New Therapeutic Strategies for COVID-19:

Identify early predictors of disease severity to guide life-saving immunotherapy interventions and discover new therapeutic strategies

Mount Sinai

The outbreak of COVID-19, a disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is the most significant health challenge of our time.

Our greatest hope for slowing this disease lies in the talents of our nation's scientists. As a leader in cutting-edge science and medical innovation, Mount Sinai Health System is focusing our extraordinary research infrastructure to confront the virus head on. One of our strongest efforts is already underway, under the expert leadership of renowned immunologist Miriam Merad, MD, PhD. **But an investment of $5 million is urgently required in order to ramp up this effort at the scale and speed required by the pandemic, saving as many lives as possible.**

KEY POINTS

- We currently lack treatment for the overwhelming number of severe cases of COVID-19 occurring across the globe daily.
- COVID-19 patients are dying of excess inflammation and immunotherapy is required to save their lives.
- We urgently need to identify and block excess inflammation at a time when patients can still be saved.
- We urgently need immune biomarkers to guide clinical strategies. This is important because dampening the immune response too soon could risk a worse infection. Not blocking the immune system could cause it to overreact with deadly consequences.
- This work will have transformative and immediate impact on the course of the pandemic.

Dr. Merad is Director of the **Precision Immunology Institute** at the Icahn School of Medicine (PrIISM), where she oversees cutting edge research in Cancer Immunotherapy, Viral Immunology and Inflammatory Disease and directs the Human Immune Monitoring Center (HIMC). The hyper-inflammatory response to COVID-19 that occurs in about 20% of patients is the cause of death in all fatalities to date. This inflammatory response is very similar to a common side effect of certain new and promising cancer immunotherapies Dr. Merad and her team are already studying.

Based on their past work, Dr. Merad's team has developed an extensive understanding of how to harness and regulate inflammation in patients. Now, PrIISM is mobilizing this knowledge and the unique resources of a deep bench of scientific colleagues who have expertise in immunology, virology, computational biology, mathematics, artificial intelligence, precision medicine, genomics and drug development to fight this pandemic. Along with other key collaborators, Dr. Merad will be drawing on the leading expertise of Dr. Adolfo Garcia-Sastre, a world virology expert and the Director of Mount Sinai's Global Health and Emerging Pathogens Institute.

PROJECT SUMMARIES

Dr. Merad and senior scientists in her team are currently working on two critically urgent goals.

Develop a rapid turn-around test to predict disease severity and inform how COVID-19 patients are treated.

Patient symptoms and severity are proving to be widely diverse—from mild to critical—despite each person being infected with the same virus. This is because COVID-19 is not just a result of the virus, but also how a patient's immune system responds to the virus. Pre-existing conditions and age are only part of the picture, as healthy young people have died as well. There are factors in each individual's immune system that cause certain patients to develop severe forms of the disease while others experience few symptoms. To fight COVID-19 and develop effective treatments, we must understand the molecular causes of these differential responses, so we can identify **who** will develop life-threatening disease early, and **how** to modulate this inflammation so as to fight infection, while keeping the patient off a ventilator.

The lethality of COVID-19 is often a result of how it triggers the immune system to produce an overblown inflammatory response, sometimes called a "cytokine storm" or "cytokine release storm" (CRS), which, at its worst, can cause organs to shut down. Our HIMC platform can measure and predict the probability and severity of a cytokine storm in an individual patient. But to ensure that this process is attuned to the particularities of COVID-19, we must **develop a rapid turn-around test** to predict, treat and monitor the cytokine storm in patients at baseline and during treatment with a drug called an IL-6 receptor blockade.

In a disease that works as quickly as COVID-19, we must be able to rapidly predict a cytokine storm in order to interrupt it. By adapting a rapid cytokine test originally developed for monitoring patients undergoing T-cell therapies, we believe we can identify the features of CRS as early as possible, thus allowing us to implement a cytokine blockade and significantly improve outcomes for patients.

Using ELLA, an advanced immune-assay instrument, we will measure four of the most commonly elevated cytokines using a test we have validated with nearly 400 specimens. We are also in the process of submitting the test to the New York State Department of Health, which will make it more widely available. Using our laboratory personnel in shifts, **we will be able to provide cytokine results within four hours of sample collection**, leading to a dramatic enhancement in monitoring and treatment.

Identify the cause of severe COVID-19 disease to inform drug re-purposing for immediate treatments.

We need treatments for COVID-19 immediately, and doctors around the world are scrambling to identify drugs that can be used to treat our sickest patients and keep them alive. The best way to achieve this goal is to map with unprecedented depth and frequency how the immune systems of different patients are reacting to the virus and identify the immunological factors responsible for the lethal response. Once these factors are found, the PrIISM team and their colleagues can select drugs that specifically target these factors, halting the deadly response. Dr. Merad and Mount Sinai's HIMC, in collaboration with Dr. Adolfo Garcia Sastre and his team, are world leaders in this area, having helped with the monitoring of immune responses to many other pathogens, including influenza and Dengue fever. This experience and knowledge positions the team to achieve progress quickly.

They will collect biological samples from thousands of infected patients throughout Mount Sinai's eight hospitals in New York City. Through the use of the specialized immunological assays and computational and analytics pipeline that Dr. Merad's group and her colleagues has spent close to a decade pioneering, they will identify the factors that are driving disease severity in humans. Once identified, specific drugs will be rationally selected and used to inform treatment of our sickest patients. Already Dr. Merad's team is working with clinicians to determine the role of specific inflammatory cytokines in COVID-19 disease, and to design strategies to clinically employ drugs that block the harmful action of these cytokines. If successful, this work could have a dramatic impact on flattening the mortality and severity curves of the disease.

Philanthropic Opportunity

Conducting the above studies at the speed necessary to meet the urgency of the outbreak will require an investment of $5 million. These funds will support the significant resources required to rapidly undertake this work, including skilled personnel, research equipment, and a broad array of assays.

This is unlike any other research effort in recent memory, and we cannot waste another moment. The COVID-19 outbreak is growing at an exponential rate, and people are dying every day. Is it an extraordinary time, and we must depend on the extraordinary generosity of bold individuals to answer this call to action. We need your partnership to pursue this work at the ambitious scale and accelerated pace that the COVID-19 pandemic demands. Few institutions can match the capabilities of Mount Sinai—and there are no better people than the heroic scientists working 24/7 across our eight campuses throughout New York City—to help us understand and conquer COVID-19.

In what has swiftly become the most pressing public health crisis of our lives, we are asking you to do what leaders in society have always done: **Rise to the challenge and make the seemingly impossible possible.** Please help our heroic researchers and scientists save lives. Thank you for your consideration.

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