriously," she adds. "This is an opportunity to realize how important they can be in monitoring individuals both at home and in a hospital setting. Right now, for example, a nurse in the infectious diseases ward of a hospital has to manually measure patients' temperatures, which puts that nurse at risk. Having these devices in a hospital setting would allow for safer and simpler care."

As the device is being built and tested, Daraio is looking ahead to how it may more broadly support public health. Together with Tapio Schneider, Caltech's Theodore Y. Wu Professor of Environmental Science and Engineering, and a team of data scientists, they envision that if enough people wear the device and send the data it collects to their smartphone, combined with proximity data, an algorithm could quantitatively predict risks of infection. This would enable people to make informed decisions about their actions (whether or not to visit a certain grocery store, for example), while also reducing the economic damage of blanket social distancing.

Daraio and Schneider, who are married, came up with the idea around the dinner table one evening early in the pandemic. "Blanket social distancing redundantly isolates too many people who are not infectious," Daraio says. "We were looking for ideas to safely return to a less socially distant life."

The Social Consequences of COVID-19

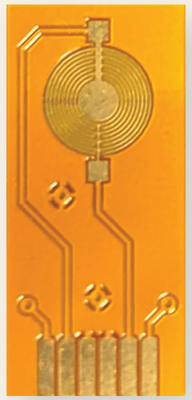
Dean Mobbs, assistant professor of cognitive neuroscience and a Chen Scholar, is studying how the viral threat has led to heightened levels of anxiety throughout the population.

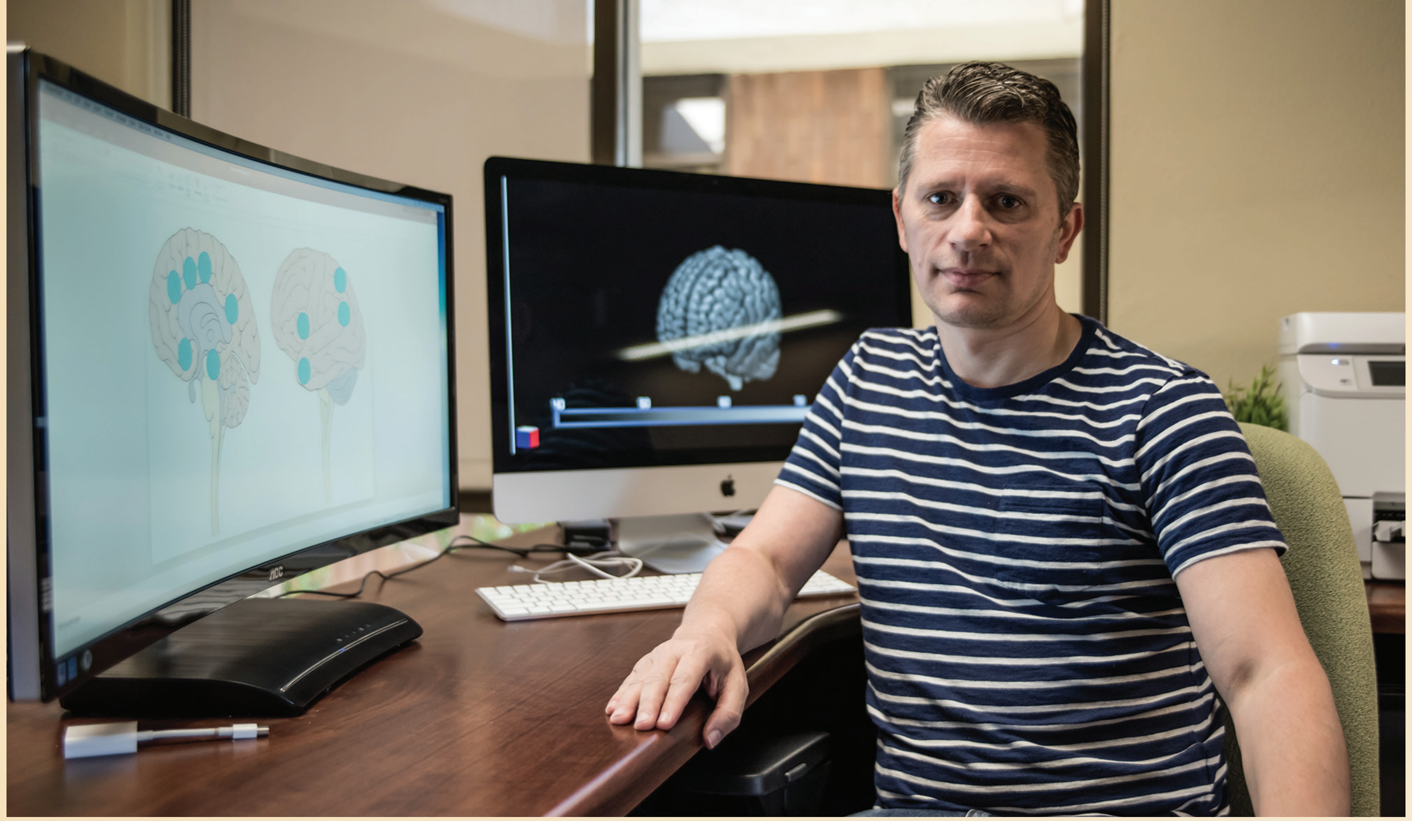
"We are coping with an unseen enemy," says Mobbs. "The human anxiety system is ramped up even higher when there's a lot of uncertainty."

When we encounter uncertainty, Mobbs says, we search for information about the threat so that we can combat it. Our brains preferentially attend to negative stories because they allow us to learn about those threats without actually experiencing them. But a constant high volume of negative information becomes overwhelming, as countless people in the midst of this pandemic can attest.

"We have this wonderful ability to think about future threats and to vicariously learn about threats in the world," Mobbs explains. "But, given the mass communication

Chiara Daraio (below) and her collaborators are developing a wearable sensor that could continuously monitor a person's temperature. Graduate student Vincenzo Costanza (MS '19) helped lead the research.





Dean Mobbs studies how the viral threat has led to heightened anxiety throughout the population.

channels that we use, it's not surprising that many of us are feeling much anxiety. That anxiety is translated into behaviors, such as panic shopping. Researchers believe there is going to be a peak to the fear and anxiety, and then, even though the danger of the threat of the virus is higher, I think we're going to see people habituate to the threat and become less anxious. You can only keep anxiety levels high for a certain period of time."

Neuroscientist Ralph Adolphs (PhD '93), Bren Professor of Psychology, Neuroscience, and Biology at Caltech, is also studying how people's psychology, biases, decision-making, behavior, and more are affected by COVID-19. He and collaborators are taking weekly surveys of approximately 1,000 people from all 50 states, with questions about their identification with various political, religious, racial, ethnic, and social groups as well as about their experiences related to COVID -19, adherence to public health recommendations, and trust in political and scientific leaders. Additionally, the researchers pose questions about various psychological factors, such as personality, mood, and coping behaviors. They are hoping to answer questions such as, "How do people's emotions reflect the COVID-related regulations in their state and county?" Adolphs hopes that the collected data and models will be useful to the people who develop public health policy.

A Pandemic's Planetary Effects

Shortly after the stay-at-home orders were issued for Los Angeles, photos of the city began to circulate on social media that suggested the skies were clearer due to people staying home; the phrase "Nature is healing; we are the virus" was a frequent caption. But Paul Wennberg, Caltech's R. Stanton Avery Professor of Atmospheric Chemistry and Environmental Science and Engineering, cautions that it's not always so straightforward to draw connections between staying home and clearer skies.

Wennberg is particularly interested in the effects of humanity's changed behavior and habits on the planet. In Los Angeles, he notes, nitrogen oxide (NOx) emissions that cause air pollution mostly come from trucks and other diesel-fueled engines rather than personal cars. In other parts of the world, the connection between the reduction in traffic associated with COVID-19 and a reduction in air pollution is easier to establish: in Europe, for example, there are far more diesel cars, which emit copious NOx. Their absence from the roads has made a much more noticeable impact.

In India, a substantial reduction in demand for electricity, a 26 percent drop in just 10 days, has led to the temporary closure of some coal plants, which in turn has led to cleaner air. In California, demand for electricity is down only about 5 to 10 percent. Many of the activities that demand electricity have not changed in the way they would in India or China, where the manufacturing sector is more dominant.

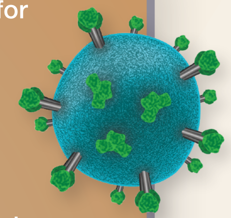
"Once you restart the activities that cause air pollution, it'll come roaring back," Wennberg says. "But there are places that have historically had really bad air pollution, and a lot of the population has never really experienced clean air. Suddenly they're experiencing it, and I just can't believe that won't have an effect. People will have seen something different, and I wouldn't be surprised if they will then demand it. We've shown in the U.S. that you can have both good air quality and substantial economic activity."

A New Day

On a sunny summer day in June, researchers (wearing masks and schooled in new safety procedures) began to slowly trickle back onto campus and into a new normal. Tables outside the Red Door Café are now spaced out for social distancing, and heightened hygiene protocols limit the number of people in any one space at a time. Custodial and dining workers have adapted to rigorous sanitizing schedules. Although campus looks and feels different than it did in early March, and the COVID-19 pandemic is far from over, the Caltech community continues to adapt to and tackle the challenges of carrying out research one day at a time. [C]

Find more articles on Caltech's COVID-19 related research at **coronavirus.caltech.edu**

Funding Rapid Responses



In April, Caltech's Richard N. Merkin Institute for Translational Research announced a call for proposals to initiate and accelerate research pertinent to COVID-19. Grants would be fast-tracked to support projects that meet urgent needs as well as initiatives focused on the long-term evolution of the virus. High-risk, high-reward projects across disciplines were encouraged.

More than 50 proposals were considered, and 21 new projects and working groups were funded. Reflecting the interdisciplinary nature of the COVID problem itself, investigators represent five of Caltech's six divisions. Two rounds of funds have been released to date, covering 19 grants. Projects include:

- The development of novel therapeutics
- Improved testing capabilities
- Structural characterization of infection processes
- Studies of the psychological impact of stress and isolation

The Merkin Institute was established in 2019 by a gift from Richard Merkin, Caltech trustee and founder of Heritage Provider Network. The institute's mission is to help Caltech scholars realize the full biomedical potential of their discoveries and inventions. It provides resources for every step in the translational science cycle, from basic discovery through clinical application and from clinical data mining to drive new basic biology.