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Miller School Researchers Find Clues for Potential 'Long COVID' Therapies

A team of researchers at the University of Miami Miller School of Medicine has uncovered a potential approach for treating patients with serious long-term COVID conditions. In two recent studies using experimental models, they found that placing a peptide "net" around the spike protein on the virus reduced deaths from organ failure and improved overall outcomes.

Having identified long-term pathological changes in mice infected with SARS-CoV-2 and demonstrated protective effects with SPIKENET, Drs. Paidas and Jayakumar are investigating the underlying cellular and molecular mechanisms by next-generation sequencing.

"With more than 600 million cases and six million deaths worldwide, we are in desperate need of effective COVID therapeutics, especially for pregnant women and children," said Michael J. Paidas, M.D., professor and chair, Department of Obstetrics, Gynecology and Reproductive Sciences.

"Despite the advances in vaccines, a significant percentage of infected patients develop long-term problems of the brain, lungs, heart, liver, or kidneys," Dr. Paidas said. "Our

laboratory research has focused on preventing the SARS-CoV-2 virus from attaching to the cell and finding a potential therapy for infected individuals fighting the lasting effects of COVID."

Dr. Paidas was the lead author on a recent study, "Long-Term Sequelae of COVID-19 in Experimental Mice," published recently in the journal *Molecular Neurobiology.*

Co-authors were Arumugam R. Jayakumar, Ph.D., research assistant professor; Daniela S. Cosio, M.S., M.D./M.P.H. candidate and research assistant; Saad Ali, M.D., Department of Pathology and Laboratory Medicine; and Norma Sue Kenyon, Ph.D., the University's vice provost for innovation, chief innovation officer at the Miller School, professor of surgery, and executive director of the Wallace H. Coulter Center for Translational Research.

"We observed pathological changes in multiple organs and blood vessels 12 months after these mice were infected with a coronavirus model," said Dr. Jayakumar. "However, treating the infected mice with a small-molecule synthetic peptide, patented as SPIKENET, prevented the binding of spike protein. That significantly reduced disease progression and pathological changes to the brain, heart, lungs, and other organs."

First Long-term Study of Its Kind

Dr. Jayakumar said that this is the first study to follow laboratory animals over a long period of time and identify pathological changes to the brain, heart and other organs in mice that would take many years to find in humans. He added that the long-term COVID study results are consistent with the

research team's prior study on the acute phase of COVID infection.

That collaborative study, "Mechanism of Multi-Organ Injury in Experimental COVID-19 and Its Inhibition by a Small Molecule Peptide," was published in May in the journal *Frontiers in Pharmacology.* Along with Drs. Paidas, Jayakumar, Cosio, and Kenyon, Miller School co-authors were Emma A. Schindler, B.A. and M.D./M.P.H. student; Chima O. Ndubizu, M.D., assistant clinical professor and former maternal fetal medicine fellow; Shamaladevi Nagarajarao, Ph.D., research scientist; Jaclyn Kwal, M.D., UM/Jackson resident; Suset Rodriguez, M.D., UM/Jackson resident; and Anis Ahmad, Ph.D., assistant research professor.

While the underlying mechanisms of SARS-CoV-2-induced multi-organ failure and death are largely unknown, the inflammatory response of the immune system can lead to edema, a rapid build-up of fluid in cells damaging tissues and organs, said Dr. Paidas.

"Using our mouse model, we found that SPIKENET treatments improved the cellular inflammatory and oxidative stress response in the acute phase of the infection. We discovered that SPIKENET also works through a novel mechanism, namely by altering aquaporins, which are critical water channels, present on cells throughout the body," Dr. Paidas said. "Through these three key mechanisms, SPIKENET reduced edema and resulted in better outcomes. We think that SPIKENET offers a one-two punch, making it an attractive therapeutic agent. It prevents the virus from entering cells and limits the damage inflicted by the virus, thus restoring organs to a more normal physiologic state."

Drs. Paidas and Jayakumar have been studying SARS-CoV-2 for more than two years, seeking a way to stop the virus from affecting pregnant women, children, and other vulnerable individuals. That led to the development of SPIKENET and subsequent laboratory studies.

“New COVID therapies are an urgent need,” said Dr. Paidas. “We hope that this will be one part of the armamentarium to treat this disease.”

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