

MIGHTY MOUSE DESIGNED TO STUDY HEPATITIS C

by LISA SPELLMAN

AS SOON AS HEPATITIS C VIRUS INVADES THE LIVER CELLS ITS UGLY JOB BEGINS.

Replicating itself as quickly as possible, the virus spreads like an inferno, invading every healthy cell in sight.

White blood cells pour in. The swollen liver fights, waging a war against an invader that mutates to stay one step ahead.

It takes years before the first sign of the virus manifests itself in the yellowing skin of its victim.

But when hepatitis C is done, the once smooth, shiny, pink liver is hardened, pitted and deformed.

“The liver can only fight for so long,” said David Mercer, M.D., Ph.D., assistant professor of surgery and one of the brightest young stars in UNMC’s organ transplantation program.

After a while, scar tissue forms, here and there at first, Dr. Mercer said, then spreads across the entire organ.

“The scar tissue squeezes off the healthy tissue in the liver leading to cirrhosis. This makes it hard for the liver to do its job, which is to detoxify the blood, and the individual begins to feel the effects: nausea, fatigue and abdominal pain,” he said.

Hepatitis C is the No. 1 reason for liver transplantation in the United States. It’s estimated that more than 3 million people in this country have the disease. For the majority of these patients, it is initially asymptomatic and goes undetected for years.

Hepatitis C is spread primarily through the blood, Dr. Mercer said.

Intravenous drug users who share needles are most at risk for contracting the disease, but health professionals also can become infected through needle sticks on the job.

The disease also can be spread from infected mothers to their infants at birth or through personal care items, like razors or

**GRAY-LA IS A MIGHTY MOUSE THAT HELPS
RESEARCHERS STUDY HEPATITIS C AND
OTHER HUMAN DISEASES.**



toothbrushes that have blood on them, and on instruments used for tattoos and body piercing that are not sanitized between uses.

Currently, there are only two drugs – interferon and ribavirin – available to treat people with chronic hepatitis C, Dr. Mercer said.

“There is no vaccine to prevent the virus,” he said.

That’s why Dr. Mercer, who specializes in transplantation and hepatitis C research, developed a novel mouse model to study the deadly disease.

Using pieces of human liver tissue that would normally be discarded after a liver operation, Dr. Mercer preserves the tissue and, in the laboratory, removes the liver cells from the surrounding tissue.

Tiny, 10-day-old mice are then anesthetized and, using a high-powered dissecting microscope, Dr. Mercer makes a small incision in the left flank of the mouse over the tip of the spleen.

Gently, the spleen is teased out into the incision and a very small needle is inserted into the tip.

A low-volume pump is then used to deliver the human liver cells into the special strain of mouse through the spleen. Once inside, the human liver cells travel to the mouse liver and multiply rapidly, eventually taking over the mouse’s liver.

“The incision is closed with a few stitches and the mice are fully awake and back to normal within a few minutes of the procedure,” Dr. Mercer said.

After 10 weeks, a miniature, humanized liver develops, which then can be infected with hepatitis C or other viruses to allow researchers to study their effect on the human liver.

Dr. Mercer’s research is considered unique because – up until now – only humans and chimpanzees had been susceptible to hepatitis C.

His work has brought heightened recognition, including the 2007 Career Development Award from the American Society of Transplant Surgeons. The \$100,000 award, combined with funding from the UNMC Department of Surgery, supports his ongoing research.

Dr. Mercer first became interested in hepatitis C research in 1996 while working at the University of Alberta in Edmonton, Canada. There, he joined a group of investigators who were developing an animal model for hepatitis C.

“As I began to learn more about it, I found virology to be a fascinating topic at a purely scientific level,” he said. “It struck me that, as a doctor, I can only help people on a one-on-one basis.

But as a scientist, there’s a possibility to impact millions of lives.”

The biggest hurdle for the research team was developing the appropriate mouse strain to support the rapid proliferation of human cells.

A series of 57 mice were transplanted using a special strain of mouse, scid/Alb-uPA, that accepts human tissue and stimulates growth of transplanted liver cells. The research team found four mice with two copies of the special transgene, Alb-uPA, that were capable of supporting the human liver sufficiently.

“All that was left was to convince the world,” Dr. Mercer said. “It wasn’t the easiest thing to do because there had been a number of earlier models that failed.”

Because hepatitis C can’t be grown in cultures, the humanized mouse models will help researchers test new therapies, understand how the virus infects healthy cells and how it replicates itself, said Lorne Tyrrell, M.D., Ph.D., a researcher at the University of Alberta who worked with Dr. Mercer on the humanized mouse model.

The mouse model is being replicated and used around the world. Researchers in Japan are testing how drugs affect the human liver. Scientists in Belgium and Germany are trying to find a treatment for hepatitis C.

Dr. Mercer plans to use the model to understand how hepatitis C affects the human liver at the earliest stages.

“I want to know what happens in the first few minutes, the first few hours, after a person becomes infected,” he said. “How long does the virus float around before it sticks to a cell and gets inside? What happens once it first gets inside? None of these answers are known.”

Dr. Mercer hopes that by finding these answers he can prevent people from becoming infected at all. 📺

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DR. DAVID MERCER WAS AMONG A GROUP OF CANADIAN RESEARCHERS WHO DISCOVERED A WAY TO TRANSPLANT HUMAN LIVER CELLS INTO A SPECIAL STRAIN OF MICE.



Hepatitis ABC's

Along with hepatitis C, there are four other strains of the virus that can cause hepatitis. These viruses are classified as hepatitis A, B, D, E and G. Each strain causes the same symptoms: jaundice, fatigue and abdominal pain, loss of appetite, nausea, diarrhea and fever. Hepatitis B and D also cause joint pain. While each can cause hepatitis in the liver and ultimately liver failure, all have unique qualities.

■ **Hepatitis A** is found in the feces of infected persons and is usually spread from person-to-person by putting something contaminated with the virus in the mouth. It is transmissible through sex, household contact with an infected person, sharing needles and traveling to countries where hepatitis A is common. Persons infected with hepatitis A can be treated with immune globulin within two weeks of coming in contact with the virus. Once you have had hepatitis A you cannot get it again. The hepatitis A vaccine, introduced in 1996, remains the best protection against the virus.

■ **Hepatitis B** is most commonly spread through unprotected sex. It is found in the blood of an infected person and can be spread through sharing contaminated needles, a needle stick exposure on the job or from an infected mother to her baby during birth. There are six drugs used to treat chronic hepatitis B. A vaccine for hepatitis B was introduced in 1982 and is the best prevention against the virus.

■ **Hepatitis D** is spread through blood or body fluid. It usually occurs as a co-infection with hepatitis B or as a super infection in persons with existing chronic hepatitis B infection. The hepatitis B vaccine is the best prevention against the virus.

■ **Hepatitis E** is found in the feces of people and animals infected with the virus. It is spread by eating or drinking contaminated food or water. Hepatitis E remains uncommon in the United States and most outbreaks in developing countries have been associated with contaminated drinking water. While there is no chronic infection, hepatitis E is more severe among pregnant women, especially in the third trimester. The best prevention: wash your hands with soap and water before preparing and eating food, and avoid drinking water of unknown purity in the developing countries of South Asia and North Africa. An experimental hepatitis E vaccine is now being studied.

■ **Hepatitis G** is very similar to hepatitis C, but has not been associated with any chronic liver disease. In fact, it seems to be a benign virus that is widely present throughout the world. There has been no association between poor outcomes of patients who are infected with hepatitis C and hepatitis G at the same time. A vaccine for Hepatitis G exists.

Sources: The Centers for Disease Control and Prevention and the Colorado Center for Digestive Disorders.