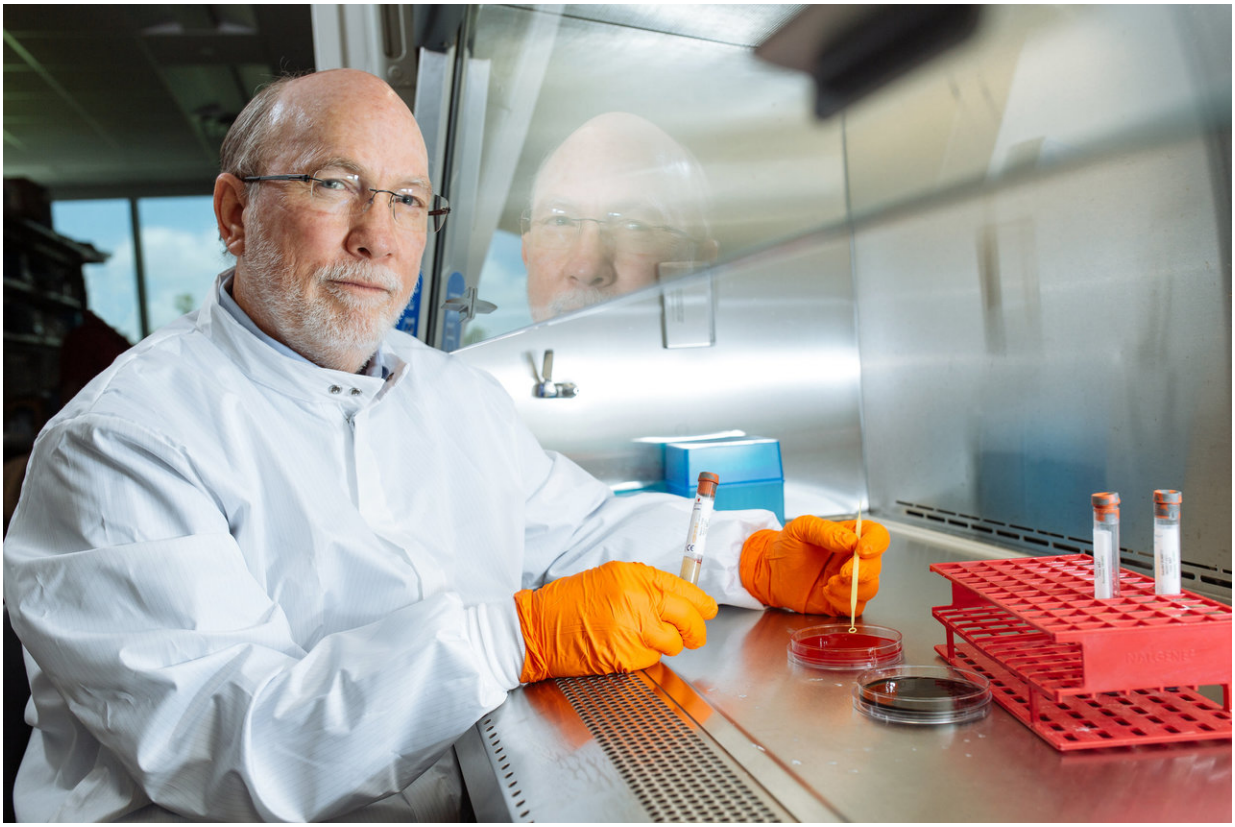
MedicalXpress

Promising new drug for hepatitis B tested

November 7 2017



Dr. Robert Lanford works in his lab at Texas Biomed. Credit: Texas Biomed

Research at the Southwest National Primate Research Center (SNPRC) on the campus of Texas Biomedical Research Institute helped advance a new treatment now in human trials for chronic hepatitis B virus (HBV) infection. Testing at SNPRC provided proof this novel therapeutic approach and drug delivery mechanism would be safe and effective, as

recently published in the international journal *Science Translational Medicine*.

The World Health Organization characterizes hepatitis B as a major global health problem. An estimated 250 to 400 million people are chronically infected with the virus. More than 800,000 people a year die from complications of cirrhosis of the liver and liver cancer. A vaccine that is 95% effective in preventing hepatitis B infections has been available since 1982, but there is currently no cure for the millions already chronically infected.

The novel therapy by Arrowhead Pharmaceuticals uses a mechanism called RNA interference to reduce the surface antigens created by chronic HBV infections. Surface antigens (called HBsAg) are small molecules involved in virus entry into liver cells. In chronic infection, they may prevent the immune response from clearing the virus. For example, a high level of HBsAg can lead to a greater risk of long-term, chronic infection with hepatitis B and life-threatening complications like cirrhosis and liver cancer. In this setting, reducing HBsAg by RNA interference will have beneficial effects.

Much of the groundbreaking work lies in the technology Arrowhead developed for delivering this small interfering RNA precisely to the liver. Experiments involving chimpanzees at the SNPRC from 2013-2015 provided the proof that this technology works and is safe for humans, laying the groundwork for the patient clinical trials that have followed. Trials of targeted HBV intervention in non-human primates showed the experimental drug was safe and effective enough to be tested in people.

The Director of the SNPRC, Robert Lanford, Ph.D., explained this novel treatment—in combination with conventional HBV therapy—could empower the immune system to kill the HBV-infected

cells and potentially cure people of the disease.

"We now have a drug that can knock down hepatitis B surface antigen and determine whether or not we can actually cure people with that," Dr. Lanford said.

The drug is delivered by subcutaneous (under the skin) injection. Scientists designed a molecule that delivers the medicine directly to the liver where it binds to a receptor. Then, another molecule that's derived from bee venom, helps break through membranes in the liver cells to deliver the medicine directly into the cytoplasm of the cells where it takes effect. The siRNA interferes with the expression of the HBV messenger RNA that produces the surface antigen.

"The idea is if you could knock the levels of surface antigens down far enough, the immune system would kick back in," Dr. Lanford said. "This technology is pretty specific for the liver right now, but there are a lot of problems in the liver that you can fix with this besides hepatitis B."

This kind of targeted therapy may someday be used to develop drugs for other chronic liver conditions like a genetic disorder called Alpha-1 antitrypsin deficiency, caused by mutated inherited genes, which can cause cancer.

The paper outlining the phase two clinical trials in people and the previous studies involving non-human primates was published in the September 27, 2017 edition of the journal *Science Translational Medicine*, an interdisciplinary medical journal established by the American Association for the Advancement of Science.

Although the SNPRC no longer uses chimpanzees for biomedical research, studies conducted with these non-human primates over decades continue to yield significant scientific information that will advance

human health.

More information: Christine I. Wooddell et al. RNAi-based treatment of chronically infected patients and chimpanzees reveals that integrated hepatitis B virus DNA is a source of HBsAg, *Science Translational Medicine* (2017). DOI: 10.1126/scitranslmed.aan0241

Provided by Texas Biomedical Research Institute