Follow-up research could also explore differential CD19 expression across brain mural cells, as well as how expression varies among individuals and how it changes with age.

"We don't really understand the big driver in causing neurotoxicity with these CD19 CAR T cells, and this paper provides a potential explanation for that—it's something that is really novel, and I think not a lot of people would have necessarily predicted it," says Lawrence Fong, MD, of the Helen Diller Family Comprehensive Cancer Center at the University of California, San Francisco, who was not involved in the research. Fong agrees that more questions need to be answered to understand the causal link between CD19 expression in brain mural cells and neurotoxicity. For example: Do CAR T cells lodge near CD19-expressing brain mural cells? Do CAR T cells damage brain mural cells and lead to an inflammatory cascade?

Beyond CD19, the team's single-cell RNA analysis approach could improve the design and development of antigen-targeting cell therapies. "This paper shows that you can use these unbiased approaches to predict off-tumor toxicities for a particular target antigen," Satpathy says, "and, on the flip side, maybe nominate better target antigens that have less off-tumor expression across the human body." *–Catherine Caruso* ■

Nobel Lauds Discovery of Hepatitis C Virus

This year's Nobel Prize in Physiology or Medicine recognizes three scientists who discovered the hepatitis C virus (HCV): Harvey Alter, MD, of the NIH; Michael Houghton, PhD, of the University of Alberta in Canada; and Charles Rice, PhD, of Rockefeller University in New York, NY. Their work has led to the development of screening tests and treatments that have dramatically reduced the incidence of hepatitis C infections worldwide and may one day eliminate the virus, a major risk factor for hepatocellular carcinoma.

"I cannot overemphasize the impact that the discovery of hepatitis C had," says Augusto Villanueva, MD, PhD, of the Tisch Cancer Institute at the Icahn School of Medicine at Mount Sinai in New York, NY, who wasn't connected to the prizewinning research.

"One nice thing about this research is how it spans from a clinical observation to a basic virology study," says Tim Greten, MD, of the NCI's Center for Cancer Research Liver Cancer Program.

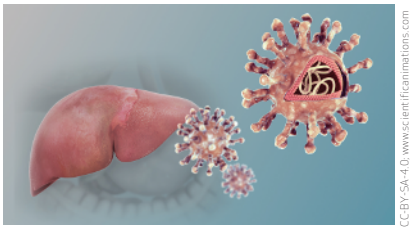
Alter made the clinical observation in the 1970s, when he was working to reduce hepatitis transmission through transfusions. At the time, improvements in donor selection and testing for the hepatitis B virus had slashed the transmission risk, but about 10% of recipients were still contracting hepatitis. In 1975, Alter and colleagues reported that 22 surgical patients who developed hepatitis after receiving transfusions tested negative for the hepatitis A and B viruses, suggesting a third disease-causing virus (N Engl J Med 1975;292:767–70). The scientists then found that blood from patients with this mysterious form of hepatitis could induce the illness in chimpanzees (Lancet 1978;311:459–63).

However, the virus proved elusive until the 1980s, when Houghton and a team that included his colleagues Qui-Lim Choo, PhD, and George Kuo, PhD, took a chance on a novel approach. They isolated pieces of RNA and DNA from infected chimpanzees and used them to make a library of DNA fragments.

To find out if any of these snippets derived from the virus, the researchers inserted each fragment into bacteria that produced the DNA-encoded protein. Then, they added serum from an infected patient—which they surmised would harbor antibodies that would latch onto viral proteins—to the bacterial colonies. They tested more than 1 million such colonies but found only one producing a viral protein, indicating that the DNA fragments these bacteria received represented a portion of the pathogen's genome (Science 1989;244:359–62).

"The isolation of the virus was a tremendous achievement with the technology of the time," says Villanueva.

In the 1990s, Rice and his colleagues answered the lingering question of whether the virus needed help from other pathogens to cause disease. That was a concern because researchers noticed that the viral clones they created in the lab did not spur cells to



Artist's rendering of hepatitis C infection, a major risk factor for hepatocellular carcinoma.

produce new virus particles in culture. Rice and his team found that the viral RNAs tested were missing a section from one end and had accrued mutations that might hamper their replication (Science 1997;277:570–4). The scientists revealed in 1997 that when they "corrected" these defects, the viral RNA induced hepatitis C in chimps, confirming that the virus acted alone.

Identification of HCV enabled researchers to design screening tests that have nearly eliminated it from the blood supply in many countries. Pharmaceutical companies have also introduced antiviral drugs, such as the combination of sofosbuvir and velpatasvir (Epclusa; Gilead), that can cure the illness in 95% of patients.

Although researchers haven't developed a vaccine against hepatitis C, the World Health Organization aims to stamp out the disease globally by 2030 through screening and treatment. If that effort succeeds, "it would be amazing that in less than 50 years we were able to isolate the virus and eliminate the disease," remarks Villanueva. *–Mitch Leslie* ■

Chemistry Nobel Honors CRISPR, an "Essential" Tool for Cancer

Two scientists who pioneered the site-specific genome-editing technology that is contributing to innovative and breath-taking cancer therapies were awarded this year's Nobel Prize in Chemistry.

Emmanuelle Charpentier, PhD, of the Max Planck Unit for the Science of Pathogens in Berlin, Germany, and Jennifer Doudna, PhD, of the University of California, Berkeley, led the team that in 2012 first showed how a bacterial immune mechanism known as CRISPR could be repurposed to edit DNA (Science 2012;337:816–21). They are the first two women to share a science Nobel without a male collaborator.