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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.

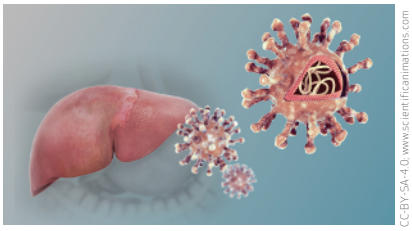
Alter made the clinical observation in the 1970s, when he was working to reduce hepatitis transmission through transfusions. At the time, improvements in donor selection and testing for the hepatitis B virus had slashed the transmission risk, but about 10% of recipients were still contracting hepatitis. 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 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.



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

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.

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Emmanuelle Charpentier, PhD (left), and Jennifer Doudna, PhD, were awarded the 2020 Nobel Prize in Chemistry for pioneering CRISPR-based genome-editing technology, a molecular tool that can precisely cut DNA. The system has myriad uses: It could, for example, be used to treat inherited diseases and develop immunotherapies for cancer.

In the years since Charpentier's and Doudna's landmark discovery, CRISPR technologies have become staples of basic research laboratories in all fields, with countless scientists adopting the simple and inexpensive tool to manipulate DNA in unprecedented ways. Cancer researchers have used the tool to precisely disrupt tumor suppressor genes or activate oncogenes to build more accurate disease models, discover drug targets, reveal basic mechanisms of tumor development, and much more.

"CRISPR really made genetic engineering methods a lot more convenient, easier, faster, and cheaper," says Jerry Li, MD, PhD, of the NCI's Division of Cancer Biology.

"For now, the most impactful outcome of this CRISPR technology is in the cancer biology world," he says, "but it's trickling into the therapeutic world," with several CRISPR-based interventions already in human testing. Some take aim at rare blood disorders, others at an inherited form of blindness. Leading the way, however, are trials of gene-edited T cells for cancer.

The first such U.S.-based trial launched in 2018 at the University of Pennsylvania in Philadelphia, where Edward Stadtmauer, MD, and his colleagues treated three patients—two with myeloma and one with liposarcoma—with an autologous NY-ESO-1–directed T-cell product in which they had disabled genes encoding T-cell receptors (TCR) and PD-1 receptors. "CRISPR was essential for the performance of our first-in-human attempt to enhance the function and activity of engineered T cells," says Stadtmauer, who reported earlier this year that the cells were well tolerated and showed durable engraftment (Science 2020;367:eaba7365).

CRISPR Therapeutics, a company cofounded by Charpentier, is also testing three allogeneic chimeric antigen receptor T-cell therapies that use the gene-editing technique to eliminate the TCR and MHC I molecules from donor cells and to precisely insert the genetic construct equipped with antigens for either CD19, BCMA, or CD70, depending on the therapy. Meanwhile, Intima Bioscience is studying whether knocking out an intracellular immune checkpoint gene called *CISH* from a patient's own tumor-infiltrating lymphocytes can enhance TCR avidity, improve neoantigen recognition, and lead to tumor regression. A phase I trial in metastatic gastrointestinal cancers kicked off earlier this year at the University of Minnesota's Masonic Cancer Center in Minneapolis.

Clinicians in China have also launched at least nine other trials of CRISPR-engineered T-cell therapies since 2017.

The various T-cell therapies under evaluation all involve gene editing *ex vivo*, but Eric Kmiec, PhD, of ChristianaCare's Gene Editing Institute in Newark, DE, hopes to soon begin testing an *in vivo* CRISPR-based treatment. He plans to disable *NRF2*—a gene involved in tumor progression and chemotherapy resistance—in patients with advanced non–small cell lung cancer to try to stall cancer growth and make tumors more susceptible to platinum-based chemotherapeutics.

Earlier this year, Kmiec's team described a unique stretch of tumor-specific DNA that allows for targeting *NRF2* in cancer cells without affecting the gene in normal tissues—and he credits Charpentier and Doudna, who helped define the various pieces of the CRISPR machinery, for making that strategy possible (Mol Cancer Res 2020;18:891–902). "Without this fundamental molecular information," Kmiec says, "it would've taken us much longer to develop our tumor-specific selective protocol for the disablement of the *NRF2* gene in squamous cell carcinoma cells." *–Elie Dolgin* ■

For more news on cancer research, visit *Cancer Discovery* online at http://cancerdiscovery.aacrjournals.org/CDNews.

NOTED

Exact Sciences will acquire Thrive Earlier Detection for $1.7 billion up front and up to $450 million more in milestone payments. Exact will gain CancerSEEK, Thrive's liquid biopsy cancer-screening test that combines genomic screening with protein analysis. Exact will also acquire Base Genomics, an epigenetics company developing technology for DNA methylation sequencing.

CRISPR Therapeutics announced positive results but concerning side effects with CTX110 in patients with relapsed/refractory B-cell malignancies. In the phase I CARBON trial, the allogeneic anti-CD19 chimeric antigen receptor T-cell therapy elicited complete responses in four of 11 patients. However, three patients developed cytokine release syndrome, one experienced immune effector cell–associated neurotoxicity syndrome, and one died due to side effects.

The FDA approved Bristol Myers Squibb's nivolumab (Opdivo) plus ipilimumab (Yervoy) for patients with newly diagnosed, inoperable malignant pleural mesothelioma. The approval was based on the phase III CheckMate-743 trial, in which patients treated with the PD-1–CTLA4 inhibitor combination had a median overall survival of 18.1 months, compared with 14.1 months in patients who received standard chemotherapy.

People living in U.S. counties with persistent poverty may have a higher risk of dying from cancer than those living in areas with less poverty (Cancer Epidemiol Biomarkers Prev 2020;29:1949–54). Between 2007 and 2011, the cancer mortality rate was 201.3 deaths per 100,000 people in counties with persistent poverty (those with poverty rates of at least 20% in Census data since 1980), compared with 179.3 deaths per 100,000 people in counties without persistent poverty.

The COVID-19 pandemic has dramatically cut cancer screenings, diagnoses, and treatments (JCO Clin Cancer Inform 2020 Oct 21 [Epub ahead of print]). Researchers analyzed 6,227,474 Medicare claims and found significant decreases in screening when comparing April 2019 with April 2020: Screening dropped by 85% for breast cancer, 75% for lung cancer, 74% for colon cancer, and 56% for prostate cancer. There were also declines in biopsies, chemotherapy treatments, and surgery.

AACR American Association for Cancer Research

CANCER DISCOVERY

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