Scientist works to rewire human immunity against COVID-19

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Many scientists across Yale have adapted their existing expertise and techniques to pursue discoveries that will positively impact the COVID-19 pandemic.

John MacMicking—an investigator of the Howard Hughes Medical Institute and associate professor of microbial pathogenesis and of immunobiology at Yale School of Medicine—spoke about work at the Yale Systems Biology Institute to identify human immune proteins that protect against SARS-CoV-2 and potentially prevent viral entry.

What COVID-19 research are you engaged in at the Systems Biology Institute?

Our laboratory is trying to identify human immune proteins that protect against SARS-CoV-2. Many of these proteins are produced in response to interferon (IFN) signaling which is one of the major antiviral mechanisms used by humans. These IFN-induced proteins could prevent viral entry by disrupting host receptor-CoV-2 viral spike protein interactions or act later on after the virus has entered target cells within the lungs and other parts of the body. Hundreds of intracellular host proteins are elicited by IFN signaling so the potential for finding anti-COVID-19 candidates is quite high. Some IFN-induced proteins are also disrupted by SARS-CoV-2 as a potential viral evasion mechanism. A search for small molecules that overcome or bypass this bottleneck would therefore be useful, especially if added to drugs that mitigate underlying hypertensive, renal and cardiovascular deficits during the disease. In addition, as we get older IFN-induced immunity starts to decline and clearly age is a major predictive factor in COVID-19 outcome. Can IFN responses be restored to full function in older patients? Pharmacologic agents that stimulate these pathways may be of clinical benefit in this group. Lastly, at a basic science level, understanding what constitutes protective immunity will inform how COVID-19 vaccines work and how they could be tailored for better effectiveness in the future.

What technology is being brought to bear in the

COVID-19 research?

West Campus has a wealth of technology and Scott Strobel, Chris Incarvito and Andre Levchenko were also very supportive in helping us set up dedicated facilities within the ISTC building to conduct work with microbial pathogens that cause human disease. Currently we are using new CRISPR-Cas9 genetic tools coupled to high-throughput microscopic imaging to track viral spike protein entry in an effort to discover what host proteins block infection. In addition, we are also enlisting super-resolution instruments to visualize these events in more detail. The SARS-CoV-2 spike protein trimer is only ~10nm in size (1/100,000 of a millimeter) and there are approximately 100 of these on the surface of a single viral particle, which itself is about 100nm in diameter. So we are talking very small scales, nanoscopic scales. You need powerful microscopes and bright fluorescent tags to follow these events in real-time and we have super-resolution instrumentation that resolves objects below 100nm within a custom-designed space to watch these processes unfold over the course of a few minutes.

How have social distancing and public safety protocols changed the way you go about this work?

At present few lab members are involved in COVID-19 research, so social distancing protocols are easy to enforce while at West campus and they are operating on a rotating schedule to avoid overlap within the laboratory. Outside of the lab they are of course adhering to public safety measures by limiting community interactions as much as possible. The people involved in this work were highly enthusiastic about doing something to help tackle the pandemic but I really want to applaud their efforts given the inherent difficulties in pursuing research under the current strictures and the risks involved. They've been exemplary so far and I hope it leads to discoveries that will impact the pandemic in a way

that benefits patients and the public alike.

How is your team holding up through these new tasks and protocols?

Based on regular communications they remain excited to be undertaking COVID-19 related work and grateful to somehow contribute to the global effort against the virus. Current information on protective immunity is scarce, so any findings that help enlighten the scientific community about how we combat SARS-CoV-2 infection and its associated sequelae is needed. It gives a sense of urgency and added impetus which are all reasons the team seem to be holding up well.

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