Hello, I'm Annalisa VanHook. Welcome to the Science Translational Medicine Podcast for November 5th, 2014. In this show, I'll be speaking with Dr. Eleanor Barnes from the University of Oxford. Her study describing a hepatitis C vaccine in humans reports that using a prime-boost vaccination strategy can induce durable T cell responses against HCV. Previous studies in mouse and human have highlighted a critical role for T cells in controlling HCV infection, and Barnes' vaccine strategy induces T cell responses that are important for viral control. This study sets the stage for the first large-scale efficacy and safety studies of a prophylactic HCV vaccine.

Interviewer – Annalisa VanHook
Hello, Dr. Barnes. Welcome to the Science Translational Medicine Podcast.

Interviewee – Eleanor Barnes
Thank you.

Interviewer – Annalisa VanHook
Why do we need new vaccine strategies for hepatitis C virus, HCV?

Interviewee – Eleanor Barnes
So hepatitis C virus is a massive global problem. Currently there are more than 118 million people infected around the globe. And in the West, hepatologists think of HCV—hepatitis C—as being a Western disease but, in fact, hepatitis C infects millions of people in resource-poor countries in Africa and Asia. Many people will have heard about the recent new drugs that we have for hepatitis C. And those are marvelous, and they're changing the field. But the issues with these is that they're very expensive. In the West, they cost between 30,000 pounds in the UK up to $80,000 in the USA per patient per course, and clearly that is unaffordable to most people around the globe. The other issue with the drugs is they need to be given to patients for many weeks. That's very difficult in resource-poor settings. And the drugs don't protect patients against reinfection and can, in some instances, be associated with viral resistance. Whereas in contrast, the vaccine—if it's effective and it's a good vaccine—can protect patients with one or two injections for the rest of their life. So vaccines really have proved themselves historically to be the very best medicine.

Interviewer – Annalisa VanHook
Right. Much better to prevent the disease than to treat it once you have it.
**Interviewee – Eleanor Barnes**
Yeah. And many patients will present for the first time to a health care physician when their disease is very advanced because the disease is a silent one until you get advanced liver disease associated with fibrosis and liver cancer.

**Interviewer – Annalisa VanHook**
Can you describe your HCV vaccination approach?

**Interviewee – Eleanor Barnes**
Yeah, so we have a new vaccine that aims to work by inducing T cells, which are one important component of the immune system. And this is a relatively new way of trying to design vaccines. So at the moment, all the existing vaccines that we have in clinical practice are based on inducing antibodies: measles, mumps, rubella, rabies, and so on. That has left us with a number of pathogens—like hepatitis C and HIV—where an antibody based approach is simply not going to work because antibodies work by targeting the outside of a virus. And in HIV and hepatitis C, these are regions of the virus that are hypervariable. And that's why an antibody approach is unlikely to work. Whereas a T cell vaccine approach can target the more conserved parts of the virus that are common between different virus particles. The way that we are doing this is using adenoviral vectors that have been disabled genetically so that these adenoviral vectors can't replicate themselves. So adenovirus is a virus that causes the common cold. We've all been exposed to these in the past. And what our vaccine does is take a component of the adenovirus and insert into that part of the hepatitis C virus. And this has been shown to induce very large numbers of T cells. One of the problems with adenovirus vectors is, as I said, we've been exposed to these in the past. So we have natural immunity against these. So to get around this problem, we're using adenoviruses in our vaccine that's derived from chimpanzees, which means that humans haven't been exposed to these before. We give that as a single injection, and then we come in with a second vector eight weeks later called a Modified Vaccinia Ankara, also known as MVA. And that effectively boosts the T cell response even higher so you end up with a superb magnitude of T cell responses to the pathogen you're interested in.

**Interviewer – Annalisa VanHook**
So you used this new vaccination approach in humans. What did you find after vaccination?

**Interviewee – Eleanor Barnes**
We were able to induce very high numbers of T cells in all subjects vaccinated; numbers up in the thousands, and that's unprecedented for a hepatitis C virus vaccine. One of the important findings was that we were able to induce T cells that could target multiple parts of the hepatitis C virus, and we think that's going to be very important for providing protection. And there's two kinds of T cells: CD4 and CD8 T cells. The advantage of this approach where you combine an adenovirus with a MVA vected approach is that you induce both CD4 and also CD8 T cells, which we think are going to be important to afford people protection over time.
Interviewer – Annalisa VanHook
How does your approach differ from previous HCV vaccine strategies?

Interviewee – Eleanor Barnes
With this approach, we're able to induce very high numbers of T cells—up in the thousands—whereas historically T cell vaccines have induced very small numbers of T cells in the tens or hundreds. And we think the magnitude of the response is going to make a difference. In addition, our T cells with our vaccine target multiple parts of the hepatitis C virus. And the vaccine induces large numbers of both CD4 and CD8 T cells. The other important thing about hepatitis C is that around the globe it exists as six major strains, and it's important for the T cells induced by vaccination to be able to target all of these strains. And the T cells induced by our vaccine we're able to some extent to target multiple strains of hepatitis C, and we think that also is going to be very important.

Interviewer – Annalisa VanHook
Based on your findings in this initial human study, what’s the next step in taking this vaccine into the clinic?

Interviewee – Eleanor Barnes
So that's already started. There's a study that's being led by Andrea Cox from Baltimore in the States and Kim Page in San Francisco taking this vaccine and vaccinating active injection drug users who are at high risk of contracting hepatitis C virus infection. In this study, half the people get the vaccine, and half get a placebo or a mock vaccine. The results from that study will not be available in 2016, but that's the next step really; it's an efficacy study to see if the vaccine works. One of the problems with the hepatitis C vaccine world is there are no good animal models in which to test vaccines. So really we're dependent on taking these vaccines through into the field to see how effective they are. And what that really calls for is establishing cohorts around the globe where we know what the prevalence rates of hepatitis C virus infection is in those environments. Because without that information, you can't design vaccine studies.

Interviewer – Annalisa VanHook
Dr. Barnes, thanks for speaking with me.

Interviewee – Eleanor Barnes
Thank you for the interview; it was a pleasure.

Host – Annalisa VanHook
That was Eleanor Barnes from the University of Oxford. Check out her group's Science Translational Medicine paper online by going to our website at stm.sciencemag.org.

I’m Annalisa VanHook, and thanks for listening!

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