A bewildering puzzle of COVID-19 is why the virus affects people so differently. Though older men seem to fare worst in the face of infection with SARS-CoV-2, younger people may unexpectedly falter too. Moreover, many people develop long-term symptoms. We don’t yet understand why.

But for Akiko Iwasaki, PhD, the Waldemar Von Zedtwitz Professor of Immunology and Molecular, Cellular and Developmental Biology, pieces of the puzzle are emerging. Genetics, gender, and even botched timing on the part of the immune response all appear important. What she learns could help us better understand not only how the virus and immune system behave, but also to study treatments and potential vaccines, they wrote, in the *Journal of Experimental Medicine*.

One of the immune system's early defenses is a group of proteins called type I interferons. Produced by immune cells in response to viruses, interferons are key to the body's initial, rapid defense against coronavirus. But some people make too much of it, others not enough, and still others neutralize it with autoantibodies—and that makes a difference.

"In the early phase of the infection, if you can generate robust interferon, you will control the virus because interferon will trigger all these antiviral genes," Dr. Iwasaki explained. That is likely how people with asymptomatic or mild disease keep it under control, she added.

On the other hand, if the immune system doesn't create interferon soon enough, the virus can replicate undisturbed. Later, caught off guard by uncontrolled viral replication, the immune system may respond by manufacturing large quantities of interferon.

But by that point, it might be too much of a good thing. Massive amounts of interferon can drive inflammation, which in turn recruits white blood cells to the lung. Long-haulers," she said. "I raised three different hypotheses, none of which are mutually exclusive.

One hypothesis is that these patients' immune systems have turned on them, resulting in long-term autoimmunity. Another possibility is that remnants of virus, such as bits of protein or genetic material, remain to stimulate the immune system. That could result in chronic inflammatory symptoms. A third scenario is that the virus in long-haulers never goes away. Instead, it may hide somewhere in the body, far from the nasal swabs that can detect it, and continue to cause infection.

"Studies like these can't take place without blood and tissue samples. Dr. Iwasaki's lab contributed to the effort of the Yale COVID-19 Biorepository, which holds samples from hundreds of COVID-19 patients, including those with cancer. The biorepository, named IMPACT for Implementing Medical and Public health Action against Coronavirus (Connecticut, CT), was launched this spring by Albert Xi, MD, Yale School of Public Health’s Chair of Epidemiology; Roy S. Herbst, MD, PhD, of the Yale Cancer Center and Smilow Cancer Hospital and a member of the IMPACT team, is leading the sample collection from cancer patients with COVID-19.

"This is the only way we could do our research," Dr. Iwasaki said of the biorepository. Thanks to these patient samples, Dr. Iwasaki, Dr. Herbst, and others are also able to study how cancer status affects COVID-19.

Understanding cancer patients' experiences with COVID-19 may help us better understand the immune system, Dr. Iwasaki explained. Some types of cancer appear to make people more susceptible to severe COVID-19, while many cancer therapies interact with specific steps in the immune response—an effect that may alter the course of COVID-19.

"We’re using this mouse model to rapidly get at these questions that people have about the importance of T cells and B cells and antibodies," she said. "Whatever it is, we can do it very quickly."

That speed is crucial. As the pandemic continues to rage around the world, clinical trials of therapies and vaccines have had to skip some steps, as Dr. Iwasaki and her co-authors recently explained in the *Journal of Experimental Medicine*. To better understand not only how the virus and immune system behave, but also to study treatments and potential vaccines, they wrote, "good mouse models are urgently needed. Good models provide a vital platform for testing prophylactic and therapeutic strategies to combat COVID-19."