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Steven Weinman, M.D., Ph.D. and his colleagues battle a virus on behalf of 3.2 million Americans

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By Alissa Poh

As diseases go, hepatitis C should be highly treatable, even curable. Like other viruses, it speedily replicates inside the cells of its host and dodges drugs by frequently mutating. One crucial difference, however, is that hepatitis C doesn't stay dormant in the body.

"If you can turn hepatitis C's replication off completely for three or more months, you're rid of it," says Steven Weinman, M.D., Ph.D., a professor of Internal Medicine and director of translational research at the University of Kansas Medical Center's Liver Center.

An estimated 3.2 million Americans, including roughly one in 33 baby boomers, are infected with hepatitis C. According to the Centers for Disease Control and Prevention, more Americans die from this infection each year than from HIV-related causes. So the fact that hepatitis C is potentially curable should be good news.

But there's a paradox. "The current drug regimen for hepatitis C is a difficult ordeal that many patients struggle to tolerate," Weinman says.

Hepatitis C patients typically undergo a year-long course of interferon and ribavirin; both boost the immune system but have major side effects. "With interferon, you feel lousy the entire time; you're weak and you have no appetite," Weinman explains. "It can cause personality changes and depression, or make pre-existing depression worse." Both interferon and ribavirin also lower a patient's blood counts, increasing the risk of other infections and causing anemia.

Two new drugs, telaprevir and boceprevir, were approved by the FDA last May. But they're only effective alongside interferon and ribavirin. Their own side effects — including a nasty rash and severe bone marrow suppression — compound the misery of the original therapy. They also need to be taken three times daily at exact eight-hour intervals and, in telaprevir's case, with a high-fat diet so it's properly absorbed.

"The ordeal's now even worse, but the new drugs do bring a cure rate that had been below 50 percent closer to 70 percent, and that's huge," Weinman says.

Hepatitis C is all the more difficult to treat because the blood-borne virus spreads most commonly through intravenous drug use, so many patients already have a history of psychiatric problems that are aggravated by the grim course of treatment. "We occasionally get patients who aren't greatly affected by therapy," Weinman says. "But many with hepatitis C are already struggling to cope with their disease *before* treatment, and the side effects of interferon alone could send them over the edge. That's why we need better treatments."

Targeting the virus

Different proteins — 10 of them, in the case of hepatitis C — make up a virus's structure. By working on HIV, scientists have learned that combinations of drugs, each aimed at a particular protein, are necessary to cut off a virus's survival strategies.

"It's a general principle of treating viruses — if you attack them at multiple sites, they can't mutate away from therapy," Weinman says. "We need potent combinations of new drugs that patients can tolerate long enough to rid themselves completely of hepatitis C."

Boceprevir and telaprevir target a class of viral proteins called proteases. Pharmaceutical companies are also busy developing and testing 20 to 30 different drugs — mostly against other parts of the virus, including its polymerase proteins.

There are additional hepatitis C viral proteins for which drugs could be developed. Weinman is studying one of these lesser-known possibilities, a protein called p7.

"It has similar properties to a protein in the influenza virus, for which the drug amantadine has worked pretty well," he says. "That's what got me interested."

Without p7, the hepatitis C virus is crippled: It can still replicate, but it can't create the packaging material needed to assemble brand-new viruses.

"For a long time, though, nobody knew p7's exact role, only that the virus could not do without it," Weinman says. He and his graduate student, Ann Wozniak, were the first to figure out what p7 actually does: it makes the interior of hepatitis C-infected cells less acid, which is necessary for the virus to function. They published their findings in the journal *PLoS Pathogens* in September 2010.

Weinman and Wozniak worked with researchers at the University of Leeds in the United Kingdom to deduce p7's function, and are continuing to collaborate to figure out how it could be stifled. In another paper in the journal *Hepatology* last summer, they described two classes of p7 inhibitors — adamantanes and alkylated imino-sugars — that attack p7 in different ways.

"Most of the current drugs target hepatitis C's early stages of replication," Weinman says. "We're trying instead to prevent replicated viral parts from being assembled." While p7 inhibitors have yet to

advance to clinical trials, he reckons it's just a matter of time.

Alcohol's clout

Hepatitis C is most often caught early in people who undergo a health screening as part of a rehabilitation program — or if an observant person notes nondescript symptoms such as fatigue and mild liver tenderness. Most infected people, though, take decades to realize that they have the disease. This is because cirrhosis, or scarring, of the liver, is a stealthy process.

With cirrhosis comes the risk of cancer. Hepatitis C is, in fact, the main cause of liver cancer in Americans.

Besides working on new ways to target the virus with drugs, Weinman wants to better understand hepatitis C's long-term effects on the liver — particularly how alcohol consumption makes hepatitis C run a more aggressive course.

"In the U.S., alcoholism is actually a minor component of liver scarring — 85 percent of people who drink heavily and regularly never get cirrhosis," Weinman says. "That's a pretty surprising statistic, and it indicates that there are natural protective mechanisms against alcohol injury."

Weinman is investigating the potential role of a protein called FOXO3 in shielding the liver from alcohol. "It's a protective factor that gets activated when we either infect laboratory-cultured liver cells with hepatitis C or treat those cells with alcohol," he says. However, feeding alcohol to mice *with* hepatitis C results in exacerbated liver injury, and under these conditions, FOXO3's activity is significantly diminished.

Like most proteins, FOXO3's surface gets different "tags" added or removed, depending on its cellular environment. These tags alter the protein's function. Weinman and his postdoctoral fellow Irina Tikhanovich have found that in the presence of hepatitis C, FOXO3 is tagged in particular ways that engage its ability to prevent liver inflammation. Alcohol, however, interferes with this process and subverts FOXO's protective function.

Weinman was recently awarded a grant from the National Institutes of Health to continue dissecting the negative impact of alcohol on hepatitis C's progression. He's using some of this funding to explore another conundrum: while FOXO3 protects the liver against hepatitis C or alcohol, it also behaves abnormally in liver cancer.

"FOXO3 normally has another role as a tumor suppressor, but it goes haywire and loses this function in the majority of liver cancer cases," he explains. "It may be that hepatitis C eventually interferes with FOXO3's ability to suppress tumor growth, but we don't know for sure."

Weinman would like to figure out how to manipulate FOXO3 so it both protects the liver from cirrhosis *and* functions fully as a tumor suppressor. Current chemotherapy drugs produce a slew of harsh side effects and are only marginally effective against liver cancer.

"Chemoprevention is not as sexy; you can't point to Mrs. Jones over there and say you got rid of her liver cancer and saved her life," he says. "But I'm more interested in preventing cancer from ever occurring in patients with cirrhosis than treating cancer that's already developed. I think we'll save more lives this way."

A different approach, and hope for a cure

Through its active liver transplant practice, the KU Medical Center has acquired more than 2,000 tissue samples from the liver biopsies of more than 1,000 patients. These samples allow KU researchers to rapidly test ideas in ways that wouldn't be possible without the multi-year specimen repository, Weinman says.

Several other Liver Center researchers are also using these samples, along with patient histories, to investigate alcohol's influence on hepatitis C. In December 2011, they published a paper in *Hepatology* showing that alcohol may mask the effects or impair the expression of several nuclear receptor genes which, among other things, regulate the formation of scar tissue that eventually leads to liver cirrhosis, which happens much faster in alcoholics with hepatitis C.

"We haven't determined if there's a direct association between alcohol's effect on nuclear receptors and the progression of hepatitis C," says Richard Gilroy, M.D., a liver transplant specialist at KU Medical Center and one of the paper's authors. "However, it's a likely reason why this disease is more aggressive in alcoholics."

Weinman, who did not contribute to this paper, considers it a good example of how hepatitis C and alcohol might individually alter gene expression in the liver, with each influencing the other's effects.

"I think it's a nice proof-of-principle that the interaction of alcohol and hepatitis C is not the sum of two parts — instead, alcohol is modifying what hepatitis C does," he says.

Ultimately, Weinman and his colleagues are looking forward to greatly improved drugs for hepatitis C, especially the dawning era of interferon-free therapy.

"It's as certain as anything can be in medicine that we're on the cusp of curing this disease in 90 to 95 percent of patients," he says.

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