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Study first to show that RNA interference can facilitate vaccine development

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Pharmaceutical companies and universities are racing to develop drugs that use the gene silencing mechanism known as RNA interference to treat a host of diseases. Now, a new study opens up an entirely new possibility for this powerful tool: Researchers at the University of Georgia have demonstrated for the first time that RNA interference can be used as a tool in the development of vaccines.

"Our data suggest that, at least in an animal model system, an RNAi prophylactic treatment can reduce infection and disease pathogenesis while also acting like a vaccine to engender immunity that protects against subsequent re-infection," said Ralph Tripp, Georgia Research Alliance Eminent Scholar in Vaccine Development at the UGA College of Veterinary Medicine.

Tripp, whose results appear in the December issue of the *Journal of Virology,* co-authored the study with doctoral student Wenliang Zhang. Previous studies by Tripp and other researchers have shown that treating mice with a small interfering RNA (siRNA) drug can reduce the replication of respiratory syncytial virus and reduce the duration of illness. RSV is a common virus that causes flu-like symptoms in otherwise healthy adults but can be fatal in infants, the elderly and people with compromised immune systems. Work from the Tripp lab has already contributed to the testing of an RNAi therapeutic for RSV infection known as ALN-RSV01, which is undergoing phase II clinical trials initiated by Cambridge, Mass.-based Alnylam Pharmaceuticals, Inc. In the latest study, Tripp explored how a related drug impacts the

body's ability to respond to later infection.

The researchers treated mice with the siRNA drug, and, for control groups, treated mice with a non-specific siRNA or saline. In prophylactic treatments in which the mice were given the drug 12 hours before RSV infection, the siRNA drug reduced the viral load by up to 80 percent compared to both controls. The drug also prevented detectable disease in the mice.

Tripp pointed out that RSV replication was reduced in a dose-dependent manner, meaning that the viral load decreased in proportion to the amount of drug administered. He said it's possible to halt viral replication entirely with higher doses of the drug, but that his goal was to expose the immune system to enough of the virus so that it could mount a strong response upon future exposure.

In the next phase of the study, the researchers took mice that three weeks earlier were exposed to RSV after being prophylactically treated with either the drug or the controls and challenged them with the virus for a second time. The researchers found that levels of specific cells associated with the memory immune response were substantially increased in the experimental group versus the control groups, while the mice treated with the siRNA drug had virus concentrations that were more than 80 percent less than the control groups and recovered an average of two days faster.

"This is the first study of its kind to show the utility of using any siRNA to improve the immune system's memory response to an infectious agent," Tripp said. "We were able to reduce virus replication enough to prevent the development of disease but still induce immunity later on."

Between 75,000 to 125,000 children under age one are hospitalized with complications of RSV annually, according to the Centers for Disease

Control and Prevention. Tripp notes that there is currently no effective vaccine for the virus. Unlike most viruses, the exact same strain of RSV can infect the same person repeatedly. Scientists are just now beginning to understand the many ways in which RSV evades the memory immune response, but Tripp's finding reveals that keeping RSV replication and protein expression at a low level prevents the virus from eluding the immune system.

Tripp said preliminary data also suggest siRNA drugs are likely to behave as effective vaccines for other common viral diseases, such as influenza and measles, and may help control outbreaks of emerging infectious diseases.

"Making siRNAs today is relatively simple because most disease-causing viruses have been sequenced or have closely-related cousins with conserved regions in their genes that can be targeted," Tripp said. "So you could prophylactically treat an animal, challenge it with the virus and see if you get reduced replication of the virus and whether that is sufficient to vaccinate against future challenge. Our data suggest that this is going to be a good strategy."

Source: University of Georgia