In 2017 Dr. Harvey Friedman of the Infectious Disease Division of the Perelman School of Medicine at the University of Pennsylvania kindly allowed me to interview him about the trivalent subunit vaccine (1) that his group was developing (See Herpes Vaccine Update: An Interview With Penn's Dr. Harvey Friedman [2]).

We have continued to evaluate our subunit trivalent herpes vaccine (THV) in animal models, and I am pleased with what we've seen. There are some technological hurdles that we are addressing, but I am confident that the THV will elicit a sufficient immune response in animals to warrant clinical trials in uninfected people to prevent genital herpes infection.

Harvey Friedman, M.D. Interview with ACSH, October, 2017

It would seem that Dr. Friedman's confidence was not misplaced. Friedman and colleagues just published a paper [3] in Science Immunology in which they describe the trivalent herpes vaccine that they developed and its efficacy in animal models. The group’s THV works like gangbusters.
Of course, these results are from animal experiments, not human trials, but there is reason to be hopeful. Not all animal models of human disease are equal, quite the opposite. Some animal models are terrible at predicting utility in humans (rodent models of cancer are awful), other models are very good, especially those for infectious diseases.

ACSH advisor Dr. David Shlaes explains:

"Certain mouse models of infection can be used to accurately predict the human dose for antibacterial and antiviral drugs. Of course, human trials are also required and may refine this prediction further."

Shlaes’ second sentence underscores the "make or break" transition from pre-clinical (animal) to clinical (human) trials, and it has tripped up many a drug. No matter how good a potential drug or vaccine looks in animal tests it can go south in a hurry once it gets into humans. Only one in seven drug candidates that sail through animal experiments will make it to the pharmacy.

**What’s in the vaccine?**

It is easier to ask "what is in that vaccine?" than to explain it, but here goes...

The Penn vaccine consists of three components, one antibody and two glycoproteins (2). The antibody, which is called gD2, binds to a protein on the surface of the virus called gD (short for glycoprotein D). The gD surface protein is responsible for allowing the virus to enter the host cell. But blocking cell entry is not sufficient to prevent infection; two other glycoproteins that do a different job are also required for the vaccine.

One is called glycoprotein C (gC2), and the other glycoprotein E (gE2). (If these names aren’t sufficient to make you crazy you should read the description of how they work – details that I have mercifully omitted.)

Both gC2 and gE2 complement gD2, albeit by a different mechanism. One of the evil strategies that viruses (especially herpes viruses) have developed is the ability to evade the human immune system. The beauty of the Penn vaccine is that it blocks cell entry as well as two key immune evasion molecules, sort of a "vaccine hat trick."

**Looking good so far**

The protection against outbreaks in mice and guinea pigs (3) was perfect. None of the animals that received the vaccine developed lesions (!). But this is only part of the job of a successful vaccine. A person with asymptomatic infection (absence of lesions) – a hallmark of herpes – can still infect others. This is also known as a subclinical infection, or asymptomatic shedding, and the vaccine also passed this test with flying colors.

The THV was this close to perfect in providing complete (no trace of infection) in mice that were challenged with HSV-2 and it was almost as good in guinea pigs.
Twenty-eight days after 64 mice were vaccinated and then infected with HSV-2, 63 out of 64 of them had no detectable virus (this is called sterilizing immunity). Of the 10 guinea pigs tested, eight showed no sign of virus after 28 days. The two that did have virus present had strains that could not infect other animals.

“Our results in mice and guinea pigs are very encouraging – better than anything we have seen in the literature... But we won’t know if this vaccine will work until it is tested in humans.”

Harvey Friedman, M.D., 9/22/19

What about a therapeutic vaccine?

This is a tougher nut to crack. There has never been a therapeutic vaccine against any infectious pathogen. Vaccines are prophylactic, not therapeutic. In 2017 Dr. Friedman told me “Right now, I don’t believe that the vaccine would work well enough to be therapeutic. However, we are addressing this.” (4)

Vaccine for herpes have been tried and failed (every time) for 100 years. We should all keep our fingers crossed for Dr. Friedman and his colleagues. An effective herpes vaccine would be a major milestone in the history of infectious disease research, especially since 11% of the world – more than 400 million people – are infected with HSV-2.

I would be cautiously optimistic at this point. The animal data look great but there is still a long way to go.

NOTES:

(1) Subunit (synthetic) vaccines contain no virus, either live or not. Instead, they contain viral proteins. While it is impossible to contract an infection from subunit vaccines they tend to offer less protection than that of vaccines that contain the virus (in a weakened or inactivated form).

(2) Glycoproteins are proteins (long chains of amino acids) which are chemically bonded to different types of sugar molecules. They are typically found on the surface of cells where they play a critical role in multiple cell functions as well as infection.

(3) Guinea pigs models are a better predictor of human infection than mice models.

(4) As far as I know, only Rational Vaccines, which is using an attenuated live virus in their vaccine, is the only company pursuing a therapeutic vaccine. I expect to hear more from them soon.