Encouraging Efforts to Develop a Vaccine Against Epstein-Barr Virus

The research is vital because Epstein-Barr virus is linked to cancers, lupus, rheumatoid arthritis, multiple sclerosis and other conditions.

July 26, 2022 By Fred Hutch News Service

Implicated in cancers, fingered as the cause of mononucleosis—and now suspected of triggering the degenerative nerve disease multiple sclerosis—Epstein-Barr virus is building a rap sheet as a seriously problematic infectious agent.

Recent findings concerning the extent of damage wrought by this common virus lend urgency to efforts to develop a first vaccine, and on June 14 in the journal Cell Reports Medicine scientists at Seattle's Fred Hutchinson Cancer Center reported encouraging results in early laboratory tests of a new concept in EBV immunization.

Hutch molecular biologist Andrew McGuire, PhD, and his team are experimenting with a vaccine made of nanoparticles, each minuscule particle studded with up to 60 copies of a pair of proteins that mimic similar pairs found on the surface of the virus. Those surface proteins—known as gH and gL—work like tiny crowbars, allowing live virus to pry through the outer membranes of cells it infects.

While the gH/gL surface proteins help the virus to infect cells, they also present a tempting target for vaccines.

Four years ago, McGuire's lab helped underscore the importance of that protein pair with research showing that immune proteins—antibodies—blocking gH/gL could stop EBV from infecting two types of human cells: epithelial cells that line the mouth, nose and throat; and B cells, our blood cells that make antibodies. Then they set out to design a vaccine.

The idea of their vaccine is to train our immune systems to recognize dummy copies of the gH/gL proteins, so that if the body encounters the same shapes on the surface of the real virus, it will raise antibodies against them. It is similar to the way COVID-19 vaccines train the immune system to attack the distinctive spikes on the surface of SARS-CoV-2—by causing the body to manufacture dummy copies of that spike.

McGuire's experimental EBV vaccine is designed to display its dummy proteins affixed to

nanoparticles, either parked one protein per particle, or displayed laid out in arrays of many copies. These dummy displays stimulate the production of antibodies that can lock onto the real gH/gL proteins on the viral surface.

Swarms of these antibodies would disrupt EBV's ability to use those crowbar proteins to muscle into healthy cells. Ideally, the immune system could summon these same antibodies repeatedly, whenever the vaccinated person is exposed in the future.

McGuire and his team—spearheaded by graduate student Harman Malhi, the lead author of the study—tested five different versions of their vaccine in laboratory mice. Each version differed by the number of copies of gH/gL proteins carried and displayed by the nanoparticles—one, four, seven, 24 or 60. McGuire said that all of the multiple-copied nanoparticles performed well, but the best results came from two of them, those carrying four copies and those carrying 60.

Next, they took serum from mice who had received the 60-copy version and tested its protective capabilities in another group of mice infected with a lethal dose of EBV. The results were dramatic: 100% of the mice given antibodies generated from the 60-copy vaccine survived; while 75% of mice given antibodies generated from the single-copy vaccine died, as did all the mice given a placebo.

"I would say that's pretty significant," McGuire said of the outcome. "I was kind of surprised, to be honest, and I was encouraged."

The two best-performing versions, carrying four and 60 copies, differed from the others in that their nanoparticle "scaffold" used to carry and display the multiple dummy proteins was "computationally designed."

The scaffolds—like most biological materials—are also protein structures, but the computer-designed versions are artificial constructs engineered for efficiency. In these experiments, the artificial protein carriers seemed to have outperformed their natural counterparts.

The four-copy scaffold was developed by Fred Hutch computational biologist Phil Bradley, PhD, and colleagues; the 60-copy version by Neil King, PhD, and the Institute for Protein Design at the University of Washington.

"They were designed to be 'tunable,'" McGuire said. In other words, they were created to carry a set number of copies chosen by the researchers.

In comparison, the less-successful scaffolds (carrying one, seven or 24 copies) were all made of naturally occurring proteins. As such, they are more likely to contain features that the immune system might have encountered before and deem a potential threat. That could prompt an unwanted immune reaction against the nanoparticle proteins rather than the dummy EBV proteins.

McGuire stressed that these laboratory studies are early steps in the vaccine development

process. The tests conducted in mice, while providing valuable insights into how an immune response can be triggered against EBV, may turn out to have little bearing on how the vaccines would work in humans.

His group is carrying out additional preclinical trials to see if the approach tested in this trial remains promising and likely safe enough to try in humans.

Increasing Concern, Investment in EBV vaccines

The 2022 study linking a high prevalence of EBV to multiple sclerosis has increased concern in the medical community about the virus, a member of the herpesvirus family that has also been tied to lethal cancers such as Burkitt lymphoma and to cancers of the nose and throat.

McGuire believes that one of the first uses of a proven EBV vaccine could be to protect patients from post-transplant lymphoproliferative disorder, a runaway growth of white blood cells and a serious complication of blood stem cell and organ transplantation. The condition is thought to be driven by reactivation of latent EBV infection in immune-suppressed patients.

“EBV pops up in a lot of places,” McGuire said. “It is a ubiquitous virus that causes many problems. Cancer is a big one. Multiple sclerosis is now huge. There are links to lupus and rheumatoid arthritis. The military is interested in an EBV vaccine because mononucleosis affects recruits and causes a lot of lost time.”

Meanwhile, renewed interest in EBV is spurring research in other laboratories hoping to find a vaccine.

In January, the University of Massachusetts and COVID-19 vaccine maker Moderna launched a human clinical trial of a potential EBV vaccine using the same mRNA technology that has performed so well against the coronavirus. It will use mRNA copies of four surface proteins found on EBV, including gH/gL, in an effort to stir antibody responses against them.

In May, the National Institutes for Allergy and Infectious Diseases Vaccine Research Center launched an early-stage human clinical trial testing the safety of a potential EBV vaccine. It targets the same surface protein that enables the virus to infect B cells, gp350, and is built using a naturally occurring scaffold well known for its ability to display a dense array of target proteins. The vaccine also contains an adjuvant, a component designed to help stir up a strong immune response to the targets.

Also in May, researchers from drugmaker Sanofi and NIAID published in the journal Science Translational Medicine results of a nanoparticle-based vaccine study in mice targeting four different EBV surface proteins. Using techniques similar to that applied by McGuire and his team, the study is testing two vaccines combined into a single formulation. The vaccines employ a naturally occurring scaffold to display different proteins found on the surface of EBV, including gH/gL. The study found that mice injected with plasma taken from mice that previously received

the vaccine were protected against a challenge from live EBV.

“They did the same thing as we did. They immunized mice with their nanoparticle vaccine, and then took the antibodies and put them into other mice that were challenged with the virus—and those mice were protected,” McGuire said. “I think the two studies agree very well, and that’s a good thing.”

This work was supported primarily by the National Institutes of Health, with additional funding from the Bill & Melinda Gates Foundation; the Audacious Project; the Washington Research Foundation; Project Violet; and by awards from Pew Biomedical Scholars and the Burroughs Wellcome Fund.

This article was originally published June 14, 2022, by Hutch News. It is republished with permission.

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