First vaccines targeting 'cruise ship virus' sail into clinical trials

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A few months ago, Charles Arntzen dined on a plate of buttery mussels. That night, he fell ill with what he believes was norovirus, a nasty bug known for causing profuse vomiting and diarrhea. It was a cruel twist of fate for someone who studies the virus at the Center for Infectious Diseases and Vaccinology at Arizona State University in Tempe. Knowing all too well that no specific medicine exists to treat norovirus illness (or even to prevent the problem), Arntzen buckled down in the bathroom and spent the better part of four days “getting rid of everything,” as he puts it. “I was so miserable I couldn’t do a thing.”

Arntzen hopes that soon others won’t have to endure the same experience. He and many other researchers are now working to develop a vaccine against the highly contagious, vomit-inducing virus, with the lead candidate already tested in humans and at least two more contenders slated to enter clinical trials in the next couple of years. And on the therapeutics front, researchers from the US National Institute of Allergy and Infectious Diseases (NIAID) reported in the September issue of the Journal of Virology that they had produced the first monoclonal antibodies proven to neutralize human norovirus and block infection in chimpanzees.

Such antibodies could potentially be used to treat vulnerable populations or to prevent the spread of outbreaks. "But we have a lot of work to do [...] before we can evaluate our therapeutic antibodies in humans," says study author Kim Green, a microbiologist at the NIAID in Bethesda, Maryland. And even if the therapy proves effective, the high price tag of monoclonal antibodies is likely to limit their use, which is why most of the field is focused on developing a cheaper, preventative vaccine.

Norovirus has made news in recent years for its terrifying tendency to tear through cruise ships, hospitals and nursing homes. According to new estimates released last month from the US Centers for Disease Control and Prevention, norovirus infects up to 21 million Americans each year, causing as many as 71,000 hospitalizations and 800 deaths. And thanks in large part to the success of the rotavirus vaccine, norovirus has surpassed rotavirus to become the most common cause of acute infectious diarrheal disease among young children in the US. It now trails only Clostridium difficile as a second leading cause of gastroenteritis-associated death in the country.

A norovirus vaccine could save lives and money. A 2012 modeling study suggests that a norovirus vaccine could avert millions of cases annually and save as much as $2.1 billion in health care costs and lost productivity in the US alone. And that's based on a vaccine that confers only up to four years of protection. Last month, another modeling paper came out showing that natural immunity against norovirus can last for as long as nine years in the absence of major strain changes. If a vaccine could achieve the same protection, the savings could be even greater.

Go viral-like

The lead norovirus vaccine contender comes from a Montana-based company called LigoCyte Pharmaceuticals, which was acquired by the Japanese drug giant Takeda in October of last year. This vaccine contains virus-like particles, or VLPs, which are hollow spheres composed of structural proteins from the virus that self assemble. In Takeda's product, the VLPs mimic two strains of naturally occurring norovirus, one from each viral subgroup that tends to sicken people. VLP-based vaccines to protect against hepatitis B and human papillomavirus are already on the market, and the technology is an attractive option for norovirus because scientists haven’t yet figured out how to grow the virus in the laboratory—a necessary first step in producing attenuated or inactivated vaccines such as are used to immunize people against most infectious agents.
Preliminary data from a 110-person trial presented at the 2012 Interscience Conference on Antimicrobial Agents and Chemotherapy in San Francisco suggest that Takeda's vaccine is safe. According to Rajeev Venkayya, head of Takeda's Vaccine Business Division, which is based in Deerfield, Illinois, the company plans to present efficacy data later this year.

Expectations are running high. In 2011, LigoCyte reported that a nasal spray version of the vaccine that contained only one type of VLP reduced the incidence of gastroenteritis from 69% for volunteers who received the placebo to 37% for volunteers who received the vaccine. “Those results were clear evidence of proof of concept,” Venkayya says. However, the company decided to pursue an injectable formulation in part because LigoCyte’s in vitro research suggested that it might be more efficacious. (The device used to deliver the nasal vaccine also had a tendency to malfunction.)

But Takeda’s experimental vaccine is not the only candidate riding the wave of interest. Two smaller companies now have comparable vaccine candidates that are scheduled to enter human testing in the next year or two.

Like Takeda, UMN Pharma is advancing an injectable vaccine that the Japanese drugmaker licensed last year from the University of Tampere Medical School’s Vaccine Research Center in Finland. In July, the Finnish group published a study showing that a combined norovirus-rotavirus vaccine elicited broad immune responses in mice. But UMN has since decided to sideline the combined vaccine and first focus on the norovirus component alone, according to Timo Vesikari, director of the Finnish vaccine center. Meanwhile, Nanotherapeutics, a company based in Alachua, Florida, is betting that a nasal norovirus vaccine will have greater efficacy. The vaccine, which Arntzen helped develop, consists of a dry powder that will be squirted into the nose with a burst of compressed air.

**Significant P value**

The lead vaccine contenders from Takeda, UMN Pharma and Nanotherapeutics all rely on VLPs, which contain many copies of the main protein found on the virus’s shell. But Xi Jason Jiang, an infectious disease researcher at the Cincinnati Children’s Hospital Medical Center in Ohio, has developed a ‘P particle’ vaccine that contains only part of the protein—a piece that protrudes and attaches to the cells that line the gut. Earlier this year, Jiang and his colleagues reported that the P particle vaccine works as well as a VLP-based product to elicit both cellular and antibody immune responses in mice. LigoCyte licensed this vaccine from Jiang’s institution in 2009, but “it’s too early to say what we’ll do with that,” Venkayya says.

Despite this progress, many questions remain. The virus is genetically diverse, and it’s not yet clear whether immunity against one or two strains will provide protection against all. “Until we get into broader scale human testing we won’t know,” Arntzen says. In Takeda’s trials to date, volunteers have been challenged only with norovirus strains that matched the VLPs included in the vaccine. A phase 3 field trial will examine whether the vaccine can protect against the wide variety of norovirus strains found in nature.

Further complicating matters, the noroviruses responsible for most outbreaks tend to evolve rapidly, giving rise to new variants every two to three years. So it’s possible that even a vaccine that is highly effective today would need to be updated and readministered periodically. Ralph Baric, a microbiologist at the University of North Carolina School of Medicine in Chapel Hill, has found a potential work-around that might extend a vaccine’s lifespan. Baric’s group created chimeric VLPs or cocktails of VLPs containing proteins from several different norovirus strains isolated over two decades. As he reported at the American Society for Virology meeting in July in State College, Pennsylvania, the more diverse vaccine constructs induced a more broadly blocking immune response in mice than standard VLP vaccine designs.

Arntzen firmly believes that any obstacles can be overcome. His mussel eating depends on it. “It’s time and money,” he says. “I honestly don’t see any scientific barriers at this point.”

**References**

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