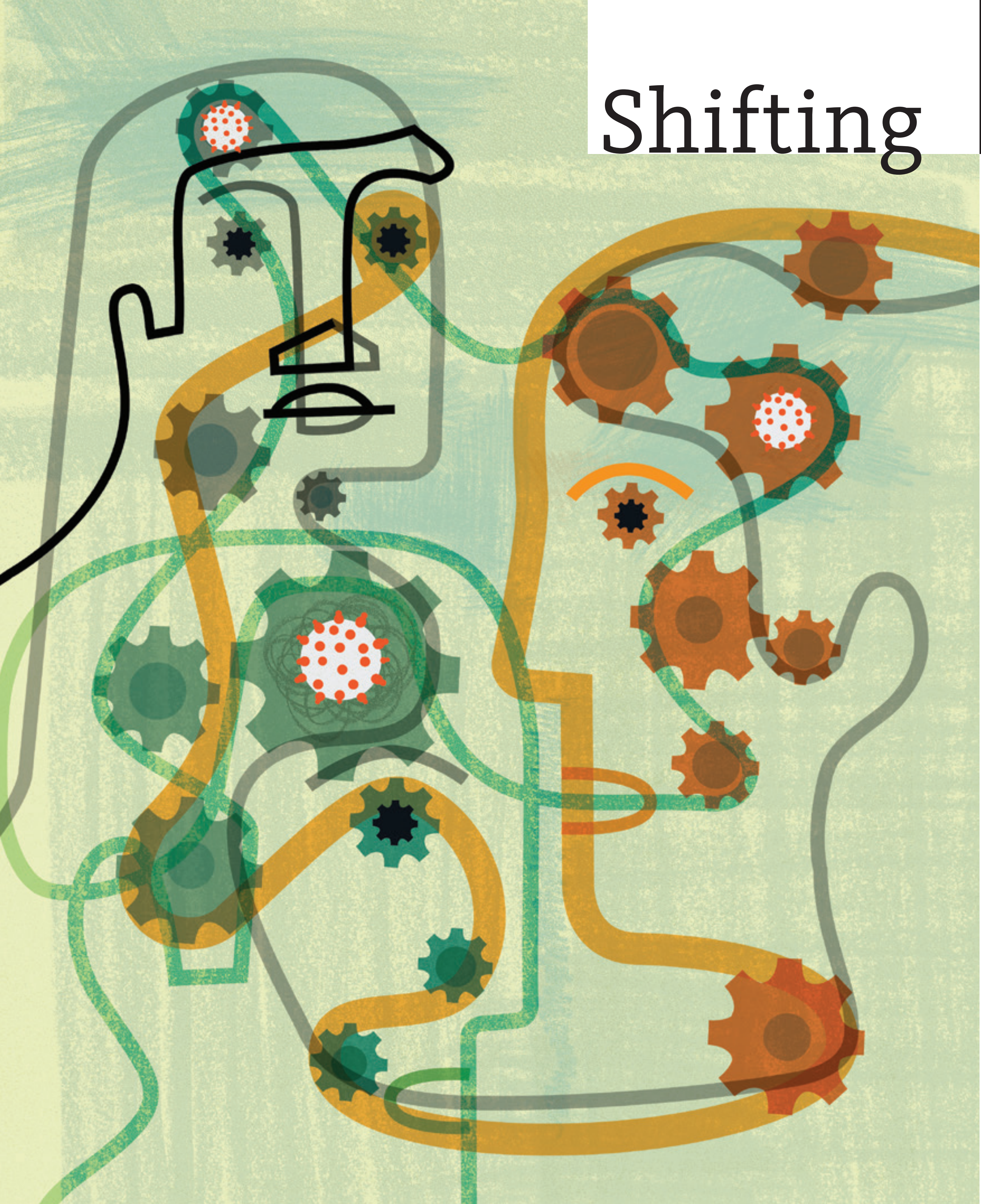


Shifting Gears

The Fight Against COVID-19 Advances

By Katie Neith

Caltech researchers have helped stem the disease's spread since the early days of the pandemic. Their work is not yet done.

When aerosol expert Richard Flagan could not come to campus to investigate the effectiveness of masks at stopping transmission of the SARS-CoV-2 virus, he brought the work home with him: specifically, to his home garage and its collection of woodworking tools. That is just one of the many ways Caltech researchers had to adjust not only the work being performed in their labs, but also the manner in which that work took place after in-person operations nearly ground to a halt in early 2020. Since then, many more intrepid scientists, engineers, and students have sought to refocus their work to address the needs of the global health crisis, despite hardships like limited capacity rules, shortages in resources, and fear of an unknown and evolving virus.

Nearly two and a half years later, these scientists have made crucial contributions to both local and national efforts to control the spread of the SARS-CoV-2 virus. These life-saving advances were made possible thanks to new funding, more public health data, a greater understanding of the virus and its effects on society, and the desire of students to help. Here are some of the major developments that have taken place in labs across campus, the unique challenges they presented, and the rewards they delivered.

Safeguarding the Workplace

Flagan, an engineer and expert in aerosol processes, flew to Helsinki in February 2020 to participate in a workshop about atmospheric particle formation experiments at the European Organization for Nuclear Research (CERN).

"I was very nervous to travel," Flagan says. "I had been aware of COVID since the first press reports, and the descriptions sounded like an airborne disease transmission, but that was not the message that was being delivered."

By the time he returned to campus, Caltech was just days away from shutting down nearly all research. Exceptions were being made, however, for studies involving COVID-19. Initially, Flagan's laboratory was involved in a study of how the first major lockdowns affected air quality. Soon, concern arose about how to open laboratories again.

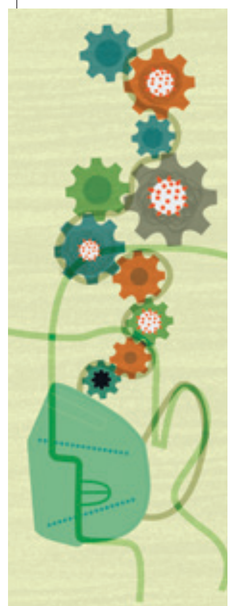
"The variability of mask effectiveness became one of the central questions," Flagan says.

Flush with state-of-the-art aerosol instruments in his laboratory, he realized that testing masks was a great match for his research group. There was just one problem: as a person over the age of 60, Flagan was up against the strong recommendation to avoid coming onto campus, even for critical projects.

Enter Buddhi Pushpawela, a postdoctoral researcher who had joined Flagan's team in November 2019. Alone in the lab, she set to work in June 2020 to build an experimental apparatus using whatever parts she could find, scouring campus for masks to test how effective they were at blocking the virus. But first, she needed to figure out how to seal the masks to the sampling instruments. In his home workshop, Flagan cut custom wood frames that Pushpawela used to clamp the masks to the plates.

"Whenever I had issues, I showed the setup to Professor Flagan through video calls and got his advice on how to do the modifications," says Pushpawela, now a clinical assistant professor of physics and astronomy at the University of Alabama in Huntsville. "I have the theoretical background and the subject knowledge, but I used some of the instruments for the first time for the face-mask testing project."

During the experiments, she measured particle penetration, breathing difficulty, and performance at different oxygen flow rates. It was a process that took nearly two hours to complete for each mask, but Pushpawela managed to test more than 400 samples, including N95s, KN95s, surgical masks, and cloth masks. Based on those results, Flagan and Pushpawela made recommendations



that guided Caltech's initial purchase of masks to help reopen campus widely for the 2021 fall semester. In addition, Flagan conducted webinars, presentations, and discussions on social media to inform the public about the effectiveness of various masks. The team published a paper with their findings in the journal *Aerosol Science and Technology* in December 2021.

"I believe we made a contribution to stopping the spread of COVID-19 and saving lives from COVID-19, at least among the Caltech community," Pushpawela says.

A Universal Vaccine?

Structural biologist Pamela Björkman is no stranger to viruses. She has dedicated her career to investigating the body's immune response to viral pathogens, and she had already received supplemental National Institutes of Health (NIH) funding to study the emerging SARS-CoV-2 virus by February 2020. But even with many similar studies under her belt, this undertaking felt different.

"Everybody knew that it was going to be very bad," Björkman says. "And running a lab was very confusing back then. We had density rules, we had to have shifts, and we had to constantly figure out who could work where and space people far apart. I was very worried that we would have an outbreak in the lab. We didn't, but I remember being very nervous about that."

Despite these stressors, the Björkman group has made significant progress in its goal to develop a universal vaccine against current and future coronaviruses.

First, Christopher Barnes, then a postdoctoral scholar in Björkman's lab and now an assistant professor of biology at Stanford, detailed the structures of antibodies produced by the body to fight COVID-19 and discovered how those antibodies bind to the virus's spike proteins (the parts that invade host cells) to stop the infection process. Barnes found that the antibodies attach to a part of the virus called the receptor-binding domain, or RBD. But not all the antibodies were binding at the same place on the RBD and the RBDs varied between the original SARS-CoV-2 virus and its newly emerging variants, as well as between related coronaviruses found in animals.

And so, Björkman says, "we did something we've been trying to do for HIV and other viruses in my lab for a long time. We made a nanoparticle that's a mosaic, meaning it co-displays different versions of the antibody target on the virus."

Alex Cohen (PhD '21), now a postdoctoral scholar in the Björkman group, designed a mosaic nanoparticle to present eight different RBDs on 60 attachment sites. Testing of the concept in animal models as a vaccine showed that the nanoparticle evokes strong immune responses to not only the viruses included in the vaccine, but also to additional coronaviruses not included in the vaccine.

Further testing has revealed the mosaic nanoparticle approach prompts antibodies to target harder-to-reach but more-conserved elements of the virus RBD, as opposed to the parts that may change with a new variant or type of coronavirus. This means the vaccine should provide broad protection regardless of how the virus mutates in the future or if new coronaviruses spill over from animals into humans, making it a strong candidate for a potent universal vaccine. The Björkman group has received funding from the Coalition for Epidemic Preparedness Initiative to conduct Phase 1 human clinical trials.

"This vaccine candidate can be used as a booster, since most people are already vaccinated or have been infected with SARS-CoV-2," Björkman explains. "It would be more protective, I believe, against possible future emerging viruses, and you wouldn't need to change it as we are confronted with more SARS-CoV-2 variants of concern."

Modeling Transmission

As the pandemic raged on and classes remained virtual, many students wanted to get involved in COVID-19 research. Yaser Abu-Mostafa (PhD '83), an expert in machine learning, decided to give students in his spring 2020 computer science class a project. The result was a model to predict the spread of the virus that consistently beat out estimates made by the Centers for Disease Control and Prevention (CDC).

"We switched the entire research and teaching effort to focus on forecasting the spread of COVID-19 in the United States," says Abu-Mostafa, who had been working on a fundamental theoretical question in deep learning prior to the pandemic. "The students are the ones who took the initiative, and I went for it based on my assessment of the value of artificial intelligence technology to help with what was clearly a national emergency."

The CDC model used data from 45 major models at universities and institutes across the country, but it did not emphasize artificial intelligence (AI), which has the power to discover patterns hidden in data that humans might miss. Early tests of Caltech's AI-driven CS156 model, named for the class where it began as a competition, showed it was more accurate than the CDC model nearly 60 percent of the time. Though it proved extremely valuable, Abu-Mostafa says it was not easy to accomplish.

"We needed to steer the whole ship in a completely new direction in short order," he explains. "This involved organizing the biggest team I have ever supervised, setting up the computational and data infrastructure, securing the funding, and, most importantly, formulating the scientific vision and the strategy to implement it successfully."

Aerosol expert **Richard Flagan** in his home garage, where he built frames used in tests to gauge the effectiveness of various masks against SARS-CoV-2.

It started with a class of more than 150 students producing 40 viable models for predicting the spread of COVID-19. From there, the top 10 models were aggregated, and a research team that included a core group of students from the class took the findings forward to create a model with an expanded scope, making rapid and precise predictions about mortality rates, numbers of infections, and test positivity rates.

"In the early days of the pandemic there were massive data gaps and uncertainties in everything from case levels to rates of mask wearing," says graduate student Dominic Yurk (BS '17, MS '21), who was the lead teaching assistant for the course and continued as a member of the research team when the class ended. "Figuring out how to make valuable predictions from highly uncertain data was a new and valuable research experience."

Shortly after initial results of the model were made public in summer 2020, the California Department of Public Health asked for access to the team's daily prediction files, which informed the department's decision-making as it managed the pandemic.

"We expected to do well given our expertise in AI, but beating all the national models put together was a surprise," Abu-Mostafa says. "While I am used to taking scientific risks, this experience encouraged me to take organizational and funding risks that are against my nature, when the opportunity arises."

The COVID-19 model also inspired him to look at other medical problems that machine learning might help solve.

"It was my first experience in research that can, and likely did, save lives," Abu-Mostafa says. "I haven't done that before in my career, and the experience made me more energized in my current focus on medical applications of AI."

Measuring Viral Load

Viruses need hosts to replicate, but exactly when a person is contagious is not always easy to pinpoint, especially with a new pathogen.

"The world clearly didn't have information on how to detect SARS-CoV-2 early, before people transmit the infection," recalls chemical engineer Rustem F. Ismagilov about the early months of the pandemic. "It was not known how much virus there was and, therefore, what sort of test would be good enough to detect it, and in which sample types, like saliva or nasal mucus, the virus was."

With the interdisciplinary team of researchers that makes up his lab, which is committed to improving global health, Ismagilov set out to answer those questions. The lab partnered with the Pasadena Public Health Department (PPHD) to launch a large community-based study to investigate how viral load changes in different sample types over time after someone has been infected.

From left: Michael Porter, Alyssa Carter, Jenny Ji, Alex Viloria Winnett, and Reid Akana, who all work in the lab of chemical engineer Rustem F. Ismagilov.

Here's how it worked: contact tracers from local public health departments, clinics, and testing sites, including Caltech's Student Wellness Services, shared study details with people recently infected with SARS-CoV-2 and their uninfected housemates. The 410 participants who enrolled self-collected their samples once or twice a day for about two weeks and sent the samples to the lab to be analyzed with a high-sensitivity research assay. The Ismagilov lab team then calculated viral load in each sample type (saliva, nasal swabs, and throat swabs) to see where the virus accumulated first and figure out how sensitive a diagnostic test would need to be to detect the virus in that sample.

Although they are still analyzing data, Ismagilov's team has released three preprints online and a publication in the *Journal of Clinical Microbiology* that outline several important findings thus far: the virus generally appears first in oral samples, which suggests that many early infections are not being detected by nasal-swab tests; viral load is highly variable among sample types, suggesting that there is no single best COVID-19 test type and better testing strategies are needed; and taking COVID-19 tests first thing in the morning helps improve test sensitivity significantly, suggesting a simple change that can make tests more reliable.

Ismagilov says performing a large study like this amid the pandemic added challenges to every aspect, from getting the study organized, designed, and launched, to running the study and securing the necessary and often scarce lab reagents.

"It would have been easier to do nothing, but the team felt very strongly they had to make this contribution," Ismagilov says.

The Ismagilov lab's COVID-19 study is already having a ripple effect on the group's future work. To make the COVID-19 study a reality, the group built a new infrastructure for conducting longitudinal community-based studies, says Natasha Shelby, scientific research manager for the Ismagilov lab and study administrator for the COVID-19 study.

"That infrastructure will open so many doors to study health conditions that have been challenging to understand," she says, adding that the group has plans to publish their study-design templates to help other labs launch similar studies and get critical data right when a new pathogen emerges.

"We answered the questions we set out to answer," Ismagilov says. "I witnessed incredible dedication and self-sacrifice, not only from our lab but from many other members of the Caltech community, including volunteers who made the study possible."

Yaser Abu-Mostafa is a professor of electrical engineering and computer science. The student research that led to the creation of the CS156 model was supported by Caltech trustee and alumnus Charles Trimble (BS '63, MS '64); the Summer Undergraduate Research Fellowship program; and the Clinard Innovation Fund, established by entrepreneur and Caltech alumnus Gary Clinard (BS '65, MS '66).

Pamela Björkman is the David Baltimore Professor of Biology and Bioengineering and a Merkin Institute Professor. Her work on a universal vaccine is funded by the Merkin Institute for Translational Research, Wellcome Leap Inc., the National Institutes of Health, and the Bill & Melinda Gates Foundation, among other supporters.

Richard Flagan is the Irma and Ross McCollum-William H. Corcoran Professor of Chemical Engineering and Environmental Science and Engineering. His face-mask studies were funded by Caltech's Jacobs Institute for Molecular Engineering for Medicine.

Rustem F. Ismagilov is the Ethel Wilson Bowles and Robert Bowles Professor of Chemistry and Chemical Engineering, a Merkin Institute Professor, and director of the Jacobs Institute for Molecular Engineering for Medicine. His COVID-19 study has been funded in part by the Bill & Melinda Gates Foundation, the Ronald and Maxine Linde Center for New Initiatives at Caltech, and the Jacobs Institute for Molecular Engineering for Medicine.

Read the online version of this story to learn about more of Caltech's COVID-19 research, including a biosensor developed by medical engineer Wei Gao:

The POWER of Observation

After a decade in space, the small but powerful NuSTAR space telescope still has more to see.

NASA's Nuclear Spectroscopic Telescope Array (NuSTAR), led by Caltech and managed by JPL, turned 10 years old in June. This space telescope detects high-energy X-ray light and studies some of the most energetic objects and processes in the universe. The mission's principal investigator is Fiona Harrison, the Harold A. Rosen Professor of Physics and the Kent and Joyce Kresa Leadership Chair of the Division of Physics, Mathematics and Astronomy at Caltech. Here are some of the ways NuSTAR has opened our eyes over the last decade:

Seeing X-Rays Close to Home

Different colors of visible light have different wavelengths and different energies; similarly, there is a range of X-ray light, or light waves with higher energies than those human eyes can detect. NuSTAR detects X-rays at the higher end of the range. There are not many objects in our solar system that emit the X-rays NuSTAR can detect, but both the sun and Jupiter do. NuSTAR's studies could help scientists explain why the sun's outer region, the corona, is many times hotter than its surface. NuSTAR's observations of Jupiter, made contemporaneously with JPL's Juno mission, found that high energy X-rays are produced as particles slam into the planet's atmosphere.

Illuminating Black Holes

Black holes do not emit light, but some of the biggest ones we know of are surrounded by disks of hot gas that glow in many different wavelengths of light. NuSTAR can show scientists what is happening to the material closest to the black hole and reveal how black holes produce bright flares and jets of hot gas that stretch for thousands of light-years into space. The mission has measured temperature variations in black hole winds that influence star formation in the rest of the galaxy. Recently, NuSTAR supported the Event Horizon Telescope (EHT) in its effort to capture the first-ever direct images of the shadows of black holes. (For more on EHT, see page 20.)

Finding Hidden Black Holes

NuSTAR has identified dozens of black holes hidden behind thick clouds of gas and dust. Visible light typically cannot penetrate those clouds, but the high-energy X-ray light observed by NuSTAR can. In recent years, scientists have used NuSTAR data to find out how black holes become surrounded by such thick clouds, how that process influences their development, and how obscuration relates to a black hole's impact on the surrounding galaxy.

Bright green sources of high-energy X-ray light captured by NuSTAR overlaid on an optical-light image of the Whirlpool galaxy and its companion galaxy, M51b (the bright greenish-white spot above).

Fiona Harrison, NuSTAR principal investigator

Revealing the Power of 'Undead' Stars

NuSTAR is a kind of zombie hunter: It finds the undead corpses of stars. Known as neutron stars, these are dense nuggets of material left over after a massive star runs out of fuel and collapses. Though neutron stars are typically the size of a large city, they are so dense that a teaspoon of one would weigh about a billion tons on Earth. Their density, combined with their powerful magnetic fields, makes these objects extremely energetic: one neutron star located in the galaxy M82 beams with the energy of 10 million suns.

Solving Supernova Mysteries

Stars are mostly spherical, but NuSTAR observations have shown that when they explode as supernovae, they become an asymmetrical mess. The space telescope solved a major mystery in the study of supernovae by mapping the radioactive material left over by two stellar explosions. It traced the shape of the debris and in both cases revealed significant deviations from a spherical shape. Because of NuSTAR's X-ray vision, astronomers now have clues about what happens in an environment that would be almost impossible to probe directly. The NuSTAR observations suggest that the inner regions of a star are extremely turbulent at the time of detonation.