New vaccine candidate shows strong potential to prevent highly contagious norovirus

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Scientists have shown that an experimental vaccine against the human norovirus – the bug behind about 90 percent of highly contagious nonbacterial illnesses that cause diarrhea and vomiting – can generate a strong immune response in mice without appearing to cause the animals any harm.

Using a novel viral vector-based method to grow and deliver the vaccine that has shown promise in other agents designed to fight such infections as HIV and hepatitis C, the researchers are the first to test this vaccine design method's effectiveness against the human norovirus.

Animals receiving the vaccine developed high levels of antibodies, a robust white blood cell response and an additional immune response in the area of the body most affected by this particular infection – the gastrointestinal system.

The researchers say this study supports the use of viral vector-based techniques as a new way to develop vaccines for human norovirus and other viruses that cannot grow in cell cultures. It also suggests that these Ohio State University scientists could be well on their way to developing a safe vaccine against a highly problematic pathogen that causes millions of gastrointestinal illnesses every year in the United States.

"The mice in our study developed a much higher antibody response to our vaccine candidate than they did to a more traditional vaccine. That's one of the keys, to have a sustained antibody response, so that when the

disease comes along, you can neutralize the virus and protect yourself," said Jianrong Li, assistant professor of food science and technology at Ohio State and senior author of the study.

Li co-authored the study with Yuanmei Ma, a graduate student in food science and technology. The research appears in the current issue of the *Journal of Virology*.

The Centers for Disease Control and Prevention estimates that more than 21 million cases of acute gastroenteritis – characterized by diarrhea, vomiting and stomach pain – each year are caused by norovirus infection. Human norovirus is transmitted primarily through fecal-oral contact, either through contaminated food or water or direct person-to-person spread. This virus is famous for being so contagious that as few as 10 viral particles may be enough to cause symptoms. No vaccine or anti-viral drug is currently available for human norovirus.

That kind of pathogenic power makes the virus a high priority for vaccine developers, said Li, who also serves on Ohio State's environmental health sciences faculty. But the process is complicated by two primary problems: The virus cannot grow in cell cultures, and no small animal models exist to mimic the infection.

Without the ability to grow the norovirus in cell cultures, the researchers instead inserted a human norovirus capsid gene – capsid refers to the virus's outer shell – into a specific location on the genome of a different virus. This process creates what is known as a recombinant virus – a new viral strain formed by recombining genetic material from other viruses.

The viral host for this vaccine candidate is called vesicular stomatitis virus, or VSV, a bullet-shaped virus that has been an attractive vector for vaccine designers, Li said. The resulting recombinant viral vector functions as both the vehicle to deliver the vaccine as well as the agent

that produces virus-like particles that mimic the human norovirus itself.

In this work, vaccination with the recombinant virus caused the norovirus capsid particles to grow continuously in animals, triggering a specific immune response. When the scientists tested these particles for their antigenic potential to look like foreign intruders in the body, the particles were neutralized by antibodies specifically designed to fight the human norovirus.

"So it looks like the virus and acts like the virus, but it's not, and that is how a vaccine designed with virus-like particles should function," Li said. "The virus-like particles can be continually produced in animals or humans for several weeks and stimulate strong immune responses. That's the advantage of using VSV."

Li said the VSV-based recombinant is also considered a powerful application because it can essentially be used as a bioreactor to facilitate large-scale production of these specific virus-like particles. In addition, it saves time: The viral vector developed virus-like particles within two days.

For comparison purposes in this study, Li and Ma also created a more traditional vaccine candidate by inserting a human norovirus gene into a different type of virus: a baculovirus, which is rod-shaped. It took six days for these viruses to grow enough to be used as a vaccine candidate, and the production level was comparatively low.

The scientists then conducted an animal study to observe what kind of immune response the VSV-based norovirus vaccine candidate could generate. Mice received either the VSV-based vaccine or various types of control substances for comparison, including one group that received the vaccine created with the more traditional technique. The substances were given orally or through the nose.

Weekly blood samples showed that two weeks after receiving the vaccines, the mice given the VSV-based norovirus vaccine had developed and sustained a high level of antibodies against the human norovirus – about 25 times higher levels of antibodies than those induced by the traditionally prepared vaccine candidate.

"This might be the most important advantage of the VSV-based norovirus vaccine candidate: It prepares a high concentration of norovirus-specific antibodies that can assist with virus detection, disease diagnosis and therapy," Li said.

In addition, the mice vaccinated with VSV-based vaccine generated a T cell immune response that was two times higher than the T cell response produced in mice receiving the traditional vaccine candidate. The immune response involving T cells, a type of white blood cell, plays an important role in efficient clearance of norovirus infection.

Li said the mucosal immune response – that involving areas covered by mucous membranes – was similar in the two vaccine types the mice received. The scientists tested fecal samples and vaginal antibody levels in the mice, and found the levels comparable between the groups of mice receiving the two different types of vaccine.

VSV is known to infect animals, especially cattle and pigs. Human infection with VSV is very rare. The VSV-based norovirus vaccine led to minimal weight loss but caused no symptoms of illness in mice. This showed that the virus strain was attenuated, or had lost its ability to spread, because of the additional gene inserted into its genome, Li explained.

Because mice will not develop traditional norovirus symptoms, this study did not involve a test of the vaccine against the pathogen itself. Li said his further research plans include enhancing the vaccine candidate by

inserting additional genes into VSV along with the human norovirus gene, which is expected to make the vaccine more potent but still safe. And he then hopes to test the vaccine candidate in a larger animal model, such as so-called germ-free pigs, animals that have never been exposed to any pathogens. These animals develop diarrhea in response to norovirus infection, as do humans..

Provided by The Ohio State University