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UMASS MEDICAL SCHOOL

COVID-19/Pandemic Research Fund

PILOT GRANTS UPDATE

Philanthropic First-Responders Enable Discoveries

In the darkest days

of a year of extraordinary hardships, the University of Massachusetts Medical School (UMMS) community radiated a light of hope. Students, faculty, staff and benefactors did not retreat from the challenge, but turned their strengths towards the pandemic to help people in the clutches of COVID-19 by prioritizing important research that is already making a difference.

Today, we have a better understanding of how the virus SARS-CoV-2 infects cells, replicates in cells and interacts with the immune system, because of the progress made so far in the UMMS labs that received pilot grants from the **COVID-19/Pandemic Research Fund**. The science revealed in these early studies is targeting potential new therapies, answering questions about the structure and life-cycle of the virus, and examining immunity to the virus that people may develop from vaccination or after recovering from COVID-19.

"We have teams working on COVID-19 across the biomedical spectrum, from basic science studies to working with patients in clinical trials," said Kate Fitzgerald, PhD, the *Worcester Foundation for Biomedical Research Chair*, professor of medicine and director of the Program in Innate Immunity. "It's a powerful network of collaboration."

The pilot grants were strategically allocated to 13 labs at UMMS to leverage their experience across disciplines and to jump-start promising early ideas. By design, the pilot grants are not duplicating efforts already underway at UMMS, but are filling knowledge gaps. The distribution of awards also draws on the synergy of having basic science, translational and clinical research programs on campus, with investigators sharing ideas, data and technologies to advance the pace of discovery. What follows are summaries of their progress to date.

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Chair of the review committee for COVID-19/Pandemic Research Fund pilot grant proposals

UMASS University of Massachusetts Medical School

Understanding the Attack

Like all viruses, SARS-CoV-2 cannot replicate on its own. It first needs to infect cells in a living organism then highjack those cells' machinery to make more copies of the virus and eventually cause disease. Several pilot grants are funding studies of those initial phases with the goal of finding ways to disrupt them.

James Munro, **PhD**, associate professor of microbiology & physiological systems, is using pilot grant funds to visualize the structure and motion of the SARS-CoV-2 spike protein, which is the tip of the viral spear for infection.

Unlike an iron spike, which is a rigid continuous form, the viral spike protein is flexible with multiple moving parts in its structure. The Munro lab is using an advanced imaging system called single-molecule fluorescence spectroscopy, which, as its name suggests, can focus at the molecular level to capture live images of the moment of first contact between the spike protein and the cell surface receptor it targets. The lab is studying how the spike protein changes its shape during this interaction and has confirmed one specific shape (or conformation) that allows it to begin the process of infecting a host cell.

Dr. Munro's team is now testing whether or not antibodies that prevent viral infection are doing so by preventing the spike protein from achieving its active form. These studies may lead to improving antibody therapies for COVID-19.

On the basis of these early findings, the Munro lab now has two federal grant applications pending for funding to continue the work.

Pre-pandemic, **David Guertin**, **PhD**, professor of molecular medicine, was working on signaling pathways in cells associated with obesity and diabetes. The pilot grant enabled his team to test how infection by SARS-CoV-2 affected some of those same pathways, and how cells were co-opted into making more copies of the virus.

To date, the Guertin lab has found that the virus takes over an important set of molecules in the cells that usually work on glucose (sugar) metabolism and lipid formation for healthy processes. The virus diverts those pathways to make more copies of itself, and in doing so, infected cells use a lot more glucose for energy.

Interestingly, this overuse of glucose in infected cells is likely associated with clinical observations that diabetic patients who suffer from hyperglycemia have worse outcomes with COVID-19. The Guertin lab is now exploring several potential points in those pathways that could be disrupted to prevent the virus from replicating in cells.

Understanding the Attack

SARS-CoV-2 may exploit several pathways when infecting a cell. In the lab of **Neal Silverman**, **PhD**, professor of medicine in the Division of Infectious Diseases and Immunology, the team is focused on epithelial cells in human lungs, since COVID-19 does the most damage in the respiratory system.

Dr. Silverman theorized that once the virus infects a cell, a particular lipid receptor on the cell's surface could play a role in helping the virus replicate. That receptor channels lipid molecules into cells for normal cellular functions. However, SARS-CoV-2 also needs lipids for its replication process. The team is testing molecules known to disrupt the lipid receptor to see if they impact the virus's ability to replicate within a cell.

The Silverman lab is also using antibodies that can bind to both the virus and the lipid receptor to serve as a marker to see if they are in close contact during cell entry and in the early stages of viral replication. Preliminary results indicate that the lipid receptor is involved in helping the virus replicate in cells. The team is now working to confirm early findings and designing experiments to move from the cellular level to a small-animal model.

Therapeutic Targets

When the first SARS virus emerged in 2003, MassBiologics of UMass Medical School, the only nonprofit FDA-licensed manufacturer of vaccines in the U.S., partnered with the National Institute of Allergy and Infectious Diseases to rapidly develop monoclonal antibodies to neutralize that virus. Thankfully, the first SARS virus was not as contagious as SARS-CoV-2 and was contained early, never becoming a global pandemic.

When COVID-19 emerged, MassBiologics researchers knew their earlier work might give them a potential head-start. Funded by a pilot grant, **Lisa Cavacini**, **PhD**, professor of medicine and senior director of product discovery, is leading a team at MassBiologics testing a class of antibodies that shows promise as a therapy to treat people infected with SARS-CoV-2, and that also may work to prevent infection.

Most antibodies fight viruses by circulating in the bloodstream. When they come in contact with a target virus, they latch on to it and block its ability to infect cells. However, there is a smaller subset of antibodies that Dr. Cavacini's research group is examining: those that attach themselves to the lining of nasal passages and the upper respiratory system, clinging to those tissues and standing guard, ready to catch a virus particle that is inhaled.

So far, Dr. Cavacini's team has identified several of those antibodies that are able to kill the SARS-CoV-2 virus in culture. The group is now scaling up to repeat tests and is working with Dr. Kate Fitzgerald's lab to test if dosing with the antibodies that cling to airway tissues could protect animals from infection when purposely challenged by the virus.

Early results have been published in *Nature Communications*.

The team is also sharing the antibodies developed with the broader research community for use as positive control antibodies for other COVID-19 experiments and diagnostic development.

Another therapeutic approach is being taken by **Celia Schiffer**, **PhD**, the *Gladys Smith Martin Chair in Oncology*, and **Paul Thompson**, **PhD**, both professors of biochemistry & molecular pharmacology. They are screening molecules they had previously developed for other programs to see if those molecules will block the function of two "proteases," which are enzymes in the host cell that help SARS-CoV-2 replicate.

Using high-throughput robotic systems, these researchers have screened several thousand molecules so far and identified a dozen that have potential to block the proteases. Those lead candidates are now being further characterized using atomic-scale resolution images showing them binding to the proteases, to study how to optimize their composition for use as an antiviral drug in humans.

Another potential therapeutic approach is being explored by **Fiachra Humphries**, **PhD**, an instructor of medicine working in the Fitzgerald lab in the Department of Medicine. The idea is to prompt a strong immune response against SARS-CoV-2 by kick-starting an innate immune pathway to block the virus from replicating.

Pilot grant funding has enabled Dr. Humphries to complete the safety training needed to work with pathogens like SARS-CoV-2, and to engineer mouse models that express the human receptor the virus exploits to infect lung cells. Dr. Humphries has found that giving mice one dose of a drug that activates the innate immune system completely protects the mice from lung disease, after they were infected with the coronavirus.

These studies have been submitted for publication and Dr. Humphries has recently applied for NIH funding to continue this work.

Javier Irazoqui, **PhD**, associate professor, and **William McDougall**, **PhD**, assistant professor, both in the Department of Microbiology & Physiological Systems, focused their pilot grant funding on analyzing how SARS-CoV-2 changes gene expression within the cells it infects. The work is being done in human epithelial lung cells.

They theorized that the virus must disarm parts of the host cells' self-defense mechanisms, so the virus could take over cellular functions to make more copies of itself. Early data points to one particular protein kinase that helps SARS-CoV-2 to remain active and replicate in cells.

Follow-up studies are planned in animal models, and the team is now working with the UMMS Office of Technology Management to patent the discovery as a potential drug target for prevention or treatment of the disease.

Therapeutic Targets

SARS-CoV-2 is a single-stranded RNA virus that carries 27 genes. **Sean Ryder, PhD**, professor of biochemistry & molecular pharmacology, and his lab team are examining sections of that RNA strand, looking for weak spots that could be targeted by new drugs to block viral replication. To date, the team has found two potential target regions along the RNA strand that are consistent across many viral variants. Those spots could become targets for drugs specifically designed to bind there, and by doing so, block viral replication.

As of mid-April 2021, those results are under peer-review, pending publication.

Enabling Technologies

Once basic science discoveries are made and confirmed at the cellular level, they need to be tested for relevance in a living model system.

Alisha Gruntman, DVM, PhD, assistant professor of pediatrics and an investigator in the UMMS Horae Gene Therapy Center, received a pilot grant to begin development of a hamster modeling core on campus, which can be used to test therapeutics and vaccines, and will facilitate study of SARS-CoV-2 clinical infection, prevention and treatment in a hamster model. Many of the pilot grant programs, and several other labs at UMMS working on potential COVID-19 therapies, will eventually use the new model core to validate their research and prepare for potential clinical trials.

The research of **René Maehr, PhD**, associate professor of molecular medicine, is also focused on lung cells. His lab is using its pilot grant to build out a system that can process human stem cells into lung epithelial cells in ways that make them ideal candidates for examining the processes of SARS-CoV-2 infection. This approach creates a larger supply of cells available for testing and is not dependent on samples from patients.

To date, the Maehr lab has successfully developed these cell lines and, in parallel, a system using the CRISPR gene-editing technology to methodically examine the virus/host interactions in those cells, one gene at a time, to establish the functions of those genes in the disease state. The Maehr lab has shared the cell lines and CRISPR technology with several other UMMS labs working on COVID-19 projects (including Dr. Humphries'), helping to accelerate their research.

The Maher lab has applied for several federal grants to expand this work. One grant written in collaboration with Robert Finberg, MD, distinguished professor of medicine and chair *emeritus* of the Department of Medicine, has been funded by the U.S. Department of Defense.

Immunity

SARS-CoV-2 is related to less severe coronaviruses that cause the common cold. There is evidence emerging that exposure to cold viruses in the past could prompt some level of protective immunity against SARS-CoV-2.

Lawrence Stern, **PhD**, professor of pathology, and his lab are using a pilot grant to analyze blood samples from people who have recovered from COVID-19 and others who are participating in a vaccine trial on campus. In each sample, the team measures levels of antibodies and several important immune system cells.

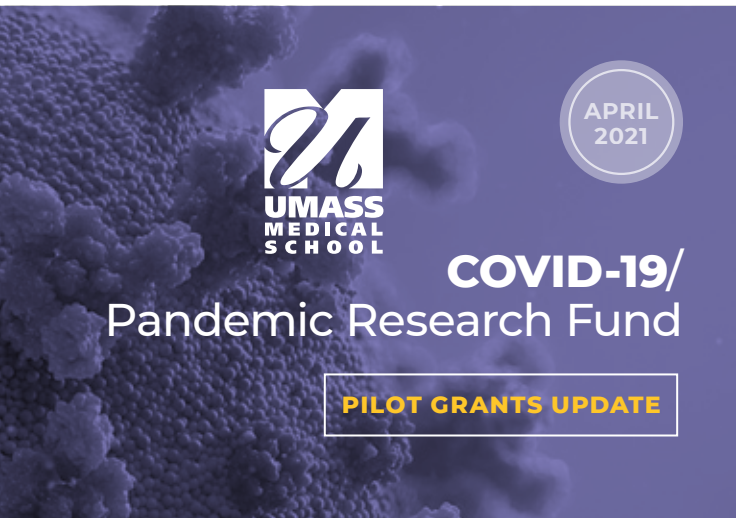
So far, all of the patients studied had some immunity to non-SARS viruses, presumably from previous colds. They also found that patients who had recovered from COVID-19 had higher levels of immune markers related to other non-SARS viruses. The Stern lab identified important immune cells called T-cells that recognized both SARS-CoV-2 and common cold viruses. This suggests "cross-reactivity," meaning the immune system uses generalized weapons to fight multiple coronaviruses.

Work continues to further characterize the immune responses in COVID-19 patients to examine whether previous immunity to common cold viruses had an impact on the severity of their disease.

In another immunity related project, **Ann Marshak-Rothstein**, **PhD**, professor of medicine, and **Kerstin Nundel**, **PhD**, assistant professor of medicine, are studying how SARS-CoV-2 immunity changes over time in hospitalized patients and in out-patients. So far, they have found that people with more severe cases of COVID-19 have more significant changes in the levels of several immune system cells and regulatory pathways.

Interestingly, and somewhat surprisingly, they have also found that some COVID-19 patients begin producing antibodies against their own healthy tissues. These so-called "auto-antibodies" can eventually lead to auto-immune diseases and may be important in the patients who suffer for an extended time after their initial infection (so-called long haulers). Work along these lines continues with more patient samples.

Rapid and intense inflammation is a hallmark of severe immune response to COVID-19. **Egil Lien**, **PhD**, professor of medicine, is using pilot grant funding to study plasma samples from COVID-19 patients to better understand the molecular pathways involved in the inflammatory response to the coronavirus. The lab is also searching for any elevated signaling molecules in the blood stream that may be correlated with elevated cell-death from infection.



Biomedical research is never predictable, but we know the best way to make rapid progress is to empower talented teams and let them follow their ideas and the science. **The early results from the work supported by donors to the COVID-19/ Pandemic Research Fund are already making a difference,** with more important benefits still to come.

Kate Fitzgerald, PhD

Chair of the review committee for COVID-19/Pandemic Research Fund pilot grant proposals

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